Micormedex NeoFax Essentials 2014

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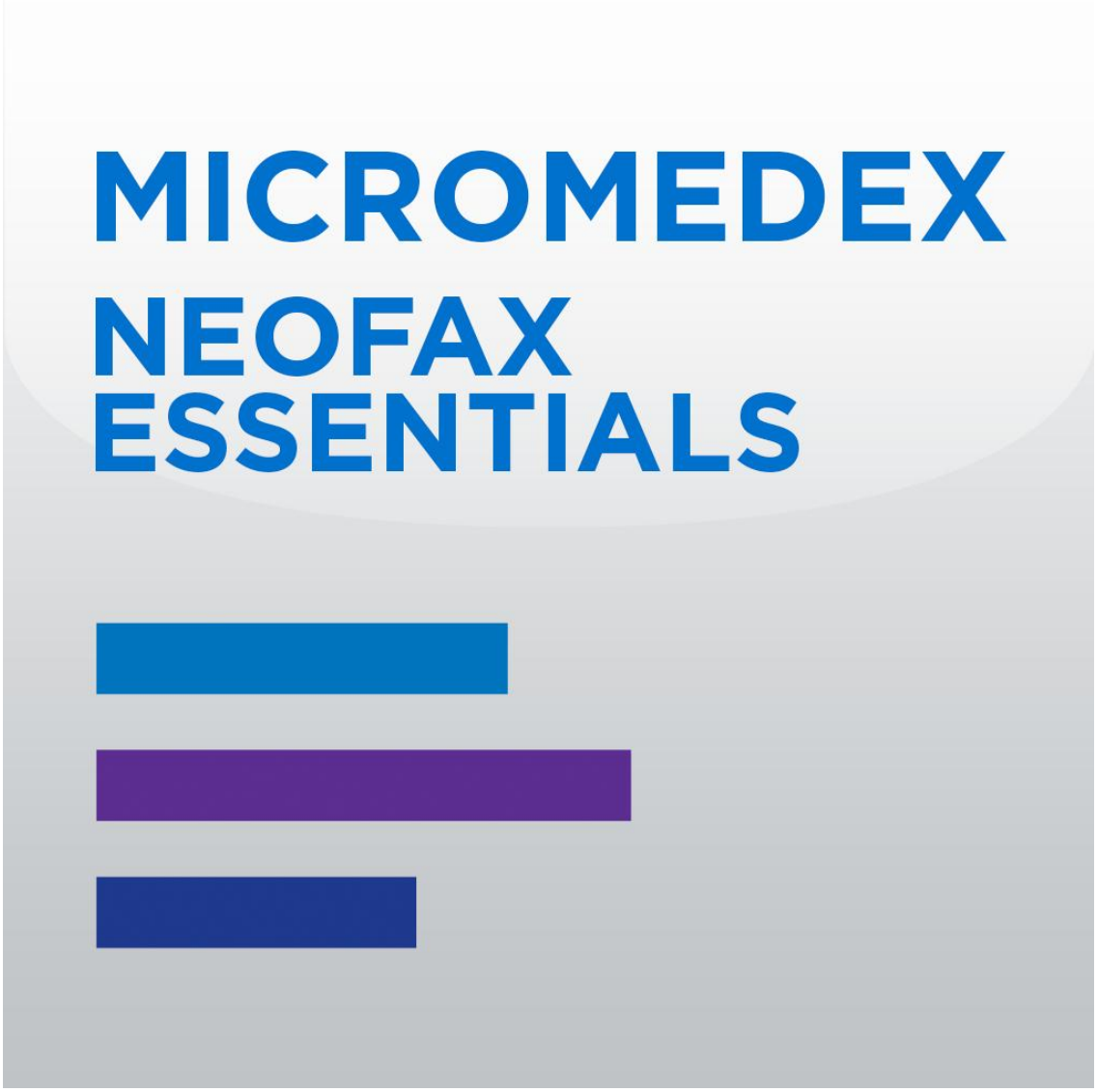
1. Micormedex NeoFax Essentials 2014



1.1 Acetaminophen

Title Acetaminophen

Dose

Intravenous
Preterm infants 32 weeks postmenstrual age or older: 10 mg/kg/dose IV every 6 hours as needed or around-the-clock. May consider a 20 mg/kg loading dose [1] [2] .
Term infants: 7.5 mg/kg/dose IV every 6 hours (**maximum 30 mg/kg/24 hours**) as needed or around the clock for pain or fever [3] [4] .

Oral
Preterm infants less than 32 weeks Postmenstrual Age: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 8 hours as needed or around-the-clock.

Term infants: 20 to 25 mg/kg orally; then 12 to 15 mg/kg/dose every 6 hours as needed or around-the-clock.

Rectal
Preterm infants less than 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 12 hours as needed or around-the-clock.
Preterm infants greater than or equal to 32 weeks Postmenstrual Age: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 8 hours as needed or around-the-clock.
Term infants: 30 mg/kg rectally; then 12 to 18 mg/kg/dose every 6 hours as needed or around-the-clock.

Administration

Intravenous: Administer IV over 15 minutes. Withdraw appropriate dose and administer in bottle, bag, or IV syringe; dose should be administered within 6 hours [5] .
Exercise caution when calculating the dose in milligrams and administering the dose in milliliters [6] [7] [8] . The administered volume in a neonate should always be 7.5 mL or less [8] .

Uses

Fever reduction and treatment of mild to moderate pain: The decision to use acetaminophen should be weighed against the epidemiological evidence of an association between acetaminophen use and asthma, atopy, rhinoconjunctivitis, or eczema; although causality has not been established [9] [10] [11] . The IV route may be considered when the oral or rectal route is not possible [4] .

Routine prophylactic use of acetaminophen at the time of vaccination is not recommended because of a potential reduction in antibody response.

Contraindications/Precautions

Intravenous formulation **contraindicated** in patients with severe hepatic impairment or severe active liver disease. Hypersensitivity reactions, including life-threatening anaphylaxis, have been reported [5] .

Rare but serious skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, have been associated with the use of acetaminophen. Reactions may occur after one use or at any time. Discontinue use immediately if rash or other hypersensitivity symptoms occur [12] .
Use with caution in patients with hepatocellular insufficiency, severe renal insufficiency, glucose 6 phosphate dehydrogenase deficiency, chronic malnutrition, or dehydration/hypovolemia [4] .
A modest reduction in blood pressure and heart rate may occur in neonates (preterm and full-term) after IV administration of acetaminophen. Neonates with pre-existing low arterial pressure may be at greater risk for hypotension [13] .

Epidemiological evidence demonstrated an association between acetaminophen use and asthma [11] , rhinoconjunctivitis, eczema [10] and atopy [9] . Confirmatory studies are

needed; however, in a meta-analysis, the odds ratio (OR) was 1.6 (95% CI, 1.48 to 1.74) for the risk of asthma in children among users of acetaminophen in the year prior to asthma diagnosis and the first year of life and 1.96 (95% CI, 1.5 to 2.56) for the risk of wheezing and acetaminophen use in the previous year of life [11] . In 2 observational studies, the OR was 3.61 (95% CI, 1.33 to 9.77) for atopy and acetaminophen exposure before the age of 15 months [9] , and up to 2.39 (95% CI, 2.24 to 2.55) for rhinoconjunctivitis symptoms or 1.99 (95% CI, 1.82 to 2.16) for eczema symptoms and acetaminophen exposure in the previous 12 months in adolescents [10]

Pharmacology

Nonnarcotic analgesic and antipyretic. Peak serum concentration occurs approximately 60 minutes after an oral dose. Absorption after rectal administration is variable and prolonged. Extensively metabolized in the liver, primarily by sulfation with a small amount by glucuronidation. Metabolites and unchanged drug are excreted by the kidney. Elimination half-life is approximately 3 hours in term neonates, 5 hours in preterm neonates greater than 32 weeks gestation, and up to 11 hours in more immature neonates. Elimination is prolonged in patients with liver dysfunction.
IV: A 20 mg/kg loading dose achieved a Cmax of 15 to 25 mg/L in 19 neonates (27 to 42 weeks gestational age) included in the PARANEO study. An effect compartment concentration of 10 mg/L was associated with a pain score reduction of 3.4 units [1] . A mean plasma concentration of 11 mg/L after acetaminophen IV 10 mg/kg every 6 hours (with or without a 20 mg/kg loading dose) was predicted from a pharmacokinetic analysis of 158 neonates (28 to 44 weeks gestation) [2] .
Oral/Rectal: Target concentrations above 10 mg/L are predicted in 50% of patients administered acetaminophen (30 mg/kg orally loading dose, 15 mg/kg/dose orally every 8 hours and 37.5 mg/kg rectally loading dose, 20 mg/kg/dose every 8 hours) in a population pharmacokinetic analysis (n=30, 1 to 90 days old, 31 to 40 weeks gestational age) [22] .

Adverse Effects

Injection site events (pain and site reactions; 15%) and vomiting (5%) occur with IV acetaminophen [4] . Rash, fever, thrombocytopenia, leukopenia, and neutropenia have been reported in children [5] [14] [15] [16] [17] . Serious skin reactions have been reported from patients who were rechallenged with acetaminophen and had a recurrence of a serious skin reaction [12] .

Hypothermia did not develop in 99 neonates (93 normothermic and 6 with fever) administered IV acetaminophen [18] .

Although data are limited for neonates, in children liver toxicity occurs with excessive doses [4] [5] or after prolonged administration (greater than 48 hours) of therapeutic doses. Hepatotoxicity occurred in less than 0.01% of children administered therapeutic doses of acetaminophen, in a systemic review (n=32,424; studies=62). The estimated risk for minor or major hepatic events was 0.031% (95% CI, 0.015% to 0.057%) [19] . No significant increases in liver enzymes were observed after a median duration of 60 hours (6 to 480 hours) and a median of 9 (2 to 80) doses of IV acetaminophen (20 mg/kg loading dose; 10 mg/kg (every 6 hours for more than 36 weeks postmenstrual age (PMA), every 8 hours for 31 to 36 weeks PMA, and every 12 hours for less than 31

weeks postmenstrual age) in 189 infants (1 day to 182 days of age; 30 to 55 weeks PMA), in a retrospective analysis [20] . Acute liver failure occurred in an 11-month-old boy who received therapeutic doses of oral acetaminophen for a prolonged duration (10 days) [21] .

Monitoring

Assess for signs of pain. Monitor temperature. Assess liver function. Serum acetaminophen concentration is obtained only to assess toxicity.

Special Considerations/Preparation

Available orally in various liquid formulations containing 32, 80, and 100 mg/mL. Some formulations are alcohol, dye, and sugar free.
Suppositories contain 80,120, 325, and 650 mg. Inaccurate dosing may occur with rectal administration because of unequal distribution of acetaminophen in the suppositories.
Intravenous formulation available in a 100-mL glass vial containing 1000 mg (10 mg/mL). Vial is for single use only and should be used within 6 hours of opening. Do not refrigerate or freeze [5] .

Treatment of Serious Acetaminophen Toxicity: N-acetylcysteine (NAC), 150 mg/kg in 5% dextrose or 1/2 NS given IV over 60 minutes (loading dose), followed by 50 mg/kg in 5% dextrose or 1/2 NS over 4 hours, then 100 mg/kg in 5% dextrose or 1/2 NS over 16 hours. NAC should be continued until clinical and biochemical markers of hepatic injury improve, and acetaminophen concentration is below the limits of detection. NAC solution concentrations of 40 mg/mL have been used to avoid fluid overload and hyponatremia in the neonate.

Solution Compatibility

D_5W; NS.

Terminal Injection Site Compatibility **Acetaminophen 10 mg/mL**

Cimetidine 12 mg/mL, dextrose 5% in lactated Ringer solution, dextrose 5% in normal saline, dextrose 10%, dexamethasone 10 mg/mL, diphenhydramine 50 mg/mL, dolasetron 20 mg/mL, fentanyl 50 mcg/mL, granisetron 0.1 mg/mL, heparin 100 units/mL, hydrocortisone 50 mg/mL, hydromorphone 4 mg/mL, ketorolac 15 mg/mL, lactated Ringer solution, lidocaine 20 mg/mL, lorazepam 0.5 mg/mL, mannitol 150 mg/mL (15%), methylprednisolone 125 mg/mL, metoclopramide 5 mg/mL, midazolam 5 mg/mL, morphine 15 mg/mL, nalbuphine 20 mg/mL, ondansetron 2 mg/mL, potassium chloride 0.1 mEq/mL.

Terminal Injection Site Incompatibility

Diazepam.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is

dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
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Monitoring

Assess for signs of pain. Monitor temperature. Assess liver function. Serum acetaminophen concentration is obtained only to assess toxicity.

Special Considerations/Preparation

Available orally in various liquid formulations containing 32, 80, and 100 mg/mL. Some formulations are alcohol, dye, and sugar free.
Suppositories contain 80,120, 325, and 650 mg. Inaccurate dosing may occur with rectal administration because of unequal distribution of acetaminophen in the suppositories.
Intravenous formulation available in a 100-mL glass vial containing 1000 mg (10 mg/mL). Vial is for single use only and should be used within 6 hours of opening. Do not refrigerate or freeze [5] .

Treatment of Serious Acetaminophen Toxicity: N-acetylcysteine (NAC), 150 mg/kg in 5% dextrose or 1/2 NS given IV over 60 minutes (loading dose), followed by 50 mg/kg in 5% dextrose or 1/2 NS over 4 hours, then 100 mg/kg in 5% dextrose or 1/2 NS over 16 hours. NAC should be continued until clinical and biochemical markers of hepatic injury improve, and acetaminophen concentration is below the limits of detection. NAC solution concentrations of 40 mg/mL have been used to avoid fluid overload and hyponatremia in the neonate.

Solution Compatibility

D_5W; NS.

Terminal Injection Site Compatibility **Acetaminophen 10 mg/mL**

Cimetidine 12 mg/mL, dextrose 5% in lactated Ringer solution, dextrose 5% in normal saline, dextrose 10%, dexamethasone 10 mg/mL, diphenhydramine 50 mg/mL, dolasetron 20 mg/mL, fentanyl 50 mcg/mL, granisetron 0.1 mg/mL, heparin 100 units/mL, hydrocortisone 50 mg/mL, hydromorphone 4 mg/mL, ketorolac 15 mg/mL, lactated Ringer solution, lidocaine 20 mg/mL, lorazepam 0.5 mg/mL, mannitol 150 mg/mL (15%), methylprednisolone 125 mg/mL, metoclopramide 5 mg/mL, midazolam 5 mg/mL, morphine 15 mg/mL, nalbuphine 20 mg/mL, ondansetron 2 mg/mL, potassium chloride 0.1 mEq/mL.

Terminal Injection Site Incompatibility

Diazepam.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
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1.2 Acyclovir

Title Acyclovir

Dose

Herpes Simplex Virus Infection, Treatment and Preemptive Therapy: 20 mg/kg/dose IV every 8 hours; infuse over 1 hour [1] [2] [3] .
Treat localized herpes simplex disease for 14 days and disseminated or CNS disease for 21 days [1] [2] [3] . Continue IV therapy for another 7 days, when repeat polymerase chain reaction (cerebrospinal fluid herpes simplex virus) is positive after approximately 21 days of acyclovir therapy. The duration for preemptive therapy without proven disease is 10 days [1] .

Herpes Simplex Virus Infection, Chronic suppression: 300 mg/m^2/dose orally 3 times a day. Begin suppressive therapy immediately after completion of IV treatment and continue for 6 months [4] [5] .

Varicella-Zoster Virus Infection:10 to 15 mg/kg/dose IV every 8 hours for 5 to 10 days [6] [7] [8] [9] .

Dose Adjustments
Preterm infant less than 33 weeks gestational age:give usual IV dose every 12 hours [10] .

Renal
CrCl 25 to 50 mL/min/1.73 m(2) or serum creatinine (SCr) 0.8 to 1.1 mg/dL: give usual IV dose every 12 hours [10] .
CrCl 10 to 25 mL/min/1.73 m(2) or SCr 1.2 to 1.5 mg/dL with decreasing urine

output: give usual IV dose every 24 hours [10] .
CrCl less than 10 mL/min/1.73 m(2) or SCr greater than 1.5 mg/dL or urine output less than 1 mL/kg/hour: decrease IV dose by 50% and give every 24 hours [10] .

Administration

Intravenous route: Administer as IV infusion over 1 hour at a concentration of 7 mg/mL or less in D_5W or NS [11] .
Oral route: take with or without food; for suspension, shake well before measuring each dose [12] .

Uses

Treatment of known or suspected neonatal herpes simplex virus (HSV) infections. Acyclovir treatment should be initiated in all infants with herpes disease. In asymptomatic neonates born to women with active herpes lesions, initiation of acyclovir is dependent on risk of transmission to the neonate [1] [2] .

Treatment of varicella-zoster virus infections with CNS and pulmonary involvement. Acyclovir treatment is recommended in infants with varicella-zoster infection having CNS or pulmonary involvement [6] [7] [8] [9] .

Chronic suppressive therapy after treatment of neonatal HSV infection.
Based on data reported from 2 parallel, phase III, double-blind, placebo-controlled studies (n=45 with CNS disease; n=29 with skin, eye, mouth (SEM) disease), 6 months of suppressive oral acyclovir therapy (300 mg/m^2/dose 3 times a day) started immediately after IV treatment for CNS HSV disease was associated with better neurological outcomes when compared with placebo. Of the 28 infants with CNS disease assessed at 12 months (acyclovir=16; placebo=12), Bayley Scales of Infant Development (2nd Edition) Mental Scores were significantly higher in patients receiving acyclovir compared with patients receiving placebo (88.24 vs 68.12; p=0.046). In patients with SEM disease receiving 6 months of suppressive oral acyclovir therapy started immediately after IV treatment, the time to 2 recurrences of skin lesions was 1.7 months longer in the treatment group compared with placebo. Of the 15 infants with SEM disease assessed at 12 months, there were no differences in Bayley scores between acyclovir and placebo. An absolute neutrophil count of 500 cells/mm^3 or less was reported in 20% to 25% of patients receiving acyclovir compared with 5% to 7% receiving placebo; no patient had complications associated with neutropenia [4] .
In one case series (n=16), infants treated for CNS or disseminated HSV disease received oral acyclovir suppressive therapy for 2 years. Starting doses were 1200 to 1600 mg/m^2 every 12 hours to achieve an acyclovir peak serum concentration greater than 2 mcg/mL [13] . There was no control group; however, the authors concluded there were improved neurological outcomes in this cohort based on comparisons with historical information from other studies. In another case series (n=9) of infants with neonatal HSV infection (n=8 with CNS disease; n=1 with recurrent dermal and ophthalmic disease) who received oral acyclovir suppressive therapy, initial oral acyclovir doses were 600 to 1400 mg/m^2 every 8 to 12 hours. The mean acyclovir dose required to achieve the target peak concentration of 2 mcg/mL or greater was 1340

mg/m^2/dose given every 12 hours. Long-term neurological development was normal in 7 of the 9 children; the 2 children who developed neurological impairment experienced a delay in oral therapy following completion of parenteral acyclovir therapy [14] .

Pharmacology

Antiviral drug that is preferentially taken up by infected cells; inhibits viral DNA synthesis. CSF concentrations are 30% to 50% of serum concentrations. Oral absorption is 15% to 30%. Most of administered dose is excreted unchanged in urine, primarily via glomerular filtration. Protein binding and metabolism are minimal. Serum half-life is 3 to 4 hours in patients with normal renal and hepatic function.

Adverse Effects

Neutropenia occurs in approximately 20% of patients; decrease dose or treat with GCSF if ANC remains less than 500/mm^3. Phlebitis may occur at IV site due to alkaline pH of 10. Risk of transient renal dysfunction and crystalluria is minimized by slow infusion rates and adequate patient hydration. Resistant viral strains may emerge during long-term therapy; these patients are at high risk for progressive life-threatening disease.

Monitoring

Periodic CBC. Follow renal and hepatic function. Monitor IV site for phlebitis--if noted, make infusion solution more dilute [15] [11] .

Special Considerations/Preparation

Intravenous formulations available as solution (50 mg/mL) or as powder for solution in 500-mg and 1-g vials. Prepare powder for solution by dissolving contents of 500-mg vial in 10 mL sterile water for injection. Reconstituted solution is stable at room temperature for 12 hours. **Do not refrigerate** [11] .

Infusion solution concentration should be no greater than 7 mg/mL [11] .

A 5-mg/mL dilution may be made by adding 1 mL of 50 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution should be used within 24 hours.

Oral suspension available in 200-mg/5 mL concentration. Store at room temperature. Shake well before administration [12] .

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Dex/AA.

Terminal Injection Site Compatibility

Amikacin, ampicillin, aminophylline, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, famotidine, fluconazole, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, nafcillin, oxacillin, penicillin G, pentobarbital, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, caspofungin, cefepime, dobutamine, dopamine, meropenem, and piperacillin-tazobactam.

References

- Whitley R, Arvin A, Prober C, et al: A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991;324:444.
- Englund JA, Zimmerman BS, Swierkosz EM, et al: Herpes simplex virus resistant to acyclovir: A study in a tertiary care center. *Ann Intern Med* 1990;112:416.
- McDonald L, Tartaglione TA, Mendelman PM, et al: Lack of toxicity in two cases of neonatal acyclovir overdose. *Pediatr Infect Dis J* 1989;8:529.
- Sullender WM, Arvin AM, Diaz PS, et al: Pharmacokinetics of acyclovir suspension in infants and children. *Antimicrob Agents Chemother* 1987;31:1722.
- Hintz M, Connor JD, Spector SA, et al: Neonatal acyclovir pharmacokinetics in patients with herpes virus infections. *Am J Med* 1982;73 (suppl):210.

1. Kimberlin DW, Baley J, Committee on Infectious Diseases et al: Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. Pediatrics Feb, 2013; 131(2): e635-e646.
2. Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010. Centers for Disease Control and Prevention, Atlanta, GA, Dec18, 2010. Available at: http://www.cdc.gov/mmwr/pdf/rr/rr5912.pdf.
3. Kimberlin DW, Lin CY, Jacobs RF et al: Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics Aug1, 2001; 108(2): 230-238.
4. Kimberlin DW, Whitley RJ, Wan W et al: Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med Oct6, 2011; 365(14): 1284-1292.
5. Kimberlin D, Powell D, Gruber W et al: Administration of oral acyclovir suppressive therapy after neonatal herpes simplex virus disease limited to the skin, eyes and mouth: results of a phase I/II trial. Pediatr Infect Dis J Mar, 1996; 15(3): 247-254.
6. Smith CK: Varicella in the fetus and newborn. Semin Fetal Neonatal Med Aug, 2009; 14(4): 209-217.
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8. Singalavanija S, Limpongsanurak W, Horpoapan S et al: Neonatal varicella: a report of 26 cases. J Med Assoc Thai Oct, 1999; 82(10): 957-962.

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10. Englund JA: Acyclovir therapy in neonates. J Pediatr Jul, 1991; 119(1 Pt 1): 129-135.
11. Product Information: acyclovir IV injection, acyclovir IV injection. APP Pharmaceuticals, LLC (per Manufacturer), Schaumburg, IL, Jan, 2008.
12. Product Information: ZOVIRAX(R) oral capsules, tablets, suspension, acyclovir oral capsules, tablets, suspension. GlaxoSmithKline, Research Triangle Park, NC, Nov1, 2007.
13. Tiffany KF, Benjamin DK, Palasanthiran P et al: Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. J Perinatol Mar, 2005; 25(3): 156-161.
14. Rudd C: Dosing considerations for oral acyclovir following neonatal herpes disease. Acta Paediatr Dec, 1994; 83(12): 1237-1243.
15. Centers for Disease Control and Prevention , National Institutes of Health , HIV Medicine Association of the Infectious Diseases Society of America et al: Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep Sep4, 2009; 58(RR11): 1-166.

Title Acyclovir

Dose

Herpes Simplex Virus Infection, Treatment and Preemptive Therapy: 20 mg/kg/dose IV every 8 hours; infuse over 1 hour [1] [2] [3] .
Treat localized herpes simplex disease for 14 days and disseminated or CNS disease for 21 days [1] [2] [3] . Continue IV therapy for another 7 days, when repeat polymerase chain reaction (cerebrospinal fluid herpes simplex virus) is positive after approximately 21 days of acyclovir therapy. The duration for preemptive therapy without proven disease is 10 days [1] .

Herpes Simplex Virus Infection, Chronic suppression: 300 mg/m^2/dose orally 3 times a day. Begin suppressive therapy immediately after completion of IV treatment and continue for 6 months [4] [5] .

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Dose Adjustments
Preterm infant less than 33 weeks gestational age:give usual IV dose every 12 hours [10] .

Renal
CrCl 25 to 50 mL/min/1.73 m(2) or serum creatinine (SCr) 0.8 to 1.1 mg/dL: give usual IV dose every 12 hours [10] .
CrCl 10 to 25 mL/min/1.73 m(2) or SCr 1.2 to 1.5 mg/dL with decreasing urine output: give usual IV dose every 24 hours [10] .

CrCl less than 10 mL/min/1.73 m(2) or SCr greater than 1.5 mg/dL or urine output less than 1 mL/kg/hour: decrease IV dose by 50% and give every 24 hours [10] .

Administration

Intravenous route: Administer as IV infusion over 1 hour at a concentration of 7 mg/mL or less in D_5W or NS [11] .
Oral route: take with or without food; for suspension, shake well before measuring each dose [12] .

Uses

Treatment of known or suspected neonatal herpes simplex virus (HSV) infections. Acyclovir treatment should be initiated in all infants with herpes disease. In asymptomatic neonates born to women with active herpes lesions, initiation of acyclovir is dependent on risk of transmission to the neonate [1] [2] .

Treatment of varicella-zoster virus infections with CNS and pulmonary involvement. Acyclovir treatment is recommended in infants with varicella-zoster infection having CNS or pulmonary involvement [6] [7] [8] [9] .

Chronic suppressive therapy after treatment of neonatal HSV infection.
Based on data reported from 2 parallel, phase III, double-blind, placebo-controlled studies (n=45 with CNS disease; n=29 with skin, eye, mouth (SEM) disease), 6 months of suppressive oral acyclovir therapy (300 mg/m^2/dose 3 times a day) started immediately after IV treatment for CNS HSV disease was associated with better neurological outcomes when compared with placebo. Of the 28 infants with CNS disease assessed at 12 months (acyclovir=16; placebo=12), Bayley Scales of Infant Development (2nd Edition) Mental Scores were significantly higher in patients receiving acyclovir compared with patients receiving placebo (88.24 vs 68.12; p=0.046). In patients with SEM disease receiving 6 months of suppressive oral acyclovir therapy started immediately after IV treatment, the time to 2 recurrences of skin lesions was 1.7 months longer in the treatment group compared with placebo. Of the 15 infants with SEM disease assessed at 12 months, there were no differences in Bayley scores between acyclovir and placebo. An absolute neutrophil count of 500 $cells/mm^3$ or less was reported in 20% to 25% of patients receiving acyclovir compared with 5% to 7% receiving placebo; no patient had complications associated with neutropenia [4] .
In one case series (n=16), infants treated for CNS or disseminated HSV disease received oral acyclovir suppressive therapy for 2 years. Starting doses were 1200 to 1600 mg/m^2 every 12 hours to achieve an acyclovir peak serum concentration greater than 2 mcg/mL [13] . There was no control group; however, the authors concluded there were improved neurological outcomes in this cohort based on comparisons with historical information from other studies. In another case series (n=9) of infants with neonatal HSV infection (n=8 with CNS disease; n=1 with recurrent dermal and ophthalmic disease) who received oral acyclovir suppressive therapy, initial oral acyclovir doses were 600 to 1400 mg/m^2 every 8 to 12 hours. The mean acyclovir dose required to achieve the target peak concentration of 2 mcg/mL or greater was 1340 mg/m^2/dose given every 12 hours. Long-term neurological development was normal in

7 of the 9 children; the 2 children who developed neurological impairment experienced a delay in oral therapy following completion of parenteral acyclovir therapy [14] .

Pharmacology

Antiviral drug that is preferentially taken up by infected cells; inhibits viral DNA synthesis. CSF concentrations are 30% to 50% of serum concentrations. Oral absorption is 15% to 30%. Most of administered dose is excreted unchanged in urine, primarily via glomerular filtration. Protein binding and metabolism are minimal. Serum half-life is 3 to 4 hours in patients with normal renal and hepatic function.

Adverse Effects

Neutropenia occurs in approximately 20% of patients; decrease dose or treat with GCSF if ANC remains less than 500/mm^3. Phlebitis may occur at IV site due to alkaline pH of 10. Risk of transient renal dysfunction and crystalluria is minimized by slow infusion rates and adequate patient hydration. Resistant viral strains may emerge during long-term therapy; these patients are at high risk for progressive life-threatening disease.

Monitoring

Periodic CBC. Follow renal and hepatic function. Monitor IV site for phlebitis--if noted, make infusion solution more dilute [15] [11] .

Special Considerations/Preparation

Intravenous formulations available as solution (50 mg/mL) or as powder for solution in 500-mg and 1-g vials. Prepare powder for solution by dissolving contents of 500-mg vial in 10 mL sterile water for injection. Reconstituted solution is stable at room temperature for 12 hours. **Do not refrigerate** [11] .

Infusion solution concentration should be no greater than 7 mg/mL [11] .

A 5-mg/mL dilution may be made by adding 1 mL of 50 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution should be used within 24 hours.

Oral suspension available in 200-mg/5 mL concentration. Store at room temperature. Shake well before administration [12] .

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Dex/AA.

Terminal Injection Site Compatibility

Amikacin, ampicillin, aminophylline, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, famotidine, fluconazole, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, nafcillin, oxacillin, penicillin G, pentobarbital, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, caspofungin, cefepime, dobutamine, dopamine, meropenem, and piperacillin-tazobactam.

References

- Whitley R, Arvin A, Prober C, et al: A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991;324:444.
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4. Kimberlin DW, Whitley RJ, Wan W et al: Oral acyclovir suppression and neurodevelopment after neonatal herpes. N Engl J Med Oct6, 2011; 365(14): 1284-1292.
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8. Singalavanija S, Limpongsanurak W, Horpoapan S et al: Neonatal varicella: a report of 26 cases. J Med Assoc Thai Oct, 1999; 82(10): 957-962.

9. Ogilvie MM: Antiviral prophylaxis and treatment in chickenpox. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. J Infect Jan, 1998; 36 Suppl 1: 31-38.
10. Englund JA: Acyclovir therapy in neonates. J Pediatr Jul, 1991; 119(1 Pt 1): 129-135.
11. Product Information: acyclovir IV injection, acyclovir IV injection. APP Pharmaceuticals, LLC (per Manufacturer), Schaumburg, IL, Jan, 2008.
12. Product Information: ZOVIRAX(R) oral capsules, tablets, suspension, acyclovir oral capsules, tablets, suspension. GlaxoSmithKline, Research Triangle Park, NC, Nov1, 2007.
13. Tiffany KF, Benjamin DK, Palasanthiran P et al: Improved neurodevelopmental outcomes following long-term high-dose oral acyclovir therapy in infants with central nervous system and disseminated herpes simplex disease. J Perinatol Mar, 2005; 25(3): 156-161.
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15. Centers for Disease Control and Prevention , National Institutes of Health , HIV Medicine Association of the Infectious Diseases Society of America et al: Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep Sep4, 2009; 58(RR11): 1-166.

1.3 Adenosine

Title Adenosine

Dose

Starting dose: 50 mcg/kg rapid IV push (1 to 2 seconds).
Increase dose in 50 mcg/kg increments every 2 minutes until return of sinus rhythm.
Usual maximum dose: 250 mcg/kg.
Infuse as close to IV site as possible. Flush IV with saline immediately.
Intraosseous administration has also been reported to be successful.

Uses

Acute treatment of sustained paroxysmal supraventricular tachycardia.
It may also be useful in establishing the cause of the SVT.

Contraindications/Precautions

Contraindicated in patients with second- or third-degree AV block and patients with sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except patients with functioning pacemaker) [1] .

Pharmacology

Adenosine is the pharmacologically active metabolite of ATP. It acts by depressing sinus node automaticity and A-V node conduction. It does **not** have negative inotropic

effects. Response should occur within 2 minutes of the dose. Estimated serum half-life is 10 seconds.

Adverse Effects

Flushing, dyspnea, and irritability occur frequently, but usually resolve within 1 minute. Transient (duration less than 1 minute) arrhythmias may occur between termination of SVT and onset of normal sinus rhythm. Apnea has been reported in one preterm infant. Recurrence of SVT occurs in approximately 30% of treated patients. Aminophylline/Theophylline and caffeine diminish adenosine's effect by competitive antagonism.

Monitoring

Continuous EKG and blood pressure monitoring.

Special Considerations/Preparation

Supplied in 2-mL vials containing 6 mg adenosine dissolved in NS. Contains no preservative. Store at room temperature. **Do not refrigerate;** crystallization will occur. Solution must be clear at the time of use.
Dilutions can be made with NS for doses less than 0.2 mL (600 mcg). Use 1 mL (3000 mcg) with 9-mL NS to make a solution with a final concentration of 300 mcg/mL.

Solution Compatibility

D_5W and NS.

References

- Paret G, Steinmetz D, Kuint J et al: Adenosine for the treatment of paroxysmal supraventricular tachycardia in full-term and preterm newborn infants.*Am J Perinatol* 1996;13:343-46.
- Friedman FD: Intraosseous adenosine for the termination of supraventricular tachycardia in an infant. *Ann Emerg Med* 1996;28:356-58.
- Crosson JE, Etheridge SP, Milstein S et al: Therapeutic and diagnostic utility of adenosine during tachycardia evaluation in children.*Am J Cardiol* 1994;74:155-60.
- Till J, Shinebourne EA, Rigby ML, et al: Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children. *Br Heart J* 1989;62:204.
- Overholt ED, Rhuban KS, Gutgesell HP, et al: Usefulness of adenosine for arrhythmias in infants and children. *Am J Cardiol* 1988;61:336.

1. Product Information: adenosine IV injection, adenosine IV injection. Abraxis Pharmaceutical Products (Per Manufacturer), Schaumburg, IL, May, 2006.

Title Adenosine

Dose

Starting dose: 50 mcg/kg rapid IV push (1 to 2 seconds).
Increase dose in 50 mcg/kg increments every 2 minutes until return of sinus rhythm.
Usual maximum dose: 250 mcg/kg.
Infuse as close to IV site as possible. Flush IV with saline immediately.
Intraosseous administration has also been reported to be successful.

Uses

Acute treatment of sustained paroxysmal supraventricular tachycardia.
It may also be useful in establishing the cause of the SVT.

Contraindications/Precautions

Contraindicated in patients with second- or third-degree AV block and patients with sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except patients with functioning pacemaker) [1] .

Pharmacology

Adenosine is the pharmacologically active metabolite of ATP. It acts by depressing sinus node automaticity and A-V node conduction. It does **not** have negative inotropic effects. Response should occur within 2 minutes of the dose. Estimated serum half-life is 10 seconds.

Adverse Effects

Flushing, dyspnea, and irritability occur frequently, but usually resolve within 1 minute.
Transient (duration less than 1 minute) arrhythmias may occur between termination of SVT and onset of normal sinus rhythm. Apnea has been reported in one preterm infant.
Recurrence of SVT occurs in approximately 30% of treated patients.
Aminophylline/Theophylline and caffeine diminish adenosine's effect by competitive antagonism.

Monitoring

Continuous EKG and blood pressure monitoring.

Special Considerations/Preparation

Supplied in 2-mL vials containing 6 mg adenosine dissolved in NS. Contains no preservative. Store at room temperature. **Do not refrigerate;** crystallization will occur.
Solution must be clear at the time of use.
Dilutions can be made with NS for doses less than 0.2 mL (600 mcg). Use 1 mL (3000 mcg) with 9-mL NS to make a solution with a final concentration of 300 mcg/mL.

Solution Compatibility

D_5W and NS.

References

- Paret G, Steinmetz D, Kuint J et al: Adenosine for the treatment of paroxysmal supraventricular tachycardia in full-term and preterm newborn infants.*Am J Perinatol* 1996;13:343-46.
- Friedman FD: Intraosseous adenosine for the termination of supraventricular tachycardia in an infant. *Ann Emerg Med* 1996;28:356-58.
- Crosson JE, Etheridge SP, Milstein S et al: Therapeutic and diagnostic utility of adenosine during tachycardia evaluation in children.*Am J Cardiol* 1994;74:155-60.
- Till J, Shinebourne EA, Rigby ML, et al: Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children. *Br Heart J* 1989;62:204.
- Overholt ED, Rhuban KS, Gutgesell HP, et al: Usefulness of adenosine for arrhythmias in infants and children. *Am J Cardiol* 1988;61:336.

1. Product Information: adenosine IV injection, adenosine IV injection. Abraxis Pharmaceutical Products (Per Manufacturer), Schaumburg, IL, May, 2006.

1.4 Albuterol

Title Albuterol

Dose

Bronchodilation: 0.1 to 0.5 mg/kg/dose every 2 to 6 hours via nebulizer.
1 MDI actuation per dose (approximately 0.1 mg or 100 mcg) every 2 to 6 hours via MDI with spacer device placed in the inspiratory limb of the ventilator circuit. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.

Oral: 0.1 to 0.3 mg/kg/dose orally every 6 to 8 hours.

Treatment of hyperkalemia
Preterm neonates: 0.4 mg/dose every 2 hours via nebulization until serum potassium decreases to desired safe level (eg, less than 5 mmol/L) [1] . Consider alternative potassium-lowering therapies for potassium levels greater than 7.5 mmol/L.

Uses

Bronchodilator.
Treatment of hyperkalemia in preterm neonates. Published data using the nebulized formulation of albuterol for the treatment of hyperkalemia in preterm neonates are limited to one randomized, placebo-controlled trial (n=19). Following administration every 2 hours until serum potassium dropped below 5 mmol/L (or a maximum of 12 doses), nebulized albuterol (n=8) was effective in lowering potassium levels at 4 and 8 hours when compared with placebo (saline via nebulization; n=11) [1] .

Pharmacology

Specific β_2-adrenergic agonist. Minimal cardiovascular effects unless used concurrently with aminophylline. Stimulates production of intracellular cyclic AMP, enhancing the

binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Enhances mucociliary clearance. Drives potassium intracellular. Studies in vitro indicate that approximately 5% of a MDI dose administered using an in-line holding chamber/spacer device, versus less than 1% of a nebulizer dose, is delivered to the lung. Optimal aerosol dose in neonates is uncertain due to differences in aerosol drug delivery techniques. The therapeutic margin appears to be wide.
Well absorbed when administered orally. Onset of action is 30 minutes; duration is 4 to 8 hours. Serum half-life is approximately 6 hours (adults). Time to peak serum concentration is 3 to 4 hours. Tolerance may develop.

Adverse Effects

Tachycardia, arrhythmias, tremor, hypokalemia, and irritable behavior.

Monitoring

Assess degree of bronchospasm. Continuous EKG monitoring. **Consider not administering when heart rate is greater than 180 beats per minute.**Serum potassium [1] .

Special Considerations/Preparation

Oral dosage form: Syrup, 2 mg/5 mL.

Inhalation solution: Available as either 5 mg/mL, 0.83 mg/mL, 0.42 mg/mL, or 0.21 mg/mL.
A 0.1 mg/mL dilution for inhalation may be made by adding 3 mL of 0.83 mg/mL albuterol concentration to 22 mL of preservative-free normal saline. Label for inhalation use only. Stable for 7 days refrigerated.

MDI: Available in a pressurized hydrofluoroalkane metered dose inhaler (contains no chlorofluorocarbons (CFC)). Proventil® HFA and Ventolin® HFA 90 mcg albuterol base per actuation.

References

- Ballard J, Lugo RA, Salyer JW: A survey of albuterol administration practices in intubated patients in the neonatal intensive care unit. *Respir Care* 2002;47:31-38.
- Lugo RA, Kenney JK, Keenan J: Albuterol delivery in a neonatal ventilated lung model: nebulization versus chlorofluorocarbon- and, hydrofluoroalkane- pressurized metered dose inhalers. *Pediatr Pulmonol* 2001;31:247-254.
- Stefano JL, Bhutani VK, Fox WW: A randomized placebo-controlled study to evaluate the effects of oral albuterol on pulmonary mechanics in ventilator-dependent infants at risk of developing BPD. *Pediatr Pulmonol* 1991;10:183-90.
- Wong CS, Pavord ID, Williams J, et al: Bronchodilator, cardiovascular, and hypokalemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990;336:1396.
- Morgan DJ, Paull JD, Richmond BH, et al: Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986;22:587.

- Beck R, Robertson C, Galdes-Sebaldt M, Levison H: Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. *J Pediatr* 1985;107:605.
- Product information, Dey, 2007.
- Product Information, GlaxoSmithKline, 2008.

1. Singh BS, Sadiq HF, Noguchi A et al: Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. J Pediatr Jul, 2002; 141(1): 16-20.

Title Albuterol

Dose

Bronchodilation: 0.1 to 0.5 mg/kg/dose every 2 to 6 hours via nebulizer.
1 MDI actuation per dose (approximately 0.1 mg or 100 mcg) every 2 to 6 hours via MDI with spacer device placed in the inspiratory limb of the ventilator circuit. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.

Oral: 0.1 to 0.3 mg/kg/dose orally every 6 to 8 hours.

Treatment of hyperkalemia
Preterm neonates: 0.4 mg/dose every 2 hours via nebulization until serum potassium decreases to desired safe level (eg, less than 5 mmol/L) [1] . Consider alternative potassium-lowering therapies for potassium levels greater than 7.5 mmol/L.

Uses

Bronchodilator.
Treatment of hyperkalemia in preterm neonates. Published data using the nebulized formulation of albuterol for the treatment of hyperkalemia in preterm neonates are limited to one randomized, placebo-controlled trial (n=19). Following administration every 2 hours until serum potassium dropped below 5 mmol/L (or a maximum of 12 doses), nebulized albuterol (n=8) was effective in lowering potassium levels at 4 and 8 hours when compared with placebo (saline via nebulization; n=11) [1] .

Pharmacology

Specific β_2-adrenergic agonist. Minimal cardiovascular effects unless used concurrently with aminophylline. Stimulates production of intracellular cyclic AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. Enhances mucociliary clearance. Drives potassium intracellular. Studies in vitro indicate that approximately 5% of a MDI dose administered using an in-line holding chamber/spacer device, versus less than 1% of a nebulizer dose, is delivered to the lung. Optimal aerosol dose in neonates is uncertain due to differences in aerosol drug delivery techniques. The therapeutic margin appears to be wide.
Well absorbed when administered orally. Onset of action is 30 minutes; duration is 4 to 8 hours. Serum half-life is approximately 6 hours (adults). Time to peak serum concentration is 3 to 4 hours. Tolerance may develop.

Adverse Effects

Tachycardia, arrhythmias, tremor, hypokalemia, and irritable behavior.

Monitoring

Assess degree of bronchospasm. Continuous EKG monitoring. **Consider not administering when heart rate is greater than 180 beats per minute.**Serum potassium [1] .

Special Considerations/Preparation

Oral dosage form: Syrup, 2 mg/5 mL.

Inhalation solution: Available as either 5 mg/mL, 0.83 mg/mL, 0.42 mg/mL, or 0.21 mg/mL.
A 0.1 mg/mL dilution for inhalation may be made by adding 3 mL of 0.83 mg/mL albuterol concentration to 22 mL of preservative-free normal saline. Label for inhalation use only. Stable for 7 days refrigerated.

MDI: Available in a pressurized hydrofluoroalkane metered dose inhaler (contains no chlorofluorocarbons (CFC)). Proventil® HFA and Ventolin® HFA 90 mcg albuterol base per actuation.

References

- Ballard J, Lugo RA, Salyer JW: A survey of albuterol administration practices in intubated patients in the neonatal intensive care unit. *Respir Care* 2002;47:31-38.
- Lugo RA, Kenney JK, Keenan J: Albuterol delivery in a neonatal ventilated lung model: nebulization versus chlorofluorocarbon- and, hydrofluoroalkane- pressurized metered dose inhalers. *Pediatr Pulmonol* 2001;31:247-254.
- Stefano JL, Bhutani VK, Fox WW: A randomized placebo-controlled study to evaluate the effects of oral albuterol on pulmonary mechanics in ventilator-dependent infants at risk of developing BPD. *Pediatr Pulmonol* 1991;10:183-90.
- Wong CS, Pavord ID, Williams J, et al: Bronchodilator, cardiovascular, and hypokalemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990;336:1396.
- Morgan DJ, Paull JD, Richmond BH, et al: Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986;22:587.
- Beck R, Robertson C, Galdes-Sebaldt M, Levison H: Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. *J Pediatr* 1985;107:605.
- Product information, Dey, 2007.
- Product Information, GlaxoSmithKline, 2008.

1. Singh BS, Sadiq HF, Noguchi A et al: Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. J Pediatr Jul, 2002; 141(1): 16-20.

1.5 Alprostadil

Title Alprostadil

Dose

Initial dose: 0.05 to 0.1 mcg/kg per minute by continuous IV infusion.
Titrate to infant's response--oxygenation *versus* adverse effects.

Maintenance dose: May be as low as 0.01 mcg/kg per minute.
Higher initial doses are usually no more effective and have a high incidence of adverse effects.
May also be given via UAC positioned near ductus arteriosus.

Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 49 mL of compatible solution (eg, D_5W) yielding a concentration of 10 mcg/mL. Infuse at a rate of 0.6 mL/kg per hour to provide a dose of 0.1 mcg/kg per minute.

Uses

To promote dilation of ductus arteriosus in infants with congenital heart disease dependent on ductal shunting for oxygenation/perfusion.

Black Box Warning

According to the manufacturer's black box warning, apnea has been reported in 10% to 12% of neonates with congenital heart defects treated with alprostadil. Apnea is seen most often in neonates weighing less than 2 kg at birth, and usually appears during the first hour of drug infusion. Monitor respiratory status throughout treatment and be prepared to intubate/resuscitate.

Pharmacology

Alprostadil causes vasodilation of **all** arterioles. Inhibition of platelet aggregation. Stimulation of uterine and intestinal smooth muscle. Maximal drug effect usually seen within 30 minutes in cyanotic lesion; may take several hours in acyanotic lesions.

Adverse Effects

Common (6% to 15%): Apnea (consider treating with aminophylline), hypotension, fever, leukocytosis, cutaneous flushing, and bradycardia. Hypokalemia reported with long-term therapy (greater than 20 days), especially with doses greater than 0.05 mcg/kg/minute. Gastric outlet obstruction and reversible cortical proliferation of the long bones after prolonged treatment (greater than 120 hours).

Uncommon (1% to 5%): Seizures, hypoventilation, tachycardia, cardiac arrest, edema, sepsis, diarrhea, and disseminated intravascular coagulation.

Rare (less than 1%): Urticaria, bronchospasm, hemorrhage, hypoglycemia, and hypocalcemia.
Musculoskeletal changes: Widened fontanels, pretibial and soft tissue swelling, and swelling of the extremities may occur after 9 days of therapy. Cortical hyperostosis and

periostitis may occur with long-term (greater than 3 months) therapy. These changes resolve over weeks after discontinuation of therapy.

Monitoring

Closely monitor respiratory and cardiovascular status. Assess for improvement in oxygenation. Closely monitor infant's temperature. Ensure reliable IV access: duration of effect is short.

Special Considerations/Preparation

Supplied in 1-mL (500-mcg) ampules that must be refrigerated. **Dilute before administration to a concentration of 20 mcg/mL or less.**Prepare fresh infusion solutions every 24 hours. Osmolality of undiluted (500 mcg/mL) is 23,250 mOsm/kg. Extravasation may cause tissue sloughing and necrosis.

Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 49 mL of compatible solution (eg, D_5W) yielding a concentration of 10 mcg/mL. Infuse at a rate of 0.6 mL/kg per hour to provide a dose of 0.1 mcg/kg per minute.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Aminophylline, ampicillin, caffeine citrate, calcium chloride, cefazolin, cefotaxime, cimetidine, clindamycin, dobutamine, dopamine, fentanyl, furosemide, gentamicin, glycopyrrolate, metoclopramide, metronidazole, nitroglycerin, nitroprusside, potassium chloride, penicillin G, tobramycin, vancomycin, and vecuronium.

References

- Meckler GD, Lowe C: To intubate or not to intubate? Transporting infants on prostaglandin E_1. *Pediatrics* 2009;123;e25-e30.
- Talosi G, Katona M, Turi S: Side-effects of long-term prostaglandin E_1 treatment in neonates. *Pediatr Int* 2007;49:335-340.
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- Lim DS, Kulik TJ, Kim DW: Aminophylline for the prevention of apnea during prostaglandin E_1 infusion. *Pediatrics* 2003;112:e27-e29.
- Arav-Boger R, Baggett HC, Spevak PJ, Willoughby RE: Leukocytosis caused by prostaglandin E_1 in neonates. *J Pediatr* 2001;138:263-265.
- Kaufman MB, El-Chaar GM: Bone and tissue changes following prostaglandin therapy in neonates. *Ann Pharmacother* 1996;30:269.
- Peled N, Dagan O, Babyn P, et al: Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992;327:505.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p250.

- Lewis AB, Freed MD, Heymann MA, et al: Side effects of therapy with prostaglandin E_1 in infants with congenital heart disease. *Circulation* 1981;64:893.
- Heymann MA: Pharmacologic use of prostaglandin E_1 in infants with congenital heart disease. *Am Heart J* 1981;101:837.
- Product Information, Pfizer, 2002.

Title Alprostadil

Dose

Initial dose: 0.05 to 0.1 mcg/kg per minute by continuous IV infusion.
Titrate to infant's response--oxygenation *versus* adverse effects.

Maintenance dose: May be as low as 0.01 mcg/kg per minute.
Higher initial doses are usually no more effective and have a high incidence of adverse effects.
May also be given via UAC positioned near ductus arteriosus.

Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 49 mL of compatible solution (eg, D_5W) yielding a concentration of 10 mcg/mL. Infuse at a rate of 0.6 mL/kg per hour to provide a dose of 0.1 mcg/kg per minute.

Uses

To promote dilation of ductus arteriosus in infants with congenital heart disease dependent on ductal shunting for oxygenation/perfusion.

Black Box Warning

According to the manufacturer's black box warning, apnea has been reported in 10% to 12% of neonates with congenital heart defects treated with alprostadil. Apnea is seen most often in neonates weighing less than 2 kg at birth, and usually appears during the first hour of drug infusion. Monitor respiratory status throughout treatment and be prepared to intubate/resuscitate.

Pharmacology

Alprostadil causes vasodilation of **all** arterioles. Inhibition of platelet aggregation. Stimulation of uterine and intestinal smooth muscle. Maximal drug effect usually seen within 30 minutes in cyanotic lesion; may take several hours in acyanotic lesions.

Adverse Effects

Common (6% to 15%): Apnea (consider treating with aminophylline), hypotension, fever, leukocytosis, cutaneous flushing, and bradycardia. Hypokalemia reported with long-term therapy (greater than 20 days), especially with doses greater than 0.05 mcg/kg/minute. Gastric outlet obstruction and reversible cortical proliferation of the long bones after prolonged treatment (greater than 120 hours).

Uncommon (1% to 5%): Seizures, hypoventilation, tachycardia, cardiac arrest, edema, sepsis, diarrhea, and disseminated intravascular coagulation.

Rare (less than 1%): Urticaria, bronchospasm, hemorrhage, hypoglycemia, and hypocalcemia.
Musculoskeletal changes: Widened fontanels, pretibial and soft tissue swelling, and swelling of the extremities may occur after 9 days of therapy. Cortical hyperostosis and periostitis may occur with long-term (greater than 3 months) therapy. These changes resolve over weeks after discontinuation of therapy.

Monitoring

Closely monitor respiratory and cardiovascular status. Assess for improvement in oxygenation. Closely monitor infant's temperature. Ensure reliable IV access: duration of effect is short.

Special Considerations/Preparation

Supplied in 1-mL (500-mcg) ampules that must be refrigerated. **Dilute before administration to a concentration of 20 mcg/mL or less.**Prepare fresh infusion solutions every 24 hours. Osmolality of undiluted (500 mcg/mL) is 23,250 mOsm/kg. Extravasation may cause tissue sloughing and necrosis.

Sample Dilution and Infusion Rate: Mix 1 ampule (500 mcg) in 49 mL of compatible solution (eg, D_5W) yielding a concentration of 10 mcg/mL. Infuse at a rate of 0.6 mL/kg per hour to provide a dose of 0.1 mcg/kg per minute.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Aminophylline, ampicillin, caffeine citrate, calcium chloride, cefazolin, cefotaxime, cimetidine, clindamycin, dobutamine, dopamine, fentanyl, furosemide, gentamicin, glycopyrrolate, metoclopramide, metronidazole, nitroglycerin, nitroprusside, potassium chloride, penicillin G, tobramycin, vancomycin, and vecuronium.

References

- Meckler GD, Lowe C: To intubate or not to intubate? Transporting infants on prostaglandin E_1. *Pediatrics* 2009;123;e25-e30.
- Talosi G, Katona M, Turi S: Side-effects of long-term prostaglandin E_1 treatment in neonates. *Pediatr Int* 2007;49:335-340.
- Dice JE: Physical compatibility of alprostadil with commonly used IV solutions and medications in the neonatal intensive care unit. *J Pediatr Pharmacol Ther* 2006;11:233-236.
- Lim DS, Kulik TJ, Kim DW: Aminophylline for the prevention of apnea during prostaglandin E_1 infusion. *Pediatrics* 2003;112:e27-e29.

- Arav-Boger R, Baggett HC, Spevak PJ, Willoughby RE: Leukocytosis caused by prostaglandin E_1 in neonates. *J Pediatr* 2001;138:263-265.
- Kaufman MB, El-Chaar GM: Bone and tissue changes following prostaglandin therapy in neonates. *Ann Pharmacother* 1996;30:269.
- Peled N, Dagan O, Babyn P, et al: Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992;327:505.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p250.
- Lewis AB, Freed MD, Heymann MA, et al: Side effects of therapy with prostaglandin E_1 in infants with congenital heart disease. *Circulation* 1981;64:893.
- Heymann MA: Pharmacologic use of prostaglandin E_1 in infants with congenital heart disease. *Am Heart J* 1981;101:837.
- Product Information, Pfizer, 2002.

1.6 Alteplase

Title Alteplase

Dose

Restoration of function to central venous catheter: Instill into dysfunctional catheter at a concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL. If catheter function is not restored in 120 minutes after 1 dose, a second dose may be instilled.
An alternative dosing regimen using a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) was used in children 10 kg or less in 1 study (n=25; infants as young as 7 weeks included).

Dissolution of intravascular thrombi: 200 mcg/kg per hour (0.2 mg/kg per hour). Duration of therapy is 6 to 48 hours. If administering directly into the thrombus, dose may be increased after 6 hours to a maximum of 500 mcg/kg per hour. If localized bleeding occurs, stop infusion for 1 hour and restart using 100 mcg/kg per hour. Discontinue heparin several hours prior to initiation of therapy.

Note: Reports in the literature are a collection of cases gathered over several years. Some authors used loading doses, others did not. Infused doses ranged from 20 to 500 mcg/kg per hour. Complications were most often linked with higher doses and longer duration of therapy.
Call 1-800-NOCLOTS for case reporting and treatment guidance.

Uses

Dissolution of intravascular thrombi of recent onset that are either intraarterial or life-threatening. Adjuvant treatment of infective endocarditis vegetations.

Restoration of function to central venous access devices as assessed by the ability to withdraw blood.

Contraindications/Precautions

Contraindications for Activase® include:
Active internal bleeding

History of cerebrovascular accident
Intracranial neoplasm, arteriovenous malformation, or aneurysm
known bleeding diathesis
Recent intracranial or intraspinal surgery or trauma (within 3 months)
Severe uncontrolled hypertension [1]

Pharmacology

Alteplase binds strongly and specifically to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Alteplase has a shorter half-life than streptokinase and does not cause anaphylactic reactions. It is cleared rapidly from the plasma, primarily via the liver.

Adverse Effects

Intracranial hemorrhage may occur, especially in premature infants treated for prolonged periods. Bleeding from venipuncture sites occurs in approximately half of treated patients. The risk of complications increases at doses above 450 mcg/kg per hour.

Monitoring

Follow coagulation studies (PT, aPTT, fibrinogen, fibrin split products) prior to therapy and at least daily during treatment. Maintain fibrinogen levels greater than 100 mg/dL and platelets greater than 50,000/mm^3. Echocardiography to assess clot lysis at least every 12 hours (every 6 hours optimal). Cranial ultrasound to assess for hemorrhage prior to therapy.

Special Considerations/Preparation

Activase® is supplied as lyophilized powder in 50 mg and 100 mg vials. Reconstitute 50- or 100-mg vial by adding 50 or 100 mL of sterile water for injection (do not use bacteriostatic water for injection) respectively, for a concentration of 1 mg/mL. Can be further diluted with NS or D_5W to a concentration of 0.5 mg/mL if necessary. Use reconstituted solution within 8 hours of mixing when stored refrigerated or at room temperature.

Cathflo® Activase® is supplied as lyophilized powder in 2-mg vials. Reconstitute by adding 2.2 mL sterile water for injection to a final concentration of 1 mg/mL. Do not use bacteriostatic water for injection. Mix by gently swirling until the contents are completely dissolved. DO NOT SHAKE. Use reconstituted solution within 8 hours of mixing. Reconstituted solution may be stored refrigerated or at room temperature.

Solution Compatibility

NS and D_5W.

Terminal Injection Site Compatibility

Lidocaine, morphine, nitroglycerin, and propranolol.

Terminal Injection Site Incompatibility

Dobutamine, dopamine, and heparin.

References

- Manco-Johnson M, Nuss R: Neonatal thrombotic disorders. *NeoReviews* 2000;1:e201.
- Hartmann J, Hussein A, Trowitzsch E, et al: Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F18-F22.
- Marks KA, Zucker N, Kapelushnik J, et al: Infective endocarditis successfully treated in extremely low birth weight infants with recombinant tissue plasminogen activator. *Pediatrics* 2002;109:153-158.
- Weiner GM, Castle VP, DiPietro MA, Faix RG: Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998;133:133-136.
- Product Information, Genentech, Inc., 2005.

1. Product Information: ACTIVASE(R) IV injection, alteplase IV injection. Genentech,Inc, South San Fransisco, CA, Dec1, 2005.

Title Alteplase

Dose

Restoration of function to central venous catheter: Instill into dysfunctional catheter at a concentration of 1 mg/mL. Use 110% of the internal lumen volume of the catheter, not to exceed 2 mg in 2 mL. If catheter function is not restored in 120 minutes after 1 dose, a second dose may be instilled.
An alternative dosing regimen using a smaller dose (0.5 mg diluted in NS to volume required to fill the central venous catheter) was used in children 10 kg or less in 1 study (n=25; infants as young as 7 weeks included).

Dissolution of intravascular thrombi: 200 mcg/kg per hour (0.2 mg/kg per hour). Duration of therapy is 6 to 48 hours. If administering directly into the thrombus, dose may be increased after 6 hours to a maximum of 500 mcg/kg per hour. If localized bleeding occurs, stop infusion for 1 hour and restart using 100 mcg/kg per hour. Discontinue heparin several hours prior to initiation of therapy.

Note: Reports in the literature are a collection of cases gathered over several years. Some authors used loading doses, others did not. Infused doses ranged from 20 to 500 mcg/kg per hour. Complications were most often linked with higher doses and longer duration of therapy.
Call 1-800-NOCLOTS for case reporting and treatment guidance.

Uses

Dissolution of intravascular thrombi of recent onset that are either intraarterial or life-threatening. Adjuvant treatment of infective endocarditis vegetations.

Restoration of function to central venous access devices as assessed by the ability to withdraw blood.

Contraindications/Precautions

Contraindications for Activase® include:
Active internal bleeding
History of cerebrovascular accident
Intracranial neoplasm, arteriovenous malformation, or aneurysm
known bleeding diathesis
Recent intracranial or intraspinal surgery or trauma (within 3 months)
Severe uncontrolled hypertension [1]

Pharmacology

Alteplase binds strongly and specifically to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Alteplase has a shorter half-life than streptokinase and does not cause anaphylactic reactions. It is cleared rapidly from the plasma, primarily via the liver.

Adverse Effects

Intracranial hemorrhage may occur, especially in premature infants treated for prolonged periods. Bleeding from venipuncture sites occurs in approximately half of treated patients. The risk of complications increases at doses above 450 mcg/kg per hour.

Monitoring

Follow coagulation studies (PT, aPTT, fibrinogen, fibrin split products) prior to therapy and at least daily during treatment. Maintain fibrinogen levels greater than 100 mg/dL and platelets greater than 50,000/mm^3. Echocardiography to assess clot lysis at least every 12 hours (every 6 hours optimal). Cranial ultrasound to assess for hemorrhage prior to therapy.

Special Considerations/Preparation

Activase® is supplied as lyophilized powder in 50 mg and 100 mg vials. Reconstitute 50- or 100-mg vial by adding 50 or 100 mL of sterile water for injection (do not use bacteriostatic water for injection) respectively, for a concentration of 1 mg/mL. Can be further diluted with NS or D_5W to a concentration of 0.5 mg/mL if necessary. Use reconstituted solution within 8 hours of mixing when stored refrigerated or at room temperature.

Cathflo® Activase® is supplied as lyophilized powder in 2-mg vials. Reconstitute by adding 2.2 mL sterile water for injection to a final concentration of 1 mg/mL. Do not use bacteriostatic water for injection. Mix by gently swirling until the contents are

completely dissolved. DO NOT SHAKE. Use reconstituted solution within 8 hours of mixing. Reconstituted solution may be stored refrigerated or at room temperature.

Solution Compatibility

NS and D_5W.

Terminal Injection Site Compatibility

Lidocaine, morphine, nitroglycerin, and propranolol.

Terminal Injection Site Incompatibility

Dobutamine, dopamine, and heparin.

References

- Manco-Johnson M, Nuss R: Neonatal thrombotic disorders. *NeoReviews* 2000;1:e201.
- Hartmann J, Hussein A, Trowitzsch E, et al: Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six years experience and review of the literature. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F18-F22.
- Marks KA, Zucker N, Kapelushnik J, et al: Infective endocarditis successfully treated in extremely low birth weight infants with recombinant tissue plasminogen activator. *Pediatrics* 2002;109:153-158.
- Weiner GM, Castle VP, DiPietro MA, Faix RG: Successful treatment of neonatal arterial thromboses with recombinant tissue plasminogen activator. *J Pediatr* 1998;133:133-136.
- Product Information, Genentech, Inc., 2005.

1. Product Information: ACTIVASE(R) IV injection, alteplase IV injection. Genentech,Inc, South San Fransisco, CA, Dec1, 2005.

1.7 Amikacin

Title Amikacin

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)

≤29*	0 to 7	18	48
	8 to 28	15	36
	≥29	15	24
30 to 34	0 to 7	18	36
	≥8	15	24
≥35	ALL	15	24

Administration

Dilute to a final concentration of 2.5 to 5 mg/mL and administer as IV infusion by syringe pump over 30 to 60 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Restricted to treatment of infections caused by gram-negative bacilli that are resistant to other aminoglycosides. Usually used in combination with a β-lactam antibiotic.

Black Box Warning According to the manufacturer's black box warning, aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of amikacin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used

with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations

Peak: 20 to 30 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
(Draw 30 minutes after end of infusion, 1 hour after IM injection.)
Trough: 2 to 5 mcg/mL

Suggested Dosing Intervals

Level at 24 hrs (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤5	~ 9	24
5.1 to 8.0	~ 12	36
8.1 to 10.5	~ 16	48
≥10.6		Measure level in 24 hours

Special Considerations/Preparation

Available in concentrations of 50 mg/mL and 250 mg/mL. For IV use, dilute with a compatible solution to a concentration of 2.5 to 5 mg/mL. After dilution, solutions are stable for 24 hours at room temperature.

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone,

enalaprilat, epinephrine, esmolol, fluconazole, furosemide, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, hyaluronidase, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nicardipine, penicillin g, pentobarbital, phenobarbital, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, vancomycin, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amphotericin B, ampicillin, azithromycin, heparin (concentrations greater than 1 unit/mL), imipenem/cilastatin, mezlocillin, nafcillin, oxacillin, phenytoin, propofol, thiopental, and ticarcillin/clavulanate.

References

- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA: Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-e118.
- Langhendries JP, Battisti O, Bertrand JM, et al: Adaptation in neonatology of the once-daily concept of aminoglycoside administration: Evaluation of a dosing chart for amikacin in an intensive care unit. *Biol Neonate* 1998;74:351-362.
- Product Information, Teva, 2009.

Title Amikacin

Dose

Antibiotic Dosing Chart:

Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29*	0 to 7	18	48
	8 to 28	15	36
	≥29	15	24
30 to 34	0 to 7	18	36
	≥8	15	24
≥35	ALL	15	24

Administration

Dilute to a final concentration of 2.5 to 5 mg/mL and administer as IV infusion by syringe pump over 30 to 60 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Restricted to treatment of infections caused by gram-negative bacilli that are resistant to other aminoglycosides. Usually used in combination with a β-lactam antibiotic.

Black Box Warning According to the manufacturer's black box warning, aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of amikacin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations

Peak: 20 to 30 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
(Draw 30 minutes after end of infusion, 1 hour after IM injection.)
Trough: 2 to 5 mcg/mL

Suggested Dosing Intervals

Level at 24 hrs (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤5	~ 9	24
5.1 to 8.0	~ 12	36
8.1 to 10.5	~ 16	48
≥10.6		Measure level in 24 hours

Special Considerations/Preparation

Available in concentrations of 50 mg/mL and 250 mg/mL. For IV use, dilute with a compatible solution to a concentration of 2.5 to 5 mg/mL. After dilution, solutions are stable for 24 hours at room temperature.

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, enalaprilat, epinephrine, esmolol, fluconazole, furosemide, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, hyaluronidase, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nicardipine, penicillin g, pentobarbital, phenobarbital, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, vancomycin, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amphotericin B, ampicillin, azithromycin, heparin (concentrations greater than 1 unit/mL), imipenem/cilastatin, mezlocillin, nafcillin, oxacillin, phenytoin, propofol, thiopental, and ticarcillin/clavulanate.

References

- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA: Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-e118.
- Langhendries JP, Battisti O, Bertrand JM, et al: Adaptation in neonatology of the once-daily concept of aminoglycoside administration: Evaluation of a dosing chart for amikacin in an intensive care unit. *Biol Neonate* 1998;74:351-362.
- Product Information, Teva, 2009.

1.8 Aminophylline

Title Aminophylline

Dose

Loading dose: 8 mg/kg IV infusion over 30 minutes, or orally.
Maintenance dose: 1.5 to 3 mg/kg/dose orally, or IV slow push every 8 to 12 hours (start maintenance dose 8 to 12 hours after the loading dose).

In preterm infants, changing from IV aminophylline to oral theophylline requires no dose adjustment.

Uses

Treatment of neonatal apnea, including post-extubation, post-anesthesia, and prostaglandin E_1-induced. Bronchodilator. May improve respiratory function.

Pharmacology

Stimulates central respiratory drive and peripheral chemoreceptor activity. May increase diaphragmatic contractility. Cerebral blood flow is acutely decreased following IV bolus dose. Renal effects include diuresis and increased urinary calcium excretion. Stimulates gastric acid secretion and may cause gastroesophageal reflux. Cardiac output is increased due to higher sensitivity to catecholamines. Elimination in preterm infants is primarily as unchanged drug, although significant interconversion to caffeine occurs. In the very immature neonate, the serum half-life of theophylline is prolonged (20 to 30 hours). Theophylline metabolism and clearance mature to adult values by 55 weeks postmenstrual age. Aminophylline salt is 78.9% theophylline. Theophylline administered orally is approximately 80% bioavailable; therefore, no dosage adjustment is necessary when changing from IV aminophylline to oral theophylline.

Adverse Effects

GI irritation. Hyperglycemia. CNS irritability and sleeplessness. May be associated with renal calcifications when used concurrently with furosemide and/or dexamethasone.
Signs of toxicity: Sinus tachycardia, failure to gain weight, vomiting, jitteriness, hyperreflexia, and seizures.

Treatment of Serious Theophylline Toxicity: Activated charcoal, 1 g/kg as a slurry by gavage tube every 2 to 4 hours. Avoid sorbitol-containing preparations: They may cause osmotic diarrhea.

Monitoring

Monitor heart rate and check blood glucose periodically with reagent strips. Assess for agitation and feeding intolerance.

Consider withholding next dose if heart rate is greater than 180 beats per minute.

When indicated by lack of efficacy or clinical signs of toxicity, serum trough concentration should be obtained. Therapeutic ranges are:
1) Apnea of prematurity: 7 to 12 mcg/mL.
2) Bronchospasm: 10 to 20 mcg/mL (older infants with bronchospasm may need these higher levels because of increased protein binding).

Special Considerations/Preparation

Available as aminophylline for IV use (25 mg/mL) in 10- and 20-mL vials. Dilute 1 mL (25 mg) with 4 mL NS or D_5W to yield a final concentration of 5 mg/mL. Stable for 4 days refrigerated.

Oral theophylline is available only as an elixir at a concentration of 80 mg/15 mL (5.33 mg/mL) and contains 20% alcohol.
Aminophylline oral solution is no longer available.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA (white precipitate forms within 2 hours) solutions. Acyclovir, ampicillin, amikacin, aztreonam, caffeine citrate, calcium gluconate, ceftazidime, chloramphenicol, cimetidine, dexamethasone, dopamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, fluconazole, flumazenil, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, meropenem, metoclopramide, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, pancuronium bromide, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, cefepime, ceftriaxone, ciprofloxacin, clindamycin, dobutamine, epinephrine, hydralazine, insulin, isoproterenol, methylprednisolone, and penicillin G.

References

- Lim DS, Kulik TJ, Kim DW: Aminophylline for the prevention of apnea during prostaglandin E_1 infusion. *Pediatrics* 2003;112:e27-e29.
- Hochwald C, Kennedy K, Chang J, Moya F: A randomized, controlled, double-blind trial comparing two loading doses of aminophylline. *J Perinatol*2002;22:275-278.

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- Aranda JV, Sitar DS, Parsons WD, et al: Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976;295:413.
- Product Information, Hospira, 2004.

Title Aminophylline

Dose

Loading dose: 8 mg/kg IV infusion over 30 minutes, or orally.
Maintenance dose: 1.5 to 3 mg/kg/dose orally, or IV slow push every 8 to 12 hours (start maintenance dose 8 to 12 hours after the loading dose).

In preterm infants, changing from IV aminophylline to oral theophylline requires no dose adjustment.

Uses

Treatment of neonatal apnea, including post-extubation, post-anesthesia, and prostaglandin E_1-induced. Bronchodilator. May improve respiratory function.

Pharmacology

Stimulates central respiratory drive and peripheral chemoreceptor activity. May increase diaphragmatic contractility. Cerebral blood flow is acutely decreased following IV bolus dose. Renal effects include diuresis and increased urinary calcium excretion. Stimulates gastric acid secretion and may cause gastroesophageal reflux. Cardiac output is increased due to higher sensitivity to catecholamines. Elimination in preterm infants is primarily as unchanged drug, although significant interconversion to caffeine occurs. In the very immature neonate, the serum half-life of theophylline is prolonged (20 to 30 hours). Theophylline metabolism and clearance mature to adult values by 55 weeks postmenstrual age. Aminophylline salt is 78.9% theophylline. Theophylline administered orally is approximately 80% bioavailable; therefore, no dosage adjustment is necessary when changing from IV aminophylline to oral theophylline.

Adverse Effects

GI irritation. Hyperglycemia. CNS irritability and sleeplessness. May be associated with renal calcifications when used concurrently with furosemide and/or dexamethasone.
Signs of toxicity: Sinus tachycardia, failure to gain weight, vomiting, jitteriness, hyperreflexia, and seizures.

Treatment of Serious Theophylline Toxicity: Activated charcoal, 1 g/kg as a slurry by gavage tube every 2 to 4 hours. Avoid sorbitol-containing preparations: They may cause osmotic diarrhea.

Monitoring

Monitor heart rate and check blood glucose periodically with reagent strips. Assess for agitation and feeding intolerance.

Consider withholding next dose if heart rate is greater than 180 beats per minute.

When indicated by lack of efficacy or clinical signs of toxicity, serum trough concentration should be obtained. Therapeutic ranges are:
1) Apnea of prematurity: 7 to 12 mcg/mL.
2) Bronchospasm: 10 to 20 mcg/mL (older infants with bronchospasm may need these higher levels because of increased protein binding).

Special Considerations/Preparation

Available as aminophylline for IV use (25 mg/mL) in 10- and 20-mL vials. Dilute 1 mL (25 mg) with 4 mL NS or D_5W to yield a final concentration of 5 mg/mL. Stable for 4 days refrigerated.

Oral theophylline is available only as an elixir at a concentration of 80 mg/15 mL (5.33 mg/mL) and contains 20% alcohol.
Aminophylline oral solution is no longer available.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA (white precipitate forms within 2 hours) solutions. Acyclovir, ampicillin, amikacin, aztreonam, caffeine citrate, calcium gluconate, ceftazidime, chloramphenicol, cimetidine, dexamethasone, dopamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, fluconazole, flumazenil, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, meropenem, metoclopramide, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, pancuronium bromide, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, cefepime, ceftriaxone, ciprofloxacin, clindamycin, dobutamine, epinephrine, hydralazine, insulin, isoproterenol, methylprednisolone, and penicillin G.

References

- Lim DS, Kulik TJ, Kim DW: Aminophylline for the prevention of apnea during prostaglandin E_1 infusion. *Pediatrics* 2003;112:e27-e29.
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- al-Omran A, al-Alaiyan S: Theophylline concentration following equal doses of intravenous aminophylline and oral theophylline in preterm infants. *Am J Perinatol* 1997;14:147-149.
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- Kraus DM, Fischer JH, Reitz SJ, et al: Alterations in theophylline metabolism during the first year of life. *Clin Pharmacol Ther*1993;54:351-59.
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- Gal P, Boer HR, Toback J, et al: Effect of asphyxia on theophylline clearance in newborns. *South Med J* 1982;75:836.
- Srinivasan G, Pildes RS, Jaspan JB, et al: Metabolic effects of theophylline in preterm infants. *J Pediatr* 1981;98:815.
- Aranda JV, Sitar DS, Parsons WD, et al: Pharmacokinetic aspects of theophylline in premature newborns. *N Engl J Med* 1976;295:413.
- Product Information, Hospira, 2004.

1.9 Amiodarone

Title Amiodarone

Dose

IV Loading Dose: 5 mg/kg IV infusion given over 30 to 60 minutes, preferably in a central vein.

Maintenance Infusion: 7 to 15 mcg/kg/minute (10 to 20 mg/kg per 24 hours). Begin at 7 mcg/kg/minute and titrate by monitoring effects. For infusions lasting longer than 1 hour, amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line.

Consider switching to oral therapy within 24 to 48 hours.

Oral: 5 to 10 mg/kg/dose every 12 hours.

Uses

Treatment of life-threatening or drug-resistant refractory supraventricular (SVT), ventricular tachyarrhythmias (VT), and postoperative junctional ectopic tachycardia (JET) - see Adverse Effects.

Contraindications/Precautions

Contraindicated in cardiogenic shock, severe sinus node dysfunction, marked sinus bradycardia, second- and third-degree AV block, and hypersensitivity to amiodarone, including iodine. Use caution when administering with other drugs that prolong QT (consider expert consultation). Polymorphic ventricular tachycardia, heart block, prolonged QT interval, and torsades de pointes VT may occur. In general, when used in combination with other antiarrhythmic agents and digoxin, their doses should be reduced and patients closely monitored [1] .

Black Box Warning According to the manufacturer's black box warning, a potentially fatal toxicity associated with amiodarone is hypersensitivity pneumonitis or interstitial/alveolar pneumonitis (reported in adults). Liver injury is common but usually mild. Amiodarone may exacerbate an existing arrhythmia.

Pharmacology

Class III antiarrhythmic agent that is an iodinated benzofuran compound. Electrophysiologic activity is accomplished by prolonging the duration of the action potential and increasing the effective refractory period. Increases cardiac blood flow and decreases cardiac work and myocardial oxygen consumption. Highly protein bound (95%) in adults. Extensively metabolized to an active metabolite by the cytochrome CYP3A4 isoenzyme system (limited in preterm infants). Drug-drug interaction potentially occur when given in combination with drugs that inhibit cytochrome CYP3A4: phenytoin, fosphenytoin, clarithromycin, erythromycin, azole antifungals (e.g. fluconazole, ketoconazole, itraconazole), protease inhibitors (e.g. indinavir, ritonavir), class IA and class III antiarrhythmics (e.g. quinidine, procainamide, sotalol) and cimetidine (amiodarone levels increase). Amiodarone prevents the elimination of digoxin resulting in high digoxin levels. Half-life reported to be 26 to 107 days in adults. No data in preterm infants. Accumulates in tissues; serum levels can be detected for months. Contains 37.3% iodine by weight. Adheres to PVC tubing: low infusion rates in neonates may lead to reduced drug delivery during continuous infusions. Oral absorption is variable with approximately 50% bioavailability.

Adverse Effects

Short-term toxicity: Bradycardia and hypotension (possibly associated with rapid rates of infusion) may occur. Hypotension may be due, in part, to the co-solvents, polysorbate 80 and benzyl alcohol, which are components of the original amiodarone product [2] [3] . In a study of pediatric patients (n=61), ages 30 days to 15 years, hypotension and bradycardia were reported in 36% and 20% of patients, respectively. AV block was reported in 15% of patients. Polymorphic ventricular tachycardia may occur. Irritating to the peripheral vessels (concentrations greater than 2 mg/mL). Administration through central vein preferred.

Long-term toxicity: Hyperthyroidism (due to inhibition of T_4 to T_3) and hypothyroidism (due to high concentration of inorganic iodine). Generic formulation contains 2% benzyl alcohol (20 mg/mL). Hepatitis and cholestatic hepatitis (rare). Photosensitivity (10%), nausea and vomiting (10%), optic neuritis (4% to 9%), and pulmonary fibrosis (4% to 9%) have been reported with prolonged oral use in adults.

Monitoring

Continuous EKG and blood pressure (for IV). Follow AST and ALT. Monitor T_3, T_4, and TSH. Observe IV site for extravasation.

Special Considerations/Preparation

IV: The preferred formulation is Nexterone®, available as 1.5 mg/mL (150 mg/100 mL) and 1.8 mg/mL (360 mg/200 mL) concentrations in premix bags. Nexterone®does not contain benzyl alcohol or polysorbate 80, and therefore does not carry a warning regarding benzyl alcohol and fatal gasping syndrome in neonates. There are also no limitations regarding compatibility and stability with plastics and isotonic infusion fluids. Store at room temperature and protect from light.
Generic amiodarone is also available as 50 mg/mL concentration in 5, 10, and 20 mL vials. Contains 2% (20 mg/mL) of benzyl alcohol and 10% (100 mg/mL) polysorbate (Tween) 80 as a preservative. Store at room temperature and protect from light.
Oral: Supplied in 100-mg, 200-mg, 300-mg, and 400-mg tablets. An oral suspension with a final concentration of 5 mg/mL may be made as follows: crush a 200-mg tablet, slowly mix in 20 mL of 1% methylcellulose, and then add in 20 mL of simple syrup to make a total volume of 40 mL. Stable for six weeks at room temperature and three months refrigerated when stored in glass or plastic.

Solution Compatibility

D_5W, and NS at concentrations of 1 to 6 mg/mL.

Solution Incompatibility

No data available for Dex/AA solutions.

Terminal Injection Site Compatibility

Amikacin, amphotericin B, atropine, calcium chloride, calcium gluconate, ceftizoxime, ceftriaxone, cefuroxime, clindamycin, dobutamine, dopamine, epinephrine, famotidine, fentanyl, fluconazole, furosemide, esmolol, erythromycin, gentamicin, insulin, isoproterenol, lidocaine, lorazepam, metronidazole, midazolam, milrinone, morphine, nitroglycerin, norepinephrine, penicillin G, phentolamine, potassium chloride, procainamide, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, ceftazidime, cefazolin, digoxin, heparin, imipenem-cilastatin, mezlocillin, micafungin, piperacillin, piperacillin-tazobactam, sodium bicarbonate, and sodium nitroprusside.

No data available for Dex/AA solutions.

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- Product Information, Prism Pharmaceuticals, 2010.

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2. Lane RD, Nguyen KT, Niemann JT et al: Amiodarone for the emergency care of children. Pediatr Emerg Care May, 2010; 26(5): 382-389.
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Title Amiodarone

Dose

IV Loading Dose: 5 mg/kg IV infusion given over 30 to 60 minutes, preferably in a central vein.

Maintenance Infusion: 7 to 15 mcg/kg/minute (10 to 20 mg/kg per 24 hours). Begin at 7 mcg/kg/minute and titrate by monitoring effects. For infusions lasting longer than 1

hour, amiodarone IV concentrations should not exceed 2 mg/mL unless using a central line.

Consider switching to oral therapy within 24 to 48 hours.

Oral: 5 to 10 mg/kg/dose every 12 hours.

Uses

Treatment of life-threatening or drug-resistant refractory supraventricular (SVT), ventricular tachyarrhythmias (VT), and postoperative junctional ectopic tachycardia (JET) - see Adverse Effects.

Contraindications/Precautions

Contraindicated in cardiogenic shock, severe sinus node dysfunction, marked sinus bradycardia, second- and third-degree AV block, and hypersensitivity to amiodarone, including iodine. Use caution when administering with other drugs that prolong QT (consider expert consultation). Polymorphic ventricular tachycardia, heart block, prolonged QT interval, and torsades de pointes VT may occur. In general, when used in combination with other antiarrhythmic agents and digoxin, their doses should be reduced and patients closely monitored [1] .

Black Box Warning According to the manufacturer's black box warning, a potentially fatal toxicity associated with amiodarone is hypersensitivity pneumonitis or interstitial/alveolar pneumonitis (reported in adults). Liver injury is common but usually mild. Amiodarone may exacerbate an existing arrhythmia.

Pharmacology

Class III antiarrhythmic agent that is an iodinated benzofuran compound. Electrophysiologic activity is accomplished by prolonging the duration of the action potential and increasing the effective refractory period. Increases cardiac blood flow and decreases cardiac work and myocardial oxygen consumption. Highly protein bound (95%) in adults. Extensively metabolized to an active metabolite by the cytochrome CYP3A4 isoenzyme system (limited in preterm infants). Drug-drug interaction potentially occur when given in combination with drugs that inhibit cytochrome CYP3A4: phenytoin, fosphenytoin, clarithromycin, erythromycin, azole antifungals (e.g. fluconazole, ketoconazole, itraconazole), protease inhibitors (e.g. indinavir, ritonavir), class IA and class III antiarrhythmics (e.g. quinidine, procainamide, sotalol) and cimetidine (amiodarone levels increase). Amiodarone prevents the elimination of digoxin resulting in high digoxin levels. Half-life reported to be 26 to 107 days in adults. No data in preterm infants. Accumulates in tissues; serum levels can be detected for months. Contains 37.3% iodine by weight. Adheres to PVC tubing: low infusion rates in neonates may lead to reduced drug delivery during continuous infusions. Oral absorption is variable with approximately 50% bioavailability.

Adverse Effects

Short-term toxicity: Bradycardia and hypotension (possibly associated with rapid rates of infusion) may occur. Hypotension may be due, in part, to the co-solvents, polysorbate 80 and benzyl alcohol, which are components of the original amiodarone product [2] [3] . In a study of pediatric patients (n=61), ages 30 days to 15 years, hypotension and bradycardia were reported in 36% and 20% of patients, respectively. AV block was reported in 15% of patients. Polymorphic ventricular tachycardia may occur. Irritating to the peripheral vessels (concentrations greater than 2 mg/mL). Administration through central vein preferred.

Long-term toxicity: Hyperthyroidism (due to inhibition of T_4 to T_3) and hypothyroidism (due to high concentration of inorganic iodine). Generic formulation contains 2% benzyl alcohol (20 mg/mL). Hepatitis and cholestatic hepatitis (rare). Photosensitivity (10%), nausea and vomiting (10%), optic neuritis (4% to 9%), and pulmonary fibrosis (4% to 9%) have been reported with prolonged oral use in adults.

Monitoring

Continuous EKG and blood pressure (for IV). Follow AST and ALT. Monitor T_3, T_4, and TSH. Observe IV site for extravasation.

Special Considerations/Preparation

IV: The preferred formulation is Nexterone®, available as 1.5 mg/mL (150 mg/100 mL) and 1.8 mg/mL (360 mg/200 mL) concentrations in premix bags. Nexterone®does not contain benzyl alcohol or polysorbate 80, and therefore does not carry a warning regarding benzyl alcohol and fatal gasping syndrome in neonates. There are also no limitations regarding compatibility and stability with plastics and isotonic infusion fluids. Store at room temperature and protect from light.
Generic amiodarone is also available as 50 mg/mL concentration in 5, 10, and 20 mL vials. Contains 2% (20 mg/mL) of benzyl alcohol and 10% (100 mg/mL) polysorbate (Tween) 80 as a preservative. Store at room temperature and protect from light.
Oral: Supplied in 100-mg, 200-mg, 300-mg, and 400-mg tablets. An oral suspension with a final concentration of 5 mg/mL may be made as follows: crush a 200-mg tablet, slowly mix in 20 mL of 1% methylcellulose, and then add in 20 mL of simple syrup to make a total volume of 40 mL. Stable for six weeks at room temperature and three months refrigerated when stored in glass or plastic.

Solution Compatibility

D_5W, and NS at concentrations of 1 to 6 mg/mL.

Solution Incompatibility

No data available for Dex/AA solutions.

Terminal Injection Site Compatibility

Amikacin, amphotericin B, atropine, calcium chloride, calcium gluconate, ceftizoxime, ceftriaxone, cefuroxime, clindamycin, dobutamine, dopamine, epinephrine, famotidine,

fentanyl, fluconazole, furosemide, esmolol, erythromycin, gentamicin, insulin, isoproterenol, lidocaine, lorazepam, metronidazole, midazolam, milrinone, morphine, nitroglycerin, norepinephrine, penicillin G, phentolamine, potassium chloride, procainamide, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, ceftazidime, cefazolin, digoxin, heparin, imipenem-cilastatin, mezlocillin, micafungin, piperacillin, piperacillin-tazobactam, sodium bicarbonate, and sodium nitroprusside.

No data available for Dex/AA solutions.

References

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- Product Information, Prism Pharmaceuticals, 2010.

1. Product Information: Cordarone(R) oral tablets, amiodarone Hydrochloride oral tablets. Wyeth Pharmaceuticals Inc, Philadelphia, PA, Aug, 2009.
2. Lane RD, Nguyen KT, Niemann JT et al: Amiodarone for the emergency care of children. Pediatr Emerg Care May, 2010; 26(5): 382-389.
3. Souney PF: PM101: intravenous amiodarone formulation changes can improve medication safety. Expert Opin Drug Saf Mar, 2010; 9(2): 319-333.

1.10 Amphotericin B

Title Amphotericin B

Dose

1 to 1.5 mg/kg every 24 hours IV infusion over 2 to 6 hours.
Dosage modification for renal dysfunction is only necessary if serum creatinine increases greater than 0.4 mg/dL from baseline during therapy - hold dose for 2 to 5 days. Alternate-day dosing recommended over decreasing daily dose in patients experiencing renal toxicity.

Uses

Treatment of systemic fungal infections and severe superficial mycoses.

Black Box Warning According to the manufacturer's black box warning, it is recommended that the product name and dosage are verified if the prescribed dose exceeds 1.5 mg/kg. Overdose can result in potentially fatal cardiac or cardiorespiratory arrest.

Pharmacology

Amphotericin B binds to ergosterol in the membrane of sensitive fungi and may be fungicidal or fungistatic. The therapeutic concentration range is not well-defined. Highly protein-bound (greater than 90%). Elimination half-life is approximately 15 days. Drug may accumulate in tissues to a significant concentration and be excreted renally for months.

Adverse Effects

Hypokalemia (serum K^+ less than 3 mmol/L) and/or a transient increase in serum creatinine occurs in approximately 16% of treated patients. Renal blood flow and GFR may be decreased by 20% to 60%. Injures tubular epithelium with resultant urinary loss of potassium and magnesium, decreased reabsorption of sodium, and renal tubular acidosis. Sodium intake greater than 4 mEq/kg per day may prevent or decrease nephrotoxicity. Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills. Consider analgesia before beginning infusion. Cardiac arrest has occurred in patients who received 10 times the recommended dose.

Monitoring

Monitor CBC, electrolytes, urine output, BUN, and serum creatinine at least every other day. Observe IV site for irritation--phlebitis is common.

Special Considerations/Preparation

Available as powder for injection in 50-mg vials. Reconstitute with 10 mL of D_5W or preservative free sterile water to a concentration of 5 mg/mL, then dilute further using D_5W to a concentration no greater than 0.1 mg/mL for infusion. Reconstituted solution stable for 24 hours at room temperature or 7 days in refrigerator. **Do not flush IV or**

mix amphotericin with saline solution; precipitation will occur. May filter if necessary; mean pore diameter should not be less than 1 micron. **Protect from light**.

Solution Compatibility

D_5W, $D_{10}W$, $D_{15}W$, and $D_{20}W$.

Solution Incompatibility

Dex/AA solutions and NS.

Terminal Injection Site Compatibility

Amiodarone, heparin, hydrocortisone, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amikacin, aztreonam, calcium chloride, calcium gluconate, cefepime, cimetidine, ciprofloxacin, dopamine, enalaprilat, fluconazole, gentamicin, linezolid, magnesium sulfate, meropenem, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, and tobramycin.

References

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- Starke JR, Mason EL, Kramer WG, Kaplan SL: Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis* 1987;155:766.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Bristol-Myers Squibb, 2006.

Title Amphotericin B

Dose

1 to 1.5 mg/kg every 24 hours IV infusion over 2 to 6 hours.
Dosage modification for renal dysfunction is only necessary if serum creatinine increases greater than 0.4 mg/dL from baseline during therapy - hold dose for 2 to 5 days. Alternate-day dosing recommended over decreasing daily dose in patients experiencing renal toxicity.

Uses

Treatment of systemic fungal infections and severe superficial mycoses.

Black Box Warning According to the manufacturer's black box warning, it is recommended that the product name and dosage are verified if the prescribed dose exceeds 1.5 mg/kg. Overdose can result in potentially fatal cardiac or cardiorespiratory arrest.

Pharmacology

Amphotericin B binds to ergosterol in the membrane of sensitive fungi and may be fungicidal or fungistatic. The therapeutic concentration range is not well-defined. Highly protein-bound (greater than 90%). Elimination half-life is approximately 15 days. Drug may accumulate in tissues to a significant concentration and be excreted renally for months.

Adverse Effects

Hypokalemia (serum K^+ less than 3 mmol/L) and/or a transient increase in serum creatinine occurs in approximately 16% of treated patients. Renal blood flow and GFR may be decreased by 20% to 60%. Injures tubular epithelium with resultant urinary loss of potassium and magnesium, decreased reabsorption of sodium, and renal tubular acidosis. Sodium intake greater than 4 mEq/kg per day may prevent or decrease nephrotoxicity. Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills. Consider analgesia before beginning infusion. Cardiac arrest has occurred in patients who received 10 times the recommended dose.

Monitoring

Monitor CBC, electrolytes, urine output, BUN, and serum creatinine at least every other day. Observe IV site for irritation--phlebitis is common.

Special Considerations/Preparation

Available as powder for injection in 50-mg vials. Reconstitute with 10 mL of D_5W or preservative free sterile water to a concentration of 5 mg/mL, then dilute further using D_5W to a concentration no greater than 0.1 mg/mL for infusion. Reconstituted solution stable for 24 hours at room temperature or 7 days in refrigerator. **Do not flush IV or mix amphotericin with saline solution; precipitation will occur.** May filter if necessary; mean pore diameter should not be less than 1 micron. **Protect from light**.

Solution Compatibility

D_5W, $D_{10}W$, $D_{15}W$, and $D_{20}W$.

Solution Incompatibility

Dex/AA solutions and NS.

Terminal Injection Site Compatibility

Amiodarone, heparin, hydrocortisone, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Amikacin, aztreonam, calcium chloride, calcium gluconate, cefepime, cimetidine, ciprofloxacin, dopamine, enalaprilat, fluconazole, gentamicin, linezolid, magnesium sulfate, meropenem, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, and tobramycin.

References

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- Le J, Adler-Shohet FC, Nguyen C, Lieberman JM: Nephrotoxicity associated with amphotericin B deoxycholate in neonates. *Pediatr Infect Dis J* 2009;28:1061-1063.
- Turcu R, Patterson MJ, Omar S: Influence of sodium intake on amphotericin B-induced nephrotoxicity among extremely premature infants. *Pediatr Nephrol* 2009;24:497-505.
- Holler B, Omar SA, Farid MD, Patterson MJ: Effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity among extremely low birth weight infants. *Pediatrics* 2004;113:e608-e616.
- Chapman RL: *Candida* infections in the neonate. *Curr Opin Pediatr* 2003;15:97-102.
- Bliss JM, Wellington M, Gigliotti F: Antifungal pharmacotherapy for neonatal candidiasis. *Semin Perinatol* 2003;27:365-374.
- Lyman CA, Walsh TJ: Systemically administered antifungal agents: A review of their clinical pharmacology and therapeutic applications. *Drugs* 1992;44:9.
- Baley JE, Meyers C, Kliegman RM, et al: Pharmacokinetics, outcome of treatment, and toxic effects of amphotericin B and 5-fluorocytosine in neonates. *J Pediatr* 1990;116:791.
- Starke JR, Mason EL, Kramer WG, Kaplan SL: Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis* 1987;155:766.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Bristol-Myers Squibb, 2006.

1.11 Amphotericin B Lipid Complex

Title Amphotericin B Lipid Complex

Dose

5 mg/kg/dose IV infusion every 24 hours.

Administration

Administer by IV infusion over 2 hours (2.5 mg/kg/hour) at a concentration of 1 to 2 mg/mL. If infusion lasts longer than 2 hours, shake the bag to mix the contents every 2 hours. Flush existing IV line with D_5W prior to infusion or administer in a separate IV line. Do not infuse with saline solutions (precipitation will occur). Do not use an in-line filter to administer [1] .

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Pharmacology

Amphotericin B lipid complex consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid ratio. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B lipid complex is nonlinear.

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output. Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.

Special Considerations/Preparation

Available as a suspension containing 100-mg Abelcet® in 20-mL (5 mg/mL). Shake the vial gently until there is no evidence of any yellow sediment on the bottom. Withdraw the appropriate dose into a syringe using an 18 gauge needle. Remove the needle and replace with the supplied 5 micron filter needle. Dilute the drug with D_5W so that the final infusion concentration is 1 to 2 mg/mL. Shake until thoroughly mixed. Check for complete dispersion. The diluted admixture is stable for 48 hours refrigerated and an additional 6 hours at room temperature [1] .
Do not freeze. Protect from light.
Do not flush IV or mix Abelcet® with saline solutions - precipitation willoccur.

Solution Compatibility

D_5W at 1 to 2 mg/mL dilution.

Solution Incompatibility

Dex/AA and NS.

Terminal Injection Site Compatibility

No available data.

References

- Adler-Shohet F, Waskin H, Lieberman J M: Amphotericin B lipid complex for neonatal invasive candidiasis . *Arch Dis Child Fetal Neonatal Ed*2001;84:F131-F133.
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- Wong-Beringer A, Jacobs RA, Guglielmo BJ: Lipid formulations of amphotericin B: Clinical efficacy and toxicities. *Clin Infect Dis* 1998;27:603-618.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Enzon, 2009.

1. Product Information: ABELCET(R) IV injection, Amphotericin B Lipid Complex IV injection. Enzon Pharmaceuticals Inc, Bridgewater, NJ, Feb, 2009.

Title Amphotericin B Lipid Complex

Dose

5 mg/kg/dose IV infusion every 24 hours.

Administration

Administer by IV infusion over 2 hours (2.5 mg/kg/hour) at a concentration of 1 to 2 mg/mL. If infusion lasts longer than 2 hours, shake the bag to mix the contents every 2 hours. Flush existing IV line with D_5W prior to infusion or administer in a separate IV line. Do not infuse with saline solutions (precipitation will occur). Do not use an in-line filter to administer [1] .

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Pharmacology

Amphotericin B lipid complex consists of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid ratio. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B lipid complex is nonlinear.

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output. Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.

Special Considerations/Preparation

Available as a suspension containing 100-mg Abelcet® in 20-mL (5 mg/mL). Shake the vial gently until there is no evidence of any yellow sediment on the bottom. Withdraw the appropriate dose into a syringe using an 18 gauge needle. Remove the needle and replace with the supplied 5 micron filter needle. Dilute the drug with D_5W so that the final infusion concentration is 1 to 2 mg/mL. Shake until thoroughly mixed. Check for complete dispersion. The diluted admixture is stable for 48 hours refrigerated and an additional 6 hours at room temperature [1] .
Do not freeze. Protect from light.
Do not flush IV or mix Abelcet® with saline solutions - precipitation willoccur.

Solution Compatibility

D_5W at 1 to 2 mg/mL dilution.

Solution Incompatibility

Dex/AA and NS.

Terminal Injection Site Compatibility

No available data.

References

- Adler-Shohet F, Waskin H, Lieberman J M: Amphotericin B lipid complex for neonatal invasive candidiasis . *Arch Dis Child Fetal Neonatal Ed*2001;84:F131-F133.
- Walsh TJ, Seibel NL, Arndt C, et al: Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J*1999;18:702-708.
- Wong-Beringer A, Jacobs RA, Guglielmo BJ: Lipid formulations of amphotericin B: Clinical efficacy and toxicities. *Clin Infect Dis* 1998;27:603-618.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Enzon, 2009.

1. Product Information: ABELCET(R) IV injection, Amphotericin B Lipid Complex IV injection. Enzon Pharmaceuticals Inc, Bridgewater, NJ, Feb, 2009.

1.12 Amphotericin B Liposome

Title Amphotericin B Liposome

Dose

5 to 7 mg/kg per dose every 24 hours IV infusion by syringe pump over 2 hours.

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Pharmacology

AmBisome® consists of amphotericin B intercalated within a single bilayer liposomal drug delivery system. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen but penetrates the CNS less than conventional amphotericin B. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B liposome is nonlinear.

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output. Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.

Special Considerations/Preparation

Available as powder for injection in 50 mg vials. Reconstitute by adding 12 mL of sterile water for injection to a yield a concentration of 4 mg/mL. Immediately shake vial vigorously for 30 seconds. Check for complete dispersion. Reconstituted suspension stable for 24 hours refrigerated.
Do not freeze. Protect from light.
Before administration, AmBisome® must be diluted with D_5W to a final concentration less than 2 mg/mL. A 1 mg/mL dilution may be made by filtering (using 5 micron filter) 1 mL of reconstituted solution into 3 mL of D_5W. Use one filter per vial of AmBisome®. Use solution within 6 hours of dilution.
Do not flush IV or mix Ambisome® with saline solutions-precipitation will occur.

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, $D_{25}W$.

Solution Incompatibility

Dex/AA and NS.

Terminal Injection Site Compatibility

No available data.

References

- Juster-Reicher A, Flidel-Rimon O, Amitay M, et al: High dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis* 2003;22:603-07.
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- Evdoridou J, Roilides E, Bibashi E, Kremenopoulos G: Multifocal osteoarthritis due to Candida albicans in a neonate: Serum level monitoring of liposomal amphotericin B and literature review. *Infection* 1997;25:112.
- Weitkamp JH, Poets CF, Sievers R, et al: Candida infection in very low birthweight infants: Outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome®). *Infection* 1998;26:11-15.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Gilead Sciences, 2005.

Title Amphotericin B Liposome

Dose

5 to 7 mg/kg per dose every 24 hours IV infusion by syringe pump over 2 hours.

Uses

Treatment of systemic fungal infections resistant to conventional amphotericin B therapy or in patients with renal or hepatic dysfunction.

Pharmacology

AmBisome® consists of amphotericin B intercalated within a single bilayer liposomal drug delivery system. Acts by binding to the sterol component of a cell membrane leading to alterations in the cell wall permeability and death. Penetrates the cell wall of susceptible fungi. Concentrates in the liver and spleen but penetrates the CNS less than conventional amphotericin B. Less nephrotoxic than conventional amphotericin B. Mean serum half-life in adults 24 to 38 hours. The pharmacokinetics of amphotericin B liposome is nonlinear.

Adverse Effects

Anemia, thrombocytopenia, hypokalemia, nausea/vomiting, and fever/chills.

Monitoring

Serum amphotericin B concentrations are not routinely followed. Monitor urine output. Periodic CBC for thrombocytopenia, electrolytes for hypokalemia, BUN, serum creatinine, and hepatic transaminases.

Special Considerations/Preparation

Available as powder for injection in 50 mg vials. Reconstitute by adding 12 mL of sterile water for injection to a yield a concentration of 4 mg/mL. Immediately shake vial vigorously for 30 seconds. Check for complete dispersion. Reconstituted suspension stable for 24 hours refrigerated.
Do not freeze. Protect from light.
Before administration, AmBisome® must be diluted with D_5W to a final concentration less than 2 mg/mL. A 1 mg/mL dilution may be made by filtering (using 5 micron filter) 1 mL of reconstituted solution into 3 mL of D_5W. Use one filter per vial of AmBisome®. Use solution within 6 hours of dilution.
Do not flush IV or mix Ambisome® with saline solutions-precipitation will occur.

Solution Compatibility

D_5W, $D_{10}W$, $D_{20}W$, $D_{25}W$.

Solution Incompatibility

Dex/AA and NS.

Terminal Injection Site Compatibility

No available data.

References

- Juster-Reicher A, Flidel-Rimon O, Amitay M, et al: High dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis* 2003;22:603-07.
- Scarcella A, Pasquariello MB, Giugliano B, et al: Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998;17:146-148.
- Evdoridou J, Roilides E, Bibashi E, Kremenopoulos G: Multifocal osteoarthritis due to Candida albicans in a neonate: Serum level monitoring of liposomal amphotericin B and literature review. *Infection* 1997;25:112.
- Weitkamp JH, Poets CF, Sievers R, et al: Candida infection in very low birthweight infants: Outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome®). *Infection* 1998;26:11-15.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Gilead Sciences, 2005.

1.13 Ampicillin

Title Ampicillin

Dose

25 to 50 mg/kg/dose by IV slow push, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Group B Streptococcal Meningitis, Empiric Therapy:
Experts recommend using higher doses for the treatment of GBS meningitis [1] [2] [3] :
7 days and younger:200 to 300 mg/kg/day IV divided every 8 hours.
8 days and older:300 mg/kg/day IV divided every 6 hours.
The addition of an aminoglycoside is also recommended [2] . Penicillin G monotherapy is recommended once the diagnosis of GBS meningitis has been established and CSF is sterile; antibiotic therapy should be continued for at least 2 weeks [2] [3] .

Administration

For IV use, the maximum concentration is 100 mg/mL to be administered slowly over 3 to 5 minutes (maximum 100 mg/min). Mix to a final concentration of 250 mg/mL for IM administration [4] .

Uses

Broad-spectrum antibiotic useful against group B *streptococcus, Listeria monocytogenes,*and susceptible *E coli* species.

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low [5] .

Pharmacology

Ampicillin is a semisynthetic penicillin that is bactericidal. Clearance is primarily by the renal route and is inversely related to postnatal age. Serum half-life in term infants younger than 7 days is approximately 4 hours.

Adverse Effects

Very large doses may result in CNS excitation or seizure activity. Moderate prolongation of bleeding times (by approximately 60 seconds) has been reported after the third or fourth dose in neonates 33 to 41 weeks GA receiving 50 to 100 mg/kg every 12 hours [6] . Prolongation of bleeding times (by approximately 2 minutes) has also been reported after at least 10 doses in preterm very low birth-weight neonates 23 to 30 weeks GA receiving 50 to 100 mg/kg every 12 hours [7] . The clinical implications of the prolonged bleeding time is unknown. Hypersensitivity reactions (maculopapular rash, urticarial rash, or fever) are rare in neonates.

Monitoring

Serum concentration can be measured but is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 125-, 250-, 500-mg, 1-g, 2-g, and 10-g vials. Reconstitute using sterile water for injection. **Maximum concentration for IV infusion is 100 mg/mL.** Mix to a final concentration of 250 mg/mL for IM administration. **Reconstituted solution must be used within 1 hour of mixing because of loss of potency**.

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Dex/AA and $D_{10}W$

Terminal Injection Site Compatibility

Fat emulsion. Acyclovir, alprostadil, aminophylline, aztreonam, calcium gluconate, cefepime, chloramphenicol, cimetidine, clindamycin, enalaprilat, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, magnesium

sulfate, metronidazole, milrinone, morphine, phytonadione, potassium chloride, propofol, ranitidine, remifentanil, and vancomycin.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, dopamine, epinephrine, erythromycin lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and tobramycin.

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- Sheffield MJ, Lambert DK, Henry E, Christensen RD: Effect of ampicillin on the bleeding time of neonatal intensive care patients. *J Perinatol*, advance online publication 31 December 2009.
- Shaffer CL, Davey AM, Ransom JL, et al: Ampicillin-induced neurotoxicity in very-low-birth-weight neonates. *Ann Pharmacother* 1998;32:482-484.
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Title Ampicillin

Dose

25 to 50 mg/kg/dose by IV slow push, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Group B Streptococcal Meningitis, Empiric Therapy:
Experts recommend using higher doses for the treatment of GBS meningitis [1] [2] [3] :
7 days and younger:200 to 300 mg/kg/day IV divided every 8 hours.
8 days and older:300 mg/kg/day IV divided every 6 hours.
The addition of an aminoglycoside is also recommended [2] . Penicillin G monotherapy is recommended once the diagnosis of GBS meningitis has been established and CSF is sterile; antibiotic therapy should be continued for at least 2 weeks [2] [3] .

Administration

For IV use, the maximum concentration is 100 mg/mL to be administered slowly over 3 to 5 minutes (maximum 100 mg/min). Mix to a final concentration of 250 mg/mL for IM administration [4] .

Uses

Broad-spectrum antibiotic useful against group B *streptococcus, Listeria monocytogenes,*and susceptible *E coli* species.

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low [5] .

Pharmacology

Ampicillin is a semisynthetic penicillin that is bactericidal. Clearance is primarily by the renal route and is inversely related to postnatal age. Serum half-life in term infants younger than 7 days is approximately 4 hours.

Adverse Effects

Very large doses may result in CNS excitation or seizure activity. Moderate prolongation of bleeding times (by approximately 60 seconds) has been reported after the third or fourth dose in neonates 33 to 41 weeks GA receiving 50 to 100 mg/kg every 12 hours [6] . Prolongation of bleeding times (by approximately 2 minutes) has also been reported after at least 10 doses in preterm very low birth-weight neonates 23 to 30 weeks GA receiving 50 to 100 mg/kg every 12 hours [7] . The clinical implications of the prolonged bleeding time is unknown. Hypersensitivity reactions (maculopapular rash, urticarial rash, or fever) are rare in neonates.

Monitoring

Serum concentration can be measured but is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 125-, 250-, 500-mg, 1-g, 2-g, and 10-g vials. Reconstitute using sterile water for injection. **Maximum concentration for IV infusion is 100 mg/mL.** Mix to a final concentration of 250 mg/mL for IM administration. **Reconstituted solution must be used within 1 hour of mixing because of loss of potency**.

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Dex/AA and $D_{10}W$

Terminal Injection Site Compatibility

Fat emulsion. Acyclovir, alprostadil, aminophylline, aztreonam, calcium gluconate, cefepime, chloramphenicol, cimetidine, clindamycin, enalaprilat, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, milrinone, morphine, phytonadione, potassium chloride, propofol, ranitidine, remifentanil, and vancomycin.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, dopamine, epinephrine, erythromycin lactobionate, fluconazole, gentamicin, hydralazine, metoclopramide, midazolam, nicardipine, sodium bicarbonate, and tobramycin.

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1.14 Anidulafungin

Title Anidulafungin

Dose

Candidiasis
Full term infants when intolerant to or resistant to fluconazole or amphotericin B
Loading dose: 3 mg/kg IV for 1 dose [1] [2] . A higher dose may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1] .
Maintenance dose: 1.5 mg/kg IV once daily [1] [2] . Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1] . Duration of therapy for proven infection, without systemic complications, is at least 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [3] .

Administration

Administer by IV Infusion over 60 minutes [1] ; not to exceed 1.1 mg/minute [4] .

Uses

Treatment of infection due to *Candida* species. *Candida* species are the most common cause of invasive fungal infection in humans; mortality in neonates and children from invasive candidiasis is 10% to 15%. Antifungal therapy should be started on all candidemic patients within 24 hours of a blood culture positive for yeast; delays are associated with increased mortality [3] .

Anidulafungin may be a useful addition or alternative to other antifungal agents for the treatment of infection due to *Candida* species, based upon safety, pharmacokinetic [1] , and limited treatment data [2] . The Infectious Diseases Society of America (IDSA) recommends that echinocandins, such as anidulafungin, be used with caution in newborn candidiasis and generally limited to cases when resistance or toxicity precludes use of fluconazole or amphotericin B [3] .
In a safety and pharmacokinetic study, doses of 1.5 mg/kg/day for 5 days in 8 neonates (6 out of 8 preterm) provided similar anidulafungin exposures compared to children and adults (100 mg/day) [1] . Despite sensitivity to amphotericin B, fungal peritonitis was not cleared in a full-term neonate until anidulafungin was added to liposomal amphotericin B; *Candida albicans* had been cultured from the peritoneum while the patient was receiving amphotericin B monotherapy [2] . Doses for hematogenous *Candida* meningoencephalitis (HCME) are expected to be much higher than those used for other indications, based upon a translational study which used neonatal (6 out of 8 were preterm) pharmacokinetic data applied to an animal model of the disease [5] .

FDA Approved Indications
Treatment of candidemia, esophageal candidiasis, and intra-abdominal abscess and peritonitis due to *Candida* in patients older than 16 years [4] .

Contraindications/Precautions

Contraindicated in patients with hypersensitivity to other echinocandins [4] .

Hepatitis, hepatic failure, and significant hepatic dysfunction have been reported. Anaphylactic reactions, including shock, have also been reported; discontinue use if reactions occur. Infusion-related reactions (eg, rash, urticaria, flushing, pruritus, bronchospasm, dyspnea, and hypotension) have been reported; to reduce occurrence, do not exceed an infusion rate of 1.1 mg/minute [4] .

Pharmacology

Anidulafungin, a semi-synthetic echinocandin, is a non-competitive inhibitor of beta-(1,3)-D-glucan synthase; this enzyme is responsible for formation of the polysaccharide, beta-(1,3)-glucan, an essential fungal cell wall component [4] .
Anidulafungin is most active (MIC_{90} in mcg/mL) against *Candida albicans* (0.06), *C glabrata* (0.12), *C tropicalis* (0.06), and *C krusei* (0.12) isolates, but less potent against *C parapsilosis* (2) and *C guilliermondii* (2). It has demonstrated activity against the

biofilms of *C. albicans* and *C. parapsilosis*. The minimum effective concentration $_{90}$ against *Aspergillus fumigatus* is 0.008 mcg/mL [6] . *Candida* isolates with reduced susceptibility to anidulafungin have been reported. The clinical relevance of these reports is unknown, but the development of drug resistance may be possible. Extensively bound to plasma proteins (greater than 99%). No hepatic metabolism; not a substrate, inducer, or inhibitor of CYP450. Undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide (inactive). In a single-dose study, less than 1% was recovered in urine and approximately 30% was recovered in the feces over 9 days, of which less than 10% was intact anidulafungin. Not removed by hemodialysis [4] .

In a pharmacokinetic and safety study following 3 to 5 days of anidulafungin (n=15; age 2 days to 2 years), neonates (n=8; 6 out of 8 premature) demonstrated a median weight adjusted clearance of 0.02 L/kg/hr (range 0.013 to 0.049), median half-life of 78 hours (range 40 to 219), and median exposure of 74.9 mcg*hr/mL (30.4 to 108.9). The lowest exposure was seen in 2 neonates who received extracorporeal membrane oxygenation (ECMO), a process which may alter volume of distribution and/or clearance, and therefore drug exposure. The inclusion of data from the ECMO patients in the calculations likely skewed the median pharmacokinetic values for the entire neonatal study population [1] .

Adverse Effects

Adverse events reported were hypotension (1), adrenal insufficiency (1), abnormal X-ray of kidneys, ureter, and bladder (1), death (1), infection (1), pulmonary edema (1), and oliguria or uremia (2) in a safety study of 8 neonates [1] .

Monitoring

Monitor blood cultures daily or every other day until yeast is cleared [3] . Monitor liver function tests. Also monitor for signs and symptoms of worsening hepatic function in patients who develop abnormal liver function tests during therapy [4] .

Special Considerations/Preparation

Available as 50-mg and 100-mg single-use vials of anidulafungin lyophilized powder for solution. The 50-mg and 100-mg vials also contain fructose (50 mg and 100 mg, respectively) and mannitol (250 mg and 500 mg, respectively). Refrigerate unopened vials between 2 and 8 degrees C (36 and 46 degrees F). Do not freeze. Excursions to 25 degrees C (77 degrees F) are permitted for 96 hours; then, vial may be returned to refrigerator [4] .

Reconstitute 50-mg and 100-mg vials with 15 mL and 30 mL, respectively, of sterile water for injection (3.33 mg/mL). Reconstituted solution may be stored up to 24 hours at 25 degrees C (77 degrees F) or less. For infusion, dilute appropriate dose in sufficient volume of D_5W or NS to final concentration of 0.8 mg/mL. Diluted solution for infusion may be stored at room temperature, up to 25 degrees C (77 degrees F), for up to 48 hours or frozen for at least 72 hours prior to administration [4] .

Solution Compatibility

D_5W, NS.

Terminal Injection Site Compatibility

Anidulafungin 0.5 mg/mL
Acyclovir (7 mg/mL), amikacin (5 mg/mL), aminocaproic acid (50 mg/mL), aminophylline (2.5 mg/mL), amiodarone (4 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20 and 10 mg/mL), argatroban (1 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), caspofungin (0.5 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin (20 mg/mL), ceftazidime (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), chloramphenicol (20 mg/mL), cimetidine (12 mg/mL), ciprofloxacin (2 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), dexmedetomidine (4 mcg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dolasetron (2 mg/mL), dopamine (3.2 mg/mL), doxycycline hyclate (1 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), ganciclovir (20 mg/mL), gentamicin (5 mg/mL), glycopyrrolate (0.2 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydralazine (1 mg/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (1 unit/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2 mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), mannitol (150 mg/mL; 15%), meropenem (2.5 mg/mL), methotrexate (12.5 mg/mL), methyldopate (10 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), midazolam (1 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), moxifloxacin (1.6 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (20 mg/mL), naloxone (0.4 mg/mL), nicardipine (1 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), norepinephrine (0.12 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), pancuronium (0.1 mg/mL), pantoprazole (0.4 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin/tazobactam (40 and 5 mg/mL), potassium chloride (0.1 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), succinylcholine (2 mg/mL), sulfamethoxazole-trimethoprim (4 and 0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vasopressin (1 unit/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), voriconazole (4 mg/mL), zidovudine (4 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B conventional colloidal, diazepam, ertapenem, magnesium sulfate, nalbuphine, phenytoin, sodium bicarbonate.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is

based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
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Title Anidulafungin

Dose

Candidiasis
Full term infants when intolerant to or resistant to fluconazole or amphotericin B
Loading dose: 3 mg/kg IV for 1 dose [1] [2] . A higher dose may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1] .
Maintenance dose: 1.5 mg/kg IV once daily [1] [2] . Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1] . Duration of therapy for proven infection, without systemic complications, is at least 2 weeks after documented clearance of *Candida* from the bloodstream and resolution of symptoms [3] .

Administration

Administer by IV Infusion over 60 minutes [1] ; not to exceed 1.1 mg/minute [4] .

Uses

Treatment of infection due to *Candida* species. *Candida* species are the most common cause of invasive fungal infection in humans; mortality in neonates and children from

invasive candidiasis is 10% to 15%. Antifungal therapy should be started on all candidemic patients within 24 hours of a blood culture positive for yeast; delays are associated with increased mortality [3] .

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Treatment of candidemia, esophageal candidiasis, and intra-abdominal abscess and peritonitis due to *Candida* in patients older than 16 years [4] .

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Contraindicated in patients with hypersensitivity to other echinocandins [4] .

Hepatitis, hepatic failure, and significant hepatic dysfunction have been reported. Anaphylactic reactions, including shock, have also been reported; discontinue use if reactions occur. Infusion-related reactions (eg, rash, urticaria, flushing, pruritus, bronchospasm, dyspnea, and hypotension) have been reported; to reduce occurrence, do not exceed an infusion rate of 1.1 mg/minute [4] .

Pharmacology

Anidulafungin, a semi-synthetic echinocandin, is a non-competitive inhibitor of beta-(1,3)-D-glucan synthase; this enzyme is responsible for formation of the polysaccharide, beta-(1,3)-glucan, an essential fungal cell wall component [4] .
Anidulafungin is most active (MIC_{90} in mcg/mL) against *Candida albicans* (0.06), *C glabrata* (0.12), *C tropicalis* (0.06), and *C krusei* (0.12) isolates, but less potent against *C parapsilosis* (2) and *C guilliermondii* (2). It has demonstrated activity against the biofilms of *C. albicans* and *C. parapsilosis*. The minimum effective concentration $_{90}$ against *Aspergillus fumigatus* is 0.008 mcg/mL [6] . *Candida* isolates with reduced susceptibility to anidulafungin have been reported. The clinical relevance of these reports is unknown, but the development of drug resistance may be possible.
Extensively bound to plasma proteins (greater than 99%). No hepatic metabolism; not a substrate, inducer, or inhibitor of CYP450. Undergoes slow chemical degradation at physiologic temperature and pH to a ring-opened peptide (inactive). In a single-dose study, less than 1% was recovered in urine and approximately 30% was recovered in

the feces over 9 days, of which less than 10% was intact anidulafungin. Not removed by hemodialysis [4] .

In a pharmacokinetic and safety study following 3 to 5 days of anidulafungin (n=15; age 2 days to 2 years), neonates (n=8; 6 out of 8 premature) demonstrated a median weight adjusted clearance of 0.02 L/kg/hr (range 0.013 to 0.049), median half-life of 78 hours (range 40 to 219), and median exposure of 74.9 mcg*hr/mL (30.4 to 108.9). The lowest exposure was seen in 2 neonates who received extracorporeal membrane oxygenation (ECMO), a process which may alter volume of distribution and/or clearance, and therefore drug exposure. The inclusion of data from the ECMO patients in the calculations likely skewed the median pharmacokinetic values for the entire neonatal study population [1] .

Adverse Effects

Adverse events reported were hypotension (1), adrenal insufficiency (1), abnormal X-ray of kidneys, ureter, and bladder (1), death (1), infection (1), pulmonary edema (1), and oliguria or uremia (2) in a safety study of 8 neonates [1] .

Monitoring

Monitor blood cultures daily or every other day until yeast is cleared [3] . Monitor liver function tests. Also monitor for signs and symptoms of worsening hepatic function in patients who develop abnormal liver function tests during therapy [4] .

Special Considerations/Preparation

Available as 50-mg and 100-mg single-use vials of anidulafungin lyophilized powder for solution. The 50-mg and 100-mg vials also contain fructose (50 mg and 100 mg, respectively) and mannitol (250 mg and 500 mg, respectively). Refrigerate unopened vials between 2 and 8 degrees C (36 and 46 degrees F). Do not freeze. Excursions to 25 degrees C (77 degrees F) are permitted for 96 hours; then, vial may be returned to refrigerator [4] .

Reconstitute 50-mg and 100-mg vials with 15 mL and 30 mL, respectively, of sterile water for injection (3.33 mg/mL). Reconstituted solution may be stored up to 24 hours at 25 degrees C (77 degrees F) or less. For infusion, dilute appropriate dose in sufficient volume of D_5W or NS to final concentration of 0.8 mg/mL. Diluted solution for infusion may be stored at room temperature, up to 25 degrees C (77 degrees F), for up to 48 hours or frozen for at least 72 hours prior to administration [4] .

Solution Compatibility

D_5W, NS.

Terminal Injection Site Compatibility

Anidulafungin 0.5 mg/mL
Acyclovir (7 mg/mL), amikacin (5 mg/mL), aminocaproic acid (50 mg/mL),

aminophylline (2.5 mg/mL), amiodarone (4 mg/mL), amphotericin B lipid complex (1 mg/mL), amphotericin B liposome (1 mg/mL), ampicillin (20 mg/mL), ampicillin/sulbactam (20 and 10 mg/mL), argatroban (1 mg/mL), atracurium (0.5 mg/mL), azithromycin (2 mg/mL), aztreonam (40 mg/mL), bivalirudin (5 mg/mL), bumetanide (40 mcg/mL), calcium chloride (40 mg/mL), calcium gluconate (40 mg/mL), caspofungin (0.5 mg/mL), cefazolin (20 mg/mL), cefepime (20 mg/mL), cefotaxime (20 mg/mL), cefotetan (20 mg/mL), cefoxitin (20 mg/mL), ceftazidime (40 mg/mL), ceftriaxone (20 mg/mL), cefuroxime (30 mg/mL), chloramphenicol (20 mg/mL), cimetidine (12 mg/mL), ciprofloxacin (2 mg/mL), cisatracurium (0.5 mg/mL), clindamycin (10 mg/mL), cyclosporine (5 mg/mL), dexamethasone (1 mg/mL), dexmedetomidine (4 mcg/mL), digoxin (0.25 mg/mL), diltiazem (5 mg/mL), diphenhydramine (2 mg/mL), dobutamine (4 mg/mL), dolasetron (2 mg/mL), dopamine (3.2 mg/mL), doxycycline hyclate (1 mg/mL), enalaprilat (0.1 mg/mL), epinephrine (50 mcg/mL), erythromycin (5 mg/mL), esmolol (10 mg/mL), famotidine (2 mg/mL), fentanyl (50 mcg/mL), fluconazole (2 mg/mL), foscarnet (24 mg/mL), fosphenytoin (20 mgPE/mL), furosemide (3 mg/mL), ganciclovir (20 mg/mL), gentamicin (5 mg/mL), glycopyrrolate (0.2 mg/mL), granisetron (50 mcg/mL), haloperidol (0.2 mg/mL), heparin (100 units/mL), hydralazine (1 mg/mL), hydrocortisone (1 mg/mL), hydromorphone (0.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (1 unit/mL), isoproterenol (20 mcg/mL), ketorolac (15 mg/mL), labetalol (2 mg/mL), levofloxacin (5 mg/mL), lidocaine (10 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), mannitol (150 mg/mL; 15%), meropenem (2.5 mg/mL), methotrexate (12.5 mg/mL), methyldopate (10 mg/mL), methylprednisolone (5 mg/mL), metoclopramide (5 mg/mL), metronidazole (5 mg/mL), midazolam (1 mg/mL), milrinone (0.2 mg/mL), morphine (15 mg/mL), moxifloxacin (1.6 mg/mL), mycophenolate mofetil (6 mg/mL), nafcillin (20 mg/mL), naloxone (0.4 mg/mL), nicardipine (1 mg/mL), nitroglycerin (0.4 mg/mL), nitroprusside (2 mg/mL), norepinephrine (0.12 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (50 mcg/mL), pancuronium (0.1 mg/mL), pantoprazole (0.4 mg/mL), pentobarbital (5 mg/mL), phenobarbital (5 mg/mL), phenylephrine (1 mg/mL), piperacillin/tazobactam (40 and 5 mg/mL), potassium chloride (0.1 mEq/mL), procainamide (20 mg/mL), propranolol (1 mg/mL), quinupristin/dalfopristin (5 mg/mL), ranitidine (2 mg/mL), rocuronium (1 mg/mL), succinylcholine (2 mg/mL), sulfamethoxazole-trimethoprim (4 and 0.8 mg/mL), tacrolimus (20 mcg/mL), ticarcillin/clavulanate (31 mg/mL), tobramycin (5 mg/mL), vancomycin (10 mg/mL), vasopressin (1 unit/mL), vecuronium (1 mg/mL), verapamil (2.5 mg/mL), voriconazole (4 mg/mL), zidovudine (4 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B conventional colloidal, diazepam, ertapenem, magnesium sulfate, nalbuphine, phenytoin, sodium bicarbonate.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details. Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 06/15/2012.

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- Product Information: ERAXIS(TM) intravenous injection, anidulafungin intravenous injection. Roerig (per FDA), New York, NY, Jul, 2012.
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1.15 AquADEKsâ„¢

Title AquADEKsâ„¢

Dose

Usual dosage: 1 dropperful (1 mL) orally every 24 hours [1] .
Percentages of the Reference Daily Intakes (%RDIs) listed in the table below are for healthy infants 0 to 6 months of age.

AquADEKs™ Pediatric Liquid

Vitamins	**% Daily value**	
-	Amount per mL	0-6 months of age
A (IU)	5751	432
C (mg)	45	113
D3 (IU)	400	200
E (IU)	50	839
E (mg)	15	*

K1 (mcg)	400	20,000
B1 (mg)	0.6	300
B2 (mg)	0.6	200
Niacin (mg)	6	300
B6 (mg)	0.6	600
Biotin (mcg)	15	300
Pantothenic acid (mg)	3	176
Zinc (mg)	5	250
Selenium (mcg)	10	67
Beta-carotene (mg)	3	*
Coenzyme Q (mg)	2	*

*Daily value not established.

Uses

Multivitamin supplement for infants with cholestasis and other conditions associated with malabsorption of fat soluble vitamins [1] .

Special Considerations/Preparation

Shake liquid well before each use [1] . Store liquid in a cool place away from direct light [1] .

References

- Product Information: AquADEKs(TM) oral liquid, antioxidant enriched multivitamin and mineral supplement oral liquid. Yasoo Health Inc. (per manufacturer), Johnson City, TN, Jul, 2006.

Title AquADEKsâ„¢

Dose

Usual dosage: 1 dropperful (1 mL) orally every 24 hours [1] .
Percentages of the Reference Daily Intakes (%RDIs) listed in the table below are for healthy infants 0 to 6 months of age.

AquADEKs™ Pediatric Liquid

Vitamins		% Daily value
-	Amount per mL	0-6 months of age
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D3 (IU)	400	200
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E (mg)	15	*
K1 (mcg)	400	20,000
B1 (mg)	0.6	300
B2 (mg)	0.6	200
Niacin (mg)	6	300
B6 (mg)	0.6	600
Biotin (mcg)	15	300
Pantothenic acid (mg)	3	176
Zinc (mg)	5	250
Selenium (mcg)	10	67
Beta-carotene (mg)	3	*
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Uses

Multivitamin supplement for infants with cholestasis and other conditions associated with malabsorption of fat soluble vitamins [1] .

Special Considerations/Preparation

Shake liquid well before each use [1] . Store liquid in a cool place away from direct light [1] .

References

- Product Information: AquADEKs(TM) oral liquid, antioxidant enriched multivitamin and mineral supplement oral liquid. Yasoo Health Inc. (per manufacturer), Johnson City, TN, Jul, 2006.

1.16 Arginine

Title Arginine

Dose

Acute Hyperammonemia - Urea Cycle Disorders
Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known CPS, OTC, or NAGS Deficiency:
Loading dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [5] [3] [4] .
Maintenance dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [5] [3] [4] .

Known ASS or ASL Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [5] [3] [4] .
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [5] [3] [4] .

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis [4] .

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Administration

For treatment of acute hyperammonemia, **must be administered through a central line.** For loading and maintenance doses, dilute arginine and sodium phenylacetate/sodium benzoate in 25 to 35 mL/kg of $D_{10}W$ prior to administration [4] .

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Sodium phenylacetate/sodium benzoate should be used concomitantly with arginine hydrochloride. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [2] [5] [3] [4] [6] .

Contraindications/Precautions

Arginine hydrochloride contains 47.5 mEq of chloride in 100 mL. Hyperchloremic metabolic acidosis has been reported in 2 pediatric patients receiving excessive arginine. Extravasation can cause tissue necrosis. Arginine is a nitric oxide precursor. Excessive arginine accumulation can result in nitric oxide overproduction with potential for vasodilation and hypotension [5] [3] [4] [7] .

Pharmacology

The use of arginine provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Arginine increases the synthesis of citrulline which contains a nitrogen from ammonia and is efficiently excreted in the urine. In addition, certain defects in the urea cycle prevent the formation of citrulline which decreases the synthesis of arginine. This results in arginine becoming an essential amino acid in patients with urea cycle disorders [5] [3] [6] .

Monitoring

Plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor electrolytes and acid-base status closely during the acute phase (eg, every 4 hours). Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal [3] [4] .

Special Considerations/Preparation

Arginine hydrochloride is supplied as a 10% solution. The product is hypertonic (950 mOsmol/liter), acidic (average pH 5.6), and contains 47.5 mEq of chloride in 100 mL. The product should be stored at room temperature. Solution that has been frozen should not be used [7] .

Solution Compatibility

$D_{10}W$ and sodium phenylacetate/sodium benzoate 10%.

References

- Product Information: Ammonul(R) IV injection, sodium phenylacetate 10% sodium benzoate 10% IV injection. Ucyclyd Pharma, Inc., Scottsdale, AZ, Jan, 2008.

- Enns GM, Berry SA, Berry GT et al: Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med May31, 2007; 356(22): 2282-2292.

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- Batshaw ML: Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr Jan, 2001; 138(1 Suppl): S46-S54.

- Brusilow SW: Arginine, an indispensable amino acid for patients with inborn errors of urea synthesis. J Clin Invest Dec, 1984; 74(6): 2144-2148.

- Product Information: R-Gene(R) 10 IV injection, arginine HCl 10% IV injection. Pharmacia & Upjohn Company (per Manufacturer), New York, NY, Feb, 2007.

Title Arginine

Dose

Acute Hyperammonemia - Urea Cycle Disorders
Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known CPS, OTC, or NAGS Deficiency:
Loading dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [5] [3] [4] .
Maintenance dose: Arginine hydrochloride 200 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [5] [3] [4] .

Known ASS or ASL Deficiency:
Loading dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [5] [3] [4] .
Maintenance dose: Arginine hydrochloride 600 mg/kg in combination with sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg as an IV infusion over 24 hours [1] [2] [5] [3] [4] .

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis [4] .

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Administration

For treatment of acute hyperammonemia, **must be administered through a central line.** For loading and maintenance doses, dilute arginine and sodium phenylacetate/sodium benzoate in 25 to 35 mL/kg of $D_{10}W$ prior to administration [4] .

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Sodium phenylacetate/sodium benzoate should be used concomitantly with arginine hydrochloride. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [2] [5] [3] [4] [6] .

Contraindications/Precautions

Arginine hydrochloride contains 47.5 mEq of chloride in 100 mL. Hyperchloremic metabolic acidosis has been reported in 2 pediatric patients receiving excessive arginine. Extravasation can cause tissue necrosis. Arginine is a nitric oxide precursor. Excessive arginine accumulation can result in nitric oxide overproduction with potential for vasodilation and hypotension [5] [3] [4] [7] .

Pharmacology

The use of arginine provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Arginine increases the synthesis of citrulline which contains a nitrogen from ammonia and is efficiently excreted in the urine. In addition, certain defects in the urea cycle prevent the formation of citrulline which decreases the synthesis of arginine. This results in arginine becoming an essential amino acid in patients with urea cycle disorders [5] [3] [6] .

Monitoring

Plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor electrolytes and acid-base status closely during the acute phase (eg, every 4 hours). Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal [3] [4] .

Special Considerations/Preparation

Arginine hydrochloride is supplied as a 10% solution. The product is hypertonic (950 mOsmol/liter), acidic (average pH 5.6), and contains 47.5 mEq of chloride in 100 mL. The product should be stored at room temperature. Solution that has been frozen should not be used [7] .

Solution Compatibility

$D_{10}W$ and sodium phenylacetate/sodium benzoate 10%.

References

- Product Information: Ammonul(R) IV injection, sodium phenylacetate 10% sodium benzoate 10% IV injection. Ucyclyd Pharma, Inc., Scottsdale, AZ, Jan, 2008.
- Enns GM, Berry SA, Berry GT et al: Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med May31, 2007; 356(22): 2282-2292.
- Summar M: Current strategies for the management of neonatal urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S30-S39.
- Urea Cycle Disorders Conference group : Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S1-S5.
- Batshaw ML: Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr Jan, 2001; 138(1 Suppl): S46-S54.
- Brusilow SW: Arginine, an indispensable amino acid for patients with inborn errors of urea synthesis. J Clin Invest Dec, 1984; 74(6): 2144-2148.
- Product Information: R-Gene(R) 10 IV injection, arginine HCl 10% IV injection. Pharmacia & Upjohn Company (per Manufacturer), New York, NY, Feb, 2007.

1.17 Aspirin

Title Aspirin

Dose

Acute Ischemic Stroke (AIS), Recurrent: 1 to 5 mg/kg orally once daily [1] [2] .

Thrombosis; Prophylaxis
1 to 5 mg/kg orally once daily [1] [3] [4] [5] .
Higher doses (6 to 10 mg/kg/day) have been used in neonates undergoing heart surgery [1] [6] [7] [8] .

Administration

Administer without regard to feedings.

Uses

Antiplatelet agent for the prophylaxis and treatment of thrombotic events. Aspirin is recommended as thromboprophylaxis after Fontan surgery, in patients with systemic-to-pulmonary shunts, in patients after ventricular assist device placement, and in patients with mechanical heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy or patients in whom there is a contraindication to full-dose vitamin K antagonists [1] [3] [4] [5] [9] . In a prospective, multicenter, randomized study (n=111) of warfarin vs aspirin for primary thromboprophylaxis in children after Fontan surgery, the thrombosis event rate at 2 years was 19% with no significant difference between warfarin and aspirin therapy (24% vs 14%; p=0.45); minor bleeding was more common in the warfarin group (33% vs 14%) [3] .

Secondary prevention of recurrent AIS [1] [2] [5] .

Contraindications/Precautions

Aspirin use has been associated with a potentially fatal condition called Reye's syndrome. Association has been shown to be mainly dose dependent, occurring with anti-inflammatory doses (greater than 40 mg/kg/day), rather than lower doses used for antiplatelet effects [11] [12] [5] [13] [14] . Use caution in patients with bleeding disorders, peptic ulcer disease, renal impairment, or severe hepatic impairment. Severe allergic reactions, including asthma, hives, and facial swelling, may occur [15] .

Pharmacology

The main mechanism of action of aspirin is through inhibition of prostaglandin biosynthesis. Prostaglandins are produced from arachidonic acid via COX (cyclooxygenase; also known as prostaglandin endoperoxide synthase). Aspirin is a more specific inhibitor against COX-1 over COX-2 [18] . Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than its other salicylic derivatives due to the acetyl group on the aspirin molecule, which inactivates cyclooxygenase via acetylation [19] . The antithrombotic effect of aspirin occurs by an irreversible inhibition of platelet cyclooxygenase. This enzyme inhibition blocks the formation of thromboxane A2 from arachidonic acid which would reduce platelet shape change, aggregation, and the release reaction [20] [21] [22] [23] . Platelet inhibition occurs at lower doses (1 to 5 mg/kg/day). Rapidly absorbed following oral administration with peak concentration achieved in 2 hours. Rapidly hydrolyzed by esterases in the liver, intestine, and blood to salicylic acid. Has a low Vd and is extensively bound to albumin (80% to 90%). Eliminated through hepatic metabolism and renal excretion with elimination pathways dependent on dose. At therapeutic doses, most elimination occurs through hepatic metabolism to 3 major metabolites (all inactive); less than 10% is excreted unchanged in the urine. At higher doses, when saturation of metabolic pathways occurs, renal excretion dominates with greater than 50% of unchanged salicylic acid eliminated in the urine. Renal excretion dependent on urinary pH (alkaline urine increases elimination). Elimination half-life is approximately 2 to 3 hours at low dose and 12 hours at anti-inflammatory doses [18] .

Adverse Effects

Mild gastrointestinal symptoms (nausea, vomiting, abdominal pain, GI upset) are the most common adverse effects. Headache and tinnitus have also been reported

frequently in children. Elevations in serum transaminases may occur [16] [17] . Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10] .

Monitoring

Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10] .

Special Considerations/Preparation

Available as 81-mg chewable tablets. Also available as 300- and 600-mg rectal suppositories.

References

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- Product Information: BUFFERIN(R) oral tablets, aspirin oral tablets. Novartis Consumer Health,Inc, Parsippany, NJ, Jan1, 2007.

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- Product Information: ZORPRIN(R) oral tablet, aspirin oral tablet. PAR Pharmaceutical, Inc, Spring Valley, NY, April, 2003.

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Title Aspirin

Dose

Acute Ischemic Stroke (AIS), Recurrent: 1 to 5 mg/kg orally once daily [1] [2] .

Thrombosis; Prophylaxis
1 to 5 mg/kg orally once daily [1] [3] [4] [5] .
Higher doses (6 to 10 mg/kg/day) have been used in neonates undergoing heart surgery [1] [6] [7] [8] .

Administration

Administer without regard to feedings.

Uses

Antiplatelet agent for the prophylaxis and treatment of thrombotic events. Aspirin is recommended as thromboprophylaxis after Fontan surgery, in patients with systemic-to-pulmonary shunts, in patients after ventricular assist device placement, and in patients with mechanical heart valves who have had thrombotic events while receiving therapeutic antithrombotic therapy or patients in whom there is a contraindication to full-dose vitamin K antagonists [1] [3] [4] [5] [9] . In a prospective, multicenter, randomized study (n=111) of warfarin vs aspirin for primary thromboprophylaxis in children after Fontan surgery, the thrombosis event rate at 2 years was 19% with no significant difference between warfarin and aspirin therapy (24% vs 14%; p=0.45); minor bleeding was more common in the warfarin group (33% vs 14%) [3] .

Secondary prevention of recurrent AIS [1] [2] [5] .

Contraindications/Precautions

Aspirin use has been associated with a potentially fatal condition called Reye's syndrome. Association has been shown to be mainly dose dependent, occurring with anti-inflammatory doses (greater than 40 mg/kg/day), rather than lower doses used for antiplatelet effects [11] [12] [5] [13] [14] . Use caution in patients with bleeding disorders, peptic ulcer disease, renal impairment, or severe hepatic impairment. Severe allergic reactions, including asthma, hives, and facial swelling, may occur [15] .

Pharmacology

The main mechanism of action of aspirin is through inhibition of prostaglandin biosynthesis. Prostaglandins are produced from arachidonic acid via COX (cyclooxygenase; also known as prostaglandin endoperoxide synthase). Aspirin is a more specific inhibitor against COX-1 over COX-2 [18] . Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than its other salicylic derivatives due to the acetyl group on the aspirin molecule, which inactivates cyclooxygenase via acetylation [19] . The antithrombotic effect of aspirin occurs by an irreversible inhibition of platelet cyclooxygenase. This enzyme inhibition blocks the formation of thromboxane A2 from arachidonic acid which would reduce platelet shape change, aggregation, and the release reaction [20] [21] [22] [23] . Platelet inhibition

occurs at lower doses (1 to 5 mg/kg/day). Rapidly absorbed following oral administration with peak concentration achieved in 2 hours. Rapidly hydrolyzed by esterases in the liver, intestine, and blood to salicylic acid. Has a low Vd and is extensively bound to albumin (80% to 90%). Eliminated through hepatic metabolism and renal excretion with elimination pathways dependent on dose. At therapeutic doses, most elimination occurs through hepatic metabolism to 3 major metabolites (all inactive); less than 10% is excreted unchanged in the urine. At higher doses, when saturation of metabolic pathways occurs, renal excretion dominates with greater than 50% of unchanged salicylic acid eliminated in the urine. Renal excretion dependent on urinary pH (alkaline urine increases elimination). Elimination half-life is approximately 2 to 3 hours at low dose and 12 hours at anti-inflammatory doses [18] .

Adverse Effects

Mild gastrointestinal symptoms (nausea, vomiting, abdominal pain, GI upset) are the most common adverse effects. Headache and tinnitus have also been reported frequently in children. Elevations in serum transaminases may occur [16] [17] . Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10] .

Monitoring

Mild salicylism is characterized by headache, dizziness, tinnitus, hearing and vision impairment, sweating, nausea, vomiting, nasal congestion, and slight hyperpyrexia. Symptoms of severe salicylate toxicity include hyperventilation, mental confusion, restlessness, irritability, hyperthermia, and alterations in acid-base balance, primarily respiratory alkalosis [10] .

Special Considerations/Preparation

Available as 81-mg chewable tablets. Also available as 300- and 600-mg rectal suppositories.

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1.18 Atropine

Title Atropine

Dose

Bradycardia
IV: 0.01 to 0.03 mg/kg/dose IV over 1 minute, or IM. Dose can be repeated every 10 to 15 minutes to achieve desired effect, with a maximum total dose of 0.04 mg/kg.
ET: 0.01 to 0.03 mg/kg/dose immediately followed by 1 mL NS.
Oral: Begin with 0.02 mg/kg/dose given every 4 to 6 hours. May increase gradually to 0.09 mg/kg/dose.

Premedication for Intubation
0.01 to 0.02 mg/kg IV over 1 minute immediately prior to other premedications [1] [2] [3] [4] [5] .

Uses

Reversal of severe sinus bradycardia, particularly when parasympathetic influences on the heart (digoxin, beta-blocker drugs, hyperactive carotid sinus reflex) predominate. Prevention of bradycardia during endotracheal or nasotracheal intubation [1] [2] [3] [4] [5] . Also used to reduce the muscarinic effects of neostigmine when reversing neuromuscular blockade.

Pharmacology

Anticholinergic. Increases heart rate by decreasing the effects of the parasympathetic system while increasing the effects of the sympathetic system. Peak tachycardia is 12 to 16 minutes after dose is given. Relaxes bronchial smooth muscle, thus reducing airway resistance and increasing dead space by 30%. Motor activity in the stomach and small and large intestines is reduced. Esophageal sphincter tone is reduced. Salivary secretion is inhibited. Duration of action is 6 hours. Primarily excreted renally unchanged.

Adverse Effects

Cardiac arrhythmias can occur, particularly during the first 2 minutes following IV administration; usually a simple A-V dissociation, more often caused by smaller rather than larger doses. Fever, especially in brain-damaged infants. Abdominal distention with decreased bowel activity. Esophageal reflux. Mydriasis and cycloplegia.

Monitoring

Heart rate.

Special Considerations/Preparation

Supplied in multiple concentrations (0.05-, 0.1-,0.4-, and 1-mg/mL) for injection. May give IV dosage form orally.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Amiodarone, cimetidine, dobutamine, famotidine, fentanyl, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, meropenem, methadone, metoclopramide, midazolam, milrinone, morphine, nafcillin, netilmicin, pentobarbital, potassium chloride, propofol, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Phenytoin, sulfamethoxazole/trimethoprim.

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Title Atropine

Dose

Bradycardia
IV: 0.01 to 0.03 mg/kg/dose IV over 1 minute, or IM. Dose can be repeated every 10 to 15 minutes to achieve desired effect, with a maximum total dose of 0.04 mg/kg.
ET: 0.01 to 0.03 mg/kg/dose immediately followed by 1 mL NS.
Oral: Begin with 0.02 mg/kg/dose given every 4 to 6 hours. May increase gradually to 0.09 mg/kg/dose.

Premedication for Intubation
0.01 to 0.02 mg/kg IV over 1 minute immediately prior to other premedications [1] [2] [3] [4] [5] .

Uses

Reversal of severe sinus bradycardia, particularly when parasympathetic influences on the heart (digoxin, beta-blocker drugs, hyperactive carotid sinus reflex) predominate. Prevention of bradycardia during endotracheal or nasotracheal intubation [1] [2] [3] [4] [5] . Also used to reduce the muscarinic effects of neostigmine when reversing neuromuscular blockade.

Pharmacology

Anticholinergic. Increases heart rate by decreasing the effects of the parasympathetic system while increasing the effects of the sympathetic system. Peak tachycardia is 12 to 16 minutes after dose is given. Relaxes bronchial smooth muscle, thus reducing airway resistance and increasing dead space by 30%. Motor activity in the stomach and small and large intestines is reduced. Esophageal sphincter tone is reduced. Salivary secretion is inhibited. Duration of action is 6 hours. Primarily excreted renally unchanged.

Adverse Effects

Cardiac arrhythmias can occur, particularly during the first 2 minutes following IV administration; usually a simple A-V dissociation, more often caused by smaller rather than larger doses. Fever, especially in brain-damaged infants. Abdominal distention with decreased bowel activity. Esophageal reflux. Mydriasis and cycloplegia.

Monitoring

Heart rate.

Special Considerations/Preparation

Supplied in multiple concentrations (0.05-, 0.1-,0.4-, and 1-mg/mL) for injection. May give IV dosage form orally.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Amiodarone, cimetidine, dobutamine, famotidine, fentanyl, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, meropenem, methadone, metoclopramide, midazolam, milrinone, morphine, nafcillin, netilmicin, pentobarbital, potassium chloride, propofol, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Phenytoin, sulfamethoxazole/trimethoprim.

References

- Miller BR, Friesen RH: Oral atropine premedication in infants attenuates cardiovascular depression during Halothane anesthesia. *Anesth Analg* 1988;67:180.
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- Unna KR, Glaser K, Lipton E, Patterson PR: Dosage of drugs in infants and children: I. Atropine. *Pediatrics* 1950;6:197.
- Product Information, Hospira, 2004.

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2. Choong K, AlFaleh K, Doucette J et al: Remifentanil for endotracheal intubation in neonates: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed Mar, 2010; 95(2): F80-F84.
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1.19 Azithromycin

Title Azithromycin

Dose

Treatment and Prophylaxis of Pertussis Infections: 10 mg/kg/dose orally once daily for 5 days.

Intravenous treatment is limited to those who cannot be treated orally. To date, no clinical studies have been conducted to evaluate the safety or efficacy of IV azithromycin in the pediatric population. Suggested IV dose: 5 mg/kg/dose once daily.

Prophylaxis of Ophthalmia Neonatorum (erythromycin ointment shortage only): 1 to 2 drops of the 1% ophthalmic solution instilled in each conjunctival sac.

Uses

Treatment and postexposure prophylaxis against Bordetella pertussis as a substitute for penicillin in situations of significant allergic intolerance.
In the event of an erythromycin ointment shortage, azithromycin ophthalmic solution is an alternative for prophylaxis of ophthalmia neonatorum.

Pharmacology

Azithromycin is classified as an azalide, a subclass of macrolide antibiotics. In vitro activity has been demonstrated against *Bordetella pertussis*, as well as Streptococci (Groups C, F, G and Viridans), *Ureaplasma urealyticum*, and Peptostreptococcus species. Eradication of *B. pertussis* in unimmunized individuals (e.g., neonates) takes longer and requires higher doses than immunized individuals. Oral bioavailability is 38% in adults and children and is not affected by food. Primarily excreted unchanged in the bile, with some hepatic metabolism to inactive metabolites. The prolonged terminal half-life (approximately 80 hours) is thought to be due to extensive uptake and subsequent release of drug from tissues.

Adverse Effects

Limited data in neonates. Diarrhea and/or vomiting occur in 5% to 12% of patients. Irritability, rash, and blood in stool have also been reported. There is one new case report of pyloric stenosis in 2 of 3 triplets treated with azithromycin for pertussis.

Monitoring

Assess gastrointestinal tolerance.

Special Considerations/Preparation

Oral suspension is available in 300, 600, 900, and 1,200 mg bottles. Reconstitute 300 mg bottle with 9 mL of water to provide a final concentration of 100 mg per 5 mL (20 mg/mL). Shake well before administration. Do not refrigerate. Use within 10 days once bottle has been opened.

Azithromycin for intravenous injection is supplied in single use vials containing 500 mg lyophilized powder. Reconstitute by adding 4.8 mL Sterile Water for Injection, then shake the vial until all the drug is dissolved. The concentration of the reconstituted

solution is 100 mg/mL. It is stable at room temperature for 24 hours. **Dilute prior to administration** using a compatible solution to a final concentration of 1 to 2 mg/mL. Diluted solution stable for 24 hours at room temperature or 7 days in refrigerator. Do not use higher concentrations due to local IV site reactions. **Infuse over at least 60 minutes.**

Solution Compatibility

D_5W, NS, 5% Dextrose in 0.45% NaCl with 20 mEq/L KCl, and Lactated Ringer's.

Terminal Injection Site Compatibility

Caspofungin.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin, famotidine, fentanyl, furosemide, gentamicin, imipenem-cilastatin, morphine, piperacillin-tazobactam, potassium chloride, ticarcillin-clavulanate, and tobramycin.

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- Product Information: Zithromax® azithromycin tablets and oral suspension, Pfizer, 2011.
- Product Information: Zithromax® azithromycin injection, Pfizer, 2011.

Title Azithromycin

Dose

Treatment and Prophylaxis of Pertussis Infections: 10 mg/kg/dose orally once daily for 5 days.

Intravenous treatment is limited to those who cannot be treated orally. To date, no clinical studies have been conducted to evaluate the safety or efficacy of IV azithromycin in the pediatric population. Suggested IV dose: 5 mg/kg/dose once daily.

Prophylaxis of Ophthalmia Neonatorum (erythromycin ointment shortage only): 1 to 2 drops of the 1% ophthalmic solution instilled in each conjunctival sac.

Uses

Treatment and postexposure prophylaxis against Bordetella pertussis as a substitute for penicillin in situations of significant allergic intolerance.
In the event of an erythromycin ointment shortage, azithromycin ophthalmic solution is an alternative for prophylaxis of ophthalmia neonatorum.

Pharmacology

Azithromycin is classified as an azalide, a subclass of macrolide antibiotics. In vitro activity has been demonstrated against *Bordetella pertussis*, as well as Streptococci (Groups C, F, G and Viridans), *Ureaplasma urealyticum*, and Peptostreptococcus species. Eradication of *B. pertussis* in unimmunized individuals (e.g., neonates) takes longer and requires higher doses than immunized individuals. Oral bioavailability is 38% in adults and children and is not affected by food. Primarily excreted unchanged in the bile, with some hepatic metabolism to inactive metabolites. The prolonged terminal half-life (approximately 80 hours) is thought to be due to extensive uptake and subsequent release of drug from tissues.

Adverse Effects

Limited data in neonates. Diarrhea and/or vomiting occur in 5% to 12% of patients. Irritability, rash, and blood in stool have also been reported. There is one new case report of pyloric stenosis in 2 of 3 triplets treated with azithromycin for pertussis.

Monitoring

Assess gastrointestinal tolerance.

Special Considerations/Preparation

Oral suspension is available in 300, 600, 900, and 1,200 mg bottles. Reconstitute 300 mg bottle with 9 mL of water to provide a final concentration of 100 mg per 5 mL (20 mg/mL). Shake well before administration. Do not refrigerate. Use within 10 days once bottle has been opened.

Azithromycin for intravenous injection is supplied in single use vials containing 500 mg lyophilized powder. Reconstitute by adding 4.8 mL Sterile Water for Injection, then shake the vial until all the drug is dissolved. The concentration of the reconstituted solution is 100 mg/mL. It is stable at room temperature for 24 hours. **Dilute prior to administration** using a compatible solution to a final concentration of 1 to 2 mg/mL. Diluted solution stable for 24 hours at room temperature or 7 days in refrigerator. Do

not use higher concentrations due to local IV site reactions. **Infuse over at least 60 minutes.**

Solution Compatibility

D_5W, NS, 5% Dextrose in 0.45% NaCl with 20 mEq/L KCl, and Lactated Ringer's.

Terminal Injection Site Compatibility

Caspofungin.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, clindamycin, famotidine, fentanyl, furosemide, gentamicin, imipenem-cilastatin, morphine, piperacillin-tazobactam, potassium chloride, ticarcillin-clavulanate, and tobramycin.

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- Friedman DS, Curtis CR, Schauer SL, et al. Surveillance for transmission and antibiotic adverse events among neonates and adults exposed to a healthcare worker with pertussis. *Infect Control Hosp Epidemiol* 2004;25:967-73.
- Jacobs RF, Maples HD, Aranda JV, et al. Pharmacokinetics of intravenously administered azithromycin in pediatric patients. *Pediatr Infect Dis J* 2005;24:34-39.
- Langley JM, Halperin SA, Boucher FD, et al. Azithromycin is as effective and better tolerated than erythromycin estolate for the treatment of pertussis. *Pediatrics* 2004;114:96-101.
- Morrison W. Infantile hypertrophic pyloric stenosis in infants treated with azithromycin. *Pediatr Infect Dis J* 2007;26:186-188.
- Product Information: Zithromax® azithromycin tablets and oral suspension, Pfizer, 2011.
- Product Information: Zithromax® azithromycin injection, Pfizer, 2011.

1.20 Aztreonam

Title Aztreonam

Dose

30 mg/kg/dose IV slow push over 5 to 10 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae*, *Klebsiella*, *Pseudomonas*,and*Serratia*). Generally used in combination with ampicillin (empirical treatment of sepsis) or an aminoglycoside (for synergism against *Pseudomonas* and *Enterobacteriaceae*).

Pharmacology

Aztreonam is a synthetically-produced monocyclic β-lactam antibiotic. Although bactericidal against aerobic gram-negative bacteria, it has virtually no activity against aerobic gram-positive and anaerobic bacteria, thereby producing little alteration of bowel flora. Good tissue and fluid penetration has been demonstrated in adults, along with protein-binding of 50 to 65%. Eliminated renally, primarily as unchanged drug. Serum half-life in neonates is 3 to 9 hours. Aztreonam does not interfere with bilirubin-albumin binding.

Adverse Effects

Aztreonam contains 780 mg L-arginine per gram of drug (23.4 mg/kg body weight per dose). Adequate amounts of glucose must be provided to prevent hypoglycemia. Side effects are rare but include eosinophilia, elevation of serum transaminases, and phlebitis at the injection site.

Monitoring

Check serum glucose one hour after administration. Measuring serum concentration is not usually necessary. Periodic CBC, AST, ALT.

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials. Reconstitute 500-mg vial with 10 mL of either sterile water for injection or NS (50 mg/mL) or 1-g vial with 10 mL of either sterile water for injection or NS (100 mg/mL). **Shake immediately and vigorously.**Reconstituted solution stable for 48 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, aminophylline, ampicillin, bumetanide, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, enalaprilat, famotidine, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem, insulin, linezolid, magnesium sulfate, metoclopramide, mezlocillin, morphine, netilmicin, nicardipine, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, tobramycin, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, azithromycin, ganciclovir, lorazepam, metronidazole, and nafcillin.

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- Product Information, Bristol-Myers Squibb, 2010
- Product Information, APP Pharmaceuticals, 2009

Title Aztreonam

Dose

30 mg/kg/dose IV slow push over 5 to 10 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual

Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of neonatal sepsis caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae*, *Klebsiella*, *Pseudomonas*,and*Serratia*). Generally used in combination with ampicillin (empirical treatment of sepsis) or an aminoglycoside (for synergism against *Pseudomonas* and *Enterobacteriaceae*).

Pharmacology

Aztreonam is a synthetically-produced monocyclic β-lactam antibiotic. Although bactericidal against aerobic gram-negative bacteria, it has virtually no activity against aerobic gram-positive and anaerobic bacteria, thereby producing little alteration of bowel flora. Good tissue and fluid penetration has been demonstrated in adults, along with protein-binding of 50 to 65%. Eliminated renally, primarily as unchanged drug. Serum half-life in neonates is 3 to 9 hours. Aztreonam does not interfere with bilirubin-albumin binding.

Adverse Effects

Aztreonam contains 780 mg L-arginine per gram of drug (23.4 mg/kg body weight per dose). Adequate amounts of glucose must be provided to prevent hypoglycemia. Side effects are rare but include eosinophilia, elevation of serum transaminases, and phlebitis at the injection site.

Monitoring

Check serum glucose one hour after administration. Measuring serum concentration is not usually necessary. Periodic CBC, AST, ALT.

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials. Reconstitute 500-mg vial with 10 mL of either sterile water for injection or NS (50 mg/mL) or 1-g vial with 10 mL of either sterile water for injection or NS (100 mg/mL). **Shake immediately and vigorously.**Reconstituted solution stable for 48 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, aminophylline, ampicillin, bumetanide, calcium gluconate, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, enalaprilat, famotidine, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem, insulin, linezolid, magnesium sulfate, metoclopramide, mezlocillin, morphine, netilmicin, nicardipine, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, tobramycin, vancomycin, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, azithromycin, ganciclovir, lorazepam, metronidazole, and nafcillin.

References

- Uauy R, Mize C, Argyle C, McCracken GH: Metabolic tolerance to arginine: Implications for the safe use of arginine salt-aztreonam combination in the neonatal period. *J Pediatr* 1991;118:965.
- Cuzzolin L, Fanos V, Zambreri D, et al: Pharmacokinetics and renal tolerance of aztreonam in premature infants. *Antimicrob Agents Chemother* 1991;35:1726.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Likitnukul S, McCracken GH, Threlkeld N, et al: Pharmacokinetics and plasma bactericidal activity of aztreonam in low-birth-weight infants. *Antimicrob Agents Chemother* 1987;31:81.
- Product Information, Bristol-Myers Squibb, 2010
- Product Information, APP Pharmaceuticals, 2009

1.21 Beractant

Title Beractant

Dose

4 mL/kg/dose intratracheally, divided into 4 aliquots [1] .
Prophylaxis: First dose is given as soon as possible after birth, with up to three additional doses in the first 48 hours of life, if indicated [1] .

Rescue treatment of RDS: Up to four doses in first 48 hours of life, no more frequently than every 6 hours [1] .

Administration

Before administration, allow to stand at room temperature for 20 minutes, or warm in the hand for at least 8 minutes. **Artificial warming methods should not be used** [1] .

Shorten a 5F end-hole catheter so tip of catheter will protrude just beyond end of ET tube above infant's carina. Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle [1] .
Do not filter or shake. Attach shortened catheter to syringe. Fill catheter with Survanta. Discard excess Survanta through catheter so only total dose to be given remains in syringe [1] .
Administer four quarter-doses with the infant in different positions to enhance distribution. The catheter can be inserted into the infant's endotracheal tube through a neonatal suction valve without interrupting ventilation. Alternatively, Survanta can be instilled through the catheter by briefly disconnecting the endotracheal tube from the ventilator. After administration of each quarter-dose, the dosing catheter is removed from the ET tube and the infant is ventilated for at least 30 seconds until stable [1] .

Uses

Prevention and treatment of respiratory distress syndrome (RDS) in premature infants [1] [2] [3] .

Contraindications/Precautions

Transient episodes of bradycardia and decreased oxygen saturation may occur during administration. Increased risk of post-treatment nosocomial sepsis was noted in Survanta®-treated infants in controlled clinical studies [1] .

Pharmacology

Survanta® is a modified natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C, to which colfosceril palmitate (DPPC), palmitic acid, and tripalmitin are added. Resulting drug provides 25 mg/mL phospholipids (including 11 to 15.5 mg/mL DPPC), 0.5 to 1.75 mg/mL triglycerides, 1.4 to 3.5 mg/mL fatty acids, and less than 1 mg/mL protein. Survanta® is suspended in NS and heat sterilized. Animal metabolism studies show that most of a dose becomes lung-associated within hours of administration, and lipids enter endogenous surfactant pathways of reuse and recycling [1] .

Adverse Effects

Most common reactions reported include transient bradycardia (11.9% of doses) and oxygen desaturation (9.8% of doses). Other adverse events include hypotension, endotracheal tube reflux or blockage, hypertension, hypercarbia, and apnea. In a pooled analysis of all controlled studies, the incidence of intracranial hemorrhage (ICH) was

not different between the Survanta® group and the control group; however, in 2 of the studies (single-dose rescue study and multiple-dose prevention study), the incidence of ICH was significantly higher in patients who received Survanta® compared with those in the control group (63.3% vs 30.8%; p=0.001 and 48.8% vs 34.2%; p=0.047, respectively) [1] .

Monitoring

Monitor systemic oxygen and carbon dioxide levels with arterial or transcutaneous measurements frequently during therapy [1] .

Special Considerations/Preparation

Available in 4- and 8-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Survanta® for discoloration; normal color is off-white to light-brown. If settling occurs during storage, **swirl** vial gently. **Do not shake.**Vials should be entered only once. Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

References

- Product Information: SURVANTA(R) intratracheal suspension, beractant intratracheal suspension. Abbott Nutrition (per DailyMed), Columbus, OH, May, 2008.

- Hoekstra R, Jackson JC, Myers TF et al: Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome.Pediatrics 1991; 88: 10-18.

- Liechty EA, Donovan E, Purohit D et al: Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome.Pediatrics July, 1991; 88(1): 19-28.

Title Beractant

Dose

4 mL/kg/dose intratracheally, divided into 4 aliquots [1] .
Prophylaxis: First dose is given as soon as possible after birth, with up to three additional doses in the first 48 hours of life, if indicated [1] .
Rescue treatment of RDS: Up to four doses in first 48 hours of life, no more frequently than every 6 hours [1] .

Administration

Before administration, allow to stand at room temperature for 20 minutes, or warm in the hand for at least 8 minutes. **Artificial warming methods should not be used** [1] .

Shorten a 5F end-hole catheter so tip of catheter will protrude just beyond end of ET tube above infant's carina. Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle [1] .
Do not filter or shake. Attach shortened catheter to syringe. Fill catheter with Survanta. Discard excess Survanta through catheter so only total dose to be given remains in syringe [1] .
Administer four quarter-doses with the infant in different positions to enhance distribution. The catheter can be inserted into the infant's endotracheal tube through a neonatal suction valve without interrupting ventilation. Alternatively, Survanta can be instilled through the catheter by briefly disconnecting the endotracheal tube from the ventilator. After administration of each quarter-dose, the dosing catheter is removed from the ET tube and the infant is ventilated for at least 30 seconds until stable [1] .

Uses

Prevention and treatment of respiratory distress syndrome (RDS) in premature infants [1] [2] [3] .

Contraindications/Precautions

Transient episodes of bradycardia and decreased oxygen saturation may occur during administration. Increased risk of post-treatment nosocomial sepsis was noted in Survanta®-treated infants in controlled clinical studies [1] .

Pharmacology

Survanta® is a modified natural bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C, to which colfosceril palmitate (DPPC), palmitic acid, and tripalmitin are added. Resulting drug provides 25 mg/mL phospholipids (including 11 to 15.5 mg/mL DPPC), 0.5 to 1.75 mg/mL triglycerides, 1.4 to 3.5 mg/mL fatty acids, and less than 1 mg/mL protein. Survanta® is suspended in NS and heat sterilized. Animal metabolism studies show that most of a dose becomes lung-associated within hours of administration, and lipids enter endogenous surfactant pathways of reuse and recycling [1] .

Adverse Effects

Most common reactions reported include transient bradycardia (11.9% of doses) and oxygen desaturation (9.8% of doses). Other adverse events include hypotension, endotracheal tube reflux or blockage, hypertension, hypercarbia, and apnea. In a pooled analysis of all controlled studies, the incidence of intracranial hemorrhage (ICH) was not different between the Survanta® group and the control group; however, in 2 of the studies (single-dose rescue study and multiple-dose prevention study), the incidence of ICH was significantly higher in patients who received Survanta® compared with those in the control group (63.3% vs 30.8%; p=0.001 and 48.8% vs 34.2%; p=0.047, respectively) [1] .

Monitoring

Monitor systemic oxygen and carbon dioxide levels with arterial or transcutaneous measurements frequently during therapy [1] .

Special Considerations/Preparation

Available in 4- and 8-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Survanta® for discoloration; normal color is off-white to light-brown. If settling occurs during storage, **swirl** vial gently. **Do not shake.**Vials should be entered only once. Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

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- Product Information: SURVANTA(R) intratracheal suspension, beractant intratracheal suspension. Abbott Nutrition (per DailyMed), Columbus, OH, May, 2008.

- Hoekstra R, Jackson JC, Myers TF et al: Improved neonatal survival following multiple doses of bovine surfactant in very premature neonates at risk for respiratory distress syndrome.Pediatrics 1991; 88: 10-18.

- Liechty EA, Donovan E, Purohit D et al: Reduction of neonatal mortality after multiple doses of bovine surfactant in low birth weight neonates with respiratory distress syndrome.Pediatrics July, 1991; 88(1): 19-28.

1.22 Bumetanide

Title Bumetanide

Dose

0.005 to 0.05 mg/kg/dose IV slow push, IM, or orally. Doses up to 0.1 mg/kg have been used in neonates; however, there are no pharmacodynamic data showing doses greater than 0.05 mg/kg provide additional benefit [1] [2] [3] .
Preterm infants less than 34 weeks gestation in the first 2 months of life: every 24 hours.
Afterward: every 12 hours.

Preterm infants 34 weeks or more gestation and term infants in the first month of life: every 24 hours.
Afterward: every 12 hours.

Infants with lung disease and normal renal function should be started on a low dose. Infants with congestive heart failure or abnormal renal function will need a higher dose.

In a dose-range evaluation of bumetanide pharmacodynamics in critically ill neonates and infants, single IV doses ranging from 0.005 to 0.1 mg/kg (increases in increments of 0.005 mg/kg) were given over 1 to 2 minutes. All doses were associated with at least a 2-fold increase in urine output and electrolyte excretion rates. The dose range corresponding to the maximal effect was 0.035 to 0.04 mg/kg. There were no

pharmacodynamic advantages (urine output and electrolyte excretion rate) to doses greater than 0.05 mg/kg [1] . Although doses of 0.05 and 0.1 mg/kg have been studied in neonates, only pharmacokinetic endpoints were determined, and no pharmacodynamic endpoints were reported [2] . In a retrospective study in preterm infants with oliguric renal failure and inadequate response to furosemide, bumetanide was effective in significantly increasing urine output in 29 of 35 infants. The mean bumetanide dose and duration of therapy were 0.03 +/- 0.016 mg/kg every 12 to 24 hours and 5.9 days, respectively. Urine output increased from 0.6 +/- 0.6 mL/kg/hour to 3 +/- 2.1 mL/kg/hour [3] .

Administration

Intravenous: Give undiluted over 1 to 2 minutes [1] .
Oral: The intravenous formulation, diluted in sterile water and given orally, has been used successfully in infants with congenital heart disease [4] .

Uses

Diuretic used in patients with renal insufficiency, congestive heart failure, or significant edema that is refractory to furosemide.

Black Box Warning According to the manufacturer's black box warning, bumetanide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion.

Pharmacology

Bumetanide is a loop diuretic with a similar mechanism of action to furosemide. Inhibits chloride reabsorption in the ascending limb of Henle's loop and inhibits tubular sodium transport, causing major loss of sodium and chloride. Increases urinary losses of potassium, calcium, and bicarbonate. Urine sodium losses are lower with bumetanide than furosemide, but urine calcium losses are higher. Decreases CSF production by weak carbonic anhydrase inhibition. Decreases pulmonary transvascular fluid filtration. Increases renal blood flow and prostaglandin secretion. Highly protein bound (greater than 97%). Data from adults indicate excellent oral bioavailability and significant hepatic metabolism (40%) via the cytochrome CYP pathway. Serum half-life varies from 4 to 19 hours in neonates, determined by gestational age, postnatal age, and disease state.

Adverse Effects

Water and electrolyte imbalances occur frequently, especially hyponatremia, hypokalemia, and hypochloremic alkalosis. Potentially ototoxic, but less so than furosemide. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods.

Monitoring

Serum electrolytes and urine output. Assess patients receiving digoxin concurrently for potassium depletion. Follow weight changes.

Special Considerations/Preparation

Supplied as 2-, 4-, and 10-mL vials (0.25-mg/mL solution). Contains 1% (10 mg/mL) benzyl alcohol; pH adjusted to 7.
A 0.125-mg/mL dilution may be made by adding 3 mL of 0.25-mg/mL injectable solution to 3 mL preservative-free normal saline for injection. Refrigerated dilution is stable for 24 hours. Discolors when exposed to light.

There is no oral dosing formulation available for neonates. The intravenous formulation, diluted in sterile water and given orally, has been used successfully in infants with congenital heart disease [4] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aztreonam, cefepime, furosemide, lorazepam, milrinone, morphine, piperacillin/tazobactam, and propofol.

Terminal Injection Site Incompatibility

Dobutamine and midazolam.

References

- Eades SK, Christensen ML: The clinical pharmacology of loop diuretics in the pediatric patient. *Pediatr Nephrol* 1998;12:603-616.
- Lopez-Samblas AM, Adams JA, Goldberg RN, Modi MW: The pharmacokinetics of bumetanide in the newborn infant. *Biol Neonate* 1997;72:265-272.
- Shankaran S, Liang K-C, Ilagan N, Fleischmann L: Mineral excretion following furosemide compared with bumetanide therapy in premature infants. *Pediatr Nephrol* 1995;9:159-62.
- Product Information, Bedford, 2005.

1. Sullivan JE, Witte MK, Yamashita TS et al: Dose-ranging evaluation of bumetanide pharmacodynamics in critically ill infants. Clin Pharmacol Ther Oct, 1996; 60(4): 424-434.
2. Lopez-Samblas AM, Adams JA, Goldberg RN et al: The pharmacokinetics of bumetanide in the newborn infant. Biol Neonate 1997; 72(5): 265-272.
3. Oliveros M, Pham JT, John E et al: The use of bumetanide for oliguric acute renal failure in preterm infants. Pediatr Crit Care Med Mar, 2011; 12(2): 210-214.
4. Ward OC: Bumetanide in heart failure in infancy. Arch Dis Child Nov, 1977; 52(11): 877-882.

Title Bumetanide

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Preterm infants 34 weeks or more gestation and term infants in the first month of life: every 24 hours.
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Intravenous: Give undiluted over 1 to 2 minutes [1] .
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Diuretic used in patients with renal insufficiency, congestive heart failure, or significant edema that is refractory to furosemide.

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sodium transport, causing major loss of sodium and chloride. Increases urinary losses of potassium, calcium, and bicarbonate. Urine sodium losses are lower with bumetanide than furosemide, but urine calcium losses are higher. Decreases CSF production by weak carbonic anhydrase inhibition. Decreases pulmonary transvascular fluid filtration. Increases renal blood flow and prostaglandin secretion. Highly protein bound (greater than 97%). Data from adults indicate excellent oral bioavailability and significant hepatic metabolism (40%) via the cytochrome CYP pathway. Serum half-life varies from 4 to 19 hours in neonates, determined by gestational age, postnatal age, and disease state.

Adverse Effects

Water and electrolyte imbalances occur frequently, especially hyponatremia, hypokalemia, and hypochloremic alkalosis. Potentially ototoxic, but less so than furosemide. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods.

Monitoring

Serum electrolytes and urine output. Assess patients receiving digoxin concurrently for potassium depletion. Follow weight changes.

Special Considerations/Preparation

Supplied as 2-, 4-, and 10-mL vials (0.25-mg/mL solution). Contains 1% (10 mg/mL) benzyl alcohol; pH adjusted to 7.
A 0.125-mg/mL dilution may be made by adding 3 mL of 0.25-mg/mL injectable solution to 3 mL preservative-free normal saline for injection. Refrigerated dilution is stable for 24 hours. Discolors when exposed to light.

There is no oral dosing formulation available for neonates. The intravenous formulation, diluted in sterile water and given orally, has been used successfully in infants with congenital heart disease [4] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aztreonam, cefepime, furosemide, lorazepam, milrinone, morphine, piperacillin/tazobactam, and propofol.

Terminal Injection Site Incompatibility

Dobutamine and midazolam.

References

- Eades SK, Christensen ML: The clinical pharmacology of loop diuretics in the pediatric patient. *Pediatr Nephrol* 1998;12:603-616.
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4. Ward OC: Bumetanide in heart failure in infancy. Arch Dis Child Nov, 1977; 52(11): 877-882.

1.23 Bupivacaine

Title Bupivacaine

Dose

The dose varies with anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Use the lowest dose and concentration to achieve the desired result [1] [2] . The USES section provides dosage ranges; however, other resources should be consulted for specific techniques and procedures.

Dose Adjustments
Cardiac Disease: Dose reduction recommended [3] [4] [1] [5] [6] .
Debilitated and Acutely Ill: Dose reduction recommended [3] [4] [1] [5] [6] .
Liver Disease: Dose reduction recommended [3] [4] [1] [5] [2] [6] .
Risk Factors for Seizures: When bupivacaine is administered by continuous infusion, reduce the rate in neonates who are at risk for seizures. Risk factors include increased uptake into the circulation (eg, pulmonary arteriovenous malformation) or lowered seizure threshold (eg, history of febrile convulsions during the postoperative period, hypomagnesemia, or hyponatremia due to free water overload) [7] .

Administration

Bupivacaine is NOT recommended for intravenous regional anesthesia (Bier Block) [1] [5] [2] [6] .
Epidural anesthesia: Use only single-dose ampules and single-dose vials for caudal or epidural anesthesia as multiple dose vials contain a preservative. Administer slowly in 3- to 5-mL incremental doses with sufficient time between doses to detect signs/symptoms of unintentional intravascular or intrathecal injection. Perform syringe

aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques. Administer a test dose, which contains epinephrine, and monitor the effects prior to the full dose and with all subsequent doses when a catheter is in place [3] [4] [1] [5] [2] [6] . The use of a local anesthetic in the test dose is probably unwarranted and may lead to toxicity [8] . Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3] [4] [1] [5] [2] [6] .
Local infiltration and peripheral nerve blocks: Check aspiration for blood or cerebrospinal fluid (when applicable) prior to injecting any local anesthetic, both initial and subsequent doses. Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3] [4] [1] [5] [2] [6] .

Uses

Epidural anesthesia: Epidural anesthesia, whether by caudal or lumbar route, is effective in the neonate [9] . Typical doses of bupivacaine 0.125% to 0.25% are 1.25 mg/kg to 2.5 mg/kg for caudal epidural anesthesia [10] , 2 mg/kg up to a maximum of 2.5 mg/kg for epidural anesthesia (other than caudal route) [10] [11] [7] , and 0.2 mg/kg/hr up to a maximum of 0.25 mg/kg/hr for continuous epidural infusion [10] [11] [12] [7] for a maximum duration of 24 to 36 hours [12] . Data are lacking in premature infants. Although, one study used 3.125 mg/kg of 0.5% bupivacaine by the caudal route as an adjunct to general anesthesia in 20 premature infants (0 to 60 days; 520 to 2750 grams). No neonate experienced elevated heart rate or blood pressure at the time of incision [13] . In a retrospective analysis of 750 children (2 days to 16 years of age), bupivacaine 0.25% provided longer postoperative pain relief (up to 5 hours) than lidocaine 0.5% or 1.5% when administered caudally [14] .

Peripheral nerve block: For neonatal circumcision a dorsal nerve block with a local anesthetic is recommended [10] . A penile nerve block is appropriate for urethral dilation and hypospadias repair [9] . Solutions containing epinephrine should NOT be used near end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [15] [3] [5] [6] . Efficacy data are lacking in neonates; however, in 2 pharmacokinetic studies bupivacaine nerve blocks were used in neonates without associated toxic concentrations or observed adverse events [16] [17] . Doses of bupivacaine were 2 mg/kg for interpleural nerve block in 8 very low birthweight infants (700 g to 1022 g) [16] and 1.5 mg/kg for intercostal block in 11 full-term neonates (1 to 27 days of age) [17] .

Spinal anesthesia: The use of spinal anesthesia is common in neonates, even preterm infants. In comparison to adults, the dose is greater in neonates [9] . Dose range is 0.5 to 1 mg/kg [9] [18] [19] with usual doses of 0.6 mg/kg of 0.75% hyperbaric bupivacaine in 8.25% dextrose [9] [19] and 0.8 mg/kg of 0.5% isobaric bupivacaine [9] . The duration of effective spinal blockade (lack of hip flexion) was 84+/-16 minutes in 11 infants (range: 0.1 to 7 months of age; 2.8 to 9.3 kg) who received 0.75% bupivacaine 0.6 mg/kg in 8.25% dextrose solution with 0.02 mL of 1:1000 epinephrine [19] . Efficacy data are lacking in premature infants.

Pediatric FDA Approved Indications
Indicated for the production of local or regional anesthesia or analgesia for surgical procedures, dental and oral surgery procedures, and diagnostic and therapeutic

procedures. Use is not recommended in pediatric patients younger than 12 years [3] [4] [1] [5] [2] [6] .
Marcaine™ Spinal: Indicated for production of subarachnoid block (spinal anesthesia). Use in patients younger than 18 years is not recommended [20] .

Contraindications/Precautions

Contraindicated in patients with hypersensitivity to other amide-type anesthetics [3] [4] [20] [1] [5] [2] [6] .

Local anesthetic solutions containing antimicrobial preservatives should NOT be used for epidural or caudal anesthesia. Inadvertent intravascular or intrathecal administration may lead to serious toxicity. Continuous bupivacaine infusions in children have resulted in high systemic bupivacaine levels and seizures; high plasma levels may also be associated with cardiovascular abnormalities. Hepatic disease, especially severe cases, and renal impairment may cause increased risk of toxic plasma concentrations. Use with caution in patients with hypotension or heart block. Patients with cardiovascular impairment may have reduced ability to compensate for functional changes associated with AV conduction prolongation. Confusion, convulsion, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression may occur with unintentional intravascular injections of large doses during head and neck area administration [3] [4] .
Glenohumeral chondrolysis has been reported in pediatric patients following intra-articular 48- to 72-hour infusions of local anesthetics with and without epinephrine. Familial malignant hyperthermia may be triggered by local anesthetics . The 0.75% concentration is not approved for local infiltration or any other peripheral nerve block, except the retrobulbar block. Retrobulbar blocks provide complete corneal anesthesia prior to onset of clinically acceptable external ocular muscle akinesia; therefore, akinesia is the determinate for initiation of surgery. Mixing bupivacaine with other local anesthetics is not recommended [3] [4] .
Formulations with epinephrine: Contain sodium metabisulfite, which may cause allergic-type reactions (eg, anaphylactic symptoms) and life-threatening or less severe asthmatic episodes in patients with sulfite sensitivity. Preparations containing a vasoconstrictor, such as epinephrine, used during or following potent inhalation anesthetics, may cause serious dose-related cardiac arrhythmias. Avoid the concomitant use of MAOIs, tricyclic antidepressants, and ergot-type oxytocic agents. Bupivacaine use in combination with vasoconstrictors may cause a risk of exaggerated vasoconstrictor response in patients with a history of hypertensive vascular disease and may cause a risk of further blood flow restriction in end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [3] [5] [6] .

Black Box Warning

Cardiac arrest with difficult resuscitation or death during use of bupivacaine for epidural anesthesia in obstetrical patients has been reported. In most cases, this has followed use of the 0.75% concentration. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection. The 0.75% concentration should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary [3] [4] [1] [5] [2] [6] .

Pharmacology

Bupivacaine is a local anesthetic agent. It acts by blocking the conduction and generation of nerve impulses, probably by increasing the threshold that produces electrical excitation in the nerve, by reducing the rate of rise of the action potential, and by slowing the nerve impulse propagation. Systemic absorption depends on total dose and concentration, route of administration, vascularity of administration site, and presence or absence of epinephrine in the anesthetic solution. Onset of action is rapid. Compared with other local anesthetics, the duration of bupivacaine is longer. Analgesia persists beyond the return of sensation. Protein binding: 95%. Distributed to some extent to all body tissue, with the highest concentrations in highly perfused organs. After regional block, time to peak is 30 to 45 minutes, followed by a decline to insignificant levels during the next 3 to 6 hours. Metabolized primarily in the liver via conjugation with glucuronic acid. Mainly excreted through kidney; 6% excreted unchanged in the urine. Half-life is 2.7 hours and 8.1 hours in adults and neonates, respectively [3] [20] [1] . The bupivacaine concentrations considered toxic are 2 to 4 mg/mL [10] .

Unbound bupivacaine did not accumulate in neonates and young infants (postmenstrual age, 40 to 59 weeks) administered single epidural injection (n=6; 1.5 mg/kg of 0.25%) and continuous epidural infusion (n=5; 0.2 mg/kg/hr starting 2 hours after single-injection). The median Cmax of unbound bupivacaine was 0.024 mg/L (0.013 to 0.12 mg/L) after a single injection and 0.052 mg/L (0.015 to 0.08 mg/L) after a continuous infusion; the corresponding values for total bupivacaine were 0.55 mg/L (0.37 to 1.61 mg/L) and 0.88 mg/L (0.58 to 1.91 mg/L), respectively [11] . Free bupivacaine concentrations were not elevated in 20 newborns (including 18 premature neonates) administered spinal anesthesia with 0.5% isobaric bupivacaine 1 mg/kg with or without epinephrine 1:200,000. Total and free bupivacaine concentrations were 0.31+/-0.17 mcg/mL and 0.047+/-0.032 mcg/mL, respectively, for the without epinephrine group and 0.25+/-0.09 mcg/mL and 0.062+/-0.025 mcg/mL, respectively, for the with epinephrine group [18] . The volume of distribution, half-life, clearance, and peak concentration were 4.67 L/kg, 453 minutes, 7.9 mL/kg/min, and 0.52 mcg/mL, respectively, in 8 very low birthweight infants (700 g to 1022 g) after interpleural nerve block with bupivacaine 2 mg/kg [16] . In comparison with 11 full-term neonates (1 to 27 days of age) administered intercostal block with 1.5 mg/kg bupivacaine 0.25% , the values were 2.56 L/kg, 132 minutes, 16.93 mL/kg/min, and 0.82 mcg/mL, respectively [17] .

Adverse Effects

As with other amide-type local anesthetics, adverse effects are related to excessive concentrations due to overdosage, inadvertent intravascular injection, or slow metabolism of bupivacaine. These adverse events are serious, typically dose-related, and generally affect the central nervous and cardiovascular system. Central nervous system reactions include restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness leading to unconsciousness and respiratory depression, nausea, vomiting, chills, and miosis. Cardiovascular reactions include depression of myocardium, decreased cardiac output, heart-block, hypotension, bradycardia, ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation), and cardiac arrest [3] [4] [20] [1] [5] [2] [6] .

Rare allergic reactions may occur. Risks with epidural and spinal anesthesia or nerve blocks near the vertebral column include underventilation or apnea with inadvertent subarachnoid injection; and hypotension secondary to loss of sympathetic tone and respiratory paralysis or underventilation when motor blockade extends cephaladly. Other risks of epidural and spinal anesthesia include urinary retention, fecal and urinary incontinence, loss of perineal sensation, persistent anesthesia, paraesthesia, weakness, paralysis of the lower extremities and loss of sphincter control, headache, backache, septic meningitis, meningismus, and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid. Risk of other routes of anesthesia include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery [3] [4] [20] [2] [6] .

In pharmacokinetic studies, no adverse events were reported in 11 neonates following intercostal nerve block with bupivacaine [17] , 8 very low birthweight infants following interpleural nerve block with bupivacaine [16] , or 20 newborns (including 18 premature neonates) administered spinal anesthesia with bupivacaine [18] .

Monitoring

Carefully monitor cardiovascular (including circulation) and respiratory vital signs and neurological status continuously during and after each injection, including during retrobulbar, dental, and stellate ganglion blocks [4] [20] [1] [5] [2] [6] . Continuously monitor for level of pain control, using an appropriate pain assessment tool [10] [21] .

In general, monitoring bupivacaine concentrations is not warranted; however, when there is a concern for accumulation then it may be appropriate. Consider monitoring concentrations when a local anesthesia is administered by continuous infusion at doses greater than 0.5 mg/kg/hr [22] .

Special Considerations/Preparation

Marcaine™: Available as 0.25% (2.5 mg/mL), 0.5% (5 mg/mL), and 0.75% (7.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials (0.25%, 0.5%, and 0.75% strengths) without methylparaben and 50-mL multidose vials (0.25% and 0.5% strengths) containing methylparaben as a preservative. May be autoclaved at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes [4] .
Marcaine™ with epinephrine 1:200,000: Available as 0.25% (2.5 mg/mL) of bupivacaine in 10-mL and 30-mL single-dose vials and a 50-mL multidose vial and as 0.5% (5 mg/mL) of bupivacaine in 3-mL single-dose ampules, 10-mL and 30-mL single-dose vials, and a 50-mL multidose vial. Each mL also contains 0.0091 mg of epinephrine and 0.5 mg of sodium metabisulfite. Multidose vials contain methylparaben as a preservative. Do not autoclave. Protect from light [3] .
Marcaine™ Spinal: Available as 2-mL single-dose ampules containing 15 mg of bupivacaine and 165 mg of dextrose. May be autoclaved once at 15-pound pressure, 121 degrees C (250 degrees F) for 15 minutes. Does not contain preservatives [20] .
Sensorcaine®: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 1 mg methylparaben (preservative). May be autoclaved [1] .
Sensorcaine®- methylparaben free (MPF): Available as 0.25%, 0.5%, and 0.75% of preservative-free bupivacaine in 10-mL and 30-mL single-dose vials and 30-mL ampules. May be autoclaved [2] .

Sensorcaine® with epinephrine 1:200,000: Available as 0.25% and 0.5% of bupivacaine in 50-mL multidose vials. Each mL contains 0.005 mg epinephrine, 0.5 mg sodium metabisulfite, and 1 mg methylparaben (preservative). Do not autoclave. Protect from light [5] .
Sensorcaine®-MPF with epinephrine 1:200,000: Available as 0.25% (10-mL and 30-mL single-dose vials), 0.5% (10-mL and 30-mL single-dose vials), and 0.75% (30-mL single-dose vial) of preservative-free bupivacaine. Each mL contains 0.005 mg epinephrine and 0.5 mg sodium metabisulfite. Do not autoclave. Protect from light [6] .

Solution Compatibility

D_5W, NS.
Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
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Title Bupivacaine

Dose

The dose varies with anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia

and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Use the lowest dose and concentration to achieve the desired result [1] [2] . The USES section provides dosage ranges; however, other resources should be consulted for specific techniques and procedures.

Dose Adjustments
Cardiac Disease: Dose reduction recommended [3] [4] [1] [5] [6] .
Debilitated and Acutely Ill: Dose reduction recommended [3] [4] [1] [5] [6] .
Liver Disease: Dose reduction recommended [3] [4] [1] [5] [2] [6] .
Risk Factors for Seizures: When bupivacaine is administered by continuous infusion, reduce the rate in neonates who are at risk for seizures. Risk factors include increased uptake into the circulation (eg, pulmonary arteriovenous malformation) or lowered seizure threshold (eg, history of febrile convulsions during the postoperative period, hypomagnesemia, or hyponatremia due to free water overload) [7] .

Administration

Bupivacaine is NOT recommended for intravenous regional anesthesia (Bier Block) [1] [5] [2] [6] .
Epidural anesthesia: Use only single-dose ampules and single-dose vials for caudal or epidural anesthesia as multiple dose vials contain a preservative. Administer slowly in 3- to 5-mL incremental doses with sufficient time between doses to detect signs/symptoms of unintentional intravascular or intrathecal injection. Perform syringe aspirations before and during each supplemental injection in continuous (intermittent) catheter techniques. Administer a test dose, which contains epinephrine, and monitor the effects prior to the full dose and with all subsequent doses when a catheter is in place [3] [4] [1] [5] [2] [6] . The use of a local anesthetic in the test dose is probably unwarranted and may lead to toxicity [8] . Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3] [4] [1] [5] [2] [6] .
Local infiltration and peripheral nerve blocks: Check aspiration for blood or cerebrospinal fluid (when applicable) prior to injecting any local anesthetic, both initial and subsequent doses. Avoid rapid injection of large volumes of anesthetic solutions. When possible, use fractional (incremental) doses [3] [4] [1] [5] [2] [6] .

Uses

Epidural anesthesia: Epidural anesthesia, whether by caudal or lumbar route, is effective in the neonate [9] . Typical doses of bupivacaine 0.125% to 0.25% are 1.25 mg/kg to 2.5 mg/kg for caudal epidural anesthesia [10] , 2 mg/kg up to a maximum of 2.5 mg/kg for epidural anesthesia (other than caudal route) [10] [11] [7] , and 0.2 mg/kg/hr up to a maximum of 0.25 mg/kg/hr for continuous epidural infusion [10] [11] [12] [7] for a maximum duration of 24 to 36 hours [12] . Data are lacking in premature infants. Although, one study used 3.125 mg/kg of 0.5% bupivacaine by the caudal route as an adjunct to general anesthesia in 20 premature infants (0 to 60 days; 520 to 2750 grams). No neonate experienced elevated heart rate or blood pressure at the time of incision [13] . In a retrospective analysis of 750 children (2 days to 16 years of age), bupivacaine 0.25% provided longer postoperative pain relief (up to 5 hours) than lidocaine 0.5% or 1.5% when administered caudally [14] .

Peripheral nerve block: For neonatal circumcision a dorsal nerve block with a local anesthetic is recommended [10] . A penile nerve block is appropriate for urethral dilation and hypospadias repair [9] . Solutions containing epinephrine should NOT be used near end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [15] [3] [5] [6] . Efficacy data are lacking in neonates; however, in 2 pharmacokinetic studies bupivacaine nerve blocks were used in neonates without associated toxic concentrations or observed adverse events [16] [17] . Doses of bupivacaine were 2 mg/kg for interpleural nerve block in 8 very low birthweight infants (700 g to 1022 g) [16] and 1.5 mg/kg for intercostal block in 11 full-term neonates (1 to 27 days of age) [17] .

Spinal anesthesia: The use of spinal anesthesia is common in neonates, even preterm infants. In comparison to adults, the dose is greater in neonates [9] . Dose range is 0.5 to 1 mg/kg [9] [18] [19] with usual doses of 0.6 mg/kg of 0.75% hyperbaric bupivacaine in 8.25% dextrose [9] [19] and 0.8 mg/kg of 0.5% isobaric bupivacaine [9] . The duration of effective spinal blockade (lack of hip flexion) was 84+/-16 minutes in 11 infants (range: 0.1 to 7 months of age; 2.8 to 9.3 kg) who received 0.75% bupivacaine 0.6 mg/kg in 8.25% dextrose solution with 0.02 mL of 1:1000 epinephrine [19] . Efficacy data are lacking in premature infants.

Pediatric FDA Approved Indications
Indicated for the production of local or regional anesthesia or analgesia for surgical procedures, dental and oral surgery procedures, and diagnostic and therapeutic procedures. Use is not recommended in pediatric patients younger than 12 years [3] [4] [1] [5] [2] [6] .
Marcaine™ Spinal: Indicated for production of subarachnoid block (spinal anesthesia). Use in patients younger than 18 years is not recommended [20] .

Contraindications/Precautions

Contraindicated in patients with hypersensitivity to other amide-type anesthetics [3] [4] [20] [1] [5] [2] [6] .

Local anesthetic solutions containing antimicrobial preservatives should NOT be used for epidural or caudal anesthesia. Inadvertent intravascular or intrathecal administration may lead to serious toxicity. Continuous bupivacaine infusions in children have resulted in high systemic bupivacaine levels and seizures; high plasma levels may also be associated with cardiovascular abnormalities. Hepatic disease, especially severe cases, and renal impairment may cause increased risk of toxic plasma concentrations. Use with caution in patients with hypotension or heart block. Patients with cardiovascular impairment may have reduced ability to compensate for functional changes associated with AV conduction prolongation. Confusion, convulsion, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression may occur with unintentional intravascular injections of large doses during head and neck area administration [3] [4] .
Glenohumeral chondrolysis has been reported in pediatric patients following intra-articular 48- to 72-hour infusions of local anesthetics with and without epinephrine. Familial malignant hyperthermia may be triggered by local anesthetics . The 0.75% concentration is not approved for local infiltration or any other peripheral nerve block, except the retrobulbar block. Retrobulbar blocks provide complete corneal anesthesia

prior to onset of clinically acceptable external ocular muscle akinesia; therefore, akinesia is the determinate for initiation of surgery. Mixing bupivacaine with other local anesthetics is not recommended [3] [4] .
Formulations with epinephrine: Contain sodium metabisulfite, which may cause allergic-type reactions (eg, anaphylactic symptoms) and life-threatening or less severe asthmatic episodes in patients with sulfite sensitivity. Preparations containing a vasoconstrictor, such as epinephrine, used during or following potent inhalation anesthetics, may cause serious dose-related cardiac arrhythmias. Avoid the concomitant use of MAOIs, tricyclic antidepressants, and ergot-type oxytocic agents. Bupivacaine use in combination with vasoconstrictors may cause a risk of exaggerated vasoconstrictor response in patients with a history of hypertensive vascular disease and may cause a risk of further blood flow restriction in end-artery areas (eg, digits, nose, external ear, penis) or areas of compromised blood supply [3] [5] [6] .

Black Box Warning

Cardiac arrest with difficult resuscitation or death during use of bupivacaine for epidural anesthesia in obstetrical patients has been reported. In most cases, this has followed use of the 0.75% concentration. Cardiac arrest has occurred after convulsions resulting from systemic toxicity, presumably following unintentional intravascular injection. The 0.75% concentration should be reserved for surgical procedures where a high degree of muscle relaxation and prolonged effect are necessary [3] [4] [1] [5] [2] [6] .

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1.24 Caffeine Citrate

Title Caffeine Citrate

Dose

Loading dose: 20 to 25 mg/kg of caffeine citrate IV over 30 minutes or orally. (Equivalent to 10 to 12.5 mg/kg caffeine base).
Maintenance dose: 5 to 10 mg/kg per dose of caffeine citrate IV slow push or orally every 24 hours. (Equivalent to 2.5 to 5 mg/kg caffeine base).
Maintenance dose should be started 24 hours after the loading dose.

May consider an additional loading dose and higher maintenance doses if able to monitor serum concentrations.

(Please note that emphasis has changed to caffeine citrate due to commercially available product. This product (Cafcit®) may be administered both intravenously and orally).

Uses

Treatment of neonatal apnea, including post-extubation and post-anesthesia. (More favorable therapeutic index than aminophylline).

Pharmacology

The pharmacological effects of caffeine are mediated by its antagonism of the actions of adenosine at cell surface receptors. It is rapidly distributed in the brain, with CNS levels approximating plasma levels. Caffeine increases the respiratory center output, chemoreceptor sensitivity to CO_2, smooth muscle relaxation, and cardiac output. Oxygen consumption may be increased and weight gain may be reduced. Renal effects include diuresis and increased urinary calcium excretion. Orally administered caffeine citrate is rapidly and completely absorbed. There is almost no first-pass metabolism. In

neonates, approximately 86% is excreted unchanged in the urine, with the remainder metabolized via the CYP1A2 enzyme system. The serum half-life of caffeine ranges from 40 to 230 hours, decreasing with advancing postmenstrual age until 60 weeks PMA. Half-life is prolonged in infants with cholestatic hepatitis.

Adverse Effects

Adverse effects are usually mild, and include restlessness, vomiting, and functional cardiac symptoms. There has been a suggested association with NEC, but causality has never been proven. Loading doses of 25 mg/kg caffeine (50 mg/kg caffeine citrate) have been reported to decrease cerebral and intestinal blood flow velocity.

Monitoring

Baseline caffeine levels are recommended in neonates previously treated with theophylline and neonates born to mothers who consumed caffeine prior to delivery. If using the suggested doses, measuring serum concentrations is probably not necessary. Monitoring of serum drug concentration should be based on a trough level determined on approximately day 5 of therapy. Therapeutic trough serum concentration is 5 to 25 mcg/mL. Concentrations greater than 40 to 50 mcg/mL are toxic. Assess for agitation. Monitor heart rate; **consider withholding dose if greater than 180 beats per minute.**

Special Considerations/Preparation

Both Cafcit® Oral Solution and Cafcit® Injection for intravenous administration are preservative free and available in 3-mL single use vials. Each mL of Cafcit® contains 20 mg of caffeine citrate (equivalent to 10 mg caffeine base). Store at room temperature.
Alternatively, an oral solution may be prepared by dissolving 2.5 g of caffeine anhydrous powder in 250 mL of water, yielding a final concentration of 10 mg/mL. Solution is stable for 4 weeks refrigerated. Crystals form when stored at low temperature but dissolve at room temperature without loss of potency. **Do not freeze.**

Solution Compatibility

D_5W and $D_{50}W$.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amikacin, aminophylline, calcium gluconate, cefotaxime, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, doxapram, epinephrine, fentanyl, gentamicin, heparin (concentration less than or equal to 1 unit/mL), isoproterenol, lidocaine, metoclopramide, morphine, nitroprusside, pancuronium, penicillin G, phenobarbital, sodium bicarbonate, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, furosemide, ibuprofen lysine, lorazepam, nitroglycerin, and oxacillin.

References

- Schmidt B, Roberts RS, Davis P, et al: Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893-1902.
- Schmidt B, Roberts RS, Davis P, et al: Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112-2121.
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- Lane AJP, Coombs RC, Evans DH, et al: Effect of caffeine on neonatal splanchnic blood flow. *Arch Dis Child Fetal Neonatal Ed*1999;80:F-128-F129.
- Lee TC, Charles B, Steer P: Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. *Clin Pharmacol Ther*1997;61:628-640.
- Falcao AC, Fernandez de Gatta MM, Delgado Iribarnegaray MF, et al: Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol*1997;52:211-217.
- Zanardo V, Dani C, Trevisanuto D: Methylxanthines increase renal calcium excretion in preterm infants. *Biol Neonate* 1995;68:169-74.
- Product Information, Bedford Laboratories, 2008

Title Caffeine Citrate

Dose

Loading dose: 20 to 25 mg/kg of caffeine citrate IV over 30 minutes or orally. (Equivalent to 10 to 12.5 mg/kg caffeine base).
Maintenance dose: 5 to 10 mg/kg per dose of caffeine citrate IV slow push or orally every 24 hours. (Equivalent to 2.5 to 5 mg/kg caffeine base).
Maintenance dose should be started 24 hours after the loading dose.

May consider an additional loading dose and higher maintenance doses if able to monitor serum concentrations.

(Please note that emphasis has changed to caffeine citrate due to commercially available product. This product (Cafcit®) may be administered both intravenously and orally).

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The pharmacological effects of caffeine are mediated by its antagonism of the actions of adenosine at cell surface receptors. It is rapidly distributed in the brain, with CNS levels approximating plasma levels. Caffeine increases the respiratory center output, chemoreceptor sensitivity to CO_2, smooth muscle relaxation, and cardiac output. Oxygen consumption may be increased and weight gain may be reduced. Renal effects include diuresis and increased urinary calcium excretion. Orally administered caffeine citrate is rapidly and completely absorbed. There is almost no first-pass metabolism. In neonates, approximately 86% is excreted unchanged in the urine, with the remainder metabolized via the CYP1A2 enzyme system. The serum half-life of caffeine ranges from 40 to 230 hours, decreasing with advancing postmenstrual age until 60 weeks PMA. Half-life is prolonged in infants with cholestatic hepatitis.

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Adverse effects are usually mild, and include restlessness, vomiting, and functional cardiac symptoms. There has been a suggested association with NEC, but causality has never been proven. Loading doses of 25 mg/kg caffeine (50 mg/kg caffeine citrate) have been reported to decrease cerebral and intestinal blood flow velocity.

Monitoring

Baseline caffeine levels are recommended in neonates previously treated with theophylline and neonates born to mothers who consumed caffeine prior to delivery. If using the suggested doses, measuring serum concentrations is probably not necessary. Monitoring of serum drug concentration should be based on a trough level determined on approximately day 5 of therapy. Therapeutic trough serum concentration is 5 to 25 mcg/mL. Concentrations greater than 40 to 50 mcg/mL are toxic. Assess for agitation. Monitor heart rate; **consider withholding dose if greater than 180 beats per minute.**

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Solution Compatibility

D_5W and $D_{50}W$.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amikacin, aminophylline, calcium gluconate, cefotaxime, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, doxapram, epinephrine, fentanyl, gentamicin, heparin (concentration less than or equal to 1 unit/mL), isoproterenol, lidocaine, metoclopramide, morphine, nitroprusside, pancuronium, penicillin G, phenobarbital, sodium bicarbonate, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, furosemide, ibuprofen lysine, lorazepam, nitroglycerin, and oxacillin.

References

- Schmidt B, Roberts RS, Davis P, et al: Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;357:1893-1902.
- Schmidt B, Roberts RS, Davis P, et al: Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112-2121.
- Steer P, Flenady V, Shearman A, et al: High dose caffeine citrate for extubation of preterm infants: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F499-F503.
- Comer AM, Perry CM, Figgitt DP: Caffeine citrate: A review of its use in apnoea of prematurity. *Paediatr Drugs* 2001;3:61-70.
- Bauer J, Maier K, Linderkamp O, Hentschel R: Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. *Pediatrics* 2001;107:660-663.
- Erenberg A, Leff RD, Haack DG, et al: Caffeine citrate for the treatment of apnea of prematurity: A double-blind, placebo-controlled study. *Pharmacotherapy*2000;20:644-652.
- Anderson BJ, Gunn TR, Holford NHG, et al: Caffeine overdose in a premature infant: Clinical course and pharmacokinetics. *Anaesth Intensive Care*1999;27:307-311.
- Lane AJP, Coombs RC, Evans DH, et al: Effect of caffeine on neonatal splanchnic blood flow. *Arch Dis Child Fetal Neonatal Ed*1999;80:F-128-F129.
- Lee TC, Charles B, Steer P: Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. *Clin Pharmacol Ther*1997;61:628-640.
- Falcao AC, Fernandez de Gatta MM, Delgado Iribarnegaray MF, et al: Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol*1997;52:211-217.
- Zanardo V, Dani C, Trevisanuto D: Methylxanthines increase renal calcium excretion in preterm infants. *Biol Neonate* 1995;68:169-74.
- Product Information, Bedford Laboratories, 2008

1.25 Calcium - Oral

Title Calcium - Oral

Dose

20 to 80 mg/kg elemental calcium per day orally in divided doses scheduled around oral feedings.

Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg per day.

Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg per day.

Calcium glubionate syrup (23 mg/mL elemental calcium): 1 to 3.5 mL/kg per day.

Uses

Treatment of non-acute hypocalcemia in babies able to tolerate oral medications.

Pharmacology

Absorption of calcium administered orally is approximately 50%. Absorption takes place throughout the small intestine, and is primarily regulated by 1,25-dihydroxy Vitamin D. Calcium carbonate significantly interferes with the absorption of levothyroxine. The osmolarity of calcium glubionate syrup is 2500 mOsm/L, and of calcium gluconate is 700 mOsm/L.

Adverse Effects

Oral calcium preparations are hypertonic, especially calcium glubionate syrup. Gastric irritation and diarrhea occur often. Use with caution in infants who are at risk for necrotizing enterocolitis.

Monitoring

Periodically measure serum calcium concentrations. Assess GI tolerance. Assess serum phosphorus and vitamin D levels when indicated.

Special Considerations/Preparation

Calcium carbonate (Roxane) is available as a 250 mg/mL suspension (equivalent to 100 mg/mL elemental calcium) in 5-mL unit dose cups.

Calcium glubionate 6.5% syrup (Rugby/Watson) yields 23 mg/mL elemental calcium (1.16 mEq/mL) and is available in 473 mL bottles. Osmolarity is 2500 mOsm/L.

References

- Hsu SC, Levine MA: Perinatal calcium metabolism: physiology and pathophysiology. *Semin Neonat* 2004;9:23-36.
- Singh N, Weisler SL, Hershman JM: The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. *Thyroid* 2001;11:967-71.
- Product information, Roxane, 1996.

Title Calcium - Oral

Dose

20 to 80 mg/kg elemental calcium per day orally in divided doses scheduled around oral feedings.

Calcium gluconate 10% IV formulation (9.3 mg/mL elemental calcium): 2 to 8 mL/kg per day.

Calcium carbonate 250 mg/mL suspension (100 mg/mL elemental calcium): 0.2 to 0.8 mL/kg per day.

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Uses

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- Hsu SC, Levine MA: Perinatal calcium metabolism: physiology and pathophysiology. *Semin Neonat* 2004;9:23-36.
- Singh N, Weisler SL, Hershman JM: The acute effect of calcium carbonate on the intestinal absorption of levothyroxine. *Thyroid* 2001;11:967-71.
- Product information, Roxane, 1996.

1.26 Calcium chloride 10%

Title Calcium chloride 10%

Dose

Cardiac Resuscitation (documented hypocalcemia, hyperkalemia, hypermagnesemia): 20 mg/kg/dose (0.2 mL/kg $CaCl_2$ 10%) slow IV push/IO; repeat dose as necessary for clinical effect [1] [2] . **Maximum single dose 2 g** [1] . Dose recommendation based on Pediatric Advanced Life Support guidelines.

Neonatal Symptomatic Hypocalcemia (eg, increased neuromuscular irritability/activity, seizures)
Acute treatment: 35 to 70 mg/kg/dose (0.35 to 0.7 mL/kg/dose, equivalent to 10 to 20 mg/kg elemental calcium) [3] [4] .
Dilute in appropriate fluid, then infuse in IV over 10 to 30 minutes while monitoring for bradycardia [3] [4] . Stop infusion if heart rate is less than 100 beats per minute.
Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis . Do not give intra-arterially [3] [4] .

Maintenance treatment: 75 to 300 mg/kg/day (0.75 to 3 mL/kg/day, equivalent to 20 to 80 mg/kg elemental calcium). Administer by continuous IV infusion. Treat for 3 to 5 days [3] .

Exchange transfusion: 33 mg per 100 mL citrated blood exchanged (equals 0.33 mL per 100 mL blood exchanged). Infuse IV over 10 to 30 minutes.

Administration

Administer by slow IV push for cardiac arrest [1] ; infuse over 30 to 60 minutes for other indications [2] . May dilute in compatible solution for intermittent infusion or continuous infusion. Infusion through central line is preferred.
Do not exceed rate of injection of 1 mL/minute (CaCl2 10% solution) [5] .
Do not administer into the cardiac muscle [5] .

Uses

Acute treatment of neonatal symptomatic hypocalcemia [3] [4] . Treatment and prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL) [4] . Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [3] [4] .

Cardiac resuscitation: Use only in cases of documented hypocalcemia, hyperkalemia, hypermagnesemia, or calcium channel blocker toxicity. Routine use of calcium in cardiac resuscitation is not recommended [1] [2] [6] .

Contraindications/Precautions

Contraindicated in patients with ventricular fibrillation [5] . Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such as parenteral nutrition) is also

contraindicated due to the risk of precipitation of ceftriaxone-calcium [7] . Rapid administration is associated with bradycardia or cardiac arrest [8] .

Pharmacology

Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss. Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%) with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QTc above 0.4 second.

Adverse Effects

Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [7] . Cutaneous necrosis or calcium deposition occurs with extravasation. Bolus infusions by UAC have been associated with intestinal bleeding and lower-extremity tissue necrosis.

Monitoring

If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses [3] [2] [4] .

Special Considerations/Preparation

Calcium chloride 10% injection yields 27 mg/mL elemental calcium (1.36 mEq/mL). Osmolarity is 2040 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely [5] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, amiodarone, chloramphenicol, dobutamine, dopamine, epinephrine, esmolol, hydrocortisone, isoproterenol, lidocaine, micafungin, milrinone,

morphine, penicillin G, pentobarbital, phenobarbital, prostaglandin E_1, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, sodium bicarbonate, and phosphate and magnesium salts when mixed directly.

References

- Rigo J, DeCurtis M: Disorders of calcium, phosphorus, and magnesium metabolism. In: Martin RJ, Fanaroff AA, Walsh MC (eds): *Neonatal-Perinatal Medicine: Diseases of the Fetus and Newborn,* ed 8. St. Louis: Mosby, 2005, pp 1508-1514.
- Broner CW, Stidham GL, Westernkirchner DF, Watson DC: A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990;117:986.
- Scott SM, Ladenson JH, Aguanna JJ, et al: Effect of calcium therapy in sick premature infants with early neonatal hypocalcemia. *J Pediatr* 1984;104:747.
- Roberts RJ: *Drug Therapy in Infants*. Philadelphia: WB Saunders Co, 1984, p 294.

1. Kleinman ME, Chameides L, Schexnayder SM et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14: pediatric advanced life support. Circulation Nov02, 2010; 122(18 Suppl.3): S876-S908.
2. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
3. Zhou P: Hypocalcemia in infants and children. Pediatr Rev May, 2009; 30(5): 190-192.
4. Mimouni F: Neonatal hypocalcemia: to treat or not to treat? (A review). J Am Coll Nutr Oct1, 1994; 13(5): 408-415.
5. Product Information: calcium chloride 10% IV injection, calcium chloride 10% IV injection. American Regent, Inc (per manufacturer), Shirley, NY, Jan, 2009.
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8. Bellazzini MA: Pediatric hypocalcemic seizures: a case of rickets. J Emerg Med Feb, 2005; 28(2): 161-164.

Title Calcium chloride 10%

Dose

Cardiac Resuscitation (documented hypocalcemia, hyperkalemia, hypermagnesemia): 20 mg/kg/dose (0.2 mL/kg $CaCl_2$ 10%) slow IV push/IO; repeat dose as necessary for clinical effect [1] [2] . **Maximum single dose 2 g** [1] . Dose recommendation based on Pediatric Advanced Life Support guidelines.

Neonatal Symptomatic Hypocalcemia (eg, increased neuromuscular irritability/activity, seizures)

Acute treatment: 35 to 70 mg/kg/dose (0.35 to 0.7 mL/kg/dose, equivalent to 10 to 20 mg/kg elemental calcium) [3] [4] .
Dilute in appropriate fluid, then infuse in IV over 10 to 30 minutes while monitoring for bradycardia [3] [4] . Stop infusion if heart rate is less than 100 beats per minute.
Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis . Do not give intra-arterially [3] [4] .

Maintenance treatment: 75 to 300 mg/kg/day (0.75 to 3 mL/kg/day, equivalent to 20 to 80 mg/kg elemental calcium). Administer by continuous IV infusion. Treat for 3 to 5 days [3] .

Exchange transfusion: 33 mg per 100 mL citrated blood exchanged (equals 0.33 mL per 100 mL blood exchanged). Infuse IV over 10 to 30 minutes.

Administration

Administer by slow IV push for cardiac arrest [1] ; infuse over 30 to 60 minutes for other indications [2] . May dilute in compatible solution for intermittent infusion or continuous infusion. Infusion through central line is preferred.
Do not exceed rate of injection of 1 mL/minute (CaCl2 10% solution) [5] .
Do not administer into the cardiac muscle [5] .

Uses

Acute treatment of neonatal symptomatic hypocalcemia [3] [4] . Treatment and prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL) [4] . Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [3] [4] .

Cardiac resuscitation: Use only in cases of documented hypocalcemia, hyperkalemia, hypermagnesemia, or calcium channel blocker toxicity. Routine use of calcium in cardiac resuscitation is not recommended [1] [2] [6] .

Contraindications/Precautions

Contraindicated in patients with ventricular fibrillation [5] . Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxone-calcium [7] . Rapid administration is associated with bradycardia or cardiac arrest [8] .

Pharmacology

Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss. Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%)

with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QTc above 0.4 second.

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Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [7] . Cutaneous necrosis or calcium deposition occurs with extravasation. Bolus infusions by UAC have been associated with intestinal bleeding and lower-extremity tissue necrosis.

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If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses [3] [2] [4] .

Special Considerations/Preparation

Calcium chloride 10% injection yields 27 mg/mL elemental calcium (1.36 mEq/mL). Osmolarity is 2040 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely [5] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, amiodarone, chloramphenicol, dobutamine, dopamine, epinephrine, esmolol, hydrocortisone, isoproterenol, lidocaine, micafungin, milrinone, morphine, penicillin G, pentobarbital, phenobarbital, prostaglandin E_1, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, sodium bicarbonate, and phosphate and magnesium salts when mixed directly.

References

- Rigo J, DeCurtis M: Disorders of calcium, phosphorus, and magnesium metabolism. In: Martin RJ, Fanaroff AA, Walsh MC (eds): *Neonatal-Perinatal Medicine: Diseases of the Fetus and Newborn,* ed 8. St. Louis: Mosby, 2005, pp 1508-1514.
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3. Zhou P: Hypocalcemia in infants and children. Pediatr Rev May, 2009; 30(5): 190-192.
4. Mimouni F: Neonatal hypocalcemia: to treat or not to treat? (A review). J Am Coll Nutr Oct1, 1994; 13(5): 408-415.
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1.27 Calcium gluconate 10%

Title Calcium gluconate 10%

Dose

Neonatal Symptomatic Hypocalcemia (eg, increased neuromuscular irritability/activity, seizures)
Acute treatment: 100 to 200 mg/kg/dose (1 to 2 mL/kg/dose, equivalent to 10 to 20 mg/kg elemental calcium) [1] [2] [3] [4] .
Dilute in appropriate fluid, then infuse in IV over 10 to 30 minutes while monitoring for bradycardia [1] [4] . Stop infusion if heart rate is less than 100 beats per minute.
Do not give intra-arterially.

Maintenance treatment: 200 to 800 mg/kg/day (2 to 8 mL/kg/day, equivalent to 20 to 80 mg/kg elemental calcium) [1] [2] .
Administer by continuous IV infusion. Treat for 3 to 5 days [2] .
May also be given orally in the same dose [4] .

Exchange transfusion: 100 mg per 100 mL citrated blood exchanged (equals 1 mL per 100 mL blood exchanged). Infuse IV over 10 minutes.

Administration

Administer by slow IV push for cardiac arrest; infuse over 30 to 60 minutes for other indications [5] . May dilute in compatible solution for intermittent or continuous infusion. Infusion through central line is preferred.
Administer slowly as bolus, about 1.5 mL over 1 minute, **do not exceed 200 mg/min as an intermittent infusion or continuous infusion** [6] .
Administer into a large vein through a small needle to avoid hypercalcemia, extravasation, and necrosis [6] [1] .
Not for IM or subQ use [6] .

Uses

Acute treatment of neonatal symptomatic hypocalcemia [1] [4] . Treatment and prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL) [4] . Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [1] [4] .
Treatment of asymptomatic infants is controversial.

Contraindications/Precautions

Calcium salts are **contraindicated** in patients with ventricular fibrillation or hypercalcemia (or when calcium levels are above normal). Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxone-calcium [7] .

Product contains aluminum that may be toxic with prolonged IV administration and in patients with impaired kidney function. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Studies showed that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Rapid administration is associated with vasodilation, hypotension, bradycardia, syncope, cardiac arrhythmias, and cardiac arrest [7] .

Pharmacology

Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%) with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QT_c above 0.4 second. Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss.

Adverse Effects

Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [7] .

Monitoring

If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses. Assess for GI intolerance when treating orally.

Special Considerations/Preparation

Calcium gluconate 10% injection yields 9.3 mg/mL elemental calcium (0.46 mEq/mL). Osmolarity is 700 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, aminophylline, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, chloramphenicol, dobutamine, enalaprilat, epinephrine, famotidine, furosemide, heparin, hydrocortisone, lidocaine, linezolid, micafungin, midazolam, milrinone, netilmicin, nicardipine, penicillin G, phenobarbital, piperacillin-tazobactam, potassium chloride, propofol, remifentanil, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, fluconazole, indomethacin, meropenem, methylprednisolone, metoclopramide, and phosphate and magnesium salts when mixed directly.

References

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4. Mimouni F: Neonatal hypocalcemia: to treat or not to treat? (A review). J Am Coll Nutr Oct1, 1994; 13(5): 408-415.
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6. Product Information: calcium gluconate 10% IV injection, calcium gluconate 10% IV injection. American Regent, Inc (per manufacturer), Shirley, NY, Jan, 2009.
7. Product Information: calcium gluconate intravenous injection, calcium gluconate intravenous injection. American Regent, Inc. (per Manufacturer), Shirley, NY, Jul, 2011.

Title Calcium gluconate 10%

Dose

Neonatal Symptomatic Hypocalcemia (eg, increased neuromuscular irritability/activity, seizures)
Acute treatment: 100 to 200 mg/kg/dose (1 to 2 mL/kg/dose, equivalent to 10 to 20 mg/kg elemental calcium) [1] [2] [3] [4] .
Dilute in appropriate fluid, then infuse in IV over 10 to 30 minutes while monitoring for bradycardia [1] [4] . Stop infusion if heart rate is less than 100 beats per minute.
Do not give intra-arterially.

Maintenance treatment: 200 to 800 mg/kg/day (2 to 8 mL/kg/day, equivalent to 20 to 80 mg/kg elemental calcium) [1] [2] .
Administer by continuous IV infusion. Treat for 3 to 5 days [2] .
May also be given orally in the same dose [4] .

Exchange transfusion: 100 mg per 100 mL citrated blood exchanged (equals 1 mL per 100 mL blood exchanged). Infuse IV over 10 minutes.

Administration

Administer by slow IV push for cardiac arrest; infuse over 30 to 60 minutes for other indications [5] . May dilute in compatible solution for intermittent or continuous infusion. Infusion through central line is preferred.
Administer slowly as bolus, about 1.5 mL over 1 minute, **do not exceed 200 mg/min as an intermittent infusion or continuous infusion** [6] .
Administer into a large vein through a small needle to avoid hypercalcemia, extravasation, and necrosis [6] [1] .
Not for IM or subQ use [6] .

Uses

Acute treatment of neonatal symptomatic hypocalcemia [1] [4] . Treatment and prevention of hypocalcemia, usually defined as a serum ionized calcium concentration less than approximately 4 mg/dL (or total serum calcium less than approximately 7 to 8 mg/dL) [4] . Calcium gluconate given at the same elemental calcium dose may be preferred as calcium chloride may cause a metabolic acidosis [1] [4] .
Treatment of asymptomatic infants is controversial.

Contraindications/Precautions

Calcium salts are **contraindicated** in patients with ventricular fibrillation or hypercalcemia (or when calcium levels are above normal). Coadministration of ceftriaxone sodium injection with calcium-containing IV solutions (including continuous calcium-containing infusions such as parenteral nutrition) is also contraindicated due to the risk of precipitation of ceftriaxone-calcium [7] .

Product contains aluminum that may be toxic with prolonged IV administration and in patients with impaired kidney function. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum. Studies showed that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration. Rapid administration is associated with vasodilation, hypotension, bradycardia, syncope, cardiac arrhythmias, and cardiac arrest [7] .

Pharmacology

Ionized calcium is the physiologically active fraction, accounting for approximately 50% of total blood calcium. The remainder is bound to albumin (40%) or complexed (10%) with citrate, phosphate, and bicarbonate. Early hypocalcemia is common in asphyxiated infants, premature infants, and infants of diabetic mothers. Significant decreases in ionized calcium may occur during acute alkalosis and following exchange transfusions with citrated blood. Clinical signs suggestive of hypocalcemia in neonates include muscle twitching, jitteriness, generalized seizures, and QT_c above 0.4 second. Calcium chloride may be more bioavailable than calcium gluconate, but it also is more likely to cause metabolic acidosis. Administration by continuous infusion is more efficacious than intermittent bolus dosing due to less renal calcium loss.

Adverse Effects

Precipitate in the infusion line with crystalline deposits in the lungs and kidneys has been reported in some deceased neonates who were coadministered ceftriaxone IV and calcium-containing fluids, sometimes in the same infusion line. At least one neonatal fatality has been reported following coadministration at different times and with separate infusion lines, though no crystalline deposits were found at autopsy in this neonate. These reports have been confined to neonates [7] .

Monitoring

If possible, measure ionized calcium directly. Avoid hypercalcemia during treatment. Correct hypomagnesemia if present. Observe IV infusion site closely for extravasation. Observe IV tubing for precipitates. Monitor continuously for bradycardia when giving bolus doses. Assess for GI intolerance when treating orally.

Special Considerations/Preparation

Calcium gluconate 10% injection yields 9.3 mg/mL elemental calcium (0.46 mEq/mL). Osmolarity is 700 mOsm/L. Injectable calcium salts should be stored at room temperature and are stable indefinitely.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, aminophylline, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, chloramphenicol, dobutamine, enalaprilat, epinephrine, famotidine, furosemide, heparin, hydrocortisone, lidocaine, linezolid, micafungin, midazolam, milrinone, netilmicin, nicardipine, penicillin G, phenobarbital, piperacillin-tazobactam, potassium chloride, propofol, remifentanil, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, ceftriaxone, fluconazole, indomethacin, meropenem, methylprednisolone, metoclopramide, and phosphate and magnesium salts when mixed directly.

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- Jain A, Agarwal R, Sankar MJ, et al: Hypocalcemia in the newborn. *Indian J Pediatr* 2008;75:165-169.
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- Scott SM, Ladenson JH, Aguanna JJ, et al: Effect of calcium therapy in sick premature infants with early neonatal hypocalcemia. *J Pediatr* 1984;104:747.
- Tsang RC, Steichen JJ, Chang GM: Neonatal hypocalcemia: Mechanisms of occurrence and management. *Crit Care Med* 1977;5:56-61.
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4. Mimouni F: Neonatal hypocalcemia: to treat or not to treat? (A review). J Am Coll Nutr Oct1, 1994; 13(5): 408-415.
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6. Product Information: calcium gluconate 10% IV injection, calcium gluconate 10% IV injection. American Regent, Inc (per manufacturer), Shirley, NY, Jan, 2009.
7. Product Information: calcium gluconate intravenous injection, calcium gluconate intravenous injection. American Regent, Inc. (per Manufacturer), Shirley, NY, Jul, 2011.

1.28 Calfactant

Title Calfactant

Dose

Initial dose: 3 mL/kg intratracheally; may be repeated if needed every 12 hours up to a total of 3 doses. For prophylactic therapy in premature infants less than 29 weeks of gestational age at significant risk for respiratory distress syndrome, Infasurf® should be given as soon as possible, preferably within 30 minutes after birth [1] .
In the Infasurf® versus Survanta® treatment trial, repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a PaO_2 of 80 torr or less [1] .

Administration

For intratracheal administration only [1] .
Calfactant intratracheal suspension may be administered by either of the following 2 methods [1] :

- 1) Administration by instilling the suspension through a side-port adapter into the endotracheal tube. Two attendants are needed to facilitate dosing; one to instill the calfactant, the other to monitor the patient and assist in positioning. The dose (3 mL/kg) should be administered in 2 aliquots of 1.5 mL/kg each. After each aliquot is instilled, the

neonate should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20 to 30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.

- 2) Administration by instilling the suspension through a 5 French feeding tube inserted into the endotracheal tube. The total dose is instilled in 4 equal aliquots with the catheter removed between each instillation and mechanical ventilation resumed for 0.5 to 2 minutes. For even distribution of calfactant, each of the aliquots should be administered with the neonate in 1 of 4 positions; prone, supine, right, and left lateral.

Uses

Neonatal FDA-Approved Indications
Infasurf® is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants less than 29 weeks of gestational age at significant risk for RDS. Treatment should be given as soon as possible, preferably within 30 minutes after birth [1] [2] [3] .

Infasurf® is indicated for infants less than 72 hours of age with RDS (confirmed by clinical and radiological findings) and requiring endotracheal intubation [1] [2] [4] .

Contraindications/Precautions

Transient episodes of reflux of surfactant into the endotracheal tube, cyanosis, bradycardia, and airway obstruction have been reported during administration. A higher rate of intraventricular hemorrhage and periventricular leukomalacia was observed in Infasurf®-treated infants compared with Exosurf®-treated infants in clinical trials [1] .

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Infasurf® is a sterile, non-pyrogenic natural surfactant extracted from calf lungs containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Preservative free. Each mL of Infasurf® contains 35 mg of total phospholipids (26 mg of phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg of proteins including 0.26 mg of SP-B [1] .

Adverse Effects

Most common adverse reactions observed in clinical trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). Reactions were usually transient and not associated with severe complications or mortality [1] .

Monitoring

Monitor closely for appropriate oxygen therapy and ventilatory support [1] .

Special Considerations/Preparation

Available in 3-mL and 6-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. **The 3 mL vial must be stored upright.** Inspect Infasurf® for discoloration; normal color is off-white, and visible flecks and foaming at the surface are normal. Suspension settles during storage; gently swirl vial in order to uniformly suspend. **Do not shake.**Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

References

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- Kendig JW, Ryan RM, Sinkin RA et al: Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics Jun, 1998; 101(6): 1006-1012.

- Hudak ML, Farrell EE, Rosenberg AA et al: A multicenter randomized, masked comparison trial of natural versus synthetic surfactant for the treatment of respiratory distress syndrome. J Pediatr Mar, 1996; 128(3): 396-406.

Title Calfactant

Dose

Initial dose: 3 mL/kg intratracheally; may be repeated if needed every 12 hours up to a total of 3 doses. For prophylactic therapy in premature infants less than 29 weeks of gestational age at significant risk for respiratory distress syndrome, Infasurf® should be given as soon as possible, preferably within 30 minutes after birth [1] .
In the Infasurf® versus Survanta® treatment trial, repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a PaO_2 of 80 torr or less [1] .

Administration

For intratracheal administration only [1] .
Calfactant intratracheal suspension may be administered by either of the following 2 methods [1] :

- 1) Administration by instilling the suspension through a side-port adapter into the endotracheal tube. Two attendants are needed to facilitate dosing; one to instill the

calfactant, the other to monitor the patient and assist in positioning. The dose (3 mL/kg) should be administered in 2 aliquots of 1.5 mL/kg each. After each aliquot is instilled, the neonate should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20 to 30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respiratory status and repositioning should separate the two aliquots.

- 2) Administration by instilling the suspension through a 5 French feeding tube inserted into the endotracheal tube. The total dose is instilled in 4 equal aliquots with the catheter removed between each instillation and mechanical ventilation resumed for 0.5 to 2 minutes. For even distribution of calfactant, each of the aliquots should be administered with the neonate in 1 of 4 positions; prone, supine, right, and left lateral.

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Transient episodes of reflux of surfactant into the endotracheal tube, cyanosis, bradycardia, and airway obstruction have been reported during administration. A higher rate of intraventricular hemorrhage and periventricular leukomalacia was observed in Infasurf®-treated infants compared with Exosurf®-treated infants in clinical trials [1] .

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Infasurf® is a sterile, non-pyrogenic natural surfactant extracted from calf lungs containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Preservative free. Each mL of Infasurf® contains 35 mg of total phospholipids (26 mg of phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg of proteins including 0.26 mg of SP-B [1] .

Adverse Effects

Most common adverse reactions observed in clinical trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (16%), and reintubation (3%). Reactions were usually transient and not associated with severe complications or mortality [1] .

Monitoring

Monitor closely for appropriate oxygen therapy and ventilatory support [1] .

Special Considerations/Preparation

Available in 3-mL and 6-mL single-use vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. **The 3 mL vial must be stored upright.** Inspect Infasurf® for discoloration; normal color is off-white, and visible flecks and foaming at the surface are normal. Suspension settles during storage; gently swirl vial in order to uniformly suspend. **Do not shake.**Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

References

- Product Information: Infasurf(R) intratracheal suspension, calfactant intratracheal suspension. Ony, Inc. (per FDA), Amherst, NY, Jun, 2011.
- Bloom BT, Kattwinkel J, Hall RT et al: Comparison of Infasurf (calf lung surfactant extract) to Survanta (Beractant) in the treatment and prevention of respiratory distress syndrome. Pediatrics Jul, 1997; 100(1): 31-38.
- Kendig JW, Ryan RM, Sinkin RA et al: Comparison of two strategies for surfactant prophylaxis in very premature infants: a multicenter randomized trial. Pediatrics Jun, 1998; 101(6): 1006-1012.
- Hudak ML, Farrell EE, Rosenberg AA et al: A multicenter randomized, masked comparison trial of natural versus synthetic surfactant for the treatment of respiratory distress syndrome. J Pediatr Mar, 1996; 128(3): 396-406.

1.29 Captopril

Title Captopril

Dose

Initial dose: 0.01 to 0.05 mg/kg/dose orally every 8 to 12 hours.
Adjust dose and interval based on response.

Administration

Administer 1 hour before feeding; food decreases absorption.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions

The use of captopril is contraindicated in patients with bilateral renovascular disease or with unilateral renal artery stenosis in a solitary kidney, as the loss of adequate renal perfusion could precipitate acute renal failure.

Pharmacology

Captopril is an angiotensin-converting enzyme (ACE) inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Captopril also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability is good in neonates, although food will decrease absorption. Onset of action is 15 minutes after a dose, with peak effects seen in 30 to 90 minutes. Duration of action is usually 2 to 6 hours, but may be significantly longer (greater than 24 hours).

Adverse Effects

Neonates are more sensitive to the effects of captopril than are older infants and children. Significant decreases in cerebral and renal blood flow have occurred in premature infants with chronic hypertension who received higher doses (0.15 to 0.30 mg/kg per dose) than those recommended above. These episodes occurred unpredictably during chronic therapy, and some were associated with neurologic (seizures, apnea, lethargy) and renal (oliguria) complications. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements [1] .

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablets.

Oral Suspension
Aqueous captopril solutions have been reported to degrade rapidly, and stability in different solutions is highly variable and dependent on many factors (pH, type of vehicle, drug concentration, addition of preservative). There have been conflicting results in various studies over the years. The data below represents some of the studies of various extemporaneously prepared captopril oral solutions.

Captopril 1 mg/mL oral solution made with tablets and undiluted syrup was stable for 30 days refrigerated (5 degrees C). In this study, different formulations of captopril solutions were made using either tablets or powder with different vehicles used (sterile water, syrup, methylcellulose); edetate disodium was added to some of the formulations. Better stability was noted when captopril tablets were used compared

with powder, with undiluted versus diluted syrup as the vehicle, and when edetate disodium was added as the preservative.

Captopril oral suspension can be made by dissolving 6.25 mg (one-half of a scored 12.5-mg tablet) in 10 mL of sterile water, adding 1000 mg of sodium ascorbate for injection (4 mL of 250-mg/mL solution) to decrease oxidation, then adding sufficient water to make a final volume of 200 mL. The final concentration is 0.03 mg/mL captopril and 5 mg/mL sodium ascorbate. Solution is stable for 14 days at room temperature, 56 days refrigerated. Some undissolved excipients will remain visible.

To overcome potential stability problems, powder papers and compounded capsules have been utilized to extemporaneously prepare captopril solutions just prior to administration.

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Title Captopril

Dose

Initial dose: 0.01 to 0.05 mg/kg/dose orally every 8 to 12 hours.
Adjust dose and interval based on response.

Administration

Administer 1 hour before feeding; food decreases absorption.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions

The use of captopril is contraindicated in patients with bilateral renovascular disease or with unilateral renal artery stenosis in a solitary kidney, as the loss of adequate renal perfusion could precipitate acute renal failure.

Pharmacology

Captopril is an angiotensin-converting enzyme (ACE) inhibitor that blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Captopril also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability is good in neonates, although food will decrease absorption. Onset of action is 15 minutes after a dose, with peak effects seen in 30 to 90 minutes. Duration of action is usually 2 to 6 hours, but may be significantly longer (greater than 24 hours).

Adverse Effects

Neonates are more sensitive to the effects of captopril than are older infants and children. Significant decreases in cerebral and renal blood flow have occurred in premature infants with chronic hypertension who received higher doses (0.15 to 0.30 mg/kg per dose) than those recommended above. These episodes occurred unpredictably during chronic therapy, and some were associated with neurologic (seizures, apnea, lethargy) and renal (oliguria) complications. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements [1] .

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Available in 12.5-mg, 25-mg, 50-mg, and 100-mg tablets.

Oral Suspension
Aqueous captopril solutions have been reported to degrade rapidly, and stability in different solutions is highly variable and dependent on many factors (pH, type of vehicle, drug concentration, addition of preservative). There have been conflicting results in various studies over the years. The data below represents some of the studies of various extemporaneously prepared captopril oral solutions.

Captopril 1 mg/mL oral solution made with tablets and undiluted syrup was stable for 30 days refrigerated (5 degrees C). In this study, different formulations of captopril solutions were made using either tablets or powder with different vehicles used (sterile water, syrup, methylcellulose); edetate disodium was added to some of the formulations. Better stability was noted when captopril tablets were used compared

with powder, with undiluted versus diluted syrup as the vehicle, and when edetate disodium was added as the preservative.

Captopril oral suspension can be made by dissolving 6.25 mg (one-half of a scored 12.5-mg tablet) in 10 mL of sterile water, adding 1000 mg of sodium ascorbate for injection (4 mL of 250-mg/mL solution) to decrease oxidation, then adding sufficient water to make a final volume of 200 mL. The final concentration is 0.03 mg/mL captopril and 5 mg/mL sodium ascorbate. Solution is stable for 14 days at room temperature, 56 days refrigerated. Some undissolved excipients will remain visible.

To overcome potential stability problems, powder papers and compounded capsules have been utilized to extemporaneously prepare captopril solutions just prior to administration.

References

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- Iafrate RP, Wall D, & Lynch SM: Oral captopril solution for neonatal hypertension (letter). *Clin Pharm* 1983; 2:395.
- Lye MYF, Yow KL, Lim LY, et al: Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997;54:2483-2487.
- Nahata MC, Morosco RS, Hipple TF: Stability of captopril in liquid containing ascorbic acid or sodium ascorbate. *Am J Hosp Pharm* 1994;1707-1708.
- O'Dea RF, Mirkin BL, Alward CT: Treatment of neonatal hypertension with captopril. *J Pediatr* 1988;113:403.
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- Tsu E & Copeland J: Powder papers for oral captopril (letter). *Clin Pharm* 1984; 3:116.

1. Product Information: captopril oral tablets, captopril oral tablets. Sandoz,Inc, Broomfield, CO, Dec1, 2003.

1.30 Carglumic Acid

Title Carglumic Acid

Dose

Acute or Chronic Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency; Adjunct: Initial, 100 to 250 mg/kg/day divided into 2 to 4 doses per day concomitantly with other ammonia lowering agents. Titrate dose to maintain within normal plasma ammonia levels for age. Normal plasma ammonia levels usually attained by day 3. Therapy is continuous and life-long [1] [2] .
Based on retrospective case series (n=22), maintenance doses were typically less than 100 mg/kg/day [1] .

Administration

Do NOT administer tablets whole or crushed. Dissolve one 200-mg tablet in 2.5-mL of water for a concentration of 80 mg/mL for oral or nasogastric (NG) tube administration. For oral administration, measure dose using an oral syringe, discard the unused portion, administer immediately, then refill the oral syringe with 1 to 2 mL of water and administer immediately to ensure complete delivery of dose. For NG tube administration, measure dose using an oral syringe, discard the unused portion, administer immediately, and flush NG tube with small volume of water. Do not use other liquids or food for preparation or administration. Administer prior to feedings [1] .

Uses

Treatment of hyperammonemia due to various metabolic disorders [2] [3] . Based upon use in newborns from case reports, carglumic acid, when administered in addition to standard therapy, acutely reduces plasma ammonia levels in patients with branched-chain organic acidemias, such as methylmalonic aciduria (MMA), propionic aciduria (PA), and isovaleric acidemia (IVA) . In these metabolic disorders, synthesis of N-acetylglutamate is inhibited due to the build up of the respective branched-chain organic acid; once standard therapy has corrected the acidemia, hyperammonemia is also resolved [4] . Doses used in these cases ranged from 70 to 200 mg/kg/day, administered as a single dose [4] or over a 48-hour period [3] .

FDA Approved Indications
Indicated as adjunctive therapy for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) from the time of birth. Also indicated as maintenance therapy for chronic hyperammonemia due to NAGS deficiency [1] .

Contraindications/Precautions

Prolonged exposure to increased plasma ammonia levels can rapidly result in brain injury or death; monitoring recommended [1] .
During initial treatment, complete protein restriction is recommended for 24 to 48 hours; supplement calories to avoid catabolism and nitrogen turnover [1] .

Pharmacology

Carglumic acid is a synthetic analogue of N-acetylglutamate (NAG), a product of N-acetylglutamate synthase (NAGS). NAG is an essential activator of carbamoyl phosphate synthetase 1 (CPS 1), which is the first enzyme in the urea cycle. Carglumic acid acts as a replacement for NAG in patients with NAGS deficiency, thereby activating CPS 1. Following administration, plasma ammonia levels are reduced within 24 hours. Tmax occurs in 2 to 4 hours. Drug partially metabolized by intestinal flora, likely to carbon dioxide, which is eliminated through the lungs. Unchanged drug is excreted in the feces (60%) and urine (9%). Mean terminal half-life is 5.6 hours [1] .

Adverse Effects

Adverse reaction which occurred in 13% or more patients from a retrospective case series include abdominal pain, anemia, diarrhea, ear infection, headache, infection, nasopharyngitis, pyrexia, tonsillitis, and vomiting [1] [2] .

Monitoring

Monitor plasma ammonia levels, neurological status, and clinical response [1] .

Special Considerations/Preparation

Available as a 200-mg tablet. Store sealed bottle in refrigerator prior to opening for the first time; do not refrigerate after opening. Discard product 1 month after first opening [1] .

References

- Product Information: CARBAGLU(R) oral tablets, carglumic acid oral tablets. Accredo Health Group, Inc. (per DailyMed), Memphis, TN, May, 2012.
- Daniotti M, la Marca G, Fiorini P et al: New developments in the treatment of hyperammonemia: emerging use of carglumic acid. Int J Gen Med 2011; 4: 21-28.
- Levrat V, Forest I, Fouilhoux A et al: Carglumic acid: an additional therapy in the treatment of organic acidurias with hyperammonemia?Orphanet J Rare Dis 2008; 3: 2-.
- Kasapkara CS, Ezgu FS, Okur I et al: N-carbamylglutamate treatment for acute neonatal hyperammonemia in isovaleric acidemia. Eur J Pediatr Jun, 2011; 170(6): 799-801.

Title Carglumic Acid

Dose

Acute or Chronic Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency; Adjunct: Initial, 100 to 250 mg/kg/day divided into 2 to 4 doses per day concomitantly with other ammonia lowering agents. Titrate dose to maintain within normal plasma ammonia levels for age. Normal plasma ammonia levels usually attained by day 3. Therapy is continuous and life-long [1] [2] .
Based on retrospective case series (n=22), maintenance doses were typically less than 100 mg/kg/day [1] .

Administration

Do NOT administer tablets whole or crushed. Dissolve one 200-mg tablet in 2.5-mL of water for a concentration of 80 mg/mL for oral or nasogastric (NG) tube administration. For oral administration, measure dose using an oral syringe, discard the unused portion, administer immediately, then refill the oral syringe with 1 to 2 mL of water and administer immediately to ensure complete delivery of dose. For NG tube administration, measure dose using an oral syringe, discard the unused portion, administer immediately, and flush NG tube with small volume of water. Do not use

other liquids or food for preparation or administration. Administer prior to feedings [1] .

Uses

Treatment of hyperammonemia due to various metabolic disorders [2] [3] . Based upon use in newborns from case reports, carglumic acid, when administered in addition to standard therapy, acutely reduces plasma ammonia levels in patients with branched-chain organic acidemias, such as methylmalonic aciduria (MMA), propionic aciduria (PA), and isovaleric acidemia (IVA) . In these metabolic disorders, synthesis of N-acetylglutamate is inhibited due to the build up of the respective branched-chain organic acid; once standard therapy has corrected the acidemia, hyperammonemia is also resolved [4] . Doses used in these cases ranged from 70 to 200 mg/kg/day, administered as a single dose [4] or over a 48-hour period [3] .

FDA Approved Indications
Indicated as adjunctive therapy for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) from the time of birth. Also indicated as maintenance therapy for chronic hyperammonemia due to NAGS deficiency [1] .

Contraindications/Precautions

Prolonged exposure to increased plasma ammonia levels can rapidly result in brain injury or death; monitoring recommended [1] .
During initial treatment, complete protein restriction is recommended for 24 to 48 hours; supplement calories to avoid catabolism and nitrogen turnover [1] .

Pharmacology

Carglumic acid is a synthetic analogue of N-acetylglutamate (NAG), a product of N-acetylglutamate synthase (NAGS). NAG is an essential activator of carbamoyl phosphate synthetase 1 (CPS 1), which is the first enzyme in the urea cycle. Carglumic acid acts as a replacement for NAG in patients with NAGS deficiency, thereby activating CPS 1. Following administration, plasma ammonia levels are reduced within 24 hours. Tmax occurs in 2 to 4 hours. Drug partially metabolized by intestinal flora, likely to carbon dioxide, which is eliminated through the lungs. Unchanged drug is excreted in the feces (60%) and urine (9%). Mean terminal half-life is 5.6 hours [1] .

Adverse Effects

Adverse reaction which occurred in 13% or more patients from a retrospective case series include abdominal pain, anemia, diarrhea, ear infection, headache, infection, nasopharyngitis, pyrexia, tonsillitis, and vomiting [1] [2] .

Monitoring

Monitor plasma ammonia levels, neurological status, and clinical response [1] .

Special Considerations/Preparation

Available as a 200-mg tablet. Store sealed bottle in refrigerator prior to opening for the first time; do not refrigerate after opening. Discard product 1 month after first opening [1] .

References

- Product Information: CARBAGLU(R) oral tablets, carglumic acid oral tablets. Accredo Health Group, Inc. (per DailyMed), Memphis, TN, May, 2012.
- Daniotti M, la Marca G, Fiorini P et al: New developments in the treatment of hyperammonemia: emerging use of carglumic acid. Int J Gen Med 2011; 4: 21-28.
- Levrat V, Forest I, Fouilhoux A et al: Carglumic acid: an additional therapy in the treatment of organic acidurias with hyperammonemia?Orphanet J Rare Dis 2008; 3: 2-.
- Kasapkara CS, Ezgu FS, Okur I et al: N-carbamylglutamate treatment for acute neonatal hyperammonemia in isovaleric acidemia. Eur J Pediatr Jun, 2011; 170(6): 799-801.

1.31 Caspofungin

Title Caspofungin

Dose

25 mg/m^2 (or approximately 2 mg/kg) per dose every 24 hours.

Administration

Administer by slow IV infusion over approximately 1 hour at a **concentration not to exceed 0.5 mg/mL.Do not dilute in dextrose-containing solutions**.

Uses

Treatment of patients with refractory Candidemia, intra-abdominal abscesses, peritonitis and pleural space infections, and those patients intolerant of amphotericin B. Treatment of invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

There are case reports, but not controlled clinical trials, treating endocarditis, osteomyelitis, and meningitis due to *Candida*.

Pharmacology

Caspofungin is the first of a new class of antifungal agents (echinocandins) that inhibit the synthesis of β-(1,3)-D-glucan, an integral component of the fungal cell wall. It is fungicidal against *Candida* species, but fungistatic against *Aspergillus*. The echinocandins are excreted primarily by the liver, presumably metabolized through an O-methyltransferase. They are not metabolized through the CYP enzyme system and therefore have significantly fewer drug-drug interactions than the azoles.

Dexamethasone, phenytoin, carbamazepine, nevirapine, and rifampin all induce caspofungin drug clearance, lowering serum concentrations.

Adverse Effects

Adverse effects reported in neonates (small number of patients): thrombophlebitis, hypercalcemia, hypokalemia, elevated liver enzymes, and isolated direct hyperbilirubinemia. In pediatric studies, the primary adverse effects were fever, hypokalemia, diarrhea, increased liver enzymes, rash, hypotension and chills.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, and hepatic transaminases.

Special Considerations/Preparation

Cancidas® is supplied as a white to off-white powder cake in single-use vials, containing either 50 or 70 mg. To prepare the 50-mg (5 mg/mL) or 70-mg (7 mg/mL) Cancidas® vial: 1) Equilibrate the refrigerated vial to room temperature. 2) Aseptically add 10.8 mL Normal Saline or Sterile Water for Injection to the vial. The powder cake will dissolve completely with gentle mixing. This reconstituted solution can be stored at room temperature for up to one hour. Visually inspect the reconstituted solution for particulate matter or discoloration. Do not use if the solution is cloudy or has precipitated. Single-use vials: discard remaining unused solution. 3) Remove desired volume of drug based on calculated dose and further dilute in compatible solution (NS, ½ NS, ¼ NS, LR) to a final concentration not to exceed 0.5 mg/mL. The infusion solution can be stored for up to 24 hours at room temperature or up to 48 hours refrigerated. **Do not use diluents containing dextrose**.

Solution Compatibility

NS, ½ NS, ¼ NS, LR.

Solution Incompatibility

All solutions containing dextrose.

Terminal Injection Site Compatibility

Azithromycin, aztreonam, dobutamine, dopamine, famotidine, fluconazole, insulin, linezolid, meropenem, metronidazole, morphine, potassium chloride, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, cefazolin, ceftriaxone, clindamycin, furosemide, heparin, and piperacillin/tazobactam.

References

- Natale F, Castronovo A, Regoli D, et al: Successful treatment with caspofungin of refractory *Candida krusei* candidemia in a very low birth weight preterm infant. *Pediatr Infect Dis J* 2009;28:452.
- Saez-Llorens X, Macias M, Maiya P, et al: Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob Agents Chemother* 2009;53:869-875.
- Condie CK, Tyler LS, Baker B, et al: Visual compatibility of caspofungin acetate with commonly used drugs during simulated y-site delivery. *Am J Health-Syst Pharm* 2008;65:454-457, 1597 (errata).
- Smith PB, Steinbach WJ, Cotton CM, et al: Caspofungin for the treatment of azole resistant candidemia in a premature infant. *J Perinatol* 2007;27:127-129.
- Manzar S, Kamat M, Pyati S: Caspofungin for refractory candidemia in neonates. *Pediatr Infect Dis J* 2006;25:282-283.
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- Steinbach WJ, Benjamin DK: New agents under development in children and neonates. *Curr Opin Infect Dis* 2005;18:484-489.
- Pannaraj PS, Walsh TJ, Baker CJ: Advances in antifungal therapy. *Pediatr Infect Dis J* 2005;10:921-923.
- Walsh TJ, Adamson PC, Seibel NL, et al: Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother* 2005;49:4536-4545.
- Dodds Ashley ES, Lewis R, Lewis JS, et al: Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Merck & Co., 2009.

Title Caspofungin

Dose

25 mg/m^2 (or approximately 2 mg/kg) per dose every 24 hours.

Administration

Administer by slow IV infusion over approximately 1 hour at a **concentration not to exceed 0.5 mg/mL.Do not dilute in dextrose-containing solutions**.

Uses

Treatment of patients with refractory Candidemia, intra-abdominal abscesses, peritonitis and pleural space infections, and those patients intolerant of amphotericin B. Treatment of invasive Aspergillosis in patients who are refractory to or intolerant of other therapies.

There are case reports, but not controlled clinical trials, treating endocarditis, osteomyelitis, and meningitis due to *Candida*.

Pharmacology

Caspofungin is the first of a new class of antifungal agents (echinocandins) that inhibit the synthesis of β-(1,3)-D-glucan, an integral component of the fungal cell wall. It is

fungicidal against *Candida* species, but fungistatic against *Aspergillus*. The echinocandins are excreted primarily by the liver, presumably metabolized through an O-methyltransferase. They are not metabolized through the CYP enzyme system and therefore have significantly fewer drug-drug interactions than the azoles. Dexamethasone, phenytoin, carbamazepine, nevirapine, and rifampin all induce caspofungin drug clearance, lowering serum concentrations.

Adverse Effects

Adverse effects reported in neonates (small number of patients): thrombophlebitis, hypercalcemia, hypokalemia, elevated liver enzymes, and isolated direct hyperbilirubinemia. In pediatric studies, the primary adverse effects were fever, hypokalemia, diarrhea, increased liver enzymes, rash, hypotension and chills.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, and hepatic transaminases.

Special Considerations/Preparation

Cancidas® is supplied as a white to off-white powder cake in single-use vials, containing either 50 or 70 mg. To prepare the 50-mg (5 mg/mL) or 70-mg (7 mg/mL) Cancidas® vial: 1) Equilibrate the refrigerated vial to room temperature. 2) Aseptically add 10.8 mL Normal Saline or Sterile Water for Injection to the vial. The powder cake will dissolve completely with gentle mixing. This reconstituted solution can be stored at room temperature for up to one hour. Visually inspect the reconstituted solution for particulate matter or discoloration. Do not use if the solution is cloudy or has precipitated. Single-use vials: discard remaining unused solution. 3) Remove desired volume of drug based on calculated dose and further dilute in compatible solution (NS, ½ NS, ¼ NS, LR) to a final concentration not to exceed 0.5 mg/mL. The infusion solution can be stored for up to 24 hours at room temperature or up to 48 hours refrigerated. **Do not use diluents containing dextrose**.

Solution Compatibility

NS, ½ NS, ¼ NS, LR.

Solution Incompatibility

All solutions containing dextrose.

Terminal Injection Site Compatibility

Azithromycin, aztreonam, dobutamine, dopamine, famotidine, fluconazole, insulin, linezolid, meropenem, metronidazole, morphine, potassium chloride, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, cefazolin, ceftriaxone, clindamycin, furosemide, heparin, and piperacillin/tazobactam.

References

- Natale F, Castronovo A, Regoli D, et al: Successful treatment with caspofungin of refractory *Candida krusei* candidemia in a very low birth weight preterm infant. *Pediatr Infect Dis J* 2009;28:452.
- Saez-Llorens X, Macias M, Maiya P, et al: Pharmacokinetics and safety of caspofungin in neonates and infants less than 3 months of age. *Antimicrob Agents Chemother* 2009;53:869-875.
- Condie CK, Tyler LS, Baker B, et al: Visual compatibility of caspofungin acetate with commonly used drugs during simulated y-site delivery. *Am J Health-Syst Pharm* 2008;65:454-457, 1597 (errata).
- Smith PB, Steinbach WJ, Cotton CM, et al: Caspofungin for the treatment of azole resistant candidemia in a premature infant. *J Perinatol* 2007;27:127-129.
- Manzar S, Kamat M, Pyati S: Caspofungin for refractory candidemia in neonates. *Pediatr Infect Dis J* 2006;25:282-283.
- Odio CM, Araya R, Pinto Le, et al: Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004;23:1093-1097.
- Steinbach WJ, Benjamin DK: New agents under development in children and neonates. *Curr Opin Infect Dis* 2005;18:484-489.
- Pannaraj PS, Walsh TJ, Baker CJ: Advances in antifungal therapy. *Pediatr Infect Dis J* 2005;10:921-923.
- Walsh TJ, Adamson PC, Seibel NL, et al: Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. *Antimicrob Agents Chemother* 2005;49:4536-4545.
- Dodds Ashley ES, Lewis R, Lewis JS, et al: Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.
- Product Information, Merck & Co., 2009.

1.32 CeFAZolin

Title CeFAZolin

Dose

25 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12

	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Administration

May be given by IV direct (bolus) injection, IV infusion, or IM injection.
For IV bolus injection, inject slowly over 3 to 5 minutes at a concentration of 100 mg/mL. For IV infusion, dilute reconstituted solution to a concentration of 5 to 20 mg/mL and infuse over 10 to 60 minutes.
For IM injection, use a concentration of 225 mg/mL. **Maximum 330 mg/mL**.

Uses

Use in neonates is generally limited to perioperative infection prophylaxis and treatment of urinary tract and soft tissue infections caused by susceptible organisms, e.g. penicillin-resistant *Staph. aureus*, *Klebsiella*, and *Proteus.*

Pharmacology

First generation cephalosporin that is bactericidal against many gram-positive and a few gram-negative organisms. Inactivated by β-lactamase producing organisms. Poor CNS penetration. Renally excreted as unchanged drug. Half-life in neonates is 3 to 5 hours.

Adverse Effects

Adverse effects are rare, but include phlebitis and eosinophilia.

Monitoring

Serum concentrations are not routinely monitored.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1000-mg vials. Reconstitute 500-mg vial using 2 mL of sterile water for injection to a concentration of 225 mg/mL. Reconstitute 1000-mg vial using 3 mL of sterile water for injection to a concentration of 330 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 10 days in refrigerator. For bolus injection, further dilute reconstituted vial with approximately 5 mL of sterile water. For intermittent or continuous infusion, further dilute reconstituted drug to a concentration of 5 to 20 mg/mL in compatible solution.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA and fat emulsion. Acyclovir, alprostadil, amikacin, aztreonam, calcium gluconate, clindamycin, enalaprilat, esmolol, famotidine, fluconazole, heparin, insulin, lidocaine, linezolid, magnesium sulfate, midazolam, milrinone, morphine, metronidazole, multivitamins, nicardipine, pancuronium bromide, propofol, prostaglandin E_1, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, caspofungin, cimetidine, and vancomycin.

References

- Saez-Llorens X, McCracken GH: Clinical pharmacology of antibacterial agents. In: Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant,*ed 5. Philadelphia: WB Saunders Co, 2001.
- Pickering LK, O'Connor DM, Anderson D, et al: Clinical and pharmacologic evaluation of cefazolin in children. *J Infect Dis* 1973;128:S407.
- Product Information, Orchid Healthcare, 2006.

Title CeFAZolin

Dose

25 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:

Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Administration

May be given by IV direct (bolus) injection, IV infusion, or IM injection.
For IV bolus injection, inject slowly over 3 to 5 minutes at a concentration of 100 mg/mL. For IV infusion, dilute reconstituted solution to a concentration of 5 to 20 mg/mL and infuse over 10 to 60 minutes.
For IM injection, use a concentration of 225 mg/mL. **Maximum 330 mg/mL**.

Uses

Use in neonates is generally limited to perioperative infection prophylaxis and treatment of urinary tract and soft tissue infections caused by susceptible organisms, e.g. penicillin-resistant *Staph. aureus*, *Klebsiella*, and *Proteus.*

Pharmacology

First generation cephalosporin that is bactericidal against many gram-positive and a few gram-negative organisms. Inactivated by β-lactamase producing organisms. Poor CNS penetration. Renally excreted as unchanged drug. Half-life in neonates is 3 to 5 hours.

Adverse Effects

Adverse effects are rare, but include phlebitis and eosinophilia.

Monitoring

Serum concentrations are not routinely monitored.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1000-mg vials. Reconstitute 500-mg vial using 2 mL of sterile water for injection to a concentration of 225 mg/mL. Reconstitute 1000-mg vial using 3 mL of sterile water for injection to a concentration of 330 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 10 days in refrigerator. For bolus injection, further dilute reconstituted vial with approximately 5 mL of sterile water. For intermittent or continuous infusion, further dilute reconstituted drug to a concentration of 5 to 20 mg/mL in compatible solution.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA and fat emulsion. Acyclovir, alprostadil, amikacin, aztreonam, calcium gluconate, clindamycin, enalaprilat, esmolol, famotidine, fluconazole, heparin, insulin, lidocaine, linezolid, magnesium sulfate, midazolam, milrinone, morphine, metronidazole, multivitamins, nicardipine, pancuronium bromide, propofol, prostaglandin E_1, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone, caspofungin, cimetidine, and vancomycin.

References

- Saez-Llorens X, McCracken GH: Clinical pharmacology of antibacterial agents. In: Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant,*ed 5. Philadelphia: WB Saunders Co, 2001.
- Pickering LK, O'Connor DM, Anderson D, et al: Clinical and pharmacologic evaluation of cefazolin in children. *J Infect Dis* 1973;128:S407.
- Product Information, Orchid Healthcare, 2006.

1.33 CefOXitin

Title CefOXitin

Dose

90 to 100 mg/kg/day IV divided every 8 hours [1] [2] [3] .

Administration

Give as an intermittent IV infusion at a concentration of 10 to 40 mg/mL over 15 to 60 minutes [4] ; [5] [1] [6] .

Uses

Use in neonates is generally limited to treatment of skin, intra-abdominal and urinary tract infections caused by susceptible bacteria - anaerobes (e.g. *Bacteroides fragilis)*, gram positives (e.g. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and other streptococci except enterococcus) and gram negatives (e.g. *Haemophilus influenzae*, *Klebsiella* species, *E. coli*, *Proteus vulgaris*, and *Neisseria gonorrhoeae*).

Pharmacology

Broad spectrum bactericidal second generation cephalosporin that has enhanced activity against anaerobic bacteria. Inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins. Not inactivated by β-lactamase. Poor CNS penetration. Highly protein bound. Renally excreted as unchanged drug (85 to 90%). Half-life in term neonates is approximately 1.4 hours, and 2.3 hours in preterm neonates --considerably longer than children (0.6 hours) and adults (0.8 hours).

Adverse Effects

Adverse effects are rare. Transient eosinophilia and elevation of hepatic transaminases have been reported in less than 3% of treated patients. Severe overdose can cause tachypnea, pallor, hypotonia, and metabolic acidosis.

Monitoring

Serum concentrations are not routinely monitored.

Special Considerations/Preparation

Available as powder for injection in 1-g and 2-g vials.

IV administration: Reconstitute 1-g vial with 9.5 mL sterile water for injection to a concentration of 100 mg/mL. A 40 mg/mL dilution may be made by adding 4 mL of reconstituted solution to 6 mL sterile water for injection, or D_5W. Stable for 18 hours at room temperature or 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA and fat emulsion. Acyclovir, amikacin, aztreonam, cimetidine, clindamycin, dopamine, famotidine, fluconazole, gentamicin, heparin, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, morphine, multivitamins, oxacillin, penicillin g, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and tobramycin.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, sodium bicarbonate, and vancomycin.

References

- Marget W: Tenfold overdose of cefoxitin in a newborn. *Infection*1982;10:243.
- Brogden RN, Heel RC, Speight TM, et al: Cefoxitin: A review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1979;17:1-37.
- Feldman WE, Moffitt S, Sprow N: Clinical and pharmacokinetic evaluation of parenteral cefoxitin in infants and children. *Antimicrob Agents Chemother* 1980;17:669-674.
- Product Information, Abraxis Pharmaceutical Products, 2006.

1. Regazzi MB, Chirico G, Cristiani D et al: Cefoxitin in newborn infants. A clinical and pharmacokinetic study. Eur J Clin Pharmacol 1983; 25(4): 507-509.
2. Farmer K: Use of cefoxitin in the newborn. N Z Med J Jun9, 1982; 95(709): 398-398.
3. Roos R, Belohradsky BH, Marget W et al: Pharmacokinetics of cefoxitin in premature and newborn infants studied by continuous serum level monitoring during combination therapy with penicillin and amikacin. Infection 1980; 8(6): 301-306.
4. Product Information: Cefoxitin IV injection, Cefoxitin IV injection. APP Pharmaceuticals LLC, Schaumburg, IL, Feb, 2008.
5. Bratzler DW: Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis Jun15, 2004; 38(12): 1706-1715.
6. Jacobson JA: Clinical and bacteriological evaluation of cefoxitin therapy in children. Antimicrob Agents Chemother Aug, 1979; 16(2): 183-185.

Title CefOXitin

Dose

90 to 100 mg/kg/day IV divided every 8 hours [1] [2] [3] .

Administration

Give as an intermittent IV infusion at a concentration of 10 to 40 mg/mL over 15 to 60 minutes [4] ; [5] [1] [6] .

Uses

Use in neonates is generally limited to treatment of skin, intra-abdominal and urinary tract infections caused by susceptible bacteria - anaerobes (e.g. *Bacteroides fragilis)*, gram positives (e.g. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and other streptococci except enterococcus) and gram negatives (e.g. *Haemophilus influenzae*, *Klebsiella* species, *E. coli, Proteus vulgaris*, and *Neisseria gonorrhoeae*).

Pharmacology

Broad spectrum bactericidal second generation cephalosporin that has enhanced activity against anaerobic bacteria. Inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins. Not inactivated by β-lactamase. Poor CNS penetration. Highly protein bound. Renally excreted as unchanged drug (85 to 90%). Half-life in term neonates is approximately 1.4 hours, and 2.3 hours in preterm neonates --considerably longer than children (0.6 hours) and adults (0.8 hours).

Adverse Effects

Adverse effects are rare. Transient eosinophilia and elevation of hepatic transaminases have been reported in less than 3% of treated patients. Severe overdose can cause tachypnea, pallor, hypotonia, and metabolic acidosis.

Monitoring

Serum concentrations are not routinely monitored.

Special Considerations/Preparation

Available as powder for injection in 1-g and 2-g vials.

IV administration: Reconstitute 1-g vial with 9.5 mL sterile water for injection to a concentration of 100 mg/mL. A 40 mg/mL dilution may be made by adding 4 mL of reconstituted solution to 6 mL sterile water for injection, or D_5W. Stable for 18 hours at room temperature or 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA and fat emulsion. Acyclovir, amikacin, aztreonam, cimetidine, clindamycin, dopamine, famotidine, fluconazole, gentamicin, heparin, insulin, lidocaine, linezolid, magnesium sulfate, metronidazole, morphine, multivitamins, oxacillin, penicillin g, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and tobramycin.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, sodium bicarbonate, and vancomycin.

References

- Marget W: Tenfold overdose of cefoxitin in a newborn. *Infection*1982;10:243.
- Brogden RN, Heel RC, Speight TM, et al: Cefoxitin: A review of its antibacterial activity, pharmacological properties and therapeutic use. *Drugs* 1979;17:1-37.
- Feldman WE, Moffitt S, Sprow N: Clinical and pharmacokinetic evaluation of parenteral cefoxitin in infants and children. *Antimicrob Agents Chemother* 1980;17:669-674.
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1. Regazzi MB, Chirico G, Cristiani D et al: Cefoxitin in newborn infants. A clinical and pharmacokinetic study. Eur J Clin Pharmacol 1983; 25(4): 507-509.
2. Farmer K: Use of cefoxitin in the newborn. N Z Med J Jun9, 1982; 95(709): 398-398.
3. Roos R, Belohradsky BH, Marget W et al: Pharmacokinetics of cefoxitin in premature and newborn infants studied by continuous serum level monitoring during combination therapy with penicillin and amikacin. Infection 1980; 8(6): 301-306.
4. Product Information: Cefoxitin IV injection, Cefoxitin IV injection. APP Pharmaceuticals LLC, Schaumburg, IL, Feb, 2008.
5. Bratzler DW: Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis Jun15, 2004; 38(12): 1706-1715.
6. Jacobson JA: Clinical and bacteriological evaluation of cefoxitin therapy in children. Antimicrob Agents Chemother Aug, 1979; 16(2): 183-185.

1.34 CefTAZidime

Title CefTAZidime

Dose

30 mg/kg/dose IV infusion by syringe pump over 30 minutes, or IM.
To reduce pain at IM injection site, ceftazidime may be mixed with 1% lidocaine without epinephrine.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	8

Uses

Treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms (e.g. *E coli, H influenzae, Neisseria, Klebsiella,* and *Proteus* species), especially *Pseudomonas aeruginosa*. Resistance among strains of*Serratia* and *Enterobacteriaceae* is increasing.

Pharmacology

Ceftazidime is one of many third-generation cephalosporins. The drug distributes widely in body tissues and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low, and it is excreted unchanged in the urine. Ceftazidime is synergistic with aminoglycosides. Serum half-life in neonates is 3 to 12 hours.

Adverse Effects

Reported adverse effects are uncommon but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coombs' test.

Monitoring

Measuring serum concentration is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, 2-g, and 6-g vials.

Intravenous solution: Reconstitute 500-mg vial with 10 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution stable for 12 hours at room temperature, 3 days refrigerated.

Intramuscular solution: Prepared by reconstituting 500-mg vial with 2.2 mL of 1% lidocaine without epinephrine or Sterile Water to a concentration of 200 mg/mL. Solution is stable for 12 hours at room temperature, 3 days refrigerated.

All vials contain sodium carbonate; when reconstituted, carbon dioxide bubbles will form. Using a vented needle may help reduce spraying and leaking.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, aztreonam, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, gentamicin, heparin, ibuprofen lysine, linezolid, metronidazole, milrinone, morphine, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amiodarone, azithromycin, erythromycin lactobionate, fluconazole, midazolam, nicardipine, phenytoin, and vancomycin.

References

- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Tessin I, Thiringer K, Trollfors B, Brorson JE: Comparison of serum concentrations of ceftazidime and tobramycin in newborn infants. *Eur J Pediatr* 1988;147:405.
- Odio CM, Umana MA, Saenz A, et al: Comparative efficacy of ceftazidime vs. carbenicillin and amikacin for treatment of neonatal septicemia. *Pediatr Infect Dis*1987;6:371.
- McCracken GH, Threlkeld N, Thomas ML: Pharmacokinetics of ceftazidime in newborn infants. *Antimicrob Agents Chemother* 1984;26:583.
- Product Information, GlaxoSmithKline, 2007.

Title CefTAZidime

Dose

30 mg/kg/dose IV infusion by syringe pump over 30 minutes, or IM.
To reduce pain at IM injection site, ceftazidime may be mixed with 1% lidocaine without epinephrine.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	8

Uses

Treatment of neonatal meningitis and sepsis caused by susceptible gram-negative organisms (e.g. *E coli, H influenzae, Neisseria, Klebsiella,* and *Proteus* species), especially *Pseudomonas aeruginosa*. Resistance among strains of*Serratia* and *Enterobacteriaceae* is increasing.

Pharmacology

Ceftazidime is one of many third-generation cephalosporins. The drug distributes widely in body tissues and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low, and it is excreted unchanged in the urine. Ceftazidime is synergistic with aminoglycosides. Serum half-life in neonates is 3 to 12 hours.

Adverse Effects

Reported adverse effects are uncommon but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coombs' test.

Monitoring

Measuring serum concentration is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, 2-g, and 6-g vials.

Intravenous solution: Reconstitute 500-mg vial with 10 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution stable for 12 hours at room temperature, 3 days refrigerated.

Intramuscular solution: Prepared by reconstituting 500-mg vial with 2.2 mL of 1% lidocaine without epinephrine or Sterile Water to a concentration of 200 mg/mL. Solution is stable for 12 hours at room temperature, 3 days refrigerated.

All vials contain sodium carbonate; when reconstituted, carbon dioxide bubbles will form. Using a vented needle may help reduce spraying and leaking.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, aztreonam, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, gentamicin, heparin, ibuprofen lysine, linezolid, metronidazole, milrinone, morphine, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amiodarone, azithromycin, erythromycin lactobionate, fluconazole, midazolam, nicardipine, phenytoin, and vancomycin.

References

- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Tessin I, Thiringer K, Trollfors B, Brorson JE: Comparison of serum concentrations of ceftazidime and tobramycin in newborn infants. *Eur J Pediatr* 1988;147:405.
- Odio CM, Umana MA, Saenz A, et al: Comparative efficacy of ceftazidime vs. carbenicillin and amikacin for treatment of neonatal septicemia. *Pediatr Infect Dis*1987;6:371.
- McCracken GH, Threlkeld N, Thomas ML: Pharmacokinetics of ceftazidime in newborn infants. *Antimicrob Agents Chemother* 1984;26:583.
- Product Information, GlaxoSmithKline, 2007.

1.35 CefTRIAXone

Title CefTRIAXone

Dose

Sepsis: 50 mg/kg IV every 24 hours.

Meningitis: 100 mg/kg IV loading dose, then 80 mg/kg IV every 24 hours.

Gonococcal Infections
Disseminated Gonococcal Infections: 25 to 50 mg/kg/day IV/IM in a single daily dose for 7 days, with a duration of 10 to 14 days if meningitis is documented.
Gonococcal Infection, Prophylaxis: 25 to 50 mg/kg **(maximum 125 mg)** IV/IM as a

single dose.
Uncomplicated Gonococcal Ophthalmia: 25 to 50 mg/kg **(maximum 125 mg)** IV/IM as a single dose. (Note: topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is given.)

Administration

Intravenous: Infusion by syringe pump over 30 minutes. Avoid administration of calcium-containing solutions or products within 48 hours of the last administration of ceftriaxone.
Intramuscular: To reduce pain at the injection site, reconstitute with 1% lidocaine without epinephrine to a final concentration of 250 mg/mL or 350 mg/mL.

Uses

Treatment of neonatal sepsis and meningitis caused by susceptible gram-negative organisms (e.g. *E coli, Pseudomonas, Klebsiella, H influenzae*). Treatment of gonococcal infections.

Contraindications/Precautions

Not recommended for use in neonates with hyperbilirubinemia. Displaces bilirubin from albumin binding sites, resulting in higher free bilirubin serum concentrations.
Concurrent administration of ceftriaxone and calcium-containing solutions or products in neonates is contraindicated. There have been 7 reported cases of cardiorespiratory arrest in young infants, with 6 deaths, associated with concurrent administration of ceftriaxone and calcium-containing intravenous solutions. In all cases, the ceftriaxone dose (150 to 200 mg/kg/day) significantly exceeded the FDA recommended dose and/or was administered IV push. Crystalline material or white precipitate was noted in vascular beds on autopsy (primarily in the lungs) in 4 of the 5 infants for which results were available.

Pharmacology

Ceftriaxone is one of many third-generation cephalosporin antibiotics. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). It is eliminated unchanged by both biliary (40%) and renal mechanisms. Serum half-life in premature infants is 5 to 16 hours. Dosage adjustment is necessary only for patients with combined hepatic and renal failure.

Adverse Effects

Eosinophilia, thrombocytosis, leukopenia. Increase in bleeding time. Diarrhea. Increase in BUN and serum creatinine. Increase in AST and ALT. Skin rash. Transient gallbladder precipitations occasionally associated with colicky abdominal pain, nausea, and vomiting.

Monitoring

CBC for eosinophilia, thrombocytosis, leukopenia. Serum electrolytes, BUN, creatinine. AST, ALT, bilirubin. Consider abdominal ultrasonography.

Special Considerations/Preparation

Intravenous solution: Available as a powder for injection in 250-mg, 500-mg, 1-g, and 2-g vials. Prepared by reconstituting powder with compatible solution (sterile water for injection, D_5W, or $D_{10}W$) to a concentration of 100 mg/mL. Reconstituted solution is stable for 2 days at room temperature, 10 days refrigerated. A dark color may appear after reconstitution; however, potency is retained.
To make 40-mg/mL solution add 6.2 mL to the 250-mg vial.

Intramuscular solution: Prepared by reconstituting 250-mg vial with 0.9 mL of 1% lidocaine without epinephrine to a concentration of 250 mg/mL. Solution is stable for 24 hours at room temperature, 3 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Solution Incompatibility

Any calcium-containing solution.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, aztreonam, clindamycin, famotidine, gentamicin, heparin, linezolid, metronidazole, morphine, potassium chloride, propofol, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, calcium chloride, calcium gluconate, caspofungin, fluconazole and vancomycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Bradley JS, Wassel RT, Lee L, Nambiar S: Intravenous ceftriaxone and calcium in the neonate: Assessing the risk for cardiopulmonary adverse events. *Pediatrics* 2009;123:e609-e613.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
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- Laga M, Naamara W, Brunham RC, et al: Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *N Engl J Med* 1986;315:1382.
- Yogev R, Shulman ST, Chadwick E, et al: Once daily ceftriaxone for central nervous system infections and other serious pediatric infections. *Pediatr Infect Dis J* 1986;5:298.
- Martin E, Koup JR, Paravicini U, Stoeckel K: Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. *J Pediatr* 1984;105:475.
- Schaad UB, Stoeckel K: Single-dose pharmacokinetics of ceftriaxone in infants and young children. *Antimicrob Agents Chemother* 1982;21:248.
- Product Information, Roche, 2009.

Title CefTRIAXone

Dose

Sepsis: 50 mg/kg IV every 24 hours.

Meningitis: 100 mg/kg IV loading dose, then 80 mg/kg IV every 24 hours.

Gonococcal Infections
Disseminated Gonococcal Infections: 25 to 50 mg/kg/day IV/IM in a single daily dose for 7 days, with a duration of 10 to 14 days if meningitis is documented.
Gonococcal Infection, Prophylaxis: 25 to 50 mg/kg **(maximum 125 mg)** IV/IM as a single dose.
Uncomplicated Gonococcal Ophthalmia: 25 to 50 mg/kg **(maximum 125 mg)** IV/IM as a single dose. (Note: topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is given.)

Administration

Intravenous: Infusion by syringe pump over 30 minutes. Avoid administration of calcium-containing solutions or products within 48 hours of the last administration of ceftriaxone.
Intramuscular: To reduce pain at the injection site, reconstitute with 1% lidocaine without epinephrine to a final concentration of 250 mg/mL or 350 mg/mL.

Uses

Treatment of neonatal sepsis and meningitis caused by susceptible gram-negative organisms (e.g. *E coli, Pseudomonas, Klebsiella, H influenzae*). Treatment of gonococcal infections.

Contraindications/Precautions

Not recommended for use in neonates with hyperbilirubinemia. Displaces bilirubin from albumin binding sites, resulting in higher free bilirubin serum concentrations.
Concurrent administration of ceftriaxone and calcium-containing solutions or products in neonates is contraindicated. There have been 7 reported cases of cardiorespiratory arrest in young infants, with 6 deaths, associated with concurrent administration of ceftriaxone and calcium-containing intravenous solutions. In all cases, the ceftriaxone dose (150 to 200 mg/kg/day) significantly exceeded the FDA

recommended dose and/or was administered IV push. Crystalline material or white precipitate was noted in vascular beds on autopsy (primarily in the lungs) in 4 of the 5 infants for which results were available.

Pharmacology

Ceftriaxone is one of many third-generation cephalosporin antibiotics. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). It is eliminated unchanged by both biliary (40%) and renal mechanisms. Serum half-life in premature infants is 5 to 16 hours. Dosage adjustment is necessary only for patients with combined hepatic and renal failure.

Adverse Effects

Eosinophilia, thrombocytosis, leukopenia. Increase in bleeding time. Diarrhea. Increase in BUN and serum creatinine. Increase in AST and ALT. Skin rash. Transient gallbladder precipitations occasionally associated with colicky abdominal pain, nausea, and vomiting.

Monitoring

CBC for eosinophilia, thrombocytosis, leukopenia. Serum electrolytes, BUN, creatinine. AST, ALT, bilirubin. Consider abdominal ultrasonography.

Special Considerations/Preparation

Intravenous solution: Available as a powder for injection in 250-mg, 500-mg, 1-g, and 2-g vials. Prepared by reconstituting powder with compatible solution (sterile water for injection, D_5W, or $D_{10}W$) to a concentration of 100 mg/mL. Reconstituted solution is stable for 2 days at room temperature, 10 days refrigerated. A dark color may appear after reconstitution; however, potency is retained.
To make 40-mg/mL solution add 6.2 mL to the 250-mg vial.

Intramuscular solution: Prepared by reconstituting 250-mg vial with 0.9 mL of 1% lidocaine without epinephrine to a concentration of 250 mg/mL. Solution is stable for 24 hours at room temperature, 3 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Solution Incompatibility

Any calcium-containing solution.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, aztreonam, clindamycin, famotidine, gentamicin, heparin, linezolid, metronidazole, morphine, potassium chloride, propofol, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, calcium chloride, calcium gluconate, caspofungin, fluconazole and vancomycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Bradley JS, Wassel RT, Lee L, Nambiar S: Intravenous ceftriaxone and calcium in the neonate: Assessing the risk for cardiopulmonary adverse events. *Pediatrics* 2009;123:e609-e613.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Schaad UB, Suter S, Gianella-Borradori A, et al: A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med* 1990;332:141.
- Fink S, Karp W, Robertson A: Ceftriaxone effect on bilirubin-albumin binding. *Pediatrics* 1987;80:873.
- Laga M, Naamara W, Brunham RC, et al: Single-dose therapy of gonococcal ophthalmia neonatorum with ceftriaxone. *N Engl J Med* 1986;315:1382.
- Yogev R, Shulman ST, Chadwick E, et al: Once daily ceftriaxone for central nervous system infections and other serious pediatric infections. *Pediatr Infect Dis J* 1986;5:298.
- Martin E, Koup JR, Paravicini U, Stoeckel K: Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. *J Pediatr* 1984;105:475.
- Schaad UB, Stoeckel K: Single-dose pharmacokinetics of ceftriaxone in infants and young children. *Antimicrob Agents Chemother* 1982;21:248.
- Product Information, Roche, 2009.

1.36 Cefepime

Title Cefepime

Dose

Term and preterm infants greater than 28 days of age: 50 mg/kg/dose IV every 12 hours.

Term and preterm infants 28 days of age and younger: 30 mg/kg/dose IV every 12 hours.

Meningitis and severe infections due to Pseudomonas aeruginosa or Enterobacter spp: 50 mg/kg/dose IV every 12 hours.

Administration

Administer via IV infusion by syringe pump over 30 minutes, or IM.
To reduce pain at IM injection site, cefepime may be mixed with 1% lidocaine without epinephrine.

Uses

Treatment of serious infections caused by susceptible gram-negative organisms (eg, *E coli, H influenzae, Enterobacter, Klebsiella,Morganella, Neisseria, Serratia,*and *Proteus* species), especially *Pseudomonas aeruginosa*that are resistant to 3rd generation cephalosporins. Treatment of serious infections caused by susceptible Gram-positive organisms (eg, *Strep pneumoniae, Strep. pyogenes, Strep. agalactiae, and Staph. aureus*).

Pharmacology

Cefepime is a fourth-generation cephalosporin with treatment efficacy equivalent to third-generation cephalosporins. Potential advantages include: more rapid penetration through the cell wall of Gram-negative pathogens; enhanced stability to hydrolysis by β-lactamases; and enhanced affinity for penicillin-binding proteins. The drug distributes widely in body tissues and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low (approximately 20%), and it is primarily excreted unchanged in the urine. Serum half-life in infants older than 2 months of age is approximately 2 hours.

Adverse Effects

Safety has been documented to be the same as commonly used second- and third-generation cephalosporins. Reported adverse effects are uncommon, but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coomb's test.

Monitoring

Measuring serum concentration is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, and 2-g vials. Reconstitute 500-mg vial with 5 mL of sterile water for injection to a concentration of 100 mg/mL. Maximum concentration for IV administration is 160 mg/mL, and for IM administration 280 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, ampicillin, aztreonam, bumetanide, calcium gluconate, clindamycin, dexamethasone, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lorazepam, methylprednisolone, metronidazole, milrinone, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, aminophylline, amphotericin B, cimetidine, diazepam, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, ganciclovir, magnesium sulfate, metoclopramide, midazolam, morphine, nicardipine, phenytoin, tobramycin, and vancomycin.

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- Capparelli E, Hochwald C, Rasmussen M, et al: Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005;49:2760-2766.
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- Kessler RE: Cefepime microbiologic profile and update. *Pediatr Infect Dis J* 2001; 20:331-336.
- Lima-Rogel V, Medina-Rojas EL, del Carmen Milan-Segovia R, et al: Population pharmacokinetics of cefepime in neonates with severe nosocomial infections. *J Clin Pharm Ther* 2008;33:295-306.
- Product Information: Maxipime®, cefepime hydrochloride for injection, Bristol-Myers Squibb, 2009.
- Saez-Llorens XO, O'Ryan M: Cefepime in the empiric treatment of meningitis in children. *Pediatr Infect Dis J* 2001;20:356-361.

Title Cefepime

Dose

Term and preterm infants greater than 28 days of age: 50 mg/kg/dose IV every 12 hours.

Term and preterm infants 28 days of age and younger: 30 mg/kg/dose IV every 12 hours.

Meningitis and severe infections due to Pseudomonas aeruginosa or Enterobacter spp: 50 mg/kg/dose IV every 12 hours.

Administration

Administer via IV infusion by syringe pump over 30 minutes, or IM.
To reduce pain at IM injection site, cefepime may be mixed with 1% lidocaine without epinephrine.

Uses

Treatment of serious infections caused by susceptible gram-negative organisms (eg, *E coli*, *H influenzae*, *Enterobacter*, *Klebsiella*,*Morganella*, *Neisseria*, *Serratia*,and *Proteus* species), especially *Pseudomonas aeruginosa*that are resistant to 3rd generation cephalosporins. Treatment of serious infections caused by susceptible Gram-positive organisms (eg, *Strep pneumoniae*, *Strep. pyogenes*, *Strep. agalactiae*, *and Staph. aureus*).

Pharmacology

Cefepime is a fourth-generation cephalosporin with treatment efficacy equivalent to third-generation cephalosporins. Potential advantages include: more rapid penetration through the cell wall of Gram-negative pathogens; enhanced stability to hydrolysis by β-lactamases; and enhanced affinity for penicillin-binding proteins. The drug distributes widely in body tissues and fluids (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Protein binding is low (approximately 20%), and it is primarily excreted unchanged in the urine. Serum half-life in infants older than 2 months of age is approximately 2 hours.

Adverse Effects

Safety has been documented to be the same as commonly used second- and third-generation cephalosporins. Reported adverse effects are uncommon, but include rash, diarrhea, elevated hepatic transaminases, eosinophilia, and positive Coomb's test.

Monitoring

Measuring serum concentration is not usually necessary.

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g, and 2-g vials. Reconstitute 500-mg vial with 5 mL of sterile water for injection to a concentration of 100 mg/mL. Maximum concentration for IV administration is 160 mg/mL, and for IM administration 280 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amikacin, ampicillin, aztreonam, bumetanide, calcium gluconate, clindamycin, dexamethasone, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lorazepam, methylprednisolone, metronidazole, milrinone, piperacillin-tazobactam, potassium chloride, ranitidine,

remifentanil, sodium bicarbonate, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, aminophylline, amphotericin B, cimetidine, diazepam, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, ganciclovir, magnesium sulfate, metoclopramide, midazolam, morphine, nicardipine, phenytoin, tobramycin, and vancomycin.

References

- Blumer JL, Reed MD, Knupp C: Review of the pharmacokinetics of cefepime in children. *Pediatr Infect Dis J* 2001;20:337-342.
- Bradley JS, Arrieta A: Empiric use of cefepime in the treatment of lower respiratory tract infections in children. *Pediatr Infect Dis J* 2001;20:343-349.
- Capparelli E, Hochwald C, Rasmussen M, et al: Population pharmacokinetics of cefepime in the neonate. *Antimicrob Agents Chemother* 2005;49:2760-2766.
- Gutierrez K: Newer antibiotics: cefepime. *NeoReviews* 2004;5:e382-386.
- Kessler RE: Cefepime microbiologic profile and update. *Pediatr Infect Dis J* 2001; 20:331-336.
- Lima-Rogel V, Medina-Rojas EL, del Carmen Milan-Segovia R, et al: Population pharmacokinetics of cefepime in neonates with severe nosocomial infections. *J Clin Pharm Ther* 2008;33:295-306.
- Product Information: Maxipime®, cefepime hydrochloride for injection, Bristol-Myers Squibb, 2009.
- Saez-Llorens XO, O'Ryan M: Cefepime in the empiric treatment of meningitis in children. *Pediatr Infect Dis J* 2001;20:356-361.

1.37 Cefotaxime

Title Cefotaxime

Dose

50 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8

30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Disseminated Gonococcal Infections: 25 mg/kg/dose IV or IM every 12 hours for 7 days, with a duration of 10 to 14 days if meningitis is documented.

Administration

May be given by IM injection, IV push (over 3 to 5 minutes), or intermittent IV infusion.
For IV push, a concentration of 50 to 100 mg/mL may be used. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 10 to 30 minutes.

Uses

Treatment of disseminated gonococcal infections.

Treatment of neonatal meningitis and sepsis. caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae*,and*Klebsiella)*. Based on a 2012 statement from the American Academy of Pediatrics (AAP), empiric or therapeutic use of cefotaxime should be limited to infants having gram-negative meningitis. Until susceptibility test are known, treatment of gram-negative meningitis with both an aminoglycoside and cefotaxime is recommended [1] .

Pharmacology

Cefotaxime is one of many third-generation cephalosporin antibiotics. The mechanism of action appears to be by bacterial cell wall disruption. Metabolized in the liver to an active compound, desacetylcefotaxime. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Excreted renally. Serum half-life in the premature infant is approximately 3 to 6 hours.

Adverse Effects

Side effects are rare but include rash, phlebitis, diarrhea, leukopenia, granulocytopenia, and eosinophilia.

Monitoring

Measuring serum concentration is not usually necessary. Periodic CBC.

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials.
The 500-mg vial is reconstituted with 10 mL sterile water for injection to yield a concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alprostadil, amikacin, aztreonam, caffeine citrate, cimetidine, clindamycin, famotidine, gentamicin, heparin, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, oxacillin, penicillin g, potassium chloride, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Azithromycin, fluconazole, protamine sulfate, sodium bicarbonate, and vancomycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Kearns GL, Jacobs RF, Thomas BR, et al: Cefotaxime and desacetylcefotaxime pharmacokinetics in very low birth weight neonates. *J Pediatr* 1989;114:461.
- de Louvois J, Mulhall A, Hurley R: The safety and pharmacokinetics of cefotaxime in the treatment of neonates. *Pediatr Pharmacol* 1982;2:275.
- Kafetzis DA, Brater DC, Kapiki AN: Treatment of severe neonatal infections with cefotaxime: Efficacy and pharmacokinetics. *J Pediatr* 1982;100:483.
- Product Information, Abraxis Pharmaceutical Products, 2006.

1. Polin RA: Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics May, 2012; 129(5): 1006-1015.

Title Cefotaxime

Dose

50 mg/kg/dose IV or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Disseminated Gonococcal Infections: 25 mg/kg/dose IV or IM every 12 hours for 7 days, with a duration of 10 to 14 days if meningitis is documented.

Administration

May be given by IM injection, IV push (over 3 to 5 minutes), or intermittent IV infusion.
For IV push, a concentration of 50 to 100 mg/mL may be used. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 10 to 30 minutes.

Uses

Treatment of disseminated gonococcal infections.

Treatment of neonatal meningitis and sepsis. caused by susceptible gram-negative organisms (e.g. *E coli*, *H influenzae,*and*Klebsiella)*. Based on a 2012 statement from the American Academy of Pediatrics (AAP), empiric or therapeutic use of cefotaxime should be limited to infants having gram-negative meningitis. Until susceptibility test are known, treatment of gram-negative meningitis with both an aminoglycoside and cefotaxime is recommended [1] .

Pharmacology

Cefotaxime is one of many third-generation cephalosporin antibiotics. The mechanism of action appears to be by bacterial cell wall disruption. Metabolized in the liver to an active compound, desacetylcefotaxime. The drug distributes widely (i.e. CSF, bile, bronchial secretions, lung tissue, ascitic fluid, middle ear). Excreted renally. Serum half-life in the premature infant is approximately 3 to 6 hours.

Adverse Effects

Side effects are rare but include rash, phlebitis, diarrhea, leukopenia, granulocytopenia, and eosinophilia.

Monitoring

Measuring serum concentration is not usually necessary. Periodic CBC.

Special Considerations/Preparation

Available as powder for injection in 500-mg, 1-g, and 2-g vials.
The 500-mg vial is reconstituted with 10 mL sterile water for injection to yield a concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 7 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alprostadil, amikacin, aztreonam, caffeine citrate, cimetidine, clindamycin, famotidine, gentamicin, heparin, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, oxacillin, penicillin g, potassium chloride, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Azithromycin, fluconazole, protamine sulfate, sodium bicarbonate, and vancomycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Kearns GL, Jacobs RF, Thomas BR, et al: Cefotaxime and desacetylcefotaxime pharmacokinetics in very low birth weight neonates. *J Pediatr* 1989;114:461.
- de Louvois J, Mulhall A, Hurley R: The safety and pharmacokinetics of cefotaxime in the treatment of neonates. *Pediatr Pharmacol* 1982;2:275.
- Kafetzis DA, Brater DC, Kapiki AN: Treatment of severe neonatal infections with cefotaxime: Efficacy and pharmacokinetics. *J Pediatr* 1982;100:483.
- Product Information, Abraxis Pharmaceutical Products, 2006.

1. Polin RA: Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics May, 2012; 129(5): 1006-1015.

1.38 Chloral hydrate

Title Chloral hydrate

Dose

25 to 75 mg/kg per dose orally or rectally.

Administration

Oral: Oral preparation should be diluted or administered after a feeding to reduce gastric irritation [1] .
Rectal: The oral preparation may be given rectally [2] [3] .

Uses

Sedative/hypnotic for short-term use only. Chloral hydrate has no analgesic properties; excitement may occur in patients with pain.

Contraindications/Precautions

Contraindicated in patients with significant hepatic or renal impairment, and in those with severe cardiac disease. Oral administration not recommended in patients with esophagitis, gastritis, or gastric or duodenal ulcers [4] [1] .

Pharmacology

Well absorbed from the oral route, with the onset of action in 10 to 15 minutes. Chloral hydrate is rapidly converted by alcohol dehydrogenase to the active and potentially toxic metabolite trichloroethanol (TCEt), which is excreted renally after glucuronidation in the liver. It is also metabolized to trichloroacetic acid (TCA), which is carcinogenic in mice when given in very high doses. Both TCEt (8 to 64 hours) and TCA (days) have long serum half-lives in neonates and accumulate with repeated doses.

Adverse Effects

Episodes of bradycardia are more frequent for up to 24 hours after a single dose in former premature infants. Gastric irritation and paradoxical excitement may also occur after a single dose. Other toxic effects have generally been reported in patients who received either repeated doses at regular intervals or acute overdoses. These effects may persist for days and include CNS, respiratory, and myocardial depression; cardiac arrhythmias; and ileus and bladder atony. Indirect hyperbilirubinemia may occur because trichloroethanol and bilirubin compete for hepatic conjugation.

Monitoring

Assess level of sedation.

Special Considerations/Preparation

Chloral hydrate is available in syrup as 100-mg/mL concentration. Osmolality is 3285 mOsm/kg of water.
The preparations are light-sensitive: Store in a dark container.

References

- Allegaert K, Daniels H, Naulaers G, et al: Pharmacodynamics of chloral hydrate in former premature infants. *Eur J Pediatr* 2005;164:403-407.
- American Academy of Pediatrics, Committee on Drugs and Committee on Environmental Health: Use of chloral hydrate for sedation in children. *Pediatrics* 1993;92:471.
- Mayers DJ, Hindmarsh KW, Gorecki DKJ, Sankaran K: Sedative/hypnotic effects of chloral hydrate in the neonate: Trichloroethanol or parent drug? *Dev Pharmacol Ther* 1992;19:141.
- Anyebuno MA, Rosenfeld CR: Chloral hydrate toxicity in a term infant. *Dev Pharmacol Ther* 1991;17:116.
- Mayers DJ, Hindmarsh KW, Sankaran K, et al: Chloral hydrate disposition following single-dose administration to critically ill neonates and children. *Dev Pharmacol Ther* 1991;16:71.
- Reimche LD, Sankaran K, Hindmarsh KW, et al: Chloral hydrate sedation in neonates and infants: Clinical and pharmacologic considerations. *Dev Pharmacol Ther* 1989;12:57.

1. Product Information: chloral hydrate oral syrup, chloral hydrate oral syrup. Vintage Pharmaceuticals,Inc, Huntsville, AL, Dec1, 1999.
2. Coskun S: Chloralhydrate in children undergoing echocardiography. Indian J Pediatr Apr, 2001; 68(4): 319-322.
3. Simpson M: Oral and rectal absorption of chloral hydrate and its betaine complex. J Pharm Sci Feb, 1980; 69(2): 227-228.
4. Product Information: SOMNOTE(R) oral capsules, chloral hydrate oral capsules. Breckenridge Pharmaceuticals,Inc, Boca Raton, FL, Dec1, 2004.

Title Chloral hydrate

Dose

25 to 75 mg/kg per dose orally or rectally.

Administration

Oral: Oral preparation should be diluted or administered after a feeding to reduce gastric irritation [1] .
Rectal: The oral preparation may be given rectally [2] [3] .

Uses

Sedative/hypnotic for short-term use only. Chloral hydrate has no analgesic properties; excitement may occur in patients with pain.

Contraindications/Precautions

Contraindicated in patients with significant hepatic or renal impairment, and in those with severe cardiac disease. Oral administration not recommended in patients with esophagitis, gastritis, or gastric or duodenal ulcers [4] [1] .

Pharmacology

Well absorbed from the oral route, with the onset of action in 10 to 15 minutes. Chloral hydrate is rapidly converted by alcohol dehydrogenase to the active and potentially toxic metabolite trichloroethanol (TCEt), which is excreted renally after glucuronidation in the liver. It is also metabolized to trichloroacetic acid (TCA), which is carcinogenic in mice when given in very high doses. Both TCEt (8 to 64 hours) and TCA (days) have long serum half-lives in neonates and accumulate with repeated doses.

Adverse Effects

Episodes of bradycardia are more frequent for up to 24 hours after a single dose in former premature infants. Gastric irritation and paradoxical excitement may also occur after a single dose. Other toxic effects have generally been reported in patients who received either repeated doses at regular intervals or acute overdoses. These effects may persist for days and include CNS, respiratory, and myocardial depression; cardiac arrhythmias; and ileus and bladder atony. Indirect hyperbilirubinemia may occur because trichloroethanol and bilirubin compete for hepatic conjugation.

Monitoring

Assess level of sedation.

Special Considerations/Preparation

Chloral hydrate is available in syrup as 100-mg/mL concentration. Osmolality is 3285 mOsm/kg of water.
The preparations are light-sensitive: Store in a dark container.

References

- Allegaert K, Daniels H, Naulaers G, et al: Pharmacodynamics of chloral hydrate in former premature infants. *Eur J Pediatr* 2005;164:403-407.
- American Academy of Pediatrics, Committee on Drugs and Committee on Environmental Health: Use of chloral hydrate for sedation in children. *Pediatrics* 1993;92:471.
- Mayers DJ, Hindmarsh KW, Gorecki DKJ, Sankaran K: Sedative/hypnotic effects of chloral hydrate in the neonate: Trichloroethanol or parent drug? *Dev Pharmacol Ther* 1992;19:141.
- Anyebuno MA, Rosenfeld CR: Chloral hydrate toxicity in a term infant. *Dev Pharmacol Ther* 1991;17:116.
- Mayers DJ, Hindmarsh KW, Sankaran K, et al: Chloral hydrate disposition following single-dose administration to critically ill neonates and children. *Dev Pharmacol Ther* 1991;16:71.
- Reimche LD, Sankaran K, Hindmarsh KW, et al: Chloral hydrate sedation in neonates and infants: Clinical and pharmacologic considerations. *Dev Pharmacol Ther* 1989;12:57.

1. Product Information: chloral hydrate oral syrup, chloral hydrate oral syrup. Vintage Pharmaceuticals,Inc, Huntsville, AL, Dec1, 1999.

2. Coskun S: Chloralhydrate in children undergoing echocardiography. Indian J Pediatr Apr, 2001; 68(4): 319-322.
3. Simpson M: Oral and rectal absorption of chloral hydrate and its betaine complex. J Pharm Sci Feb, 1980; 69(2): 227-228.
4. Product Information: SOMNOTE(R) oral capsules, chloral hydrate oral capsules. Breckenridge Pharmaceuticals,Inc, Boca Raton, FL, Dec1, 2004.

1.39 Chloramphenicol

Title Chloramphenicol

Dose

Loading dose: 20 mg/kg IV infusion by syringe pump over 30 minutes.

Maintenance dose: (Begin 12 hours after loading dose.)
Premature infants under 1 month of age: 2.5 mg/kg/dose every 6 hours.
Full-term infants under 1 week of age and premature infants over 1 month of age: 5 mg/kg/dose every 6 hours.
Full-term infants over 1 week of age: 12.5 mg/kg/dose every 6 hours.
(Absorption of oral chloramphenicol palmitate is erratic in newborns.)

Uses

A wide-spectrum antimicrobial bacteriostatic agent. May be bactericidal to species such as *H influenzae* and *Neisseria meningitidis*.

Black Box Warning According to the manufacturer's black box warning, serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur. There have been reports of aplastic anemia which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. It is essential that adequate blood studies be made during treatment. If blood dyscrasias occur, therapy should be discontinued.

Pharmacology

Both esters (succinate and palmitate) are biologically inactive prodrugs. Hydrolysis to the active compound is erratic in newborns. Metabolized by hepatic glucuronyl transferase. Hepatically and renally eliminated. Inhibits metabolism of phenobarbital, phenytoin, and other agents.

Adverse Effects

Reversible bone marrow suppression, irreversible aplastic anemia. Serum concentration greater than 50 mcg/mL has been associated with the "gray baby" syndrome (ie, abdominal distention, pallid cyanosis, vasomotor collapse; may lead to death within hours of onset). Fungal overgrowth.

Monitoring

Close monitoring of serum concentration is mandatory. Small changes in dose and interval can lead to disproportionately large changes in serum concentration. Therapeutic peak serum concentration: 10 to 25 mcg/mL. Monitor CBC and reticulocyte counts. Assess hepatic and renal function.

Special Considerations/Preparation

Chloramphenicol succinate is available as powder for injection in a 1-g vial. Contains 52 mg (2.25 mEq) of sodium per gram. Reconstitute with 10 mL sterile water for injection or D_5W to a concentration of 100 mg/mL. For IV intermittent infusion, further dilute to a concentration of 20 to 25 mg/mL in compatible solution.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, aminophylline, ampicillin, calcium chloride, calcium gluconate, dopamine, enalaprilat, esmolol, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nafcillin, nicardipine, oxacillin, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, fluconazole, metoclopramide, phenytoin, and vancomycin.

References

- Roberts RJ: *Drug Therapy in Infants.* Philadelphia: WB Saunders Co, 1984, p 70.
- Rajchgot P, Prober CG, Soldin S: Initiation of chloramphenicol therapy in the newborn infant. *J Pediatr* 1982;101:1018.
- Glazer JP, Danish MA, Plotkin SA, Yaffe SJ: Disposition of chloramphenicol in low birth weight infants. *Pediatrics* 1980;66:573.
- Product Information, Abraxis, 2006.

Title Chloramphenicol

Dose

Loading dose: 20 mg/kg IV infusion by syringe pump over 30 minutes.

Maintenance dose: (Begin 12 hours after loading dose.)
Premature infants under 1 month of age: 2.5 mg/kg/dose every 6 hours.
Full-term infants under 1 week of age and premature infants over 1 month of age: 5 mg/kg/dose every 6 hours.
Full-term infants over 1 week of age: 12.5 mg/kg/dose every 6 hours.
(Absorption of oral chloramphenicol palmitate is erratic in newborns.)

Uses

A wide-spectrum antimicrobial bacteriostatic agent. May be bactericidal to species such as *H influenzae* and *Neisseria meningitidis*.

Black Box Warning According to the manufacturer's black box warning, serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur. There have been reports of aplastic anemia which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. It is essential that adequate blood studies be made during treatment. If blood dyscrasias occur, therapy should be discontinued.

Pharmacology

Both esters (succinate and palmitate) are biologically inactive prodrugs. Hydrolysis to the active compound is erratic in newborns. Metabolized by hepatic glucuronyl transferase. Hepatically and renally eliminated. Inhibits metabolism of phenobarbital, phenytoin, and other agents.

Adverse Effects

Reversible bone marrow suppression, irreversible aplastic anemia. Serum concentration greater than 50 mcg/mL has been associated with the "gray baby" syndrome (ie, abdominal distention, pallid cyanosis, vasomotor collapse; may lead to death within hours of onset). Fungal overgrowth.

Monitoring

Close monitoring of serum concentration is mandatory. Small changes in dose and interval can lead to disproportionately large changes in serum concentration. Therapeutic peak serum concentration: 10 to 25 mcg/mL. Monitor CBC and reticulocyte counts. Assess hepatic and renal function.

Special Considerations/Preparation

Chloramphenicol succinate is available as powder for injection in a 1-g vial. Contains 52 mg (2.25 mEq) of sodium per gram. Reconstitute with 10 mL sterile water for injection or D_5W to a concentration of 100 mg/mL. For IV intermittent infusion, further dilute to a concentration of 20 to 25 mg/mL in compatible solution.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, aminophylline, ampicillin, calcium chloride, calcium gluconate, dopamine, enalaprilat, esmolol, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine,

nafcillin, nicardipine, oxacillin, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Erythromycin lactobionate, fluconazole, metoclopramide, phenytoin, and vancomycin.

References

- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p 70.
- Rajchgot P, Prober CG, Soldin S: Initiation of chloramphenicol therapy in the newborn infant. *J Pediatr* 1982;101:1018.
- Glazer JP, Danish MA, Plotkin SA, Yaffe SJ: Disposition of chloramphenicol in low birth weight infants. *Pediatrics* 1980;66:573.
- Product Information, Abraxis, 2006.

1.40 Chlorothiazide

Title Chlorothiazide

Dose

Diuresis: 10 to 20 mg/kg/dose orally every 12 hours.

Adjuvant treatment of central diabetes insipidus: 5 mg/kg/dose orally every 12 hours.
Administer with food (improves absorption).
IV administration not recommended because of a lack of data.
Note: Do not confuse with hydrochlorothiazide.

Uses

Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone. May improve pulmonary function in patients with BPD. Adjuvant treatment of central diabetes insipidus.

Pharmacology

Limited data in neonates. Variable absorption from GI tract. Onset of action within 1 hour. Elimination half-life depends on GFR, and is approximately 5 hours. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, bicarbonate, and phosphorus. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin binding sites.

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia.
Do not use in patients with significant impairment of renal or hepatic function.

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

Special Considerations/Preparation

Available as a 250 mg/5mL suspension for oral use.

Injectable formulation available in 500-mg vial as lyophilized powder for reconstitution. Reconstitute 500-mg vial with 18 mL (never less) of sterile water for injection to make a concentration of 28 mg/mL. Use solution immediately after reconstitution; discard unused portion. May further dilute in compatible solution for IV infusion (D_5W and NS).

Solution Compatibility D_5W and NS.

Terminal Injection Site Compatibility Alprostadil.

References

- Dice JE: Physical compatibility of alprostadil with commonly used IV solutions and medications in the neonatal intensive care unit. *J Pediatr Pharmacol Ther* 2006;11:233-236.
- Pogacar PR, Mahnke S, SA: Management of central diabetes insipidus in infancy with low renal solute load formula and chlorothiazide. *Curr Opin Pediatr* 2000;12:405-411.
- Wells TG: The pharmacology and therapeutics of diuretics in the pediatric patient. *Pediatr Clin North Am* 1990;37:463.
- Albersheim SG, Solimano AJ, Sharma AK, et al: Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989;115:615.
- Roberts RJ: *Drug Therapy in Infants*. Philadelphia: WB Saunders Co, 1984, p 244.
- Kao LC, Warburton D, Cheng MH, et al: Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: Results of a double-blind, crossover, sequential trial. *Pediatrics* 1984;74:37.
- Product Information, Merck, 2007.

Title Chlorothiazide

Dose

Diuresis: 10 to 20 mg/kg/dose orally every 12 hours.

Adjuvant treatment of central diabetes insipidus: 5 mg/kg/dose orally every 12 hours.
Administer with food (improves absorption).
IV administration not recommended because of a lack of data.
Note: Do not confuse with hydrochlorothiazide.

Uses

Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone. May improve pulmonary function in patients with BPD. Adjuvant treatment of central diabetes insipidus.

Pharmacology

Limited data in neonates. Variable absorption from GI tract. Onset of action within 1 hour. Elimination half-life depends on GFR, and is approximately 5 hours. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, bicarbonate, and phosphorus. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin binding sites.

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia. **Do not use in patients with significant impairment of renal or hepatic function.**

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

Special Considerations/Preparation

Available as a 250 mg/5mL suspension for oral use.

Injectable formulation available in 500-mg vial as lyophilized powder for reconstitution. Reconstitute 500-mg vial with 18 mL (never less) of sterile water for injection to make a concentration of 28 mg/mL. Use solution immediately after reconstitution; discard unused portion. May further dilute in compatible solution for IV infusion (D_5W and NS).

Solution Compatibility D_5W and NS.

Terminal Injection Site Compatibility Alprostadil.

References

- Dice JE: Physical compatibility of alprostadil with commonly used IV solutions and medications in the neonatal intensive care unit. *J Pediatr Pharmacol Ther* 2006;11:233-236.
- Pogacar PR, Mahnke S, SA: Management of central diabetes insipidus in infancy with low renal solute load formula and chlorothiazide. *Curr Opin Pediatr* 2000;12:405-411.
- Wells TG: The pharmacology and therapeutics of diuretics in the pediatric patient. *Pediatr Clin North Am* 1990;37:463.
- Albersheim SG, Solimano AJ, Sharma AK, et al: Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989;115:615.
- Roberts RJ: *Drug Therapy in Infants*. Philadelphia: WB Saunders Co, 1984, p 244.

- Kao LC, Warburton D, Cheng MH, et al: Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: Results of a double-blind, crossover, sequential trial. *Pediatrics* 1984;74:37.
- Product Information, Merck, 2007.

1.41 Cimetidine

Title Cimetidine

Dose

2.5 to 5 mg/kg/dose every 6 to 12 hours orally or IV infusion over 15 to 30 minutes.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Contraindications/Precautions

Contraindicated in patients receiving cisapride due to precipitation of life-threatening arrhythmias. Cardiac arrhythmias and hypotension have been reported following the rapid IV bolus administration of cimetidine [1] .

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Peak inhibition occurs in 15 to 60 minutes after both oral and IV administration. Metabolized in the liver via sulfation and hydroxylation to inactive compounds that are 90% renally eliminated. Half-life in neonates is 1.1 to 3.4 hours, and is prolonged in patients with renal or hepatic insufficiency. The sulfoxide metabolite may accumulate in the CNS and cause toxicity. Antacids interfere with absorption; therefore, concomitant administration is not recommended.

Adverse Effects

Known adverse effects of cimetidine in adults include mental confusion, seizures, thrombocytopenia, neutropenia, nausea, vomiting, diarrhea, gynecomastia, rash, and muscular pain. Cimetidine has been reported to increase the serum level and potentiate toxicity of other drugs such as chlordiazepoxide, diazepam, lidocaine, metronidazole, nifedipine, phenytoin, propranolol, theophylline, warfarin, and certain tricyclic antidepressants [1] [2] [3] .

Monitoring

Gastric pH may be measured to assess efficacy. Observe for impaired consciousness and reduced spontaneous movements.

Special Considerations/Preparation

Available as a 150-mg/mL injectable solution in 2-mL single-use vials and 8-mL multidose vials. A 15-mg/mL dilution may be made by adding 1 mL of 150 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution stable for 48 hours. Manufacturer's oral solution (60 mg/mL) contains 2.8% alcohol. A 2.4 mg/mL oral dilution may be prepared by adding 1 mL (60 mg) of manufacturer's oral solution to 24 mL of sterile water. Stable for 14 days refrigerated. Also available in 200-, 300-, 400-, and 800-mg tablets.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acetazolamide, acyclovir, amikacin, aminophylline, ampicillin, atropine, aztreonam, caffeine citrate, cefotaxime, cefoxitin, ceftazidime, clindamycin, dexamethasone, diazepam, digoxin, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meperidine, meropenem, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroprusside, pancuronium, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1 , protamine, remifentanil, sodium bicarbonate, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B (Immediate precipitation occurs), cefazolin, cefepime, indomethacin, and pentobarbital.

References

- Vandenplas Y, Sacre L: The use of cimetidine in newborns. *Am J Perinatol* 1987;4:131.
- Lloyd CW, Martin WJ, Taylor BD: The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985;19:203.
- Ziemniak JA, Wynn RJ, Aranda JV, et al: The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984;7:30.
- Aranda JV, Outerbridge EW, Shentag JJ: Pharmacodynamics and kinetics of cimetidine in a premature newborn. *Am J Dis Child* 1983;137:1207.
- Product Information, Hospira, 2004.

1. Product Information: TAGAMET (R), cimetidine tablet. GlaxoSmithKline, Research Triangle Park, North Carolina, USA, December, 2005.
2. Rudolph CD, Mazur LJ, Liptak GS et al: Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32 Suppl 2: S1-S31.
3. Dohil M: Treatment of molluscum contagiosum with oral cimetidine: clinical experience in 13 patients.Pediatr Dermatol 1996; 13: 310-312.

Title Cimetidine

Dose

2.5 to 5 mg/kg/dose every 6 to 12 hours orally or IV infusion over 15 to 30 minutes.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Contraindications/Precautions

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Monitoring

Gastric pH may be measured to assess efficacy. Observe for impaired consciousness and reduced spontaneous movements.

Special Considerations/Preparation

Available as a 150-mg/mL injectable solution in 2-mL single-use vials and 8-mL multidose vials. A 15-mg/mL dilution may be made by adding 1 mL of 150 mg/mL concentration to 9 mL of preservative-free normal saline. Dilution stable for 48 hours. Manufacturer's oral solution (60 mg/mL) contains 2.8% alcohol. A 2.4 mg/mL oral dilution may be prepared by adding 1 mL (60 mg) of manufacturer's oral solution to 24 mL of sterile water. Stable for 14 days refrigerated. Also available in 200-, 300-, 400-, and 800-mg tablets.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acetazolamide, acyclovir, amikacin, aminophylline, ampicillin, atropine, aztreonam, caffeine citrate, cefotaxime, cefoxitin, ceftazidime, clindamycin, dexamethasone, diazepam, digoxin, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meperidine, meropenem, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, nitroprusside, pancuronium, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1 , protamine, remifentanil, sodium bicarbonate, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B (Immediate precipitation occurs), cefazolin, cefepime, indomethacin, and pentobarbital.

References

- Vandenplas Y, Sacre L: The use of cimetidine in newborns. *Am J Perinatol* 1987;4:131.
- Lloyd CW, Martin WJ, Taylor BD: The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985;19:203.
- Ziemniak JA, Wynn RJ, Aranda JV, et al: The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984;7:30.
- Aranda JV, Outerbridge EW, Shentag JJ: Pharmacodynamics and kinetics of cimetidine in a premature newborn. *Am J Dis Child* 1983;137:1207.
- Product Information, Hospira, 2004.

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2. Rudolph CD, Mazur LJ, Liptak GS et al: Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32 Suppl 2: S1-S31.
3. Dohil M: Treatment of molluscum contagiosum with oral cimetidine: clinical experience in 13 patients.Pediatr Dermatol 1996; 13: 310-312.

1.42 Clindamycin

Title Clindamycin

Dose

5 to 7.5 mg/kg/dose IV infusion by syringe pump over 30 minutes, or orally.

Increase dosing interval in patients with significant liver dysfunction.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Bacteriostatic antibiotic used for the treatment of bacteremia and pulmonary and deep tissue infections caused by anaerobic bacteria and some gram-positive cocci. Clindamycin should not be used in the treatment of meningitis.

Black Box Warning Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin. If pseudomembranous colitis is suspected or confirmed, consider discontinuation of clindamycin and initiate appropriate fluid and electrolyte management, protein supplementation, *C. difficile* antibiotic treatment, and surgical evaluation as clinically indicated.

Pharmacology

Clindamycin inhibits bacterial protein synthesis and is primarily bacteriostatic at therapeutically attainable concentrations. Widely distributed into most tissues, especially the lung. Poor cerebrospinal fluid penetration. Oral clindamycin is completely absorbed from the gastrointestinal tract. Highly protein bound. Almost complete metabolism in the liver, with excretion via bile and feces. Available data in neonates suggest extremely variable clearance, especially in premature infants. No data are available regarding conversion of ester to active drug.

Adverse Effects

Hypersensitivity reactions, and jaundice and liver function test abnormalities have been reported in association with clindamycin therapy. Should not be used in combination with topical or oral erythromycin-containing products due to possible antagonism.

Monitoring

Assess liver function. Monitor GI status closely. Therapeutic serum concentration ranges from 2 to 10 mcg/mL (bioassay yields variable results).

Special Considerations/Preparation

Oral preparation (clindamycin palmitate) is reconstituted with sterile water for injection, yielding a 75 mg per 5 mL solution.
Do not refrigerate. Stable at room temperature for 2 weeks.

IV preparation (clindamycin phosphate) is available as a 150 mg/mL solution in 2-mL, 4-mL, and 6-mL vials containing 9.45 mg/mL benzyl alcohol. It should be diluted using D_5W, NS, or LR to a maximum concentration of 18 mg/mL, and infused at a rate no greater than 30 mg/min. Also available in premixed bags (50 mL) without benzyl alcohol containing 300 mg, 600 mg or 900 mg of clindamycin.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, enalaprilat, esmolol, gentamicin, heparin, hydrocortisone succinate, linezolid, magnesium sulfate, metoclopramide, metronidazole, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Aminophylline, azithromycin, barbiturates, caspofungin, fluconazole, and phenytoin.

References

- Koren G, Zarfin Y, Maresky D, et al: Pharmacokinetics of intravenous clindamycin in newborn infants. *Pediatr Pharmacol* 1986;5:287.
- Bell MJ, Shackelford P, Smith R, Schroeder K: Pharmacokinetics of clindamycin phosphate in the first year of life. *J Pediatr* 1984;105:482.
- Feigin RD, Pickering LK, Anderson D, et al: Clindamycin treatment of osteomyelitis and septic arthritis in children. *Pediatrics* 1975;55:213.
- Lwin N, Collipp PJ: Absorption and tolerance of clindamycin 2-palmitate in infants below 6 months of age. *Curr Ther Res Clin Exp* 1970;12:648.
- Product Information, Pfizer, 2003.

Title Clindamycin

Dose

5 to 7.5 mg/kg/dose IV infusion by syringe pump over 30 minutes, or orally.

Increase dosing interval in patients with significant liver dysfunction.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

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Uses

Bacteriostatic antibiotic used for the treatment of bacteremia and pulmonary and deep tissue infections caused by anaerobic bacteria and some gram-positive cocci. Clindamycin should not be used in the treatment of meningitis.

Black Box Warning Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clindamycin, and may range in severity from mild to life-threatening. Because clindamycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin. If pseudomembranous colitis is suspected or confirmed, consider discontinuation of clindamycin and initiate appropriate fluid and electrolyte management, protein supplementation, *C. difficile* antibiotic treatment, and surgical evaluation as clinically indicated.

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especially the lung. Poor cerebrospinal fluid penetration. Oral clindamycin is completely absorbed from the gastrointestinal tract. Highly protein bound. Almost complete metabolism in the liver, with excretion via bile and feces. Available data in neonates suggest extremely variable clearance, especially in premature infants. No data are available regarding conversion of ester to active drug.

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Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, amiodarone, ampicillin, aztreonam, caffeine citrate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, enalaprilat, esmolol, gentamicin, heparin, hydrocortisone succinate, linezolid, magnesium sulfate, metoclopramide, metronidazole, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, tobramycin, and zidovudine.

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- Koren G, Zarfin Y, Maresky D, et al: Pharmacokinetics of intravenous clindamycin in newborn infants. *Pediatr Pharmacol* 1986;5:287.
- Bell MJ, Shackelford P, Smith R, Schroeder K: Pharmacokinetics of clindamycin phosphate in the first year of life. *J Pediatr* 1984;105:482.
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- Lwin N, Collipp PJ: Absorption and tolerance of clindamycin 2-palmitate in infants below 6 months of age. *Curr Ther Res Clin Exp* 1970;12:648.
- Product Information, Pfizer, 2003.

1.43 CloNIDine

Title CloNIDine

Dose

Neonatal Abstinence Syndrome; Adjunct
35 weeks GA and older:0.5 to 1 mcg/kg orally every 4 to 6 hours [1] [2] [3] .
Discontinue based on NAS scores and patient stability.

Administration

Oral: Some experts recommend using a dilution of the epidural formulation of clonidine for use in neonates with NAS due to concerns about extemporaneous compounded oral suspensions and accuracy of dosing [2] [3] . The epidural formulation (100 mcg/mL) was diluted in NS to a concentration of 5 mcg/mL and used orally in a randomized controlled trial [3] .

Uses

Treatment of neonatal abstinence syndrome, as adjunct to opioids. Clonidine has been used as an adjunct to tincture of opium (DTO) in neonates with intrauterine exposure to heroin or methadone. In a prospective, randomized, double-blind, placebo-controlled trial, infants 35 weeks GA and older receiving DTO with oral clonidine experienced fewer treatment failures, a shorter duration of treatment and observation, and required less DTO than infants receiving DTO with placebo. There were no clinically important changes in blood pressure and heart rate in the clonidine group [3] .

Contraindications/Precautions

Epidural Injection
Contraindicated in patients with an injection site infection, patients with a bleeding diathesis, and patients on concurrent anticoagulant therapy. Epidural administration above the C4 dermatome is also contraindicated [4] .

Abrupt discontinuation may result in symptoms of withdrawal (eg, agitation, headache, tremor, rapid rise of blood pressure); a gradual reduction of dosage is recommended when therapy is discontinued [5] .

Pharmacology

Clonidine is a centrally acting alpha-2-adrenergic agonist. Stimulation of these alpha-adrenoreceptors in the brain stem results in decreased sympathetic outflow from the CNS and in reductions in peripheral resistance, heart rate, and blood pressure. Its action in ADHD is unknown. After oral administration, onset of action of hypotension occurs within 30 to 60 minutes with a peak effect within 2 to 4 hours. Peak concentrations occur 3 to 5 hours after dosing of immediate-release formulation. Food does not affect the pharmacokinetics [5] . Approximately 50% of a dose is metabolized in the liver and approximately 40% to 60% of a dose is eliminated in the urine as unchanged drug. Elimination half-life in neonates is 44 to 72 hours [2] and is prolonged in patients with renal impairment [5] [10] . In neonates, clearance of clonidine rapidly increases with postnatal age over the first month of life. Pharmacokinetic modelling showed that by the age of 1 month, neonates had achieved 70% of adult clearance [11] .

Adverse Effects

The use of clonidine as an adjunct with local anesthetics for caudal or spinal anesthesia/analgesia has been associated with apnea and respiratory depression in neonates and premature infants [6] [7] [8] [9] . The use of clonidine for treatment of NAS has not been associated with clinically important changes in blood pressure or heart rate; however, close monitoring is imperative [3] .

Monitoring

Monitor heart rate and blood pressure every 4 hours the first 2 days of therapy and every 12 hours thereafter; monitor blood pressure closely for 48 hours after discontinuing clonidine to access for rebound hypertension. Monitor NAS scores every 3 to 4 hours during treatment using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1] [3] .

Special Considerations/Preparation

Oral formulations available as 0.1-, 0.2- and 0.3-mg immediate-release tablets. An extemporaneous oral suspension can be prepared using the directions below [5] .

Extemporaneous Preparation
Clonidine 0.1 mg/mL oral suspension can be prepared by grinding thirty (30) 0.2 mg-clonidine tablets, adding 2 mL of Purified Water, USP, to make a fine paste, and adding enough Simple Syrup, NF, for a final volume of 60 mL. The suspension is stable for 28 days when refrigerated (4 degrees C) [12] .

Clonidine for epidural injection is available in concentrations of 100 mcg/mL and 500 mcg/mL in 10-mL single-dose vials. Vials are preservative free. The 500 mcg/mL-strength must be diluted with NS to a final concentration not exceeding 100 mcg/mL prior to use. Do not use with preservative-containing diluents [4] .

References

- Hudak ML: Neonatal Drug Withdrawal. Pediatrics Feb, 2012; 129(2): e540-e560.

- Bio LL: Update on the pharmacologic management of neonatal abstinence syndrome. J Perinatol Aug25, 2011; EPub: EPub-.

- Agthe AG, Kim GR, Mathias KB et al: Clonidine as an adjunct therapy to opioids for neonatal abstinence syndrome: a randomized, controlled trial. Pediatrics May, 2009; 123(5): e849-e856.

- Product Information: clonidine HCl epidural injection, clonidine HCl epidural injection. APP Pharmaceuticals, LLC (per manufacturer), Schaumburg, IL, Jun, 2011.

- Product Information: CATAPRES oral tablet, clonidine hydrochloride oral tablet. Boehringer Ingelheim Promeco SA de CV, Mexico, Mexico, Jan, 2010.

- Galante D: Preoperative apnea in a preterm infant after caudal block with ropivacaine and clonidine. Paediatr Anaesth Aug, 2005; 15(8): 708-709.

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- Breschan C, Krumpholz R, Likar R et al: Can a dose of 2microg.kg(-1) caudal clonidine cause respiratory depression in neonates. Paediatr Anaesth 1999; 9(1): 81-83.

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- Levinson ML: Stability of an extemporaneously compounded clonidine hydrochloride oral liquid. Am J Hosp Pharm Jan, 1992; 49(1): 122-125.

Title CloNIDine

Dose

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35 weeks GA and older:0.5 to 1 mcg/kg orally every 4 to 6 hours [1] [2] [3] .
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Administration

Oral: Some experts recommend using a dilution of the epidural formulation of clonidine for use in neonates with NAS due to concerns about extemporaneous compounded oral suspensions and accuracy of dosing [2] [3] . The epidural formulation (100 mcg/mL) was diluted in NS to a concentration of 5 mcg/mL and used orally in a randomized controlled trial [3] .

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Contraindications/Precautions

Epidural Injection
Contraindicated in patients with an injection site infection, patients with a bleeding diathesis, and patients on concurrent anticoagulant therapy. Epidural administration above the C4 dermatome is also contraindicated [4] .

Abrupt discontinuation may result in symptoms of withdrawal (eg, agitation, headache, tremor, rapid rise of blood pressure); a gradual reduction of dosage is recommended when therapy is discontinued [5] .

Pharmacology

Clonidine is a centrally acting alpha-2-adrenergic agonist. Stimulation of these alpha-adrenoreceptors in the brain stem results in decreased sympathetic outflow from the CNS and in reductions in peripheral resistance, heart rate, and blood pressure. Its action in ADHD is unknown. After oral administration, onset of action of hypotension occurs within 30 to 60 minutes with a peak effect within 2 to 4 hours. Peak concentrations occur 3 to 5 hours after dosing of immediate-release formulation. Food does not affect the pharmacokinetics [5] . Approximately 50% of a dose is metabolized in the liver and approximately 40% to 60% of a dose is eliminated in the urine as unchanged drug. Elimination half-life in neonates is 44 to 72 hours [2] and is prolonged in patients with renal impairment [5] [10] . In neonates, clearance of clonidine rapidly increases with postnatal age over the first month of life. Pharmacokinetic modelling showed that by the age of 1 month, neonates had achieved 70% of adult clearance [11] .

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Clonidine for epidural injection is available in concentrations of 100 mcg/mL and 500 mcg/mL in 10-mL single-dose vials. Vials are preservative free. The 500 mcg/mL-strength must be diluted with NS to a final concentration not exceeding 100 mcg/mL prior to use. Do not use with preservative-containing diluents [4] .

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- Product Information: CATAPRES oral tablet, clonidine hydrochloride oral tablet. Boehringer Ingelheim Promeco SA de CV, Mexico, Mexico, Jan, 2010.
- Galante D: Preoperative apnea in a preterm infant after caudal block with ropivacaine and clonidine. Paediatr Anaesth Aug, 2005; 15(8): 708-709.
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1.44 Clopidogrel

Title Clopidogrel

Dose

Thrombosis; Prophylaxis
35 weeks of gestation or greater:initial, 0.2 mg/kg orally once daily [1] .
In the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial (n=73; neonates 30 days and younger (n=34) and infants greater than 30 days (n=39)), a clopidogrel dose of 0.2 mg/kg/day given to infants and children (aged 0 to 24 months; 35 weeks of gestation or greater) at risk of arterial thrombosis achieved a similar antiplatelet effect (30% to 50% inhibition of 5 mcmol/L adenosine diphosphate (ADP)-induced platelet aggregation) as a 75 mg/day regimen in adults. A total of 79% of the subjects were taking low-dose aspirin 81 mg or less per day (aspirin mean dose, 8.8 +/- 14 mg/kg/day) [1] .

Discontinuation
Clopidogrel should be discontinued 5 days prior to elective surgery if an antiplatelet effect is not desired [2] .

Administration

May be given without regard to feedings [2] .

Uses

Antiplatelet agent for the prophylaxis of thrombotic events [3] [4] [1] . Has been used successfully for the prophylaxis of thrombosis in cardiac disease and cardiac conditions associated with a high risk for arterial thrombosis [3] [1] [4] .

Pediatric FDA Approved Indications
Not FDA approved in pediatric patients [2] .

Contraindications/Precautions

Contraindicated in patients with active, pathological bleeding (eg, peptic ulcer or intracranial hemorrhage). Bleeding risk is increased with the concomitant use of clopidogrel, NSAIDs or warfarin [2] . In one pediatric clinical study (n=17), significant intracranial hemorrhage was reported in 25% of pediatric patients (n=2/9) when clopidogrel was used concomitantly with aspirin [6] . In another study (n=46), 1 case each of severe epistaxis and gastrointestinal bleeding was reported in the 2 children receiving concomitant warfarin and clopidogrel therapy [4] . There was 1 report of

massive upper GI bleeding in a child on concomitant clopidogrel, low-dose aspirin, and warfarin in another study (n=15) [5] . Thrombotic thrombocytopenic purpura, some cases fatal, has been reported [2] .

Concomitant use with the CYP2C19 inhibitors omeprazole and esomeprazole should be avoided as platelet activity may be reduced [2] . In a subgroup analysis (n=49) of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) trial, children who were receiving clopidogrel in combination with a proton pump inhibitor (PPI; n=5) displayed reduced platelet inhibition overall compared to those children receiving clopidogrel alone (n=44; median 6%; interquartile range, 0 to 44% vs 49%; interquartile range, 19% to 63%; p=0.09); there was also a significant reduction in the clopidogrel responders sub-group (median 25%; interquartile range, 3% to 45% vs 53%, interquartile range, 38% to 65%; p=0.04). The combination group consisted of 4 patients taking omeprazole and 1 patient taking lansoprazole [7] .

Allergic cross-reactivity may occur among thienopyridines (eg, ticlopidine, prasugrel). Evaluate patients for prior hypersensitivity reactions [8] .

Black Box Warning

Clopidogrel efficacy is dependent on its activation to an active metabolite by CYP2C19. In patients who are CYP2C19 poor metabolizers, clopidogrel at recommended doses forms less of that metabolite and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype; these tests can help determine therapeutic strategy. Consider alternative treatment or treatment strategies in CYP2C19 poor metabolizers [2] .

Pharmacology

Clopidogrel is a prodrug that is metabolized to the active form (thiol derivative) which inhibits platelet aggregation by selectively and irreversibly binding to the adenosine diphosphate (ADP) P2Y12 receptor on platelets. This binding prevents activation of the ADP-mediated glycoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation. This action is irreversible for the remainder of the platelet lifespan (7 to 10 days). Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses. Platelet inhibition reaches steady state at days 3 to 7 after therapy initiation. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days. Bioavailability is at least 50%; food does not affect absorption. Peak concentration achieved 30 to 60 minutes after administration. Extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes (CYP2C19, CYP3A, CYP2B6 and CYP1A2). The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelets. Approximately 50% and 46% is eliminated in the urine and feces, respectively. Elimination half-life is approximately 6 hours (75-mg dose in adults). The half-life of the active metabolite is about 30 minutes [2] .

Adverse Effects

Bleeding and thrombotic thrombocytopenic purpura are the most common hematological adverse events [2] [4] . Anemia, neutropenia, and leukopenia have also been reported [4] .

Monitoring

Measure bleeding time prior to therapy initiation and 3 to 7 days after therapy initiation to assess drug efficacy. Platelet aggregation assay studies may be useful in some patients to evaluate response [5] . Monitor hematological parameters closely during the first few months of therapy and every 2 to 3 months in patients on long-term therapy [4] .

Special Considerations/Preparation

Available as 75-mg and 300-mg tablets [2] . An extemporaneous clopidogrel oral suspension can be compounded by triturating four 75-mg tablets in a mortar and mixing with 30 mL of Ora-Plus and 30 mL of Ora-Sweet for a final concentration of 5 mg/mL. Suspension is stable for 60 days at room temperature or refrigerated.**Shake well** before use [9] .

References

- Li JS, Yow E, Berezny KY et al: Dosing of clopidogrel for platelet inhibition in infants and young children: primary results of the Platelet Inhibition in Children On cLOpidogrel (PICOLO) Trial. Circulation Jan29, 2008; 117(4): 553-559.
- Product Information: PLAVIX(R) oral tablets, clopidogrel bisulfate oral tablets. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership (per FDA), Bridgewater, NJ, Dec, 2011.
- Maltz LA, Gauvreau K, Connor JA et al: Clopidogrel in a pediatric population: prescribing practice and outcomes from a single center. Pediatr Cardiol Feb, 2009; 30(2): 99-105.
- Mertens L, Eyskens B, Boshoff D et al: Safety and efficacy of clopidogrel in children with heart disease. J Pediatr Jul, 2008; 153(1): 61-64.
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- Pasquali SK, Yow E, Jennings LK et al: Platelet activity associated with concomitant use of clopidogrel and proton pump inhibitors in children with cardiovascular disease. Congenit Heart Dis Nov, 2010; 5(6): 552-555.
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- Skillman KL: Stability of an extemporaneously prepared clopidogrel oral suspension. Am J Health Syst Pharm Apr1, 2010; 67(7): 559-561.

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Adverse Effects

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1.45 Cyclopentolate (Ophthalmic)

Title Cyclopentolate (Ophthalmic)

Dose

1 or 2 drops instilled in the eye 10 to 30 minutes prior to funduscopy.
Use solutions containing concentrations of 0.5% or less in neonates.
May be used in conjunction with 1 drop of phenylephrine 2.5% ophthalmic solution.

Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.

Pharmacology

Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Maximal mydriasis occurs 30 to 60 minutes following administration. Recovery of accommodation occurs in 6 to 24 hours. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

Adverse Effects

Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth, restlessness, delayed gastric emptying and decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.

Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

Special Considerations/Preparation

Supplied as ophthalmic solution 0.5% in 15-mL Drop-tainers, and 1% and 2% concentrations in 2-, 5- and 15-mL Drop-tainers. Store away from heat. **Do not refrigerate.**A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 5-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.

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Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

Special Considerations/Preparation

Supplied as ophthalmic solution 0.5% in 15-mL Drop-tainers, and 1% and 2% concentrations in 2-, 5- and 15-mL Drop-tainers. Store away from heat. **Do not refrigerate.**A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 5-mL Drop-tainers.
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- Isenberg S, Everett S: Cardiovascular effects of mydriatics in low-birth-weight infants. *J Pediatr* 1984;105:111-112.
- Product Information, Falcon, 2004

1.46 DOBUTamine

Title DOBUTamine

Dose

2 to 25 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects. Use a large vein for IV.

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Dobutamine): Mix 30 mL of 800 mcg/mL solution using dobutamine concentration of 12.5 mg/mL.
800 mcg/mL = 0.8 mg/mL
0.8 mg/mL x 30 mL = 24 mg dobutamine
***24 mg ÷ 12.5 mg/mL = 1.9 mL of dobutamine**
Add 1.9 mL of dobutamine (12.5 mg/mL) to 28.1 mL of compatible solution (eg, D_5 W) to yield 30 mL of infusion solution with a concentration of 800 mcg/mL.

Dobutamine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
500	2.5	0.3
	5	0.6
	7.5	0.9

	10	1.2
800	2.5	0.19
	5	0.38
	7.5	0.56
	10	0.75
1000	2.5	0.15
	5	0.3
	7.5	0.45
	10	0.6
1600	2.5	0.094
	5	0.19
	7.5	0.28
	10	0.38
2000	2.5	0.075
	5	0.15
	7.5	0.23
	10	0.3
3200	2.5	0.047
	5	0.094
	7.5	0.14
	10	0.19
4000	2.5	0.038
	5	0.075
	7.5	0.11
	10	0.15

Uses

Treatment of hypoperfusion and hypotension, especially if related to myocardial dysfunction.

Pharmacology

Synthetic catecholamine with primarily β_1-adrenergic activity. Inotropic vasopressor. Increases myocardial contractility, cardiac index, oxygen delivery, and oxygen consumption. Decreases systemic and pulmonary vascular resistance (adults). Dobutamine has a more prominent effect on cardiac output than dopamine but less of an effect on blood pressure. Onset of action is 1 to 2 minutes after IV administration, with peak effect in 10 minutes. Must be administered by continuous IV infusion because of rapid metabolism of drug. Serum half-life is several minutes. Metabolized in

the liver by sulfoconjugation to an inactive compound. There is wide interpatient variability in plasma clearance due to differences in metabolism and renal excretion.

Adverse Effects

May cause hypotension if patient is hypovolemic. Volume loading is recommended before starting dobutamine therapy. Tachycardia occurs at high dosage. Arrhythmias, hypertension, and cutaneous vasodilation. Increases myocardial oxygen consumption. Tissue ischemia occurs with infiltration.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring preferable. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Supplied as 250 mg per 20-mL vial (12.5 mg/mL) and premixed bags in concentrations of 1, 2, and 4 mg/mL. Diluted solutions for infusion should be used within 24 hours. Solutions containing dobutamine and dextrose may exhibit a pink color which will increase with time due to oxidation of the drug. There is no significant loss of potency.

There are no specific data regarding the compatibility of dobutamine and fat emulsions. Dobutamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dobutamine and fat emulsion together; dobutamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amiodarone, atropine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, caspofungin, ceftazidime, ciprofloxacin, dopamine, enalaprilat, epinephrine, famotidine, fentanyl, fluconazole, flumazenil, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, phentolamine, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, aminophylline, cefepime, bumetanide, diazepam, digoxin, furosemide, ibuprofen lysine, indomethacin, micafungin, phenytoin, phytonadione, piperacillin-tazobactam, and sodium bicarbonate.

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	10	0.75

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	5	0.3
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1600	2.5	0.094
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	10	0.38
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Uses

Treatment of hypoperfusion and hypotension, especially if related to myocardial dysfunction.

Pharmacology

Synthetic catecholamine with primarily β_1-adrenergic activity. Inotropic vasopressor. Increases myocardial contractility, cardiac index, oxygen delivery, and oxygen consumption. Decreases systemic and pulmonary vascular resistance (adults). Dobutamine has a more prominent effect on cardiac output than dopamine but less of an effect on blood pressure. Onset of action is 1 to 2 minutes after IV administration, with peak effect in 10 minutes. Must be administered by continuous IV infusion because of rapid metabolism of drug. Serum half-life is several minutes. Metabolized in the liver by sulfoconjugation to an inactive compound. There is wide interpatient variability in plasma clearance due to differences in metabolism and renal excretion.

Adverse Effects

May cause hypotension if patient is hypovolemic. Volume loading is recommended before starting dobutamine therapy. Tachycardia occurs at high dosage. Arrhythmias, hypertension, and cutaneous vasodilation. Increases myocardial oxygen consumption. Tissue ischemia occurs with infiltration.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring preferable. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Supplied as 250 mg per 20-mL vial (12.5 mg/mL) and premixed bags in concentrations of 1, 2, and 4 mg/mL. Diluted solutions for infusion should be used within 24 hours. Solutions containing dobutamine and dextrose may exhibit a pink color which will increase with time due to oxidation of the drug. There is no significant loss of potency.

There are no specific data regarding the compatibility of dobutamine and fat emulsions. Dobutamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dobutamine and fat emulsion together; dobutamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amiodarone, atropine, aztreonam, caffeine citrate, calcium chloride, calcium gluconate, caspofungin, ceftazidime, ciprofloxacin, dopamine, enalaprilat, epinephrine, famotidine, fentanyl, fluconazole, flumazenil, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, phentolamine, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, aminophylline, cefepime, bumetanide, diazepam, digoxin, furosemide, ibuprofen lysine, indomethacin, micafungin, phenytoin, phytonadione, piperacillin-tazobactam, and sodium bicarbonate.

References

- Noori S, Friedlich P, Seri I: The use of dobutamine in the treatment of neonatal cardiovascular compromise. *NeoReviews* 2004;5:e22-e26.
- Berg RA, Donnerstein RL, Padbury JF: Dobutamine infusion in stable, critically ill children: pharmacokinetics and hemodynamic actions. *Crit Care Med* 1993;21:678-86.
- Martinez AM, Padbury JF, Thio S: Dobutamine pharmacokinetics and cardiovascular responses in critically ill neonates. *Pediatrics* 1992;89:47.
- Leier CV, Unverferth DV: Dobutamine. *Ann Intern Med* 1983;99:490.
- Perkin RM, Levin DL, Webb R, et al: Dobutamine: A hemodynamic evaluation in children with shock. *J Pediatr* 1982;100:977.

- Product Information, Bedford, 2005.

1.47 DOPamine

Title DOPamine

Dose

2 to 20 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects. Use a large vein for IV.

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Dopamine): Mix 30 mL of 800 mcg/mL solution using dopamine concentration of 40 mg/mL.
800 mcg/mL = 0.8 mg/mL
0.8 mg/mL x 30 mL = 24 mg dopamine
***24 mg ÷ 40 mg/mL = 0.6 mL of dopamine**
Add 0.6 mL of dopamine (40 mg/mL) to 29.4 mL of compatible solution (eg, D_5W) to yield 30 mL of infusion solution with a concentration of 800 mcg/mL.

Dopamine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
500	2.5	0.3
	5	0.6
	7.5	0.9
	10	1.2
800	2.5	0.19
	5	0.38
	7.5	0.56
	10	0.75
1000	2.5	0.15
	5	0.3
	7.5	0.45
	10	0.6
1600	2.5	0.094
	5	0.19
	7.5	0.28

	10	0.38
2000	2.5	0.075
	5	0.15
	7.5	0.23
	10	0.3
3200	2.5	0.047
	5	0.094
	7.5	0.14
	10	0.19

Uses

Treatment of hypotension.

Black Box Warning

Tissue sloughing may occur with IV infiltration. According to the manufacturer's black box warning, to prevent sloughing and necrosis in areas of extravasation, the area should be infiltrated as soon as possible with a saline solution containing phentolamine mesylate.
Suggested treatment for extravasation: Inject a 0.5 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Pharmacology

Catecholamine that is metabolized rapidly. Serum half-life is 2 to 5 minutes, but clearance is quite variable. Dopamine increases blood pressure primarily by increasing systemic vascular resistance via Î±-adrenergic effects. Effects on cardiac output vary with gestational age and baseline stroke volume. Selective renal vasodilation associated with increases in urine output has been noted in preterm neonates at doses of 2 to 5 mcg/kg/minute. No changes in mesenteric or cerebral blood flow were observed. Mechanism of action in neonates is controversial. Relative effects of dopamine at different doses are uncertain because of developmental differences in 1) endogenous norepinephrine stores, 2) Î±-adrenergic, β-adrenergic, and dopaminergic receptor functions, and 3) the ability of the neonatal heart to increase stroke volume. Responses tend to be individualized. Use higher doses with caution in patients with persistent pulmonary hypertension of the newborn.

Adverse Effects

Tachycardia and arrhythmias. May increase pulmonary artery pressure. Reversible suppression of prolactin and thyrotropin secretion.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is preferable. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and infiltration.

Special Considerations/Preparation

Available in 40-mg/mL, 80-mg/mL, and 160-mg/mL vials for injection and premixed bags in concentrations of 800, 1600, and 3200 mcg/mL. Diluted solutions stable for 24 hours. **Admixtures exhibiting a color change should not be used.**

There are no specific data regarding the compatibility of dopamine and fat emulsions. Dopamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dopamine and fat emulsion together; dopamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, chloramphenicol, dobutamine, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, flumazenil, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, lidocaine, linezolid, lorazepam, meropenem, metronidazole, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, oxacillin, pancuronium bromide, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, tobramycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, amphotericin B, ampicillin, cefepime, furosemide, indomethacin, insulin, penicillin G, and sodium bicarbonate.

References

- Valverde E, Pellicer A, Madero R, et al: Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. *Pediatrics* 2006;117:e1213-e1222.
- Lynch SK, Lemley KV, Polak MJ: The effect of dopamine on glomerular filtration rate in normotensive, oliguric premature neonates. *Pediatr Nephrol* 2003;18:649-652.
- Seri I, Abbasi S, Wood DC, Gerdes JS: Regional hemodynamic effects of dopamine in the sick preterm neonate. *J Pediatr* 1998;133:728-734.
- Seri I: Cardiovascular, renal, and endocrine actions of dopamine in neonates and children. *J Pediatr* 1995;126:333.
- Filippi L, Pezzati M, Cecchi A, et al: Dopamine infusion and anterior pituitary gland function in very low birth weight infants. *Biol Neonate* 2006;89:274-280.

- Van den Berghe G, de Zegher F, Lauwers P: Dopamine suppresses pituitary function in infants and children. *Crit Care Med* 1994;22:1747.
- Roze JC, Tohier C, Maingueneau C, et al : Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;69:59-63.
- Padbury JF, Agata Y, Baylen BG, et al: Dopamine pharmacokinetics in critically ill newborn infants. *J Pediatr* 1987;110:293.
- DiSessa TG, Leitner M, Ti CC, et al: The cardiovascular effects of dopamine in the severely asphyxiated neonate. *J Pediatr* 1981;99:772.
- Product Information, American Regent, 2001.

Title DOPamine

Dose

2 to 20 mcg/kg per minute continuous IV infusion. Begin at a low dose and titrate by monitoring effects. Use a large vein for IV.

Solution Preparation Calculations

To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

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Example (for Dopamine): Mix 30 mL of 800 mcg/mL solution using dopamine concentration of 40 mg/mL.
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Dopamine Titration Chart

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	5	0.38
	7.5	0.56
	10	0.75
1000	2.5	0.15
	5	0.3

	7.5	0.45
	10	0.6
1600	2.5	0.094
	5	0.19
	7.5	0.28
	10	0.38
2000	2.5	0.075
	5	0.15
	7.5	0.23
	10	0.3
3200	2.5	0.047
	5	0.094
	7.5	0.14
	10	0.19

Uses

Treatment of hypotension.

Black Box Warning

Tissue sloughing may occur with IV infiltration. According to the manufacturer's black box warning, to prevent sloughing and necrosis in areas of extravasation, the area should be infiltrated as soon as possible with a saline solution containing phentolamine mesylate.
Suggested treatment for extravasation: Inject a 0.5 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Pharmacology

Catecholamine that is metabolized rapidly. Serum half-life is 2 to 5 minutes, but clearance is quite variable. Dopamine increases blood pressure primarily by increasing systemic vascular resistance via Î±-adrenergic effects. Effects on cardiac output vary with gestational age and baseline stroke volume. Selective renal vasodilation associated with increases in urine output has been noted in preterm neonates at doses of 2 to 5 mcg/kg/minute. No changes in mesenteric or cerebral blood flow were observed. Mechanism of action in neonates is controversial. Relative effects of dopamine at different doses are uncertain because of developmental differences in 1) endogenous norepinephrine stores, 2) Î±-adrenergic, β-adrenergic, and dopaminergic receptor functions, and 3) the ability of the neonatal heart to increase stroke volume. Responses tend to be individualized. Use higher doses with caution in patients with persistent pulmonary hypertension of the newborn.

Adverse Effects

Tachycardia and arrhythmias. May increase pulmonary artery pressure. Reversible suppression of prolactin and thyrotropin secretion.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is preferable. Assess urine output and peripheral perfusion frequently. Observe IV site closely for blanching and infiltration.

Special Considerations/Preparation

Available in 40-mg/mL, 80-mg/mL, and 160-mg/mL vials for injection and premixed bags in concentrations of 800, 1600, and 3200 mcg/mL. Diluted solutions stable for 24 hours. **Admixtures exhibiting a color change should not be used.**

There are no specific data regarding the compatibility of dopamine and fat emulsions. Dopamine is most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dopamine and fat emulsion together; dopamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, D_5NS, $D_{10}W$, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aminophylline, amiodarone, aztreonam, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, chloramphenicol, dobutamine, enalaprilat, epinephrine, esmolol, famotidine, fentanyl, fluconazole, flumazenil, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, lidocaine, linezolid, lorazepam, meropenem, metronidazole, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, oxacillin, pancuronium bromide, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, tobramycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, alteplase, amphotericin B, ampicillin, cefepime, furosemide, indomethacin, insulin, penicillin G, and sodium bicarbonate.

References

- Valverde E, Pellicer A, Madero R, et al: Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. *Pediatrics* 2006;117:e1213-e1222.
- Lynch SK, Lemley KV, Polak MJ: The effect of dopamine on glomerular filtration rate in normotensive, oliguric premature neonates. *Pediatr Nephrol* 2003;18:649-652.

- Seri I, Abbasi S, Wood DC, Gerdes JS: Regional hemodynamic effects of dopamine in the sick preterm neonate. *J Pediatr* 1998;133:728-734.
- Seri I: Cardiovascular, renal, and endocrine actions of dopamine in neonates and children. *J Pediatr* 1995;126:333.
- Filippi L, Pezzati M, Cecchi A, et al: Dopamine infusion and anterior pituitary gland function in very low birth weight infants. *Biol Neonate* 2006;89:274-280.
- Van den Berghe G, de Zegher F, Lauwers P: Dopamine suppresses pituitary function in infants and children. *Crit Care Med* 1994;22:1747.
- Roze JC, Tohier C, Maingueneau C, et al : Response to dobutamine and dopamine in the hypotensive very preterm infant. *Arch Dis Child* 1993;69:59-63.
- Padbury JF, Agata Y, Baylen BG, et al: Dopamine pharmacokinetics in critically ill newborn infants. *J Pediatr* 1987;110:293.
- DiSessa TG, Leitner M, Ti CC, et al: The cardiovascular effects of dopamine in the severely asphyxiated neonate. *J Pediatr* 1981;99:772.
- Product Information, American Regent, 2001.

1.48 DT\Td Vaccine

Title DT/Td Vaccine

Dose

0.5 mL IM [1] . Immunize premature infants according to their postnatal age. Please refer to most recent AAP/ACIP immunization schedule.

Administration

DT Vaccine
Administer IM in the anterolateral thigh. **When giving multiple vaccines, use a separate syringe for each and give at different sites.**Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [1] .

Uses

Immunoprophylaxis against diphtheria and tetanus for infants who have a contraindication for pertussis vaccine [1] .

Contraindications/Precautions **Contraindicated** in infants and children with a history of systemic allergic reaction (eg, anaphylaxis) associated with a previous dose of DT or vaccine component. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [2] .

Pharmacology

Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins. DT vaccine is an aluminum-salt-adsorbed preparation. Contains 6.7 Lf (flocculation units) of diphtheria toxoid and 5 Lf of tetanus toxoid [1] .

Adverse Effects

Fever (less than 39 degrees C; less than 102.2 degrees F) and/or small local reactions are common (35% to 55%). Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [1] .

Monitoring

Observe injection site for erythema, induration (common), palpable nodule (uncommon), or sterile abscess (rare).

Special Considerations/Preparation

DT vaccine (for pediatric use) is available as 0.5-mL single-dose vials. Store refrigerated. **Do not freeze**. Shake vial well before withdrawing each dose. Do not use if product contains clumps that cannot be resuspended with vigorous shaking. Normal appearance is a turbid whitish suspension [1] .

References

- Product Information: diphtheria toxoid tetanus toxoid adsorbed (for pediatric use) intramuscular injection, diphtheria toxoid tetanus toxoid adsorbed (for pediatric use) intramuscular injection. sanofi pasteur (per manufacturer), Swiftwater, PA, Dec, 2005.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

Title DT/Td Vaccine

Dose

0.5 mL IM [1] . Immunize premature infants according to their postnatal age. Please refer to most recent AAP/ACIP immunization schedule.

Administration

DT Vaccine
Administer IM in the anterolateral thigh. **When giving multiple vaccines, use a separate syringe for each and give at different sites.**Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [1] .

Uses

Immunoprophylaxis against diphtheria and tetanus for infants who have a contraindication for pertussis vaccine [1] .

Contraindications/Precautions **Contraindicated** in infants and children with a history of systemic allergic reaction (eg, anaphylaxis) associated with a previous dose of DT or vaccine component. Vaccination should be deferred in patients with moderate or severe acute illness,

with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [2] .

Pharmacology

Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins. DT vaccine is an aluminum-salt-adsorbed preparation. Contains 6.7 Lf (flocculation units) of diphtheria toxoid and 5 Lf of tetanus toxoid [1] .

Adverse Effects

Fever (less than 39 degrees C; less than 102.2 degrees F) and/or small local reactions are common (35% to 55%). Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [1] .

Monitoring

Observe injection site for erythema, induration (common), palpable nodule (uncommon), or sterile abscess (rare).

Special Considerations/Preparation

DT vaccine (for pediatric use) is available as 0.5-mL single-dose vials. Store refrigerated. **Do not freeze**. Shake vial well before withdrawing each dose. Do not use if product contains clumps that cannot be resuspended with vigorous shaking. Normal appearance is a turbid whitish suspension [1] .

References

- Product Information: diphtheria toxoid tetanus toxoid adsorbed (for pediatric use) intramuscular injection, diphtheria toxoid tetanus toxoid adsorbed (for pediatric use) intramuscular injection. sanofi pasteur (per manufacturer), Swiftwater, PA, Dec, 2005.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

1.49 DTaP Vaccine

Title DTaP Vaccine

Dose

0.5 mL IM in the anterolateral thigh. Five-dose series is started at 2 months of age (minimum age, 6 weeks) [1] [2] [3] [4] . Immunize premature infants according to their postnatal age.

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] [3] [4] .

Uses

Preferred immunoprophylaxis against diphtheria, tetanus, and pertussis [2] [3] [4] [5] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine, including yeast, neomycin, and polymyxin B. **Contraindications** to further DTaP vaccination: in children who develop encephalopathy within 7 days following any DTP vaccination, DT vaccine should be substituted for the remaining doses; in children who develop an immediate anaphylactic reaction, further immunization with any of the three antigens should be deferred; and in children with a progressive neurologic disorder, it is prudent to delay the initial dose of DTaP vaccine until further observation and study have clarified their neurologic status and the effect of treatment [6] .
Some infants born prematurely have experience apnea following IM vaccination [7] .
For infants and children with progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, and progressive encephalopathy, defer vaccination until neurologic status is clarified and stabilized. Those infants with stable neurologic conditions, including well-controlled seizures, may be vaccinated [6] .
Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [6] .
Precautions to further DTaP vaccination (the benefits of administering DTaP may exceed risks in areas with a high incidence of pertussis; otherwise administer DT vaccine) include [6] :

- Temperature 40.5 degrees C (105 degrees F) or greater within 48 hours with no other cause
- Hypotonic-hyporesponsive collapse or shock-like state within 48 hours
- Inconsolable crying (3 hours or greater) occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

Pharmacology

DTaP vaccines are aluminum-salt-adsorbed preparations. All acellular pertussis vaccines contain inactivated pertussis toxoid, but vary in the inclusion and concentration of four other pertussis antigens. Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins. Daptacel®, Infanrix® and Tripedia® are thimerosal-free. Each dose of Daptacel®contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 5 mcg fimbriae types 2 and 3, 5 mcg FHA, and 3 mcg pertactin, with 3.3 mg 2-phenoxyethanol as a preservative. Each dose of Infanrix® contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 mcg inactivated toxin, 25 mcg FHA, and 8 mcg pertactin, with 2.5 mg 2-phenoxyethanol as a preservative. Each dose of Tripedia® contains 6.7 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 23.4 mcg inactivated toxin, and 23.4 mcg FHA [2] [3] [4] .

Adverse Effects

Fever, drowsiness, loss of appetite, and/or small local reactions are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [2] [3] [4] .

Monitoring

Observe injection site for pain, erythema, and induration (common).

Special Considerations/Preparation

FDA-licensed DTaP vaccines:
Infanrix® (GlaxoSmithKline), available in single-dose vials and single-dose prefilled syringes.
Daptacel® (Sanofi Pasteur), available in single-dose vials and multi-dose vials.
Tripedia® (Sanofi Pasteur), available in single-dose vials.

Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze.**Shake vial well before withdrawing dose. Do not use if product contains clumps that cannot be resuspended with vigorous shaking. Normal appearance is a homogeneous (Tripedia® and Daptacel®) or turbid (Infanrix®) white suspension [2] [3] [4] .

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: INFANRIX(R) IM injection, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2010.

- Product Information: DAPTACEL(R) suspension for IM injection, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed suspension for IM injection. Sanofi Pasteur Inc (per Manufacturer), Swiftwater, PA, Jan, 2009.

- Product Information: TRIPEDIA(R) IM injection, diphtheria, tetanus toxoids, acellular pertussis adsorbed vaccine IM injection. Sanofi Pasteur Inc, Swiftwater, PA, Dec1, 2005.

- CDC : Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committe on Immunization Practices (ACIP). MMWR 1997; 46(RR-): 1-25.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

- Product Information: DAPTACEL(R) intramuscular injection, diphtheria tetanus toxoids acellular pertussis vaccine adsorbed intramuscular injection. Sanofi Pasteur Inc. (per FDA), Swiftwater, PA, Jul, 2012.

Title DTaP Vaccine

Dose

0.5 mL IM in the anterolateral thigh. Five-dose series is started at 2 months of age (minimum age, 6 weeks) [1] [2] [3] [4] . Immunize premature infants according to their postnatal age.

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] [3] [4] .

Uses

Preferred immunoprophylaxis against diphtheria, tetanus, and pertussis [2] [3] [4] [5] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine, including yeast, neomycin, and polymyxin B. **Contraindications** to further DTaP vaccination: in children who develop encephalopathy within 7 days following any DTP vaccination, DT vaccine should be substituted for the remaining doses; in children who develop an immediate anaphylactic reaction, further immunization with any of the three antigens should be deferred; and in children with a progressive neurologic disorder, it is prudent to delay the initial dose of DTaP vaccine until further observation and study have clarified their neurologic status and the effect of treatment [6] .
Some infants born prematurely have experience apnea following IM vaccination [7] .
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Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [6] .
Precautions to further DTaP vaccination (the benefits of administering DTaP may exceed risks in areas with a high incidence of pertussis; otherwise administer DT vaccine) include [6] :

- Temperature 40.5 degrees C (105 degrees F) or greater within 48 hours with no other cause
- Hypotonic-hyporesponsive collapse or shock-like state within 48 hours
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- Convulsions with or without fever occurring within 3 days

Pharmacology

DTaP vaccines are aluminum-salt-adsorbed preparations. All acellular pertussis vaccines contain inactivated pertussis toxoid, but vary in the inclusion and concentration of four other pertussis antigens. Diphtheria and tetanus toxoids are prepared by formaldehyde treatment of the respective toxins. Daptacel®, Infanrix® and Tripedia® are thimerosal-free. Each dose of Daptacel®contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 5 mcg fimbriae types 2 and 3, 5 mcg FHA, and 3 mcg pertactin, with 3.3 mg 2-phenoxyethanol as a preservative. Each dose of Infanrix® contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 mcg inactivated toxin, 25 mcg FHA, and 8 mcg pertactin, with 2.5 mg 2-phenoxyethanol as a preservative. Each dose of Tripedia® contains 6.7 Lf diphtheria toxoid, 5 Lf tetanus toxoid, 23.4 mcg inactivated toxin, and 23.4 mcg FHA [2] [3] [4] .

Adverse Effects

Fever, drowsiness, loss of appetite, and/or small local reactions are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [2] [3] [4] .

Monitoring

Observe injection site for pain, erythema, and induration (common).

Special Considerations/Preparation

FDA-licensed DTaP vaccines:
Infanrix® (GlaxoSmithKline), available in single-dose vials and single-dose prefilled syringes.
Daptacel® (Sanofi Pasteur), available in single-dose vials and multi-dose vials.
Tripedia® (Sanofi Pasteur), available in single-dose vials.

Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze.**Shake vial well before withdrawing dose. Do not use if product contains clumps that cannot be resuspended with vigorous shaking. Normal appearance is a homogeneous (Tripedia® and Daptacel®) or turbid (Infanrix®) white suspension [2] [3] [4] .

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: INFANRIX(R) IM injection, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2010.

- Product Information: DAPTACEL(R) suspension for IM injection, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed suspension for IM injection. Sanofi Pasteur Inc (per Manufacturer), Swiftwater, PA, Jan, 2009.

- Product Information: TRIPEDIA(R) IM injection, diphtheria, tetanus toxoids, acellular pertussis adsorbed vaccine IM injection. Sanofi Pasteur Inc, Swiftwater, PA, Dec1, 2005.

- CDC : Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committe on Immunization Practices (ACIP). MMWR 1997; 46(RR-): 1-25.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

- Product Information: DAPTACEL(R) intramuscular injection, diphtheria tetanus toxoids acellular pertussis vaccine adsorbed intramuscular injection. Sanofi Pasteur Inc. (per FDA), Swiftwater, PA, Jul, 2012.

1.50 DTaP-HepB-IPV Combination Vaccine

Title DTaP-HepB-IPV Combination Vaccine

Dose

0.5 mL IM in the anterolateral thigh. Shake vial vigorously before withdrawing dose [1] .

Pediarix® should not be administered to any infant before the age of 6 weeks. Only monovalent hepatitis B vaccine can be used for the birth dose [1] .

Please refer to the most recent AAP/ACIP immunization schedule. It is recommended that premature infants should be immunized according to their postnatal age; however, inadequate seroconversion against hepatitis B may occur in chronically ill premature infants.

Uses

Immunoprophylaxis against diphtheria, tetanus, pertussis, hepatitis B, and polio. Using Pediarix® to complete the hepatitis B vaccination series in infants who were born of HBsAg-positive mothers and who received monovalent Hepatitis B vaccine (Recombinant) has not been studied [1] [2] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine, including yeast, neomycin, and polymyxin B. **Contraindications** to further DTaP vaccination: in children who develop encephalopathy within 7 days following any DTP vaccination, DT vaccine should be substituted for the remaining doses; in children who develop an immediate anaphylactic reaction, further immunization with any of the three antigens should be deferred; and in children with a progressive neurologic disorder, it is prudent to delay the initial dose of DTaP

vaccine until further observation and study have clarified their neurologic status and the effect of treatment [3] [4] .
For infants and children with progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, and progressive encephalopathy, defer vaccination until neurologic status is clarified and stabilized. Those infants with stable neurologic conditions, including well-controlled seizures, may be vaccinated [3] .
Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [3] .
Syncope, at times associated other neurologic signs such as tonic-clonic movements, paresthesias, and visual disturbances, has been reported; monitoring recommended [1] .
Use caution in patients with latex allergy; tip cap and rubber plunger of the needleless prefilled syringes may contain dry natural latex rubber; vials do not contain latex [1] .
Precautions to further DTaP vaccination (the benefits of administering DTaP may exceed risks in areas with a high incidence of pertussis; otherwise administer DT vaccine) include [3] :

- Temperature 40.5 degrees C (105 degrees F) or greater within 48 hours with no other cause
- Hypotonic-hyporesponsive collapse or shock-like state within 48 hours
- Inconsolable crying (3 hours or greater) occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

Pharmacology

Each dose of Pediarix® contains the type and amount of diphtheria and tetanus toxoids and pertussis antigens as Infanrix®, and hepatitis B virus antigens as Engerix-B ®. The poliovirus component of DTaP-HepB-IPV contains the same strains and quantity of inactivated poliovirus Types 1, 2, and 3 as IPV from a different manufacturer (IPOL®, Sanofi Pasteur). The immunologic responses following 3 doses of DTaP-HepB-IPV were generally similar to those following 3 doses of the individual vaccines administered separately [1] .

Adverse Effects

Fever is more common (approximately 20%) after Pediarix® than with the individual component vaccines administered separately [1] . Other local and systemic adverse events occur at similar rates. Apnea, bradycardia, and desaturation events are common in premature infants for 48 hours after vaccination [5] .

Monitoring

Cardiorespiratory monitoring and pulse oximetry are recommended for premature infants who remain hospitalized at the time of vaccination.

Special Considerations/Preparation

Pediarix® is supplied as a turbid white suspension in single dose (0.5 mL) vials (contain no latex), and in disposable prefilled Tip-Lock® syringes, which contain latex. Shake

well prior to administration. Do not use if resuspension does not occur after vigorous shaking. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze**. Discard if the vaccine has been frozen [1] .

References

- Product Information: PEDIARIX(R) intramuscular injection suspension, diphtheria tetanus toxoids acellular pertussis adsorbed hepatitis B recombinant inactivated poliovirus vaccine intramuscular injection suspension. GlaxoSmithKline (per FDA), Research Triangle Park, NC, Jul, 2012.

- CDC : Notice to readers: FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (Pediarix(TM)) for use in infants. MMWR 2003; 52(10): 203-204.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

- Product Information: PEDIARIX(R) IM injection, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis b [recombinant] and inactivated poliovirus vaccine IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2010.

- Pfister RE, Aeschbach V, Niksic-Stuber V et al: Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. J Pediatr Jul, 2004; 145(1): 58-66.

Title DTaP-HepB-IPV Combination Vaccine

Dose

0.5 mL IM in the anterolateral thigh. Shake vial vigorously before withdrawing dose [1] .

Pediarix® should not be administered to any infant before the age of 6 weeks. Only monovalent hepatitis B vaccine can be used for the birth dose [1] .

Please refer to the most recent AAP/ACIP immunization schedule. It is recommended that premature infants should be immunized according to their postnatal age; however, inadequate seroconversion against hepatitis B may occur in chronically ill premature infants.

Uses

Immunoprophylaxis against diphtheria, tetanus, pertussis, hepatitis B, and polio. Using Pediarix® to complete the hepatitis B vaccination series in infants who were born of HBsAg-positive mothers and who received monovalent Hepatitis B vaccine (Recombinant) has not been studied [1] [2] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine, including yeast, neomycin, and polymyxin B. **Contraindications** to further DTaP vaccination: in children who develop encephalopathy within 7 days following any DTP vaccination, DT vaccine should be substituted for the remaining doses; in children who develop an immediate anaphylactic reaction, further immunization with any of the three antigens should be deferred; and in children with a progressive neurologic disorder, it is prudent to delay the initial dose of DTaP vaccine until further observation and study have clarified their neurologic status and the effect of treatment [3] [4] .
For infants and children with progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, and progressive encephalopathy, defer vaccination until neurologic status is clarified and stabilized. Those infants with stable neurologic conditions, including well-controlled seizures, may be vaccinated [3] .
Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [3] .
Syncope, at times associated other neurologic signs such as tonic-clonic movements, paresthesias, and visual disturbances, has been reported; monitoring recommended [1] .
Use caution in patients with latex allergy; tip cap and rubber plunger of the needleless prefilled syringes may contain dry natural latex rubber; vials do not contain latex [1] .
Precautions to further DTaP vaccination (the benefits of administering DTaP may exceed risks in areas with a high incidence of pertussis; otherwise administer DT vaccine) include [3] :

- Temperature 40.5 degrees C (105 degrees F) or greater within 48 hours with no other cause
- Hypotonic-hyporesponsive collapse or shock-like state within 48 hours
- Inconsolable crying (3 hours or greater) occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

Pharmacology

Each dose of Pediarix® contains the type and amount of diphtheria and tetanus toxoids and pertussis antigens as Infanrix®, and hepatitis B virus antigens as Engerix-B ®. The poliovirus component of DTaP-HepB-IPV contains the same strains and quantity of inactivated poliovirus Types 1, 2, and 3 as IPV from a different manufacturer (IPOL®, Sanofi Pasteur). The immunologic responses following 3 doses of DTaP-HepB-IPV were generally similar to those following 3 doses of the individual vaccines administered separately [1] .

Adverse Effects

Fever is more common (approximately 20%) after Pediarix® than with the individual component vaccines administered separately [1] . Other local and systemic adverse events occur at similar rates. Apnea, bradycardia, and desaturation events are common in premature infants for 48 hours after vaccination [5] .

Monitoring

Cardiorespiratory monitoring and pulse oximetry are recommended for premature infants who remain hospitalized at the time of vaccination.

Special Considerations/Preparation

Pediarix® is supplied as a turbid white suspension in single dose (0.5 mL) vials (contain no latex), and in disposable prefilled Tip-Lock® syringes, which contain latex. Shake well prior to administration. Do not use if resuspension does not occur after vigorous shaking. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze**. Discard if the vaccine has been frozen [1] .

References

- Product Information: PEDIARIX(R) intramuscular injection suspension, diphtheria tetanus toxoids acellular pertussis adsorbed hepatitis B recombinant inactivated poliovirus vaccine intramuscular injection suspension. GlaxoSmithKline (per FDA), Research Triangle Park, NC, Jul, 2012.

- CDC : Notice to readers: FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (Pediarix(TM)) for use in infants. MMWR 2003; 52(10): 203-204.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

- Product Information: PEDIARIX(R) IM injection, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis b [recombinant] and inactivated poliovirus vaccine IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2010.

- Pfister RE, Aeschbach V, Niksic-Stuber V et al: Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. J Pediatr Jul, 2004; 145(1): 58-66.

1.51 Dexamethasone

Title Dexamethasone

Dose

DART Trial Protocol: 0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 3 days, 0.025 mg/kg/dose every 12 hours for 2 days, and 0.01 mg/kg/dose every 12 hours for 2 days. Doses may be administered IV slow push or orally.

Uses

Low-dose dexamethasone has been used successfully to facilitate extubation and improve lung function acutely in preterm infants at high risk for developing chronic lung disease. Low doses have not been associated with substantial effects with regard to

mortality or development of bronchopulmonary dysplasia (BPD) at 36 weeks [1] [2] [3] . High-dose dexamethasone (eg, 0.5 mg/kg/day) has been associated with a reduction in the incidence of BPD, but also an increased risk for short-term adverse effects (hyperglycemia, hypertension, gastrointestinal perforation, infection risk) and adverse long-term neurodevelopmental outcomes (cerebral palsy (CP)) [1] [4] [5] . A review of meta-analyses looking at the timing and dosage of postnatal steroids found the development of CP was associated with early steroid use (first week of life) in patients at lower risk for BPD [1] . A prospective cohort study found that higher steroid exposure was associated with an increased risk for CP [6] . High-dose dexamethasone in the first week of life is generally not recommended for the prevention of BPD or for the treatment of BPD after the first week of life [7] [4] ; however, the judicious use of late dexamethasone may be considered for infants who cannot be weaned from the ventilator [7] [8] .

Pharmacology

Stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves integrity of alveolar-capillary barrier, inhibits prostaglandin and leukotriene production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm. Hyperglycemia is caused by inhibition of glucose uptake into cells and decreased glucokinase activity. Increased triglyceride synthesis is due to hyperinsulinemia and increased acetyl-CoA carboxylase activity. Blood pressure is increased due to increased responsiveness to endogenous catecholamines. Increases protein catabolism with potential loss of muscle tissue, increases urinary calcium excretion because of bone resorption, and suppresses pituitary ACTH secretion. Biologic half-life is 36 to 54 hours.

Adverse Effects

The February 2002 AAP and CPS statement strongly discourages routine use of dexamethasone. If dexamethasone is used for CLD risk reduction, 1) Treat only those infants at highest risk; 2) Use lower than traditional pharmacologic doses; 3) Begin treatment after Day 7 but before Day 14 of life; 4) Do not give concurrently with indomethacin; 5) Use preservative-free drug wherever possible.
The DART trial found no association with long-term morbidity, but other studies have reported an increased risk of cerebral palsy. Most evidence suggests no increase in the incidence of ROP or the need for cryotherapy. Gastrointestinal perforation and GI hemorrhage occur more frequently in patients treated beginning on Day 1 and in those also being treated concurrently with indomethacin. Hyperglycemia and glycosuria occur frequently after the first few doses, and one case of diabetic ketoacidosis has been reported. Blood pressure increases are common, and hypertension occurs occasionally. Cardiac effects noted by Day 14 of therapy include increased left ventricular wall thickness with outflow tract obstruction and transient impairment of left ventricular filling, systolic anterior motion of the mitral valve, and ST-segment depression. Other potential short-term adverse effects include sodium and water retention, hypokalemia, hypocalcemia, hypertriglyceridemia, increased risk of sepsis, renal stones (in patients receiving furosemide), osteopenia, and inhibition of growth. Adrenal insufficiency may occur secondary to pituitary suppression.

Monitoring

Assess for hyperglycemia and hyperlipidemia. Monitor blood pressure. Guaiac gastric aspirates. Echocardiogram if treating longer than 7 days.

Special Considerations/Preparation

Dexamethasone sodium phosphate for injection is available in concentrations of 4 mg/mL (benzyl alcohol preservative 10 mg/mL) and 10 mg/mL (preservative free or benzyl alcohol preservative 10 mg/mL). Stable for 30 days under refrigeration at dilutions of 0.2 mg/mL and 0.4 mg/mL in NS in PVC minibags [9] . Stable for 22 days at room temperature at dilutions of 0.1 mg/mL and 1 mg/mL in NS in polypropylene syringes [10] . Stable for 28 days under refrigeration and at room temperature at a dilution of 1 mg/mL in bacteriostatic NS in glass vials [11] . Stable for up to 14 days at room temperature at dilutions of 0.08 mg/mL and 0.6 mg/mL in D_5W in polyvinyl chloride bags [12] .
Oral solution is available in 0.5-mg/5 mL (0.1-mg/mL) and 1-mg/mL (Intensol™ concentrate) concentrations. Intensol™ concentrate contains alcohol 30%. Discard opened bottle of Intensol™ after 90 days. Tablets are available in the following strengths: 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg [13] [14] .
A 0.5 mg/mL oral suspension can be made by diluting 1 mL of the 4 mg/mL IV solution up to a total volume of 8 mL with a 1:1 mixture of Ora-Sweet® and Ora-Plus®. The oral suspension is physically and chemically stable for up to 91 days with or without refrigeration [15] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, aztreonam, caffeine citrate, cefepime, cimetidine, famotidine, fentanyl, fluconazole, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, meropenem, methadone, metoclopramide, milrinone, morphine, nafcillin, netilmicin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Glycopyrrolate, midazolam, and vancomycin.

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Title Dexamethasone

Dose

DART Trial Protocol: 0.075 mg/kg/dose every 12 hours for 3 days, 0.05 mg/kg/dose every 12 hours for 3 days, 0.025 mg/kg/dose every 12 hours for 2 days, and 0.01 mg/kg/dose every 12 hours for 2 days. Doses may be administered IV slow push or orally.

Uses

Low-dose dexamethasone has been used successfully to facilitate extubation and improve lung function acutely in preterm infants at high risk for developing chronic lung disease. Low doses have not been associated with substantial effects with regard to mortality or development of bronchopulmonary dysplasia (BPD) at 36 weeks [1] [2] [3] . High-dose dexamethasone (eg, 0.5 mg/kg/day) has been associated with a reduction in the incidence of BPD, but also an increased risk for short-term adverse effects (hyperglycemia, hypertension, gastrointestinal perforation, infection risk) and adverse long-term neurodevelopmental outcomes (cerebral palsy (CP)) [1] [4] [5] . A review of meta-analyses looking at the timing and dosage of postnatal steroids found the development of CP was associated with early steroid use (first week of life) in patients at lower risk for BPD [1] . A prospective cohort study found that higher steroid exposure was associated with an increased risk for CP [6] . High-dose dexamethasone

in the first week of life is generally not recommended for the prevention of BPD or for the treatment of BPD after the first week of life [7] [4] ; however, the judicious use of late dexamethasone may be considered for infants who cannot be weaned from the ventilator [7] [8] .

Pharmacology

Stabilizes lysosomal and cell membranes, inhibits complement-induced granulocyte aggregation, improves integrity of alveolar-capillary barrier, inhibits prostaglandin and leukotriene production, rightward shifts oxygen-hemoglobin dissociation curve, increases surfactant production, decreases pulmonary edema, relaxes bronchospasm. Hyperglycemia is caused by inhibition of glucose uptake into cells and decreased glucokinase activity. Increased triglyceride synthesis is due to hyperinsulinemia and increased acetyl-CoA carboxylase activity. Blood pressure is increased due to increased responsiveness to endogenous catecholamines. Increases protein catabolism with potential loss of muscle tissue, increases urinary calcium excretion because of bone resorption, and suppresses pituitary ACTH secretion. Biologic half-life is 36 to 54 hours.

Adverse Effects

The February 2002 AAP and CPS statement strongly discourages routine use of dexamethasone. If dexamethasone is used for CLD risk reduction, 1) Treat only those infants at highest risk; 2) Use lower than traditional pharmacologic doses; 3) Begin treatment after Day 7 but before Day 14 of life; 4) Do not give concurrently with indomethacin; 5) Use preservative-free drug wherever possible.
The DART trial found no association with long-term morbidity, but other studies have reported an increased risk of cerebral palsy. Most evidence suggests no increase in the incidence of ROP or the need for cryotherapy. Gastrointestinal perforation and GI hemorrhage occur more frequently in patients treated beginning on Day 1 and in those also being treated concurrently with indomethacin. Hyperglycemia and glycosuria occur frequently after the first few doses, and one case of diabetic ketoacidosis has been reported. Blood pressure increases are common, and hypertension occurs occasionally. Cardiac effects noted by Day 14 of therapy include increased left ventricular wall thickness with outflow tract obstruction and transient impairment of left ventricular filling, systolic anterior motion of the mitral valve, and ST-segment depression. Other potential short-term adverse effects include sodium and water retention, hypokalemia, hypocalcemia, hypertriglyceridemia, increased risk of sepsis, renal stones (in patients receiving furosemide), osteopenia, and inhibition of growth. Adrenal insufficiency may occur secondary to pituitary suppression.

Monitoring

Assess for hyperglycemia and hyperlipidemia. Monitor blood pressure. Guaiac gastric aspirates. Echocardiogram if treating longer than 7 days.

Special Considerations/Preparation

Dexamethasone sodium phosphate for injection is available in concentrations of 4 mg/mL (benzyl alcohol preservative 10 mg/mL) and 10 mg/mL (preservative free or

benzyl alcohol preservative 10 mg/mL). Stable for 30 days under refrigeration at dilutions of 0.2 mg/mL and 0.4 mg/mL in NS in PVC minibags [9] . Stable for 22 days at room temperature at dilutions of 0.1 mg/mL and 1 mg/mL in NS in polypropylene syringes [10] . Stable for 28 days under refrigeration and at room temperature at a dilution of 1 mg/mL in bacteriostatic NS in glass vials [11] . Stable for up to 14 days at room temperature at dilutions of 0.08 mg/mL and 0.6 mg/mL in D_5W in polyvinyl chloride bags [12] .
Oral solution is available in 0.5-mg/5 mL (0.1-mg/mL) and 1-mg/mL (Intensol™ concentrate) concentrations. Intensol™ concentrate contains alcohol 30%. Discard opened bottle of Intensol™ after 90 days. Tablets are available in the following strengths: 0.5, 0.75, 1, 1.5, 2, 4, and 6 mg [13] [14] .
A 0.5 mg/mL oral suspension can be made by diluting 1 mL of the 4 mg/mL IV solution up to a total volume of 8 mL with a 1:1 mixture of Ora-Sweet® and Ora-Plus®. The oral suspension is physically and chemically stable for up to 91 days with or without refrigeration [15] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, aztreonam, caffeine citrate, cefepime, cimetidine, famotidine, fentanyl, fluconazole, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, meropenem, methadone, metoclopramide, milrinone, morphine, nafcillin, netilmicin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Glycopyrrolate, midazolam, and vancomycin.

References

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1.52 Dextrose

Title Dextrose

Dose

Hypoglycemia
Initial Dose: 0.2 g/kg IV (2 mL/kg) as $D_{10}W$ [1] [2] [3] .
Maintenance Dose: Continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes at an initial glucose infusion rate of 5 to 8 mg/kg/minute. Titrate rate to attain normoglycemia [1] [2] . Higher doses may be necessary (10 to 20 mg/kg/minute) to maintain acceptable blood glucose levels, particularly in patients with persistent hyperinsulinemic hypoglycemia. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia [4] .

Hyperkalemia
Initial, continuous IV infusion of 0.5 g/kg/hour dextrose and 0.1 to 0.2 units/kg/hour regular insulin. Dextrose and insulin dosages are adjusted based on serum glucose and potassium concentrations.

Parenteral Nutrition Recommendations
An initial dextrose infusion rate of 6 to 8 mg/kg/minute, advanced as tolerated to a goal rate of 10 to 12 mg/kg/minute, is recommended in neonates. An initial rate of 4 to 8 mg/kg/minute should be considered in preterm neonates.

Administration

Generally, glucose concentrations greater than 15% should be administered via a central vein to minimize risk of phlebitis and thrombosis. However, in one study in term neonates (n=121), peripheral infusion of a 20% glucose solution did not cause a

higher rate or severity of phlebitis compared with peripheral infusion of a 15% glucose solution. Bolus doses should be administered only by slow IV injection. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia.

Uses

Treatment of hypoglycemia.

Treatment of hyperkalemia in combination with insulin.

Nutritional supplement in parenteral nutrition solutions.

Contraindications/Precautions

Contraindicated when intracranial or intraspinal hemorrhage is present. Concentrated dextrose solutions (ie, 25% and 50%) are hypertonic and may cause phlebitis and thrombosis at injection site. Rapid administration may cause significant hyperglycemia and possible hyperosmolar syndrome.

Pharmacology

Dextrose restores blood glucose levels in hypoglycemia and provides a source of carbohydrate calories. Intravenous dextrose provides 3.4 kcal/g [6] . When combined with insulin for the treatment of hyperkalemia, dextrose stimulates the sodium-potassium (Na-K) adenosine triphosphatase pump (ATP) leading to an intracellular shift of potassium.

Adverse Effects Excessive glucose provided by parenteral nutrition is associated with promotion of fat deposition, liver impairment and steatosis, and impairment of protein metabolism [5] .

Monitoring

Frequent monitoring of blood glucose is recommended; reasonable goal is blood glucose between 40 and 50 mg/dL. Monitor sodium and potassium levels closely. Obtain urine glucose and electrolytes periodically during therapy. Monitor acid-base balance and fluid status.

Special Considerations/Preparation

Available as 50% concentrated solution in 50-mL single-dose vials and syringes, and 25% concentrated solution in single-use 10-mL syringes. Also available in various other concentrations in large-volume IV solutions.

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Caspofungin, erythromycin, phenytoin, and procainamide.

References

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6. Product Information: dextrose 25% IV injection, dextrose 25% IV injection. Hospira, Inc (per DailyMed), Lake Forest, IL, Nov, 2009.

Title Dextrose

Dose

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Maintenance Dose: Continuous infusion of a 5% to 10% dextrose IV solution with appropriate maintenance electrolytes at an initial glucose infusion rate of 5 to 8 mg/kg/minute. Titrate rate to attain normoglycemia [1] [2] . Higher doses may be necessary (10 to 20 mg/kg/minute) to maintain acceptable blood glucose levels, particularly in patients with persistent hyperinsulinemic hypoglycemia. Abruptly discontinuing a dextrose infusion is not recommended due the risk for rebound hypoglycemia [4] .

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Uses

Treatment of hypoglycemia.

Treatment of hyperkalemia in combination with insulin.

Nutritional supplement in parenteral nutrition solutions.

Contraindications/Precautions

Contraindicated when intracranial or intraspinal hemorrhage is present. Concentrated dextrose solutions (ie, 25% and 50%) are hypertonic and may cause phlebitis and thrombosis at injection site. Rapid administration may cause significant hyperglycemia and possible hyperosmolar syndrome.

Pharmacology

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Adverse Effects Excessive glucose provided by parenteral nutrition is associated with promotion of fat deposition, liver impairment and steatosis, and impairment of protein metabolism [5] .

Monitoring

Frequent monitoring of blood glucose is recommended; reasonable goal is blood glucose between 40 and 50 mg/dL. Monitor sodium and potassium levels closely. Obtain urine glucose and electrolytes periodically during therapy. Monitor acid-base balance and fluid status.

Special Considerations/Preparation

Available as 50% concentrated solution in 50-mL single-dose vials and syringes, and 25% concentrated solution in single-use 10-mL syringes. Also available in various other concentrations in large-volume IV solutions.

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Caspofungin, erythromycin, phenytoin, and procainamide.

References

- Ahee P, Crowe AV: The management of hyperkalaemia in the emergency department. *J Accid Emerg Med* 2000;17:188-191.
- ASPEN Board of Directors and the Clinical Guidelines Task Force: Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN* 2002;26 (1 Suppl):1-138.
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6. Product Information: dextrose 25% IV injection, dextrose 25% IV injection. Hospira, Inc (per DailyMed), Lake Forest, IL, Nov, 2009.

1.53 Diazoxide

Title Diazoxide

Dose

2 to 5 mg/kg/dose orally given every 8 hours. Begin therapy at the higher dosage and taper by response.

Uses

Treatment of persistent (more than a few days) or severe hypoglycemia due to hyperinsulinism. Positive responses are usually seen within 48 to 72 hours, and occur in less than 50% of neonates.

Pharmacology

Diazoxide inhibits insulin release by opening ATP-sensitive potassium channels in normal pancreatic beta cells. The opening of these channels also occurs in cardiac and vascular smooth muscle, leading to decreases in blood pressure and the potential for other rare toxic cardiovascular effects. Diazoxide also reduces insulin release and counters the peripheral actions of insulin via catecholamine stimulation. The serum half-life is 10 to 24 hours in infants. Protein binding is more than 90% in adults, and it is primarily excreted unchanged by the kidneys.

Adverse Effects

Sodium and fluid retention is common--consider concurrent treatment with chlorothiazide (which may also potentiate the hyperglycemic action of diazoxide). There are a few case reports of pulmonary hypertension and cardiac failure, perhaps due to a direct toxic vascular injury. Hyperuricemia, leukopenia, and neutropenia are rare complications. Excessive hair growth and coarse facial features develop with long term use. Ketoacidosis may occur during times of intercurrent illness.

Monitoring

Periodic CBC and serum uric acid concentrations if treating long term.

Special Considerations/Preparation

Proglycem® is available as an oral suspension, 50 mg/mL concentration. Alcohol content is 7.25%. Shake well before use. Protect from light. Store at room temperature.

References

- Arnoux JB, de Lonlay P, Ribeiro MJ, et al: Congenital hyperinsulinism. *Early Hum Dev* 2010;86:287-294.
- Nebesio TD, Hoover WC, Caldwell RL, et al: Development of pulmonary hypertension in an infant treated with diazoxide. *J Pediatr Endocrinol Metab* 2007;20:939-44.
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- Product Information, Ivax, 2003

Title Diazoxide

Dose

2 to 5 mg/kg/dose orally given every 8 hours. Begin therapy at the higher dosage and taper by response.

Uses

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- Hoe FM, Thornton PS, Wanner LA, et al. Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. *J Pediatr* 2006;148:207-212.
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- Stanley CA: Hyperinsulinism in infants and children. *Pediatr Clin North Am* 1997;44:363-374.
- Product Information, Ivax, 2003

1.54 Didanosine

Title Didanosine

Dose

HIV Infection
14 days or older: The manufacturer recommends 100 mg/m^2 orally twice daily [1] ; however, guidelines for the treatment of HIV-infected children recommend that a dose of 50 mg/m^2 twice daily may be more appropriate for neonates [2] .

Administration

Preferably, administer on an empty stomach (30 minutes before or 2 hours after a feeding); however, to improve adherence, may be given with a feeding [2] . Shake well before measuring dose [1] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents. If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). Didanosine plus lamivudine or emtricitabine is considered an alternative dual-NRTI backbone option for initial therapy. The preferred dual-NRTI backbone option in neonates (as long as zidovudine resistance is not detected) is zidovudine plus lamivudine/emtricitabine [2] .

Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children 2 weeks or older [1] .

Contraindications/Precautions

Contraindicated with the coadministration of allopurinol or ribavirin [1] . Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported mainly in adults. Pancreatitis has been reported less commonly in children than in adults [2] ; suspend or discontinue treatment if signs or symptoms occur. Non-cirrhotic portal hypertension has been reported, including fatalities or cases requiring liver transplantation; the onset occurred months to years after start of therapy; discontinue therapy if signs or symptoms occur. Hepatic toxicity, worsening of hepatic dysfunction, and peripheral neuropathy have been reported; discontinuation of therapy may be warranted. Retinal changes and optic neuritis have also been reported in children as well as adults. Inflammatory response (immune reconstitution syndrome) to indolent or residual opportunistic infections may occur during initial phase of treatment [1] .

Black Box Warning

Fatal and nonfatal pancreatitis has occurred during therapy with didanosine. Didanosine should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (in adults) [1] .

Pharmacology

Didanosine is a nucleoside reverse transcriptase inhibitor active against HIV type 1. The AUC is equivalent for buffered or enteric-coated formulations. Mean bioavailability is approximately 25% in children. Cmax occurs from 0.25 to 1.5 hours following oral administration of the pediatric powder for solution. Food decreases absorption. Protein binding is less than 5%. Primarily eliminated renally (50%). A population pharmacokinetic analysis from 9 clinical trials in 106 pediatric (neonate to 18 years of age) showed that body weight is the primary factor associated with oral clearance. Clearance was not affected by dosing schedule (once vs twice daily) or formulation (powder for oral solution, tablet, and delayed-release capsule). Mean elimination half-life in children (8 months or older) is 0.8 hours [1] [2] .

Adverse Effects

Pancreatitis occurred in 3% (2 out of 60) of pediatric patients during a clinical trial at doses below 300 mg/m(2)/day [1] . Common adverse events include diarrhea, abdominal pain, vomiting, rash, and increased liver enzymes [1] [2] . Electrolyte abnormalities, hyperuricemia, and insulin resistance/diabetes mellitus have also been reported in pediatric patients [2] .

Monitoring

Monitor viral load (plasma HIV-RNA) and CD4 cell counts, as well as CBC with differential, serum chemistries, and liver and renal function tests at baseline, at 4 to 8 weeks after initiating or changing therapy, and at least every 3 to 4 months thereafter. Screen for clinical adverse effects and assess regimen adherence within 1 to 2 weeks of initiating therapy, at 4 to 8 weeks after initiating or changing therapy, and at least every 3 to 4 months thereafter. Lipid panel and urinalysis are recommended at baseline and every 6 to 12 months during therapy [2] . Monitor for early signs and symptoms of portal hypertension (eg, thrombocytopenia and splenomegaly). Perform retinal examinations periodically to screen for retinal changes and optic neuritis [1] . Resistance testing is recommended prior to initiation of antiretroviral therapy, and in patients experiencing treatment failure [2] .

Special Considerations/Preparation

Available in pediatric powder for oral solution in 4- and 8-ounce glass bottles containing 2 g and 4 g of didanosine, respectively. Reconstitute each 2-g or 4-g bottle with 100 mL or 200 mL of purified water, USP, respectively, for an initial concentration of 20 mg/mL. This solution should be immediately mixed with one part Maximum Strength Mylanta® Liquid, resulting in a final concentration of didanosine 10 mg/mL. Shake well before use. Refrigerate admixture at 2 to 8 degrees C (36 to 46 degrees F) for up to 30 days, and discard any unused portion after this time [1] .

References

- Product Information: VIDEX(R) oral powder for solution, didanosine oral powder for solution. Bristol-Myers Squibb (per FDA), Princeton, NJ, Nov, 2011.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. National Institute of Health, Bethesda, MD, Aug11, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.

Title Didanosine

Dose

HIV Infection
14 days or older: The manufacturer recommends 100 mg/m^2 orally twice daily [1] ; however, guidelines for the treatment of HIV-infected children recommend that a dose of 50 mg/m^2 twice daily may be more appropriate for neonates [2] .

Administration

Preferably, administer on an empty stomach (30 minutes before or 2 hours after a feeding); however, to improve adherence, may be given with a feeding [2] . Shake well before measuring dose [1] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents. If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). Didanosine plus lamivudine or emtricitabine is considered an alternative dual-NRTI backbone option for initial therapy. The preferred dual-NRTI backbone option in neonates (as long as zidovudine resistance is not detected) is zidovudine plus lamivudine/emtricitabine [2] .

Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children 2 weeks or older [1] .

Contraindications/Precautions

Contraindicated with the coadministration of allopurinol or ribavirin [1] . Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported mainly in adults. Pancreatitis has been reported less commonly in children than in adults [2] ; suspend or discontinue treatment if signs or symptoms occur. Non-cirrhotic portal hypertension has been reported, including fatalities or cases requiring liver transplantation; the onset occurred months to years after start of therapy; discontinue therapy if signs or symptoms occur. Hepatic toxicity, worsening of hepatic dysfunction, and peripheral neuropathy have been reported; discontinuation of therapy may be warranted. Retinal changes and optic neuritis have also been reported in children as well as adults. Inflammatory response (immune reconstitution syndrome) to

indolent or residual opportunistic infections may occur during initial phase of treatment [1] .

Black Box Warning

Fatal and nonfatal pancreatitis has occurred during therapy with didanosine. Didanosine should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (in adults) [1] .

Pharmacology

Didanosine is a nucleoside reverse transcriptase inhibitor active against HIV type 1. The AUC is equivalent for buffered or enteric-coated formulations. Mean bioavailability is approximately 25% in children. Cmax occurs from 0.25 to 1.5 hours following oral administration of the pediatric powder for solution. Food decreases absorption. Protein binding is less than 5%. Primarily eliminated renally (50%). A population pharmacokinetic analysis from 9 clinical trials in 106 pediatric (neonate to 18 years of age) showed that body weight is the primary factor associated with oral clearance. Clearance was not affected by dosing schedule (once vs twice daily) or formulation (powder for oral solution, tablet, and delayed-release capsule). Mean elimination half-life in children (8 months or older) is 0.8 hours [1] [2] .

Adverse Effects

Pancreatitis occurred in 3% (2 out of 60) of pediatric patients during a clinical trial at doses below 300 mg/m(2)/day [1] . Common adverse events include diarrhea, abdominal pain, vomiting, rash, and increased liver enzymes [1] [2] . Electrolyte abnormalities, hyperuricemia, and insulin resistance/diabetes mellitus have also been reported in pediatric patients [2] .

Monitoring

Monitor viral load (plasma HIV-RNA) and CD4 cell counts, as well as CBC with differential, serum chemistries, and liver and renal function tests at baseline, at 4 to 8 weeks after initiating or changing therapy, and at least every 3 to 4 months thereafter. Screen for clinical adverse effects and assess regimen adherence within 1 to 2 weeks of initiating therapy, at 4 to 8 weeks after initiating or changing therapy, and at least every 3 to 4 months thereafter. Lipid panel and urinalysis are recommended at baseline and every 6 to 12 months during therapy [2] . Monitor for early signs and symptoms of portal hypertension (eg, thrombocytopenia and splenomegaly). Perform retinal examinations periodically to screen for retinal changes and optic neuritis [1] . Resistance testing is recommended prior to initiation of antiretroviral therapy, and in patients experiencing treatment failure [2] .

Special Considerations/Preparation

Available in pediatric powder for oral solution in 4- and 8-ounce glass bottles containing 2 g and 4 g of didanosine, respectively. Reconstitute each 2-g or 4-g bottle

with 100 mL or 200 mL of purified water, USP, respectively, for an initial concentration of 20 mg/mL. This solution should be immediately mixed with one part Maximum Strength Mylanta® Liquid, resulting in a final concentration of didanosine 10 mg/mL. Shake well before use. Refrigerate admixture at 2 to 8 degrees C (36 to 46 degrees F) for up to 30 days, and discard any unused portion after this time [1] .

References

- Product Information: VIDEX(R) oral powder for solution, didanosine oral powder for solution. Bristol-Myers Squibb (per FDA), Princeton, NJ, Nov, 2011.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. National Institute of Health, Bethesda, MD, Aug11, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.

1.55 Digoxin

Title Digoxin

Dose

Loading dose ("Digitalization"): Generally used only when treating arrhythmias and acute congestive heart failure. Give over 24 hours as 3 divided doses.
Oral doses should be 25% greater than IV doses. Do not administer IM.

Note: These beginning doses are based primarily on studies that measured echocardiographic changes and EKG signs of toxicity and take into account renal maturation. Titrate dosage based on clinical response. Decrease dose proportional to the reduction in creatinine clearance.

Total Loading Dose

Divide into 3 doses over 24 hours.

PMA weeks	IV mcg/kg	Oral mcg/kg
≤29	15	20
30 to 36	20	25
37 to 48	30	40
≥49	40	50

Maintenance Doses

Titrate based on clinical response.

PMA weeks	IV mcg/kg	Oral mcg/kg	Interval hours
≤29	4	5	24
30 to 36	5	6	24
37 to 48	4	5	12
≥49	5	6	12

Administration

Intravenous: Administer IV slow push over 5 to 10 minutes. Rapid administration may result in systemic and coronary arteriolar constriction. May be given undiluted or diluted **at least** 4-fold in compatible diluents or precipitation may occur. For small dose volumes, a 1:10 dilution of the 100 mcg/mL concentration to provide a final concentration of 10 mcg/mL may be required. Do not administer IM [1] .
Oral: Give consistently with regard to feedings [2] .

Uses

Treatment of heart failure caused by diminished myocardial contractility. Treatment of SVT, atrial flutter, and atrial fibrillation.

Contraindications/Precautions

Contraindicated in ventricular fibrillation. Increased risk for digoxin toxicity in patients with low body weight, hypokalemia, hypomagnesemia, hypercalcemia, and renal impairment; monitoring and dose adjustment may be required. Wolff-Parkinson-White syndrome patients with atrial fibrillation have an increased risk of ventricular fibrillation. Severe sinus bradycardia or sinoatrial block may occur, especially in patients with preexisting sinus node disease or incomplete atrioventricular block; consider pacemaker placement before initiating treatment. Decreased cardiac output may develop with use in patients with heart failure associated with preserved left ventricular systolic function. May induce ventricular arrhythmias in patients undergoing electrical cardioversion; consider reducing dose or discontinuing use 1 to 2 days prior to procedure. Avoid use in patients with myocarditis [3] [2] .

Pharmacology

Digitalis glycoside with positive inotropic and negative chronotropic actions. Increases myocardial catecholamine levels (low doses) and inhibits sarcolemmal sodium-potassium-ATPase (higher doses) to enhance contractility by increasing systolic intracellular calcium-ion concentrations. Indirectly increases vagal activity, thereby slowing S-A node firing and A-V node conduction. Other effects include peripheral, splanchnic, and perhaps, pulmonary vasoconstriction, and reduced CSF production. Serum concentration peaks 30 to 90 minutes after an oral dose, with myocardial peak occurring in 4 to 6 hours. Large volume of distribution that increases with age during

infancy. Rapid absorption of oral dose from small intestine; reduced by antacids and rapid transit times. 20% protein bound. Probably not significantly metabolized. Glomerular filtration and tubular secretion account for most of the total body clearance of digoxin, although significant nonrenal elimination has been proposed.

Adverse Effects

Toxic Cardiac Effects:

- PR interval prolongation
- Sinus bradycardia or SA block
- Atrial or nodal ectopic beats
- Ventricular arrhythmias**Nontoxic Cardiac Effects:**
- QTc interval shortening
- ST segment sagging
- T-wave amplitude dampening
- Heart rate slowing

Other Effects: Feeding intolerance, vomiting, diarrhea, and lethargy.

Treatment of Life-Threatening Digoxin Toxicity:
Digibind® Digoxin Immune Fab, IV over 30 minutes through 0.22-micron filter.

Dose (# of vials) = (weight [kg]) x (serum digoxin concentration)/100

Each vial of digibind contains 38 mg (enough to bind 0.5 mg Digoxin).

Monitoring

Follow heart rate and rhythm closely. Periodic EKGs to assess both desired effects and signs of toxicity. Follow closely (especially in patients receiving diuretics or amphotericin B) for decreased serum potassium and magnesium, or increased calcium and magnesium, all of which predispose to digoxin toxicity. Assess renal function. Be aware of drug interactions. May follow serum drug concentrations if assay is available that excludes endogenous digoxin-like substances. Therapeutic serum concentration is 1 to 2 nanograms/mL.

Special Considerations/Preparation

Pediatric dosage forms: Injectable (100 mcg/mL) and elixir (50 mcg/mL).
Store at room temperature and protect from light.
Dilute injectable as follows:
1) Draw up digoxin into syringe.

2) Inject desired amount of drug into second syringe containing a 4-fold or greater volume of solution-compatible diluent. Use diluted product immediately.

Drug Interactions: Amiodarone, indomethacin, spironolactone, quinidine, and verapamil decrease digoxin clearance. Cisapride and metoclopramide decrease digoxin absorption. Spironolactone interferes with radioimmunoassay. Erythromycin may increase digoxin absorption.

Solution Compatibility

(only when diluted 4-fold or greater): D_5W, $D_{10}W$, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Cimetidine, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, meropenem, midazolam, milrinone, morphine, potassium chloride, ranitidine, and remifentanil.

Terminal Injection Site Incompatibility

Amiodarone, dobutamine, fluconazole, and propofol.

References

- Smith TW: Digitalis: Mechanisms of action and clinical use. *N Engl J Med* 1988;318:358.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p 138.
- Johnson GL, Desai NS, Pauly TH, Cunningham MD: Complications associated with digoxin in low-birth-weight infants. *Pediatrics* 1982;69:463.
- Nyberg L, Wettrell G: Pharmacokinetics and dosage of digoxin in neonates and infants. *Eur J Clin Pharmacol* 1980;18:69.
- Pinsky WW, Jacobsen JR, Gillette PC, et al: Dosage of digoxin in premature infants. *J Pediatr* 1979;96:639.

1. Product Information: LANOXIN(R) IV, IM injection, digoxin IV, IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2009.
2. Product Information: digoxin oral solution, digoxin oral solution. Roxane Laboratories, Inc, Columbus, OH, Nov, 2009.
3. Product Information: LANOXIN(R) intravenous injection, intramuscular injection, digoxin intravenous injection, intramuscular injection. Covis Pharmaceuticals, Inc. (per FDA), Cary, NC, May, 2013.

Title Digoxin

Dose

Loading dose ("Digitalization"): Generally used only when treating arrhythmias and acute congestive heart failure. Give over 24 hours as 3 divided doses.
Oral doses should be 25% greater than IV doses. Do not administer IM.

Note: These beginning doses are based primarily on studies that measured echocardiographic changes and EKG signs of toxicity and take into account renal maturation. Titrate dosage based on clinical response. Decrease dose proportional to the reduction in creatinine clearance.

Total Loading Dose

Divide into 3 doses over 24 hours.

PMA weeks	IV mcg/kg	Oral mcg/kg
≤29	15	20
30 to 36	20	25
37 to 48	30	40
≥49	40	50

Maintenance Doses

Titrate based on clinical response.

PMA weeks	IV mcg/kg	Oral mcg/kg	Interval hours
≤29	4	5	24
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Administration

Intravenous: Administer IV slow push over 5 to 10 minutes. Rapid administration may result in systemic and coronary arteriolar constriction. May be given undiluted or diluted **at least** 4-fold in compatible diluents or precipitation may occur. For small dose volumes, a 1:10 dilution of the 100 mcg/mL concentration to provide a final concentration of 10 mcg/mL may be required. Do not administer IM [1] .
Oral: Give consistently with regard to feedings [2] .

Uses

Treatment of heart failure caused by diminished myocardial contractility. Treatment of SVT, atrial flutter, and atrial fibrillation.

Contraindications/Precautions

Contraindicated in ventricular fibrillation. Increased risk for digoxin toxicity in patients with low body weight, hypokalemia, hypomagnesemia, hypercalcemia, and renal impairment; monitoring and dose adjustment may be required. Wolff-Parkinson-White syndrome patients with atrial fibrillation have an increased risk of ventricular fibrillation. Severe sinus bradycardia or sinoatrial block may occur, especially in patients with preexisting sinus node disease or incomplete atrioventricular block; consider pacemaker placement before initiating treatment. Decreased cardiac output may develop with use in patients with heart failure associated with preserved left ventricular systolic function. May induce ventricular arrhythmias in patients undergoing electrical cardioversion; consider reducing dose or discontinuing use 1 to 2 days prior to procedure. Avoid use in patients with myocarditis [3] [2] .

Pharmacology

Digitalis glycoside with positive inotropic and negative chronotropic actions. Increases myocardial catecholamine levels (low doses) and inhibits sarcolemmal sodium-potassium-ATPase (higher doses) to enhance contractility by increasing systolic intracellular calcium-ion concentrations. Indirectly increases vagal activity, thereby slowing S-A node firing and A-V node conduction. Other effects include peripheral, splanchnic, and perhaps, pulmonary vasoconstriction, and reduced CSF production. Serum concentration peaks 30 to 90 minutes after an oral dose, with myocardial peak occurring in 4 to 6 hours. Large volume of distribution that increases with age during infancy. Rapid absorption of oral dose from small intestine; reduced by antacids and rapid transit times. 20% protein bound. Probably not significantly metabolized. Glomerular filtration and tubular secretion account for most of the total body clearance of digoxin, although significant nonrenal elimination has been proposed.

Adverse Effects

Toxic Cardiac Effects:

- PR interval prolongation
- Sinus bradycardia or SA block
- Atrial or nodal ectopic beats
- Ventricular arrhythmias**Nontoxic Cardiac Effects:**
- QTc interval shortening
- ST segment sagging
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- Heart rate slowing

Other Effects: Feeding intolerance, vomiting, diarrhea, and lethargy.

Treatment of Life-Threatening Digoxin Toxicity:
Digibind® Digoxin Immune Fab, IV over 30 minutes through 0.22-micron filter.

Dose (# of vials) = (weight [kg]) x (serum digoxin concentration)/100

Each vial of digibind contains 38 mg (enough to bind 0.5 mg Digoxin).

Monitoring

Follow heart rate and rhythm closely. Periodic EKGs to assess both desired effects and signs of toxicity. Follow closely (especially in patients receiving diuretics or amphotericin B) for decreased serum potassium and magnesium, or increased calcium and magnesium, all of which predispose to digoxin toxicity. Assess renal function. Be aware of drug interactions. May follow serum drug concentrations if assay is available that excludes endogenous digoxin-like substances. Therapeutic serum concentration is 1 to 2 nanograms/mL.

Special Considerations/Preparation

Pediatric dosage forms: Injectable (100 mcg/mL) and elixir (50 mcg/mL).
Store at room temperature and protect from light.
Dilute injectable as follows:
1) Draw up digoxin into syringe.
2) Inject desired amount of drug into second syringe containing a 4-fold or greater volume of solution-compatible diluent. Use diluted product immediately.

Drug Interactions: Amiodarone, indomethacin, spironolactone, quinidine, and verapamil decrease digoxin clearance. Cisapride and metoclopramide decrease digoxin absorption. Spironolactone interferes with radioimmunoassay. Erythromycin may increase digoxin absorption.

Solution Compatibility

(only when diluted 4-fold or greater): D_5W, $D_{10}W$, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Cimetidine, famotidine, furosemide, heparin, hydrocortisone succinate, insulin, lidocaine, linezolid, meropenem, midazolam, milrinone, morphine, potassium chloride, ranitidine, and remifentanil.

Terminal Injection Site Incompatibility

Amiodarone, dobutamine, fluconazole, and propofol.

References

- Smith TW: Digitalis: Mechanisms of action and clinical use. *N Engl J Med* 1988;318:358.
- Roberts RJ: *Drug Therapy in Infants.* Philadelphia: WB Saunders Co, 1984, p 138.
- Johnson GL, Desai NS, Pauly TH, Cunningham MD: Complications associated with digoxin in low-birth-weight infants. *Pediatrics* 1982;69:463.
- Nyberg L, Wettrell G: Pharmacokinetics and dosage of digoxin in neonates and infants. *Eur J Clin Pharmacol* 1980;18:69.
- Pinsky WW, Jacobsen JR, Gillette PC, et al: Dosage of digoxin in premature infants. *J Pediatr* 1979;96:639.

1. Product Information: LANOXIN(R) IV, IM injection, digoxin IV, IM injection. GlaxoSmithKline, Research Triangle Park, NC, Aug, 2009.
2. Product Information: digoxin oral solution, digoxin oral solution. Roxane Laboratories, Inc, Columbus, OH, Nov, 2009.
3. Product Information: LANOXIN(R) intravenous injection, intramuscular injection, digoxin intravenous injection, intramuscular injection. Covis Pharmaceuticals, Inc. (per FDA), Cary, NC, May, 2013.

1.56 Digoxin Immune Fab (Ovine)

Title Digoxin Immune Fab (Ovine)

Dose

Digoxin Toxicity
There are limited safety data in neonatal patients. Dosing estimates are based on calculations derived for adult dosing [1] .
Each vial of digoxin immune Fab (40 mg purified digoxin-specific Fab fragments) will bind approximately 0.5 mg of digoxin or digitoxin [1] .

Acute Ingestion of Known Amount
Dose (in vials) = (digoxin ingested (mg) X bioavailability)/0.5 mg of digitalis bound per vial [1] (bioavailability of digoxin solution = 0.85 [2] ; bioavailability of digoxin tablets = 0.8). If in any case, the dose estimated based on ingested amount differs considerably from that calculated based on the serum digoxin, it may be preferable to use the higher dose estimate [1] .

Chronic Digoxin Toxicity
Unknown digoxin level: single vial (40 mg) IV initially [1] .
Known digoxin level: dose in mg = 40 mg x (serum digoxin concentration in nanogram (ng)/mL x weight in kg)/100 [1] .

If toxicity has not adequately reversed after several hours, or appears to recur, readministration of digoxin immune Fab may be required [1] .

Administration

Reconstitute the vial (40 mg) with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL (see Special Considerations section for storage and stability of the reconstituted vial). May dilute the reconstituted solution to an appropriate volume of NS for administration. Very small doses (less than

1 mL) may be given undiluted via a tuberculin syringe or the reconstituted solution may be further diluted with 36 mL of NS to achieve a 1 mg/mL concentration. Administer by slow IV infusion over 30 minutes; if cardiac arrest is imminent, the solution can be given by bolus injection [1] .
Stop temporarily the IV infusion for any infusion-rate related anaphylactoid reactions (eg, hypotension, wheezing, urticaria) and restart at a lower rate. Incidence of infusion-related reactions may be increased with bolus injection [1] .

Uses

Pediatric FDA Approved Indications
Digoxin immune Fab is indicated for life-threatening or potentially life-threatening digoxin toxicity or overdose in children, including the following situations: ingestion of fatal doses of 4 mg (or 0.1 mg/kg) or more, or amounts leading to serum concentrations of 10 ng/mL or greater; chronic ingestions leading to levels greater than 4 ng/mL; and in the presence of severe ventricular arrhythmias, bradycardia, second/third degree heart block that is unresponsive to atropine, or potassium levels greater than 6 mEq/L with rapidly progressive signs of toxicity [1] [3] [4] [5] [6] .
ECG abnormalities [1] [4] and hyperkalemia typically resolve within 4 hours after digoxin immune Fab administration [4] .

Contraindications/Precautions

Anaphylaxis and hypersensitivity reactions may occur; higher risk in patients with sheep protein allergies or who have previously received intact ovine antibodies or ovine Fab. Patients with poor cardiac function may deteriorate upon loss of inotropic effect of digoxin. Hypokalemia may occur; monitoring recommended [1] .

Pharmacology

Digoxin immune Fab (ovine) is a sterile, lyophilized preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep. Digoxin immune Fab referentially binds molecules of digoxin or digitoxin, and the complex is then excreted by the kidneys. As free serum digoxin is removed, tissue-bound digoxin is also released into the serum to maintain the equilibrium and is bound and removed by digoxin immune Fab. The net result is a reduction in serum and tissue digoxin. Distributes extensively in the extracellular fluid. Digoxin-specific Fab fragments are excreted in the urine. The elimination half-life in patients with normal renal function is approximately 15 hours. In patients with renal impairment, the half-life may be increased by up to 10-fold [1] . Poorly removed by hemodialysis [3] .

Adverse Effects

The most common adverse reactions are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%) [1] .

Monitoring

Monitor serum digoxin serum concentration before digoxin immune Fab administration, if possible, to establish the digitalis intoxication diagnosis. Serum digoxin concentrations may be inaccurate for a period of time (several days or a week, or more in patients with renal impairment) after administration due to interference with digitalis immunoassay measurements. Monitor temperature, blood pressure, and ECG during and after administration. Monitor potassium levels frequently, particularly during the first several hours after administration. Consider assessing free digoxin levels after administration in patients with renal failure to detect a possible recurrence of toxicity. Monitor for signs and symptoms of hypersensitivity reactions [1] .

Special Considerations/Preparation

Available as a vial containing 40 mg of digoxin immune Fab protein. Store in refrigerator; do not freeze. Reconstitute the vial with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL. May dilute the reconstituted solution with NS to a concentration of 1 mg/mL for small doses or to an appropriate volume of NS for administration. Use reconstituted product immediately; if not used immediately, refrigerate and use within 4 hours [1] .

References

- Product Information: DigiFab(R) intravenous injection lyophilized powder for solution, digoxin immune fab ovine intravenous injection lyophilized powder for solution. BTG International Inc. (per manufacturer), West Conshohocken, PA, Jan, 2012.

- Product Information: digoxin oral solution, digoxin oral solution. Roxane Laboratories, Inc. (per FDA), Columbus, OH, Nov, 2011.

- Berkovitch M, Akilesh MR, Gerace R et al: Acute digoxin overdose in a newborn with renal failure: use of digoxin immune Fab and peritoneal dialysis. Ther Drug Monit Oct1, 1994; 16(5): 531-533.

- Woolf AD: Results of multicenter studies of digoxin-specific antibody fragments in managing digitalis intoxication in the pediatric population. Am J Emerg Med Mar, 1991; 9(2 Suppl 1): 16-20.

- Kaufman J: Use of digoxin fab immune fragments in a seven-day-old infant. Pediatr Emerg Care Jun, 1990; 6(2): 118-121.

- Telang V: Topics in neonatal metabolism. Metabolic effects of digitalis intoxication in a premature infant: treatment with digoxin-specific Fab fragments. J Perinatol 1987; 7(3): 259-261.

Title Digoxin Immune Fab (Ovine)

Dose

Digoxin Toxicity
There are limited safety data in neonatal patients. Dosing estimates are based on calculations derived for adult dosing [1] .

Each vial of digoxin immune Fab (40 mg purified digoxin-specific Fab fragments) will bind approximately 0.5 mg of digoxin or digitoxin [1] .

Acute Ingestion of Known Amount
Dose (in vials) = (digoxin ingested (mg) X bioavailability)/0.5 mg of digitalis bound per vial [1] (bioavailability of digoxin solution = 0.85 [2] ; bioavailability of digoxin tablets = 0.8). If in any case, the dose estimated based on ingested amount differs considerably from that calculated based on the serum digoxin, it may be preferable to use the higher dose estimate [1] .

Chronic Digoxin Toxicity
Unknown digoxin level: single vial (40 mg) IV initially [1] .
Known digoxin level: dose in mg = 40 mg x (serum digoxin concentration in nanogram (ng)/mL x weight in kg)/100 [1] .

If toxicity has not adequately reversed after several hours, or appears to recur, readministration of digoxin immune Fab may be required [1] .

Administration

Reconstitute the vial (40 mg) with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL (see Special Considerations section for storage and stability of the reconstituted vial). May dilute the reconstituted solution to an appropriate volume of NS for administration. Very small doses (less than 1 mL) may be given undiluted via a tuberculin syringe or the reconstituted solution may be further diluted with 36 mL of NS to achieve a 1 mg/mL concentration. Administer by slow IV infusion over 30 minutes; if cardiac arrest is imminent, the solution can be given by bolus injection [1] .
Stop temporarily the IV infusion for any infusion-rate related anaphylactoid reactions (eg, hypotension, wheezing, urticaria) and restart at a lower rate. Incidence of infusion-related reactions may be increased with bolus injection [1] .

Uses

Pediatric FDA Approved Indications
Digoxin immune Fab is indicated for life-threatening or potentially life-threatening digoxin toxicity or overdose in children, including the following situations: ingestion of fatal doses of 4 mg (or 0.1 mg/kg) or more, or amounts leading to serum concentrations of 10 ng/mL or greater; chronic ingestions leading to levels greater than 4 ng/mL; and in the presence of severe ventricular arrhythmias, bradycardia, second/third degree heart block that is unresponsive to atropine, or potassium levels greater than 6 mEq/L with rapidly progressive signs of toxicity [1] [3] [4] [5] [6] .
ECG abnormalities [1] [4] and hyperkalemia typically resolve within 4 hours after digoxin immune Fab administration [4] .

Contraindications/Precautions

Anaphylaxis and hypersensitivity reactions may occur; higher risk in patients with sheep protein allergies or who have previously received intact ovine antibodies or ovine

Fab. Patients with poor cardiac function may deteriorate upon loss of inotropic effect of digoxin. Hypokalemia may occur; monitoring recommended [1] .

Pharmacology

Digoxin immune Fab (ovine) is a sterile, lyophilized preparation of digoxin-immune ovine Fab (monovalent) immunoglobulin fragments obtained from the blood of healthy sheep. Digoxin immune Fab referentially binds molecules of digoxin or digitoxin, and the complex is then excreted by the kidneys. As free serum digoxin is removed, tissue-bound digoxin is also released into the serum to maintain the equilibrium and is bound and removed by digoxin immune Fab. The net result is a reduction in serum and tissue digoxin. Distributes extensively in the extracellular fluid. Digoxin-specific Fab fragments are excreted in the urine. The elimination half-life in patients with normal renal function is approximately 15 hours. In patients with renal impairment, the half-life may be increased by up to 10-fold [1] . Poorly removed by hemodialysis [3] .

Adverse Effects

The most common adverse reactions are worsening congestive heart failure (13%), hypokalemia (13%) and worsening atrial fibrillation (7%) [1] .

Monitoring

Monitor serum digoxin serum concentration before digoxin immune Fab administration, if possible, to establish the digitalis intoxication diagnosis. Serum digoxin concentrations may be inaccurate for a period of time (several days or a week, or more in patients with renal impairment) after administration due to interference with digitalis immunoassay measurements. Monitor temperature, blood pressure, and ECG during and after administration. Monitor potassium levels frequently, particularly during the first several hours after administration. Consider assessing free digoxin levels after administration in patients with renal failure to detect a possible recurrence of toxicity. Monitor for signs and symptoms of hypersensitivity reactions [1] .

Special Considerations/Preparation

Available as a vial containing 40 mg of digoxin immune Fab protein. Store in refrigerator; do not freeze. Reconstitute the vial with 4 mL of Sterile Water for Injection and mix gently; the final concentration will be approximately 10 mg/mL. May dilute the reconstituted solution with NS to a concentration of 1 mg/mL for small doses or to an appropriate volume of NS for administration. Use reconstituted product immediately; if not used immediately, refrigerate and use within 4 hours [1] .

References

- Product Information: DigiFab(R) intravenous injection lyophilized powder for solution, digoxin immune fab ovine intravenous injection lyophilized powder for solution. BTG International Inc. (per manufacturer), West Conshohocken, PA, Jan, 2012.

- Product Information: digoxin oral solution, digoxin oral solution. Roxane Laboratories, Inc. (per FDA), Columbus, OH, Nov, 2011.

- Berkovitch M, Akilesh MR, Gerace R et al: Acute digoxin overdose in a newborn with renal failure: use of digoxin immune Fab and peritoneal dialysis. Ther Drug Monit Oct1, 1994; 16(5): 531-533.

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1.57 Dornase alfa

Title Dornase alfa

Dose

1.25 mL to 2.5 mL via nebulizer, or 0.2 mL/kg instilled directly into the endotracheal tube.
Administer once or twice per day.

Uses

Treatment of atelectasis, secondary to mucus plugging, that is unresponsive to conventional therapies.

Pharmacology

Pulmozyme® is a highly purified solution of recombinant human deoxyribonuclease (rhDNase, an enzyme that selectively cleaves DNA). The protein is produced by genetically engineered Chinese hamster ovary cells. Purulent pulmonary secretions contain very high concentrations of extracellular DNA released by degenerating leukocytes. rhDNase hydrolyzes this DNA to decrease the viscoelasticity of the secretions. Clinical improvements in the thickness of secretions and ventilation usually occur within 3 hours of administration.

Adverse Effects

Desaturation and/or airway obstruction may occur due to rapid mobilization of secretions.

Monitoring

Monitor airway patency. Suction the airway as needed.

Special Considerations/Preparation

Pulmozyme® is supplied in single-use ampules. Each ampule contains 2.5 mL of a sterile, clear, colorless, aqueous solution containing 1 mg/mL dornase alfa (2.5 mg per ampule), 0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/mL sodium chloride (22 mg per ampule) with no preservative. The nominal pH of the solution is 6.3. The ampules should be stored in their protective foil pouch under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) and protected from strong light. Do not use beyond the expiration date on the ampule.

References

- Erdeve O, Uras N, Atasay B, Arsan S: Efficacy and safety of nebulized recombinant human DNase as rescue treatment for persistent atelectasis in newborns: case-series. *Croat Med J* 2007;48:234-239.
- Riethmueller J, Borth-Bruhns T, Kumpf M, et al: Recombinant human deoxyribonuclease shortens ventilation time in young, mechanically ventilated children. *Pediatr Pulmonol* 2006;41:61-66.
- Hendriks T, de Hoog M, Lequin MH, et al: DNase and atelectasis in non-cystic fibrosis patients. *Crit Care* 2005;9:R351-R356.
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- Kupeli S, Teksam O, Dogru D, Yurdakok M: Use of recombinant human DNase in a premature infant with recurrent atelectasis. *Pediatrics International* 2003;45:584-586.
- El Hassan NO, Chess PR, Huysman MWA, et al: Rescue use of DNase in critical lung atelectasis and mucus retention in premature neonates. *Pediatrics* 2001;108:468-471.
- Reiter PD, Townsend SF, Velasquez R: Dornase alfa in premature infants with severe respiratory distress and early bronchopulmonary dysplasia. *J Perinatol* 2000;20:530-534.
- Product information, Genentech, 2005.

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- Product information, Genentech, 2005.

1.58 EMLAÂ®

Title EMLAÂ®

Dose

Apply 1 to 2 g to distal half of the penis, then wrap with occlusive dressing. Allow dressing to remain intact for 60 to 90 minutes, remove and clean treated area completely prior to circumcision to avoid systemic absorption.

Uses

Topical analgesia for circumcision. Not effective for heel lancing.

Pharmacology

EMLA cream, containing 2.5% lidocaine and 2.5% prilocaine, attenuates the pain response to circumcision when applied 60 to 90 minutes before the procedure. The analgesic effect is limited during the phases associated with extensive tissue trauma such as during lysis of adhesions and tightening of the clamp. Stabilizes the neuronal membranes by inhibiting the ionic fluxes required for conduction and initiation of nerve impulses. There is a theoretic concern about the potential for neonates to develop methemoglobinemia after the application of EMLA cream, because a metabolite of prilocaine can oxidize hemoglobin to methemoglobin. Neonates are deficient in methemoglobin NADH cytochrome b_5 reductase. Lidocaine is metabolized rapidly by the liver to a number of active metabolites and then excreted renally.

Adverse Effects

Blanching and redness resolve without treatment. When measured, blood levels of methemoglobin in neonates after the application of 1 g of EMLA cream have been well below toxic levels. Two cases of methemoglobinemia in infants occurred after greater than 3 g of EMLA cream was applied; in 1 of these cases, the infant also was receiving sulfamethoxazole. EMLA cream should not be used in neonates with congenital or idiopathic methemoglobinemia, or who are receiving other drugs known to induce methemoglobinemia: sulfonamides, acetaminophen, nitrates, nitroglycerin, nitroprusside, phenobarbital, and phenytoin.

Monitoring

Blood methemoglobin concentration if concerned about toxicity.

Special Considerations/Preparation

Available in 5-g and 30-g tubes with Tegaderm dressing. Each gram of EMLA contains lidocaine 25 mg and prilocaine 25 mg in a eutectic mixture. pH of the product is 9. Contains no preservatives.

References

- American Academy of Pediatrics, Task Force on Circumcision. Circumcision policy statement. *Pediatrics* 1999;103:686-693.
- Taddio A, Ohlsson A, Einarson TR, et al: A systematic review of lidocaine-prilocaine cream (EMLA) in the treatment of acute pain in neonates. *Pediatrics* 1998;101:1-9.
- Lander J, Brady-Fryer B, Metcalfe JB, et al: Comparison of ringblock, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: A randomized controlled trial. *JAMA* 1997;278:2157-2162.
- Taddio A, Stevens B, Craig K, et al: Efficacy and safety of lidocaine-prilocaine cream for pain during circumcision. *N Engl J Med* 1997;336:1197-1201.
- Product Information, APP Pharmaceuticals, 2006.

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- Product Information, APP Pharmaceuticals, 2006.

1.59 EPINEPHrine (Adrenaline)

Title EPINEPHrine (Adrenaline)

Dose

Intravenous
Resuscitation and severe bradycardia: 0.1 to 0.3 mL/kg **1:10,000 concentration** IV push; equal to 0.01 to 0.03 mg/kg (10 to 30 mcg/kg). Follow IV administration with 0.5 to 1 mL flush of normal saline [1] .

IV continuous infusion: Start at 0.1 mcg/kg per minute and adjust to desired response, to a maximum of 1 mcg/kg per minute.
If possible, correct acidosis before administration of epinephrine to enhance the effectiveness of the drug.

Endotracheal
Resuscitation and severe bradycardia: 0.5 to 1 mL/kg **1:10,000 concentration** via ET tube; equal to 0.05 to 0.1 mg/kg (50 to 100 mcg/kg). Follow ET administration with several positive pressure ventilations [1] . Do **not** administer these higher doses of epinephrine intravenously.

Administration

Intravenous: When giving IV push, follow administration with 0.5 to 1 mL flush of normal saline. Always use the 1:10,000 (0.1 mg/mL) concentration for individual doses and the 1:1000 (1 mg/mL) concentration to prepare continuous infusion solution. For continuous infusion, dilute in compatible diluent to a concentration of 10 to 60 mcg/mL.
Endotracheal: Instill directly into ET tube and follow with several positive-pressure ventilations [1] .

Intravenous infusion:
Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Epinephrine): Mix 50 mL of 20 mcg/mL solution using epinephrine concentration of 1 mg/mL.

20 mcg/mL = 0.02 mg/mL
0.02 mg/mL Ã— 50 mL = 1 mg epinephrine
***1 mg ÷ 1 mg/mL = 1 mL of epinephrine**
Add 1 mL of epinephrine (1:1000) to 49 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 20 mcg/mL.
Maximum concentration 60 mcg/mL.

Epinephrine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
10	0.05	0.3
	0.1	0.6
	0.5	3
	1	6
20	0.05	0.15
	0.1	0.3
	0.5	1.5
	1	3
30	0.05	0.1
	0.1	0.2
	0.5	1
	1	2
40	0.05	0.075
	0.1	0.15
	0.5	0.75
	1	1.5
50	0.05	0.06
	0.1	0.12
	0.5	0.6
	1	1.2
60	0.05	0.05
	0.1	0.1
	0.5	0.5
	1	1

Uses

Acute cardiovascular collapse. Short-term use for treatment of systemic hypotension. Despite the widespread use of epinephrine/adrenaline during resuscitation, no placebo-controlled studies have evaluated either the tracheal or intravenous administration of

epinephrine at any stage during cardiac arrest in human neonates. Nonetheless, it is reasonable to continue to use epinephrine when adequate ventilation and chest compressions have failed to increase the heart rate to greater than 60 beats per minute [1] .

Pharmacology

Epinephrine (adrenaline) is the major hormone secreted by the adrenal medulla. It is a potent stimulator of both alpha and beta adrenergic receptors, with complex effects on body organ systems. Low doses are associated with systemic and pulmonary vasodilation. Higher doses increase blood pressure by direct myocardial stimulation, increases in heart rate, and vasoconstriction. Myocardial oxygen consumption is increased. Blood flow to skeletal muscle, brain, liver, and myocardium is increased. However, blood flow to the kidney is decreased due to increased vascular resistance.

Adverse Effects

Compared to dopamine, continuous infusions at doses yielding similar changes in blood pressure are more likely to cause hyperglycemia, tachycardia, and elevations in serum lactate. Cardiac arrhythmias (PVCs and ventricular tachycardia) are also more likely. Renal vascular ischemia may occur at higher doses. Bolus doses are associated with severe hypertension and intracranial hemorrhage. Increased myocardial oxygen requirements.
IV infiltration may cause tissue ischemia and necrosis. Suggested treatment: Inject a 1 mg/mL solution of phentolamine into the affected area. The usual amount needed is 1 to 5 mL, depending on the size of the infiltrate.

Monitoring

Monitor heart rate and blood pressure continuously. Observe IV site for signs of infiltration.

Special Considerations/Preparation

Available as a 1:10,000 concentration (0.1 mg/mL) and 1:1000 (1 mg/mL) concentration. **Always use the 1:10,000 concentration for individual doses and the 1:1000 (1 mg/mL) concentration to prepare continuous infusion solution.** Protect from light.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, ceftazidime, cimetidine, dobutamine, dopamine, famotidine, fentanyl, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, lorazepam, midazolam, milrinone,

morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, and vitamin K_1.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, hyaluronidase, micafungin, and sodium bicarbonate.

References

- Barber CA, Wyckoff MH: Use and efficacy of endotracheal versus intravenous epinephrine during neonatal cardiopulmonary resuscitation in the delivery room. *Pediatrics* 2006;118:1028-1034.
- Valverde E, Pellicer A, Madero R, et al: Dopamine versus epinephrine for cardiovascular support in low birth weight infants: analysis of systemic effects and neonatal clinical outcomes. *Pediatrics* 2006;117(6):e1213-22. URL: http://www.pediatrics.org/cgi/content/full/117/6/e1213.
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	0.5	1
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50	0.05	0.06
	0.1	0.12

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	1	1.2
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	1	1

Uses

Acute cardiovascular collapse. Short-term use for treatment of systemic hypotension. Despite the widespread use of epinephrine/adrenaline during resuscitation, no placebo-controlled studies have evaluated either the tracheal or intravenous administration of epinephrine at any stage during cardiac arrest in human neonates. Nonetheless, it is reasonable to continue to use epinephrine when adequate ventilation and chest compressions have failed to increase the heart rate to greater than 60 beats per minute [1] .

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1:1000 (1 mg/mL) concentration to prepare continuous infusion solution. Protect from light.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, ceftazidime, cimetidine, dobutamine, dopamine, famotidine, fentanyl, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, vecuronium, and vitamin K_1.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, hyaluronidase, micafungin, and sodium bicarbonate.

References

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- Pellicer A, Valverde E, Elorza MD, et al: Cardiovascular support for low birth weight infants and cerebral hemodynamics: a randomized, blinded clinical trial. *Pediatrics* 2005; 115: 1501-1512.
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1.60 Emtricitabine

Title Emtricitabine

Dose

HIV Infection
3 mg/kg orally once daily [1] [2] .

Dose Adjustments
Renal Impairment
There are no published recommendations available for dose adjustment in neonatal patients with renal impairment. Since elimination of emtricitabine is primarily dependent on CrCl, dose adjustments in neonates should be similar to CrCl-based dose

adjustments for adults. The following dose adjustments are consistent with recommendations in adult patients with renal impairment [1] :
CrCl 30 to 49 mL/min: 1.5 mg/kg (0.15 mL/kg) every 24 hours.
CrCl 15 to 29 mL/min: 1 mg/kg (0.1 mL/kg) every 24 hours.
CrCl less than 15 mL/min or receiving hemodialysis: 0.75 mg/kg (0.075 mL/kg) every 24 hours; give dose after hemodialysis on hemodialysis days.

Administration

May be administered with or without feedings [1] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-NRTI backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). The preferred dual-NRTI backbone option in neonates (as long as zidovudine resistance is not detected) is zidovudine plus lamivudine or emtricitabine [2] .

Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children starting at birth [1] .

Contraindications/Precautions

Do not administer with other products containing lamivudine. Fatal lactic acidosis and severe hepatomegaly with steatosis have been reported (in adults). Increased risk in patients with liver disease; suspend or discontinue treatment if signs or symptoms occur even in the absence of marked transaminase elevations. May cause new onset or worsening of renal impairment. Inflammatory response (immune reconstitution syndrome) to indolent or residual opportunistic infections may occur during initial phase of treatment [1] .

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals (in adults) [1] .

Pharmacology

Emtricitabine a synthetic nucleoside analog with activity against HIV-1 reverse transcriptase and HBV DNA polymerase, and is consistently 4 to 10 times more potent than lamivudine, the other NRTI with similar activity. Mean absolute bioavailability of emtricitabine is 93% and 75% for the capsules and the oral solution, respectively, and

the relative bioavailability of the oral solution is approximately 80% of the capsules [1] [4] . In a pharmacokinetic study in neonates (n=20), after receipt of two short course of emtricitabine oral solution (each 3 mg/kg once daily for 4 days) during the first 3 months of life, emtricitabine exposure was similar to the exposures achieved in patients 3 months to 17 years of age with a 6 mg/kg-dose and adults with a 200-mg dose. Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug [2] . Rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Protein binding is less than 4%. Primarily eliminated renally. Following emtricitabine administration, approximately 86% and 14% of the dose was recovered in the urine and feces, respectively. Clearance is decreased in patients with renal impairment. Half-life is approximately 12 hours in neonates [1] .

Adverse Effects

Safety data for emtricitabine in neonatal patients are limited. In a small pharmacokinetic study in neonates (n=20), no safety issues were noted [2] . In a 96-week, phase 2, open-label, non-randomized, multicenter study of HIV-infected pediatric patients 3 months to 17 years of age (n=116), skin discoloration, presenting as small, asymptomatic maculae on the palms or soles, occurred in 13% (annual incidence rate) of patients. All cases were mild (grade 1) and self-limiting with one exception (moderate, grade 2). Other common adverse events (all reported as annual incidence rates) were the following: infection (26%), increased cough (17%), otitis media (13%), rhinitis (13%), vomiting (12%), rash (11%), diarrhea (10%), pneumonia (8%), and gastroenteritis (8%). Grade 3 or 4 adverse events considered to be probably or possibly related to emtricitabine included leukopenia, anemia, gastroenteritis, and pancreatitis, all occurring at a frequency of less than 1% (annual incidence rate) [3] .

Monitoring

Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch
Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X
Chemistries	X		X	X		X
Electrolytes	X			X		X
Glucose	X			X		X

AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X
Lipid Panel	X				X	
Urinalysis	X				X	

KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count

* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days.
** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months).
# For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.
# # May be too early to detect immunological response in the CD4 count/percentage

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo

Special Considerations/Preparation

Available in an oral solution with a concentration of 10 mg/mL. Refrigerate oral solution at 2 to 8 degrees C (36 to 46 degrees F). If stored at room temperature, the oral solution is stable for up to 90 days, and any unused portion must be discarded after this time [1] .

References

- Product Information: EMTRIVA(R) oral capsules solution, emtricitabine oral capsules solution. Gilead Sciences, Inc. (per FDA), Foster City, CA, Nov, 2011.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

- Saez-Llorens X, Violari A, Ndiweni D et al: Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. Pediatrics Apr1, 2008; 121(4): e827-e835.

- Wang LH, Wiznia AA, Rathore MH et al: Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. Antimicrob Agents Chemother Jan, 2004; 48(1): 183-191.

Title Emtricitabine

Dose

HIV Infection
3 mg/kg orally once daily [1] [2] .

Dose Adjustments
Renal Impairment
There are no published recommendations available for dose adjustment in neonatal patients with renal impairment. Since elimination of emtricitabine is primarily dependent on CrCl, dose adjustments in neonates should be similar to CrCl-based dose adjustments for adults. The following dose adjustments are consistent with recommendations in adult patients with renal impairment [1] :
CrCl 30 to 49 mL/min: 1.5 mg/kg (0.15 mL/kg) every 24 hours.
CrCl 15 to 29 mL/min: 1 mg/kg (0.1 mL/kg) every 24 hours.
CrCl less than 15 mL/min or receiving hemodialysis: 0.75 mg/kg (0.075 mL/kg) every 24 hours; give dose after hemodialysis on hemodialysis days.

Administration

May be administered with or without feedings [1] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-NRTI backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). The preferred dual-NRTI backbone option in neonates (as

long as zidovudine resistance is not detected) is zidovudine plus lamivudine or emtricitabine [2] .

Pediatric FDA Approved Indications
Treatment of HIV-1 infection, in combination with other antiretroviral agents, in children starting at birth [1] .

Contraindications/Precautions

Do not administer with other products containing lamivudine. Fatal lactic acidosis and severe hepatomegaly with steatosis have been reported (in adults). Increased risk in patients with liver disease; suspend or discontinue treatment if signs or symptoms occur even in the absence of marked transaminase elevations. May cause new onset or worsening of renal impairment. Inflammatory response (immune reconstitution syndrome) to indolent or residual opportunistic infections may occur during initial phase of treatment [1] .

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals (in adults) [1] .

Pharmacology

Emtricitabine a synthetic nucleoside analog with activity against HIV-1 reverse transcriptase and HBV DNA polymerase, and is consistently 4 to 10 times more potent than lamivudine, the other NRTI with similar activity. Mean absolute bioavailability of emtricitabine is 93% and 75% for the capsules and the oral solution, respectively, and the relative bioavailability of the oral solution is approximately 80% of the capsules [1] [4] . In a pharmacokinetic study in neonates (n=20), after receipt of two short course of emtricitabine oral solution (each 3 mg/kg once daily for 4 days) during the first 3 months of life, emtricitabine exposure was similar to the exposures achieved in patients 3 months to 17 years of age with a 6 mg/kg-dose and adults with a 200-mg dose. Emtricitabine AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug [2] . Rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Protein binding is less than 4%. Primarily eliminated renally. Following emtricitabine administration, approximately 86% and 14% of the dose was recovered in the urine and feces, respectively. Clearance is decreased in patients with renal impairment. Half-life is approximately 12 hours in neonates [1] .

Adverse Effects

Safety data for emtricitabine in neonatal patients are limited. In a small pharmacokinetic study in neonates (n=20), no safety issues were noted [2] . In a 96-week, phase 2, open-label, non-randomized, multicenter study of HIV-infected pediatric patients 3 months to 17 years of age (n=116), skin discoloration, presenting as small, asymptomatic maculae on the palms or soles, occurred in 13% (annual incidence

rate) of patients. All cases were mild (grade 1) and self-limiting with one exception (moderate, grade 2). Other common adverse events (all reported as annual incidence rates) were the following: infection (26%), increased cough (17%), otitis media (13%), rhinitis (13%), vomiting (12%), rash (11%), diarrhea (10%), pneumonia (8%), and gastroenteritis (8%). Grade 3 or 4 adverse events considered to be probably or possibly related to emtricitabine included leukopenia, anemia, gastroenteritis, and pancreatitis, all occurring at a frequency of less than 1% (annual incidence rate) [3] .

Monitoring

Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch
Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X
Chemistries	X		X	X		X
Electrolytes	X			X		X
Glucose	X			X		X
AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X

Lipid Panel	X				X	
Urinalysis	X				X	
KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count						
* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days. ** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months). # For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter. # # May be too early to detect immunological response in the CD4 count/percentage						
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo						

Special Considerations/Preparation

Available in an oral solution with a concentration of 10 mg/mL. Refrigerate oral solution at 2 to 8 degrees C (36 to 46 degrees F). If stored at room temperature, the oral solution is stable for up to 90 days, and any unused portion must be discarded after this time [1] .

References

- Product Information: EMTRIVA(R) oral capsules solution, emtricitabine oral capsules solution. Gilead Sciences, Inc. (per FDA), Foster City, CA, Nov, 2011.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

- Saez-Llorens X, Violari A, Ndiweni D et al: Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. Pediatrics Apr1, 2008; 121(4): e827-e835.

- Wang LH, Wiznia AA, Rathore MH et al: Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. Antimicrob Agents Chemother Jan, 2004; 48(1): 183-191.

1.61 Enalapril maleate

Title Enalapril maleate

Dose

Begin with 40 mcg/kg per dose (0.04 mg/kg per dose) given orally every 24 hours. Usual maximum dose 150 mcg/kg per dose (0.15 mg/kg per dose), as frequently as every 6 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Pharmacology

Enalapril is a prodrug that is hydrolyzed in the liver to form the active ACE inhibitor enalaprilat, which blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability of oral dosage form is uncertain in neonates, but is significantly less than the 60% reported in adults. Onset of action after oral dose is 1 to 2 hours. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

Adverse Effects

Hypotension occurs primarily in patients who are volume depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Supplied in 2.5-mg, 5-mg, 10-mg, and 20-mg tablets. Enalapril oral suspension (200 mL total) can be prepared by crushing ten 20-mg tablets and adding 50 mL of isotonic citrate buffer (Bicitra®). Mixture should be placed in a bottle and shaken for at least 2 minutes, left to stand for 60 minutes, and then shaken for an additional minute. Add 150 mL of Ora-Sweet SF®, yielding a final concentration of 1 mg/mL. Suspension is stable for 30 days refrigerated.

Title Enalapril maleate

Dose

Begin with 40 mcg/kg per dose (0.04 mg/kg per dose) given orally every 24 hours. Usual maximum dose 150 mcg/kg per dose (0.15 mg/kg per dose), as frequently as every 6 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Pharmacology

Enalapril is a prodrug that is hydrolyzed in the liver to form the active ACE inhibitor enalaprilat, which blocks the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Bioavailability of oral dosage form is uncertain in neonates, but is significantly less than the 60% reported in adults. Onset of action after oral dose is 1 to 2 hours. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

Adverse Effects

Hypotension occurs primarily in patients who are volume depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Supplied in 2.5-mg, 5-mg, 10-mg, and 20-mg tablets. Enalapril oral suspension (200 mL total) can be prepared by crushing ten 20-mg tablets and adding 50 mL of isotonic citrate buffer (Bicitra®). Mixture should be placed in a bottle and shaken for at least 2 minutes, left to stand for 60 minutes, and then shaken for an additional minute. Add 150 mL of Ora-Sweet SF®, yielding a final concentration of 1 mg/mL. Suspension is stable for 30 days refrigerated.

1.62 Enalaprilat

Title Enalaprilat

Dose

Begin with 10 mcg/kg per dose (0.01 mg/kg per dose) IV over 5 minutes every 24 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Pharmacology

Enalaprilat is an ACE inhibitor which blocks the production of the potent vasoconstrictor angiotensin II. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

Adverse Effects

Hypotension occurs primarily in patients who are volume-depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Enalaprilat is supplied as a 1.25-mg/mL solution for injection in 1-mL and 2-mL vials. Benzyl alcohol content is 9 mg/mL. To make a dilution for IV use, take 1 mL (1.25 mg) of solution and add 49 mL NS to make a final concentration of 25 mcg/mL (0.025 mg/mL). Dilution stable for 24 hours.

Solution Compatibility

D_5W, D_5NS, NS, and D_5LR.

Terminal Injection Site Compatibility

Amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin, hydrocortisone succinate, lidocaine, linezolid, magnesium sulfate, meropenem, metronidazole, morphine, nafcillin, nicardipine, nitroprusside, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sulfamethoxazole/trimethoprim, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, cefepime, and phenytoin.

References

- Schilder JLAM, Van den Anker JN: Use of enalapril in neonatal hypertension. *Acta Paediatr* 1995;84:1426.
- Mason T, Polak MJ, Pyles L, et al: Treatment of neonatal renovascular hypertension with intravenous enalapril. *Am J Perinatol* 1992;9:254.
- Rasoulpour M, Marinelli KA: Systemic hypertension. *Clin Perinatol* 1992;19:121.
- Wells TG, Bunchman TE, Kearns GL: Treatment of neonatal hypertension with enalaprilat. *J Pediatr* 1990;117:665.
- Frenneaux M, Stewart RAH, Newman CMH, Hallidie-Smith KA: Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989;64:219.
- Product Information, Hospira, 2006.

Title Enalaprilat

Dose

Begin with 10 mcg/kg per dose (0.01 mg/kg per dose) IV over 5 minutes every 24 hours. Titrate subsequent doses and interval based on amount and duration of response. Dosage may need to be increased every few days.

Uses

Treatment of moderate to severe hypertension. Afterload reduction in patients with congestive heart failure.

Contraindications/Precautions Use with extreme caution in patients with impaired renal function: oliguria and increased serum creatinine occur frequently.

Pharmacology

Enalaprilat is an ACE inhibitor which blocks the production of the potent vasoconstrictor angiotensin II. It thereby decreases plasma and tissue concentrations of angiotensin II and aldosterone, and increases plasma and tissue renin activity. Enalaprilat also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Beneficial effects are thought to be caused by a combination of afterload reduction and long-term inhibition of salt and water retention. Duration of action is quite variable in neonates, ranging from 8 to 24 hours.

Adverse Effects

Hypotension occurs primarily in patients who are volume-depleted. Hyperkalemia occurs primarily in patients receiving potassium-sparing diuretics or potassium supplements. Cough has been reported frequently in adults.

Monitoring

Frequent assessment of blood pressure, particularly after the first dose. Periodic assessment of renal function and serum potassium.

Special Considerations/Preparation

Enalaprilat is supplied as a 1.25-mg/mL solution for injection in 1-mL and 2-mL vials. Benzyl alcohol content is 9 mg/mL. To make a dilution for IV use, take 1 mL (1.25 mg) of solution and add 49 mL NS to make a final concentration of 25 mcg/mL (0.025 mg/mL). Dilution stable for 24 hours.

Solution Compatibility

D_5W, D_5NS, NS, and D_5LR.

Terminal Injection Site Compatibility

Amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin, hydrocortisone succinate, lidocaine, linezolid, magnesium sulfate, meropenem, metronidazole, morphine, nafcillin, nicardipine, nitroprusside, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, ranitidine, remifentanil, sulfamethoxazole/trimethoprim, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Amphotericin B, cefepime, and phenytoin.

References

- Schilder JLAM, Van den Anker JN: Use of enalapril in neonatal hypertension. *Acta Paediatr* 1995;84:1426.
- Mason T, Polak MJ, Pyles L, et al: Treatment of neonatal renovascular hypertension with intravenous enalapril. *Am J Perinatol* 1992;9:254.
- Rasoulpour M, Marinelli KA: Systemic hypertension. *Clin Perinatol* 1992;19:121.
- Wells TG, Bunchman TE, Kearns GL: Treatment of neonatal hypertension with enalaprilat. *J Pediatr* 1990;117:665.
- Frenneaux M, Stewart RAH, Newman CMH, Hallidie-Smith KA: Enalapril for severe heart failure in infancy. *Arch Dis Child* 1989;64:219.
- Product Information, Hospira, 2006.

1.63 EnfamilÂ® Human Milk Fortifier

Title EnfamilÂ® Human Milk Fortifier

Table

Enfamil® Human Milk Fortifier

Nutrient	per 1 pk	per 4 pks
Energy, Cal	3.5	14
Protein, g	0.28	1.1
Fat, g	0.25	1
Linoleic acid, mg	35	140
Carbohydrate, g	less than 0.1	less than 0.4
Minerals		
Calcium, mg (mEq)	22.5 (1.13)	90 (4.49)
Phosphorus, mg (mEq)	12.5 (0.4)	50 (1.61)
Magnesium, mg	0.25	1
Iron, mg	0.36*	1.44*
Zinc, mg	0.18	0.72
Manganese, mcg	2.5	10
Copper, mcg	11	44
Iodine, mcg	-	-
Selenium, mcg	-	-
Sodium, mg (mEq)	4 (0.17)	16 (0.7)
Potassium, mg (mEq)	7.25 (0.19)	29 (0.74)
Chloride, mg (mEq)	3.25 (0.09)	13 (0.37)
Vitamins		
Vitamin A, IU	237.5	950

Vitamin D, IU	37.5	150
Vitamin E, IU	1.15	4.6
Vitamin K, mcg	1.1	4.4
Thiamine (B 1), mcg	37.5	150
Riboflavin (B 2), mcg	55	220
Vitamin B 6 , mcg	28.75	115
Vitamin B 12 , mcg	0.05	0.18
Niacin, mcg	750	3000
Folic acid (Folacin), mcg	6.25	25
Pantothenic acid, mcg	182.5	730
Biotin, mcg	0.68	2.7
Vitamin C (Ascorbic acid), mg	3	12
Renal Solute Load, mOsm	2.45	9.8

*Additional iron should be supplied from other sources.

Precautions: Nutritionally incomplete. Tolerance to enteral feedings should be confirmed by offering small volumes of unfortified human milk. Once enteral feeding is well established, Enfamil Human Milk Fortifier can be added.

Title EnfamilÂ® Human Milk Fortifier

Table

Enfamil® Human Milk Fortifier

Nutrient	**per 1 pk**	**per 4 pks**
Energy, Cal	3.5	14
Protein, g	0.28	1.1
Fat, g	0.25	1

Linoleic acid, mg	35	140
Carbohydrate, g	less than 0.1	less than 0.4
Minerals		
Calcium, mg (mEq)	22.5 (1.13)	90 (4.49)
Phosphorus, mg (mEq)	12.5 (0.4)	50 (1.61)
Magnesium, mg	0.25	1
Iron, mg	0.36*	1.44*
Zinc, mg	0.18	0.72
Manganese, mcg	2.5	10
Copper, mcg	11	44
Iodine, mcg	-	-
Selenium, mcg	-	-
Sodium, mg (mEq)	4 (0.17)	16 (0.7)
Potassium, mg (mEq)	7.25 (0.19)	29 (0.74)
Chloride, mg (mEq)	3.25 (0.09)	13 (0.37)
Vitamins		
Vitamin A, IU	237.5	950
Vitamin D, IU	37.5	150
Vitamin E, IU	1.15	4.6
Vitamin K, mcg	1.1	4.4
Thiamine (B 1), mcg	37.5	150
Riboflavin (B 2), mcg	55	220
Vitamin B 6 , mcg	28.75	115
Vitamin B 12 , mcg	0.05	0.18

Niacin, mcg	750	3000
Folic acid (Folacin), mcg	6.25	25
Pantothenic acid, mcg	182.5	730
Biotin, mcg	0.68	2.7
Vitamin C (Ascorbic acid), mg	3	12
Renal Solute Load, mOsm	2.45	9.8

*Additional iron should be supplied from other sources.

Precautions: Nutritionally incomplete. Tolerance to enteral feedings should be confirmed by offering small volumes of unfortified human milk. Once enteral feeding is well established, Enfamil Human Milk Fortifier can be added.

1.64 Enoxaparin

Title Enoxaparin

Dose

Treatment of Thrombosis:
Term infants: initial, 1.7 mg/kg per dose subQ every 12 hours.
Preterm infants: initial, 2 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor X_a level between 0.5 and 1.0 unit/mL. It will usually take several days to attain levels in the target range.
Dosage requirements to maintain target anti-factor X_a levels in preterm infants are quite variable, ranging from 0.8 to 3 mg/kg every 12 hours.
Infants 2 months of age and older: initial, 1 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor Xa level between 0.5 and 1 unit/mL. It will usually take several days to attain levels in the target range. A suggested dosage adjustment is 0.125 mg/kg/dose until therapeutic anti-Xa level is achieved.

Dosing Issues
Several retrospective studies have suggested that higher initial doses are required to more quickly achieve therapeutic anti-Xa levels and reduce the number of dosage adjustments. In one retrospective study in children (n=192), higher initial doses (1.7 mg/kg every 12 hours for children 3 months of age and younger; 1.2 mg/kg every 12 hours for children greater than 3 months of age) achieved more rapid therapeutic anti-factor Xa levels resulting in fewer venipunctures, without an increase in adverse events, compared with standard doses. Treatment outcomes (resolution or reduction of thrombus) were not different between groups. The authors concluded a higher starting dose of 1.8 mg/kg every 12 hours for infants less than 3 months of age and 1.5 mg/kg

every 12 hours for children 3 to 12 months of age may be considered [1] . Another retrospective study (n=150) found that only 41% of patients attained therapeutic anti-Xa levels with initial dosing consistent with current standard treatment guidelines. The following doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than one month of age, 1.8 mg/kg; one month to 1 year, 1.64 mg/kg [2] . A third retrospective study (n=140) also revealed that less than half of the population achieved therapeutic anti-Xa levels following the initial dose with the current standard treatment guidelines. The following higher doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than 2 months of age, 1.6 mg/kg; 2 months to 1 year, 1.5 mg/kg [3] .

In a retrospective study, whole-milligram enoxaparin dosing using insulin syringes (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) was associated with therapeutic anti-Xa levels and no reported dose measurement errors. The study included neonates, infants and children (n=514); 27% were infants less than 3 months of age (900 to 4700 g in weight). Five children (less than 1%) had a supra-therapeutic initial anti-Xa level without hemorrhagic consequences. No patients needed decimal dosing to attain therapeutic levels [4] .

Low-risk prophylaxis: 0.75 mg/kg per dose subQ every 12 hours.
Infants 2 months of age and older: 0.5 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor X_a level between 0.1 and 0.4 units/mL.

Administration

Administer by deep subQ injection. **Not for IM administration.**

Administration may be aided by using a small plastic indwelling subcutaneous catheter (Insuflon®, Hypoguard USA). Adverse events related to these catheters are much more frequent in ELBW infants.

Uses

Anticoagulation. Advantages over standard unfractionated heparin:
(1) May be given subcutaneously,
(2) More predictable pharmacokinetics,
(3) Minimal monitoring,
(4) Dosing every 12 hours,
(5) Less frequent bleeding complications. One disadvantage is the inability to quickly and completely reverse its anticoagulant effects.

Call 1-800-NOCLOTS for case reporting and treatment guidance.

Contraindications/Precautions

Contraindicated in presence of active major bleeding or in patients with thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin.
Major bleeding may occur even with anti-factor X_a levels in the therapeutic range. The overall incidence is approximately 4%. Reported complications include major bleeding

or hematoma at the administration site, compartment syndrome, intracranial hemorrhage, and gastrointestinal hemorrhage.

Black Box Warning Epidural or spinal hematomas, which may result in long-term or permanent paralysis, may occur in patients who are anticoagulated with low molecular weight heparins or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. Factors that can increase the risk of developing these hematomas include: use of indwelling epidural catheters, concomitant use of drugs affecting hemostasis such as NSAIDs, platelet inhibitors, or other anticoagulants, or history of traumatic or repeated epidural or spinal puncture, spinal deformity, or spinal surgery. Monitor patients frequently for neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider risks/benefits before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Pharmacology

Enoxaparin is a low-molecular weight heparin that has considerably less activity against thrombin than does standard heparin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. It is also much less likely to interfere with platelet function or cause osteoporosis. It activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Bioavailability is almost 100% after subcutaneous administration, with peak activity 2.5 to 4 hours later. The apparent half-life of anti-$X_a$activity is 4 to 5 hours. Clearance in neonates is more rapid than in older infants, children or adults.

Monitoring

Measure anti-factor Xa concentrations 4 to 6 hours after a dose (therapeutic range, 0.5 and 1 unit/mL). If measured 2 to 6 hours after a dose, target therapeutic range is 0.5 to 0.8 units/mL. Preterm infants are likely to require several dosage adjustments to achieve the target levels. Obtain anti-factor Xa levels initially, weekly during hospitalization, and then every 3 to 4 weeks in stable patients. After attaining target levels, dosage adjustments will be necessary once or twice a month, perhaps more often in preterm infants and infants with hepatic or renal dysfunction. Obtain CBC (including platelet count) and liver function tests during therapy. Monitor blood pressure. Monitor patients with renal impairment closely during therapy (dose reduction necessary). Assess for signs of bleeding and thrombosis. Patients undergoing concomitant neuraxial anesthesia or spinal puncture should be monitored frequently for neurological impairment indicating possible spinal or epidural hematoma [5] [6] [7] [8] .

Special Considerations/Preparation

Available as 100-mg/mL concentration as 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL in preservative-free prefilled syringes. Multidose vial available in 100-mg/mL concentration with 15 mg benzyl alcohol per 1 mL as a preservative.
Undiluted enoxaparin (100 mg/mL) transferred to tuberculin syringes and stored under

refrigeration retained anti-Xa activity for 10 days. Syringes stored at room temperature did not retain anti-Xa activity.

Enoxaparin Dilution

A 20-mg/mL enoxaparin dilution (in preservative-free sterile water) was stable for 4 weeks in glass vials stored at room temperature. The same dilution was stable in 1-mL tuberculin syringes (6 mg/0.3 mL) for 2 weeks stored at room temperature or under refrigeration. The stability end-point was significant loss of anti-Xa activity; sterility and pyrogenicity tests were not performed [9] .

In another stability study, enoxaparin (20 mg/mL in 1-mL tuberculin syringes) diluted in 4% glucose retained greater than 99% of the baseline anti-Xa activity when stored under refrigeration (4 degrees C) for 31 days. A decrease of 10% (statistically significant) of the initial anti-Xa activity was noted when enoxaparin (20 mg/mL in 1 mL tuberculin syringes) was diluted with sterile water and stored under the same conditions. Stability of enoxaparin in commercially available 5% glucose solution was not tested in this study; however, the authors suggest that an increase in glucose concentration would not affect the stability of the dilution [10] .

A 20-mg/mL enoxaparin dilution in 0.9% normal saline (in 1-mL polypropylene syringes; 10 mg/0.5 mL) was stable for up to 43 days when stored at room temperature or under refrigeration (2 to 8 degrees C). At least 90% of the baseline anti-Xa activity was retained under these conditions [11] .

Enoxaparin 120 mg (1.2 mL) diluted to 100 mL in 0.9% normal saline (1.2 mg/mL final concentration) in polyvinyl chloride containers was stable for up to 48 hours at room temperature; greater than 94% of the baseline anti-Xa activity was retained during the time period [12] .

Solution Compatibility

NS, D_5W, and sterile water.

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Title Enoxaparin

Dose

Treatment of Thrombosis:
Term infants: initial, 1.7 mg/kg per dose subQ every 12 hours.
Preterm infants: initial, 2 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor X_a level between 0.5 and 1.0 unit/mL. It will usually take several days to attain levels in the target range.
Dosage requirements to maintain target anti-factor X_a levels in preterm infants are quite variable, ranging from 0.8 to 3 mg/kg every 12 hours.
Infants 2 months of age and older: initial, 1 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor Xa level between 0.5 and 1 unit/mL. It will usually take several days to attain levels in the target range. A suggested dosage adjustment is 0.125 mg/kg/dose until therapeutic anti-Xa level is achieved.

Dosing Issues
Several retrospective studies have suggested that higher initial doses are required to more quickly achieve therapeutic anti-Xa levels and reduce the number of dosage adjustments. In one retrospective study in children (n=192), higher initial doses (1.7 mg/kg every 12 hours for children 3 months of age and younger; 1.2 mg/kg every 12 hours for children greater than 3 months of age) achieved more rapid therapeutic anti-factor Xa levels resulting in fewer venipunctures, without an increase in adverse events, compared with standard doses. Treatment outcomes (resolution or reduction of thrombus) were not different between groups. The authors concluded a higher starting dose of 1.8 mg/kg every 12 hours for infants less than 3 months of age and 1.5 mg/kg every 12 hours for children 3 to 12 months of age may be considered [1] . Another retrospective study (n=150) found that only 41% of patients attained therapeutic anti-Xa levels with initial dosing consistent with current standard treatment guidelines. The following doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than one month of age, 1.8 mg/kg; one month to 1 year, 1.64 mg/kg [2] . A third retrospective study (n=140) also revealed that less than half of the population achieved therapeutic anti-Xa levels following the initial dose with the current standard treatment guidelines. The following higher doses were required to achieve a therapeutic anti-Xa level (dose given every 12 hours): less than 2 months of age, 1.6 mg/kg; 2 months to 1 year, 1.5 mg/kg [3] .

In a retrospective study, whole-milligram enoxaparin dosing using insulin syringes (undiluted 100 mg/mL; 1 mg enoxaparin = 0.01 mL = 1 unit) was associated with therapeutic anti-Xa levels and no reported dose measurement errors. The study included neonates, infants and children (n=514); 27% were infants less than 3 months of age (900 to 4700 g in weight). Five children (less than 1%) had a supra-therapeutic initial anti-Xa level without hemorrhagic consequences. No patients needed decimal dosing to attain therapeutic levels [4] .

Low-risk prophylaxis: 0.75 mg/kg per dose subQ every 12 hours.
Infants 2 months of age and older: 0.5 mg/kg per dose subQ every 12 hours.
Adjust dosage to maintain anti-factor X_a level between 0.1 and 0.4 units/mL.

Administration

Administer by deep subQ injection. **Not for IM administration.**

Administration may be aided by using a small plastic indwelling subcutaneous catheter (Insuflon®, Hypoguard USA). Adverse events related to these catheters are much more frequent in ELBW infants.

Uses

Anticoagulation. Advantages over standard unfractionated heparin:
(1) May be given subcutaneously,
(2) More predictable pharmacokinetics,
(3) Minimal monitoring,
(4) Dosing every 12 hours,
(5) Less frequent bleeding complications. One disadvantage is the inability to quickly and completely reverse its anticoagulant effects.

Call 1-800-NOCLOTS for case reporting and treatment guidance.

Contraindications/Precautions

Contraindicated in presence of active major bleeding or in patients with thrombocytopenia associated with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin.
Major bleeding may occur even with anti-factor X_a levels in the therapeutic range. The overall incidence is approximately 4%. Reported complications include major bleeding or hematoma at the administration site, compartment syndrome, intracranial hemorrhage, and gastrointestinal hemorrhage.

Black Box Warning Epidural or spinal hematomas, which may result in long-term or permanent paralysis, may occur in patients who are anticoagulated with low molecular weight heparins or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. Factors that can increase the risk of developing these hematomas include: use of indwelling epidural catheters, concomitant use of drugs affecting hemostasis such as NSAIDs, platelet inhibitors, or other anticoagulants, or history of traumatic or repeated epidural or spinal puncture, spinal deformity, or spinal surgery. Monitor patients frequently for neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider risks/benefits before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

Pharmacology

Enoxaparin is a low-molecular weight heparin that has considerably less activity against thrombin than does standard heparin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. It is also much less likely to interfere with platelet function or cause osteoporosis. It activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Bioavailability is almost 100%

after subcutaneous administration, with peak activity 2.5 to 4 hours later. The apparent half-life of anti-$X_a$activity is 4 to 5 hours. Clearance in neonates is more rapid than in older infants, children or adults.

Monitoring

Measure anti-factor Xa concentrations 4 to 6 hours after a dose (therapeutic range, 0.5 and 1 unit/mL). If measured 2 to 6 hours after a dose, target therapeutic range is 0.5 to 0.8 units/mL. Preterm infants are likely to require several dosage adjustments to achieve the target levels. Obtain anti-factor Xa levels initially, weekly during hospitalization, and then every 3 to 4 weeks in stable patients. After attaining target levels, dosage adjustments will be necessary once or twice a month, perhaps more often in preterm infants and infants with hepatic or renal dysfunction. Obtain CBC (including platelet count) and liver function tests during therapy. Monitor blood pressure. Monitor patients with renal impairment closely during therapy (dose reduction necessary). Assess for signs of bleeding and thrombosis. Patients undergoing concomitant neuraxial anesthesia or spinal puncture should be monitored frequently for neurological impairment indicating possible spinal or epidural hematoma [5] [6] [7] [8] .

Special Considerations/Preparation

Available as 100-mg/mL concentration as 30 mg/0.3 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL in preservative-free prefilled syringes. Multidose vial available in 100-mg/mL concentration with 15 mg benzyl alcohol per 1 mL as a preservative.
Undiluted enoxaparin (100 mg/mL) transferred to tuberculin syringes and stored under refrigeration retained anti-Xa activity for 10 days. Syringes stored at room temperature did not retain anti-Xa activity.

Enoxaparin Dilution
A 20-mg/mL enoxaparin dilution (in preservative-free sterile water) was stable for 4 weeks in glass vials stored at room temperature. The same dilution was stable in 1-mL tuberculin syringes (6 mg/0.3 mL) for 2 weeks stored at room temperature or under refrigeration. The stability end-point was significant loss of anti-Xa activity; sterility and pyrogenicity tests were not performed [9] .
In another stability study, enoxaparin (20 mg/mL in 1-mL tuberculin syringes) diluted in 4% glucose retained greater than 99% of the baseline anti-Xa activity when stored under refrigeration (4 degrees C) for 31 days. A decrease of 10% (statistically significant) of the initial anti-Xa activity was noted when enoxaparin (20 mg/mL in 1 mL tuberculin syringes) was diluted with sterile water and stored under the same conditions. Stability of enoxaparin in commercially available 5% glucose solution was not tested in this study; however, the authors suggest that an increase in glucose concentration would not affect the stability of the dilution [10] .
A 20-mg/mL enoxaparin dilution in 0.9% normal saline (in 1-mL polypropylene syringes; 10 mg/0.5 mL) was stable for up to 43 days when stored at room temperature or under refrigeration (2 to 8 degrees C). At least 90% of the baseline anti-Xa activity was retained under these conditions [11] .
Enoxaparin 120 mg (1.2 mL) diluted to 100 mL in 0.9% normal saline (1.2 mg/mL final concentration) in polyvinyl chloride containers was stable for up to 48 hours at room

temperature; greater than 94% of the baseline anti-Xa activity was retained during the time period [12] .

Solution Compatibility

NS, D_5W, and sterile water.

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1.65 Epoetin alfa

Title Epoetin alfa

Dose

200 to 400 units/kg/dose, 3 to 5 times per week, for 2 to 6 weeks.
Total dose **per week** is 600 to 1400 units per kg.

Short course: 300 units/kg/dose daily for 10 days.

Administer subQ, or IV over at least 4 hours (even continuously in total parenteral nutrition).
Supplemental iron therapy should be initiated concurrently.

Administration

Note: Do not use epoetin alfa from multidose vials in neonates or infants; contains benzyl alcohol. Do not use single-dose vials admixed with bacteriostatic saline containing benzyl alcohol in neonates and infants.

Uses

To stimulate erythropoiesis and decrease the need for erythrocyte transfusions in high-risk preterm infants. Those most likely to benefit are infants with birth weights less than 800 g and phlebotomy losses greater than 30 mL/kg.

Contraindications/Precautions

Contraindicated in patients with a known hypersensitivity to mammalian cell-derived products or albumin (human), patients with uncontrolled hypertension, or in patients with pure red cell aplasia that develops with epoetin or other erythropoietin protein drugs.
Multidose formulation contains benzyl alcohol; use single-dose vials in neonates.

Black Box Warning According to the manufacturer's black box warning, (adult) patients with renal failure experienced greater risks for death, serious cardiovascular events, and stroke when higher hemoglobin levels were achieved (greater than 11 g/dL). It is recommended that for (adult) patients with renal failure, the lowest dose should be used that will maintain hemoglobin levels sufficient to reduce the need for red blood cell transfusions. The relevance of this finding to the neonatal population is unknown.

Pharmacology

Epoetin alfa is a 165-amino acid glycoprotein manufactured by recombinant DNA technology that has the same biological effects as endogenous erythropoietin. It acts on mature erythroid progenitors, CFU-E, by binding to cell surface receptors and stimulating differentiation and cell division. Noticeable effects on hematocrit and reticulocyte counts occur within 2 weeks. Adequate iron and protein intake is necessary for epoetin to be effective (additional Vitamin E intake may be necessary as well). Subcutaneously administered drug appears to be pharmacodynamically as effective as IV, despite only 40% bioavailability. Half-life of r-HuEPO in preterm infants is approximately 12 hours. Doses reported in the literature are all stated as units/kg **per week**. Efficacy may be dose dependent in the range of 500 to 1500 units/kg per week (see meta-analysis by Garcia et al), but no differences were observed in the randomized trial by Maier et al.

Adverse Effects

The only adverse effect in premature neonates is neutropenia, which occurs rarely and resolves with discontinuation of the drug.

Monitoring

Weekly CBC to check for neutropenia and monitor RBC response.

Special Considerations/Preparation

Available in preservative-free, single-use, 1-mL vials containing 2000, 3000, 4000, 10,000, or 40,000 units formulated in an isotonic, sodium chloride/sodium citrate

buffered solution with 2.5 mg human albumin. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze or shake.** Undiluted epoetin is stable in plastic syringes for 2 weeks. For IV infusion, dilute epoetin in 2 mL of solutions containing at least 0.05% protein and infuse over 4 hours. These dilutions are stable for 24 hours. Product support for use in neonates is handled by Ortho Biotech, Inc. (Procrit®). Multidose 1-mL (20,000 units/mL) and 2-mL (10,000 units/mL) vials are also available from both Ortho Biotech (Procrit®) and Amgen (Epogen®) containing 1% (10 mg/mL) benzyl alcohol solution with 2.5-mg albumin per mL. Discard multidose vials 21 days after initial entry.

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- Product Information: Procrit® epoetin alfa, Ortho Biotech, 2011.

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Administration

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Uses

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Weekly CBC to check for neutropenia and monitor RBC response.

Special Considerations/Preparation

Available in preservative-free, single-use, 1-mL vials containing 2000, 3000, 4000, 10,000, or 40,000 units formulated in an isotonic, sodium chloride/sodium citrate buffered solution with 2.5 mg human albumin. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze or shake.** Undiluted epoetin is stable in plastic syringes for 2 weeks. For IV infusion, dilute epoetin in 2 mL of solutions containing at least 0.05% protein and infuse over 4 hours. These dilutions are stable for 24 hours. Product support for use in neonates is handled by Ortho Biotech, Inc. (Procrit®). Multidose 1-mL (20,000 units/mL) and 2-mL (10,000 units/mL) vials are also available from both Ortho Biotech (Procrit®) and Amgen (Epogen®) containing 1% (10 mg/mL) benzyl alcohol solution with 2.5-mg albumin per mL. Discard multidose vials 21 days after initial entry.

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- Meyer MP, Meyer JH, Commerford A, et al: Recombinant erythropoietin in the treatment of the anemia of prematurity: Results of a double-blind, placebo-controlled study. *Pediatrics* 1994;93:918.
- Product Information: Epogen® epoetin alfa, Amgen, 2011.
- Product Information: Procrit® epoetin alfa, Ortho Biotech, 2011.

1.66 Erythromycin

Title Erythromycin

Dose

Oral
Treatment of pneumonitis and conjunctivitis due to Chlamydia trachomatis: 12.5 mg/kg per dose orally every 6 hours for 14 days.

Treatment and prophylaxis of pertussis: 12.5 mg/kg per dose orally every 6 hours for 14 days. The drug of choice in infants younger than 1 month of age is azithromycin. Administer with infant formula to enhance absorption of the ethylsuccinate and reduce possible GI side effects.

Treatment of feeding intolerance due to dysmotility: 10 mg/kg per dose orally every 6 hours for 2 days, followed by 4 mg/kg per dose orally every 6 hours for 5 days.

Other infections and prophylaxis: 10 mg/kg per dose orally every 6 hours.

Intravenous
Severe infections when oral route unavailable: 5 to 10 mg/kg per dose IV infusion by syringe pump over at least 60 minutes every 6 hours.
Do not administer IM.

Ophthalmic
Prophylaxis of ophthalmia neonatorum: Ribbon of 0.5% ointment instilled in each conjunctival sac.

Administration

Intravenous: Give as intermittent infusion over at least 60 minutes at a concentration of 1 to 5 mg/mL. IV push administration is not recommended [1] .

Uses

Treatment of infections caused by *Chlamydia, Mycoplasma,*and *Ureaplasma.*Treatment for and prophylaxis against *Bordetella pertussis.*As a substitute for penicillin in situations of significant allergic intolerance. As a prokinetic agent in cases of feeding intolerance.

Contraindications/Precautions

Contraindicated in patients receiving terfenadine, astemizole, pimozide, cisapride, ergotamine, or dihydroergotamine [2] [3] [4] .

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported. Infantile hypertropic pyloric stenosis occurred in 5% of infants receiving erythromycin for pertussis prophylaxis. QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, have been reported with erythromycin. Risk factors include electrolyte imbalances, liver impairment, myocardial ischemia, left ventricular dysfunction, idiopathic QT prolongation, and concurrent antiarrhythmic therapy. Reversible hearing loss (mainly in patients with renal impairment or patients receiving high doses) has been reported [1] [2] [3] [4] . Clindamycin should not be used in

combination with topical or oral erythromycin-containing products due to possible antagonism [5] .

Pharmacology

Erythromycin may be bacteriostatic or bactericidal depending on the tissue concentration of drug and the microorganism involved. IV administration of E. lactobionate to preterm infants, using doses of 6.25 to 10 mg/kg, yielded peak serum concentrations of 1.9 to 3.7 mcg/mL and a half-life of 2 hours. The drug penetrates poorly into the CNS, is concentrated in the liver and bile, and is excreted via the bowel. It is a motilin receptor agonist and induces stomach and small intestine motor activity. Plasma clearance of midazolam is reduced by 50%. Digoxin, midazolam, theophylline and carbamazepine serum concentrations may be significantly increased because of prolongation of their half-life.

Adverse Effects

The risk of hypertrophic pyloric stenosis is increased 10-fold in neonates under 2 weeks of age who receive oral erythromycin for pertussis prophylaxis (1 additional case per every 42 infants treated). No studies of premature infants with feeding intolerance have been large enough to assess safety. Two reported cases of severe bradycardia and hypotension occurring during IV administration of erythromycin lactobionate. Intrahepatic cholestasis. Loose stools occur infrequently. Bilateral sensorineural hearing loss has been reported rarely in adults, usually associated with intravenous administration and renal or hepatic dysfunction. The hearing loss occurred after the first few doses and was reversible after discontinuing the drug. Venous irritation is common when using the IV dosage form.

Monitoring

Watch for diarrhea and signs of abdominal discomfort. CBC for eosinophilia. **Monitor heart rate and blood pressure closely during IV administration.** Observe IV site for signs of infiltration.

Special Considerations/Preparation

Erythromycin ethylsuccinate oral suspension is available in concentrations of 200 mg- and 400 mg per 5 mL. Refrigeration not required except to preserve taste. Shake suspension well before administering. To prepare a 20 mg/mL dilution of the oral suspension, dilute 5 mL of the 200 mg/5 mL (40 mg/mL) erythromycin ethylsuccinate suspension (suspension made from powder for suspension only) up to a final volume of 10 mL with sterile water. Erythromycin ethylsuccinate suspension made from powder for suspension, at usual concentrations of 40 mg/mL and 80 mg/mL, is stable for 35 days at room temperature.

Available as powder for injection in 500-mg and 1-g vials. Reconstitute 500-mg vial with 10 mL of sterile water for injection to concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 2 weeks in refrigerator. After reconstitution, dilute to a concentration of 1 to 5 mg/mL for infusion. To make a 5-

mg/mL dilution, add 1 mL of reconstituted solution to 9 mL sterile water for injection. Use diluted drug within 8 hours [1] .

Erythromycin ophthalmic is available as a 0.5% ointment. In the event of a shortage, the CDC recommends azithromycin ophthalmic solution 1%. Tobramycin ophthalmic ointment may be used if azithromycin solution is not available .

Solution Compatibility

NS and sterile water for injection.

Solution Incompatibility

D_5W and $D_{10}W$ (unless buffered with 4% sodium bicarbonate to maintain stability).

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, aminophylline, amiodarone, cimetidine, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, lidocaine, lorazepam, magnesium sulfate, midazolam, morphine, nicardipine, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefotaxime, ceftazidime, chloramphenicol, fluconazole, furosemide, linezolid, and metoclopramide.

References

- American Academy of Pediatrics. Chlamydia trachomatis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: p255.
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- Centers for Disease Control and Prevention. CDC guidance on shortage of erythromycin (0.5%) ophthalmic ointment-September 2009. Available at: http://www.cdc.gov/std/treatment/2006/erythromycinointmentshortage.htm.
- Eichenwald H: Adverse reactions to erythromycin. *Pediatr Infect Dis* 1986;5:147.
- Farrar HC, Walsh-Sukys MC, Kyllonen K, Blumer JL: Cardiac toxicity associated with intravenous erythromycin lactobionate: Two case reports and a review of the literature. *Pediatr Infect Dis J* 1993;12:688.
- Ginsburg CM: Pharmacology of erythromycin in infants and children. *Pediatr Infect Dis* 1986;5:124.
- Gouyon JB, Benoit A, Betremieux P, et al: Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994;13:840-841.
- Honein MA, Paulozzi LJ, Himelright IM, et al: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet*1999;354:2101-2105.
- Ng PC: Use of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Neonatology* 2009;95:97-104.

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- Nuntnarumit P, Kiatchoosakun P, Tantiprapa W, Boonkasidecha S: Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006;148:600-605.
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- Patole S, Rao S, Doherty D: Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F301-F306.
- Waites KB, Sims PJ, Crouse DT, et al: Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for *Ureaplasma* urealyticum infection. *Pediatr Infect Dis J* 1994;13:287.

1. Product Information: Erythrocin(R) Lactobionate-IV intravenous injection, erythromycin lactobionate intravenous injection. Hospira Inc. (per FDA), Lake Forest, IL, Dec, 2011.
2. Product Information: Eryped oral suspension, erythromycin ethylsuccinate oral suspension. Abbott Laboratories, North Chicago, IL, Jan, 2011.
3. Product Information: PCE oral tablets, erythromycin oral tablets. Abbott Laboratories, North Chicago, IL, Nov, 2010.
4. Product Information: E.E.S.(R) oral suspension, oral film-coated tablets, erythromycin ethylsuccinate oral suspension, oral film-coated tablets. Arbor Pharmaceuticals, Inc. (per FDA), Atlanta, GA, Jan, 2012.
5. Product Information: CLEOCIN PHOSPHATE IV, IM solution, clindamycin phosphate IV,IM solution. Pfizer Inc, New York, NY, Jun1, 2007.

Title Erythromycin

Dose

Oral

Treatment of pneumonitis and conjunctivitis due to Chlamydia trachomatis: 12.5 mg/kg per dose orally every 6 hours for 14 days.

Treatment and prophylaxis of pertussis: 12.5 mg/kg per dose orally every 6 hours for 14 days. The drug of choice in infants younger than 1 month of age is azithromycin. Administer with infant formula to enhance absorption of the ethylsuccinate and reduce possible GI side effects.

Treatment of feeding intolerance due to dysmotility: 10 mg/kg per dose orally every 6 hours for 2 days, followed by 4 mg/kg per dose orally every 6 hours for 5 days.

Other infections and prophylaxis: 10 mg/kg per dose orally every 6 hours.

Intravenous

Severe infections when oral route unavailable: 5 to 10 mg/kg per dose IV infusion by syringe pump over at least 60 minutes every 6 hours.

Do not administer IM.

Ophthalmic
Prophylaxis of ophthalmia neonatorum: Ribbon of 0.5% ointment instilled in each conjunctival sac.

Administration

Intravenous: Give as intermittent infusion over at least 60 minutes at a concentration of 1 to 5 mg/mL. IV push administration is not recommended [1] .

Uses

Treatment of infections caused by *Chlamydia, Mycoplasma,*and *Ureaplasma.*Treatment for and prophylaxis against *Bordetella pertussis.*As a substitute for penicillin in situations of significant allergic intolerance. As a prokinetic agent in cases of feeding intolerance.

Contraindications/Precautions

Contraindicated in patients receiving terfenadine, astemizole, pimozide, cisapride, ergotamine, or dihydroergotamine [2] [3] [4] .

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported. Infantile hypertropic pyloric stenosis occurred in 5% of infants receiving erythromycin for pertussis prophylaxis. QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes, have been reported with erythromycin. Risk factors include electrolyte imbalances, liver impairment, myocardial ischemia, left ventricular dysfunction, idiopathic QT prolongation, and concurrent antiarrhythmic therapy. Reversible hearing loss (mainly in patients with renal impairment or patients receiving high doses) has been reported [1] [2] [3] [4] . Clindamycin should not be used in combination with topical or oral erythromycin-containing products due to possible antagonism [5] .

Pharmacology

Erythromycin may be bacteriostatic or bactericidal depending on the tissue concentration of drug and the microorganism involved. IV administration of E. lactobionate to preterm infants, using doses of 6.25 to 10 mg/kg, yielded peak serum concentrations of 1.9 to 3.7 mcg/mL and a half-life of 2 hours. The drug penetrates poorly into the CNS, is concentrated in the liver and bile, and is excreted via the bowel. It is a motilin receptor agonist and induces stomach and small intestine motor activity. Plasma clearance of midazolam is reduced by 50%. Digoxin, midazolam, theophylline and carbamazepine serum concentrations may be significantly increased because of prolongation of their half-life.

Adverse Effects

The risk of hypertrophic pyloric stenosis is increased 10-fold in neonates under 2 weeks of age who receive oral erythromycin for pertussis prophylaxis (1 additional case per

every 42 infants treated). No studies of premature infants with feeding intolerance have been large enough to assess safety. Two reported cases of severe bradycardia and hypotension occurring during IV administration of erythromycin lactobionate. Intrahepatic cholestasis. Loose stools occur infrequently. Bilateral sensorineural hearing loss has been reported rarely in adults, usually associated with intravenous administration and renal or hepatic dysfunction. The hearing loss occurred after the first few doses and was reversible after discontinuing the drug. Venous irritation is common when using the IV dosage form.

Monitoring

Watch for diarrhea and signs of abdominal discomfort. CBC for eosinophilia. **Monitor heart rate and blood pressure closely during IV administration.** Observe IV site for signs of infiltration.

Special Considerations/Preparation

Erythromycin ethylsuccinate oral suspension is available in concentrations of 200 mg- and 400 mg per 5 mL. Refrigeration not required except to preserve taste. Shake suspension well before administering. To prepare a 20 mg/mL dilution of the oral suspension, dilute 5 mL of the 200 mg/5 mL (40 mg/mL) erythromycin ethylsuccinate suspension (suspension made from powder for suspension only) up to a final volume of 10 mL with sterile water. Erythromycin ethylsuccinate suspension made from powder for suspension, at usual concentrations of 40 mg/mL and 80 mg/mL, is stable for 35 days at room temperature.

Available as powder for injection in 500-mg and 1-g vials. Reconstitute 500-mg vial with 10 mL of sterile water for injection to concentration of 50 mg/mL. Reconstituted solution stable for 24 hours at room temperature or 2 weeks in refrigerator. After reconstitution, dilute to a concentration of 1 to 5 mg/mL for infusion. To make a 5-mg/mL dilution, add 1 mL of reconstituted solution to 9 mL sterile water for injection. Use diluted drug within 8 hours [1] .

Erythromycin ophthalmic is available as a 0.5% ointment. In the event of a shortage, the CDC recommends azithromycin ophthalmic solution 1%. Tobramycin ophthalmic ointment may be used if azithromycin solution is not available .

Solution Compatibility

NS and sterile water for injection.

Solution Incompatibility

D_5W and $D_{10}W$ (unless buffered with 4% sodium bicarbonate to maintain stability).

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, aminophylline, amiodarone, cimetidine, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, lidocaine,

lorazepam, magnesium sulfate, midazolam, morphine, nicardipine, penicillin G, pentobarbital, potassium chloride, ranitidine, sodium bicarbonate, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefotaxime, ceftazidime, chloramphenicol, fluconazole, furosemide, linezolid, and metoclopramide.

References

- American Academy of Pediatrics. Chlamydia trachomatis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: p255.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Centers for Disease Control and Prevention. CDC guidance on shortage of erythromycin (0.5%) ophthalmic ointment-September 2009. Available at: http://www.cdc.gov/std/treatment/2006/erythromycinointmentshortage.htm.
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- Farrar HC, Walsh-Sukys MC, Kyllonen K, Blumer JL: Cardiac toxicity associated with intravenous erythromycin lactobionate: Two case reports and a review of the literature. *Pediatr Infect Dis J* 1993;12:688.
- Ginsburg CM: Pharmacology of erythromycin in infants and children. *Pediatr Infect Dis* 1986;5:124.
- Gouyon JB, Benoit A, Betremieux P, et al: Cardiac toxicity of intravenous erythromycin lactobionate in preterm infants. *Pediatr Infect Dis J* 1994;13:840-841.
- Honein MA, Paulozzi LJ, Himelright IM, et al: Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. *Lancet*1999;354:2101-2105.
- Ng PC: Use of oral erythromycin for the treatment of gastrointestinal dysmotility in preterm infants. *Neonatology* 2009;95:97-104.
- Ng PC, Lee CH, Wong SP, et al: High-dose oral erythromycin decreased the incidence of parenteral nutrition-associated cholestasis in preterm infants. *Gastroenterology* 2007;132:1726-1739.
- Nuntnarumit P, Kiatchoosakun P, Tantiprapa W, Boonkasidecha S: Efficacy of oral erythromycin for treatment of feeding intolerance in preterm infants. *J Pediatr* 2006;148:600-605.
- Oei J, Lui K: A placebo-controlled trial of low-dose erythromycin to promote feed tolerance in preterm infants. *ActaPaediatr*2001;90:904-908.
- Pai MP, Graci DM, Amsden GW: Macrolide drug interactions: an update. *Ann Pharmacother* 2000;34:495-513.
- Patole S, Rao S, Doherty D: Erythromycin as a prokinetic agent in preterm neonates: a systematic review. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F301-F306.
- Waites KB, Sims PJ, Crouse DT, et al: Serum concentrations of erythromycin after intravenous infusion in preterm neonates treated for *Ureaplasma* urealyticum infection. *Pediatr Infect Dis J* 1994;13:287.

1. Product Information: Erythrocin(R) Lactobionate-IV intravenous injection, erythromycin lactobionate intravenous injection. Hospira Inc. (per FDA), Lake Forest, IL, Dec, 2011.

2. Product Information: Eryped oral suspension, erythromycin ethylsuccinate oral suspension. Abbott Laboratories, North Chicago, IL, Jan, 2011.
3. Product Information: PCE oral tablets, erythromycin oral tablets. Abbott Laboratories, North Chicago, IL, Nov, 2010.
4. Product Information: E.E.S.(R) oral suspension, oral film-coated tablets, erythromycin ethylsuccinate oral suspension, oral film-coated tablets. Arbor Pharmaceuticals, Inc. (per FDA), Atlanta, GA, Jan, 2012.
5. Product Information: CLEOCIN PHOSPHATE IV, IM solution, clindamycin phosphate IV,IM solution. Pfizer Inc, New York, NY, Jun1, 2007.

1.67 Esmolol

Title Esmolol

Dose

Starting IV doses:
Supraventricular tachycardia (SVT): 100 mcg/kg per minute continuous infusion. Increase in increments of 50 to 100 mcg/kg per minute every 5 minutes until control of the ventricular rate is achieved.

Acute management of postoperative hypertension: 50 mcg/kg per minute continuous infusion. Increase in increments of 25 to 50 mcg/kg per minute every 5 minutes until desired blood pressure is achieved.

Usual maximum dosage: 200 mcg/kg per minute.
Doses greater than 300 mcg/kg per minute are likely to cause hypotension.

Uses

Short term treatment of postoperative hypertension, supraventricular tachycardia (SVT), and ventricular tachycardia (VT).

Contraindications/Precautions

Contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure [1] .

Pharmacology

Esmolol is a potent cardio-selective beta-blocking agent with a uniquely short half-life (2.8 to 4.5 minutes) and a brief (10 to 15 minute) duration of action. There appears to be no correlation between age and pharmacodynamic response or pharmacokinetic profile. Esmolol is cleared primarily by red blood cell esterases. Renal or hepatic failure does not effect elimination.

Adverse Effects

May cause hypotension in high doses. Adverse effects reversible with discontinuation of drug. Monitor IV site closely for vein irritation and phlebitis, especially at high concentrations (greater than 10 mg/mL).

Monitoring

Continuous EKG monitoring during acute treatment of arrhythmias. Measure systemic blood pressure and heart rate frequently.

Special Considerations/Preparation

Esmolol is supplied in preservative-free 10-mL (10 mg/mL) vials, and 2500 mg/250 mL and 2000 mg/100 mL ready-to-use premixed bags. The pH is approximately 4.5 to 5.5. Osmolarity is 312 mOsm/L. Store at room temperature. Stable for at least 24 hours at room temperature or refrigeration when diluted in compatible solutions to a concentration of 10 mg/mL.

Solution Compatibility

D_5W, LR, D_5LR, NS, ½ NS, D_5 ½ NS, and D_5NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, atracurium, calcium chloride, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, gentamicin, heparin, hydrocortisone, insulin, linezolid, magnesium sulfate, metronidazole, micafungin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, norepinephrine, pancuronium, penicillin G, phenytoin, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, furosemide, procainamide, and sodium bicarbonate 5% injection.

References

- Cuneo B, Zales VR, Blahunka PC, et al: Pharmacodynamics and pharmacokinetics of esmolol, a short-acting β-blocking agent, in children. *Pediatr Cardiol* 1994;15:296-301.
- Trippel MD, Wiest DB, Gillette PC: Cardiovascular and antiarrhythmic effects of esmolol in children. *J Pediatr* 1991;119:142-147.
- Wiest DB, Garner SS, Uber WE, et al: Esmolol for the management of pediatric hypertension after cardiac operations. *J Thoracic Cardiov Surg* 1998;115:890-897.
- Wiest DB, Trippel MD, Gillette PC, et al: Pharmacokinetics of esmolol in children. *Clin Pharmacol Ther*1991;49:618-623.

1. Product Information: BREVIBLOC IV injection, esmolol hcl IV injection. Baxter Healthcare Corporation, Deerfield, IL, Nov6, 2007.

Title Esmolol

Dose

Starting IV doses:
Supraventricular tachycardia (SVT): 100 mcg/kg per minute continuous infusion. Increase in increments of 50 to 100 mcg/kg per minute every 5 minutes until control of the ventricular rate is achieved.

Acute management of postoperative hypertension: 50 mcg/kg per minute continuous infusion. Increase in increments of 25 to 50 mcg/kg per minute every 5 minutes until desired blood pressure is achieved.

Usual maximum dosage: 200 mcg/kg per minute.
Doses greater than 300 mcg/kg per minute are likely to cause hypotension.

Uses

Short term treatment of postoperative hypertension, supraventricular tachycardia (SVT), and ventricular tachycardia (VT).

Contraindications/Precautions

Contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure [1] .

Pharmacology

Esmolol is a potent cardio-selective beta-blocking agent with a uniquely short half-life (2.8 to 4.5 minutes) and a brief (10 to 15 minute) duration of action. There appears to be no correlation between age and pharmacodynamic response or pharmacokinetic profile. Esmolol is cleared primarily by red blood cell esterases. Renal or hepatic failure does not effect elimination.

Adverse Effects

May cause hypotension in high doses. Adverse effects reversible with discontinuation of drug. Monitor IV site closely for vein irritation and phlebitis, especially at high concentrations (greater than 10 mg/mL).

Monitoring

Continuous EKG monitoring during acute treatment of arrhythmias. Measure systemic blood pressure and heart rate frequently.

Special Considerations/Preparation

Esmolol is supplied in preservative-free 10-mL (10 mg/mL) vials, and 2500 mg/250 mL and 2000 mg/100 mL ready-to-use premixed bags. The pH is approximately 4.5 to 5.5. Osmolarity is 312 mOsm/L. Store at room temperature. Stable for at least 24 hours at room temperature or refrigeration when diluted in compatible solutions to a concentration of 10 mg/mL.

Solution Compatibility

D_5W, LR, D_5LR, NS, ½ NS, D_5 ½ NS, and D_5NS.

Terminal Injection Site Compatibility

Amikacin, aminophylline, atracurium, calcium chloride, cefazolin, ceftazidime, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, gentamicin, heparin, hydrocortisone, insulin, linezolid, magnesium sulfate, metronidazole, micafungin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, norepinephrine, pancuronium, penicillin G, phenytoin, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, furosemide, procainamide, and sodium bicarbonate 5% injection.

References

- Cuneo B, Zales VR, Blahunka PC, et al: Pharmacodynamics and pharmacokinetics of esmolol, a short-acting β-blocking agent, in children. *Pediatr Cardiol* 1994;15:296-301.
- Trippel MD, Wiest DB, Gillette PC: Cardiovascular and antiarrhythmic effects of esmolol in children. *J Pediatr* 1991;119:142-147.
- Wiest DB, Garner SS, Uber WE, et al: Esmolol for the management of pediatric hypertension after cardiac operations. *J Thoracic Cardiov Surg* 1998;115:890-897.
- Wiest DB, Trippel MD, Gillette PC, et al: Pharmacokinetics of esmolol in children. *Clin Pharmacol Ther*1991;49:618-623.

1. Product Information: BREVIBLOC IV injection, esmolol hcl IV injection. Baxter Healthcare Corporation, Deerfield, IL, Nov6, 2007.

1.68 Famotidine

Title Famotidine

Dose

IV: 0.25 to 0.5 mg/kg/dose IV slow push every 24 hours.
Continuous infusion of the daily dose in adults provides better gastric acid suppression than intermittent dosing.
Oral: 0.5 to 1 mg/kg/dose orally every 24 hours.

Administration

IV push: Dilute to concentration of 2 to 4 mg/mL with 0.9% NS; give over a period of at least 2 minutes.
Oral: Shake oral suspension vigorously for 5 to 10 seconds prior to each use.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Elimination half-life is dependent on renal function, and decreases with age from 11 hours (range 5 to 22) in neonates to 8 hours (range 4 to 12) by 3 months of age. Oral bioavailability is 42 to 50%.

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for late-onset bacterial and fungal sepsis. Routine gastric acid suppression in neonates should be avoided. No short term adverse effects have been reported in infants and children, although data are limited to a few small studies. The most common (less than 5% of patients) adverse effects noted in adults were headache, dizziness, constipation, and diarrhea.

Monitoring

Gastric pH may be measured to assess efficacy (greater than 4).

Special Considerations/Preparation

Available as 10-mg/mL solution for intravenous use in 2-mL preservative-free single-dose vials, and 4-mL multidose vials containing 0.9% (9 mg/mL) benzyl alcohol as a preservative. A 1-mg/mL dilution may be made by adding 1 mL of the 10 mg/mL concentrated solution to 9 mL of sterile water for injection. Dilution stable for 7 days at room temperature. Although diluted Pepcid® Injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of Pepcid® Injection should be refrigerated and used within 48 hours.

Pepcid® for oral suspension is supplied as a powder containing 400 mg famotidine. Constitute by slowly adding 46 mL Purified Water and shaking vigorously for 5-10 seconds. Final concentration 40 mg/5 mL (8 mg/mL). Stable at room temperature for 30 days. Shake bottle before each use.

Solution Compatibility

D_5W, $D_{10}W$, NS, and Dex/AA solutions.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, ampicillin, atropine, aztreonam, calcium gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fluconazole, flumazenil, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, metoclopramide, mezlocillin, midazolam, morphine, nafcillin, nicardipine, nitroglycerin, oxacillin, phenytoin, piperacillin, potassium chloride, procainamide, propofol, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Azithromycin, cefepime and piperacillin/tazobactam.

References

- Graham PL, Begg MD, Larson E, et al: Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J* 2006;25:113-117.
- Saiman L, Ludington E, Pfaller M, et al: Risk factors for candidemia in neonatal intensive care unit patients. *Pediatr Infect Dis J* 2000;19:319-324.
- Wenning LA, Murphy MG, James LP, et al: Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005;44:395-406.
- James LP, Marotti T, Stowe CD, et al: Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998;38:1089-1095.
- James LP, Marshall JD, Heulitt MJ, et al: Pharmacokinetics and pharmacodynamics of famotidine in children. *J Clin Pharmacol* 1996;21:48-54.
- Bullock L, Fitzgerald JF, Glick MR: Stability of famotidine 20 and 50 mg/L in total nutrient admixtures. *Am J Hosp Pharm* 1989;46:2326-29.
- Product information, Merck Inc., 2006.
- Product information, Salix, 2007.

Title Famotidine

Dose

IV: 0.25 to 0.5 mg/kg/dose IV slow push every 24 hours.
Continuous infusion of the daily dose in adults provides better gastric acid suppression than intermittent dosing.
Oral: 0.5 to 1 mg/kg/dose orally every 24 hours.

Administration

IV push: Dilute to concentration of 2 to 4 mg/mL with 0.9% NS; give over a period of at least 2 minutes.
Oral: Shake oral suspension vigorously for 5 to 10 seconds prior to each use.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Elimination half-life is dependent on renal function, and decreases with age from 11 hours (range 5 to 22) in neonates to 8 hours (range 4 to 12) by 3 months of age. Oral bioavailability is 42 to 50%.

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for late-onset bacterial and fungal sepsis. Routine gastric acid suppression in neonates should be avoided. No short term adverse effects have been reported in infants and children, although data are limited to a few small studies. The most common (less than 5% of patients) adverse effects noted in adults were headache, dizziness, constipation, and diarrhea.

Monitoring

Gastric pH may be measured to assess efficacy (greater than 4).

Special Considerations/Preparation

Available as 10-mg/mL solution for intravenous use in 2-mL preservative-free single-dose vials, and 4-mL multidose vials containing 0.9% (9 mg/mL) benzyl alcohol as a preservative. A 1-mg/mL dilution may be made by adding 1 mL of the 10 mg/mL concentrated solution to 9 mL of sterile water for injection. Dilution stable for 7 days at room temperature. Although diluted Pepcid® Injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of Pepcid® Injection should be refrigerated and used within 48 hours.

Pepcid® for oral suspension is supplied as a powder containing 400 mg famotidine. Constitute by slowly adding 46 mL Purified Water and shaking vigorously for 5-10 seconds. Final concentration 40 mg/5 mL (8 mg/mL). Stable at room temperature for 30 days. Shake bottle before each use.

Solution Compatibility

D_5W, $D_{10}W$, NS, and Dex/AA solutions.

Terminal Injection Site Compatibility

Acyclovir, aminophylline, amiodarone, ampicillin, atropine, aztreonam, calcium gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, fluconazole, flumazenil, furosemide, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium sulfate, metoclopramide, mezlocillin, midazolam,

morphine, nafcillin, nicardipine, nitroglycerin, oxacillin, phenytoin, piperacillin, potassium chloride, procainamide, propofol, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Azithromycin, cefepime and piperacillin/tazobactam.

References

- Graham PL, Begg MD, Larson E, et al: Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J* 2006;25:113-117.
- Saiman L, Ludington E, Pfaller M, et al: Risk factors for candidemia in neonatal intensive care unit patients. *Pediatr Infect Dis J* 2000;19:319-324.
- Wenning LA, Murphy MG, James LP, et al: Pharmacokinetics of famotidine in infants. *Clin Pharmacokinet* 2005;44:395-406.
- James LP, Marotti T, Stowe CD, et al: Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol* 1998;38:1089-1095.
- James LP, Marshall JD, Heulitt MJ, et al: Pharmacokinetics and pharmacodynamics of famotidine in children. *J Clin Pharmacol* 1996;21:48-54.
- Bullock L, Fitzgerald JF, Glick MR: Stability of famotidine 20 and 50 mg/L in total nutrient admixtures. *Am J Hosp Pharm* 1989;46:2326-29.
- Product information, Merck Inc., 2006.
- Product information, Salix, 2007.

1.69 Fat Emulsion

Title Fat Emulsion

Dose

Begin at 0.5 g/kg per day IV increasing by 0.5 g/kg per day to a maximum of 3 g/kg per day. Infusion rate should not exceed 0.15 g/kg per hour. 24 hour infusion times are preferred. Essential fatty acid deficiency may be prevented with 0.5 to 1 g/kg per day.

Fat Emulsion

	Intralipid ® 20%	**Liposyn II ® 20%**	**Liposyn III ® 20%**
Oils (%)			
Safflower	0	10	0
Soybean	20	10	20
Fatty Acid Content (%)			

Linoleic	50	65.8	54.5
Oleic	26	17.7	22.4
Palmitic	10	8.8	10.5
Linolenic	9	4.2	8.3
Stearic	3.5	3.4	4.2
Egg yolk phospholipid (%)	1.2	1.2	1.2
Glycerine (%)	2.25	2.5	2.5
Calories (per mL)	2	2	2
Osmolarity (mOsm/L)	260	258	292

Uses

Parenteral nutrition source of calories and essential fatty acids.

Black Box Warning According to the manufacturer's black box warning, deaths due to intravascular fat accumulation in the lungs of preterm infants after infusion of IV fat emulsion have been reported. Strict adherence to the recommended total daily dose and hourly infusion rates is recommended. Infusion rates should not exceed 1 g/kg in four hours.

Pharmacology

Intravenous fat emulsions are high caloric (2 calories/mL) isotonic emulsions of either soybean or safflower oil. Fat particle size is between 0.4 and 0.5 microns in diameter, similar to endogenous chylomicrons. Clearance is via endogenous lipoprotein lipase activity, which is limited in very premature (less than 28 weeks gestation) and infected infants. Twenty percent emulsions are preferred due to lower total phospholipid and liposome content per gram of triglyceride. Ten percent emulsions have been associated with hypercholesterolemia and hyperphospholipidemia. Destabilization of lipid emulsions (flocculation and separation) may occur when they are co-infused with Dex/AA solutions containing calcium and high concentrations (greater than 1 unit/mL) of heparin. This risk may be decreased by 1) minimizing the contact time; 2) using low (1 unit/mL or less) concentrations of heparin; and 3) adding a multivitamin preparation to the Dex/AA solution.

Adverse Effects

Hypertriglyceridemia and hyperglycemia. The minimum dose should be used in infants with severe hyperbilirubinemia, sepsis, or severe pulmonary dysfunction. Extravasation may cause tissue inflammation and necrosis.

Monitoring

Monitor serum triglycerides (less than 200 mg/dL), liver function test, platelet count, albumin, glucose, and bilirubin.

Special Considerations/Preparation

Liposyn® and Intralipid® are available in 10% and 20% concentrations in 50-, 100-, 250-, and 500-mL bottles. Store at room temperature. Do not freeze. Use within 24 hours when dispensed in syringes.

There are no specific data regarding the compatibility of dobutamine or dopamine and fat emulsions. Dobutamine and dopamine are most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dobutamine or dopamine and fat emulsion together; dobutamine or dopamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Ampicillin, cefazolin, cefotaxime, cefoxitin, chloramphenicol, clindamycin, digoxin, erythromycin lactobionate, famotidine, furosemide, gentamicin, heparin (1 unit/mL or less), isoproterenol, lidocaine, meropenem, netilmicin, norepinephrine, oxacillin, penicillin G, piperacillin/tazobactam, potassium chloride, sulfamethoxazole/trimethoprim, ticarcillin, and tobramycin.

Terminal Injection Site Incompatibility

Acyclovir, amikacin, amphotericin B, ganciclovir, lorazepam, magnesium chloride, midazolam, octreotide acetate, pentobarbital, phenobarbital, and phenytoin.

References

- Silvers KM, Darlow BA, Winterbourn CC: Pharmacologic levels of heparin do not destabilize neonatal parenteral nutrition. *J Parenter Enteral Nutr* 1998;22:311-314.
- Lipsky CL, Spear ML: Recent advances in parenteral nutrition. *Clin Perinatol* 1995;22:141-155.
- Haumont D, Deckelbaum RJ, Richelle M, Dahlan W, et al: Plasma lipid and plasma lipoprotein concentration in low birth weight infants given parenteral nutrition with twenty or ten percent lipid emulsion. *J Pediatr* 1989;115:787-93.
- Brans YW, Andrews DS, Carrillo DW, Dutton EP, et al: Tolerance of fat emulsions in very-low-birth-weight neonates. *Am J Dis Child* 1988;142:145-152.
- Kao LC, Cheng MH, Warburton D: Triglycerides, free fatty acids, free fatty acids/albumin molar ratio, and cholesterol levels in serum of neonates receiving long-term lipid infusions: Controlled trial of continuous and intermittent regimens. *J Pediatr* 1984;104:429-435.
- Product Information, Hospira, 2005.

Title Fat Emulsion

Dose

Begin at 0.5 g/kg per day IV increasing by 0.5 g/kg per day to a maximum of 3 g/kg per day. Infusion rate should not exceed 0.15 g/kg per hour. 24 hour infusion times are preferred. Essential fatty acid deficiency may be prevented with 0.5 to 1 g/kg per day.

Fat Emulsion

	Intralipid ® 20%	**Liposyn II ® 20%**	**Liposyn III ® 20%**
Oils (%)			
Safflower	0	10	0
Soybean	20	10	20
Fatty Acid Content (%)			
Linoleic	50	65.8	54.5
Oleic	26	17.7	22.4
Palmitic	10	8.8	10.5
Linolenic	9	4.2	8.3
Stearic	3.5	3.4	4.2
Egg yolk phospholipid (%)	1.2	1.2	1.2
Glycerine (%)	2.25	2.5	2.5
Calories (per mL)	2	2	2
Osmolarity (mOsm/L)	260	258	292

Uses

Parenteral nutrition source of calories and essential fatty acids.

Black Box Warning According to the manufacturer's black box warning, deaths due to intravascular fat accumulation in the lungs of preterm infants after infusion of IV fat emulsion have been reported. Strict adherence to the recommended total daily dose and hourly infusion rates is recommended. Infusion rates should not exceed 1 g/kg in four hours.

Pharmacology

Intravenous fat emulsions are high caloric (2 calories/mL) isotonic emulsions of either soybean or safflower oil. Fat particle size is between 0.4 and 0.5 microns in diameter, similar to endogenous chylomicrons. Clearance is via endogenous lipoprotein lipase activity, which is limited in very premature (less than 28 weeks gestation) and infected infants. Twenty percent emulsions are preferred due to lower total phospholipid and liposome content per gram of triglyceride. Ten percent emulsions have been associated with hypercholesterolemia and hyperphospholipidemia. Destabilization of lipid emulsions (flocculation and separation) may occur when they are co-infused with Dex/AA solutions containing calcium and high concentrations (greater than 1 unit/mL) of heparin. This risk may be decreased by 1) minimizing the contact time; 2) using low (1 unit/mL or less) concentrations of heparin; and 3) adding a multivitamin preparation to the Dex/AA solution.

Adverse Effects

Hypertriglyceridemia and hyperglycemia. The minimum dose should be used in infants with severe hyperbilirubinemia, sepsis, or severe pulmonary dysfunction. Extravasation may cause tissue inflammation and necrosis.

Monitoring

Monitor serum triglycerides (less than 200 mg/dL), liver function test, platelet count, albumin, glucose, and bilirubin.

Special Considerations/Preparation

Liposyn® and Intralipid® are available in 10% and 20% concentrations in 50-, 100-, 250-, and 500-mL bottles. Store at room temperature. Do not freeze. Use within 24 hours when dispensed in syringes.

There are no specific data regarding the compatibility of dobutamine or dopamine and fat emulsions. Dobutamine and dopamine are most stable in solutions with a pH at or below 5. In alkaline solutions, the catechol moieties are oxidized, cyclized, and polymerized to colored materials. All fat emulsions have pH ranges from 6 to 9. Caution is urged when co-infusing dobutamine or dopamine and fat emulsion together; dobutamine or dopamine may degrade over time in this alkaline pH resulting in lower than expected clinical effects.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Ampicillin, cefazolin, cefotaxime, cefoxitin, chloramphenicol, clindamycin, digoxin, erythromycin lactobionate, famotidine, furosemide, gentamicin, heparin (1 unit/mL or less), isoproterenol, lidocaine, meropenem, netilmicin, norepinephrine, oxacillin, penicillin G, piperacillin/tazobactam, potassium chloride, sulfamethoxazole/trimethoprim, ticarcillin, and tobramycin.

Terminal Injection Site Incompatibility

Acyclovir, amikacin, amphotericin B, ganciclovir, lorazepam, magnesium chloride, midazolam, octreotide acetate, pentobarbital, phenobarbital, and phenytoin.

References

- Silvers KM, Darlow BA, Winterbourn CC: Pharmacologic levels of heparin do not destabilize neonatal parenteral nutrition. *J Parenter Enteral Nutr* 1998;22:311-314.
- Lipsky CL, Spear ML: Recent advances in parenteral nutrition. *Clin Perinatol* 1995;22:141-155.
- Haumont D, Deckelbaum RJ, Richelle M, Dahlan W, et al: Plasma lipid and plasma lipoprotein concentration in low birth weight infants given parenteral nutrition with twenty or ten percent lipid emulsion. *J Pediatr* 1989;115:787-93.
- Brans YW, Andrews DS, Carrillo DW, Dutton EP, et al: Tolerance of fat emulsions in very-low-birth-weight neonates. *Am J Dis Child* 1988;142:145-152.
- Kao LC, Cheng MH, Warburton D: Triglycerides, free fatty acids, free fatty acids/albumin molar ratio, and cholesterol levels in serum of neonates receiving long-term lipid infusions: Controlled trial of continuous and intermittent regimens. *J Pediatr* 1984;104:429-435.
- Product Information, Hospira, 2005.

1.70 FentaNYL

Title FentaNYL

Dose

Sedation and Analgesia: 0.5 to 4 mcg/kg per dose IV slow push.
Repeat as required (usually every 2 to 4 hours).

Infusion rate: 1 to 5 mcg/kg per hour.
Tolerance may develop rapidly following constant infusion.

Anesthesia: 5 to 50 mcg/kg per dose.

Uses

Analgesia. Sedation. Anesthesia.

Pharmacology

Synthetic opioid narcotic analgesic that is 50 to 100 times more potent than morphine on a weight basis. Extremely lipid soluble. Penetrates the CNS rapidly. Transient rebound in fentanyl serum concentration may reflect sequestration and subsequent release of fentanyl from body fat. Metabolized extensively in the liver by CYP 3A4 enzyme system and then excreted by the kidney. Serum half-life is prolonged in patients with liver failure. Highly protein bound. Wide variability in apparent volume of distribution (10 to 30 L/kg) and serum half-life (1 to 15 hours).

Adverse Effects

Respiratory depression occurs when anesthetic doses (greater than 5 mcg/kg) are used and may also occur unexpectedly because of redistribution. Chest wall rigidity has occurred in 4% of neonates who received 2.2 to 6.5 mcg/kg per dose, occasionally associated with laryngospasm. This was reversible with administration of naloxone. Urinary retention may occur when using continuous infusions. Tolerance may develop to analgesic doses with prolonged use. Significant withdrawal symptoms have been reported in patients treated with continuous infusion for 5 days or longer.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention, loss of bowel sounds, and muscle rigidity.

Special Considerations/Preparation

Naloxone should be readily available to reverse adverse effects.
Available in 2-, 5-, 10-, and 20-mL ampules in a concentration of 50 mcg/mL. A 10-mcg/mL dilution may be made by adding 1 mL of the 50-mcg/mL concentration to 4 mL preservative-free normal saline. Stable for 24 hours refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amiodarone, atropine, caffeine citrate, cimetidine, dexamethasone, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Azithromycin, pentobarbital and phenytoin.

References

- Anand KJS and the International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;155:173-180.
- Fahnenstich H, Steffan J, Kau N, Bartmann P: Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000;28:836-839.
- Saarenmaa E, Neuvonen PJ, Fellman V: Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. *J Pediatr* 2000;136:767-770.
- Muller P and Vogtmann C: Three cases with different presentation of fentanyl-induced muscle rigidity-A rare problem in intensive care of neonates. *Am J Perinatol* 2000;17:23-26.
- Santeiro ML, Christie J, Stromquist C, et al: Pharmacokinetics of continuous infusion fentanyl in newborns. *J Perinatol* 1997;17:135-139.

- Arnold JH, Truog RD, Orav EJ, et al: Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology* 1990;73:1136.
- Koehntop DE, Rodman JH, Brundage DM, et al: Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986;65:227.
- Johnson KL, Erickson JP, Holley FO, Scott JC: Fentanyl pharmacokinetics in the pediatric population. *Anesthesiology* 1984;61:A441.
- Reilly CS, Wood AJ, Wood M: Variability of fentanyl pharmacokinetics in man. *Anaesthesia* 1984;40:837.
- Mather LE: Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983;8:422.
- Product Information, Hospira, 2005.

Title FentaNYL

Dose

Sedation and Analgesia: 0.5 to 4 mcg/kg per dose IV slow push.
Repeat as required (usually every 2 to 4 hours).

Infusion rate: 1 to 5 mcg/kg per hour.
Tolerance may develop rapidly following constant infusion.

Anesthesia: 5 to 50 mcg/kg per dose.

Uses

Analgesia. Sedation. Anesthesia.

Pharmacology

Synthetic opioid narcotic analgesic that is 50 to 100 times more potent than morphine on a weight basis. Extremely lipid soluble. Penetrates the CNS rapidly. Transient rebound in fentanyl serum concentration may reflect sequestration and subsequent release of fentanyl from body fat. Metabolized extensively in the liver by CYP 3A4 enzyme system and then excreted by the kidney. Serum half-life is prolonged in patients with liver failure. Highly protein bound. Wide variability in apparent volume of distribution (10 to 30 L/kg) and serum half-life (1 to 15 hours).

Adverse Effects

Respiratory depression occurs when anesthetic doses (greater than 5 mcg/kg) are used and may also occur unexpectedly because of redistribution. Chest wall rigidity has occurred in 4% of neonates who received 2.2 to 6.5 mcg/kg per dose, occasionally associated with laryngospasm. This was reversible with administration of naloxone. Urinary retention may occur when using continuous infusions. Tolerance may develop to analgesic doses with prolonged use. Significant withdrawal symptoms have been reported in patients treated with continuous infusion for 5 days or longer.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention, loss of bowel sounds, and muscle rigidity.

Special Considerations/Preparation

Naloxone should be readily available to reverse adverse effects.
Available in 2-, 5-, 10-, and 20-mL ampules in a concentration of 50 mcg/mL. A 10-mcg/mL dilution may be made by adding 1 mL of the 50-mcg/mL concentration to 4 mL preservative-free normal saline. Stable for 24 hours refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, amiodarone, atropine, caffeine citrate, cimetidine, dexamethasone, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, furosemide, heparin, hydrocortisone succinate, lidocaine, linezolid, lorazepam, metoclopramide, midazolam, milrinone, morphine, nafcillin, nicardipine, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Azithromycin, pentobarbital and phenytoin.

References

- Anand KJS and the International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med* 2001;155:173-180.
- Fahnenstich H, Steffan J, Kau N, Bartmann P: Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000;28:836-839.
- Saarenmaa E, Neuvonen PJ, Fellman V: Gestational age and birth weight effects on plasma clearance of fentanyl in newborn infants. *J Pediatr* 2000;136:767-770.
- Muller P and Vogtmann C: Three cases with different presentation of fentanyl-induced muscle rigidity-A rare problem in intensive care of neonates. *Am J Perinatol* 2000;17:23-26.
- Santeiro ML, Christie J, Stromquist C, et al: Pharmacokinetics of continuous infusion fentanyl in newborns. *J Perinatol* 1997;17:135-139.
- Arnold JH, Truog RD, Orav EJ, et al: Tolerance and dependence in neonates sedated with fentanyl during extracorporeal membrane oxygenation. *Anesthesiology* 1990;73:1136.
- Koehntop DE, Rodman JH, Brundage DM, et al: Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986;65:227.
- Johnson KL, Erickson JP, Holley FO, Scott JC: Fentanyl pharmacokinetics in the pediatric population. *Anesthesiology* 1984;61:A441.
- Reilly CS, Wood AJ, Wood M: Variability of fentanyl pharmacokinetics in man. *Anaesthesia* 1984;40:837.

- Mather LE: Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983;8:422.
- Product Information, Hospira, 2005.

1.71 Ferrous sulfate

Title Ferrous sulfate

Dose

2 mg/kg/day of elemental iron for growing premature infants. **(Maximum of 15 mg/day)**.
Begin therapy after 2 weeks of age.

Infants with birthweights less than 1000 grams may need 4 mg/kg/day.

6 mg/kg/day of elemental iron for patients receiving erythropoietin.
Administer orally in 1 or 2 divided doses, preferably diluted in formula.

Uses

Iron supplementation for prevention and treatment of anemia.

Pharmacology

Well absorbed from stomach.

Adverse Effects

In growing premature infants, iron supplementation should not be started until adequate vitamin E is supplied in the diet; otherwise, iron may increase hemolysis. Nausea, constipation, black stools, lethargy, hypotension, and erosion of gastric mucosa.

Monitoring

Monitor hemoglobin and reticulocyte counts during therapy.
Observe stools, check for constipation.

Special Considerations/Preparation

Drops: Ferrous sulfate drops available as 15 mg elemental iron per 1 mL (0.2% alcohol). **Confirm product concentration.**
Elixir: Contains 44 mg elemental iron per 5 mL (some with 5% alcohol).

References

- Rao R, Georgieff M: Microminerals. In: Tsang R, Uauy R, Koletzko B, Zlotkin S. *Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines.* Cincinnati, Ohio: Digital Publishing Inc; 2005: pp 277-288.
- Rao R, Georgieff MK: Neonatal iron nutrition. *Semin Neonatol*2001;6:425-35.

- Siimes MA, Jarvenpaa A-L: Prevention of anemia and iron deficiency in very low-birth-weight infants. *J Pediatr* 1982;101:277-280.
- Oski FA: Iron requirements of the premature infant, in Tsang R (ed): *Vitamin and Mineral Requirements in Preterm Infants*. New York: Marcel Dekker, 1985, p 18.
- Product Information, Mead Johnson, 2011

Title Ferrous sulfate

Dose

2 mg/kg/day of elemental iron for growing premature infants. **(Maximum of 15 mg/day)**.
Begin therapy after 2 weeks of age.

Infants with birthweights less than 1000 grams may need 4 mg/kg/day.

6 mg/kg/day of elemental iron for patients receiving erythropoietin.
Administer orally in 1 or 2 divided doses, preferably diluted in formula.

Uses

Iron supplementation for prevention and treatment of anemia.

Pharmacology

Well absorbed from stomach.

Adverse Effects

In growing premature infants, iron supplementation should not be started until adequate vitamin E is supplied in the diet; otherwise, iron may increase hemolysis. Nausea, constipation, black stools, lethargy, hypotension, and erosion of gastric mucosa.

Monitoring

Monitor hemoglobin and reticulocyte counts during therapy.
Observe stools, check for constipation.

Special Considerations/Preparation

Drops: Ferrous sulfate drops available as 15 mg elemental iron per 1 mL (0.2% alcohol). **Confirm product concentration.**
Elixir: Contains 44 mg elemental iron per 5 mL (some with 5% alcohol).

References

- Rao R, Georgieff M: Microminerals. In: Tsang R, Uauy R, Koletzko B, Zlotkin S. *Nutrition of the Preterm Infant. Scientific Basis and Practical Guidelines.* Cincinnati, Ohio: Digital Publishing Inc; 2005: pp 277-288.
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- Siimes MA, Jarvenpaa A-L: Prevention of anemia and iron deficiency in very low-birth-weight infants. *J Pediatr* 1982;101:277-280.
- Oski FA: Iron requirements of the premature infant, in Tsang R (ed): *Vitamin and Mineral Requirements in Preterm Infants*. New York: Marcel Dekker, 1985, p 18.
- Product Information, Mead Johnson, 2011

1.72 Flecainide

Title Flecainide

Dose

Begin at 2 mg/kg per dose every 12 hours orally. Adjust dose based on response and serum concentrations to a maximum of 4 mg/kg per dose every 12 hours. Correct preexisting hypokalemia or hyperkalemia before administration. Optimal effect may take 2 to 3 days of therapy to achieve, and steady-state plasma levels may not be reached until 3 to 5 days at a given dosage in patients with normal renal and hepatic function. Therefore, do not increase dosage more frequently than approximately once every 4 days.

Administration

Infant formulas and milk may decrease absorption. If milk is removed from the infant's diet, a reduction in dose should be considered [1] [2] [3] .

Uses

Treatment of supraventricular arrhythmias not responsive to conventional therapies. Not recommended in patients with structurally abnormal hearts.

Contraindications/Precautions

Contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock, unless a pacemaker is present. Also contraindicated in the presence of cardiogenic shock [1] .

Black Box Warning An excessive mortality or non-fatal cardiac arrest rate was seen in patients (adults) with asymptomatic non-life-threatening ventricular arrhythmias and a history of myocardial infarction treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group in the Cardiac Arrhythmia Suppression Trial (CAST). It is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. Flecainide is not recommended for use in patients with chronic atrial fibrillation. Case reports of ventricular proarrhythmic effects in patients treated with flecainide for atrial fibrillation/flutter have included increased PVCs, VT, ventricular fibrillation (VF), and death.

Pharmacology

Flecainide is a class IC antiarrhythmic that produces a dose-related decrease in intracardiac conduction in all parts of the heart, thereby increasing PR, QRS and QT intervals. Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times are less pronounced than those on the ventricle. Peak serum concentrations occur 2 to 3 hours after an oral dose. Infant formula and milk products interfere with drug absorption. Plasma protein binding is about 40% in adults and is independent of plasma drug level. Children under 1 year of age have elimination half-life values of 11 to 12 hours. Elimination half-life in newborns after maternal administration is as long as 29 hours.

Adverse Effects

Flecainide can cause new or worsened arrhythmias, including AV block, bradycardia, ventricular tachycardia, torsades de pointes. There is also a negative inotropic effect. Dizziness, blurred vision, and headache have been reported in children.

Monitoring

Continuous EKG during initiation of therapy, as this is the most common time to see drug-induced arrhythmias. Follow trough serum concentrations closely at initiation, 3 to 5 days after any dose change, and with any significant change in clinical status or diet. Therapeutic trough levels are 200 to 800 nanograms/mL.

Special Considerations/Preparation

Supplied in 50-mg, 100-mg, and 150-mg tablets. An oral suspension with a final concentration of 5 mg/mL can be made as follows: crush 6 (six) 100-mg tablets, slowly mix in 20 mL of a 1:1 mixture of Ora-Sweet® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) to form a uniform paste, then add to this mixture enough vehicle to make a final volume of 120 mL. Shake well and protect from light. Stable for 45 days refrigerated and at room temperature when stored in amber glass or plastic [4] .

An oral suspension with a final concentration of 20 mg/mL may also be compounded. Extemporaneously compounded flecainide acetate 20 mg/mL prepared in either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) and placed in a 120-mL amber polyethylene terephthalate bottle is stable, retaining a mean of at least 92% of the initial drug concentration, for up to 60 days when stored without light at 5 and 25 degrees C [5] .

References

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- Luedtke SA, Kuhn RJ, McCaffrey FM: Pharmacologic management of supraventricular tachycardia in children. *Ann Pharmacother* 1997;31:1227-43.
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Title Flecainide

Dose

Begin at 2 mg/kg per dose every 12 hours orally. Adjust dose based on response and serum concentrations to a maximum of 4 mg/kg per dose every 12 hours. Correct preexisting hypokalemia or hyperkalemia before administration. Optimal effect may take 2 to 3 days of therapy to achieve, and steady-state plasma levels may not be reached until 3 to 5 days at a given dosage in patients with normal renal and hepatic function. Therefore, do not increase dosage more frequently than approximately once every 4 days.

Administration

Infant formulas and milk may decrease absorption. If milk is removed from the infant's diet, a reduction in dose should be considered [1] [2] [3] .

Uses

Treatment of supraventricular arrhythmias not responsive to conventional therapies. Not recommended in patients with structurally abnormal hearts.

Contraindications/Precautions

Contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock, unless a pacemaker is present. Also contraindicated in the presence of cardiogenic shock [1] .

Black Box Warning An excessive mortality or non-fatal cardiac arrest rate was seen in patients (adults) with asymptomatic non-life-threatening ventricular arrhythmias and a history of myocardial infarction treated with flecainide compared with that seen in patients assigned to a carefully matched placebo-treated group in the Cardiac Arrhythmia Suppression Trial (CAST). It is prudent to consider the risks of Class IC agents (including flecainide), coupled with the lack of any evidence of improved survival, generally unacceptable in patients without life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs. Flecainide is not recommended for use in patients with chronic atrial fibrillation. Case reports of ventricular proarrhythmic effects in patients treated

with flecainide for atrial fibrillation/flutter have included increased PVCs, VT, ventricular fibrillation (VF), and death.

Pharmacology

Flecainide is a class IC antiarrhythmic that produces a dose-related decrease in intracardiac conduction in all parts of the heart, thereby increasing PR, QRS and QT intervals. Effects upon atrioventricular (AV) nodal conduction time and intra-atrial conduction times are less pronounced than those on the ventricle. Peak serum concentrations occur 2 to 3 hours after an oral dose. Infant formula and milk products interfere with drug absorption. Plasma protein binding is about 40% in adults and is independent of plasma drug level. Children under 1 year of age have elimination half-life values of 11 to 12 hours. Elimination half-life in newborns after maternal administration is as long as 29 hours.

Adverse Effects

Flecainide can cause new or worsened arrhythmias, including AV block, bradycardia, ventricular tachycardia, torsades de pointes. There is also a negative inotropic effect. Dizziness, blurred vision, and headache have been reported in children.

Monitoring

Continuous EKG during initiation of therapy, as this is the most common time to see drug-induced arrhythmias. Follow trough serum concentrations closely at initiation, 3 to 5 days after any dose change, and with any significant change in clinical status or diet. Therapeutic trough levels are 200 to 800 nanograms/mL.

Special Considerations/Preparation

Supplied in 50-mg, 100-mg, and 150-mg tablets. An oral suspension with a final concentration of 5 mg/mL can be made as follows: crush 6 (six) 100-mg tablets, slowly mix in 20 mL of a 1:1 mixture of Ora-Sweet® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) to form a uniform paste, then add to this mixture enough vehicle to make a final volume of 120 mL. Shake well and protect from light. Stable for 45 days refrigerated and at room temperature when stored in amber glass or plastic [4] .

An oral suspension with a final concentration of 20 mg/mL may also be compounded. Extemporaneously compounded flecainide acetate 20 mg/mL prepared in either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup) and placed in a 120-mL amber polyethylene terephthalate bottle is stable, retaining a mean of at least 92% of the initial drug concentration, for up to 60 days when stored without light at 5 and 25 degrees C [5] .

References

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- Luedtke SA, Kuhn RJ, McCaffrey FM: Pharmacologic management of supraventricular tachycardia in children. *Ann Pharmacother* 1997;31:1227-43.
- Perry JC, Garson A: Flecainide acetate for treatment of tachyarrhythmias in children: Review of world literature on efficacy, safety, and dosing. *Am Heart J* 1992;124:1614-21.

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4. Wiest DB, Garner SS, Pagacz LR et al: Stability of flecainide acetate in an extemporaneously compounded oral suspension. Am J Hosp Pharm Jun, 1992; 49(6): 1467-1470.
5. Allen LV: Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. Am J Health Syst Pharm Sep15, 1996; 53(18): 2179-2184.

1.73 Fluconazole

Title Fluconazole

Dose

Invasive Candidiasis: 12 to 25 mg/kg loading dose, then 6 to 12 mg/kg per dose IV, or orally.
Consider the higher doses for treating severe infections or *Candida* strains with higher MICs (4 to 8 mcg/mL). Extended dosing intervals should be considered for neonates with renal insufficiency (serum creatinine greater than 1.3 mg/dL).
Higher doses may be required in patients receiving extracorporeal membrane oxygenation (ECMO) [1] .
Note: The higher doses are based on recent pharmacokinetic data but have not been prospectively tested for efficacy or safety.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Invasive Candidiasis Dosing Interval Chart

Gest. Age (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 14	48
	>14	24
30 and older	0 to 7	48
	>7	24

Prophylaxis: 3 mg/kg per dose via IV infusion twice weekly, or orally.
A dose of 6 mg/kg twice weekly may be considered if targeting *Candida* strains with higher MICs (4 to 8 mcg/mL).
Consider prophylaxis only in VLBW infants at high risk for invasive fungal disease.

Thrush: 6 mg/kg on Day 1, then 3 mg/kg per dose every 24 hours orally.

Administration

Intravenous: Infuse at concentration of 2 mg/mL over 1 to 2 hours **(maximum rate 200 mg/hour)**. Solutions for intravenous infusion are supplied premade (glass bottle or Viaflex® plastic bag) in a concentration of 2 mg/mL [2] .

Oral: May be given with or without food [2] .

Uses

Treatment of systemic infections, meningitis, and severe superficial mycoses caused by *Candida* species. Resistance has been reported with *C glabrata* and *C krusei* and in patients receiving long-term suppressive therapy.

Contraindications/Precautions

Contraindicated in patients receiving **cisapride** due to precipitation of life-threatening arrhythmias [2] [3] .

Pharmacology

Water-soluble triazole antifungal agent. Inhibits cytochrome P-450-dependent ergosterol synthesis. Well absorbed after oral administration, with peak serum concentrations reached within 1 to 2 hours. Less than 12% protein binding. Good penetration into CSF after both oral and IV administration. Serum half-life is 30 to 180 hours in severely ill VLBW infants in the first 2 weeks of life and approximately 17 hours in children. Primarily excreted unchanged in the urine.

Adverse Effects

Data in neonates are limited. Reversible elevations of transaminases have occurred in 12% of children. A retrospective study using historical controls reports direct hyperbilirubinemia in the absence of elevated transaminases in some infants treated prophylactically for 6 weeks. Interferes with metabolism of barbiturates and phenytoin. May also interfere with metabolism of aminophylline, caffeine, theophylline, and midazolam.

Monitoring

Serum fluconazole concentrations are not routinely followed. Assess renal function. Follow AST, ALT, and direct bilirubin, especially in patients on the higher doses. Periodic CBC for eosinophilia.

Special Considerations/Preparation

Available as a premixed solution for IV injection in concentrations of 200 mg/100 mL and 400 mg/200 mL in Viaflex® bags or glass bottles (2 mg/mL). Do not remove overwrap from Viaflex® bag until ready for use. **Store at room temperature.Do not freeze**.

Oral dosage form is available as a powder for suspension in concentrations of 10 mg/mL and 40 mg/mL. Prepare both concentrations by adding 24 mL distilled water to bottle of powder and shaking vigorously. Each bottle will deliver 35 mL of suspension. Suspension is stable at room temperature for 2 weeks. **Do not freeze**.

Solution Compatibility

D_5W and $D_{10}W$.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, amiodarone, aztreonam, caspofungin, cefazolin, cefepime, cefoxitin, cimetidine, dexamethasone, dobutamine, dopamine, famotidine, ganciclovir, gentamicin, heparin, hydrocortisone succinate, intravenous immune globulin (human), linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, morphine, nafcillin, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenytoin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, calcium gluconate, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, digoxin, erythromycin lactobionate, furosemide, imipenem, piperacillin, ticarcillin, and trimethoprim/sulfamethoxazole.

References

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- Wade KC, Wu D, Kaufman DA, et al: Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother* 2008;52:4043-4049.
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- Huttova M, Hartmanova I, Kralinsky K, et al: Candida fungemia in neonates treated with fluconazole: report of forty cases, including eight with meningitis. *Pediatr Infect Dis J* 1998;17:1012-1015.

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- Saxen H, Hoppu K, Pohjavuori M: Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993;54:269.
- Dodds Ashley ES, Lewis R, Lewis JS, et al. Pharmacology of systemic antifungal agents. *Clin Infect Dis* 2006;43:S29-39.

1. Watt KM, Benjamin DK, Cheifetz IM et al: Pharmacokinetics and safety of fluconazole in young infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J Oct, 2012; 31(10): 1042-1047.
2. Product Information: DIFLUCAN(R) oral tablets, powder for oral suspension, solution for intravenous infusion, fluconazole oral tablets, powder for oral suspension, solution for intravenous infusion. Roerig, New York, NY, Aug, 2010.
3. Novelli V: Safety and tolerability of fluconazole in children. Antimicrob Agents Chemother Aug, 1999; 43(8): 1955-1960.

Title Fluconazole

Dose

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Consider the higher doses for treating severe infections or *Candida* strains with higher MICs (4 to 8 mcg/mL). Extended dosing intervals should be considered for neonates with renal insufficiency (serum creatinine greater than 1.3 mg/dL).
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Consider prophylaxis only in VLBW infants at high risk for invasive fungal disease.

Thrush: 6 mg/kg on Day 1, then 3 mg/kg per dose every 24 hours orally.

Administration

Intravenous: Infuse at concentration of 2 mg/mL over 1 to 2 hours **(maximum rate 200 mg/hour)**. Solutions for intravenous infusion are supplied premade (glass bottle or Viaflex® plastic bag) in a concentration of 2 mg/mL [2] .

Oral: May be given with or without food [2] .

Uses

Treatment of systemic infections, meningitis, and severe superficial mycoses caused by *Candida* species. Resistance has been reported with *C glabrata* and *C krusei* and in patients receiving long-term suppressive therapy.

Contraindications/Precautions

Contraindicated in patients receiving **cisapride** due to precipitation of life-threatening arrhythmias [2] [3] .

Pharmacology

Water-soluble triazole antifungal agent. Inhibits cytochrome P-450-dependent ergosterol synthesis. Well absorbed after oral administration, with peak serum concentrations reached within 1 to 2 hours. Less than 12% protein binding. Good penetration into CSF after both oral and IV administration. Serum half-life is 30 to 180 hours in severely ill VLBW infants in the first 2 weeks of life and approximately 17 hours in children. Primarily excreted unchanged in the urine.

Adverse Effects

Data in neonates are limited. Reversible elevations of transaminases have occurred in 12% of children. A retrospective study using historical controls reports direct hyperbilirubinemia in the absence of elevated transaminases in some infants treated prophylactically for 6 weeks. Interferes with metabolism of barbiturates and phenytoin. May also interfere with metabolism of aminophylline, caffeine, theophylline, and midazolam.

Monitoring

Serum fluconazole concentrations are not routinely followed. Assess renal function. Follow AST, ALT, and direct bilirubin, especially in patients on the higher doses. Periodic CBC for eosinophilia.

Special Considerations/Preparation

Available as a premixed solution for IV injection in concentrations of 200 mg/100 mL and 400 mg/200 mL in Viaflex® bags or glass bottles (2 mg/mL). Do not remove overwrap from Viaflex® bag until ready for use. **Store at room temperature.Do not freeze**.

Oral dosage form is available as a powder for suspension in concentrations of 10 mg/mL and 40 mg/mL. Prepare both concentrations by adding 24 mL distilled water to bottle of powder and shaking vigorously. Each bottle will deliver 35 mL of suspension. Suspension is stable at room temperature for 2 weeks. **Do not freeze**.

Solution Compatibility

D_5W and $D_{10}W$.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, amiodarone, aztreonam, caspofungin, cefazolin, cefepime, cefoxitin, cimetidine, dexamethasone, dobutamine, dopamine, famotidine, ganciclovir, gentamicin, heparin, hydrocortisone succinate, intravenous immune globulin (human), linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, morphine, nafcillin, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenytoin, piperacillin/tazobactam, potassium chloride, propofol, quinupristin/dalfopristin, ranitidine, remifentanil, ticarcillin/clavulanate, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, calcium gluconate, cefotaxime, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, digoxin, erythromycin lactobionate, furosemide, imipenem, piperacillin, ticarcillin, and trimethoprim/sulfamethoxazole.

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- Saxen H, Hoppu K, Pohjavuori M: Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther* 1993;54:269.
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3. Novelli V: Safety and tolerability of fluconazole in children. Antimicrob Agents Chemother Aug, 1999; 43(8): 1955-1960.

1.74 Flucytosine

Title Flucytosine

Dose

12.5 to 37.5 mg/kg per dose every 6 hours orally. Increase dosing interval if renal dysfunction is present.

Uses

Antifungal agent used in combination with amphotericin B or fluconazole for treatment of infections caused by *Candida*, *Cryptococcus*, and other sensitive fungi.

Black Box Warning According to the manufacturer's black box warning, extreme caution is recommended in patients with impaired renal function. Close monitoring of hematologic, renal, and hepatic status of all patients is essential.

Pharmacology

Well absorbed orally. Transformed within cell to fluorouracil, which interferes with RNA synthesis. Excellent penetration into CSF and body tissues. 90% renal elimination

of unchanged drug, proportional to GFR. Serum half-life in adults is 3 to 5 hours if renal function is normal, but 30 to 250 hours if renal impairment is present. Limited pharmacokinetic data in premature infants. Resistance develops frequently if used alone. Synergistic with amphotericin even if treating resistant strain.

Adverse Effects

Toxicities are related to serum concentration above 100 mcg/mL, and are usually reversible if the drug is stopped or the dose is reduced. Fatal bone marrow depression (related to fluorouracil production), hepatitis, severe diarrhea, rash. Amphotericin B may increase toxicity by decreasing renal excretion.

Monitoring

Desired peak serum concentration ranges from 50 to 80 mcg/mL. Assess renal function. Follow GI status closely. Twice-weekly CBC and platelet counts. Periodic AST, ALT.

Special Considerations/Preparation

Flucytosine is available as 250- and 500-mg capsules. A pediatric suspension (10 mg/mL) may be prepared by mixing contents of four 250-mg capsules with enough vehicle (1:1 mixture of Ora-Sweet® (or Ora-Sweet SF®) and Ora-Plus® or cherry syrup) to make a final volume of 100 mL. Suspension is stable for 60 days at room temperature or under refrigeration. Shake well before use and **protect from light**.

A 50-mg/mL suspension may be prepared by mixing six 500-mg capsules with enough vehicle (1:1 mixture of Ora-Plus® and Ora-Sweet NF® (or other syrup)) to make a final volume of 60 mL. Suspension is stable for at least 90 days when stored at room temperature or under refrigeration. Shake well before use.

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Title Flucytosine

Dose

12.5 to 37.5 mg/kg per dose every 6 hours orally. Increase dosing interval if renal dysfunction is present.

Uses

Antifungal agent used in combination with amphotericin B or fluconazole for treatment of infections caused by *Candida*, *Cryptococcus*, and other sensitive fungi.

Black Box Warning According to the manufacturer's black box warning, extreme caution is recommended in patients with impaired renal function. Close monitoring of hematologic, renal, and hepatic status of all patients is essential.

Pharmacology

Well absorbed orally. Transformed within cell to fluorouracil, which interferes with RNA synthesis. Excellent penetration into CSF and body tissues. 90% renal elimination of unchanged drug, proportional to GFR. Serum half-life in adults is 3 to 5 hours if renal function is normal, but 30 to 250 hours if renal impairment is present. Limited pharmacokinetic data in premature infants. Resistance develops frequently if used alone. Synergistic with amphotericin even if treating resistant strain.

Adverse Effects

Toxicities are related to serum concentration above 100 mcg/mL, and are usually reversible if the drug is stopped or the dose is reduced. Fatal bone marrow depression (related to fluorouracil production), hepatitis, severe diarrhea, rash. Amphotericin B may increase toxicity by decreasing renal excretion.

Monitoring

Desired peak serum concentration ranges from 50 to 80 mcg/mL. Assess renal function. Follow GI status closely. Twice-weekly CBC and platelet counts. Periodic AST, ALT.

Special Considerations/Preparation

Flucytosine is available as 250- and 500-mg capsules. A pediatric suspension (10 mg/mL) may be prepared by mixing contents of four 250-mg capsules with enough vehicle (1:1 mixture of Ora-Sweet® (or Ora-Sweet SF®) and Ora-Plus® or cherry syrup) to make a final volume of 100 mL. Suspension is stable for 60 days at room temperature or under refrigeration. Shake well before use and **protect from light**.

A 50-mg/mL suspension may be prepared by mixing six 500-mg capsules with enough vehicle (1:1 mixture of Ora-Plus® and Ora-Sweet NF® (or other syrup)) to make a final volume of 60 mL. Suspension is stable for at least 90 days when stored at room temperature or under refrigeration. Shake well before use.

References

- Marr B, Gross S, Cunningham C, et al: Candidal sepsis and meningitis in a very-low-birth-weight infant successfully treated with fluconazole and flucytosine. *Clin Infect Dis*1994;19:795.
- Smego RA, Perfect JR, Durack DT: Combined therapy with amphotericin B and 5-fluorocytosine for *Candida* meningitis. *Rev Infect Dis* 1984;6:791.
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- Koldin MH, Medoff G: Antifungal chemotherapy. *Pediatr Clin North Am* 1983;30:49.
- Product Information, Valeant Pharmaceuticals, 2005.

1.75 Flumazenil

Title Flumazenil

Dose

IV: 5 to 10 mcg/kg/dose IV over 15 seconds. May repeat every 45 seconds until the patient is awake. Maximum total cumulative dose should not exceed 50 mcg/kg (0.05 mg/kg) or 1 mg in infants, whichever is smaller (data in infants older than 1 year). No reported maximum dose in neonates has been tested. Administer intravenously through a freely running large vein to minimize pain upon injection.

Intranasal: 40 mcg/kg/dose divided equally between both nostrils. Administer via TB syringe for accurate equal dosing.

Rectal:15 to 30 mcg/kg/dose, may repeat if sedation not reversed within 15 to 20 minutes.

Uses

Reversal of sedative effect from benzodiazepines, in cases of suspected benzodiazepines overdose, and in neonatal apnea secondary to prenatal benzodiazepine exposure.

Black Box Warning According to the manufacturer's black box warning, the use of flumazenil has been associated with the occurrence of seizures. Seizures are most frequent in patients who have been on benzodiazepines for long-term sedation.

Pharmacology

Imidazobenzodiazepine that is a benzodiazepine receptor antagonist. Competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor. Eliminated rapidly by hepatic metabolism to three inactive metabolites. Highly lipid soluble and penetrates the brain rapidly. Elimination half-life in children 20 to 75 minutes. Peak concentration reached in 3 minutes when delivered intravenously (children). Limited pharmacokinetic data in neonates.

Adverse Effects

The reported experience in neonates is very limited. Use with caution in neonates with preexisting seizure disorders. Hypotension has been reported in adults following rapid administration. Resedation has been reported in 10% of treated pediatric patients, occurring 19 to 50 minutes after initial dosing. May cause pain on injection. Observe IV site for extravasation.

Monitoring

Monitor for the return of sedation and respiratory depression. Continuous EKG and blood pressure.

Special Considerations/Preparation

Available in an injectable form as a 0.1 mg/mL concentration in 5- and 10-mL multidose vials. If drawn into a syringe or mixed with D_5W, LR, or NS, discard solution after 24 hours. Discard opened vials within 24 hours. Store at room temperature. Injectable preparation may be given intranasally or rectally.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Aminophylline, cimetidine, dobutamine, dopamine, famotidine, heparin, lidocaine, procainamide, and ranitidine.

References

- Phelps SJ, Hak EB: *Pediatric Injectable Drugs.*Maryland: American Society of Health System Pharmacists, 2004, p176.
- Zaw W, Knoppert DC, da Silva O: Flumazenil's reversal of myoclonic-like movements associated with midazolam in term newborns. *Pharmacotherapy*2001;21:642-6.
- Carbajal R, Simon N, Blanc P, et al: Rectal flumazenil to reverse midazolam sedation in children. *Anest Analog* 1996;82:895.
- Richard P, Autret E, Bardol J, et al: The use of flumazenil in a neonate. *Clin Toxicol* 1991;29:137-40.
- Brogden RN, Goa KL: Flumazenil. A review of its benzodiazepine antagonist properties, intrinsic activity and therapeutic use. *Drugs* 1988;35:448-67.
- Product Information, Roche, 2007.

Title Flumazenil

Dose

IV: 5 to 10 mcg/kg/dose IV over 15 seconds. May repeat every 45 seconds until the patient is awake. Maximum total cumulative dose should not exceed 50 mcg/kg (0.05 mg/kg) or 1 mg in infants, whichever is smaller (data in infants older than 1 year). No reported maximum dose in neonates has been tested. Administer intravenously through a freely running large vein to minimize pain upon injection.

Intranasal: 40 mcg/kg/dose divided equally between both nostrils. Administer via TB syringe for accurate equal dosing.

Rectal:15 to 30 mcg/kg/dose, may repeat if sedation not reversed within 15 to 20 minutes.

Uses

Reversal of sedative effect from benzodiazepines, in cases of suspected benzodiazepines overdose, and in neonatal apnea secondary to prenatal benzodiazepine exposure.

Black Box Warning According to the manufacturer's black box warning, the use of flumazenil has been associated with the occurrence of seizures. Seizures are most frequent in patients who have been on benzodiazepines for long-term sedation.

Pharmacology

Imidazobenzodiazepine that is a benzodiazepine receptor antagonist. Competitively inhibits the activity at the benzodiazepine recognition site on the GABA/benzodiazepine receptor. Eliminated rapidly by hepatic metabolism to three inactive metabolites. Highly lipid soluble and penetrates the brain rapidly. Elimination half-life in children 20 to 75 minutes. Peak concentration reached in 3 minutes when delivered intravenously (children). Limited pharmacokinetic data in neonates.

Adverse Effects

The reported experience in neonates is very limited. Use with caution in neonates with preexisting seizure disorders. Hypotension has been reported in adults following rapid administration. Resedation has been reported in 10% of treated pediatric patients, occurring 19 to 50 minutes after initial dosing. May cause pain on injection. Observe IV site for extravasation.

Monitoring

Monitor for the return of sedation and respiratory depression. Continuous EKG and blood pressure.

Special Considerations/Preparation

Available in an injectable form as a 0.1 mg/mL concentration in 5- and 10-mL multidose vials. If drawn into a syringe or mixed with D_5W, LR, or NS, discard solution after 24 hours. Discard opened vials within 24 hours. Store at room temperature. Injectable preparation may be given intranasally or rectally.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Aminophylline, cimetidine, dobutamine, dopamine, famotidine, heparin, lidocaine, procainamide, and ranitidine.

References

- Phelps SJ, Hak EB: *Pediatric Injectable Drugs.*Maryland: American Society of Health System Pharmacists, 2004, p176.
- Zaw W, Knoppert DC, da Silva O: Flumazenil's reversal of myoclonic-like movements associated with midazolam in term newborns. *Pharmacotherapy*2001;21:642-6.
- Carbajal R, Simon N, Blanc P, et al: Rectal flumazenil to reverse midazolam sedation in children. *Anest Analog* 1996;82:895.
- Richard P, Autret E, Bardol J, et al: The use of flumazenil in a neonate. *Clin Toxicol* 1991;29:137-40.
- Brogden RN, Goa KL: Flumazenil. A review of its benzodiazepine antagonist properties, intrinsic activity and therapeutic use. *Drugs* 1988;35:448-67.
- Product Information, Roche, 2007.

1.76 Fosphenytoin

Title Fosphenytoin

Dose

Note: Fosphenytoin dosing is expressed in phenytoin equivalents (PE). (Fosphenytoin 1 mg PE = phenytoin 1 mg) [1] .

Loading dose: 15 to 20 mg PE/kg IM or IV infusion over at least 10 minutes.

Maintenance dose: 4 to 8 mg PE/kg every 24 hours IM or IV slow push. Begin maintenance 24 hours after loading dose.
Term infants older than 1 week of age may require up to 8 mg PE/kg per dose every 8 to 12 hours.

Administration

Intravenous: Administer loading dose as an IV infusion at a rate of 1 to 3 mg PE/kg per minute (**maximum 150 mg PE/minute**) at a concentration of 1.5 to 25 mg PE/mL. Dilute in 5% dextrose or normal saline. May administer maintenance dose slow IV push (undiluted) at the same rate (1 to 3 mg PE/kg per minute; **maximum 150 mg PE/minute**) [1] [2] [3] [4] [5] .
Intramuscular: Administer undiluted. May divide dose and give in more than one site [1] [5] [6] .

Uses

Anticonvulsant. Generally used to treat seizures that are refractory to phenobarbital. Can be administered with lorazepam for rapid onset of seizure control.

Black Box Warning

The rate of intravenous fosphenytoin administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous fosphenytoin. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these

events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [1] .

Pharmacology

Fosphenytoin is a water-soluble prodrug of phenytoin rapidly converted by phosphatases in blood and tissue. It has no known intrinsic pharmacologic activity before conversion to phenytoin. Each 1.5 mg of fosphenytoin is metabolically converted to 1 mg phenytoin. Nonlinear (zero order) kinetics (as dose increases, saturation of elimination mechanisms occur leading to progressive accumulation of phenytoin). After IV administration, peak concentration is reached at end of infusion. After IM administration, peak is reached in approximately 20 to 30 minutes. Conversion half-life of fosphenytoin administered intravenously to infants and children is approximately 8 minutes. No drugs have been identified to interfere with the conversion of fosphenytoin to phenytoin. Fosphenytoin is highly protein bound (adults 95% to 99%); only free fraction can cross blood-brain barrier. Primarily eliminated through hepatic metabolism. Potent inducer of cytochrome P450 enzyme systems resulting in a reduction of serum levels of drugs metabolized by this system. Renal excretion is negligible. Serum half-life reflects that of phenytoin (18 to 70 hours) due to rapid conversion. The conversion of fosphenytoin to phenytoin yields very small amounts of formaldehyde and phosphate. This is only significant in cases of large overdosage. Phenytoin serum concentrations measured up to two hours after IV and four hours after IM dose may be falsely elevated due to fosphenytoin interaction with immunoanalytic methods (eg, TDx fluorescence polarization) [7] [3] [10] [11] [12] [6] .

Adverse Effects

Fewer infusion-related reactions and tissue damage (eg, purple glove syndrome) compared with phenytoin. Hypotension and cardiac arrhythmias have been reported. Dose related adverse events include nystagmus (total level, 15 to 25 mg/L) and ataxia and mental status changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Minor venous irritation upon IV administration. Vomiting is common in children. Long-term effects of therapy include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Fosphenytoin drug interactions are similar to phenytoin (ie, carbamazepine, cimetidine, corticosteroids, digoxin, furosemide, phenobarbital, and valproate) [7] [3] .
Use with caution in infants and children with hyperbilirubinemia: both fosphenytoin and bilirubin displace phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [8] .

Serious and sometimes fatal skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, have been reported with phenytoin therapy. Onset of symptoms is typically within 28 days, but can occur later. Limited data suggests that a particular human leukocyte antigen (HLA) allele, HLA-B*1502, found in patients of Asian ancestry may be a risk factor for the development of SJS/TEN in patients taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502 [9] . Because fosphenytoin is a prodrug and is converted to phenytoin after administration, any concern regarding this association is also applicable to fosphenytoin.

Monitoring

Monitor electrocardiogram, blood pressure, and respiratory function continuously during infusion and for 10 to 20 minutes after end of infusion [1] [5] . Measure serum phenytoin (not fosphenytoin) concentration 2 hours after IV dose and 4 hours after IM dose. For maintenance therapy, a trough measurement is suggested. Therapeutic serum phenytoin concentration is 10 to 20 mg/L for total phenytoin and 1 to 2 mg/L for unbound phenytoin. Collect blood samples in EDTA tubes to minimize fosphenytoin to phenytoin conversion in the tube [1] [5] .

Special Considerations/Preparation

Available as an injectable solution in a concentration equivalent to 50 mg PE/mL, in 2- and 10-mL vials. Administer IM undiluted. Administer IV after diluting in NS or D_5W to a concentration of 1.5 to 25 mg PE/mL. The pH is 8.6 to 9 [1] .
Store unopened vials refrigerated. Stable for 48 hours at room temperature. Do not use vials containing particulate matter [1] .
Phosphate load: Provides 0.0037 mmol phosphate/mg PE [1] .

Solution Compatibility

D_5W, $D_{10}W$ and NS.

Terminal Injection Site Compatibility

Lorazepam, phenobarbital, and potassium chloride.

Terminal Injection Site Incompatibility

Midazolam.

References

- Takeoka M, Krishnamoorthy KS, Soman TB, et al: Fosphenytoin in infants. *J Child Neurol*1998;13:537-540.

1. Product Information: CEREBYX(R) intravenous injection, fosphenytoin sodium intravenous injection. Parke-Davis (per FDA), New York, NY, Nov, 2011.
2. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
3. Abend NS, Huh JW, Helfaer MA et al: Anticonvulsant medications in the pediatric emergency room and intensive care unit. Pediatr Emerg Care Oct, 2008; 24(10): 705-718.
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6. Morton LD: Clinical experience with fosphenytoin in children. J Child Neurol Oct, 1998; 13 Suppl 1: S19-S22.
7. Eriksson K: Fosphenytoin. Expert Opin Drug Metab Toxicol Jun, 2009; 5(6): 695-701.
8. Battino D: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet Nov, 1995; 29(5): 341-369.
9. Product Information: Dilantin(R) intravenous injection solution, phenytoin sodium intravenous injection solution. Pfizer (Per FDA), New York, NY, Oct, 2011.
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11. Fischer JH: Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clin Pharmacokinet Jan1, 2003; 42(1): 33-58.
12. Wheless JW: New formulations of drugs in epilepsy. Expert Opin Pharmacother Nov, 1999; 1(1): 49-60.

Title Fosphenytoin

Dose

Note: Fosphenytoin dosing is expressed in phenytoin equivalents (PE). (Fosphenytoin 1 mg PE = phenytoin 1 mg) [1] .

Loading dose: 15 to 20 mg PE/kg IM or IV infusion over at least 10 minutes.

Maintenance dose: 4 to 8 mg PE/kg every 24 hours IM or IV slow push. Begin maintenance 24 hours after loading dose.
Term infants older than 1 week of age may require up to 8 mg PE/kg per dose every 8 to 12 hours.

Administration

Intravenous: Administer loading dose as an IV infusion at a rate of 1 to 3 mg PE/kg per minute (**maximum 150 mg PE/minute**) at a concentration of 1.5 to 25 mg PE/mL. Dilute in 5% dextrose or normal saline. May administer maintenance dose slow IV push (undiluted) at the same rate (1 to 3 mg PE/kg per minute; **maximum 150 mg PE/minute**) [1] [2] [3] [4] [5] .
Intramuscular: Administer undiluted. May divide dose and give in more than one site [1] [5] [6] .

Uses

Anticonvulsant. Generally used to treat seizures that are refractory to phenobarbital. Can be administered with lorazepam for rapid onset of seizure control.

Black Box Warning

The rate of intravenous fosphenytoin administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous fosphenytoin. Although the risk of cardiovascular

toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [1] .

Pharmacology

Fosphenytoin is a water-soluble prodrug of phenytoin rapidly converted by phosphatases in blood and tissue. It has no known intrinsic pharmacologic activity before conversion to phenytoin. Each 1.5 mg of fosphenytoin is metabolically converted to 1 mg phenytoin. Nonlinear (zero order) kinetics (as dose increases, saturation of elimination mechanisms occur leading to progressive accumulation of phenytoin). After IV administration, peak concentration is reached at end of infusion. After IM administration, peak is reached in approximately 20 to 30 minutes. Conversion half-life of fosphenytoin administered intravenously to infants and children is approximately 8 minutes. No drugs have been identified to interfere with the conversion of fosphenytoin to phenytoin. Fosphenytoin is highly protein bound (adults 95% to 99%); only free fraction can cross blood-brain barrier. Primarily eliminated through hepatic metabolism. Potent inducer of cytochrome P450 enzyme systems resulting in a reduction of serum levels of drugs metabolized by this system. Renal excretion is negligible. Serum half-life reflects that of phenytoin (18 to 70 hours) due to rapid conversion. The conversion of fosphenytoin to phenytoin yields very small amounts of formaldehyde and phosphate. This is only significant in cases of large overdosage. Phenytoin serum concentrations measured up to two hours after IV and four hours after IM dose may be falsely elevated due to fosphenytoin interaction with immunoanalytic methods (eg, TDx fluorescence polarization) [7] [3] [10] [11] [12] [6] .

Adverse Effects

Fewer infusion-related reactions and tissue damage (eg, purple glove syndrome) compared with phenytoin. Hypotension and cardiac arrhythmias have been reported. Dose related adverse events include nystagmus (total level, 15 to 25 mg/L) and ataxia and mental status changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Minor venous irritation upon IV administration. Vomiting is common in children. Long-term effects of therapy include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Fosphenytoin drug interactions are similar to phenytoin (ie, carbamazepine, cimetidine, corticosteroids, digoxin, furosemide, phenobarbital, and valproate) [7] [3] .
Use with caution in infants and children with hyperbilirubinemia: both fosphenytoin and bilirubin displace phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [8] .

Serious and sometimes fatal skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, have been reported with phenytoin therapy. Onset of symptoms is typically within 28 days, but can occur later. Limited data suggests that a particular human leukocyte antigen (HLA) allele, HLA-B*1502, found in patients of Asian ancestry may be a risk factor for the development of SJS/TEN in patients taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502 [9] . Because fosphenytoin is a

prodrug and is converted to phenytoin after administration, any concern regarding this association is also applicable to fosphenytoin.

Monitoring

Monitor electrocardiogram, blood pressure, and respiratory function continuously during infusion and for 10 to 20 minutes after end of infusion [1] [5] . Measure serum phenytoin (not fosphenytoin) concentration 2 hours after IV dose and 4 hours after IM dose. For maintenance therapy, a trough measurement is suggested. Therapeutic serum phenytoin concentration is 10 to 20 mg/L for total phenytoin and 1 to 2 mg/L for unbound phenytoin. Collect blood samples in EDTA tubes to minimize fosphenytoin to phenytoin conversion in the tube [1] [5] .

Special Considerations/Preparation

Available as an injectable solution in a concentration equivalent to 50 mg PE/mL, in 2- and 10-mL vials. Administer IM undiluted. Administer IV after diluting in NS or D_5W to a concentration of 1.5 to 25 mg PE/mL. The pH is 8.6 to 9 [1] .
Store unopened vials refrigerated. Stable for 48 hours at room temperature. Do not use vials containing particulate matter [1] .
Phosphate load: Provides 0.0037 mmol phosphate/mg PE [1] .

Solution Compatibility

D_5W, $D_{10}W$ and NS.

Terminal Injection Site Compatibility

Lorazepam, phenobarbital, and potassium chloride.

Terminal Injection Site Incompatibility

Midazolam.

References

- Takeoka M, Krishnamoorthy KS, Soman TB, et al: Fosphenytoin in infants. *J Child Neurol*1998;13:537-540.

1. Product Information: CEREBYX(R) intravenous injection, fosphenytoin sodium intravenous injection. Parke-Davis (per FDA), New York, NY, Nov, 2011.
2. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
3. Abend NS, Huh JW, Helfaer MA et al: Anticonvulsant medications in the pediatric emergency room and intensive care unit. Pediatr Emerg Care Oct, 2008; 24(10): 705-718.
4. Glauser TA: Designing practical evidence-based treatment plans for children with prolonged seizures and status epilepticus. J Child Neurol May, 2007; 22(5 Suppl): 38S-46S.

5. Meek PD, Davis SN, Collins DM et al: Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. Panel on Nonemergency Use of Parenteral Phenytoin Products. Arch Intern Med Dec13, 1999; 159(22): 2639-2644.
6. Morton LD: Clinical experience with fosphenytoin in children. J Child Neurol Oct, 1998; 13 Suppl 1: S19-S22.
7. Eriksson K: Fosphenytoin. Expert Opin Drug Metab Toxicol Jun, 2009; 5(6): 695-701.
8. Battino D: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet Nov, 1995; 29(5): 341-369.
9. Product Information: Dilantin(R) intravenous injection solution, phenytoin sodium intravenous injection solution. Pfizer (Per FDA), New York, NY, Oct, 2011.
10. Ogutu BR, Newton CR, Muchohi SN et al: Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. Br J Clin Pharmacol Jul1, 2003; 56(1): 112-119.
11. Fischer JH: Fosphenytoin: clinical pharmacokinetics and comparative advantages in the acute treatment of seizures. Clin Pharmacokinet Jan1, 2003; 42(1): 33-58.
12. Wheless JW: New formulations of drugs in epilepsy. Expert Opin Pharmacother Nov, 1999; 1(1): 49-60.

1.77 Furosemide

Title Furosemide

Dose

Initial Dose: 1 mg/kg IV slow push, IM, or orally.
May increase to a maximum of 2 mg/kg/dose IV or 6 mg/kg/dose orally.
Initial Intervals:
Premature infant: every 24 hours.
Full-term infant: every 12 hours.
Full-term infant older than 1 month: every 6 to 8 hours.
Consider alternate-day therapy for long-term use.

Uses

Diuretic that may also improve pulmonary function [1] . Based on results from a systematic review of the use of furosemide in infants with (or developing) chronic lung disease (CLD), furosemide was associated with no or inconsistent effects on lung function in preterm infants less than 3 weeks of age. For preterm infants greater than 3 weeks of age with CLD, single IV doses were associated with short-term (less than 1 hour) improvement in lung compliance and airway resistance. Infants receiving chronic diuretic therapy had improved oxygenation and lung compliance. There are no data to support the routine or sustained use of loop diuretics based on duration of ventilatory support, duration of hospitalization, long-term outcomes, or survival in infants with CLD [2] [3] .

Contraindications/Precautions

Contraindicated in patients with anuria [5] .

Black Box Warning According to the manufacturer's black box warning, furosemide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion [5] .

Pharmacology

The diuretic actions of furosemide are primarily at the ascending limb of Henle's loop, and are directly related to renal tubular drug concentration. Furosemide causes major urinary losses of sodium, potassium, and chloride. Urinary calcium and magnesium excretion, and urine pH are also increased. Prostaglandin production is stimulated, with increases in renal blood flow and renin secretion. Free water clearance is increased and CSF production is decreased by weak carbonic anhydrase inhibition. Nondiuretic effects include decreased pulmonary transvascular fluid filtration and improved pulmonary function. Protein binding is extensive, but bilirubin displacement is negligible when using normal doses. Oral bioavailability is good. Time to peak effect when given IV is 1 to 3 hours; duration of effect is approximately 6 hours, although half-life may be as long as 67 hours in the most immature neonates.

Adverse Effects

Furosemide therapy may lead to increased hyponatremia and a significant rise in serum creatinine in patients receiving indomethacin for PDA closure [6] [7] . Ototoxicity (tinnitus and reversible or irreversible hearing impairment) has been reported, especially with rapid injection, severe renal impairment, higher than recommended doses, hypoproteinemia, or concomitant therapy with aminoglycosides, ethacrynic acid, or other ototoxic drugs. Controlled intravenous infusion is recommended for high-dose parenteral therapy. Avoid concomitant use of aminoglycosides (except in life-threatening cases) and ethacrynic acid. Water and electrolyte imbalances occur frequently, especially hypokalemia, hyponatremia, and hypochloremic alkalosis. Risk for hypokalemia increased with brisk diuresis, inadequate oral intake, presence of cirrhosis, concomitant therapy with corticosteroids, ACTH, or prolonged use of laxatives. Acute urinary retention may occur in patients with symptoms of underlying urinary retention; careful monitoring recommended. In patients at high risk for radiocontrast nephropathy, a higher risk of deterioration of renal function may occur with furosemide therapy. Nephrocalcinosis and nephrolithiasis may occur due to high urinary calcium excretion. This has been reported mainly in premature infants and a cumulative dose of 10 mg/kg or greater was associated with an increased risk [4] . Cases have also occurred in infants with no history of prematurity; monitoring recommended [8] . Hypercalciuria and development of bone demineralization and renal calculi occur with long-term therapy. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods. Cholestatic jaundice and cholelithiasis have also been reported with loop diuretics (mainly in preterm infants receiving long-term TPN and furosemide therapy. Other adverse events include hypotension, fatigue, nausea, and muscle cramps.

Monitoring

Monitor serum and urine electrolytes and renal function periodically during therapy. Consider performing renal ultrasonography in premature infants as furosemide may precipitate nephrocalcinosis/nephrolithiasis [4] . Follow serum potassium levels closely

at initiation, in patients receiving concomitant diuretics or digoxin, and during long-term therapy. Monitor urine output and weight changes. Monitor for signs/symptoms of fluid/electrolyte imbalance [5] .

Special Considerations/Preparation

Furosemide oral solution is available in 8-mg/mL and 10-mg/mL concentrations. Protect from light and discard open bottle after 90 days. The injectable solution may also be used for oral administration.
Furosemide for injection is available as a 10-mg/mL concentration in 2-, 4-, and 10-mL single use vials.
A 2-mg/mL dilution may be made by adding 2 mL of the 10-mg/mL injectable solution to 8-mL preservative-free normal saline for injection. Dilution should be used within 24 hours. Protect from light and do not refrigerate.

Solution Compatibility

NS, D_5W, $D_{10}W$, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA Solutions, fat emulsion. Amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, calcium gluconate, cefepime, ceftazidime, cimetidine, dexamethasone, digoxin, epinephrine, famotidine, fentanyl, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, lidocaine, lorazepam, linezolid, meropenem, micafungin, morphine, nitroglycerin, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, and tobramycin.

Terminal Injection Site Incompatibility

Azithromycin, caspofungin, ciprofloxacin, dobutamine, dopamine, erythromycin lactobionate, esmolol, fluconazole, gentamicin, hydralazine, isoproterenol, metoclopramide, midazolam, milrinone, netilmicin, nicardipine, and vecuronium.

References

- Mirochnick MH, Miceli JJ, Kramer PA, et al: Furosemide pharmacokinetics in very low birth weight infants. *J Pediatr* 1988;112:653.
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- Ross BS, Pollak A, Oh W: The pharmacological effects of furosemide therapy in the low-birth-weight infant. *J Pediatr* 1978;92:149.
- Ghanekar AG, Das Gupta V, Gibbs CW Jr: Stability of furosemide in aqueous systems. *J Pharm Sci* 1978;67:808.
- Product Information, Sanofi-Aventis, 2010.
- Product Information, APP Pharmaceuticals, 2008.

1. Rush MG, Engelhardt B, Parker RA et al: Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. J Pediatr Jul, 1990; 117(1 Pt 1): 112-118.
2. Stewart A: Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Cochrane Database Syst Rev 2011; 2011(9): 1.
3. Hagadorn JI, Sanders MR, Staves C et al: Diuretics for very low birth weight infants in the first 28 days: a survey of the U.S. neonatologists. J Perinatol Oct, 2011; 31(10): 677-681.
4. Gimpel C, Krause A, Franck P et al: Exposure to furosemide as the strongest risk factor for nephrocalcinosis in preterm infants. Pediatr Int Feb, 2010; 52(1): 51-56.
5. Product Information: LASIX(R) oral tablets, furosemide oral tablets. sanofi-aventis U.S. LLC, Bridgewater, NJ, Sep, 2010.
6. Lee BS, Byun SY, Chung ML et al: Effect of furosemide on ductal closure and renal function in indomethacin-treated preterm infants during the early neonatal period. Neonatology 2010; 98(2): 191-199.
7. Andriessen P, Struis NC, Niemarkt H et al: Furosemide in preterm infants treated with indomethacin for patent ductus arteriosus. Acta Paediatr May, 2009; 98(5): 797-803.
8. Product Information: furosemide IV, IM injection, furosemide IV, IM injection. American Regent, Inc.(per FDA), Shirley, NY, Jun, 2011.

Title Furosemide

Dose

Initial Dose: 1 mg/kg IV slow push, IM, or orally.
May increase to a maximum of 2 mg/kg/dose IV or 6 mg/kg/dose orally.
Initial Intervals:
Premature infant: every 24 hours.
Full-term infant: every 12 hours.
Full-term infant older than 1 month: every 6 to 8 hours.
Consider alternate-day therapy for long-term use.

Uses

Diuretic that may also improve pulmonary function [1] . Based on results from a systematic review of the use of furosemide in infants with (or developing) chronic lung disease (CLD), furosemide was associated with no or inconsistent effects on lung function in preterm infants less than 3 weeks of age. For preterm infants greater than 3 weeks of age with CLD, single IV doses were associated with short-term (less than 1 hour) improvement in lung compliance and airway resistance. Infants receiving chronic diuretic therapy had improved oxygenation and lung compliance. There are no data to support the routine or sustained use of loop diuretics based on duration of ventilatory support, duration of hospitalization, long-term outcomes, or survival in infants with CLD [2] [3] .

Contraindications/Precautions

Contraindicated in patients with anuria [5] .

Black Box Warning According to the manufacturer's black box warning, furosemide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion [5] .

Pharmacology

The diuretic actions of furosemide are primarily at the ascending limb of Henle's loop, and are directly related to renal tubular drug concentration. Furosemide causes major urinary losses of sodium, potassium, and chloride. Urinary calcium and magnesium excretion, and urine pH are also increased. Prostaglandin production is stimulated, with increases in renal blood flow and renin secretion. Free water clearance is increased and CSF production is decreased by weak carbonic anhydrase inhibition. Nondiuretic effects include decreased pulmonary transvascular fluid filtration and improved pulmonary function. Protein binding is extensive, but bilirubin displacement is negligible when using normal doses. Oral bioavailability is good. Time to peak effect when given IV is 1 to 3 hours; duration of effect is approximately 6 hours, although half-life may be as long as 67 hours in the most immature neonates.

Adverse Effects

Furosemide therapy may lead to increased hyponatremia and a significant rise in serum creatinine in patients receiving indomethacin for PDA closure [6] [7] . Ototoxicity (tinnitus and reversible or irreversible hearing impairment) has been reported, especially with rapid injection, severe renal impairment, higher than recommended doses, hypoproteinemia, or concomitant therapy with aminoglycosides, ethacrynic acid, or other ototoxic drugs. Controlled intravenous infusion is recommended for high-dose parenteral therapy. Avoid concomitant use of aminoglycosides (except in life-threatening cases) and ethacrynic acid. Water and electrolyte imbalances occur frequently, especially hypokalemia, hyponatremia, and hypochloremic alkalosis. Risk for hypokalemia increased with brisk diuresis, inadequate oral intake, presence of cirrhosis, concomitant therapy with corticosteroids, ACTH, or prolonged use of laxatives. Acute urinary retention may occur in patients with symptoms of underlying urinary retention; careful monitoring recommended. In patients at high risk for radiocontrast nephropathy, a higher risk of deterioration of renal function may occur with furosemide therapy. Nephrocalcinosis and nephrolithiasis may occur due to high urinary calcium excretion. This has been reported mainly in premature infants and a cumulative dose of 10 mg/kg or greater was associated with an increased risk [4] . Cases have also occurred in infants with no history of prematurity; monitoring recommended [8] . Hypercalciuria and development of bone demineralization and renal calculi occur with long-term therapy. May displace bilirubin from albumin binding sites when given in high doses or for prolonged periods. Cholestatic jaundice and cholelithiasis have also been reported with loop diuretics (mainly in preterm infants receiving long-term TPN and furosemide therapy. Other adverse events include hypotension, fatigue, nausea, and muscle cramps.

Monitoring

Monitor serum and urine electrolytes and renal function periodically during therapy. Consider performing renal ultrasonography in premature infants as furosemide may precipitate nephrocalcinosis/nephrolithiasis [4] . Follow serum potassium levels closely

at initiation, in patients receiving concomitant diuretics or digoxin, and during long-term therapy. Monitor urine output and weight changes. Monitor for signs/symptoms of fluid/electrolyte imbalance [5] .

Special Considerations/Preparation

Furosemide oral solution is available in 8-mg/mL and 10-mg/mL concentrations. Protect from light and discard open bottle after 90 days. The injectable solution may also be used for oral administration.
Furosemide for injection is available as a 10-mg/mL concentration in 2-, 4-, and 10-mL single use vials.
A 2-mg/mL dilution may be made by adding 2 mL of the 10-mg/mL injectable solution to 8-mL preservative-free normal saline for injection. Dilution should be used within 24 hours. Protect from light and do not refrigerate.

Solution Compatibility

NS, D_5W, $D_{10}W$, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA Solutions, fat emulsion. Amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, calcium gluconate, cefepime, ceftazidime, cimetidine, dexamethasone, digoxin, epinephrine, famotidine, fentanyl, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, lidocaine, lorazepam, linezolid, meropenem, micafungin, morphine, nitroglycerin, penicillin G, piperacillin/tazobactam, potassium chloride, propofol, prostaglandin E_1, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, and tobramycin.

Terminal Injection Site Incompatibility

Azithromycin, caspofungin, ciprofloxacin, dobutamine, dopamine, erythromycin lactobionate, esmolol, fluconazole, gentamicin, hydralazine, isoproterenol, metoclopramide, midazolam, milrinone, netilmicin, nicardipine, and vecuronium.

References

- Mirochnick MH, Miceli JJ, Kramer PA, et al: Furosemide pharmacokinetics in very low birth weight infants. *J Pediatr* 1988;112:653.
- Green TP: The pharmacologic basis of diuretic therapy in the newborn. *Clin Perinatol* 1987;14:951.
- Hufnagle KG, Khan SN, Penn D: Renal calcifications: A complication of long-term furosemide therapy in preterm infants. *Pediatrics* 1982;70:360.
- Ross BS, Pollak A, Oh W: The pharmacological effects of furosemide therapy in the low-birth-weight infant. *J Pediatr* 1978;92:149.
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1. Rush MG, Engelhardt B, Parker RA et al: Double-blind, placebo-controlled trial of alternate-day furosemide therapy in infants with chronic bronchopulmonary dysplasia. J Pediatr Jul, 1990; 117(1 Pt 1): 112-118.
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4. Gimpel C, Krause A, Franck P et al: Exposure to furosemide as the strongest risk factor for nephrocalcinosis in preterm infants. Pediatr Int Feb, 2010; 52(1): 51-56.
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7. Andriessen P, Struis NC, Niemarkt H et al: Furosemide in preterm infants treated with indomethacin for patent ductus arteriosus. Acta Paediatr May, 2009; 98(5): 797-803.
8. Product Information: furosemide IV, IM injection, furosemide IV, IM injection. American Regent, Inc.(per FDA), Shirley, NY, Jun, 2011.

1.78 Ganciclovir

Title Ganciclovir

Dose

6 mg/kg/dose IV every 12 hours. Treat for a minimum of 6 weeks if possible. Reduce the dose by half for significant neutropenia (less than 500 cells/mm^3).

Chronic Oral Suppression: 30 to 40 mg/kg/dose orally every 8 hours.

Administration

Use proper procedures for handling and disposal of chemotherapy; drug is potentially carcinogenic and mutagenic.

Intravenous: Infuse over a period of 1 hour in compatible solution at a concentration not to exceed 10 mg/mL. Phlebitis and/or pain may occur at intravenous infusion site due to high pH (11) of solution; infuse into veins with adequate blood flow, permitting rapid dilution and distribution.

Uses

Prevention of progressive hearing loss and lessening of developmental delays in babies with symptomatic congenital cytomegalovirus infection involving the central nervous system.

Black Box Warning According to the manufacturer's black box warning, the clinical toxicity of ganciclovir includes granulocytopenia, anemia, and thrombocytopenia.

Pharmacology

Ganciclovir is an acyclic nucleoside analog of guanine that inhibits replication of herpes viruses in vivo. There is large interpatient variability in pharmacokinetic parameters. Mean half-life in infants less than 49 days postnatal age is 2.4 hours. Metabolism is minimal; almost all drug is excreted unchanged in the urine via glomerular filtration and active tubular secretion.

Adverse Effects

Significant neutropenia will occur in the majority of treated patients. Discontinue treatment if the neutropenia does not resolve after reducing the dosage by half.

Monitoring

CBC every 2 to 3 days during first 3 weeks of therapy, weekly thereafter if stable.

Special Considerations/Preparation

Cytovene® is supplied as lyophilized powder for injection, 500 mg per vial. Reconstitute by injecting 10 mL of sterile water for injection into the vial. Do not use bacteriostatic water for injection containing parabens; it is incompatible with ganciclovir and may cause precipitation. Shake the vial to dissolve the drug. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution. Discard the vial if particulate matter or discoloration is observed.
Reconstituted solution in the vial is stable at room temperature for 12 hours. **Do not refrigerate,** may cause precipitation. The pH is approximately 11; use caution when handling. Osmolarity is 320 mOsm/kg.

Based on patient weight, remove the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) from the vial and add to a compatible diluent fluid to make a final infusion concentration less than 10 mg/mL. Although stable for 14 days, the infusion solution must be used within 24 hours of dilution to reduce the risk of bacterial contamination. Refrigerate the infusion solution. **Do not freeze**.

Available as 250-mg and 500-mg capsules. Prepare oral suspension in a vertical-flow laminar hood. Oral suspension (100 mg/mL) may be prepared by emptying eighty (80) 250-mg capsules into a glass mortar wetted and triturated with Oral-Sweet® to a smooth paste. Add 50-mL of Oral-Sweet® to the paste, mix, and transfer contents to an amber polyethylene terephthalate bottle. Rinse the mortar with another 50 mL of Oral-Sweet® and transfer contents to the bottle. Add enough Oral-Sweet® to make a final volume of 200 mL. Stable for 123 days when stored at 23 to 25 degrees C. **Protect from light**.

Solution Compatibility

NS, D_5W, and LR.

Solution Incompatibility

Dex/AA.

Terminal Injection Site Compatibility

Enalaprilat, fluconazole, linezolid, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, cefepime, and piperacillin/tazobactam.

References

- Oliver SE, Cloud GA, Sanchez PJ, et al: Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009;46S:S22-S26.
- Marshall BC, Koch WC: Antivirals for cytomegalovirus infection in neonates and infants. *Pediatr Drugs* 2009;11:309-321.
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- Frenkel LM, Capparelli EV, Dankner WM, et al: Oral ganciclovir in children: pharmacokinetics, safety, tolerance, and antiviral effects. *J Infect Dis* 2000;182:1616-24.
- Anaizi NH, Swenson CF, and Dentinger PJ: Stability of ganciclovir in extemporaneously compounded oral liquids. *Am J Health Syst Pharm* 1999;56:1738-41.
- Product Information, Roche, 2006.

Title Ganciclovir

Dose

6 mg/kg/dose IV every 12 hours. Treat for a minimum of 6 weeks if possible. Reduce the dose by half for significant neutropenia (less than 500 cells/mm^3).

Chronic Oral Suppression: 30 to 40 mg/kg/dose orally every 8 hours.

Administration

Use proper procedures for handling and disposal of chemotherapy; drug is potentially carcinogenic and mutagenic.

Intravenous: Infuse over a period of 1 hour in compatible solution at a concentration not to exceed 10 mg/mL. Phlebitis and/or pain may occur at intravenous infusion site due to high pH (11) of solution; infuse into veins with adequate blood flow, permitting rapid dilution and distribution.

Uses

Prevention of progressive hearing loss and lessening of developmental delays in babies with symptomatic congenital cytomegalovirus infection involving the central nervous system.

Black Box Warning According to the manufacturer's black box warning, the clinical toxicity of ganciclovir includes granulocytopenia, anemia, and thrombocytopenia.

Pharmacology

Ganciclovir is an acyclic nucleoside analog of guanine that inhibits replication of herpes viruses in vivo. There is large interpatient variability in pharmacokinetic parameters. Mean half-life in infants less than 49 days postnatal age is 2.4 hours. Metabolism is minimal; almost all drug is excreted unchanged in the urine via glomerular filtration and active tubular secretion.

Adverse Effects

Significant neutropenia will occur in the majority of treated patients. Discontinue treatment if the neutropenia does not resolve after reducing the dosage by half.

Monitoring

CBC every 2 to 3 days during first 3 weeks of therapy, weekly thereafter if stable.

Special Considerations/Preparation

Cytovene® is supplied as lyophilized powder for injection, 500 mg per vial. Reconstitute by injecting 10 mL of sterile water for injection into the vial. Do not use bacteriostatic water for injection containing parabens; it is incompatible with ganciclovir and may cause precipitation. Shake the vial to dissolve the drug. Visually inspect the reconstituted solution for particulate matter and discoloration prior to proceeding with infusion solution. Discard the vial if particulate matter or discoloration is observed.
Reconstituted solution in the vial is stable at room temperature for 12 hours. **Do not refrigerate,** may cause precipitation. The pH is approximately 11; use caution when handling. Osmolarity is 320 mOsm/kg.

Based on patient weight, remove the appropriate volume of the reconstituted solution (ganciclovir concentration 50 mg/mL) from the vial and add to a compatible diluent fluid to make a final infusion concentration less than 10 mg/mL. Although stable for 14 days, the infusion solution must be used within 24 hours of dilution to reduce the risk of bacterial contamination. Refrigerate the infusion solution. **Do not freeze**.

Available as 250-mg and 500-mg capsules. Prepare oral suspension in a vertical-flow laminar hood. Oral suspension (100 mg/mL) may be prepared by emptying eighty (80) 250-mg capsules into a glass mortar wetted and triturated with Oral-Sweet® to a smooth paste. Add 50-mL of Oral-Sweet® to the paste, mix, and transfer contents to an amber polyethylene terephthalate bottle. Rinse the mortar with another 50 mL of Oral-Sweet® and transfer contents to the bottle. Add enough Oral-Sweet® to make a final volume of 200 mL. Stable for 123 days when stored at 23 to 25 degrees C. **Protect from light**.

Solution Compatibility

NS, D_5W, and LR.

Solution Incompatibility

Dex/AA.

Terminal Injection Site Compatibility

Enalaprilat, fluconazole, linezolid, propofol, and remifentanil.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, cefepime, and piperacillin/tazobactam.

References

- Oliver SE, Cloud GA, Sanchez PJ, et al: Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009;46S:S22-S26.
- Marshall BC, Koch WC: Antivirals for cytomegalovirus infection in neonates and infants. *Pediatr Drugs* 2009;11:309-321.
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- Michaels MG, Greenberg DP, Sabo DL, Wald ER: Treatment of children with cytomegalovirus infection with ganciclovir. *Pediatr Infect Dis J* 2003;22:504-08.
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- Anaizi NH, Swenson CF, and Dentinger PJ: Stability of ganciclovir in extemporaneously compounded oral liquids. *Am J Health Syst Pharm* 1999;56:1738-41.
- Product Information, Roche, 2006.

1.79 Gentamicin

Title Gentamicin

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)

≤29*	0 to 7	5	48
	8 to 28	4	36
	≥29	4	24
30 to 34	0 to 7	4.5	36
	≥8	4	24
≥35	ALL	4	24

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Treatment of infections caused by aerobic gram-negative bacilli (eg, *Pseudomonas*, *Klebsiella*, *E coli*). Usually used in combination with a β-lactam antibiotic.

Optimal treatment for suspected, early-onset sepsis is broad-spectrum antimicrobial coverage using a combination of ampicillin and an aminoglycoside (usually gentamicin); once a pathogen is identified, therapy should be narrowed unless synergism is required. Therapy should be discontinued at 48 hours if the probability of sepsis is low [1] .

Black Box Warning According to the manufacturer's black box warning, aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of gentamicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (eg, furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (ie, neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia. The use of gentamicin ointment for newborn ocular prophylaxis has been associated with periocular ulcerative dermatitis.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max}/MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

Suggested Dosing Intervals

Level at 24 hours (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3		Measure level in 24 hours

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions and fat emulsion. Acyclovir, alprostadil, amiodarone, aztreonam, caffeine citrate, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dopamine, enalaprilat, esmolol, famotidine, fluconazole, gentamicin, heparin (concentrations of 1 unit/mL or less), insulin, linezolid, lorazepam, magnesium sulfate, meropenem, metronidazole, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, penicillin g, prostaglandin E_1, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, azithromycin, furosemide, imipenem/cilastatin, heparin (concentrations greater than 1 unit/mL), indomethacin, mezlocillin, nafcillin, oxacillin, propofol, and ticarcillin/clavulanate.

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Title Gentamicin

Dose

Antibiotic Dosing Chart:

Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

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Administration

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Uses

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Black Box Warning According to the manufacturer's black box warning, aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of gentamicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

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Peak: 5 to 12 mcg/mL (or C_{max}/MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

Suggested Dosing Intervals

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2.4 to 3.2	~ 15	48
≥3.3		Measure level in 24 hours

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions and fat emulsion. Acyclovir, alprostadil, amiodarone, aztreonam, caffeine citrate, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, cimetidine, clindamycin, dopamine, enalaprilat, esmolol, famotidine, fluconazole, gentamicin, heparin (concentrations of 1 unit/mL or less), insulin, linezolid, lorazepam, magnesium sulfate, meropenem, metronidazole, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, penicillin g, prostaglandin E_1, ranitidine, remifentanil, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, ampicillin, azithromycin, furosemide, imipenem/cilastatin, heparin (concentrations greater than 1 unit/mL), indomethacin, mezlocillin, nafcillin, oxacillin, propofol, and ticarcillin/clavulanate.

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1.80 Glucagon

Title Glucagon

Dose

Hypoglycemia, Refractory
200 mcg/kg/dose (0.2 mg/kg/dose) IV push, IM, or subQ.
Maximum dose: 1 mg.

Continuous infusion: Begin with 10 to 20 mcg/kg/hour; doses of 0.5 to 1 mg per day regardless of age or weight have been used, given as a continuous infusion. Rise in blood glucose should occur within one hour of starting infusion.

Administration May administer subQ, IM, or IV push (only for hypoglycemia). Should not be used at concentrations greater than 1 mg/mL; use 1 mL of diluent provided or Sterile Water for Injection.
For continuous infusion, glucagon in 10% dextrose has been used successfully in infants with persistent hypoglycemia. There are no stability data available for glucagon in 10% dextrose.

Uses

Treatment of hypoglycemia refractory to intravenous dextrose infusions, or when dextrose infusion is unavailable, or in cases of documented glucagon deficiency.

Contraindications/Precautions

Contraindicated in patients with pheochromocytoma, insulinoma, and in those with known hypersensitivity to lactose [1] .

Pharmacology

Glucagon stimulates synthesis of cyclic AMP, especially in liver and adipose tissue. Stimulates gluconeogenesis. In high doses, glucagon has a cardiac inotropic effect. Inhibits small-bowel motility and gastric-acid secretion.

Adverse Effects

Nausea and vomiting, tachycardia, and ileus. Hyponatremia and thrombocytopenia have also been reported.

Monitoring

Follow blood glucose concentration closely. Watch for rebound hypoglycemia. Rise in blood glucose will last approximately 2 hours.

Special Considerations/Preparation

Supplied in 1-mg single-dose vials. Dissolve the lyophilized product in the supplied diluent or in Sterile Water for Injection (GlucaGen®). Should not be used at concentrations greater than 1 mg/mL. One unit of glucagon and 1 mg of glucagon are equivalent. Use immediately after reconstitution. Discard any unused portion.

Solution Compatibility

No data are currently available on Dex/AA and other intravenous solutions.

Terminal Injection Site Compatibility

No data are currently available.

References

- Carter PE, Lloyd DJ, Duffty P: Glucagon for hypoglycaemia in infants small for gestational age. Arch Dis Child 1988;63:1264-1266.
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- Product Information, Novo Nordisk Inc., 2010.
- Product Information, Eli Lilly, 2005.

1. Product Information: GlucaGen(R) intravenous intramuscular subcutaneous injection, glucagon rDNA origin intravenous intramuscular subcutaneous injection. Novo Nordisk Inc., Princeton, NJ, Dec, 2010.

Title Glucagon

Dose

Hypoglycemia, Refractory
200 mcg/kg/dose (0.2 mg/kg/dose) IV push, IM, or subQ.
Maximum dose: 1 mg.

Continuous infusion: Begin with 10 to 20 mcg/kg/hour; doses of 0.5 to 1 mg per day regardless of age or weight have been used, given as a continuous infusion. Rise in blood glucose should occur within one hour of starting infusion.

Administration May administer subQ, IM, or IV push (only for hypoglycemia). Should not be used at concentrations greater than 1 mg/mL; use 1 mL of diluent provided or Sterile Water for Injection.
For continuous infusion, glucagon in 10% dextrose has been used successfully in infants with persistent hypoglycemia. There are no stability data available for glucagon in 10% dextrose.

Uses

Treatment of hypoglycemia refractory to intravenous dextrose infusions, or when dextrose infusion is unavailable, or in cases of documented glucagon deficiency.

Contraindications/Precautions

Contraindicated in patients with pheochromocytoma, insulinoma, and in those with known hypersensitivity to lactose [1] .

Pharmacology

Glucagon stimulates synthesis of cyclic AMP, especially in liver and adipose tissue. Stimulates gluconeogenesis. In high doses, glucagon has a cardiac inotropic effect. Inhibits small-bowel motility and gastric-acid secretion.

Adverse Effects

Nausea and vomiting, tachycardia, and ileus. Hyponatremia and thrombocytopenia have also been reported.

Monitoring

Follow blood glucose concentration closely. Watch for rebound hypoglycemia. Rise in blood glucose will last approximately 2 hours.

Special Considerations/Preparation

Supplied in 1-mg single-dose vials. Dissolve the lyophilized product in the supplied diluent or in Sterile Water for Injection (GlucaGen®). Should not be used at concentrations greater than 1 mg/mL. One unit of glucagon and 1 mg of glucagon are equivalent. Use immediately after reconstitution. Discard any unused portion.

Solution Compatibility

No data are currently available on Dex/AA and other intravenous solutions.

Terminal Injection Site Compatibility

No data are currently available.

References

- Carter PE, Lloyd DJ, Duffty P: Glucagon for hypoglycaemia in infants small for gestational age. Arch Dis Child 1988;63:1264-1266.
- Charsha DS, McKinley PS, Whitfield JM: Glucagon infusion for treatment of hypoglycemia: efficacy and safety in sick, preterm neonates. *Pediatrics* 2003;111:220-1.
- Davis SN, Granner DK: Insulin and oral hypoglycemic agents and the pharmacology of the endocrine pancreas, in Hardman JG, Limbird LE, Gilman AG (eds): *The Pharmacological Basis of Therapeutics*, ed 10. New York: Macmillan Co, 2001, pp 1707-08.
- Hawdon JM, Aynsley-Green A, Ward Platt MP: Neonatal blood glucose concentrations: metabolic effect of intravenous glucagon and intragastric medium chain triglyceride. *Arch Dis Child*1993;68:255.
- Mehta A, Wootton R, Cheng KN, et al: Effect of diazoxide or glucagon on hepatic production rate during extreme neonatal hypoglycemia. *Arch Dis Child* 1987;62:924.
- Miralles RE, Lodha A, Perlman M, Moore AM: Experience with intravenous glucagon infusions as a treatment for resistant neonatal hypoglycemia. *Arch Pediatr Adolesc Med* 2002;156:99-1004.

- Product Information, Novo Nordisk Inc., 2010.
- Product Information, Eli Lilly, 2005.

1. Product Information: GlucaGen(R) intravenous intramuscular subcutaneous injection, glucagon rDNA origin intravenous intramuscular subcutaneous injection. Novo Nordisk Inc., Princeton, NJ, Dec, 2010.

1.81 Haemophilus b (Hib) Conjugate Vaccine

Title Haemophilus b (Hib) Conjugate Vaccine

Dose

0.5 mL IM in the anterolateral thigh or deltoid x 4 doses. Give at 2, 4, and 6 months of age and a booster dose at 12 to 15 months of age [1] [2] [3] .

If PRP-OMP (PedvaxHIB® or Comvax® (HepB-Hib)) is given at 2 and 4 months of age, a dose at 6 months is not necessary; the third dose is given at 12 to 15 months of age [1] .

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] [3] .

Uses

Immunoprophylaxis against invasive disease caused by *Haemophilus influenzae* type b [2] [3] .

Contraindications/Precautions **Contraindicated**in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine. Also contraindicated in infants less than 6 weeks of age. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [4] .

Pharmacology

Three conjugate vaccines are currently approved for use in infants older than 2 months of age. These vaccines are derived from*H influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP), which is linked to a T-cell-dependent protein antigen to enhance immunogenicity [2] [3] .

Adverse Effects

Fever and injection site reactions (ie, local erythema, swelling, and tenderness) are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [2] [3] .

Monitoring

Observe injection site for local reactions.

Special Considerations/Preparation

ActHIB® is supplied as lyophilized powder. Store the lyophilized vaccine and diluent refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze.**Reconstitute using only the 0.4% saline diluent provided in single-use 0.6-mL vials and use immediately. Reconstituted vaccine is a clear, colorless solution [3] .

Liquid PedvaxHIB® is supplied in single-dose vials. It is a slightly opaque white suspension. Shake well before withdrawal and use. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze** [2] .

Hib Conjugate Vaccine

(PI ActHIB®, 2009; PI PedvaxHIB®, 2010; PI Hiberix®, 2010)

Manufacturer	Abbreviation	Trade Name	Carrier Protein
Sanofi Pasteur	PRP-T	ActHIB®	Tetanus toxoid
Merck & Co, Inc	PRP-OMP Liquid	PedvaxHIB®	OMP (an outer membrane protein comp
GlaxoSmithKline	none	Hiberix®	Tetanus toxoid

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: Liquid PedvaxHIB(R) IM injection, haemophilus b conjugate vaccine (meningococcal protein conjugate) IM injection. Merck Sharp & Dohme Corp., Whitehouse Station, PA, Dec, 2010.

- Product Information: ActHIB(R) lyophilized powder for intramuscular injection, haemophilus b conjugate vaccine lyophilized powder for intramuscular injection. Sanofi Pasteur, Swiftwater, PA, May, 2009.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

Title Haemophilus b (Hib) Conjugate Vaccine

Dose

0.5 mL IM in the anterolateral thigh or deltoid x 4 doses. Give at 2, 4, and 6 months of age and a booster dose at 12 to 15 months of age [1] [2] [3] .

If PRP-OMP (PedvaxHIB® or Comvax® (HepB-Hib)) is given at 2 and 4 months of age, a dose at 6 months is not necessary; the third dose is given at 12 to 15 months of age [1] .

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] [3] .

Uses

Immunoprophylaxis against invasive disease caused by *Haemophilus influenzae* type b [2] [3] .

Contraindications/Precautions **Contraindicated**in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine. Also contraindicated in infants less than 6 weeks of age. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [4] .

Pharmacology

Three conjugate vaccines are currently approved for use in infants older than 2 months of age. These vaccines are derived from*H influenzae* type b capsular polysaccharide, polyribosylribitol phosphate (PRP), which is linked to a T-cell-dependent protein antigen to enhance immunogenicity [2] [3] .

Adverse Effects

Fever and injection site reactions (ie, local erythema, swelling, and tenderness) are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [2] [3] .

Monitoring

Observe injection site for local reactions.

Special Considerations/Preparation

ActHIB® is supplied as lyophilized powder. Store the lyophilized vaccine and diluent refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze.**Reconstitute using only the 0.4% saline diluent provided in single-use 0.6-mL vials and use immediately. Reconstituted vaccine is a clear, colorless solution [3] .

Liquid PedvaxHIB® is supplied in single-dose vials. It is a slightly opaque white suspension. Shake well before withdrawal and use. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze** [2] .

Hib Conjugate Vaccine

(PI ActHIB®, 2009; PI PedvaxHIB®, 2010; PI Hiberix®, 2010)

Manufacturer	Abbreviation	Trade Name	Carrier Protein
Sanofi Pasteur	PRP-T	ActHIB®	Tetanus toxoid
Merck & Co, Inc	PRP-OMP Liquid	PedvaxHIB®	OMP (an outer membrane protein comp
GlaxoSmithKline	none	Hiberix®	Tetanus toxoid

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: Liquid PedvaxHIB(R) IM injection, haemophilus b conjugate vaccine (meningococcal protein conjugate) IM injection. Merck Sharp & Dohme Corp., Whitehouse Station, PA, Dec, 2010.

- Product Information: ActHIB(R) lyophilized powder for intramuscular injection, haemophilus b conjugate vaccine lyophilized powder for intramuscular injection. Sanofi Pasteur, Swiftwater, PA, May, 2009.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

1.82 Heparin

Title Heparin

Dose

Maintaining patency of central vascular catheters:
0.5 units/kg/hour [1] [2] .

Maintaining patency of peripheral vascular catheters:
0.5 to 1 unit/mL of IV fluid.

Treatment of thrombosis: 75 units/kg bolus over 10 minutes, followed by 28 units/kg per hour continuous infusion. Four hours after initiating therapy, measure aPTT, then adjust dose to achieve an aPTT that corresponds to an anti-factor X_a level of 0.35 to 0.7

(this is usually equivalent to an aPTT of 60 to 85 seconds). Treatment should be limited to 10 to 14 days. Some experts recommend switching to low molecular weight heparin after 3 to 5 days. For renal vein thrombosis requiring treatment, 6 weeks to 3 months of heparin/low molecular weight heparin therapy is recommended [1] .

Administration

Intravenous: Administer loading doses as IV bolus over 10 minutes. Administer maintenance infusion by continuous IV infusion in compatible solution (various concentrations may be used).
Make certain correct concentration is used.
Avoid intramuscular administration due to possibility of hematoma formation.

Effective October 1, 2009, a revised United States Pharmacopeia (USP) reference standard and test method has resulted in an approximately 10% reduction in heparin potency per USP unit. It is unlikely that the change in potency will have clinical significance. Clinicians should be aware of this change in potency in the event that there are any differences in response to heparin therapy in practice. Manufacturers will provide an identifier (an 'N' next to the lot number) on heparin products made under the new USP standards.

Uses

Maintenance of peripheral arterial and central venous catheter patency. Only continuous infusions (rather than intermittent flushes) have been demonstrated to maintain catheter patency. Treatment of thrombosis. Unilateral renal vein thrombosis (without renal impairment or extension to inferior vena cava) may be managed with supportive care and radiologic monitoring or heparin/low molecular weight heparin. Bilateral renal vein thromboses should be managed with heparin/low molecular weight heparin [1] . Although data are limited, enoxaparin may be preferable to heparin for treatment of thromboses.

Call 1-800-NOCLOTS for case reporting and treatment guidance.

Contraindications/Precautions

Contraindicated in infants with evidence of intracranial or GI bleeding or thrombocytopenia (below 50,000/mm^3). Data are insufficient to make specific recommendations regarding anticoagulation therapy. Heparin-induced thrombocytopenia (HIT) has been reported to occur in approximately 1% of newborns exposed to heparin. Heparin-associated antiplatelet antibodies were found in half of the newborns who were both thrombocytopenic and heparin-exposed. Although the thrombocytopenia resolved spontaneously in most patients upon stopping the heparin, a high incidence of ultrasonographic-documented aortic thrombosis was seen. Long term use of therapeutic doses of heparin can lead to osteoporosis.
Confirm heparin vial concentration prior to administration of the drug. Fatal hemorrhages have occurred in pediatric patients when the incorrect heparin concentration was administered.

Pharmacology

Activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. Metabolized by liver. Renal excretion should occur within 6 hours, but may be delayed. Clearance in neonates is more rapid than in children or adults. Half-life is dose-dependent, but averages 1 to 3 hours.

Monitoring

Follow platelet counts every 2 to 3 days. When treating thromboses, maintain a prolonged aPTT in a range corresponding to an anti-factor X_a level of 0.3 to 0.7 units/mL (usually equivalent to an aPTT of 60 to 85 seconds). Assess for signs of bleeding and thrombosis.

Special Considerations/Preparation

Keep protamine sulfate on hand to manage hemorrhage (see Protamine monograph for appropriate dosing).
Heparin available in 10 units/mL (for IV reservoirs); 100 units/mL; 1000 units/mL (for central catheters); 5000 units/mL, 10,000 units/mL, and 20,000 units/mL. Also available in premixed infusion bags in D_5W, NS, and ½ NS in various concentrations.

Solution Compatibility

D_5W, $D_{10}W$, NS, and ½ NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, caffeine citrate, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, flumazenil, furosemide, micafungin, hydralazine, hydrocortisone succinate, ibuprofen lysine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, milrinone, morphine, nafcillin, naloxone, neostigmine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, phytonadione, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Alteplase, amikacin, amiodarone, caspofungin, diazepam, gentamicin, hyaluronidase, methadone, netilmicin, phenytoin, tobramycin, and vancomycin.

References

- Chang GY, Leuder FL, DiMichele DM, et al: Heparin and the risk of intraventricular hemorrhage in premature infants. *J Pediatr*1997;131:362-66.
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2. Shah PS: Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. Cochrane Database Syst Rev 2008; 2008(2): 1.

Title Heparin

Dose

Maintaining patency of central vascular catheters:
0.5 units/kg/hour [1] [2] .

Maintaining patency of peripheral vascular catheters:
0.5 to 1 unit/mL of IV fluid.

Treatment of thrombosis: 75 units/kg bolus over 10 minutes, followed by 28 units/kg per hour continuous infusion. Four hours after initiating therapy, measure aPTT, then adjust dose to achieve an aPTT that corresponds to an anti-factor X_a level of 0.35 to 0.7

(this is usually equivalent to an aPTT of 60 to 85 seconds). Treatment should be limited to 10 to 14 days. Some experts recommend switching to low molecular weight heparin after 3 to 5 days. For renal vein thrombosis requiring treatment, 6 weeks to 3 months of heparin/low molecular weight heparin therapy is recommended [1] .

Administration

Intravenous: Administer loading doses as IV bolus over 10 minutes. Administer maintenance infusion by continuous IV infusion in compatible solution (various concentrations may be used).
Make certain correct concentration is used.
Avoid intramuscular administration due to possibility of hematoma formation.

Effective October 1, 2009, a revised United States Pharmacopeia (USP) reference standard and test method has resulted in an approximately 10% reduction in heparin potency per USP unit. It is unlikely that the change in potency will have clinical significance. Clinicians should be aware of this change in potency in the event that there are any differences in response to heparin therapy in practice. Manufacturers will provide an identifier (an 'N' next to the lot number) on heparin products made under the new USP standards.

Uses

Maintenance of peripheral arterial and central venous catheter patency. Only continuous infusions (rather than intermittent flushes) have been demonstrated to maintain catheter patency. Treatment of thrombosis. Unilateral renal vein thrombosis (without renal impairment or extension to inferior vena cava) may be managed with supportive care and radiologic monitoring or heparin/low molecular weight heparin. Bilateral renal vein thromboses should be managed with heparin/low molecular weight heparin [1] . Although data are limited, enoxaparin may be preferable to heparin for treatment of thromboses.

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Confirm heparin vial concentration prior to administration of the drug. Fatal hemorrhages have occurred in pediatric patients when the incorrect heparin concentration was administered.

Pharmacology

Activates antithrombin III, which progressively inactivates both thrombin and factor X_a, key proteolytic enzymes in the formation of fibrinogen and activation of prothrombin. Efficacy in neonates is decreased due to low antithrombin plasma concentrations. Metabolized by liver. Renal excretion should occur within 6 hours, but may be delayed. Clearance in neonates is more rapid than in children or adults. Half-life is dose-dependent, but averages 1 to 3 hours.

Monitoring

Follow platelet counts every 2 to 3 days. When treating thromboses, maintain a prolonged aPTT in a range corresponding to an anti-factor X_a level of 0.3 to 0.7 units/mL (usually equivalent to an aPTT of 60 to 85 seconds). Assess for signs of bleeding and thrombosis.

Special Considerations/Preparation

Keep protamine sulfate on hand to manage hemorrhage (see Protamine monograph for appropriate dosing).
Heparin available in 10 units/mL (for IV reservoirs); 100 units/mL; 1000 units/mL (for central catheters); 5000 units/mL, 10,000 units/mL, and 20,000 units/mL. Also available in premixed infusion bags in D_5W, NS, and ½ NS in various concentrations.

Solution Compatibility

D_5W, $D_{10}W$, NS, and ½ NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, caffeine citrate, calcium gluconate, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, flumazenil, furosemide, micafungin, hydralazine, hydrocortisone succinate, ibuprofen lysine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, midazolam, milrinone, morphine, nafcillin, naloxone, neostigmine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, phytonadione, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, trimethoprim/sulfamethoxazole, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Alteplase, amikacin, amiodarone, caspofungin, diazepam, gentamicin, hyaluronidase, methadone, netilmicin, phenytoin, tobramycin, and vancomycin.

References

- Chang GY, Leuder FL, DiMichele DM, et al: Heparin and the risk of intraventricular hemorrhage in premature infants. *J Pediatr*1997;131:362-66.
- Edstrom CS, Christensen RD: Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clin Perinatol*2000;27:623-41.
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1.83 Hepatitis B Immune Globulin (Human)

Title Hepatitis B Immune Globulin (Human)

Dose

0.5 mL IM in the anterolateral thigh.

Term and preterm newborns born to HBsAg-positive mother: Give within 12 hours of birth.

Term and preterm newborns born to HBsAg status unknown mother with BW greater than or equal to 2000 g: Give as soon as it is determined that the mother is HBsAg-positive, within 7 days of birth.

Preterm newborns born to HBsAg status unknown mother with BW less than 2000 g: If mother's status unavailable, give within 12 hours of birth.

When given at the same time as the first dose of hepatitis B vaccine, use a separate syringe and a different site. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel.

Uses

Passive immunization of newborns whose mothers have acute hepatitis B infection at the time of delivery, or who are HBsAg-positive. Infants born to mothers who are HBeAg-positive have the highest risk.

Pharmacology

Hepatitis B Immune Globulin (human) is a hyperimmune globulin solution prepared from pooled plasma of individuals with high titers of antibody to hepatitis B surface antigen (anti-HBsAg). All donors are HBsAg-negative and HIV-antibody negative. Nabi-HB® (Nabi) is a solvent detergent treated and thimerosal free hepatitis B immune globulin preparation [1] [2] .

Adverse Effects

Local pain and tenderness may occur at the injection site.
Do not administer IV because of the risk of serious systemic reactions. Serious complications of IM injections are rare. Universal precautions should be used with neonates born to HBsAg-positive mothers until they have been bathed carefully to remove maternal blood and secretions.

Special Considerations/Preparation

Refrigerate. Supplied in 1-mL and 5-mL single-dose vials and 0.5-mL and 1-mL unit-dose syringes. Approximate potency of Nabi-HB® and HepaGam® is 312 international units/mL. Use within 6 hours after vial has been entered [1] [2] .

References

- American Academy of Pediatrics. Hepatitis B. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: pp 343-350.
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- Product Information, Cangene, 2006.

1. Product Information: HepaGam B(R) intravenous intramuscular injection, hepatitis B immune globulin (human) intravenous intramuscular injection. Cangene bioPharma, Inc. (per FDA), Baltimore, MD, Jan, 2012.
2. Product Information: Nabi-HB(R) IM injection, hepatitis B immune globulin (human) IM injection. Biotest Pharmaceuticals Corporation (per manufacturer), Boca Raton, FL, Apr, 2008.

Title Hepatitis B Immune Globulin (Human)

Dose

0.5 mL IM in the anterolateral thigh.

Term and preterm newborns born to HBsAg-positive mother: Give within 12 hours of birth.

Term and preterm newborns born to HBsAg status unknown mother with BW greater than or equal to 2000 g: Give as soon as it is determined that the mother is HBsAg-positive, within 7 days of birth.

Preterm newborns born to HBsAg status unknown mother with BW less than 2000 g: If mother's status unavailable, give within 12 hours of birth.

When given at the same time as the first dose of hepatitis B vaccine, use a separate syringe and a different site. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel.

Uses

Passive immunization of newborns whose mothers have acute hepatitis B infection at the time of delivery, or who are HBsAg-positive. Infants born to mothers who are HBeAg-positive have the highest risk.

Pharmacology

Hepatitis B Immune Globulin (human) is a hyperimmune globulin solution prepared from pooled plasma of individuals with high titers of antibody to hepatitis B surface antigen (anti-HBsAg). All donors are HBsAg-negative and HIV-antibody negative. Nabi-HB® (Nabi) is a solvent detergent treated and thimerosal free hepatitis B immune globulin preparation [1] [2] .

Adverse Effects

Local pain and tenderness may occur at the injection site.
Do not administer IV because of the risk of serious systemic reactions. Serious complications of IM injections are rare. Universal precautions should be used with neonates born to HBsAg-positive mothers until they have been bathed carefully to remove maternal blood and secretions.

Special Considerations/Preparation

Refrigerate. Supplied in 1-mL and 5-mL single-dose vials and 0.5-mL and 1-mL unit-dose syringes. Approximate potency of Nabi-HB® and HepaGam® is 312 international units/mL. Use within 6 hours after vial has been entered [1] [2] .

References

- American Academy of Pediatrics. Hepatitis B. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: pp 343-350.
- Crumpacker CS: Hepatitis, in Remington JS, Klein JO (eds): *Infectious Diseases of the Fetus and Newborn Infant*, ed 5. Philadelphia: WB Saunders Co, 2001, pp 932-33.
- Product Information, Cangene, 2006.

1. Product Information: HepaGam B(R) intravenous intramuscular injection, hepatitis B immune globulin (human) intravenous intramuscular injection. Cangene bioPharma, Inc. (per FDA), Baltimore, MD, Jan, 2012.
2. Product Information: Nabi-HB(R) IM injection, hepatitis B immune globulin (human) IM injection. Biotest Pharmaceuticals Corporation (per manufacturer), Boca Raton, FL, Apr, 2008.

1.84 Hepatitis B Vaccine (Recombinant)

Title Hepatitis B Vaccine (Recombinant)

Dose

Engerix-B® 10 mcg (0.5 mL) or Recombivax HB® 5 mcg (0.5 mL) IM [1] [2] .

Maternal HBsAg-Positive: Administer first dose before 12 hours of age regardless of birth weight. Administer in combination with 0.5 mL of hepatitis B immune globulin. These infants should be tested for HBsAg and HBsAg antibodies 1 to 2 months after receiving the last dose of the hepatitis B vaccine series [3] .
Maternal HBsAg Unknown: Administer first dose before 12 hours of age. If birthweight less than 2000 g, administer in combination with hepatitis B immune globulin if mother's HBsAg result is not available within 12 hours of age. If birthweight 2000 g of greater and mother subsequently tests HBsAg positive, administer hepatitis B immune globulin to infant within 7 days of birth [3] .

Maternal HBsAg Negative: Administer first dose shortly after birth, before hospital discharge [3] . If birthweight less than 2000 g and medically stable, administer first dose at 30 days of chronologic age or at time of hospital discharge if before 30 days of chronologic age [4] .

The usual immunization schedule is Engerix-B® 10 mcg (0.5 mL) or Recombivax HB® 5 mcg (0.5 mL) given IM in the anterolateral thigh; first dose at elected date (preferably at birth), second dose 1 to 2 months later, and third dose 6 months after first dose. Monovalent or a combination vaccine containing HepB may be used to complete the series; 4 doses may be given if combination vaccine is used. Monovalent HepB vaccine should be used for doses administered before 6 weeks of age [3] [1] [2] .
A minimum of 4 weeks should elapse between the first and second doses, and 8 weeks between the second and third doses. The last dose (third or fourth) should be

administered no earlier than 6 months of age and at least 4 months after the first dose [3] .
Infants who did not receive a birth dose should be started on a 3-dose series of HepB-containing vaccine as soon as it is feasible [3] .

Administration

The vaccine may be administered subcutaneously in patients at risk for hemorrhage following IM injection, but the immune response may be lower [1] [2] [5] .
A 22- to 25-gauge needle should be used. The appropriate needle length is 7/8" to 1" for infants [5] .

Uses

Immunoprophylaxis against hepatitis B [1] [2] . Safe for use in infants born to HIV-positive mothers, although it may be less effective [6] .

Pharmacology

Recombinant hepatitis B vaccines are produced by *Saccharomyces cerevisiae* (common baker's yeast) that has been genetically modified to synthesize HBsAg. Both vaccines are inactivated (noninfective) products that contain HBsAg protein adsorbed to aluminum hydroxide, and may be interchanged with comparable efficacy [1] [2] .

Adverse Effects

The only common side effect is soreness at the injection site. Fever greater than 37.7 degrees C occurs in 1% to 6%.

Monitoring

Testing for immunity 3 months after completion of the vaccination series is recommended for infants born to HBsAg-positive mothers [5] and, perhaps, for premature infants who received an early first dose.

Special Considerations/Preparation

Recombivax HB® for infant use is supplied in 0.5-mL single-dose vials and single-dose prefilled syringes containing 5 mcg. Engerix-B® is supplied in 0.5-mL single-dose vials and 0.5-mL single-dose prefilled disposable syringes containing 10 mcg per 0.5 mL. Preservative free. The vaccine should be used as supplied; do not dilute. **Shake well before withdrawal and use.**Store refrigerated at **2 to 8 degrees C (36 to 46 degrees F)**. **Do not freeze**-destroys potency [1] [2] .

References

- Product Information: RECOMBIVAX HB(R) IM injection, hepatitis B vaccine (recombinant) IM injection. Merck Sharp & Dohme Corp. (per Manufacturer), Whitehouse Station, NJ, July, 2011.

- Product Information: ENGERIX-B suspension for intramuscular injection, hepatitis B vaccine (recombinant) suspension for intramuscular injection. GlaxoSmithKline, Research Triangle Park, NC, Dec, 2010.

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Committee on Infectious Diseases, American Academy of Pediatrics , Pickering LK, Baker CJ et al: Red Book(R): 2009 Report of the Committee on Infectious Diseases, 28th ed., 28th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.

- Mast EE, Margolis HS, Fiore AE et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep 12/23/2005; 54(RR-16): 1-31.

- Saari TN: Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics Jul1, 2003; 112(1 Pt 1): 193-198.

Title Hepatitis B Vaccine (Recombinant)

Dose

Engerix-B® 10 mcg (0.5 mL) or Recombivax HB® 5 mcg (0.5 mL) IM [1] [2] .

Maternal HBsAg-Positive: Administer first dose before 12 hours of age regardless of birth weight. Administer in combination with 0.5 mL of hepatitis B immune globulin. These infants should be tested for HBsAg and HBsAg antibodies 1 to 2 months after receiving the last dose of the hepatitis B vaccine series [3] .
Maternal HBsAg Unknown: Administer first dose before 12 hours of age. If birthweight less than 2000 g, administer in combination with hepatitis B immune globulin if mother's HBsAg result is not available within 12 hours of age. If birthweight 2000 g of greater and mother subsequently tests HBsAg positive, administer hepatitis B immune globulin to infant within 7 days of birth [3] .

Maternal HBsAg Negative: Administer first dose shortly after birth, before hospital discharge [3] . If birthweight less than 2000 g and medically stable, administer first dose at 30 days of chronologic age or at time of hospital discharge if before 30 days of chronologic age [4] .

The usual immunization schedule is Engerix-B® 10 mcg (0.5 mL) or Recombivax HB® 5 mcg (0.5 mL) given IM in the anterolateral thigh; first dose at elected date (preferably at birth), second dose 1 to 2 months later, and third dose 6 months after first dose. Monovalent or a combination vaccine containing HepB may be used to complete the series; 4 doses may be given if combination vaccine is used. Monovalent HepB vaccine should be used for doses administered before 6 weeks of age [3] [1] [2] .
A minimum of 4 weeks should elapse between the first and second doses, and 8 weeks

between the second and third doses. The last dose (third or fourth) should be administered no earlier than 6 months of age and at least 4 months after the first dose [3] .
Infants who did not receive a birth dose should be started on a 3-dose series of HepB-containing vaccine as soon as it is feasible [3] .

Administration

The vaccine may be administered subcutaneously in patients at risk for hemorrhage following IM injection, but the immune response may be lower [1] [2] [5] .
A 22- to 25-gauge needle should be used. The appropriate needle length is 7/8" to 1" for infants [5] .

Uses

Immunoprophylaxis against hepatitis B [1] [2] . Safe for use in infants born to HIV-positive mothers, although it may be less effective [6] .

Pharmacology

Recombinant hepatitis B vaccines are produced by *Saccharomyces cerevisiae* (common baker's yeast) that has been genetically modified to synthesize HBsAg. Both vaccines are inactivated (noninfective) products that contain HBsAg protein adsorbed to aluminum hydroxide, and may be interchanged with comparable efficacy [1] [2] .

Adverse Effects

The only common side effect is soreness at the injection site. Fever greater than 37.7 degrees C occurs in 1% to 6%.

Monitoring

Testing for immunity 3 months after completion of the vaccination series is recommended for infants born to HBsAg-positive mothers [5] and, perhaps, for premature infants who received an early first dose.

Special Considerations/Preparation

Recombivax HB® for infant use is supplied in 0.5-mL single-dose vials and single-dose prefilled syringes containing 5 mcg. Engerix-B® is supplied in 0.5-mL single-dose vials and 0.5-mL single-dose prefilled disposable syringes containing 10 mcg per 0.5 mL. Preservative free. The vaccine should be used as supplied; do not dilute. **Shake well before withdrawal and use.**Store refrigerated at **2 to 8 degrees C (36 to 46 degrees F)**. **Do not freeze**-destroys potency [1] [2] .

References

- Product Information: RECOMBIVAX HB(R) IM injection, hepatitis B vaccine (recombinant) IM injection. Merck Sharp & Dohme Corp. (per Manufacturer), Whitehouse Station, NJ, July, 2011.

- Product Information: ENGERIX-B suspension for intramuscular injection, hepatitis B vaccine (recombinant) suspension for intramuscular injection. GlaxoSmithKline, Research Triangle Park, NC, Dec, 2010.

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Committee on Infectious Diseases, American Academy of Pediatrics , Pickering LK, Baker CJ et al: Red Book(R): 2009 Report of the Committee on Infectious Diseases, 28th ed., 28th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.

- Mast EE, Margolis HS, Fiore AE et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep 12/23/2005; 54(RR-16): 1-31.

- Saari TN: Immunization of preterm and low birth weight infants. American Academy of Pediatrics Committee on Infectious Diseases. Pediatrics Jul1, 2003; 112(1 Pt 1): 193-198.

1.85 Hib Conjugate\Hepatitis B Combination Vaccine

Title Hib Conjugate/Hepatitis B Combination Vaccine

Dose

0.5 mL IM in the anterolateral thigh [1] .

Please refer to the most recent AAP/ACIP immunization schedule. It is recommended that premature infants should be immunized according to their postnatal age; some data, however, suggest delaying the first dose in chronically ill premature infants due to inadequate seroconversion against *H influenzae*.

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [1] .

Uses

Comvax® is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born to HBsAg-negative mothers. Comvax® should not be used in infants younger than 6 weeks of age [1] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine. Also **contraindicated** in infants less than 6 weeks of age (due to Hib component). Vaccination

should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [2] .

Pharmacology

Comvax® (preservative-free) combines the antigenic components of Recombivax HB® and PedvaxHIB®. Each 0.5 mL dose contains 5 mcg HBsAg and 7.5 mcg *Haemophilus b*-PRP (conjugated to meningococcal protein). Immune response is produced through formation of protective antibodies (anti-HBs) and formation of a T-dependent antigen from the PRP-conjugate that stimulates an enhanced antibody response and immunologic memory [1] .

Adverse Effects

Fever, irritability, somnolence, and injection site reactions (ie, local erythema, swelling, and tenderness) are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [1] .

Monitoring

Observe injection site for local reactions.

Special Considerations/Preparation

Supplied in 0.5-mL single-dose vial. Store refrigerated. **Do not freeze** [1] .

References

- Product Information: COMVAX(R) IM injection, haemophilus b conjugate [meningococcal protein conjugate] and hepatitis b [recombinant] vaccine IM injection. Merck Sharp & Dohme Corp, Whitehouse Station, NJ, Dec, 2010.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

Title Hib Conjugate/Hepatitis B Combination Vaccine

Dose

0.5 mL IM in the anterolateral thigh [1] .

Please refer to the most recent AAP/ACIP immunization schedule. It is recommended that premature infants should be immunized according to their postnatal age; some data, however, suggest delaying the first dose in chronically ill premature infants due to inadequate seroconversion against *H influenzae*.

Administration

When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [1] .

Uses

Comvax® is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born to HBsAg-negative mothers. Comvax® should not be used in infants younger than 6 weeks of age [1] .

Contraindications/Precautions **Contraindicated** in patients with a serious allergic reaction (eg, anaphylaxis) after a previous vaccine dose or to a component of the vaccine. Also **contraindicated** in infants less than 6 weeks of age (due to Hib component). Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine [2] .

Pharmacology

Comvax® (preservative-free) combines the antigenic components of Recombivax HB® and PedvaxHIB®. Each 0.5 mL dose contains 5 mcg HBsAg and 7.5 mcg *Haemophilus b*-PRP (conjugated to meningococcal protein). Immune response is produced through formation of protective antibodies (anti-HBs) and formation of a T-dependent antigen from the PRP-conjugate that stimulates an enhanced antibody response and immunologic memory [1] .

Adverse Effects

Fever, irritability, somnolence, and injection site reactions (ie, local erythema, swelling, and tenderness) are common. Rare anaphylactic reactions (ie, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported [1] .

Monitoring

Observe injection site for local reactions.

Special Considerations/Preparation

Supplied in 0.5-mL single-dose vial. Store refrigerated. **Do not freeze** [1] .

References

- Product Information: COMVAX(R) IM injection, haemophilus b conjugate [meningococcal protein conjugate] and hepatitis b [recombinant] vaccine IM injection. Merck Sharp & Dohme Corp, Whitehouse Station, NJ, Dec, 2010.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

1.86 Hyaluronidase

Title Hyaluronidase

Dose

Inject 1 mL (150 units) as 5 separate 0.2-mL subcutaneous injections around the periphery of the extravasation site. Use 25- or 26-gauge needle and change after each injection.

The chances of therapeutic success may be increased by:
1) Initiating treatment within 1 hour of extravasation;
2) Providing small exit stab incisions and subcutaneously flushing the affected area with up to 500 mL of normal saline after the hyaluronidase treatment (technique described by Gault 1993 [1]);
3) Covering with a hydrogel dressing for 48 hours.

Uses

Prevention of tissue injury caused by IV extravasation. Suggested indications (some anecdotal) are for extravasations involving drugs that are irritating to veins because of hyperosmolarity or extreme pH (e.g. aminophylline, amphotericin B, calcium, diazepam, erythromycin, gentamicin, methicillin, nafcillin, oxacillin, phenytoin, potassium chloride, rifampin, sodium bicarbonate, tromethamine, vancomycin, and TPN, and concentrated IV solutions). Hyaluronidase is **not** indicated for treatment of extravasations of vasoconstrictive agents (e.g. dopamine, epinephrine, and norepinephrine).

Contraindications/Precautions

Not recommended for IV use. Discontinue use if sensitization occurs. Should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist agents. Do not inject near area of infection or acutely inflamed area because of the risk of spreading a localized infection.

Pharmacology

Hyaluronidase is a mucolytic enzyme that disrupts the normal intercellular barrier and allows rapid dispersion of extravasated fluids through tissues.

Adverse Effects

The most frequent adverse events reported are injection site reactions. Allergic reactions have occurred rarely.

Monitoring

No specific monitoring required.

Special Considerations/Preparation

Amphadase® and Hydase™ are purified bovine hyaluronidase, and Hylenex® is a recombinant human hyaluronidase.
Amphadase®, Hydase™, and Hylenex® are supplied as 150 USP units/mL in 2 mL glass vials. Store refrigerated. Do not freeze.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Incompatibility

Epinephrine, heparin, and phenytoin.

References

- Ramasethu J: Prevention and management of extravasation injuries in neonates. *NeoReviews* 2004;5:e491-e497.
- Lehr VT, Lulic-Botica M, Lindblad WJ, et al: Management of infiltration injury in neonates using duoderm hydroactive gel. *Am J Perinatol* 2004;21:409-414.
- Casanova D, Bardot J, Magalon G: Emergency treatment of accidental infusion leakage in the newborn: report of 14 cases. *Br J Plast Surg*2001;545:396-399.
- Davies J, Gault D, Buchdahl: Preventing the scars of neonatal intensive care. *Arch Dis Child* 1994;70:F50-F51.
- Gault DT: Extravasation injuries. *Br J Plast Surg* 1993;46:91-96.
- Raszka WV, Kueser TK, Smith FR, Bass JW: The use of hyaluronidase in the treatment of intravenous extravasation injuries. *J Perinatol* 1990;10:146.
- Product information, Amphastar Pharmaceuticals, Inc., 2005
- Product information, Akorn, 2007
- Product information, Baxter Healthcare, 2008

1. Gault DT: Extravasation injuries. Br J Plast Surg Mar, 1993; 46(2): 91-96.

Title Hyaluronidase

Dose

Inject 1 mL (150 units) as 5 separate 0.2-mL subcutaneous injections around the periphery of the extravasation site. Use 25- or 26-gauge needle and change after each injection.

The chances of therapeutic success may be increased by:
1) Initiating treatment within 1 hour of extravasation;
2) Providing small exit stab incisions and subcutaneously flushing the affected area with up to 500 mL of normal saline after the hyaluronidase treatment (technique described by Gault 1993 [1]);
3) Covering with a hydrogel dressing for 48 hours.

Uses

Prevention of tissue injury caused by IV extravasation. Suggested indications (some anecdotal) are for extravasations involving drugs that are irritating to veins because of

hyperosmolarity or extreme pH (e.g. aminophylline, amphotericin B, calcium, diazepam, erythromycin, gentamicin, methicillin, nafcillin, oxacillin, phenytoin, potassium chloride, rifampin, sodium bicarbonate, tromethamine, vancomycin, and TPN, and concentrated IV solutions). Hyaluronidase is **not** indicated for treatment of extravasations of vasoconstrictive agents (e.g. dopamine, epinephrine, and norepinephrine).

Contraindications/Precautions

Not recommended for IV use. Discontinue use if sensitization occurs. Should not be used to enhance the absorption and dispersion of dopamine and/or alpha agonist agents. Do not inject near area of infection or acutely inflamed area because of the risk of spreading a localized infection.

Pharmacology

Hyaluronidase is a mucolytic enzyme that disrupts the normal intercellular barrier and allows rapid dispersion of extravasated fluids through tissues.

Adverse Effects

The most frequent adverse events reported are injection site reactions. Allergic reactions have occurred rarely.

Monitoring

No specific monitoring required.

Special Considerations/Preparation

Amphadase® and Hydase™ are purified bovine hyaluronidase, and Hylenex® is a recombinant human hyaluronidase.
Amphadase®, Hydase™, and Hylenex® are supplied as 150 USP units/mL in 2 mL glass vials. Store refrigerated. Do not freeze.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Incompatibility

Epinephrine, heparin, and phenytoin.

References

- Ramasethu J: Prevention and management of extravasation injuries in neonates. *NeoReviews* 2004;5:e491-e497.
- Lehr VT, Lulic-Botica M, Lindblad WJ, et al: Management of infiltration injury in neonates using duoderm hydroactive gel. *Am J Perinatol* 2004;21:409-414.

- Casanova D, Bardot J, Magalon G: Emergency treatment of accidental infusion leakage in the newborn: report of 14 cases. *Br J Plast Surg*2001;545:396-399.
- Davies J, Gault D, Buchdahl: Preventing the scars of neonatal intensive care. *Arch Dis Child* 1994;70:F50-F51.
- Gault DT: Extravasation injuries. *Br J Plast Surg* 1993;46:91-96.
- Raszka WV, Kueser TK, Smith FR, Bass JW: The use of hyaluronidase in the treatment of intravenous extravasation injuries. *J Perinatol* 1990;10:146.
- Product information, Amphastar Pharmaceuticals, Inc., 2005
- Product information, Akorn, 2007
- Product information, Baxter Healthcare, 2008

1. Gault DT: Extravasation injuries. Br J Plast Surg Mar, 1993; 46(2): 91-96.

1.87 HydrALAZINE

Title HydrALAZINE

Dose

Parenteral: Begin with 0.1 to 0.5 mg/kg/dose every 6 to 8 hours. Dose may be gradually increased as required for blood pressure control to a maximum of 2 mg/kg/dose every 6 hours.
Oral: 0.25 to 1 mg/kg/dose every 6 to 8 hours, or approximately twice the required IV dose. Administer with food to enhance absorption.

Note: Use with a beta-blocking agent is often recommended to enhance the antihypertensive effect and decrease the magnitude of the reflex tachycardia. This is expected to reduce hydralazine IV dosage requirements to less than 0.15 mg/kg per dose.

Uses

Treatment of mild to moderate neonatal hypertension by vasodilation. Afterload reduction in patients with congestive heart failure.

Pharmacology

Causes direct relaxation of smooth muscle in the arteriolar resistance vessels. Major hemodynamic effects: Decrease in systemic vascular resistance and a resultant increase in cardiac output. Increases renal, coronary, cerebral, and splanchnic blood flow. When administered orally, hydralazine has low bioavailability because of extensive first-pass metabolism by the liver and intestines. The rate of enzymatic metabolism is genetically determined by the acetylator phenotype--slow acetylators have higher plasma concentrations and a higher incidence of adverse effects.

Adverse Effects

Diarrhea, emesis, and temporary agranulocytosis have been reported in neonates. Tachycardia, postural hypotension, headache, nausea, and a lupus-like syndrome occur in 10% to 20% of adults. Uncommon reactions in adults include GI irritation and bleeding, drug fever, rash, conjunctivitis, and bone marrow suppression.

Monitoring

Frequent assessment of blood pressure and heart rate. Guaiac stools. Periodic CBC during long-term use.

Special Considerations/Preparation

Hydralazine hydrochloride injection for IV use (20 mg/mL) is available in 1-mL vial. A 1-mg/mL dilution may be made by diluting 0.5 mL of the 20-mg/mL concentrate with 9.5 mL of preservative-free normal saline for injection. Dilution is stable for 24 hours. Oral tablet strengths include 10-, 25-, 50-, and 100-mg. Oral formulations using simple syrups containing dextrose, fructose, or sucrose are unstable. To prepare an oral suspension, crush a 50 mg tablet and dissolve in 4 mL of 5% mannitol, then add 46 mL of sterile water to make a final concentration of 1 mg/mL. Protect from light. Stable for 7 days refrigerated.

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Dobutamine, heparin, hydrocortisone succinate, and potassium chloride.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, diazoxide, furosemide, and phenobarbital.

References

- Artman M, Graham TP Jr: Guidelines for vasodilator therapy of congestive heart failure in infants and children. *Am Heart J*1987;113:995.
- Gupta VD, Stewart KR, Bethea C: Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986;11:215.
- Beekman RH, Rocchini AP, Rosenthal A: Hemodynamic effects of hydralazine in infants with a large ventricular septal defect. *Circulation* 1982;65:523.
- Fried R, Steinherz LJ, Levin AR, et al: Use of hydralazine for intractable cardiac failure in childhood. *J Pediatr* 1980;97:1009.
- Product Information, American Regent, 2003.

Title HydrALAZINE

Dose

Parenteral: Begin with 0.1 to 0.5 mg/kg/dose every 6 to 8 hours. Dose may be gradually increased as required for blood pressure control to a maximum of 2 mg/kg/dose every 6 hours.
Oral: 0.25 to 1 mg/kg/dose every 6 to 8 hours, or approximately twice the required IV dose. Administer with food to enhance absorption.

Note: Use with a beta-blocking agent is often recommended to enhance the antihypertensive effect and decrease the magnitude of the reflex tachycardia. This is expected to reduce hydralazine IV dosage requirements to less than 0.15 mg/kg per dose.

Uses

Treatment of mild to moderate neonatal hypertension by vasodilation. Afterload reduction in patients with congestive heart failure.

Pharmacology

Causes direct relaxation of smooth muscle in the arteriolar resistance vessels. Major hemodynamic effects: Decrease in systemic vascular resistance and a resultant increase in cardiac output. Increases renal, coronary, cerebral, and splanchnic blood flow. When administered orally, hydralazine has low bioavailability because of extensive first-pass metabolism by the liver and intestines. The rate of enzymatic metabolism is genetically determined by the acetylator phenotype--slow acetylators have higher plasma concentrations and a higher incidence of adverse effects.

Adverse Effects

Diarrhea, emesis, and temporary agranulocytosis have been reported in neonates. Tachycardia, postural hypotension, headache, nausea, and a lupus-like syndrome occur in 10% to 20% of adults. Uncommon reactions in adults include GI irritation and bleeding, drug fever, rash, conjunctivitis, and bone marrow suppression.

Monitoring

Frequent assessment of blood pressure and heart rate. Guaiac stools. Periodic CBC during long-term use.

Special Considerations/Preparation

Hydralazine hydrochloride injection for IV use (20 mg/mL) is available in 1-mL vial. A 1-mg/mL dilution may be made by diluting 0.5 mL of the 20-mg/mL concentrate with 9.5 mL of preservative-free normal saline for injection. Dilution is stable for 24 hours. Oral tablet strengths include 10-, 25-, 50-, and 100-mg. Oral formulations using simple syrups containing dextrose, fructose, or sucrose are unstable. To prepare an oral suspension, crush a 50 mg tablet and dissolve in 4 mL of 5% mannitol, then add 46 mL of sterile water to make a final concentration of 1 mg/mL. Protect from light. Stable for 7 days refrigerated.

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Dobutamine, heparin, hydrocortisone succinate, and potassium chloride.

Terminal Injection Site Incompatibility

Aminophylline, ampicillin, diazoxide, furosemide, and phenobarbital.

References

- Artman M, Graham TP Jr: Guidelines for vasodilator therapy of congestive heart failure in infants and children. *Am Heart J*1987;113:995.
- Gupta VD, Stewart KR, Bethea C: Stability of hydralazine hydrochloride in aqueous vehicles. *J Clin Hosp Pharm* 1986;11:215.
- Beekman RH, Rocchini AP, Rosenthal A: Hemodynamic effects of hydralazine in infants with a large ventricular septal defect. *Circulation* 1982;65:523.
- Fried R, Steinherz LJ, Levin AR, et al: Use of hydralazine for intractable cardiac failure in childhood. *J Pediatr* 1980;97:1009.
- Product Information, American Regent, 2003.

1.88 Hydrochlorothiazide

Title Hydrochlorothiazide

Dose

1 to 2 mg/kg/dose orally every 12 hours.
Administer with food (improves absorption).

Note: Do not confuse with chlorothiazide.

Uses

Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone. May improve pulmonary function in patients with BPD.

Pharmacology

Limited data in neonates. Rapidly absorbed from GI tract. Onset of action is within 1 hour. Elimination half-life depends on GFR and is longer than that of chlorothiazide. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, phosphorus, and bicarbonate. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin.

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia.
Do not use in patients with significant impairment of renal or hepatic function.

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

Special Considerations/Preparation

Supplied as 12.5-mg capsule and 25-, 50-, and 100-mg tablets. Extemporaneous formulation for single ingredient hydrochlorothiazide oral suspension is not available. Below are the extemporaneous compounding instructions for the combination product of spironolactone PLUS hydrochlorothiazide.

Spironolactone/hydrochlorothiazide 5-mg/5 mg per mL oral solution can be prepared by using 24 tablets of spironolactone/hydrochlorothiazide 25 mg/25 mg in 120 mL of either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup). Crush tablets to a fine powder, add 25 mL of vehicle, and mix to create a uniform paste. Add vehicle to almost volume, transfer to amber bottle and add vehicle to final volume of 120 mL. Label "shake well" and "protect from light", with expiration date of 60 days. In the stability study, at least 91% of the initial hydrochlorothiazide and spironolactone concentration was retained for up to 60 days when stored without light at 5 and 25 degrees C [1] .

References

- Allen LV, Erickson MA III: Stability of labetalol hydrochloride, metoprolol tartrate, verapamil hydrochloride, and spironolactone with hydrochlorothiazide in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996;53:2304-2309.
- Albersheim SG, Solimano AJ, Sharma AK, et al: Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989;115:615.
- Roberts RJ: *Drug Therapy in Infants*. Philadelphia: WB Saunders Co, 1984, p 244.

1. Allen LV: Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. Am J Health Syst Pharm Sep1, 1996; 53(17): 2073-2078.

Title Hydrochlorothiazide

Dose

1 to 2 mg/kg/dose orally every 12 hours.
Administer with food (improves absorption).

Note: Do not confuse with chlorothiazide.

Uses

Diuretic used in treating both mild to moderate edema and mild to moderate hypertension. Effects increased when used in combination with furosemide or spironolactone. May improve pulmonary function in patients with BPD.

Pharmacology

Limited data in neonates. Rapidly absorbed from GI tract. Onset of action is within 1 hour. Elimination half-life depends on GFR and is longer than that of chlorothiazide. Major diuretic effect results from inhibition of sodium reabsorption in the distal nephron. Increases urinary losses of sodium, potassium, magnesium, chloride, phosphorus, and bicarbonate. Decreases renal excretion of calcium. Inhibits pancreatic release of insulin. Displaces bilirubin from albumin.

Adverse Effects

Hypokalemia and other electrolyte abnormalities. Hyperglycemia. Hyperuricemia. **Do not use in patients with significant impairment of renal or hepatic function.**

Monitoring

Serum electrolytes, calcium, phosphorus, and glucose; urine output and blood pressure.

Special Considerations/Preparation

Supplied as 12.5-mg capsule and 25-, 50-, and 100-mg tablets. Extemporaneous formulation for single ingredient hydrochlorothiazide oral suspension is not available. Below are the extemporaneous compounding instructions for the combination product of spironolactone PLUS hydrochlorothiazide.

Spironolactone/hydrochlorothiazide 5-mg/5 mg per mL oral solution can be prepared by using 24 tablets of spironolactone/hydrochlorothiazide 25 mg/25 mg in 120 mL of either a 1:1 mixture of Ora-Sweet® and Ora-Plus®, a 1:1 mixture of Ora-Sweet SF® and Ora-Plus®, or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup). Crush tablets to a fine powder, add 25 mL of vehicle, and mix to create a uniform paste. Add vehicle to almost volume, transfer to amber bottle and add vehicle to final volume of 120 mL. Label “shake well” and “protect from light”, with expiration date of 60 days. In the stability study, at least 91% of the initial hydrochlorothiazide and spironolactone concentration was retained for up to 60 days when stored without light at 5 and 25 degrees C [1] .

References

- Allen LV, Erickson MA III: Stability of labetalol hydrochloride, metoprolol tartrate, verapamil hydrochloride, and spironolactone with hydrochlorothiazide in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996;53:2304-2309.
- Albersheim SG, Solimano AJ, Sharma AK, et al: Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989;115:615.
- Roberts RJ: *Drug Therapy in Infants*. Philadelphia: WB Saunders Co, 1984, p 244.

1. Allen LV: Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. Am J Health Syst Pharm Sep1, 1996; 53(17): 2073-2078.

1.89 Hydrocortisone

Title Hydrocortisone

Dose

Physiologic replacement: 7 to 9 mg/m^2 per day IV or orally, in 2 or 3 doses.

Treatment of pressor- and volume-resistant hypotension (Stress doses):
20 to 30 mg/m^2 per day IV, in 2 or 3 doses, or approximately 1 mg/kg per dose every 8 hours.

Body Surface Area

BSA (m(2)) = (0.05 x kg) + 0.05

Weight (kg)	Body Surface Area (m(2))
0.6	0.08
1	0.1
1.4	0.12
2	0.15
3	0.2
4	0.25

Treatment of chorioamnionitis-exposed ELBW infants to decrease risk of CLD:
Initial dose: 0.5 mg/kg/dose IV every 12 hours for 12 days, followed by 0.25 mg/kg IV every 12 hours for 3 days [1] .

Administration

Intravenous: Administer over a period of 30 seconds (eg, 100 mg) to 10 minutes (eg, 500 mg or more). The reconstituted solution may be given without further dilution. For intravenous infusion, may dilute to 1 mg/mL in D_5W or NS for infusion [2] .
Oral: Guideline recommendations suggest crushing the tablet formulation and mixing with small amount of liquid just prior to administration [3] .

Uses

Prevention of bronchopulmonary dysplasia (BPD) in ELBW neonates. In a randomized, placebo-controlled clinical trial of ELBW neonates receiving low-dose hydrocortisone or placebo (started within the first 48 hours of life), babies exposed to chorioamnioitis receiving hydrocortisone had significantly improved survival without BPD and

decreased mortality before 36 weeks PMA when compared to those receiving placebo (OR 2.84; 95% CI, 1.21 to 6.67). There were no differences in these outcomes for infants without chorioamnioitis exposure receiving hydrocortisone when compared with placebo (OR 0.72; 95% CI, 0.31 to 1.65). The trial was stopped early due to an increased incidence of spontaneous GI perforation in the group receiving hydrocortisone (calculated sample size=712 births; actual final enrollment=360 births) [1] . Low-dose hydrocortisone for the first 2 weeks of life should be considered for infants with evidence of fetal inflammation; however, there are insufficient data to support its use in all babies at risk for BPD [4] [5] .
Treatment of cortisol deficiency. Treatment of pressor-resistant hypotension. Adjunctive therapy for persistent hypoglycemia.

Pharmacology

Hydrocortisone is the main adrenal corticosteroid, with primarily glucocorticoid effects. It increases the expression of adrenergic receptors in the vascular wall, thereby enhancing vascular reactivity to other vasoactive substances, such as norepinephrine and angiotensin II. Hypotensive babies who are cortisol deficient (less than 15 mcg/dL) are most likely to respond, and blood pressure will increase within 2 hours of the first dose. Hydrocortisone also stimulates the liver to form glucose from amino acids and glycerol, and stimulates the deposition of glucose as glycogen. Peripheral glucose utilization is diminished, protein breakdown is increased, and lipolysis is activated. The net result is an increase in blood glucose levels. Renal effects include increased calcium excretion. The apparent half-life in premature infants is 9 hours.

Adverse Effects

Hyperglycemia, hypertension, salt and water retention. There is an increased risk of GI perforations when treating concurrently with indomethacin. There is also an increased risk of disseminated *Candida*infections. Early, low-dose hydrocortisone treatment was not associated with increased cerebral palsy [6] . Treated infants had indicators of improved developmental outcome.

Monitoring

Measure blood pressure and blood glucose frequently during acute illness.

Special Considerations/Preparation

Hydrocortisone sodium succinate is available as powder for injection in 2-mL vials containing 100 mg. Reconstitute using preservative-free sterile water for injection to 50 mg/mL. Also available in 2-, 4-, and 8-mL vials with a concentration of 125 mg/mL after reconstitution. The reconstituted solution may be given without further dilution. Reconstituted solution stable for 3 days refrigerated. For intravenous infusion, may dilute to 1 mg/mL in D_5W or NS for infusion. Dilutions stable for at least 4 hours [2] .

A hydrocortisone oral suspension (2.5 mg/mL; made from tablets, 250 mg total) prepared in a vehicle containing sodium carboxymethylcellulose (1 g), methyl hydroxybenzoate (0.02 g), propyl hydroxybenzoate (0.08 g), polysorbate 80 (0.5 mL), syrup BP (10 mL), citric acid monohydrate (0.6 g) and water to 100 mL was stable for

at least 30 days when stored in the dark at room temperature (25 degrees C) and under refrigeration (5 degrees C). The vehicle was prepared by dissolving the methylhydroxybenzoate, propyl hydroxybenzoate, citric acid, and syrup in hot water. The cooled solution was triturated with the sodium carboxymethylcellulose and left overnight. Ground hydrocortisone tablets were triturated with polysorbate 80 and the vehicle was added; water was added to 100 mL [7] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, calcium chloride, calcium gluconate, cefepime, chloramphenicol, clindamycin, dexamethasone, digoxin, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, furosemide, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium, metoclopramide, metronidazole, morphine, neostigmine, netilmicin, nicardipine, oxacillin, pancuronium, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, remifentanil, sodium bicarbonate, vecuronium and vitamin K_1.

Terminal Injection Site Incompatibility

Midazolam, nafcillin, pentobarbital, phenobarbital, and phenytoin.

References

- Ng PC, Lee CH, Bnur FL, et al: A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. *Pediatrics* 2006;117:367-375.
- Fernandez E, Schrader R, Watterberg K: Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol* 2004;25:114-118.
- Seri I, Tan R, Evans J: Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics* 2001;107:1070-1074.
- Botas CM, Kurlat I, Young SM, Sola A: Disseminated candidal infections and intravenous hydrocortisone in preterm infants. *Pediatrics* 1995;95:883.
- Briars GL, Bailey BJ: Surface area estimation: pocket calculator versus nomogram. *Arch Dis Child* 1994;70:246-247.

1. Watterberg KL, Gerdes JS, Cole CH et al: Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics Dec, 2004; 114(6): 1649-1657.
2. Product Information: Solu-Cortef(R) IV, IM injection, powder for solution, hydrocortisone sodium succinate IV, IM injection, powder for solution. Pharmacia & Upjohn Company (per DailyMed), New York, NY, Jul, 2010.

3. Speiser PW, Azziz R, Baskin LS et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab Sep, 2010; 95(9): 4133-4160.
4. Watterberg KL: Policy statement--postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics Oct, 2010; 126(4): 800-808.
5. Doyle LW: Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology 2010; 98(2): 111-117.
6. Watterberg KL, Shaffer ML, Mishefske MJ et al: Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants. Pediatrics Jul, 2007; 120(1): 40-48.
7. Fawcett JP, Boulton DW, Jiang R et al: Stability of hydrocortisone oral suspensions prepared from tablets and powder. Ann Pharmacother Oct, 1995; 29(10): 987-990.

Title Hydrocortisone

Dose

Physiologic replacement: 7 to 9 mg/m^2 per day IV or orally, in 2 or 3 doses.

Treatment of pressor- and volume-resistant hypotension (Stress doses):
20 to 30 mg/m^2 per day IV, in 2 or 3 doses, or approximately 1 mg/kg per dose every 8 hours.

Body Surface Area

BSA (m(2)) = (0.05 x kg) + 0.05

Weight (kg)	Body Surface Area (m(2))
0.6	0.08
1	0.1
1.4	0.12
2	0.15
3	0.2
4	0.25

Treatment of chorioamnionitis-exposed ELBW infants to decrease risk of CLD:
Initial dose: 0.5 mg/kg/dose IV every 12 hours for 12 days, followed by 0.25 mg/kg IV every 12 hours for 3 days [1] .

Administration

Intravenous: Administer over a period of 30 seconds (eg, 100 mg) to 10 minutes (eg, 500 mg or more). The reconstituted solution may be given without further dilution. For intravenous infusion, may dilute to 1 mg/mL in D_5W or NS for infusion [2] .
Oral: Guideline recommendations suggest crushing the tablet formulation and mixing with small amount of liquid just prior to administration [3] .

Uses

Prevention of bronchopulmonary dysplasia (BPD) in ELBW neonates. In a randomized, placebo-controlled clinical trial of ELBW neonates receiving low-dose hydrocortisone or placebo (started within the first 48 hours of life), babies exposed to chorioamnioitis receiving hydrocortisone had significantly improved survival without BPD and decreased mortality before 36 weeks PMA when compared to those receiving placebo (OR 2.84; 95% CI, 1.21 to 6.67). There were no differences in these outcomes for infants without chorioamnioitis exposure receiving hydrocortisone when compared with placebo (OR 0.72; 95% CI, 0.31 to 1.65). The trial was stopped early due to an increased incidence of spontaneous GI perforation in the group receiving hydrocortisone (calculated sample size=712 births; actual final enrollment=360 births) [1] . Low-dose hydrocortisone for the first 2 weeks of life should be considered for infants with evidence of fetal inflammation; however, there are insufficient data to support its use in all babies at risk for BPD [4] [5] .
Treatment of cortisol deficiency. Treatment of pressor-resistant hypotension. Adjunctive therapy for persistent hypoglycemia.

Pharmacology

Hydrocortisone is the main adrenal corticosteroid, with primarily glucocorticoid effects. It increases the expression of adrenergic receptors in the vascular wall, thereby enhancing vascular reactivity to other vasoactive substances, such as norepinephrine and angiotensin II. Hypotensive babies who are cortisol deficient (less than 15 mcg/dL) are most likely to respond, and blood pressure will increase within 2 hours of the first dose. Hydrocortisone also stimulates the liver to form glucose from amino acids and glycerol, and stimulates the deposition of glucose as glycogen. Peripheral glucose utilization is diminished, protein breakdown is increased, and lipolysis is activated. The net result is an increase in blood glucose levels. Renal effects include increased calcium excretion. The apparent half-life in premature infants is 9 hours.

Adverse Effects

Hyperglycemia, hypertension, salt and water retention. There is an increased risk of GI perforations when treating concurrently with indomethacin. There is also an increased risk of disseminated *Candida*infections. Early, low-dose hydrocortisone treatment was not associated with increased cerebral palsy [6] . Treated infants had indicators of improved developmental outcome.

Monitoring

Measure blood pressure and blood glucose frequently during acute illness.

Special Considerations/Preparation

Hydrocortisone sodium succinate is available as powder for injection in 2-mL vials containing 100 mg. Reconstitute using preservative-free sterile water for injection to 50 mg/mL. Also available in 2-, 4-, and 8-mL vials with a concentration of 125 mg/mL after reconstitution. The reconstituted solution may be given without further dilution. Reconstituted solution stable for 3 days refrigerated. For intravenous infusion, may dilute to 1 mg/mL in D_5W or NS for infusion. Dilutions stable for at least 4 hours [2] .

A hydrocortisone oral suspension (2.5 mg/mL; made from tablets, 250 mg total) prepared in a vehicle containing sodium carboxymethylcellulose (1 g), methyl hydroxybenzoate (0.02 g), propyl hydroxybenzoate (0.08 g), polysorbate 80 (0.5 mL), syrup BP (10 mL), citric acid monohydrate (0.6 g) and water to 100 mL was stable for at least 30 days when stored in the dark at room temperature (25 degrees C) and under refrigeration (5 degrees C). The vehicle was prepared by dissolving the methylhydroxybenzoate, propyl hydroxybenzoate, citric acid, and syrup in hot water. The cooled solution was triturated with the sodium carboxymethylcellulose and left overnight. Ground hydrocortisone tablets were triturated with polysorbate 80 and the vehicle was added; water was added to 100 mL [7] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, aminophylline, amphotericin B, ampicillin, atropine, aztreonam, calcium chloride, calcium gluconate, cefepime, chloramphenicol, clindamycin, dexamethasone, digoxin, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, furosemide, heparin, hydralazine, insulin, isoproterenol, lidocaine, linezolid, lorazepam, magnesium, metoclopramide, metronidazole, morphine, neostigmine, netilmicin, nicardipine, oxacillin, pancuronium, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, procainamide, propofol, propranolol, remifentanil, sodium bicarbonate, vecuronium and vitamin K_1.

Terminal Injection Site Incompatibility

Midazolam, nafcillin, pentobarbital, phenobarbital, and phenytoin.

References

- Ng PC, Lee CH, Bnur FL, et al: A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. *Pediatrics* 2006;117:367-375.
- Fernandez E, Schrader R, Watterberg K: Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol* 2004;25:114-118.
- Seri I, Tan R, Evans J: Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics* 2001;107:1070-1074.
- Botas CM, Kurlat I, Young SM, Sola A: Disseminated candidal infections and intravenous hydrocortisone in preterm infants. *Pediatrics* 1995;95:883.

- Briars GL, Bailey BJ: Surface area estimation: pocket calculator versus nomogram. *Arch Dis Child* 1994;70:246-247.

1. Watterberg KL, Gerdes JS, Cole CH et al: Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics Dec, 2004; 114(6): 1649-1657.
2. Product Information: Solu-Cortef(R) IV, IM injection, powder for solution, hydrocortisone sodium succinate IV, IM injection, powder for solution. Pharmacia & Upjohn Company (per DailyMed), New York, NY, Jul, 2010.
3. Speiser PW, Azziz R, Baskin LS et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab Sep, 2010; 95(9): 4133-4160.
4. Watterberg KL: Policy statement--postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics Oct, 2010; 126(4): 800-808.
5. Doyle LW: Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology 2010; 98(2): 111-117.
6. Watterberg KL, Shaffer ML, Mishefske MJ et al: Growth and neurodevelopmental outcomes after early low-dose hydrocortisone treatment in extremely low birth weight infants. Pediatrics Jul, 2007; 120(1): 40-48.
7. Fawcett JP, Boulton DW, Jiang R et al: Stability of hydrocortisone oral suspensions prepared from tablets and powder. Ann Pharmacother Oct, 1995; 29(10): 987-990.

1.90 INFUVITEÂ® Pediatric

Title INFUVITEÂ® Pediatric

Dose

Intravenous: Infuvite® Pediatric is a sterile product consisting of two vials: a 4 mL vial labeled **Vial 1** and a 1 mL vial labeled **Vial 2**. The daily dose is a function of infant weight as indicated in the following table [1] .
Do not exceed this daily dose.

Infuvite Dosing

	< 1 kg	**> 1 kg and < 3 kg**	**≥ 3 kg**
Vial 1	1.2 mL	2.6 mL	4 mL
Vial 2	0.3 mL	0.65 mL	1 mL

Uses

Pediatric FDA Approved Indications
Multivitamin maintenance dosage for infants and children up to 11 years of age receiving parenteral nutrition or in patients in “stress situations” where administration by the IV route is necessary (eg, surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states) to prevent tissue depletion of nutrients [1] .

Pharmacology See table below for nutrient amounts.

INFUVITE® Pediatric

Vial 1 (4 mL)	**Amt***
Vitamin A** (as palmitate)	2300 IU (0.7 mg)
Vitamin D** (IU) (cholecalciferol)	400 IU (10 mcg)
Ascorbic Acid (vitamin C)	80 mg
Vitamin E** (dl -alpha tocopheryl acetate)	7 IU (7 mg)
Thiamine (as hydrochloride) B 1	1.2 mg
Riboflavin (as phosphate) B 2	1.4 mg
Niacinamide B 3	17 mg
Pyridoxine hydrochloride B 6	1 mg
d -Panthenol	5 mg
Vitamin K 1 **	0.2 mg
Vial 2 (1 mL)	
Biotin	20 mcg
Folic Acid	140 mcg
Vitamin B 12 (cyanocobalamin)	1 mcg

* Amounts based upon guidelines published by the American Medical. Association Department of Foods and Nutrition, JPEN 3(4);25862:1979.

Vial 1 (4 mL) Inactive ingredients: 50 mg polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection.

** Polysorbate 80 is used to water solubilize the oil-soluble vitamins A, D, E, and K.

Vial 2 (1 mL) Inactive ingredients: 75 mg mannitol, citric acid and/or sodium citrate for pH adjustment and water for injection.

Adverse Effects

Infuvite® Pediatric is administered in intravenous solutions, which may contain aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired [1] . Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solution, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration [1] .

Anaphylactic reactions following parenteral multivitamin administration have been reported rarely [1] .

Should not be given as a direct, undiluted intravenous injection.

Monitoring

Assess blood vitamin concentrations periodically in patients on long-term therapy to monitor for vitamin deficiencies or excesses [1] .

Special Considerations/Preparation

After Infuvite® Pediatric is diluted in an intravenous infusion, the resulting solution is ready for immediate use. Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Exposure to light should be minimized. Discard any unused portion. **Store between 2 and 8 degrees C (36 and 46 degrees F). Contains no more than 30 mcg/L of aluminum (vials 1 and 2 combined)** [1] .

Solution Compatibility

D_5W, $D_{10}W$, NS, D_5NS, Dex/AA solutions

Terminal Injection Site Incompatibility

Alkaline solutions or moderately alkaline drugs (acetazolamide, aminophylline, chlorothiazide, and sodium bicarbonate), ampicillin, tetracycline.
Direct addition to intravenous fat emulsions is not recommended [1] .

References

- Product Information: INFUVITE(R) Pediatric Pharmacy Bulk Package intravenous infusion, multiple vitamins intravenous infusion. Baxter Healthcare Corporation (per manufacturer), Deerfield, IL, Sep, 2007.

Title INFUVITEÂ® Pediatric

Dose

Intravenous: Infuvite® Pediatric is a sterile product consisting of two vials: a 4 mL vial labeled **Vial 1** and a 1 mL vial labeled **Vial 2**. The daily dose is a function of infant weight as indicated in the following table [1] .
Do not exceed this daily dose.

Infuvite Dosing

	< 1 kg	**> 1 kg and < 3 kg**	**≥ 3 kg**
Vial 1	1.2 mL	2.6 mL	4 mL
Vial 2	0.3 mL	0.65 mL	1 mL

Uses

Pediatric FDA Approved Indications
Multivitamin maintenance dosage for infants and children up to 11 years of age receiving parenteral nutrition or in patients in "stress situations" where administration by the IV route is necessary (eg, surgery, extensive burns, fractures and other trauma, severe infectious diseases, and comatose states) to prevent tissue depletion of nutrients [1] .

Pharmacology See table below for nutrient amounts.

INFUVITE® Pediatric

Vial 1 (4 mL)	**Amt***
Vitamin A** (as palmitate)	2300 IU (0.7 mg)
Vitamin D** (IU) (cholecalciferol)	400 IU (10 mcg)
Ascorbic Acid (vitamin C)	80 mg
Vitamin E** (dl -alpha tocopheryl acetate)	7 IU (7 mg)
Thiamine (as hydrochloride) B 1	1.2 mg
Riboflavin (as phosphate) B 2	1.4 mg
Niacinamide B 3	17 mg
Pyridoxine hydrochloride B 6	1 mg
d -Panthenol	5 mg

Vitamin K 1 **	0.2 mg
Vial 2 (1 mL)	
Biotin	20 mcg
Folic Acid	140 mcg
Vitamin B 12 (cyanocobalamin)	1 mcg

* Amounts based upon guidelines published by the American Medical. Association Department of Foods and Nutrition, JPEN 3(4);25862:1979.

Vial 1 (4 mL) Inactive ingredients: 50 mg polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection.

** Polysorbate 80 is used to water solubilize the oil-soluble vitamins A, D, E, and K.

Vial 2 (1 mL) Inactive ingredients: 75 mg mannitol, citric acid and/or sodium citrate for pH adjustment and water for injection.

Adverse Effects

Infuvite® Pediatric is administered in intravenous solutions, which may contain aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired [1] . Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solution, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration [1] .

Anaphylactic reactions following parenteral multivitamin administration have been reported rarely [1] .

Should not be given as a direct, undiluted intravenous injection.

Monitoring

Assess blood vitamin concentrations periodically in patients on long-term therapy to monitor for vitamin deficiencies or excesses [1] .

Special Considerations/Preparation

After Infuvite® Pediatric is diluted in an intravenous infusion, the resulting solution is ready for immediate use. Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Exposure to light should be minimized. Discard any unused portion. **Store between 2 and 8 degrees C (36 and 46**

degrees F). Contains no more than 30 mcg/L of aluminum (vials 1 and 2 combined) [1] .

Solution Compatibility

D_5W, $D_{10}W$, NS, D_5NS, Dex/AA solutions

Terminal Injection Site Incompatibility

Alkaline solutions or moderately alkaline drugs (acetazolamide, aminophylline, chlorothiazide, and sodium bicarbonate), ampicillin, tetracycline.
Direct addition to intravenous fat emulsions is not recommended [1] .

References

- Product Information: INFUVITE(R) Pediatric Pharmacy Bulk Package intravenous infusion, multiple vitamins intravenous infusion. Baxter Healthcare Corporation (per manufacturer), Deerfield, IL, Sep, 2007.

1.91 Ibuprofen Lysine

Title Ibuprofen Lysine

Dose

First dose: 10 mg/kg IV [1] .
Second and third doses: 5 mg/kg IV [1] .
Administer at 24 hour intervals [1] [2] .

Administration

Dilute prior to administration in an appropriate volume of dextrose or saline and give over 15 minutes [2] .

Uses

Closure of Patent Ductus Arteriosus (PDA). According to a review of 20 studies, ibuprofen was found to be as effective as indomethacin for closure of PDA. Additionally, ibuprofen was associated with a decreased risk for development of necrotizing enterocolitis (RR 0.68; 95% CI, 0.47, 0.99) and less evidence for transient renal impairment when compared with indomethacin [3] . In a clinical trial including preterm neonates less than 30 weeks GA with an asymptomatic PDA, treatment with ibuprofen within the first 72 hours of life was associated with a decreased need for rescue therapy when compared with placebo [1] . In another randomized, controlled, single-center study, the use of early ibuprofen therapy for PDA closure in patients who were mildly symptomatic was not associated with a reduction in supplemental oxygen needs in the first 28 days of life or oxygen requirements at 36 weeks PMA when compared with ibuprofen therapy provided once a PDA became symptomatic and required treatment. This study was terminated early due to a recall of the intravenous ibuprofen lysine product; 105 of the needed 168 infants were enrolled by study

termination [4] .
Not indicated for IVH prophylaxis.

Contraindications/Precautions

Ibuprofen lysine is **contraindicated** in preterm neonates with 1) untreated infection, 2) active bleeding, 3) thrombocytopenia or coagulation defects, 4) NEC, 5) significant renal dysfunction, and 6) congenital heart disease with ductal-dependent systemic blood flow [2] .

Pharmacology

Ibuprofen lysine is a lysine salt solution of racemic ibuprofen, an inhibitor of prostaglandin synthesis. In adults (no data in neonates), metabolism is primarily via hydroxylation by hepatic CYP 2C9 and 2C8, with renal elimination of unchanged drug (10% to 15%) and metabolites. The mean half-life in premature neonates is approximately 43 hours, with large interpatient variability. Clearance increases rapidly with postnatal age and PDA closure [2] [10] .

Adverse Effects

Decreased urine output is less severe and occurs less frequently than with indomethacin [3] [5] . Although the available (and few) data suggest that the displacement of bilirubin from albumin is minimal with an ibuprofen dosing regimen of 10-, 5-, 5-mg/kg (every 24 hr), a more significant increase in unbound bilirubin can be expected in those infants with a high unconjugated bilirubin/albumin ratio and those in whom high ibuprofen concentrations are achieved [6] . A retrospective cohort study (ibuprofen for PDA [n=418] versus no ibuprofen [n=288]) found an increased total serum bilirubin (9 mg/dL versus 7.3 mg/dL) and an increased need for phototherapy (95% versus 87.6%) in babies receiving ibuprofen. The cohorts were from 2 separate decades which could introduce historical bias [7] . There is one recent case report of pulmonary hypertension in a 32-week gestation infant in Italy who received ibuprofen lysine (not NeoProfen®) for treatment of PDA [8] . Several studies have demonstrated an increased risk of oxygen dependency at 28 days postnatal age, but not 36 weeks PMA. Ibuprofen, like other NSAID drugs, can inhibit platelet aggregation. According to a meta-analysis, ibuprofen was associated with a decreased risk for development of NEC when compared with indomethacin (RR=0.68; 95% CI, 0.47 to 0.99). No other significant differences were noted [3] . In another meta-analysis, no difference in risk was found for NEC between ibuprofen and indomethacin; however, an increased risk for chronic lung disease was found for ibuprofen (RR=1.28; 95% CI, 1.03 to 1.6) [9] .

Monitoring

Assess for ductal closure. Monitor urine output and delay further doses if urine output falls below 0.6 mL/kg/hour [2] . Assess for signs of bleeding.

Special Considerations/Preparation

Supplied as a 10-mg/mL sterile solution for injection in 2-mL single use vials. Should be diluted prior to administration in an appropriate volume of dextrose or saline. Contains no preservatives and is not buffered. Administer within 30 minutes of preparation. The pH is adjusted to 7. Store at room temperature. **Protect from light** [2] .

Solution Compatibility

NS and D_5W.

Terminal Injection Site Compatibility

Ceftazidime, dopamine, epinephrine, furosemide, heparin, insulin, morphine, phenobarbital, potassium chloride, sodium bicarbonate.

Terminal Injection Site Incompatibility

Dex/AA. Caffeine citrate, dobutamine, and vecuronium.

References

- Lundbeck Inc.: Compatibility data on file as of October 2009.

1. Aranda JV, Clyman R, Cox B et al: A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol Mar, 2009; 26(3): 235-245.
2. Product Information: NeoProfen IV injection, ibuprofen lysine IV injection. Lundbeck Inc. (per Manufacturer), Deerfield, IL, Jan, 2010.
3. Ohlsson A: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev Apr14, 2010; 4: 1-.
4. Sosenko IR, Fajardo MF, Claure N et al: Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr Jun, 2012; 160(6): 929-935.
5. Thomas RL, Parker GC, VanOvermeire B et al: A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 03/00/2005; 164(3): 135-140.
6. Ambat MT: Effect of ibuprofen L-lysinate on bilirubin binding to albumin as measured by saturation index and horseradish peroxidase assays. J Perinatol Apr, 2008; 28(4): 287-290.
7. Zecca E, Romagnoli C, De Carolis MP et al: Does Ibuprofen increase neonatal hyperbilirubinemia?Pediatrics Aug, 2009; 124(2): 480-484.
8. Bellini C: Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ Jun20, 2006; 174(13): 1843-1844.
9. Jones LJ, Craven PD, Attia J et al: Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. Arch Dis Child Fetal Neonatal Ed Jan, 2011; 96(1): F45-F52.
10. Van Overmeire B, Touw D, Schepens PJ et al: Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther Oct, 2001; 70(4): 336-343.

Title Ibuprofen Lysine

Dose

First dose: 10 mg/kg IV [1] .
Second and third doses: 5 mg/kg IV [1] .
Administer at 24 hour intervals [1] [2] .

Administration

Dilute prior to administration in an appropriate volume of dextrose or saline and give over 15 minutes [2] .

Uses

Closure of Patent Ductus Arteriosus (PDA). According to a review of 20 studies, ibuprofen was found to be as effective as indomethacin for closure of PDA. Additionally, ibuprofen was associated with a decreased risk for development of necrotizing enterocolitis (RR 0.68; 95% CI, 0.47, 0.99) and less evidence for transient renal impairment when compared with indomethacin [3] . In a clinical trial including preterm neonates less than 30 weeks GA with an asymptomatic PDA, treatment with ibuprofen within the first 72 hours of life was associated with a decreased need for rescue therapy when compared with placebo [1] . In another randomized, controlled, single-center study, the use of early ibuprofen therapy for PDA closure in patients who were mildly symptomatic was not associated with a reduction in supplemental oxygen needs in the first 28 days of life or oxygen requirements at 36 weeks PMA when compared with ibuprofen therapy provided once a PDA became symptomatic and required treatment. This study was terminated early due to a recall of the intravenous ibuprofen lysine product; 105 of the needed 168 infants were enrolled by study termination [4] .
Not indicated for IVH prophylaxis.

Contraindications/Precautions

Ibuprofen lysine is **contraindicated** in preterm neonates with 1) untreated infection, 2) active bleeding, 3) thrombocytopenia or coagulation defects, 4) NEC, 5) significant renal dysfunction, and 6) congenital heart disease with ductal-dependent systemic blood flow [2] .

Pharmacology

Ibuprofen lysine is a lysine salt solution of racemic ibuprofen, an inhibitor of prostaglandin synthesis. In adults (no data in neonates), metabolism is primarily via hydroxylation by hepatic CYP 2C9 and 2C8, with renal elimination of unchanged drug (10% to 15%) and metabolites. The mean half-life in premature neonates is approximately 43 hours, with large interpatient variability. Clearance increases rapidly with postnatal age and PDA closure [2] [10] .

Adverse Effects

Decreased urine output is less severe and occurs less frequently than with indomethacin [3] [5] . Although the available (and few) data suggest that the displacement of bilirubin from albumin is minimal with an ibuprofen dosing regimen of 10-, 5-, 5-mg/kg (every 24 hr), a more significant increase in unbound bilirubin can be expected in those infants with a high unconjugated bilirubin/albumin ratio and those in whom high ibuprofen concentrations are achieved [6] . A retrospective cohort study (ibuprofen for PDA [n=418] versus no ibuprofen [n=288]) found an increased total serum bilirubin (9 mg/dL versus 7.3 mg/dL) and an increased need for phototherapy (95% versus 87.6%) in babies receiving ibuprofen. The cohorts were from 2 separate decades which could introduce historical bias [7] . There is one recent case report of pulmonary hypertension in a 32-week gestation infant in Italy who received ibuprofen lysine (not NeoProfen®) for treatment of PDA [8] . Several studies have demonstrated an increased risk of oxygen dependency at 28 days postnatal age, but not 36 weeks PMA. Ibuprofen, like other NSAID drugs, can inhibit platelet aggregation. According to a meta-analysis, ibuprofen was associated with a decreased risk for development of NEC when compared with indomethacin (RR=0.68; 95% CI, 0.47 to 0.99). No other significant differences were noted [3] . In another meta-analysis, no difference in risk was found for NEC between ibuprofen and indomethacin; however, an increased risk for chronic lung disease was found for ibuprofen (RR=1.28; 95% CI, 1.03 to 1.6) [9] .

Monitoring

Assess for ductal closure. Monitor urine output and delay further doses if urine output falls below 0.6 mL/kg/hour [2] . Assess for signs of bleeding.

Special Considerations/Preparation

Supplied as a 10-mg/mL sterile solution for injection in 2-mL single use vials. Should be diluted prior to administration in an appropriate volume of dextrose or saline. Contains no preservatives and is not buffered. Administer within 30 minutes of preparation. The pH is adjusted to 7. Store at room temperature. **Protect from light** [2] .

Solution Compatibility

NS and D_5W.

Terminal Injection Site Compatibility

Ceftazidime, dopamine, epinephrine, furosemide, heparin, insulin, morphine, phenobarbital, potassium chloride, sodium bicarbonate.

Terminal Injection Site Incompatibility

Dex/AA. Caffeine citrate, dobutamine, and vecuronium.

References

- Lundbeck Inc.: Compatibility data on file as of October 2009.

1. Aranda JV, Clyman R, Cox B et al: A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol Mar, 2009; 26(3): 235-245.
2. Product Information: NeoProfen IV injection, ibuprofen lysine IV injection. Lundbeck Inc. (per Manufacturer), Deerfield, IL, Jan, 2010.
3. Ohlsson A: Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev Apr14, 2010; 4: 1-.
4. Sosenko IR, Fajardo MF, Claure N et al: Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr Jun, 2012; 160(6): 929-935.
5. Thomas RL, Parker GC, VanOvermeire B et al: A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. Eur J Pediatr 03/00/2005; 164(3): 135-140.
6. Ambat MT: Effect of ibuprofen L-lysinate on bilirubin binding to albumin as measured by saturation index and horseradish peroxidase assays. J Perinatol Apr, 2008; 28(4): 287-290.
7. Zecca E, Romagnoli C, De Carolis MP et al: Does Ibuprofen increase neonatal hyperbilirubinemia?Pediatrics Aug, 2009; 124(2): 480-484.
8. Bellini C: Pulmonary hypertension following L-lysine ibuprofen therapy in a preterm infant with patent ductus arteriosus. CMAJ Jun20, 2006; 174(13): 1843-1844.
9. Jones LJ, Craven PD, Attia J et al: Network meta-analysis of indomethacin versus ibuprofen versus placebo for PDA in preterm infants. Arch Dis Child Fetal Neonatal Ed Jan, 2011; 96(1): F45-F52.
10. Van Overmeire B, Touw D, Schepens PJ et al: Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther Oct, 2001; 70(4): 336-343.

1.92 Imipenem\Cilastatin

Title Imipenem/Cilastatin

Dose

20 to 25 mg/kg/dose IV every 12 hours.

Administration

Administer by IV infusion over 15 to 30 minutes at a concentration of 5 mg/mL or less [1] .

Uses

Restricted to treatment of non-CNS infections caused by bacteria, primarily Enterobacteriaceae and anaerobes, resistant to other antibiotics.

Pharmacology

Imipenem is a broad-spectrum carbapenem antibiotic combined in a 1:1 ratio with cilastatin, a renal dipeptidase inhibitor with no intrinsic antibacterial activity. Bactericidal activity is due to inhibition of cell wall synthesis. Clearance is directly

related to renal function. Serum half-life of imipenem in neonates is 2.5 hours; the half-life of cilastatin is 9 hours.

Adverse Effects

Seizures occur frequently in patients with meningitis, preexisting CNS pathology, and severe renal dysfunction. Local reactions at the injection site and increased platelet counts are the most frequent adverse effects. Other reactions, including eosinophilia, elevated hepatic transaminases, and diarrhea, also occur in more than 5% of patients.

Monitoring

Periodic CBC and hepatic transaminases. Assess IV site for signs of phlebitis.

Special Considerations/Preparation

Available as powder for injection in 250-mg, and 500-mg vials. Reconstitute with 10 mL of compatible diluent. When reconstituted with compatible diluent, solution is stable for 4 hours at room temperature, 24 hours refrigerated. Maximum concentration for infusion is 5 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aztreonam, cefepime, famotidine, insulin, linezolid, midazolam, propofol, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, azithromycin, fluconazole, gentamicin, lorazepam, milrinone, sodium bicarbonate, and tobramycin.

References

- Ahonkhai VI, Cyhan GM, Wilson SE, Brown KR: Imipenem-cilastatin in pediatric patients: an overview of safety and efficacy in studies conducted in the United States. *Pediatr Infect Dis J* 1989;8:740.
- Garges HP, Alexander KA: Newer antibiotics: imipenem/cilastatin and meropenem. *NeoReviews* 2003;4:e364-68.
- Nalin DR, Jacobsen CA: Imipenem/cilastatin therapy for serious infections in neonates and infants. *Scand J Infect Dis* 1987;Suppl.2:46.
- Product Information: Primaxin® IV, imipenem and cilastatin IV injection. Merck & Co., 2009.
- Reed MD, Kliegman RM, Yamashita TS, et al: Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990;34:1172.

- Stuart RL, Turnidge J, Grayson ML: Safety of imipenem in neonates. *Pediatr Infect Dis J* 1995;14:804.

1. Product Information: PRIMAXIN(R)IV IV injection, imipenem and cilastatin IV injection. Merck and Co Inc, Whitehouse Station, NJ, Aug, 2009.

Title Imipenem/Cilastatin

Dose

20 to 25 mg/kg/dose IV every 12 hours.

Administration

Administer by IV infusion over 15 to 30 minutes at a concentration of 5 mg/mL or less [1] .

Uses

Restricted to treatment of non-CNS infections caused by bacteria, primarily Enterobacteriaceae and anaerobes, resistant to other antibiotics.

Pharmacology

Imipenem is a broad-spectrum carbapenem antibiotic combined in a 1:1 ratio with cilastatin, a renal dipeptidase inhibitor with no intrinsic antibacterial activity. Bactericidal activity is due to inhibition of cell wall synthesis. Clearance is directly related to renal function. Serum half-life of imipenem in neonates is 2.5 hours; the half-life of cilastatin is 9 hours.

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Seizures occur frequently in patients with meningitis, preexisting CNS pathology, and severe renal dysfunction. Local reactions at the injection site and increased platelet counts are the most frequent adverse effects. Other reactions, including eosinophilia, elevated hepatic transaminases, and diarrhea, also occur in more than 5% of patients.

Monitoring

Periodic CBC and hepatic transaminases. Assess IV site for signs of phlebitis.

Special Considerations/Preparation

Available as powder for injection in 250-mg, and 500-mg vials. Reconstitute with 10 mL of compatible diluent. When reconstituted with compatible diluent, solution is stable for 4 hours at room temperature, 24 hours refrigerated. Maximum concentration for infusion is 5 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, aztreonam, cefepime, famotidine, insulin, linezolid, midazolam, propofol, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, azithromycin, fluconazole, gentamicin, lorazepam, milrinone, sodium bicarbonate, and tobramycin.

References

- Ahonkhai VI, Cyhan GM, Wilson SE, Brown KR: Imipenem-cilastatin in pediatric patients: an overview of safety and efficacy in studies conducted in the United States. *Pediatr Infect Dis J* 1989;8:740.
- Garges HP, Alexander KA: Newer antibiotics: imipenem/cilastatin and meropenem. *NeoReviews* 2003;4:e364-68.
- Nalin DR, Jacobsen CA: Imipenem/cilastatin therapy for serious infections in neonates and infants. *Scand J Infect Dis* 1987;Suppl.2:46.
- Product Information: Primaxin® IV, imipenem and cilastatin IV injection. Merck & Co., 2009.
- Reed MD, Kliegman RM, Yamashita TS, et al: Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. *Antimicrob Agents Chemother* 1990;34:1172.
- Stuart RL, Turnidge J, Grayson ML: Safety of imipenem in neonates. *Pediatr Infect Dis J* 1995;14:804.

1. Product Information: PRIMAXIN(R)IV IV injection, imipenem and cilastatin IV injection. Merck and Co Inc, Whitehouse Station, NJ, Aug, 2009.

1.93 Indomethacin

Title Indomethacin

Dose

Closure of Ductus Arteriosus:
Usually three doses per course, maximum two courses. Give at 12- to 24-hour intervals with close monitoring of urine output. If anuria or severe oliguria occurs, subsequent doses should be delayed [1] .
Longer treatment courses may be used: 0.2 mg/kg every 24 hours for a total of 5 to 7 days.

PDA Closure Dose (mg/kg)

Age at 1st dose	1st	2nd	3rd

	0.2	0.1	0.1
2 to 7 days	0.2	0.2	0.2
> 7 days	0.2	0.25	0.25

Prevention of Intraventricular Hemorrhage (IVH): 0.1 mg/kg every 24 hours for 3 doses, beginning at 6 to 12 hours of age.

Administration

IV infusion by syringe pump over at least 30 minutes to minimize adverse effects on cerebral, gastrointestinal, and renal blood flow velocities.

Uses

Closure of ductus arteriosus [1] . Prevention of intraventricular hemorrhage.

Contraindications/Precautions

Contraindicated in active bleeding, significant thrombocytopenia or coagulation defects, necrotizing enterocolitis, untreated proven or suspected infection, and/or significantly impaired renal function [1] . If oliguria occurs, observe for hyponatremia and hypokalemia, and consider prolonging the dosing interval of renally excreted drugs (eg, gentamicin). Consider withholding feedings. Concomitant therapy with furosemide may lead to increased hyponatremia and a significant rise in serum creatinine [2] [3] .

Pharmacology

Inhibitor of prostaglandin synthesis. Decreases cerebral, renal and gastrointestinal blood flow. Metabolized in the liver to inactive compounds and excreted in the urine and feces. Serum half-life is approximately 30 hours, with a range of 15 to 50 hours, partially dependent on postnatal age. In most studies, the response of the ductus and adverse effects of indomethacin are only weakly correlated with plasma concentration.

Adverse Effects

Hypoglycemia is common, usually preventable by increasing the glucose infusion rate by 2 mg/kg per minute. Causes platelet dysfunction. Rapid (less than 5-minute) infusions are associated with reductions in organ blood flow. Gastrointestinal perforations occur frequently if used concurrently with corticosteroids.

Monitoring

Monitor urine output, serum electrolytes, glucose, creatinine and BUN, and platelet counts. Assess murmur, pulse pressure. Assess for gastrointestinal bleeding by gastric and fecal occult blood testing. Observe for prolonged bleeding from puncture sites.

Special Considerations/Preparation

Supplied as a lyophilized powder in 1-mg single-dose vials [1] .
Indomethacin sodium trihydrate salt is not buffered, and is insoluble in solutions with pH less than 6; the manufacturer therefore recommends against continuous infusion in typical IV solutions. Reconstitute using 1 to 2 mL of preservative-free NS or sterile water for injection. Reconstituted indomethacin is stable in polypropylene syringes and glass vials for 12 days when stored at room temperature or refrigerated. Observe for precipitation.

Solution Compatibility

Sterile water for injection.
(No visual precipitation in 24 hours): $D_{2.5}W$, D_5W, and NS.

Solution Incompatibility

$D_{7.5}W$, $D_{10}W$, and Dex/AA Solutions.

Terminal Injection Site Compatibility

Furosemide, insulin, nitroprusside, potassium chloride, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Calcium gluconate, cimetidine, dobutamine, dopamine, gentamicin, and tobramycin.

References

- Fowlie PW, Davis PG: Prophylactic indomethacin for preterm infants: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*2003;88:F464-66.
- Itabashi K, Ohno T, Nishida H: Indomethacin responsiveness of patent ductus arteriosus and renal abnormalities in preterm infants treated with indomethacin. *J Pediatr* 2003;143:203-7.
- Clyman RI: Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies. *J Pediatr* 1996;128:601.
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3. Andriessen P, Struis NC, Niemarkt H et al: Furosemide in preterm infants treated with indomethacin for patent ductus arteriosus. Acta Paediatr May, 2009; 98(5): 797-803.

Title Indomethacin

Dose

Closure of Ductus Arteriosus:
Usually three doses per course, maximum two courses. Give at 12- to 24-hour intervals with close monitoring of urine output. If anuria or severe oliguria occurs, subsequent doses should be delayed [1] .
Longer treatment courses may be used: 0.2 mg/kg every 24 hours for a total of 5 to 7 days.

PDA Closure Dose (mg/kg)

Age at 1st dose	1st	2nd	3rd
	0.2	0.1	0.1
2 to 7 days	0.2	0.2	0.2
> 7 days	0.2	0.25	0.25

Prevention of Intraventricular Hemorrhage (IVH): 0.1 mg/kg every 24 hours for 3 doses, beginning at 6 to 12 hours of age.

Administration

IV infusion by syringe pump over at least 30 minutes to minimize adverse effects on cerebral, gastrointestinal, and renal blood flow velocities.

Uses

Closure of ductus arteriosus [1] . Prevention of intraventricular hemorrhage.

Contraindications/Precautions

Contraindicated in active bleeding, significant thrombocytopenia or coagulation defects, necrotizing enterocolitis, untreated proven or suspected infection, and/or significantly impaired renal function [1] . If oliguria occurs, observe for hyponatremia and hypokalemia, and consider prolonging the dosing interval of renally excreted drugs (eg, gentamicin). Consider withholding feedings. Concomitant therapy with furosemide may lead to increased hyponatremia and a significant rise in serum creatinine [2] [3] .

Pharmacology

Inhibitor of prostaglandin synthesis. Decreases cerebral, renal and gastrointestinal blood flow. Metabolized in the liver to inactive compounds and excreted in the urine and feces. Serum half-life is approximately 30 hours, with a range of 15 to 50 hours, partially dependent on postnatal age. In most studies, the response of the ductus and adverse effects of indomethacin are only weakly correlated with plasma concentration.

Adverse Effects

Hypoglycemia is common, usually preventable by increasing the glucose infusion rate by 2 mg/kg per minute. Causes platelet dysfunction. Rapid (less than 5-minute) infusions are associated with reductions in organ blood flow. Gastrointestinal perforations occur frequently if used concurrently with corticosteroids.

Monitoring

Monitor urine output, serum electrolytes, glucose, creatinine and BUN, and platelet counts. Assess murmur, pulse pressure. Assess for gastrointestinal bleeding by gastric and fecal occult blood testing. Observe for prolonged bleeding from puncture sites.

Special Considerations/Preparation

Supplied as a lyophilized powder in 1-mg single-dose vials [1] .
Indomethacin sodium trihydrate salt is not buffered, and is insoluble in solutions with pH less than 6; the manufacturer therefore recommends against continuous infusion in typical IV solutions. Reconstitute using 1 to 2 mL of preservative-free NS or sterile water for injection. Reconstituted indomethacin is stable in polypropylene syringes and glass vials for 12 days when stored at room temperature or refrigerated. Observe for precipitation.

Solution Compatibility

Sterile water for injection.
(No visual precipitation in 24 hours): $D_{2.5}W$, D_5W, and NS.

Solution Incompatibility

$D_{7.5}W$, $D_{10}W$, and Dex/AA Solutions.

Terminal Injection Site Compatibility

Furosemide, insulin, nitroprusside, potassium chloride, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Calcium gluconate, cimetidine, dobutamine, dopamine, gentamicin, and tobramycin.

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- Ment LR, Oh W, Ehrenkranz RA, et al: Low-dose indomethacin and prevention of intraventricular hemorrhage: A multicenter randomized trial. *Pediatrics* 1994;93:543.

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1.94 Insulin

Title Insulin

Dose

Hyperglycemia:
Continuous IV infusion: 0.01 to 0.1 unit/kg/hour.
Titrate using blood glucose concentration/reagent strips.
Intermittent dose: 0.1 to 0.2 unit/kg subQ every 6 to 12 hours.

Hyperkalemia:
Initial: Regular insulin 0.1 to 0.2 units/kg/hour in combination with 0.5 g/kg/hour of dextrose given as continuous IV infusion. Insulin and dextrose dosages are adjusted based on serum glucose and potassium concentrations.

Administration

Intravenous:
Only regular insulin for injection may be administered intravenously. For continuous infusion, dilute **regular insulin** in compatible solution to a concentration of 0.05 to 1 unit/mL.
To saturate plastic tubing binding sites, fill IV tubing with insulin solution and wait for at least 20 minutes before infusing (preconditioning). The use of higher insulin concentrations and longer wait times will shorten the time to steady-state. Other studies have examined preconditioning and/or priming volumes; running a certain volume of insulin infusion through the tubing prior to initiation. A recent study found that 20 mL of priming volume was sufficient to minimize adsorption losses for a 1 unit/mL insulin infusion. Results show that preflushing IV administration sets leads to greater and more predictable insulin delivery over time and that the combination of preconditioning and flushing offers the best combination to reduce insulin adsorption.

Uses

Treatment of VLBW hyperglycemic infants with persistent glucose intolerance.

Treatment of hyperkalemia in combination with dextrose.

Pharmacology

Degraded in liver and kidney. Enhances cellular uptake of glucose, conversion of glucose to glycogen, amino acid uptake by muscle tissue, synthesis of fat, and cellular uptake of potassium. Inhibits lipolysis and conversion of protein to glucose. Plasma half-life in adults is 9 minutes.

Adverse Effects

May rapidly induce hypoglycemia. Insulin resistance may develop, causing a larger dose requirement. Euglycemic hyperinsulinemia due to exogenous insulin administration may cause metabolic acidosis.
The most recent randomized controlled trial (Beardsall) and systematic review (Raney) concluded that routine use of insulin in VLBW infants to promote growth is not warranted.

Monitoring

Follow blood glucose concentration frequently (every 15 to 30 minutes) after starting insulin infusion and after changes in infusion rate. Monitor potassium concentrations closely when treating hyperkalemia.

Special Considerations/Preparation

Regular human insulin [rDNA origin] is available as a 100-unit/mL concentration in 10-mL vials. For subcutaneous administration, dilute with sterile water or NS to a concentration of 0.5 or 1 unit/mL. For IV administration, make a 10 units/mL dilution with sterile water, then further dilute in compatible solution to a concentration of 0.05 to 1 unit/mL. **Keep refrigerated.**

Solution Compatibility

D_5W, and $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amiodarone, ampicillin, aztreonam, caspofungin, cefazolin, cefoxitin, cimetidine, digoxin, dobutamine, esmolol, famotidine, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, imipenem, indomethacin, lidocaine, meropenem, midazolam, milrinone, morphine, nitroglycerin, pentobarbital, potassium chloride, propofol, ranitidine, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Aminophylline, dopamine, micafungin, nafcillin, phenobarbital, and phenytoin.

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Title Insulin

Dose

Hyperglycemia:
Continuous IV infusion: 0.01 to 0.1 unit/kg/hour.
Titrate using blood glucose concentration/reagent strips.
Intermittent dose: 0.1 to 0.2 unit/kg subQ every 6 to 12 hours.

Hyperkalemia:
Initial: Regular insulin 0.1 to 0.2 units/kg/hour in combination with 0.5 g/kg/hour of

dextrose given as continuous IV infusion. Insulin and dextrose dosages are adjusted based on serum glucose and potassium concentrations.

Administration

Intravenous:
Only regular insulin for injection may be administered intravenously. For continuous infusion, dilute **regular insulin** in compatible solution to a concentration of 0.05 to 1 unit/mL.
To saturate plastic tubing binding sites, fill IV tubing with insulin solution and wait for at least 20 minutes before infusing (preconditioning). The use of higher insulin concentrations and longer wait times will shorten the time to steady-state. Other studies have examined preconditioning and/or priming volumes; running a certain volume of insulin infusion through the tubing prior to initiation. A recent study found that 20 mL of priming volume was sufficient to minimize adsorption losses for a 1 unit/mL insulin infusion. Results show that preflushing IV administration sets leads to greater and more predictable insulin delivery over time and that the combination of preconditioning and flushing offers the best combination to reduce insulin adsorption.

Uses

Treatment of VLBW hyperglycemic infants with persistent glucose intolerance.

Treatment of hyperkalemia in combination with dextrose.

Pharmacology

Degraded in liver and kidney. Enhances cellular uptake of glucose, conversion of glucose to glycogen, amino acid uptake by muscle tissue, synthesis of fat, and cellular uptake of potassium. Inhibits lipolysis and conversion of protein to glucose. Plasma half-life in adults is 9 minutes.

Adverse Effects

May rapidly induce hypoglycemia. Insulin resistance may develop, causing a larger dose requirement. Euglycemic hyperinsulinemia due to exogenous insulin administration may cause metabolic acidosis.
The most recent randomized controlled trial (Beardsall) and systematic review (Raney) concluded that routine use of insulin in VLBW infants to promote growth is not warranted.

Monitoring

Follow blood glucose concentration frequently (every 15 to 30 minutes) after starting insulin infusion and after changes in infusion rate. Monitor potassium concentrations closely when treating hyperkalemia.

Special Considerations/Preparation

Regular human insulin [rDNA origin] is available as a 100-unit/mL concentration in 10-mL vials. For subcutaneous administration, dilute with sterile water or NS to a concentration of 0.5 or 1 unit/mL. For IV administration, make a 10 units/mL dilution with sterile water, then further dilute in compatible solution to a concentration of 0.05 to 1 unit/mL. **Keep refrigerated.**

Solution Compatibility

D_5W, and $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Amiodarone, ampicillin, aztreonam, caspofungin, cefazolin, cefoxitin, cimetidine, digoxin, dobutamine, esmolol, famotidine, gentamicin, heparin, hydrocortisone succinate, ibuprofen lysine, imipenem, indomethacin, lidocaine, meropenem, midazolam, milrinone, morphine, nitroglycerin, pentobarbital, potassium chloride, propofol, ranitidine, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, tobramycin, and vancomycin.

Terminal Injection Site Incompatibility

Aminophylline, dopamine, micafungin, nafcillin, phenobarbital, and phenytoin.

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1.95 Intravenous Immune Globulin (Human)

Title Intravenous Immune Globulin (Human)

Dose

Usual Dosage: 500 to 750 mg/kg per dose over 2 to 6 hours.

For neonatal alloimmune thrombocytopenia, doses have ranged from 400 mg/kg to 1 g/kg.

Most studies have used a single dose, although additional doses have been given at 24 hour intervals.

See "Special Considerations/Preparation" for product-specific information.

Administration Rate of administration varies by product; refer to the IVIG Product-Specific Administration table below for specific information.

IVIG Product-Specific Administration

sol'n = solution

Brand	Infusion Rate	Infusion Rate in Re Disease/Thromboti Complications
Bivigam(R) 10% (Biotest)	Initial, 0.5 mg/kg/min (0.005 mL/kg/min) for the first 10 minutes; increase by 0.8 mg/kg/min every 20 minutes if tolerated to a maximum of 6 mg/kg/min	Minimum rate practicable.
Carimune(R) NF	Use the 3% solution for	Maximum rate less

(CSL Behring AG)	the first infusion at initial rate of 0.5 mg/kg/min; increase to 1 mg/kg/min after 30 minutes; up gradually to a maximum of 3 mg/kg/min.	than 2 mg/kg/min.
Flebogamma(R) 5% and 10% DIF (Grifols)	Initial, 0.01 mL/kg/min; increase gradually during the first 30 minutes to a maximum of 0.1 mL/kg/min for 5% solution and 0.08 mL/kg/min for 10% solution.	Minimum rate practicable.
GAMMAGARD Liquid 10% (Baxter)	Initial, 0.5 mL/kg/hr; increase every 30 minutes to a rate of 5 mL/kg/hr.	Maximum rate less than 2 mL/kg/hr.
GAMMAGARD S/D (Baxter)	Initial, infuse 5% sol'n at rate of 0.5 mL/kg/hr; increase gradually to 4 mL/kg/hr if tolerated; subsequent infusion of 10% sol'n starts at 0.5 mL/kg/hr, increase to 8 mL/kg/hr as tolerated. Antecubital veins for 10% sol'n.	Maximum rate less than 4 mL/kg/hr of a 5% solution, or less than 2 mL/kg of a 10% solution.
GAMMAKED(TM) 10% (Grifols Therapeutics)	Initial, infuse 10% sol'n at rate of 0.01 mL/kg/min; increase gradually to 0.08 mL/kg/min if tolerated	Minimum rate practicable.
Gammaplex(R) 5% (Bio Products Lab)	Initial, 0.01 mL/kg/min for 15 minutes; increase every 15 minutes to 0.08 mL/kg/min.	Minimum rate practicable.
Gamunex(R) 10% (Talecris)	Initial, 0.01 mL/kg/min (1 mg/kg/min) for the first 30 minutes and gradually increase up to 0.08 mL/kg/min (8 mg/kg/min) if tolerated.	Minimum rate practicable.
Octagam 5% (Octapharma)	Initial, 0.01 mL/kg/min (0.5 mg/kg/min) for first 30 minutes; if tolerated, increase to 0.02 mL/kg/min (1 mg/kg/min) for next 30 minutes; increase to (0.04 mL/kg/min (2 mg/kg/min)	Minimum rate practicable, not to exceed 3.33 mg/kg/minute

	for the next 30 minutes if tolerated then can maintain rate up to 0.07 mL/kg/min (3.33 mg/kg/min).	
Privigen(R) 10% (CSL Behring AG)	Initial, 0.005 mL/kg/min and increase gradually to 0.04 mL/kg/min (maximum 0.08 mL/kg/min).	Minimum rate practicable.

Uses

Adjuvant treatment of fulminant neonatal sepsis, hemolytic jaundice, and neonatal alloimmune thrombocytopenia.

Contraindications/Precautions

Contraindicated in patients with selective IgA deficiency [1] . Serious immediate anaphylactic and hypersensitivity reactions have been reported rarely. Hemolysis and thrombotic events have also been reported in association with IVIG [2] [1] . All donor units are nonreactive to HBsAg and HIV. The manufacturing process of these products now includes a solvent/detergent treatment to inactivate hepatitis C and other membrane-enveloped viruses [1] .

Black Box Warning According to the manufacturer's black box warning, immune globulin intravenous (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Use caution in patients predisposed to acute renal failure and administer at the minimum concentration available and the minimum rate of infusion practicable in such patients. Higher rates of renal failure were associated with IGIV products containing sucrose. Gammaked™ does not contain sucrose.

Pharmacology

IVIG is a plasma-derived, concentrated form of IgG antibodies present in the donor population. Significant lot-to-lot variation of specific antibodies may occur with all products. No significant differences in clinical outcomes using the different products have been seen. All preparations are reported to contain more than 92% IgG monomers and a normal distribution of IgG subclasses. Total IgG titers in treated, septic neonates remain elevated for approximately 10 days.

Adverse Effects

Rare cases of hypoglycemia, transient tachycardia, and hypotension that resolved after stopping the infusion have been reported. The risk of necrotizing enterocolitis may be increased in term and late preterm infants treated for isoimmune hemolytic jaundice. Animal studies have demonstrated reticuloendothelial system blockade when higher doses (greater than 1 g/kg) have been used. All donor units are nonreactive to HBsAg and HIV. The manufacturing process of these products now includes a

solvent/detergent treatment to inactivate hepatitis C and other membrane-enveloped viruses.

Monitoring

Frequent monitoring of heart rate and blood pressure. Check IV site for signs of phlebitis.

Special Considerations/Preparation

Reconstitute lyophilized products with supplied diluent. DO NOT SHAKE vials; swirl gently to mix. All products are preservative free. DO NOT FREEZE; products that have been frozen should not be used. Shelf life varies, but is at least 2 years, when stored properly. Do not mix IVIG products from different manufacturers.

IVIG Preparations

Brand	Form	Sugar	Preparation/Storage/St
Bivigam Liquid 10% (Biotest)	10% read-for-use solution	None (glycine stabilized)	Store refrigerated. Should be at room temperature for adm been entered and discard any unused portion. Not recom products, IV solutions, or medications
Carimune NF (CSL Behring AG)	3, 6, and 12 g lyophilized vials	1.67 g sucrose/g IVIG	Store at room temperature. Use immediately after reconstit air flow hood. Solution is stable for 24 hours with aseptic Compatible with NS and D5W (PI Ca
Flebogamma 5% and 10% DIF (Grifols)	5% and 10% ready-for-use solution	50 mg/mL D-sorbitol	Store at room temperature or refrigerated. Use immediately unused portion. Not recommended to be mixed with ar Flebogamma®, 2010; PI Fleboga
Gammagard Liquid 10% (Baxter)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. Should be at r Compatible with D5W (not compatible with NS)
Gammagard S/D (Baxter)	2.5, 5, and 10 g lyophilized vials	2% glucose	Store at room temperature. Use immediately (no more tha outside of sterile laminar air flow hood). Stable for 24 hours v not mix with other IV solutions or medications
Gammaked 10% (Grifols)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. Use immediately unused portion. Do not mix with other IV solutions or

Gammaplex 5% (Bio Products Lab)	5% ready-for-use solution	50 mg/mL D-sorbitol	Room temperature or refrigerated. Use immediately once via Infuse within 2 hours if vials are pooled for large doses. Do no Gammaplex®, 2013
Gamunex 10% (Talecris)	10% ready-for-use solution	None (glycine stabilized)	Room temperature or refrigerated. Use immediately once via Vials pooled under aseptic conditions must be used within 8 h Compatible with D5W, but not with NS
Octagam 5% (Baxter)	5% ready-for-use solution	100 mg/mL maltose	Store at room temperature or refrigerated. Use immediately portion. Infuse within 8 hours if vials are pooled for large dos not mix with other IV fluids or medicati
Privigen 10% (CSL Behring AG)	10% ready-for-use solution	None (L-proline stabilized)	Store at room temperature. Use immediately once vial ha portion. Contents of vials pooled under aseptic conditions components are latex free. Compatible with

Solution Compatibility

D_5W, $D_{15}W$, and Dex/AA.

Terminal Injection Site Compatibility

Fluconazole.

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- Christensen RD, Brown MS, Hall DC, et al: Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991;118:606.
- Figueras-Aloy J, Rodriguez-Miguelez JM, Iriondo-Sanz M, et al. Intravenous immunoglobulin and necrotizing enterocolitis in newborns with hemolytic disease. *Pediatrics* 2010;125:136-141.
- Gottstein R, Cooke RWI: Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F6-F10.

- Tanyer G, Suklar Z, Dallar Y, et al: Multiple dose IVIG treatment of neonatal immune hemolytic jaundice. *J Trop Pediatr* 2001:47:50-53.

1. Product Information: GAMMAGARD S/D(R) IV injection, immune globulin human IV injection. Baxter Healthcare Corporation, Westlake Village, CA, Dec, 2009.
2. Gadient P: Juvenile myasthenia gravis: three case reports and a literature review. J Child Neurol May, 2009; 24(5): 584-590.

Title Intravenous Immune Globulin (Human)

Dose

Usual Dosage: 500 to 750 mg/kg per dose over 2 to 6 hours.

For neonatal alloimmune thrombocytopenia, doses have ranged from 400 mg/kg to 1 g/kg.

Most studies have used a single dose, although additional doses have been given at 24 hour intervals.

See "Special Considerations/Preparation" for product-specific information.

Administration Rate of administration varies by product; refer to the IVIG Product-Specific Administration table below for specific information.

IVIG Product-Specific Administration

sol'n = solution

Brand	Infusion Rate	Infusion Rate in Re Disease/Thromboti Complications
Bivigam(R) 10% (Biotest)	Initial, 0.5 mg/kg/min (0.005 mL/kg/min) for the first 10 minutes; increase by 0.8 mg/kg/min every 20 minutes if tolerated to a maximum of 6 mg/kg/min	Minimum rate practicable.
Carimune(R) NF (CSL Behring AG)	Use the 3% solution for the first infusion at initial rate of 0.5 mg/kg/min; increase to 1 mg/kg/min after 30 minutes; up gradually to a maximum of 3 mg/kg/min.	Maximum rate less than 2 mg/kg/min.
Flebogamma(R) 5% and 10% DIF (Grifols)	Initial, 0.01 mL/kg/min; increase gradually during the first 30 minutes to a maximum of 0.1 mL/kg/min for	Minimum rate practicable.

	5% solution and 0.08 mL/kg/min for 10% solution.	
GAMMAGARD Liquid 10% (Baxter)	Initial, 0.5 mL/kg/hr; increase every 30 minutes to a rate of 5 mL/kg/hr.	Maximum rate less than 2 mL/kg/hr.
GAMMAGARD S/D (Baxter)	Initial, infuse 5% sol'n at rate of 0.5 mL/kg/hr; increase gradually to 4 mL/kg/hr if tolerated; subsequent infusion of 10% sol'n starts at 0.5 mL/kg/hr, increase to 8 mL/kg/hr as tolerated. Antecubital veins for 10% sol'n.	Maximum rate less than 4 mL/kg/hr of a 5% solution, or less than 2 mL/kg of a 10% solution.
GAMMAKED(TM) 10% (Grifols Therapeutics)	Initial, infuse 10% sol'n at rate of 0.01 mL/kg/min; increase gradually to 0.08 mL/kg/min if tolerated	Minimum rate practicable.
Gammaplex(R) 5% (Bio Products Lab)	Initial, 0.01 mL/kg/min for 15 minutes; increase every 15 minutes to 0.08 mL/kg/min.	Minimum rate practicable.
Gamunex(R) 10% (Talecris)	Initial, 0.01 mL/kg/min (1 mg/kg/min) for the first 30 minutes and gradually increase up to 0.08 mL/kg/min (8 mg/kg/min) if tolerated.	Minimum rate practicable.
Octagam 5% (Octapharma)	Initial, 0.01 mL/kg/min (0.5 mg/kg/min) for first 30 minutes; if tolerated, increase to 0.02 mL/kg/min (1 mg/kg/min) for next 30 minutes; increase to (0.04 mL/kg/min (2 mg/kg/min) for the next 30 minutes if tolerated then can maintain rate up to 0.07 mL/kg/min (3.33 mg/kg/min).	Minimum rate practicable, not to exceed 3.33 mg/kg/minute
Privigen(R) 10% (CSL Behring AG)	Initial, 0.005 mL/kg/min and increase gradually to 0.04 mL/kg/min (maximum 0.08 mL/kg/min).	Minimum rate practicable.

Uses

Adjuvant treatment of fulminant neonatal sepsis, hemolytic jaundice, and neonatal alloimmune thrombocytopenia.

Contraindications/Precautions

Contraindicated in patients with selective IgA deficiency [1] . Serious immediate anaphylactic and hypersensitivity reactions have been reported rarely. Hemolysis and thrombotic events have also been reported in association with IVIG [2] [1] . All donor units are nonreactive to HBsAg and HIV. The manufacturing process of these products now includes a solvent/detergent treatment to inactivate hepatitis C and other membrane-enveloped viruses [1] .

Black Box Warning According to the manufacturer's black box warning, immune globulin intravenous (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Use caution in patients predisposed to acute renal failure and administer at the minimum concentration available and the minimum rate of infusion practicable in such patients. Higher rates of renal failure were associated with IGIV products containing sucrose. Gammaked™ does not contain sucrose.

Pharmacology

IVIG is a plasma-derived, concentrated form of IgG antibodies present in the donor population. Significant lot-to-lot variation of specific antibodies may occur with all products. No significant differences in clinical outcomes using the different products have been seen. All preparations are reported to contain more than 92% IgG monomers and a normal distribution of IgG subclasses. Total IgG titers in treated, septic neonates remain elevated for approximately 10 days.

Adverse Effects

Rare cases of hypoglycemia, transient tachycardia, and hypotension that resolved after stopping the infusion have been reported. The risk of necrotizing enterocolitis may be increased in term and late preterm infants treated for isoimmune hemolytic jaundice. Animal studies have demonstrated reticuloendothelial system blockade when higher doses (greater than 1 g/kg) have been used. All donor units are nonreactive to HBsAg and HIV. The manufacturing process of these products now includes a solvent/detergent treatment to inactivate hepatitis C and other membrane-enveloped viruses.

Monitoring

Frequent monitoring of heart rate and blood pressure. Check IV site for signs of phlebitis.

Special Considerations/Preparation

***Reconstitute lyophilized products with supplied diluent. DO NOT SHAKE vials; swirl gently to mix. All products are preservative free. DO NOT FREEZE; products that have been frozen should not be used. Shelf life varies, but is at least**

2 years, when stored properly. Do not mix IVIG products from different manufacturers.*

IVIG Preparations

Brand	Form	Sugar	Preparation/Storage/St
Bivigam Liquid 10% (Biotest)	10% read-for-use solution	None (glycine stabilized)	Store refrigerated. Should be at room temperature for adm been entered and discard any unused portion. Not recom products, IV solutions, or medications
Carimune NF (CSL Behring AG)	3, 6, and 12 g lyophilized vials	1.67 g sucrose/g IVIG	Store at room temperature. Use immediately after reconstit air flow hood. Solution is stable for 24 hours with aseptic Compatible with NS and D5W (PI Ca
Flebogamma 5% and 10% DIF (Grifols)	5% and 10% ready-for-use solution	50 mg/mL D-sorbitol	Store at room temperature or refrigerated. Use immediately unused portion. Not recommended to be mixed with ar Flebogamma®, 2010; PI Fleboga
Gammagard Liquid 10% (Baxter)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. Should be at r Compatible with D5W (not compatible with NS)
Gammagard S/D (Baxter)	2.5, 5, and 10 g lyophilized vials	2% glucose	Store at room temperature. Use immediately (no more tha outside of sterile laminar air flow hood). Stable for 24 hours v not mix with other IV solutions or medications
Gammaked 10% (Grifols)	10% ready-for-use solution	None (glycine stabilized)	Store at room temperature or refrigerated. Use immediately unused portion. Do not mix with other IV solutions or
Gammaplex 5% (Bio Products Lab)	5% ready-for-use solution	50 mg/mL D-sorbitol	Room temperature or refrigerated. Use immediately once via Infuse within 2 hours if vials are pooled for large doses. Do no Gammaplex®, 2013
Gamunex 10% (Talecris)	10% ready-for-use solution	None (glycine stabilized)	Room temperature or refrigerated. Use immediately once via Vials pooled under aseptic conditions must be used within 8 h Compatible with D5W, but not with NS
Octagam 5% (Baxter)	5% ready-for-use solution	100 mg/mL maltose	Store at room temperature or refrigerated. Use immediately portion. Infuse within 8 hours if vials are pooled for large dos not mix with other IV fluids or medicati
Privigen 10%	10% ready-for-	None (L-	Store at room temperature. Use immediately once vial ha

(CSL Behring AG) use solution proline stabilized) portion. Contents of vials pooled under aseptic conditions components are latex free. Compatible with

Solution Compatibility

D_5W, $D_{15}W$, and Dex/AA.

Terminal Injection Site Compatibility

Fluconazole.

References

- Figueras-Aloy J, Rodriguez-Miguelez JM, Iriondo-Sanz M, et al: Intravenous immunoglobulin and necrotizing enterocolitis in newborns with hemolytic disease. *Pediatrics* 2010;125:139-144.
- Kreymann KG, de Heer G, Nierhaus A, Kluge S: Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock. *Crit Care Med* 2007;35:2677-2685.
- Sandberg K, Fasth A, Berger A, et al: Preterm infants with low immunoglobulin G levels have increased risk for neonatal sepsis but do not benefit from prophylactic immunoglobulin G. *J Pediatr* 2000;137:623-628.
- Jenson HB, Pollock BH: Meta-analyses of the effectiveness of intravenous immune globulin for prevention and treatment of neonatal sepsis. *Pediatrics* 1997;99(2):e2.
- Blanchette VS, Rand ML: Platelet disorders in newborn infants: diagnosis and management. *Semin Perinatol* 1997;21:53-62.
- Weisman LE, Stoll BJ, Kueser TJ: Intravenous immunoglobulin therapy for early-onset sepsis in premature neonates. *J Pediatr* 1992;121:434.
- Christensen RD, Brown MS, Hall DC, et al: Effect on neutrophil kinetics and serum opsonic capacity of intravenous administration of immune globulin to neonates with clinical signs of early-onset sepsis. *J Pediatr* 1991;118:606.
- Figueras-Aloy J, Rodriguez-Miguelez JM, Iriondo-Sanz M, et al. Intravenous immunoglobulin and necrotizing enterocolitis in newborns with hemolytic disease. *Pediatrics* 2010;125:136-141.
- Gottstein R, Cooke RWI: Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F6-F10.
- Tanyer G, Suklar Z, Dallar Y, et al: Multiple dose IVIG treatment of neonatal immune hemolytic jaundice. *J Trop Pediatr* 2001:47:50-53.

1. Product Information: GAMMAGARD S/D(R) IV injection, immune globulin human IV injection. Baxter Healthcare Corporation, Westlake Village, CA, Dec, 2009.
2. Gadient P: Juvenile myasthenia gravis: three case reports and a literature review. J Child Neurol May, 2009; 24(5): 584-590.

1.96 Ipratropium

Title Ipratropium

Dose

Administer every 6 to 8 hours as a metered dose inhaler (MDI) or nebulized solution. Doses studied in intubated neonates range from 2 puffs (34 mcg) to 4 puffs (68 mcg)

via MDI with spacer device placed in the inspiratory limb of the ventilator circuit, and 75 to 175 mcg via jet nebulizer. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.

Optimal dose in neonates has yet to be determined due to differences in aerosol drug delivery techniques, although the therapeutic margin appears to be wide.

Uses

Anticholinergic bronchodilator for primary treatment of chronic obstructive pulmonary diseases and adjunctive treatment of acute bronchospasm. Ipratropium is not useful in the treatment of bronchiolitis.

Pharmacology

Ipratropium bromide is a quaternary ammonium derivative of atropine. It produces primarily large airway bronchodilation by antagonizing the action of acetylcholine at its receptor site. It is relatively bronchospecific when administered by inhalation because of limited absorption through lung tissue. Peak effect occurs 1 to 2 hours after administration. Duration of effect is 4 to 6 hours in children. The combination of ipratropium with a beta-agonist produces more bronchodilation than either drug individually.

Adverse Effects

Temporary blurring of vision, precipitation of narrow-angle glaucoma, or eye pain may occur if solution comes into direct contact with the eyes.

Monitoring

Assess degree of bronchospasm.

Special Considerations/Preparation

Metered-dose inhaler: Atrovent® HFA is available in a pressurized metered-dose aerosol unit (contains no chlorofluorocarbons (CFC)) providing 200 actuations per each 12.9-g canister. Each actuation delivers 21 mcg of ipratropium from the valve and 17 mcg from the mouthpiece.

Solution for inhalation: Supplied in 2.5-mL vials, containing ipratropium bromide 0.02% (200 mcg/mL) in a sterile, preservative-free, isotonic saline solution that is pH-adjusted to 3.4 with hydrochloric acid. It may be mixed with albuterol or metaproterenol if used within 1 hour. Store at room temperature in foil pouch provided. Protect from light.

References

- Fayon M, Tayara N, Germain C et al: Efficacy and tolerance of high-dose ipratropium bromide vs. terbutaline in intubated premature human neonates. *Neonatology* 2007;91:167-173.
- Lee H, Arnon S, Silverman M: Bronchodilator aerosol administered by metered dose inhaler and spacer in subacute neonatal respiratory distress syndrome. *Arch Dis Child* 1994;70:F218.
- Consensus Conference in Aerosol Delivery: Aerosol Consensus Statement. *Respir Care* 1991;36:916.
- Brundage KL, Mohsini Kj Froese AB, Fisher JT: Bronchodilator response to ipratropium bromide in infants with bronchopulmonary dysplasia. *Am Rev Respir Dis* 1990;142:1137.
- Gross NJ: Ipratropium bromide. *N Engl J Med* 1988;319:486.
- Product Information, Dey, 2006.
- Product Information, Boehringer-Ingelheim, 2008.

Title Ipratropium

Dose

Administer every 6 to 8 hours as a metered dose inhaler (MDI) or nebulized solution. Doses studied in intubated neonates range from 2 puffs (34 mcg) to 4 puffs (68 mcg) via MDI with spacer device placed in the inspiratory limb of the ventilator circuit, and 75 to 175 mcg via jet nebulizer. Simulated neonatal lung models suggest greater delivery when using a spacer with the MDI. Use chlorofluorocarbon free preparations when administering to neonates.

Optimal dose in neonates has yet to be determined due to differences in aerosol drug delivery techniques, although the therapeutic margin appears to be wide.

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References

- Fayon M, Tayara N, Germain C et al: Efficacy and tolerance of high-dose ipratropium bromide vs. terbutaline in intubated premature human neonates. *Neonatology* 2007;91:167-173.
- Lee H, Arnon S, Silverman M: Bronchodilator aerosol administered by metered dose inhaler and spacer in subacute neonatal respiratory distress syndrome. *Arch Dis Child* 1994;70:F218.
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- Gross NJ: Ipratropium bromide. *N Engl J Med* 1988;319:486.
- Product Information, Dey, 2006.
- Product Information, Boehringer-Ingelheim, 2008.

1.97 Iron Dextran

Title Iron Dextran

Dose

0.4 to 1 mg/kg (400 to 1000 mcg/kg) per day IV continuous infusion in Dex/AA solutions containing at least 2% amino acids.

Uses

Iron supplementation in patients unable to tolerate oral iron, especially those also being treated with erythropoietin.

Black Box Warning Anaphylactic-type reactions, including fatalities, have followed parenteral administration. Resuscitation equipment and trained personnel must be readily available during iron dextran administration. **Must perform test dose.** Observe for signs/symptoms of anaphylactic-type reactions. Fatal reactions have occurred following the test dose and have

occurred in situations where the test dose was tolerated. Patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions.

Pharmacology

Iron dextran for intravenous use is a complex of ferric hydroxide and low molecular mass dextran. The dextran serves as a protective lipophilic colloid. Radiolabeled iron dextran injected into adult subjects localized to the liver and spleen before being incorporated into RBC hemoglobin. Complete clearance occurred by 3 days. Approximately 40% of the labeled iron was bound to transferrin within 11 hours. The addition of iron dextran to Dex/AA solutions inhibits the spontaneous generation of peroxides.

Adverse Effects

No adverse effects have been observed in patients who have received low doses infused continuously. Large (50-mg) intramuscular doses administered to infants were associated with increased risk of infection. Retrospective reviews of adult patients who received larger doses injected over a few minutes report a 0.7% risk of immediate serious allergic reactions, and a 5% risk of delayed such as myalgia, arthralgia, phlebitis, and lymphadenopathy.

Monitoring

Periodic CBC and reticulocyte count. Observe Dex/AA solution for rust-colored precipitates.

Special Considerations/Preparation

Available as a 50 mg/mL concentration in 2-mL single-dose vials. Store at room temperature.

References

- Mayhew SL, Quick MW: Compatibility of iron dextran with neonatal parenteral nutrition solutions. *Am J Health-Syst Pharm* 1997;54:570-1.
- Lavoie J-C, Chessex P: Bound iron admixture prevents the spontaneous generation of peroxides in total parenteral nutrition solutions. *J Pediatr Gastroenterol Nutr* 1997;25:307-11.
- Friel JK, Andrews WL, Hall MS, et al: Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition. *JPEN*1995;19:114-18.
- Burns DL, Mascioli EA, Bistrian BR: Parenteral iron dextran therapy: a review. *Nutrition* 1995;11:163-68.
- Kanakakorn K, Cavill I, Jacobs A: The metabolism of intravenously administered iron-dextran. *Br J Haematol* 1973;25:637-43.
- Product Information, Watson, 2009.

Title Iron Dextran

Dose

0.4 to 1 mg/kg (400 to 1000 mcg/kg) per day IV continuous infusion in Dex/AA solutions containing at least 2% amino acids.

Uses

Iron supplementation in patients unable to tolerate oral iron, especially those also being treated with erythropoietin.

Black Box Warning Anaphylactic-type reactions, including fatalities, have followed parenteral administration. Resuscitation equipment and trained personnel must be readily available during iron dextran administration. **Must perform test dose.** Observe for signs/symptoms of anaphylactic-type reactions. Fatal reactions have occurred following the test dose and have occurred in situations where the test dose was tolerated. Patients with a history of drug allergy or multiple drug allergies may be at increased risk of anaphylactic-type reactions.

Pharmacology

Iron dextran for intravenous use is a complex of ferric hydroxide and low molecular mass dextran. The dextran serves as a protective lipophilic colloid. Radiolabeled iron dextran injected into adult subjects localized to the liver and spleen before being incorporated into RBC hemoglobin. Complete clearance occurred by 3 days. Approximately 40% of the labeled iron was bound to transferrin within 11 hours. The addition of iron dextran to Dex/AA solutions inhibits the spontaneous generation of peroxides.

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Monitoring

Periodic CBC and reticulocyte count. Observe Dex/AA solution for rust-colored precipitates.

Special Considerations/Preparation

Available as a 50 mg/mL concentration in 2-mL single-dose vials. Store at room temperature.

References

- Mayhew SL, Quick MW: Compatibility of iron dextran with neonatal parenteral nutrition solutions. *Am J Health-Syst Pharm* 1997;54:570-1.

- Lavoie J-C, Chessex P: Bound iron admixture prevents the spontaneous generation of peroxides in total parenteral nutrition solutions. *J Pediatr Gastroenterol Nutr* 1997;25:307-11.
- Friel JK, Andrews WL, Hall MS, et al: Intravenous iron administration to very-low-birth-weight newborns receiving total and partial parenteral nutrition. *JPEN*1995;19:114-18.
- Burns DL, Mascioli EA, Bistrian BR: Parenteral iron dextran therapy: a review. *Nutrition* 1995;11:163-68.
- Kanakakorn K, Cavill I, Jacobs A: The metabolism of intravenously administered iron-dextran. *Br J Haematol* 1973;25:637-43.
- Product Information, Watson, 2009.

1.98 Isoproterenol

Title Isoproterenol

Dose

0.05 to 0.5 mcg/kg per minute continuous IV infusion.
Maximum dose 2 mcg/kg per minute.
Dosage often titrated according to heart rate.
Acidosis should be corrected before infusion.

Solution Preparation Calculations

To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)

Example (for Isoproterenol): Mix 50 mL of 10-mcg/mL solution using isoproterenol concentration of 0.2 mg/mL.
10 mcg/mL = 0.01 mg/mL
0.01 mg/mL x 50 mL = 0.5 mg isoproterenol
***0.5 mg ÷ 0.2 mg/mL = 2.5 mL of isoproterenol**

Add 2.5 mL of isoproterenol (0.2 mg/mL) to 47.5 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 10 mcg/mL.

Maximum concentration 20 mcg/mL.

Isoproterenol Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
5	0.05	0.6
	0.1	1.2

	0.5	6
	1	12
10	0.05	0.3
	0.1	0.6
	0.5	3
	1	6
15	0.05	0.2
	0.1	0.4
	0.5	2
	1	4
20	0.05	0.15
	0.1	0.3
	0.5	1.5
	1	3

Uses

Increases cardiac output in patients with cardiovascular shock. Pulmonary vasodilator (older infants).

Pharmacology

β-receptor stimulant, sympathomimetic. Increases cardiac output by 1) increasing rate (major) and 2) increasing strength of contractions (minor). Insulin secretion is stimulated. Afterload reduction via β_2 effects on arterioles.

Adverse Effects

Cardiac arrhythmias. Tachycardia severe enough to cause CHF. Decreases venous return to heart. Systemic vasodilation. May cause hypoxemia by increasing intrapulmonary shunt. Hypoglycemia.

Monitoring

Continuous vital signs, intra-arterial blood pressure, CVP monitoring preferable. Periodic blood glucose reagent strips.

Special Considerations/Preparation

Supplied as 0.2-mg/mL (1:5000) solution in 1-mL and 5-mL ampuls.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Amiodarone, caffeine citrate, calcium chloride, calcium gluceptate, cimetidine, dobutamine, famotidine, heparin, hydrocortisone succinate, milrinone, netilmicin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide and sodium bicarbonate.

References

- Cabal LA, Devaskar U, Siassi B, et al: Cardiogenic shock associated with perinatal asphyxia in preterm infants. *J Pediatr* 1980;96:705.
- Daoud FS, Reeves JT, Kelly DB: Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension. *Am J Cardiol* 1978;42:817.
- Product Information, Hospira, 2006.

Title Isoproterenol

Dose

0.05 to 0.5 mcg/kg per minute continuous IV infusion.
Maximum dose 2 mcg/kg per minute.
Dosage often titrated according to heart rate.
Acidosis should be corrected before infusion.

Solution Preparation Calculations

To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).

To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)

Example (for Isoproterenol): Mix 50 mL of 10-mcg/mL solution using isoproterenol concentration of 0.2 mg/mL.
10 mcg/mL = 0.01 mg/mL
0.01 mg/mL x 50 mL = 0.5 mg isoproterenol
***0.5 mg ÷ 0.2 mg/mL = 2.5 mL of isoproterenol**

Add 2.5 mL of isoproterenol (0.2 mg/mL) to 47.5 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 10 mcg/mL.

Maximum concentration 20 mcg/mL.

Isoproterenol Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
5	0.05	0.6
	0.1	1.2
	0.5	6
	1	12
10	0.05	0.3
	0.1	0.6
	0.5	3
	1	6
15	0.05	0.2
	0.1	0.4
	0.5	2
	1	4
20	0.05	0.15
	0.1	0.3
	0.5	1.5
	1	3

Uses

Increases cardiac output in patients with cardiovascular shock. Pulmonary vasodilator (older infants).

Pharmacology

β-receptor stimulant, sympathomimetic. Increases cardiac output by 1) increasing rate (major) and 2) increasing strength of contractions (minor). Insulin secretion is stimulated. Afterload reduction via β_2 effects on arterioles.

Adverse Effects

Cardiac arrhythmias. Tachycardia severe enough to cause CHF. Decreases venous return to heart. Systemic vasodilation. May cause hypoxemia by increasing intrapulmonary shunt. Hypoglycemia.

Monitoring

Continuous vital signs, intra-arterial blood pressure, CVP monitoring preferable. Periodic blood glucose reagent strips.

Special Considerations/Preparation

Supplied as 0.2-mg/mL (1:5000) solution in 1-mL and 5-mL ampuls.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Amiodarone, caffeine citrate, calcium chloride, calcium gluceptate, cimetidine, dobutamine, famotidine, heparin, hydrocortisone succinate, milrinone, netilmicin, nitroprusside, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide and sodium bicarbonate.

References

- Cabal LA, Devaskar U, Siassi B, et al: Cardiogenic shock associated with perinatal asphyxia in preterm infants. *J Pediatr* 1980;96:705.
- Daoud FS, Reeves JT, Kelly DB: Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension. *Am J Cardiol* 1978;42:817.
- Product Information, Hospira, 2006.

1.99 LORazepam

Title LORazepam

Dose

0.05 to 0.1 mg/kg per dose IV slow push. Repeat doses based on clinical response.

Uses

Anticonvulsant, acute management of patients with seizures refractory to conventional therapy.

Pharmacology

Dose-dependent CNS depression. Onset of action within 5 minutes; peak serum concentration within 45 minutes. Duration of action is 3 to 24 hours. Mean half-life in term neonates is 40 hours. Metabolized to an inactive glucuronide, which is excreted by the kidneys. Highly lipid-soluble.

Adverse Effects

Respiratory depression. Rhythmic myoclonic jerking has occurred in premature neonates receiving lorazepam for sedation.

Monitoring

Monitor respiratory status closely. Observe IV site for signs of phlebitis or extravasation.

Special Considerations/Preparation

Limited data are available for neonates. Available in 2-mg/mL and 4-mg/mL concentrations (1 mL preservative free vial) and 2 mg/mL multidose vial (10 mL). Some available products contain 2% (20 mg/mL) benzyl alcohol and 18% polyethylene glycol 400 in propylene glycol. A dilution of 0.4 mg/mL may be prepared by adding 1 mL of 4 mg/mL concentration in 9 mL of preservative-free sterile water for injection. This will make it easier to measure the dose and decrease the benzyl alcohol content to 0.5 mg/kg per dose.
Solutions should not be used if they are discolored or contain a precipitate.

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, bumetanide, cefepime, cefotaxime, cimetidine, dexamethasone, dobutamine, dopamine, epinephrine, erythromycin lactobionate, famotidine, fentanyl, fluconazole, fosphenytoin, furosemide, gentamicin, heparin, hydrocortisone succinate, labetalol, levetiracetam, linezolid, methadone, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium bromide, piperacillin, piperacillin-tazobactam, potassium chloride, propofol, ranitidine, remifentanil, trimethoprim-sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, and imipenem/cilastatin.

References

- Sexson WR, Thigpen J, Stajich GV: Stereotypic movements after lorazepam administration in premature neonates: a series and review of the literature. *J Perinatol* 1995;15:146-49.
- McDermott CA, Kowalczyk AL, Schnitzler ER, et al: Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992;120:479.
- Deshmukh A, Wittert W, Schnitzler E, Mangurten HH: Lorazepam in the treatment of refractory neonatal seizures. *Am J Dis Child* 1986;140:1042.
- Product Information, Bedford, 2004.

Title LORazepam

Dose

0.05 to 0.1 mg/kg per dose IV slow push. Repeat doses based on clinical response.

Uses

Anticonvulsant, acute management of patients with seizures refractory to conventional therapy.

Pharmacology

Dose-dependent CNS depression. Onset of action within 5 minutes; peak serum concentration within 45 minutes. Duration of action is 3 to 24 hours. Mean half-life in term neonates is 40 hours. Metabolized to an inactive glucuronide, which is excreted by the kidneys. Highly lipid-soluble.

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Respiratory depression. Rhythmic myoclonic jerking has occurred in premature neonates receiving lorazepam for sedation.

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Monitor respiratory status closely. Observe IV site for signs of phlebitis or extravasation.

Special Considerations/Preparation

Limited data are available for neonates. Available in 2-mg/mL and 4-mg/mL concentrations (1 mL preservative free vial) and 2 mg/mL multidose vial (10 mL). Some available products contain 2% (20 mg/mL) benzyl alcohol and 18% polyethylene glycol 400 in propylene glycol. A dilution of 0.4 mg/mL may be prepared by adding 1 mL of 4 mg/mL concentration in 9 mL of preservative-free sterile water for injection. This will make it easier to measure the dose and decrease the benzyl alcohol content to 0.5 mg/kg per dose.
Solutions should not be used if they are discolored or contain a precipitate.

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, bumetanide, cefepime, cefotaxime, cimetidine, dexamethasone, dobutamine, dopamine, epinephrine, erythromycin lactobionate, famotidine, fentanyl, fluconazole, fosphenytoin, furosemide, gentamicin, heparin, hydrocortisone succinate, labetalol, levetiracetam, linezolid, methadone, metronidazole, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium bromide, piperacillin, piperacillin-tazobactam, potassium chloride, propofol, ranitidine, remifentanil, trimethoprim-sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Fat emulsion. Aztreonam, caffeine citrate, and imipenem/cilastatin.

References

- Sexson WR, Thigpen J, Stajich GV: Stereotypic movements after lorazepam administration in premature neonates: a series and review of the literature. *J Perinatol* 1995;15:146-49.
- McDermott CA, Kowalczyk AL, Schnitzler ER, et al: Pharmacokinetics of lorazepam in critically ill neonates with seizures. *J Pediatr* 1992;120:479.
- Deshmukh A, Wittert W, Schnitzler E, Mangurten HH: Lorazepam in the treatment of refractory neonatal seizures. *Am J Dis Child* 1986;140:1042.
- Product Information, Bedford, 2004.

1.100 LamiVUDine

Title LamiVUDine

Dose

HIV Infection; Prevention of Transmission or Treatment: 2 mg/kg orally every 12 hours [1] .

Dose Adjustments
Renal Impairment: Although there are no dosing recommendations available for neonates or pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered [2] .

Administration

Can be given without regard to meals [2] .

Uses

HIV-1 infection; Prevention of transmission or Treatment: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-NRTI backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). Lamivudine (or emtricitabine) plus zidovudine is the preferred dual-NRTI backbone option in neonates [1] .

Pediatric FDA Approved Indications
Epivir®
Treatment of HIV-1 infection in combination with other antiretroviral agents in children 3 months of age and older [2] .

Contraindications/Precautions

Dual-NRTI therapy with emtricitabine and lamivudine is NOT recommended in children due to similar resistance patterns and no additive benefit [4] [1] .

Black Box Warning

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (in adults). Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus and HIV-1 and have discontinued lamivudine. Epivir® (for treatment of HIV-1 infection) has a higher dose of lamivudine than Epivir-HBV® (for treatment of chronic hepatitis B virus infection). Patients should receive the lamivudine product appropriate to their diagnosis [2] [3] .

Pharmacology

Lamivudine (3TC) is a synthetic nucleoside analog that inhibits HIV and HBV replication by interfering with viral reverse transcriptase. It is intracellularly converted in several steps to the active compound, and then renally excreted. Poor CNS penetration with a percent CSF to serum drug concentration of approximately 12%. The oral solution is well-absorbed, with 66% bioavailability in children. Peak reached in 0.5 to 1.5 hours. Primarily eliminated as unchanged drug in the urine. The serum half-life in children is approximately 2.2 +/- 2 hours. Clearance reduced in renal impairment; dose reduction recommended. Viral resistance develops rapidly to monotherapy with lamivudine (3TC) [2] [5] .
In 36 infants up to 1 week of age administered lamivudine and zidovudine, lamivudine clearance was substantially reduced in 1-week-old neonates compared with children older than 3 months of age [2] .

Adverse Effects

Adverse effects reported in neonates were increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, gastroenteritis (with associated convulsions), and transient renal insufficiency associated with dehydration. Deaths (1 from gastroenteritis with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes) were reported in 3 neonates. [2] .

Monitoring

Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch
Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X

Chemistries	X		X	X		X
Electrolytes	X			X		X
Glucose	X			X		X
AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X
Lipid Panel	X				X	
Urinalysis	X				X	

KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count

* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days.
** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months).
# For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.
# # May be too early to detect immunological response in the CD4 count/percentage

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo

Monitor for signs/symptoms of pancreatitis (eg, persistent abdominal pain, fever, nausea, vomiting, or diarrhea) [2] .

Special Considerations/Preparation

Available as an oral solution in concentrations of 5 mg/mL (Epivir-HBV®) and 10 mg/mL (Epivir®). Oral tablets available in 100-mg (Epivir-HBV®), 150-mg (Epivir®), and 300-mg (Epivir®) strengths. **Store at room temperature.** [2] [3] .

References

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

- Product Information: EPIVIR(R) oral tablets, solution, lamivudine oral tablets, solution. ViiV Healthcare (per manufacturer), Research Triangle Park, NC, Sep, 2010.

- Product Information: EPIVIR-HBV(R) oral tablets, solution, lamivudine oral tablets, solution. GlaxoSmithKline, Research Triangle Park, NC, Oct1, 2007.

- Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Feb12, 2013. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

- Mueller BU, Lewis LL, Yuen GJ et al: Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. Antimicrob Agents Chemother Dec, 1998; 42(12): 3187-3192.

Title LamiVUDine

Dose

HIV Infection; Prevention of Transmission or Treatment: 2 mg/kg orally every 12 hours [1] .

Dose Adjustments
Renal Impairment: Although there are no dosing recommendations available for neonates or pediatric patients with renal impairment, a reduction in the dose and/or an increase in the dosing interval should be considered [2] .

Administration

Can be given without regard to meals [2] .

Uses

HIV-1 infection; Prevention of transmission or Treatment: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. The preferred antiretroviral regimen in neonates is a dual-NRTI backbone in combination with lopinavir/ritonavir (postmenstrual age of 42 weeks and postnatal age of 14 days). Lamivudine (or emtricitabine) plus zidovudine is the preferred dual-NRTI backbone option in neonates [1] .

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Lamivudine (3TC) is a synthetic nucleoside analog that inhibits HIV and HBV replication by interfering with viral reverse transcriptase. It is intracellularly converted in several steps to the active compound, and then renally excreted. Poor CNS penetration with a percent CSF to serum drug concentration of approximately 12%. The oral solution is well-absorbed, with 66% bioavailability in children. Peak reached in 0.5 to 1.5 hours. Primarily eliminated as unchanged drug in the urine. The serum half-life in children is approximately 2.2 +/- 2 hours. Clearance reduced in renal impairment; dose reduction recommended. Viral resistance develops rapidly to monotherapy with lamivudine (3TC) [2] [5] .
In 36 infants up to 1 week of age administered lamivudine and zidovudine, lamivudine clearance was substantially reduced in 1-week-old neonates compared with children older than 3 months of age [2] .

Adverse Effects

Adverse effects reported in neonates were increased liver function tests, anemia, diarrhea, electrolyte disturbances, hypoglycemia, jaundice and hepatomegaly, rash, respiratory infections, sepsis, gastroenteritis (with associated convulsions), and transient renal insufficiency associated with dehydration. Deaths (1 from gastroenteritis

with acidosis and convulsions, 1 from traumatic injury, and 1 from unknown causes) were reported in 3 neonates. [2] .

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Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch
Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X
Chemistries	X		X	X		X
Electrolytes	X			X		X
Glucose	X			X		X
AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X
Lipid Panel	X				X	
Urinalysis	X				X	

KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count
* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days. ** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months). # For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter. # # May be too early to detect immunological response in the CD4 count/percentage
Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo

Monitor for signs/symptoms of pancreatitis (eg, persistent abdominal pain, fever, nausea, vomiting, or diarrhea) [2] .

Special Considerations/Preparation

Available as an oral solution in concentrations of 5 mg/mL (Epivir-HBV®) and 10 mg/mL (Epivir®). Oral tablets available in 100-mg (Epivir-HBV®), 150-mg (Epivir®), and 300-mg (Epivir®) strengths. **Store at room temperature.** [2] [3] .

References

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

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- Mueller BU, Lewis LL, Yuen GJ et al: Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. Antimicrob Agents Chemother Dec, 1998; 42(12): 3187-3192.

1.101 Lansoprazole

Title Lansoprazole

Dose

0.73 to 1.66 mg/kg/dose orally once daily.

Administration

The contents of a capsule can be mixed in 40 mL of apple juice and administered by NG tube. Do not use other liquids. The NG tube should be flushed with additional apple juice after administration. Data for successfully supplying patient-specific, partial doses of lansoprazole through pediatric/neonatal feeding tubes are lacking. In one study attempting to provide a partial dose (orally disintegrating tablet formulation) through a feeding tube, a 7.5 mg dose was administered successfully through an 8 French pediatric feeding tube; however, the same dose partially clogged a 6 French pediatric feeding tube (was able to clear with NS flush) and completely clogged a 5 French pediatric feeding tube.

There have been reports to the FDA of Teva's lansoprazole delayed-release orally-disintegrating tablets causing clogged and blocked oral syringes, and gastric and jejunostomy feeding tubes requiring patients to seek emergency medical assistance to have feeding tubes unclogged or removed and replaced. Tablets may not disintegrate entirely when water is added to form a suspension, and/or the tablets may disintegrate but later form clumps which can adhere to the inside walls of the tubes. The FDA recommends that the Teva brand of delayed-release orally-disintegrating lansoprazole tablets not be dispensed to patients with feeding tubes.

Uses

Treatment of reflux esophagitis.

Contraindications/Precautions

Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year) of proton pump inhibitors. Concomitant use of drugs that cause hypomagnesemia may increase the risk. Monitoring is recommended during therapy. In some cases, hypomagnesemia was not reversed with magnesium supplementation and discontinuation of the proton pump inhibitor was necessary.
An increased risk of *Clostridium difficile*-associated diarrhea (CDAD) has been associated with proton pump inhibitor (PPI) use [1] [2] . Although not reported in neonates, a higher risk of CDAD was seen in children who received PPI therapy. In a retrospective, single-center, observational, case-control study of children (1 year of age and older) having protracted diarrhea and stool analysis for *C. difficile*, 68 cases of CDAD were identified and then randomly matched to 68 control subjects who tested*C. difficile* negative. The use of PPI therapy was significantly higher in the patients with CDAD (22%; n=15) compared to the control group (6%; n=4), resulting in an odds ratio of 4.5 (95% CI, 1.4 to 14.4; p=0.006) [2] .

Pharmacology

Lansoprazole inhibits gastric acid secretion by inhibition of hydrogen-potassium ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Extensively metabolized in the liver by CYP 2C19 and 3A4. Onset of action is within one hour of administration, maximal effect is at approximately 1.5 hours. Average elimination half-life is 1.5 hours. Inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours. The absorption of weakly acidic drugs (eg, digoxin, furosemide) is enhanced. The absorption of weakly basic drugs (eg, ketoconazole) is inhibited.

Adverse Effects

Hypergastrinemia and mild transaminase elevations are the only adverse effects reported in children who received lansoprazole for extended periods of time. Available data are limited to small studies of infants and children.

Monitoring

Observe for symptomatic improvement within 3 days. Consider intraesophageal pH monitoring to assess for efficacy (pH greater than 4.0). Measure AST and ALT if duration of therapy is greater than 8 weeks. Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year). Monitor magnesium levels prior to initiation of therapy and periodically during therapy in patients expected to be on long-term therapy or patients receiving concomitant drugs such as digoxin or those that may cause hypomagnesemia.

Special Considerations/Preparation

Prevacid® is supplied as a delayed-release capsule and a delayed-release orally disintegrating tablet (ODT) containing either 15 mg or 30 mg lansoprazole for oral administration [3] [4] .

References

- Franco M, Salvia G, Terrin G, Spadaro R, et al: Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood. *Dig Liver Dis*2000;32:660-6.
- Gibbons TE, Gold BD: The use of proton pump inhibitors in children: a comprehensive review. *Paediatr Drugs* 2003;5:25-40.
- Johnson CE, Cober MP, Ludwig JL: Stability of partial doses of omeprazole-sodium bicarbonate oral suspension. *Ann Pharmacother* 2007;41:1954-1961.
- Product Information: Prevacid®, Prevacid® Solu Tab, lansoprazole delayed-release capsules and orally disintegrating tablets, Takeda Pharmaceuticals, 2010.
- Scott LJ: Lansoprazole in the management of gastroesophageal reflux disease in children. *Paediatr Drugs* 2003;5:57-61.
- Tran A, Rey E, Pons G, Pariente-Khayat A, et al: Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther*2002;71:359-67.
- U.S. Food and Drug Administration: FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of proton pump inhibitors (PPIs). U.S. Food and Drug Administration. Silver Spring, MD. 2011. Available from URL: http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm. As accessed 2011-03-02.

- U.S. Food and Drug Administration: FDA Drug Safety Communication: Lansoprazole delayed-release orally disintegrating tablets by Teva Pharmaceuticals: Letter to Healthcare Professionals - Clogged, blocked oral syringes and feeding tubes. U.S. Food and Drug Administration. Silver Spring, MD. 2011. Available from URL: http://www.fda.gov/Drugs/DrugSafety/ucm251485.htm. As accessed 2011-04-15.

1. US Food and Drug Administration: FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). US Food and Drug Administration, Silver Spring, MD, Jan08, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm#data.
2. Turco R, Martinelli M, Miele E et al: Proton pump inhibitors as a risk factor for paediatric Clostridium difficile infection. Aliment Pharmacol Ther Apr, 2010; 31(7): 754-759.
3. Product Information: PREVACID(R) SoluTab oral delayed-release disintegrating tablets, lansoprazole oral delayed-release disintegrating tablets. Takeda Pharmaceuticals America, Inc. (per FDA), Deerfield, IL, May, 2012.
4. Product Information: PREVACID(R) oral delayed-release capsules, lansoprazole oral delayed-release capsules. Takeda Pharmaceuticals America, Inc. (per FDA), Deerfield, IL, May, 2012.

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References

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1. US Food and Drug Administration: FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). US Food and Drug Administration, Silver Spring, MD, Jan08, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm#data.
2. Turco R, Martinelli M, Miele E et al: Proton pump inhibitors as a risk factor for paediatric Clostridium difficile infection. Aliment Pharmacol Ther Apr, 2010; 31(7): 754-759.
3. Product Information: PREVACID(R) SoluTab oral delayed-release disintegrating tablets, lansoprazole oral delayed-release disintegrating tablets. Takeda Pharmaceuticals America, Inc. (per FDA), Deerfield, IL, May, 2012.
4. Product Information: PREVACID(R) oral delayed-release capsules, lansoprazole oral delayed-release capsules. Takeda Pharmaceuticals America, Inc. (per FDA), Deerfield, IL, May, 2012.

1.102 LevETIRAcetam

Title LevETIRAcetam

Dose

Initial dose: 10 mg/kg/dose IV or orally every 24 hours in the neonatal period, every 12 hours later in infancy.
Adjust dosage upward as needed every 1 to 2 weeks to a maximum of 30 mg/kg/dose.

Administration

Intravenous: Dilute to a concentration of 5 to 15 mg/mL and infuse over 15 minutes [1] .
Oral: May be given without regards to feedings [2] .

Uses

Anticonvulsant. In the neonatal period, it has been used as a second line of therapy for seizures refractory to phenobarbital and other anticonvulsants.

Pharmacology

Rapidly and completely absorbed after oral administration, with the onset of action by 30 minutes and peak concentration within 2 hours. Bioavailability is not affected by food. Half-life in the immediate neonatal period is approximately 18 hours, decreasing to 6 hours by 6 months of age. Minimal protein binding. Linear pharmacokinetics. Primarily (66%) excreted unchanged in the urine, with some metabolism via enzymatic hydrolysis to inactive metabolites (no cytochrome p450 involvement). Dose should be adjusted in patients with renal impairment. The precise mechanism of action is unknown. Levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. There are no known significant drug interactions.

Adverse Effects

Data in neonates are limited to case reports and abstracts. Sedation and irritability have been reported in neonates and young infants. When discontinuing therapy, wean the dose gradually to minimize the potential of increased seizure frequency.

Monitoring

Serum trough concentrations are not routinely monitored, although they may be useful when determining the magnitude of dosing adjustments. Therapeutic concentrations are approximately 10 to 40 mcg/mL.

Special Considerations/Preparation

Keppra® injection for intravenous use is available in single-use 5 mL vials containing 500 mg (100 mg/mL). Must be further diluted to a concentration of 5 to 15 mg/mL in compatible diluent prior to administration. Diluted solution is stable for 24 hours at room temperature [1] .

Keppra® oral solution is available in a concentration of 100 mg/mL (dye- and alcohol-free). Store at room temperature [2] [3] .

Solution Compatibility

NS, LR, and D_5W.

Terminal Injection Site Compatibility

Diazepam, lorazepam, and valproate sodium.

References

- Shoemaker MT, Rotenberg JS: Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007;22:95-98.
- Grosso S, Cordelli DM, Franzoni E, et al: Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. *Seizure* 2007;16:345-350.
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- Allegaert K, Lewi L, Naulaers G, et al: Levetiracetam pharmacokinetics in neonates at birth. *Epilepsia*2006;47:1068-1069.
- Glauser TA, Mitchell WG, Weinstock A, et al: Pharmacokinetics of levetiracetam in infants and children with epilepsy. *Epilepsia* 2007;48:1117-22.
- Tomson T, Palm R, Kallen K, et al: Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;48:1111-1116.
- De Smedt T, Raedt R, Vonck K, Boon P: Levetiracetam: Part II, the clinical profile of a novel anticonvulsant drug. *CNS Reviews* 2007;13:57-78.
- Product information, UCB, 2008.

1. Product Information: KEPPRA(R) intravenous injection, levetiracetam intravenous injection. UCB,Inc., Smyrna, GA, May1, 2008.
2. Product Information: KEPPRA(R) oral tablets, oral solution, levetiracetam oral tablets, oral solution. UCB, Inc. (per FDA), Smyrna, GA, Dec, 2011.
3. Product Information: KEPPRA XR(TM) extended-release oral tablet, levetiracetam extended-release oral tablet. UCB, Inc., Smyrna, GA, Feb, 2009.

Title LevETIRAcetam

Dose

Initial dose: 10 mg/kg/dose IV or orally every 24 hours in the neonatal period, every 12 hours later in infancy.
Adjust dosage upward as needed every 1 to 2 weeks to a maximum of 30 mg/kg/dose.

Administration

Intravenous: Dilute to a concentration of 5 to 15 mg/mL and infuse over 15 minutes [1] .
Oral: May be given without regards to feedings [2] .

Uses

Anticonvulsant. In the neonatal period, it has been used as a second line of therapy for seizures refractory to phenobarbital and other anticonvulsants.

Pharmacology

Rapidly and completely absorbed after oral administration, with the onset of action by 30 minutes and peak concentration within 2 hours. Bioavailability is not affected by food. Half-life in the immediate neonatal period is approximately 18 hours, decreasing to 6 hours by 6 months of age. Minimal protein binding. Linear pharmacokinetics. Primarily (66%) excreted unchanged in the urine, with some metabolism via enzymatic hydrolysis to inactive metabolites (no cytochrome p450 involvement). Dose should be adjusted in patients with renal impairment. The precise mechanism of action is unknown. Levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity. There are no known significant drug interactions.

Adverse Effects

Data in neonates are limited to case reports and abstracts. Sedation and irritability have been reported in neonates and young infants. When discontinuing therapy, wean the dose gradually to minimize the potential of increased seizure frequency.

Monitoring

Serum trough concentrations are not routinely monitored, although they may be useful when determining the magnitude of dosing adjustments. Therapeutic concentrations are approximately 10 to 40 mcg/mL.

Special Considerations/Preparation

Keppra® injection for intravenous use is available in single-use 5 mL vials containing 500 mg (100 mg/mL). Must be further diluted to a concentration of 5 to 15 mg/mL in compatible diluent prior to administration. Diluted solution is stable for 24 hours at room temperature [1] .

Keppra® oral solution is available in a concentration of 100 mg/mL (dye- and alcohol-free). Store at room temperature [2] [3] .

Solution Compatibility

NS, LR, and D_5W.

Terminal Injection Site Compatibility

Diazepam, lorazepam, and valproate sodium.

References

- Shoemaker MT, Rotenberg JS: Levetiracetam for the treatment of neonatal seizures. *J Child Neurol* 2007;22:95-98.

- Grosso S, Cordelli DM, Franzoni E, et al: Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. *Seizure* 2007;16:345-350.
- Striano P, Coppola A, Pezzella M, et al: An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 2007;69:250-254.
- Allegaert K, Lewi L, Naulaers G, et al: Levetiracetam pharmacokinetics in neonates at birth. *Epilepsia*2006;47:1068-1069.
- Glauser TA, Mitchell WG, Weinstock A, et al: Pharmacokinetics of levetiracetam in infants and children with epilepsy. *Epilepsia* 2007;48:1117-22.
- Tomson T, Palm R, Kallen K, et al: Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia* 2007;48:1111-1116.
- De Smedt T, Raedt R, Vonck K, Boon P: Levetiracetam: Part II, the clinical profile of a novel anticonvulsant drug. *CNS Reviews* 2007;13:57-78.
- Product information, UCB, 2008.

1. Product Information: KEPPRA(R) intravenous injection, levetiracetam intravenous injection. UCB,Inc., Smyrna, GA, May1, 2008.
2. Product Information: KEPPRA(R) oral tablets, oral solution, levetiracetam oral tablets, oral solution. UCB, Inc. (per FDA), Smyrna, GA, Dec, 2011.
3. Product Information: KEPPRA XR(TM) extended-release oral tablet, levetiracetam extended-release oral tablet. UCB, Inc., Smyrna, GA, Feb, 2009.

1.103 Levothyroxine

Title Levothyroxine

Dose

Initial oral dose: 10 to 14 mcg/kg/dose orally every 24 hours.
(37.5 to 50 mcg/dose for an average term infant).
Dosage is adjusted in 12.5-mcg increments. Always round upward.

Initial IV dose: 5 to 8 mcg/kg/dose every 24 hours.

Uses

Treatment of hypothyroidism.

Pharmacology

Tissue deiodination converts T_4 to T_3, the active metabolite. Elimination of both T_4 and T_3 is equal in the urine and feces. Clinical effects will persist for 1 week after discontinuation of the drug. Levothyroxine prepared as an oral suspension is 50% to 80% bioavailable. Oral dosing produces effects within 3 to 5 days, while IV dosing produces effects in 6 to 8 hours.

Adverse Effects

Prolonged over-treatment can produce premature craniosynostosis and acceleration of bone age.

Monitoring

After 2 weeks of treatment, serum levothyroxine (T_4) concentration should be in the high normal range (10 to 16 mcg/dL) and should be maintained in this range for the first year of life. Serum triiodothyronine (T_3) concentration should be normal (70 to 220 nanograms/dL), and TSH should have declined from initial value. After 12 weeks of treatment, serum TSH concentration should be in the normal range, less than 15 milliunits/L. Serum T_4 and TSH concentrations should be measured at two weeks of age, then every 1 to 2 months, or 2 weeks after any change in dosage. Assess for signs of hypothyroidism: Lethargy, poor feeding, constipation, intermittent cyanosis, and prolonged neonatal jaundice. Assess for signs of thyrotoxicosis: hyperreactivity, altered sleep pattern, tachycardia, tachypnea, fever, exophthalmos, and goiter. Periodically assess growth, development, and bone-age advancement.

Special Considerations/Preparation

Oral suspension is not commercially available. Available as scored tablets ranging from 25 to 300 mcg per tablet. Also available in capsules that contain a viscous liquid ranging from 13 to 150 mcg per capsule. **Capsules cannot be crushed, suspended in water, or dissolved by placing in water before use**. Monitor patient closely when switching brand of drug due to some differences in bioavailability.

To prepare a 15-mcg/mL levothyroxine oral suspension: Crush levothyroxine 100-mcg tablets in glycerol and add sterile water up to desired volume. Shake well before dispensing. Product stability is 10 days when refrigerated between 2 and 8 degrees C. Stability tests demonstrated a 12% decline in levothyroxine concentration in the prepared suspension over 11 days.

An oral liquid formulation of levothyroxine sodium 25 mcg/mL in 40% glycerol compounded from crushed tablets and distilled water with no preservatives added was stable for 8 days when stored in amber bottles at 4 degrees C. Degradation occurred faster in the formulation with preservative (methylparaben).

Injectable form is available as lyophilized powder in vials containing 100 or 500 mcg. **Use only NS for reconstitution.** Following reconstitution with 5 mL of NS, final concentrations are approximately 20 mcg/mL and 100 mcg/mL **Use immediately. Do not add to any other IV solution** Reconstituted solution is preservative free and stable for 4 hours [1] .

References

- Mathai S, Cutfield WS, Gunn AJ, et al: A novel therapeutic paradigm to treat congenital hypothyroidism. *Clin Endocrinol* (Oxf) 2008; 69(1):142-147.
- Selva KA, Mandel SH, Rien L, et al: Initial treatment of L-thyroxine in congenital hypothyroidism. *J Pediatr* 2002;141:786-92.
- Boulton DW, Fawcett JP, & Woods DJ: Stability of an extemporaneously compounded levothyroxine sodium oral liquid. *Am J Health-Syst Pharm* 1996; 53:1157-1161.
- AAP Section on Endocrinology and Committee on Genetics, and Committee on Public Health, American Thyroid Association: Newborn screening for congenital hypothyroidism: Recommended guidelines. *Pediatrics* 1993;91:1203-1209.

- Germak JA, Foley TP: Longitudinal assessment of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1990;117:211.
- Product Information, Bedford, 2003.

1. Product Information: levothyroxine sodium intravenous injection, levothyroxine sodium intravenous injection. APP Pharmaceuticals, LLC (per FDA), Schaumburg, IL, Dec, 2012.

Title Levothyroxine

Dose

Initial oral dose: 10 to 14 mcg/kg/dose orally every 24 hours.
(37.5 to 50 mcg/dose for an average term infant).
Dosage is adjusted in 12.5-mcg increments. Always round upward.

Initial IV dose: 5 to 8 mcg/kg/dose every 24 hours.

Uses

Treatment of hypothyroidism.

Pharmacology

Tissue deiodination converts T_4 to T_3, the active metabolite. Elimination of both T_4 and T_3 is equal in the urine and feces. Clinical effects will persist for 1 week after discontinuation of the drug. Levothyroxine prepared as an oral suspension is 50% to 80% bioavailable. Oral dosing produces effects within 3 to 5 days, while IV dosing produces effects in 6 to 8 hours.

Adverse Effects

Prolonged over-treatment can produce premature craniosynostosis and acceleration of bone age.

Monitoring

After 2 weeks of treatment, serum levothyroxine (T_4) concentration should be in the high normal range (10 to 16 mcg/dL) and should be maintained in this range for the first year of life. Serum triiodothyronine (T_3) concentration should be normal (70 to 220 nanograms/dL), and TSH should have declined from initial value. After 12 weeks of treatment, serum TSH concentration should be in the normal range, less than 15 milliunits/L. Serum T_4 and TSH concentrations should be measured at two weeks of age, then every 1 to 2 months, or 2 weeks after any change in dosage. Assess for signs of hypothyroidism: Lethargy, poor feeding, constipation, intermittent cyanosis, and prolonged neonatal jaundice. Assess for signs of thyrotoxicosis: hyperreactivity, altered sleep pattern, tachycardia, tachypnea, fever, exophthalmos, and goiter. Periodically assess growth, development, and bone-age advancement.

Special Considerations/Preparation

Oral suspension is not commercially available. Available as scored tablets ranging from 25 to 300 mcg per tablet. Also available in capsules that contain a viscous liquid ranging from 13 to 150 mcg per capsule. **Capsules cannot be crushed, suspended in water, or dissolved by placing in water before use**. Monitor patient closely when switching brand of drug due to some differences in bioavailability.

To prepare a 15-mcg/mL levothyroxine oral suspension: Crush levothyroxine 100-mcg tablets in glycerol and add sterile water up to desired volume. Shake well before dispensing. Product stability is 10 days when refrigerated between 2 and 8 degrees C. Stability tests demonstrated a 12% decline in levothyroxine concentration in the prepared suspension over 11 days.

An oral liquid formulation of levothyroxine sodium 25 mcg/mL in 40% glycerol compounded from crushed tablets and distilled water with no preservatives added was stable for 8 days when stored in amber bottles at 4 degrees C. Degradation occurred faster in the formulation with preservative (methylparaben).

Injectable form is available as lyophilized powder in vials containing 100 or 500 mcg. **Use only NS for reconstitution.** Following reconstitution with 5 mL of NS, final concentrations are approximately 20 mcg/mL and 100 mcg/mL **Use immediately. Do not add to any other IV solution** Reconstituted solution is preservative free and stable for 4 hours [1] .

References

- Mathai S, Cutfield WS, Gunn AJ, et al: A novel therapeutic paradigm to treat congenital hypothyroidism. *Clin Endocrinol* (Oxf) 2008; 69(1):142-147.
- Selva KA, Mandel SH, Rien L, et al: Initial treatment of L-thyroxine in congenital hypothyroidism. *J Pediatr* 2002;141:786-92.
- Boulton DW, Fawcett JP, & Woods DJ: Stability of an extemporaneously compounded levothyroxine sodium oral liquid. *Am J Health-Syst Pharm* 1996; 53:1157-1161.
- AAP Section on Endocrinology and Committee on Genetics, and Committee on Public Health, American Thyroid Association: Newborn screening for congenital hypothyroidism: Recommended guidelines. *Pediatrics* 1993;91:1203-1209.
- Germak JA, Foley TP: Longitudinal assessment of L-thyroxine therapy for congenital hypothyroidism. *J Pediatr* 1990;117:211.
- Product Information, Bedford, 2003.

1. Product Information: levothyroxine sodium intravenous injection, levothyroxine sodium intravenous injection. APP Pharmaceuticals, LLC (per FDA), Schaumburg, IL, Dec, 2012.

1.104 Lidocaine - Antiarrhythmic

Title Lidocaine - Antiarrhythmic

Dose

Initial bolus dose: 0.5 to 1 mg/kg IV push over 5 minutes. Repeat every 10 minutes as necessary to control arrhythmia. **Maximum total bolus dose should not exceed 5 mg/kg.**

Maintenance IV infusion: 10 to 50 mcg/kg per minute. Premature neonates should receive lowest dosage.

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Lidocaine): Mix 50 mL of 2400 mcg/mL solution using lidocaine concentration of 20 mg/mL.
2400 mcg/mL = 2.4 mg/mL
2.4 mg/mL x 50 mL = 120 mg lidocaine
***120 mg ÷ 20 mg/mL = 6 mL of lidocaine**
Add 6 mL of lidocaine (20 mg/mL) to 44 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 2400 mcg/mL.
Maximum concentration is 8000 mcg/mL.

Lidocaine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
800	10	0.75
	20	1.5
	30	2.25
	40	3
	50	3.75
1600	10	0.375
	20	0.75
	30	1.125
	40	1.5
	50	1.875
2400	10	0.25
	20	0.5
	30	0.75
	40	1
	50	1.25
4000	10	0.15
	20	0.3
	30	0.45
	40	0.6
	50	0.75

	10	0.1
	20	0.2
6000	30	0.3
	40	0.4
	50	0.5
	10	0.075
	20	0.15
8000	30	0.225
	40	0.3
	50	0.375

Uses

Short-term control of ventricular arrhythmias, including ventricular tachycardia, premature ventricular contractions, and arrhythmias resulting from digitalis intoxication.

Contraindications/Precautions

Contraindicated in complete heart block and wide complex tachycardia attributable to accessory conduction pathways [3] [4] .

Pharmacology

Lidocaine is a type 1b antiarrhythmic agent used intravenously. Onset of action is 1 to 2 minutes after bolus administration. Plasma half-life in neonates is 3 hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by Î±$_1$-acid glycoprotein. Transformed in the liver to metabolites with antiarrhythmic activity; approximately 30% is excreted unchanged in neonates.

Adverse Effects

Early signs of CNS toxicity are drowsiness, agitation, vomiting, and muscle twitching. Later signs include seizures, loss of consciousness, respiratory depression, and apnea. Cardiac toxicity is associated with excessive doses and includes bradycardia, hypotension, heart block, and cardiovascular collapse.

Monitoring

Continuous monitoring of ECG, heart rate, and blood pressure should be performed. Assess level of consciousness. Observe for seizure activity. Therapeutic drug concentration is 1.5 to 6 mg/L, with toxicity associated with concentrations greater than 9 mg/L [1] [2] .

Special Considerations/Preparation

Use only preservative-free lidocaine without epinephrine. Available in multiple concentrations ranging from 1% to 20%. To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1-mg/mL final concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, methicillin, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Lerman J, Strong A, LeDez KM, et al: Effects of age on the serum concentration of Î±$_1$-acid glycoprotein and the binding of lidocaine in pediatric patients. *Clin Pharmacol Ther* 1989;46:219.
- Mihaly GW, Moore RG, Thomas J: The pharmacokinetics and metabolism of the anilide local anesthetics in neonates. I. Lignocaine. *Eur J Clin Pharmacol* 1978;13:143.
- Gelband H, Rosen MR: Pharmacologic basis for the treatment of cardiac arrhythmias. *Pediatrics* 1975;55:59.

1. Rademaker CMA: Pharmacology Review: Lidocaine for Neonatal Seizure Management. NeoReviews 2008; 9: e585-e589.
2. Product Information: Lidocaine HCl and 5% Dextrose intravenous injection solution, lidocaine HCl and 5% dextrose intravenous injection solution. B Braun (per manufacturer), Irvine, CA, 2004.
3. Kleinman ME, Chameides L, Schexnayder SM et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14: pediatric advanced life support. Circulation Nov02, 2010; 122(18 Suppl.3): S876-S908.
4. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.

Title Lidocaine - Antiarrhythmic

Dose

Initial bolus dose: 0.5 to 1 mg/kg IV push over 5 minutes. Repeat every 10 minutes as necessary to control arrhythmia. **Maximum total bolus dose should not exceed 5 mg/kg.**

Maintenance IV infusion: 10 to 50 mcg/kg per minute. Premature neonates should receive lowest dosage.

Solution Preparation Calculations
To calculate the AMOUNT of drug needed per defined final fluid volume:
Desired final concentration (mg/mL) x defined final fluid volume (mL) = AMOUNT of drug to add to final infusion solution (mg).
To calculate the VOLUME of drug needed per defined final fluid volume:
*AMOUNT of drug to add (mg) ÷ drug (vial) concentration (mg/mL) = VOLUME of drug to add (mL)
Example (for Lidocaine): Mix 50 mL of 2400 mcg/mL solution using lidocaine concentration of 20 mg/mL.
2400 mcg/mL = 2.4 mg/mL
2.4 mg/mL x 50 mL = 120 mg lidocaine
***120 mg ÷ 20 mg/mL = 6 mL of lidocaine**
Add 6 mL of lidocaine (20 mg/mL) to 44 mL of compatible solution (eg, D_5W) to yield 50 mL of infusion solution with a concentration of 2400 mcg/mL.
Maximum concentration is 8000 mcg/mL.

Lidocaine Titration Chart

Concentration (mcg/mL)	Dose (mcg/kg/min)	IV Rate (mL/kg/hour)
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	20	1.5
	30	2.25
	40	3
	50	3.75
1600	10	0.375
	20	0.75
	30	1.125
	40	1.5
	50	1.875
2400	10	0.25
	20	0.5
	30	0.75
	40	1
	50	1.25
4000	10	0.15
	20	0.3

	30	0.45
	40	0.6
	50	0.75
	10	0.1
	20	0.2
6000	30	0.3
	40	0.4
	50	0.5
	10	0.075
	20	0.15
8000	30	0.225
	40	0.3
	50	0.375

Uses

Short-term control of ventricular arrhythmias, including ventricular tachycardia, premature ventricular contractions, and arrhythmias resulting from digitalis intoxication.

Contraindications/Precautions

Contraindicated in complete heart block and wide complex tachycardia attributable to accessory conduction pathways [3] [4] .

Pharmacology

Lidocaine is a type 1b antiarrhythmic agent used intravenously. Onset of action is 1 to 2 minutes after bolus administration. Plasma half-life in neonates is 3 hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by Î±$_1$-acid glycoprotein. Transformed in the liver to metabolites with antiarrhythmic activity; approximately 30% is excreted unchanged in neonates.

Adverse Effects

Early signs of CNS toxicity are drowsiness, agitation, vomiting, and muscle twitching. Later signs include seizures, loss of consciousness, respiratory depression, and apnea. Cardiac toxicity is associated with excessive doses and includes bradycardia, hypotension, heart block, and cardiovascular collapse.

Monitoring

Continuous monitoring of ECG, heart rate, and blood pressure should be performed. Assess level of consciousness. Observe for seizure activity. Therapeutic drug

concentration is 1.5 to 6 mg/L, with toxicity associated with concentrations greater than 9 mg/L [1] [2] .

Special Considerations/Preparation

Use only preservative-free lidocaine without epinephrine. Available in multiple concentrations ranging from 1% to 20%. To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1-mg/mL final concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, methicillin, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Lerman J, Strong A, LeDez KM, et al: Effects of age on the serum concentration of Î±$_1$-acid glycoprotein and the binding of lidocaine in pediatric patients. *Clin Pharmacol Ther* 1989;46:219.
- Mihaly GW, Moore RG, Thomas J: The pharmacokinetics and metabolism of the anilide local anesthetics in neonates. I. Lignocaine. *Eur J Clin Pharmacol* 1978;13:143.
- Gelband H, Rosen MR: Pharmacologic basis for the treatment of cardiac arrhythmias. *Pediatrics* 1975;55:59.

1. Rademaker CMA: Pharmacology Review: Lidocaine for Neonatal Seizure Management. NeoReviews 2008; 9: e585-e589.
2. Product Information: Lidocaine HCl and 5% Dextrose intravenous injection solution, lidocaine HCl and 5% dextrose intravenous injection solution. B Braun (per manufacturer), Irvine, CA, 2004.
3. Kleinman ME, Chameides L, Schexnayder SM et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14: pediatric advanced life support. Circulation Nov02, 2010; 122(18 Suppl.3): S876-S908.
4. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.

1.105 Lidocaine - CNS

Title Lidocaine - CNS

Dose

Term, normothermic newborns:
Loading dose: 2 mg/kg IV over 10 minutes, followed immediately by a
Maintenance infusion: 6 mg/kg per hour for 6 hours, then 4 mg/kg per hour for 12 hours, then 2 mg/kg per hour for 12 hours.

Caution: Preterm newborns and term newborns undergoing hypothermia treatment are at risk for drug accumulation due to slower drug clearance. Precise dosing in these infants is uncertain.

Uses

Treatment of severe recurrent or prolonged seizures that do not respond to first-line therapies.

Pharmacology

The mode of action for lidocaine as an anticonvulsant drug is unknown. Lidocaine is metabolized in the liver into 2 active metabolites: monoethylglycinexylidide (MEGX) and glycinxylidide (GX). Approximately 30% is excreted unchanged in the urine. The half-life in neonates is at least 3 hours, and clearance is dose-dependent. The clinically effective dose of 6 mg/kg/hr will lead to accumulation of both lidocaine and metabolites within several hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by alpha 1-acid glycoprotein.

Adverse Effects

Do not use concurrently with phenytoin due to cardiac effects. Stop infusion immediately if significant cardiac arrhythmia occurs. Arrhythmias and significant bradycardia have occurred in 5% of reported cases. Slowing of the heart rate is common.

Monitoring

Continuous monitoring of EKG, heart rate, and blood pressure. Observe for worsening of seizure activity. Measuring blood concentrations is not clinically useful except when accumulation is suspected.

Special Considerations/Preparation

Use only preservative-free lidocaine without epinephrine. Available in multiple concentrations ranging from 1% to 20%. To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1 mg/mL final concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Shany E, Benzaqen O, Watemberg N: Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007;22:255-259.
- Rademaker CMA, de Vries LS: Lidocaine for neonatal seizure management. *NeoReviews* 2008;9:e585-e589.
- Malingre MM, Van Rooij LGM, Rademaker CMA, et al: Development of an optimal lidocaine infusion strategy for neonatal seizures. *Eur J Pediatr* 2006;165:598-604.
- Van Rooij LGM, Toet MC, Rademaker KMA, et al: Cardiac arrhythmias in neonates receiving lidocaine as anticonvulsive treatment. *Eur J Pediatr* 2004;163:637-641.
- Hellstrom-Westas L, Svenningsen NW, Westgren U, et al: Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion. *Acta Paediatr* 1992;81:35-39.
- Hellstrom-Westas L, Westgren U, Rosen I, Svenningsen NW: Lidocaine for treatment of severe seizures in newborn infants. I. Clinical effects and cerebral electrical activity monitoring. *Acta Paediatr Scand* 1988;77:79-84.
- Rey E, Radvanyi-Bouvet MF, Bodiou C, et al: Intravenous lidocaine in the treatment of convulsions in the neonatal period: Monitoring plasma levels. *Ther Drug Monit* 1990;12:316-320.

Compatibilities updated 7/2009
Dose & Administration and References updated 1/2009
Added 3/2006

Title Lidocaine - CNS

Dose

Term, normothermic newborns:
Loading dose: 2 mg/kg IV over 10 minutes, followed immediately by a

Maintenance infusion: 6 mg/kg per hour for 6 hours, then 4 mg/kg per hour for 12 hours, then 2 mg/kg per hour for 12 hours.

Caution: Preterm newborns and term newborns undergoing hypothermia treatment are at risk for drug accumulation due to slower drug clearance. Precise dosing in these infants is uncertain.

Uses

Treatment of severe recurrent or prolonged seizures that do not respond to first-line therapies.

Pharmacology

The mode of action for lidocaine as an anticonvulsant drug is unknown. Lidocaine is metabolized in the liver into 2 active metabolites: monoethylglycinexylidide (MEGX) and glycinxylidide (GX). Approximately 30% is excreted unchanged in the urine. The half-life in neonates is at least 3 hours, and clearance is dose-dependent. The clinically effective dose of 6 mg/kg/hr will lead to accumulation of both lidocaine and metabolites within several hours. Free drug fraction in both term and premature neonates is approximately twice that found in older children because of significantly reduced protein binding by alpha 1-acid glycoprotein.

Adverse Effects

Do not use concurrently with phenytoin due to cardiac effects. Stop infusion immediately if significant cardiac arrhythmia occurs. Arrhythmias and significant bradycardia have occurred in 5% of reported cases. Slowing of the heart rate is common.

Monitoring

Continuous monitoring of EKG, heart rate, and blood pressure. Observe for worsening of seizure activity. Measuring blood concentrations is not clinically useful except when accumulation is suspected.

Special Considerations/Preparation

Use only preservative-free lidocaine without epinephrine. Available in multiple concentrations ranging from 1% to 20%. To make a dilution for bolus dosing, dilute 10 mg lidocaine (0.5 mL of 2% solution) in 9.5 mL NS or D_5W, yielding a 1 mg/mL final concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Alteplase, aminophylline, amiodarone, ampicillin, caffeine citrate, calcium chloride, calcium gluconate, cefazolin, cefoxitin, chloramphenicol, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, erythromycin lactobionate, famotidine, fentanyl, flumazenil, furosemide, glycopyrrolate, heparin, hydrocortisone succinate, insulin, linezolid, metoclopramide, micafungin, morphine, nafcillin, nicardipine, nitroglycerin, penicillin G, pentobarbital, potassium chloride, procainamide, ranitidine, sodium bicarbonate, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Shany E, Benzaqen O, Watemberg N: Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007;22:255-259.
- Rademaker CMA, de Vries LS: Lidocaine for neonatal seizure management. *NeoReviews* 2008;9:e585-e589.
- Malingre MM, Van Rooij LGM, Rademaker CMA, et al: Development of an optimal lidocaine infusion strategy for neonatal seizures. *Eur J Pediatr* 2006;165:598-604.
- Van Rooij LGM, Toet MC, Rademaker KMA, et al: Cardiac arrhythmias in neonates receiving lidocaine as anticonvulsive treatment. *Eur J Pediatr* 2004;163:637-641.
- Hellstrom-Westas L, Svenningsen NW, Westgren U, et al: Lidocaine for treatment of severe seizures in newborn infants. II. Blood concentrations of lidocaine and metabolites during intravenous infusion. *Acta Paediatr* 1992;81:35-39.
- Hellstrom-Westas L, Westgren U, Rosen I, Svenningsen NW: Lidocaine for treatment of severe seizures in newborn infants. I. Clinical effects and cerebral electrical activity monitoring. *Acta Paediatr Scand* 1988;77:79-84.
- Rey E, Radvanyi-Bouvet MF, Bodiou C, et al: Intravenous lidocaine in the treatment of convulsions in the neonatal period: Monitoring plasma levels. *Ther Drug Monit* 1990;12:316-320.

Compatibilities updated 7/2009
Dose & Administration and References updated 1/2009
Added 3/2006

1.106 Linezolid

Title Linezolid

Dose

10 mg/kg/dose IV or orally every 8 hours [1] [2] .
Preterm newborns less than 1 week of age: 10 mg/kg/dose IV or orally every 12 hours [1] .

Administration

IV: Give as an intermittent IV infusion over 30 to 120 minutes. Supplied as ready-to-use infusion bags (2 mg/mL); no further dilution is necessary [1] .
Oral: May administer without regard to timing of feedings. Before administering oral suspension, gently mix by inverting bottle 3 to 5 times. Do not shake [1] .

Uses

Limited to treatment of infections, including endocarditis and ventriculitis, caused by gram positive organisms (eg, methicillin-resistant *Staph. aureus*,, penicillin-resistant *Strep. pneumoniae*, and vancomycin-resistant *Enterococcus faecium)* that are refractory to conventional therapy with vancomycin and other antibiotics [3] [4] [5] [2] . Do not use as empiric treatment or in any patient with infections caused by gram-negative organisms.

Contraindications/Precautions

Contraindicated in patients with carcinoid syndrome, uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and/or patients receiving concurrent serotonergic agents, sympathomimetic agents, vasopressive agents, or dopaminergic agents unless monitored closely [1] .
Use not recommended in pediatric patients with central nervous system (CSF) infections due to variable linezolid CSF concentrations. Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported. Symptomatic hypoglycemia has been reported in patients with diabetes receiving insulin. Serotonin syndrome may occur with concurrent use of serotonergic agents. Peripheral and optic neuropathy have been reported in pediatric patients, mainly in patients treated for longer than 28 days. Convulsions have been reported [1] .
Lactic acidosis has been reported in a case series of 3 children aged 6 months, 6 months, and 16 years receiving linezolid for 53, 31 and 7 days of treatment, respectively. All 3 children had liver dysfunction and complicated medical courses while receiving linezolid therapy. Two patients developed multiple system organ failure and metabolic acidosis, and the third patient developed pressor-refractory shock and metabolic acidosis. The role of linezolid in the development of lactic acidosis in these patients is unknown [6] .
Safety and efficacy of linezolid therapy for greater than 28 days has not been evaluated in controlled clinical trials [1] .
The FDA issued an alert regarding Zyvox (linezolid) on March 16, 2007. Patients in an open-label, randomized trial comparing linezolid with vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Patients with Gram positive infections had no difference in mortality according to their antibiotic treatment. In contrast, mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study. See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm101503.htm.

Pharmacology

Linezolid is an oxazolidinone agent that has a unique mechanism of inhibition of bacterial protein synthesis. It is usually bacteriostatic, although it may be bactericidal against *S. pneumoniae*, *B. fragilis*, and *C. perfringens*. Resistance to linezolid has been reported for vancomycin-resistant *E. faecium* and methicillin-resistant *S. aureus* [9] [10] [11] [12] [13] . Outbreaks of linezolid-resistant *S. aureus*, *S. epidermidis*, and *S. haemolyticus* have been reported in adult ICU settings. The majority of patients had received linezolid previously [14] [15] [9] . Rapidly penetrates osteoarticular tissues and synovial fluid. CSF concentrations were 70% of plasma concentrations in older patients with non-inflamed meninges. Completely and rapidly absorbed when administered orally to adults and children. Metabolized by oxidation without cytochrome CYP induction. Excreted in the urine as unchanged drug (30%) and two inactive metabolites. Serum half-life in most neonates is 2 to 3 hours, with the exception of preterm neonates less than one week of age, who have a serum half-life of 5 to 6 hours [1] [16] [17] .

Adverse Effects

Elevated transaminases and diarrhea occur in approximately 5% of treated patients; thrombocytopenia and anemia occur in 2% to 5% [2] [8] .

Monitoring

Monitor CBC weekly, especially in patients receiving linezolid for longer than 2 weeks, those with myelosuppression, those receiving concurrent myelosuppressive drugs, or those with a chronic infection who have received previous or concomitant antibiotic therapy [1] . Monitor lactate concentrations in patients receiving extended courses of linezolid therapy or in patients with pre-existing hepatic or renal dysfunction [6] . Patients receiving an extended course of therapy (eg, over 28 days) should be monitored for signs and symptoms of neuropathy [7] . Monitor for signs and symptoms of serotonin syndrome (hyperpyrexia, hyperreflexia, and incoordination) in patients receiving concomitant serotonergic agents. Visual function should be assessed in patients receiving long-term linezolid (3 months or greater) and in all patients experiencing visual impairment. Monitor blood pressure in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and/or in patients receiving sympathomimetic agents, vasopressive agents, or dopaminergic agents [1] .

Special Considerations/Preparation

Linezolid IV injection is supplied as a 2-mg/mL solution in single-use, ready-to-use 100-mL, 200-mL, and 300-mL plastic infusion bags in a foil laminate overwrap. Keep in the overwrap until use. **Store at room temperature.Do not freeze.** IV injection may exhibit a yellow color that can intensify over time without affecting potency [1] .
An oral suspension is available, and after reconstitution with 123 mL of distilled water (in 2 portions) provides 20 mg/mL. **Store at room temperature.** Use within 21 days after reconstitution. **Protect from light** [1] .

Solution Compatibility

D_5W, NS, Lactated Ringers.

Terminal Injection Site Compatibility

Dex/AA. Acyclovir, amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, caspofungin, cefazolin, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, furosemide, ganciclovir, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lidocaine, lorazepam, magnesium sulfate, meropenem, methylprednisolone, metoclopramide, metronidazole, mezlocillin, midazolam, morphine, naloxone, netilmicin, nicardipine, nitroglycerin, pentobarbital, phenobarbital, piperacillin, piperacillin-tazobactam, potassium chloride, propranolol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, erythromycin lactobionate, phenytoin, and trimethoprim/sulfamethoxazole.

References

- Product Information: ZYVOX(R) intravenous injection, oral tablets, oral suspension, linezolid intravenous injection, oral tablets, oral suspension. Pharmacia & Upjohn Company (per FDA), New York, NY, Nov, 2011.

- Deville JG, Adler S, Azimi PH et al: Linezolid versus vancomycin in the treatment of known or suspected resistant gram-positive infections in neonates. Pediatr Infect Dis J Sep1, 2003; 22(9 Suppl): S158-S163.

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- Scheetz MH, Knechtel SA, Malczynski M et al: Increasing incidence of linezolid-intermediate or -resistant, vancomycin-resistant Enterococcus faecium strains parallels increasing linezolid consumption. Antimicrob Agents Chemother Jun, 2008; 52(6): 2256-2259.

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- Seral C, Saenz Y, Algarate S et al: Nosocomial outbreak of methicillin- and linezolid-resistant Staphylococcus epidermidis associated with catheter-related infections in intensive care unit patients. Int J Med Microbiol Apr, 2011; 301(4): 354-358.

- Mazzariol A, Lo Cascio G, Kocsis E et al: Outbreak of linezolid-resistant Staphylococcus haemolyticus in an Italian intensive care unit. Eur J Clin Microbiol Infect Dis Jul27, 2011; Epub: Epub.

- Jungbluth GL: Linezolid pharmacokinetics in pediatric patients: an overview. Pediatr Infect Dis J Sep, 2003; 22(9 Suppl): S153-S157.

- Kearns GL, Abdel-Rahman SM, Blumer JL et al: Single dose pharmacokinetics of linezolid in infants and children. Pediatr Infect Dis J Dec, 2000; 19(12): 1178-1184.

Title Linezolid

Dose

10 mg/kg/dose IV or orally every 8 hours [1] [2] .
Preterm newborns less than 1 week of age: 10 mg/kg/dose IV or orally every 12 hours [1] .

Administration

IV: Give as an intermittent IV infusion over 30 to 120 minutes. Supplied as ready-to-use infusion bags (2 mg/mL); no further dilution is necessary [1] .
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Uses

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Pharmacology

Linezolid is an oxazolidinone agent that has a unique mechanism of inhibition of bacterial protein synthesis. It is usually bacteriostatic, although it may be bactericidal against *S. pneumoniae*, *B. fragilis*, and *C. perfringens*. Resistance to linezolid has been reported for vancomycin-resistant *E. faecium* and methicillin-resistant *S. aureus* [9] [10] [11] [12] [13] . Outbreaks of linezolid-resistant *S. aureus*, *S. epidermidis*, and *S. haemolyticus* have been reported in adult ICU settings. The majority of patients had

received linezolid previously [14] [15] [9] . Rapidly penetrates osteoarticular tissues and synovial fluid. CSF concentrations were 70% of plasma concentrations in older patients with non-inflamed meninges. Completely and rapidly absorbed when administered orally to adults and children. Metabolized by oxidation without cytochrome CYP induction. Excreted in the urine as unchanged drug (30%) and two inactive metabolites. Serum half-life in most neonates is 2 to 3 hours, with the exception of preterm neonates less than one week of age, who have a serum half-life of 5 to 6 hours [1] [16] [17] .

Adverse Effects

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Linezolid IV injection is supplied as a 2-mg/mL solution in single-use, ready-to-use 100-mL, 200-mL, and 300-mL plastic infusion bags in a foil laminate overwrap. Keep in the overwrap until use. **Store at room temperature.Do not freeze.** IV injection may exhibit a yellow color that can intensify over time without affecting potency [1] .
An oral suspension is available, and after reconstitution with 123 mL of distilled water (in 2 portions) provides 20 mg/mL. **Store at room temperature.** Use within 21 days after reconstitution. **Protect from light** [1] .

Solution Compatibility

D_5W, NS, Lactated Ringers.

Terminal Injection Site Compatibility

Dex/AA. Acyclovir, amikacin, aminophylline, ampicillin, aztreonam, calcium gluconate, caspofungin, cefazolin, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat,

esmolol, famotidine, fentanyl, fluconazole, furosemide, ganciclovir, gentamicin, heparin, hydrocortisone succinate, imipenem/cilastatin, lidocaine, lorazepam, magnesium sulfate, meropenem, methylprednisolone, metoclopramide, metronidazole, mezlocillin, midazolam, morphine, naloxone, netilmicin, nicardipine, nitroglycerin, pentobarbital, phenobarbital, piperacillin, piperacillin-tazobactam, potassium chloride, propranolol, ranitidine, remifentanil, sodium bicarbonate, theophylline, ticarcillin, tobramycin, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, erythromycin lactobionate, phenytoin, and trimethoprim/sulfamethoxazole.

References

- Product Information: ZYVOX(R) intravenous injection, oral tablets, oral suspension, linezolid intravenous injection, oral tablets, oral suspension. Pharmacia & Upjohn Company (per FDA), New York, NY, Nov, 2011.

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- Langgartner M, Mutenthaler A, Haiden N et al: Linezolid for treatment of catheter-related cerebrospinal fluid infections in preterm infants. Arch Dis Child Fetal Neonatal Ed Sep, 2008; 93(5): F397-F397.

- Kumar S, Kohlhoff S, Valencia G et al: Treatment of vancomycin-resistant Enterococcus faecium ventriculitis in a neonate. Int J Antimicrob Agents Jun, 2007; 29(6): 740-741.

- Su E, Crowley K, Carcillo JA et al: Linezolid and Lactic Acidosis: A Role for Lactate Monitoring With Long-term Linezolid Use in Children. Pediatr Infect Dis J Sep, 2011; 30(9): 804-806.

- Nambiar S, Rellosa N, Wassel RT et al: Linezolid-associated peripheral and optic neuropathy in children. Pediatrics Jun, 2011; 127(6): e1528-e1532.

- Saiman L, Goldfarb J, Kaplan SA et al: Safety and tolerability of linezolid in children. Pediatr Infect Dis J Sep, 2003; 22(9 Suppl): S193-S200.

- Garcia MS, De la Torre MA, Morales G et al: Clinical outbreak of linezolid-resistant Staphylococcus aureus in an intensive care unit. JAMA Jun9, 2010; 303(22): 2260-2264.

- Scheetz MH, Knechtel SA, Malczynski M et al: Increasing incidence of linezolid-intermediate or -resistant, vancomycin-resistant Enterococcus faecium strains parallels increasing linezolid consumption. Antimicrob Agents Chemother Jun, 2008; 52(6): 2256-2259.

- Gales AC, Sader HS, Andrade SS et al: Emergence of linezolid-resistant Staphylococcus aureus during treatment of pulmonary infection in a patient with cystic fibrosis. Int J Antimicrob Agents Apr, 2006; 27(4): 300-302.

- Herrero IA: Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. N Engl J Med Mar14, 2002; 346(11): 867-869.

- Tsiodras S, Gold HS, Sakoulas G et al: Linezolid resistance in a clinical isolate of Staphylococcus aureus. Lancet Jul21, 2001; 358(9277): 207-208.

- Seral C, Saenz Y, Algarate S et al: Nosocomial outbreak of methicillin- and linezolid-resistant Staphylococcus epidermidis associated with catheter-related infections in intensive care unit patients. Int J Med Microbiol Apr, 2011; 301(4): 354-358.

- Mazzariol A, Lo Cascio G, Kocsis E et al: Outbreak of linezolid-resistant Staphylococcus haemolyticus in an Italian intensive care unit. Eur J Clin Microbiol Infect Dis Jul27, 2011; Epub: Epub.

- Jungbluth GL: Linezolid pharmacokinetics in pediatric patients: an overview. Pediatr Infect Dis J Sep, 2003; 22(9 Suppl): S153-S157.

- Kearns GL, Abdel-Rahman SM, Blumer JL et al: Single dose pharmacokinetics of linezolid in infants and children. Pediatr Infect Dis J Dec, 2000; 19(12): 1178-1184.

1.107 Lopinavir\Ritonavir

Title Lopinavir/Ritonavir

Dose

HIV Infection
14 days and older: lopinavir 16 mg/ritonavir 4 mg/kg orally twice daily OR lopinavir 300 mg/ritonavir 75 mg/m^2 orally twice daily [1] [2] [3] . **Do not use until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Oral solution contains ethanol (42.4% v/v) and propylene glycol (15.3% w/v) which may lead to serious adverse events in neonates, particularly preterm neonates** [1] [2] .

Once-daily lopinavir/ritonavir is NOT recommended in any pediatric patient [1] [2] .

Co-administration with efavirenz, nevirapine, fosamprenavir, or nelfinavir is NOT recommended in patients less than 6 months of age [1] [2] .

When used in infants and young children, especially those 14 days to 6 months of age, it is critical to ensure that dose calculation, transcription of the medication order, and dosing instructions are accurate, and that total amounts of alcohol and propylene glycol from all concomitant medications are accounted for [4] .

Administration Administer with a feeding. Use a calibrated dosing syringe to administer the oral solution dose [4] .

If coadministered with didanosine, give didanosine 1 hour before or 2 hours after lopinavir/ritonavir dose [4] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. Lopinavir/ritonavir, in combination with a preferred dual nucleoside reverse transcriptase inhibitor (NRTI) component, is the preferred protease inhibitor-based regimen for treatment-naive, HIV-infected neonates with postmenstrual age of 42 weeks and postnatal age of 14 days and older. A lopinavir/ritonavir-based regimen is preferred over a nevirapine-based regimen due to higher rates of virological failure observed with nevirapine (regardless of previous exposure to nevirapine as part of maternal-infant prophylaxis). The preferred dual-NRTI backbone option in neonates (as long as zidovudine resistance is not detected) is zidovudine plus lamivudine/emtricitabine [1] .

Pediatric FDA Approved Indications
Lopinavir/ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 14 days of age or older [4] .

Contraindications/Precautions

Due to cardiovascular toxicity observed in preterm infants, lopinavir/ritonavir should NOT be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Serious reactions, such as complete atrioventricular block, bradycardia, and cardiomyopathy, lactic acidosis, acute renal failure, CNS depression, and respiratory complications, including fatal cases, have been reported, and are suspected to be caused by ethanol (42.4% v/v) and propylene glycol (15.3% w/v) present in the oral solution [4] .
Contraindicated when coadministered with alfuzosin, astemizole, cisapride, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, oral midazolam, pimozide, rifampin, sildenafil (when dosed for the treatment of pulmonary arterial hypertension), simvastatin, St. John's wort, terfenadine, and triazolam. QT interval prolongation and torsade de pointes have been reported; avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval [4] [5] .

Use with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. Pancreatitis (including fatal cases) and large increases in total cholesterol and triglycerides have also been reported; monitoring recommended and interruption or discontinuation of therapy may be necessary. Severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis) have been reported; discontinue if severe rash develops. May cause hepatotoxicity; patients with hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk. Exacerbation or new development of diabetes mellitus/hyperglycemia

may occur. Spontaneous bleeding may occur, requiring additional factor VIII, in patients with hemophilia type A and B. Immune reconstitution syndrome may occur during initial phase of treatment; monitor for opportunistic infections [4] [5]

Pharmacology

Lopinavir inhibits the HIV protease and prevents cleavage of the Gag-Pol polyprotein, thus reducing the probability of viral particles reaching a mature, infectious state. Ritonavir is administered solely to increase lopinavir plasma levels. Tmax following oral administration of lopinavir/ritonavir is approximately 4 hours. Food increases bioavailability of oral solution; therefore, lopinavir/ritonavir oral solution should be administered with feedings. Protein binding is approximately 98% to 99% and is primarily to alpha-1-acid glycoprotein (higher affinity) and albumin. Lopinavir is extensively metabolized in the liver, primarily by the CYP3A4 enzyme system. Ritonavir is a potent inhibitor of CYP3A4 and inhibits the metabolism of lopinavir, thereby increasing lopinavir concentrations. There are many drug interactions with lopinavir involving CYP3A4. Approximately 2% and 20% of lopinavir is excreted unchanged in the urine and feces, respectively [4] . In HIV-infected infants less than 6 weeks of age (range, 3.6 to 5.9 weeks) receiving oral solution of lopinavir 300 mg/ritonavir 75 mg/m^2 twice daily, the mean elimination half life was 3.7 hours (range 2.1 to 5.8 hours; n=9), according to a prospective, phase I/II, open-label study [3] . A pharmacokinetic study showed that the clearance of lopinavir/ritonavir was dependent on weight and postmenstrual age in neonates and infants from birth to less than 2 years of age (weight range from 1.16 to 10.4 kg; n=96) [6] .

Adverse Effects

Commonly reported adverse events are diarrhea, vomiting, rash, asthenia, and hyperlipidemia, especially hypertriglyceridemia. Elevations in liver transaminases and lipodystrophy have also been reported [1] .

Monitoring

Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch
Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X
Chemistries	X		X	X		X
Electrolytes	X			X		X

Glucose	X			X		X
AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X
Lipid Panel	X				X	
Urinalysis	X				X	

KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count

* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days.
** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months).
# For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.
# # May be too early to detect immunological response in the CD4 count/percentage

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo

Antiretroviral Monitoring in Adolescents

	ART initiation or modificati	2-to 8 weeks post-initiation	Every 3 to 6 months	Every 6 months	Every 12 months	Treatment Failure	Clinically Indicat

	on	or modification					ed
CD4 count	X		X	In clinically stable patients with suppressed viral load, can be monitored every 6-12 months.			X
HIV viral load	X	X *	X **			X	X
Resistance testing	X ***					X	X
Hepatitis B serology ^	X						X
Hepatitis C serology, with confirmation of positive result							X
Basic chemistry ^^, ~	X	X	X				X
AST/ALT/total bilirubin	X	X	X				X
CBC with differential	X	X If on zidovudine	X				X
Fasting lipid profile	X	X 4 to 8 weeks after new ART regimen		X If abnormal at last measurement	X If normal at last measurement		X

		affecting lipids					
Fasting glucose or HbA1C	X		X If abnormal at last measurement	X If normal at last measurement			X
Urinalysis	X			X~~ If on tenofovir	X		X
Pregnancy test	X If starting efavirenz						X

KEY: ART = antiretroviral, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, CBC = complete blood count.

* If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until suppression to less than 200 copies/mL, then every 3 to 6 months.
** Viral load is typically measured every 3 to 4 months in patients on ART. However, for adherent patients with suppressed viral load and stable immunological status for more than 2 to 3 years, monitoring at 6 months intervals may be considered.
*** In ART-naive patients, if resistance testing was performed at entry into care, repeat testing before initiation of ART is optional. The exception is pregnant women; repeat testing is recommended in this case. For virologically suppressed patients who are switching therapy for toxicity or convenience, viral amplification will not be possible and therefore resistance testing should not be performed. Results from prior resistance testing can be used to help in the construction of a new regimen.
^ If HBsAg is positive at baseline or before initiation of ART, tenofovir plus either emtricitabine or lamivudine should be used as part of the ART regimen to treat both hepatitis B virus and HIV infections. If HBsAG, and HBsAb, and anti-HBc are negative at baseline, hepatitis B vaccine series should be administered.
^^ Serum sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, glucose (preferably fasting). May consider monitoring the phosphorus concentrations in patients on tenofovir. Renal function determination by Cockcroft-Gault equation (CrCl) or Modification of Diet in Renal Disease (MDRD) equation (glomerular filtration rate).
~ For patients with renal disease, consult with the Guidelines on the Management of Chronic Kidney Disease in HIV-infected Patients: Recommendations of the HIV medicine Association of the Infectious Diseases Society of America.
~~ More frequent monitoring may be indicated for patients with evidence of kidney disease or increased risk of renal insufficiency.

Guidelines for the Use of Antiretroviral Agents in Adolescents HIV Infection, 2013; AIDSinfo

Special Considerations/Preparation

Available as an oral solution in a concentration of 80 mg lopinavir/20 mg ritonavir per mL that also contains 42.4% alcohol (v/v) and propylene glycol (15.3% w/v). Preferably, store oral solution refrigerated. Refrigerated oral solution is stable until the expiration date printed on the label; if stored at room temperature up to 25 degrees C (77 degrees F), oral solution should be used within 2 months [4] .

References

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

- Product Information: KALETRA(R) oral tablets, oral solution, lopinavir ritonavir oral tablets, oral solution. Abbott Laboratories (per FDA), North Chicago, IL, Jan, 2013.

- Chadwick EG, Pinto J, Yogev R et al: Early Initiation of Lopinavir/Ritonavir in Infants Less Than 6 Weeks of Age: Pharmacokinetics and 24-Week Safety and Efficacy. Pediatr Infect Dis J Feb9, 2009; Epub: --.

- Product Information: KALETRA oral film coated tablets, oral solution, lopinavir ritonavir oral film coated tablets, oral solution. Abbott Laboratories (Per manufacturer), North Chicago, IL, Feb, 2012.

- Rudin C, Burri M, Shen Y et al: Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. Pediatr Infect Dis J May, 2008; 27(5): 431-437.

- Urien S, Firtion G, Anderson ST et al: Lopinavir/ritonavir population pharmacokinetics in neonates and infants. Br J Clin Pharmacol Jun, 2011; 71(6): 956-960.

Title Lopinavir/Ritonavir

Dose

HIV Infection
14 days and older: lopinavir 16 mg/ritonavir 4 mg/kg orally twice daily OR lopinavir 300 mg/ritonavir 75 mg/m^2 orally twice daily [1] [2] [3] . **Do not use until a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Oral solution contains ethanol (42.4% v/v) and propylene glycol (15.3% w/v) which may lead to serious adverse events in neonates, particularly preterm neonates** [1] [2] .

Once-daily lopinavir/ritonavir is NOT recommended in any pediatric patient [1] [2] .

Co-administration with efavirenz, nevirapine, fosamprenavir, or nelfinavir is NOT recommended in patients less than 6 months of age [1] [2] .

When used in infants and young children, especially those 14 days to 6 months of age, it is critical to ensure that dose calculation, transcription of the medication order, and dosing instructions are accurate, and that total amounts of alcohol and propylene glycol from all concomitant medications are accounted for [4] .

Administration Administer with a feeding. Use a calibrated dosing syringe to administer the oral solution dose [4] .
If coadministered with didanosine, give didanosine 1 hour before or 2 hours after lopinavir/ritonavir dose [4] .

Uses

Treatment of HIV-1 infection, in combination with other antiretroviral agents: If an infant is definitively diagnosed with HIV infection while receiving prophylactic treatment for prevention of mother-to-child transmission of HIV, prophylactic antiretrovirals should be discontinued immediately and treatment initiated with a 3-drug combination regimen. Lopinavir/ritonavir, in combination with a preferred dual nucleoside reverse transcriptase inhibitor (NRTI) component, is the preferred protease inhibitor-based regimen for treatment-naive, HIV-infected neonates with postmenstrual age of 42 weeks and postnatal age of 14 days and older. A lopinavir/ritonavir-based regimen is preferred over a nevirapine-based regimen due to higher rates of virological failure observed with nevirapine (regardless of previous exposure to nevirapine as part of maternal-infant prophylaxis). The preferred dual-NRTI backbone option in neonates (as long as zidovudine resistance is not detected) is zidovudine plus lamivudine/emtricitabine [1] .

Pediatric FDA Approved Indications
Lopinavir/ritonavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 14 days of age or older [4] .

Contraindications/Precautions

Due to cardiovascular toxicity observed in preterm infants, lopinavir/ritonavir should NOT be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Serious reactions, such as complete atrioventricular block, bradycardia, and cardiomyopathy, lactic acidosis, acute renal failure, CNS depression, and respiratory complications, including fatal cases, have been reported, and are suspected to be caused by ethanol (42.4% v/v) and propylene glycol (15.3% w/v) present in the oral solution [4] .
Contraindicated when coadministered with alfuzosin, astemizole, cisapride, ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine), lovastatin, oral midazolam, pimozide, rifampin, sildenafil (when dosed for the treatment of pulmonary arterial hypertension), simvastatin, St. John's wort, terfenadine, and triazolam. QT interval prolongation and torsade de pointes have been reported; avoid use in patients with congenital long QT syndrome, those with hypokalemia, and with other drugs that prolong the QT interval [4] [5] .

Use with caution in patients with underlying structural heart disease, pre-existing conduction system abnormalities, ischemic heart disease or cardiomyopathies, as these patients may be at increased risk for developing cardiac conduction abnormalities. Pancreatitis (including fatal cases) and large increases in total cholesterol and triglycerides have also been reported; monitoring recommended and interruption or discontinuation of therapy may be necessary. Severe skin reactions (eg, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis) have been reported; discontinue if severe rash develops. May cause hepatotoxicity; patients with hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk. Exacerbation or new development of diabetes mellitus/hyperglycemia may occur. Spontaneous bleeding may occur, requiring additional factor VIII, in patients with hemophilia type A and B. Immune reconstitution syndrome may occur during initial phase of treatment; monitor for opportunistic infections [4] [5]

Pharmacology

Lopinavir inhibits the HIV protease and prevents cleavage of the Gag-Pol polyprotein, thus reducing the probability of viral particles reaching a mature, infectious state. Ritonavir is administered solely to increase lopinavir plasma levels. Tmax following oral administration of lopinavir/ritonavir is approximately 4 hours. Food increases bioavailability of oral solution; therefore, lopinavir/ritonavir oral solution should be administered with feedings. Protein binding is approximately 98% to 99% and is primarily to alpha-1-acid glycoprotein (higher affinity) and albumin. Lopinavir is extensively metabolized in the liver, primarily by the CYP3A4 enzyme system. Ritonavir is a potent inhibitor of CYP3A4 and inhibits the metabolism of lopinavir, thereby increasing lopinavir concentrations. There are many drug interactions with lopinavir involving CYP3A4. Approximately 2% and 20% of lopinavir is excreted unchanged in the urine and feces, respectively [4] . In HIV-infected infants less than 6 weeks of age (range, 3.6 to 5.9 weeks) receiving oral solution of lopinavir 300 mg/ritonavir 75 mg/m^2 twice daily, the mean elimination half life was 3.7 hours (range 2.1 to 5.8 hours; n=9), according to a prospective, phase I/II, open-label study [3] . A pharmacokinetic study showed that the clearance of lopinavir/ritonavir was dependent on weight and postmenstrual age in neonates and infants from birth to less than 2 years of age (weight range from 1.16 to 10.4 kg; n=96) [6] .

Adverse Effects

Commonly reported adverse events are diarrhea, vomiting, rash, asthenia, and hyperlipidemia, especially hypertriglyceridemia. Elevations in liver transaminases and lipodystrophy have also been reported [1] .

Monitoring

Antiretroviral Monitoring in Children

	Baseline*	1 to 2 weeks on therapy	4 to 8 weeks on therapy	Every 3 to 4 months **	Every 6 to 12 months	Therapy Switch

Adverse Effects	X	X	X	X	X	X
CBC with differential	X		X	X		X
Chemistries	X		X	X		X
Electrolytes	X			X		X
Glucose	X			X		X
AST/ALT	X	X #	X #	X		X
Bilirubin	X			X		X
BUN/Creatinine	X			X		X
Albumin/total protein	X				X	X
Calcium/Phosphate	X				X	X
CD4 count/%	X		X # #	X		X
HIV RNA	X	X	X	X		X
Resistance Testing	X					X
Adherence Evaluation		X	X	X		X
Lipid Panel	X				X	
Urinalysis	X				X	

KEY: AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen CBC = complete blood count

* Baseline may not be necessary if pre-therapy monitoring was performed within 30 to 45 days.
** May consider monitoring every 6 months, in children who are in stable treatment status (non-detectable HIV RNA and normal CD4 count/percentage for at least 12 months).
# For nevirapine, obtain serum transaminase concentrations every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, and every 3 to 4 months thereafter.
# # May be too early to detect immunological response in the CD4 count/percentage

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, 2012; AIDSinfo

Antiretroviral Monitoring in Adolescents

	ART initiation or modification	2-to 8 weeks post-initiation or modification	Every 3 to 6 months	Every 6 months	Every 12 months	Treatment Failure	Clinically Indicated
CD4 count	X		X	In clinically stable patients with suppressed viral load, can be monitored every 6-12 months.			X
HIV viral load	X	X *	X **			X	X
Resistance testing	X ***					X	X
Hepatitis B serology ^	X						X
Hepatitis C serology, with confirmation of positive result							X
Basic chemistry ^^, ~	X	X	X				X
AST/ALT/total bilirubin	X	X	X				X
CBC with differential	X	X If on zidovudin	X				X

		e					
Fasting lipid profile	X	X 4 to 8 weeks after new ART regimen affecting lipids		X If abnormal at last measurement	X If normal at last measurement		X
Fasting glucose or HbA1C	X		X If abnormal at last measurement	X If normal at last measurement			X
Urinalysis	X			X~~ If on tenofovir	X		X
Pregnancy test	X If starting efavirenz						X

KEY: ART = antiretroviral, AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, CBC = complete blood count.

* If HIV RNA is detectable at 2 to 8 weeks, repeat every 4 to 8 weeks until suppression to less than 200 copies/mL, then every 3 to 6 months.
** Viral load is typically measured every 3 to 4 months in patients on ART. However, for adherent patients with suppressed viral load and stable immunological status for more than 2 to 3 years, monitoring at 6 months intervals may be considered.
*** In ART-naive patients, if resistance testing was performed at entry into care, repeat testing before initiation of ART is optional. The exception is pregnant women; repeat testing is recommended in this case. For virologically suppressed patients who are switching therapy for toxicity or convenience, viral amplification will not be possible and therefore resistance testing should not be performed. Results from prior resistance testing can be used to help in the construction of a new regimen.
^ If HBsAg is positive at baseline or before initiation of ART, tenofovir plus either emtricitabine or lamivudine should be used as part of the ART regimen to treat both hepatitis B virus and HIV infections. If HBsAG, and HBsAb, and anti-HBc are negative at baseline, hepatitis B vaccine series should be administered.
^^ Serum sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, glucose

(preferably fasting). May consider monitoring the phosphorus concentrations in patients on tenofovir. Renal function determination by Cockcroft-Gault equation (CrCl) or Modification of Diet in Renal Disease (MDRD) equation (glomerular filtration rate). ~ For patients with renal disease, consult with the Guidelines on the Management of Chronic Kidney Disease in HIV-infected Patients: Recommendations of the HIV medicine Association of the Infectious Diseases Society of America. ~~ More frequent monitoring may be indicated for patients with evidence of kidney disease or increased risk of renal insufficiency.
Guidelines for the Use of Antiretroviral Agents in Adolescents HIV Infection, 2013; AIDSinfo

Special Considerations/Preparation

Available as an oral solution in a concentration of 80 mg lopinavir/20 mg ritonavir per mL that also contains 42.4% alcohol (v/v) and propylene glycol (15.3% w/v). Preferably, store oral solution refrigerated. Refrigerated oral solution is stable until the expiration date printed on the label; if stored at room temperature up to 25 degrees C (77 degrees F), oral solution should be used within 2 months [4] .

References

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Nov05, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf.

- Product Information: KALETRA(R) oral tablets, oral solution, lopinavir ritonavir oral tablets, oral solution. Abbott Laboratories (per FDA), North Chicago, IL, Jan, 2013.

- Chadwick EG, Pinto J, Yogev R et al: Early Initiation of Lopinavir/Ritonavir in Infants Less Than 6 Weeks of Age: Pharmacokinetics and 24-Week Safety and Efficacy. Pediatr Infect Dis J Feb9, 2009; Epub: --.

- Product Information: KALETRA oral film coated tablets, oral solution, lopinavir ritonavir oral film coated tablets, oral solution. Abbott Laboratories (Per manufacturer), North Chicago, IL, Feb, 2012.

- Rudin C, Burri M, Shen Y et al: Long-term safety and effectiveness of ritonavir, nelfinavir, and lopinavir/ritonavir in antiretroviral-experienced HIV-infected children. Pediatr Infect Dis J May, 2008; 27(5): 431-437.

- Urien S, Firtion G, Anderson ST et al: Lopinavir/ritonavir population pharmacokinetics in neonates and infants. Br J Clin Pharmacol Jun, 2011; 71(6): 956-960.

1.108 Lucinactant

Title Lucinactant

Dose

Respiratory Distress Syndrome; Prophylaxis
5.8 mL/kg birth weight intratracheally in 4 equal aliquots (with infant repositioned between each aliquot). Up to 4 doses may be given in the first 48 hours of life; give no more frequently than every 6 hours [1] . In clinical trials, lucinactant was administered within 20 to 30 minutes after birth [2] [3] .

Administration

Preparation
Prior to administration, warm the lucinactant intratracheal suspension vial for 15 minutes in a preheated dry block heater set at 44 degrees C (111 degrees F). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. After withdrawn into a syringe for administration, the temperature of the suspension will be about 37 degrees C (99 degrees F). Warmed vials should not be refrigerated after warming but may be stored in the carton at room temperature for no more than 2 hours [1] .

Administration
For intratracheal administration only. Using a 16- or 18-gauge needle, slowly draw up the dose of warmed and vigorously shaken lucinactant intratracheal suspension into an appropriately sized syringe [1] .
Before administration of the suspension, ensure patency and proper placement of the endotracheal tube. The endotracheal tube may be suctioned before lucinactant administration if necessary. Allow the infant to stabilize before administration [1] .
The infant should be positioned in the right lateral decubitus position with head and thorax at a 30 degree upward inclined position. A 5-French end-hole catheter with the syringe of lucinactant attached should be threaded through a Bodai valve (or equivalent device) to allow maintenance of positive end-expiratory pressure. The tip of the catheter should be advanced into the endotracheal tube and positioned so that it is slightly distal to the end of the endotracheal tube [1] .
The lucinactant dose should be delivered in 4 equal aliquots (each aliquot equal to one-fourth of the total dose). Administer the first aliquot while continuing positive pressure mechanical ventilation and maintaining a positive end-expiratory pressure of 4 to 5 cm H_2O. Adjust ventilator settings as necessary to maintain appropriate oxygenation and ventilation until the infant is stable (oxygen saturation of at least 90% and heart rate greater than 120 beats/minute) [1] .
Maintain adequate positive pressure ventilation, move the infant to the left decubitus position, and repeat the administration procedure for the second aliquot. Pause between administration of each aliquot to evaluate the infant's respiratory status. Move the infant to the right decubitus position for administration of the third aliquot, and to the left decubitus position for administration of the fourth aliquot [1] .
Remove the catheter after administration of the fourth aliquot, and resume usual ventilator management. Keep the head of the infant's bed elevated at least 10 degrees for at least 1 to 2 hours. Unless the infant develops significant airway obstruction, do not suction the infant for the first hour after dosing [1] .

Uses

Prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS [4] [2] [3] .

Lucinactant reduced the occurrence of RDS among premature neonates (32 weeks gestational age or younger) at high risk for developing RDS more effectively than colfosceril palmitate (47.2% vs 39.1%; p=0.005) and also reduced the number of RDS-related deaths compared with colfosceril palmitate and beractant treatment groups (4.7% vs 9.4% (p=0.002) vs 10.5% (p=0.001), respectively) in a multicenter, randomized comparison trial (n=1294) [3] . Lucinactant and poractant alfa were similar in terms of efficacy in premature infants (24 to 28 weeks gestation) at high risk for developing RDS in a multicenter randomized noninferiority trial (n=252). The rate of survival without BPD at 28 days (primary outcome) was 37.8% vs 33.1%, respectively [2] . In a one-year follow-up of these 2 studies (n=1546), lucinactant had similar efficacy to the animal-derived and synthetic exogenous surfactant products for decreasing mortality and morbidity rates in premature neonates at risk for RDS. Neurologic function was similar in infants who received lucinactant and those that received other surfactants [4] .

Pediatric FDA Approved Indications

Lucinactant intratracheal suspension is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS [1] .

Contraindications/Precautions

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube (ETT) may occur; if reactions occur, interrupt treatment until resolved. Suctioning of the ETT or reintubation may be necessary for persistent airway obstruction. Respiratory status may change rapidly with administration; monitoring recommended, oxygen and ventilatory support modifications may be required [1] .

Pharmacology

Lucinactant is a synthetic, non-pyrogenic pulmonary surfactant which acts like endogenous surfactant by restoring surface activity to the lung of premature infants deficient in pulmonary surfactant. It consists of phospholipids, a fatty acid, and sinapultide (21-amino acid synthetic peptide). No pharmacokinetic data are available regarding the absorption, distribution, metabolism, or elimination of lucinactant [1] .

Adverse Effects

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube are common adverse events. In clinical trials, rates of bradycardia and oxygen desaturation have ranged from 3% to 23% and 8% to 58%, respectively. Endotracheal tube reflux occurred at an incidence of 18% to 27% [1] [5] . The incidence of pulmonary hemorrhage, pulmonary leaks, patent ductus arteriosus, sepsis, intraventricular hemorrhage, necrotizing enterocolitis (grade 2 or higher), retinopathy of prematurity (grade 3 or 4), and periventricular leukomalacia was not significantly different between lucinactant and the comparators in clinical trials [3] [2] .

Monitoring

Monitor oxygen saturation and ventilatory support frequently and modify according to changes in respiratory status [1] .

Special Considerations/Preparation

Available as an intratracheal suspension containing 8.5 mL in a glass vial. Each mL contains 30 mg phospholipids (22.50 mg dipalmitoylphosphatidylcholine and 7.50 mg palmitoyloleoyl-phosphatidylglycerol, sodium salt), 4.05 mg palmitic acid, and 0.862 mg sinapultide. Contains no preservatives; single-use vials only. Store in refrigerator and protect from light; do not freeze [1] .
Prior to administration, warm the lucinactant intratracheal suspension vial for 15 minutes in a preheated dry block heater set at 44 degrees C (111 degrees F). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. After withdrawn into a syringe for administration, the temperature of the suspension will be about 37 degrees C (99 degrees F). Warmed vials should not be refrigerated after warming but may be stored in the carton at room temperature for no more than 2 hours [1] .

References

- Product Information: SURFAXIN(R) intratracheal suspension, lucinactant intratracheal suspension. Discovery Laboratories, Inc. (Per FDA), Warrington, PA, Mar, 2012.

- Sinha SK, Lacaze-Masmonteil T, Valls i Soler A et al: A multicenter, randomized, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics Apr1, 2005; 115(4): 1030-1038.

- Moya FR, Gadzinowski J, Bancalari E et al: A multicenter, randomized, masked, comparison trial of lucinactant, colfosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. Pediatrics Apr1, 2005; 115(4): 1018-1029.

- Moya F, Sinha S, Gadzinowski J et al: One-year follow-up of very preterm infants who received lucinactant for prevention of respiratory distress syndrome: results from 2 multicenter randomized, controlled trials. Pediatrics Jun1, 2007; 119(6): e1361-e1370.

- Laughon M, Bose C, Moya F et al: A pilot randomized, controlled trial of later treatment with a Peptide-containing, synthetic surfactant for the prevention of bronchopulmonary dysplasia. Pediatrics Jan, 2009; 123(1): 89-96.

Title Lucinactant

Dose

Respiratory Distress Syndrome; Prophylaxis
5.8 mL/kg birth weight intratracheally in 4 equal aliquots (with infant repositioned between each aliquot). Up to 4 doses may be given in the first 48 hours of life; give no more frequently than every 6 hours [1] . In clinical trials, lucinactant was administered within 20 to 30 minutes after birth [2] [3] .

Administration

Preparation
Prior to administration, warm the lucinactant intratracheal suspension vial for 15

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For intratracheal administration only. Using a 16- or 18-gauge needle, slowly draw up the dose of warmed and vigorously shaken lucinactant intratracheal suspension into an appropriately sized syringe [1] .
Before administration of the suspension, ensure patency and proper placement of the endotracheal tube. The endotracheal tube may be suctioned before lucinactant administration if necessary. Allow the infant to stabilize before administration [1] .
The infant should be positioned in the right lateral decubitus position with head and thorax at a 30 degree upward inclined position. A 5-French end-hole catheter with the syringe of lucinactant attached should be threaded through a Bodai valve (or equivalent device) to allow maintenance of positive end-expiratory pressure. The tip of the catheter should be advanced into the endotracheal tube and positioned so that it is slightly distal to the end of the endotracheal tube [1] .
The lucinactant dose should be delivered in 4 equal aliquots (each aliquot equal to one-fourth of the total dose). Administer the first aliquot while continuing positive pressure mechanical ventilation and maintaining a positive end-expiratory pressure of 4 to 5 cm H_2O. Adjust ventilator settings as necessary to maintain appropriate oxygenation and ventilation until the infant is stable (oxygen saturation of at least 90% and heart rate greater than 120 beats/minute) [1] .
Maintain adequate positive pressure ventilation, move the infant to the left decubitus position, and repeat the administration procedure for the second aliquot. Pause between administration of each aliquot to evaluate the infant's respiratory status. Move the infant to the right decubitus position for administration of the third aliquot, and to the left decubitus position for administration of the fourth aliquot [1] .
Remove the catheter after administration of the fourth aliquot, and resume usual ventilator management. Keep the head of the infant's bed elevated at least 10 degrees for at least 1 to 2 hours. Unless the infant develops significant airway obstruction, do not suction the infant for the first hour after dosing [1] .

Uses

Prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS [4] [2] [3] .
Lucinactant reduced the occurrence of RDS among premature neonates (32 weeks gestational age or younger) at high risk for developing RDS more effectively than colfosceril palmitate (47.2% vs 39.1%; p=0.005) and also reduced the number of RDS-related deaths compared with colfosceril palmitate and beractant treatment groups (4.7% vs 9.4% (p=0.002) vs 10.5% (p=0.001), respectively) in a multicenter, randomized comparison trial (n=1294) [3] . Lucinactant and poractant alfa were similar in terms of efficacy in premature infants (24 to 28 weeks gestation) at high risk for developing RDS in a multicenter randomized noninferiority trial (n=252). The rate of survival without BPD at 28 days (primary outcome) was 37.8% vs 33.1%, respectively [2] . In a one-year follow-up of these 2 studies (n=1546), lucinactant had similar

efficacy to the animal-derived and synthetic exogenous surfactant products for decreasing mortality and morbidity rates in premature neonates at risk for RDS. Neurologic function was similar in infants who received lucinactant and those that received other surfactants [4] .

Pediatric FDA Approved Indications
Lucinactant intratracheal suspension is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS [1] .

Contraindications/Precautions

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube (ETT) may occur; if reactions occur, interrupt treatment until resolved. Suctioning of the ETT or reintubation may be necessary for persistent airway obstruction. Respiratory status may change rapidly with administration; monitoring recommended, oxygen and ventilatory support modifications may be required [1] .

Pharmacology

Lucinactant is a synthetic, non-pyrogenic pulmonary surfactant which acts like endogenous surfactant by restoring surface activity to the lung of premature infants deficient in pulmonary surfactant. It consists of phospholipids, a fatty acid, and sinapultide (21-amino acid synthetic peptide). No pharmacokinetic data are available regarding the absorption, distribution, metabolism, or elimination of lucinactant [1] .

Adverse Effects

Bradycardia, hypoxemia, airway obstruction, and reflux of drug into the endotracheal tube are common adverse events. In clinical trials, rates of bradycardia and oxygen desaturation have ranged from 3% to 23% and 8% to 58%, respectively. Endotracheal tube reflux occurred at an incidence of 18% to 27% [1] [5] . The incidence of pulmonary hemorrhage, pulmonary leaks, patent ductus arteriosus, sepsis, intraventricular hemorrhage, necrotizing enterocolitis (grade 2 or higher), retinopathy of prematurity (grade 3 or 4), and periventricular leukomalacia was not significantly different between lucinactant and the comparators in clinical trials [3] [2] .

Monitoring

Monitor oxygen saturation and ventilatory support frequently and modify according to changes in respiratory status [1] .

Special Considerations/Preparation

Available as an intratracheal suspension containing 8.5 mL in a glass vial. Each mL contains 30 mg phospholipids (22.50 mg dipalmitoylphosphatidylcholine and 7.50 mg palmitoyloleoyl-phosphatidylglycerol, sodium salt), 4.05 mg palmitic acid, and 0.862 mg sinapultide. Contains no preservatives; single-use vials only. Store in refrigerator and protect from light; do not freeze [1] .
Prior to administration, warm the lucinactant intratracheal suspension vial for 15

minutes in a preheated dry block heater set at 44 degrees C (111 degrees F). Remove the vial from the heater and shake vigorously until the suspension is uniform and free-flowing. After withdrawn into a syringe for administration, the temperature of the suspension will be about 37 degrees C (99 degrees F). Warmed vials should not be refrigerated after warming but may be stored in the carton at room temperature for no more than 2 hours [1] .

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1.109 MCT Oil

Title MCT Oil

Dose

Medium Chain Triglyceride Oil

Medium chain triglycerides (MCT) are lipid fractions of coconut oil consisting of triglycerides with chain lengths of 6 to 10 carbons. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

Pharmacology

Osmolality (mOsm/kg water): Not Available

Supplied: 1 quart glass bottles.

Ingredients: Medium chain triglycerides.

MCT Oil

Nutrient	per mL	per 15 mL (1 tbsp)	per 89 mL (3 fl oz)
Calories	7.7	115	685.3
Protein, g	0	0	0
Fat, g	0.94	14	44.5
Carbohydrate, g	0	0	0
Water, g	0	0	0
Linoleic Acid, g	0.367	5.5	32.63

Fatty Acid Distribution

Shorter than carbon 8	
Caprylic C8:0	67%
Capric C10:0	23%
Longer than C10:0	

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Use within 60 to 90 days after a bottle is opened. Do not store in plastic container. MCT may break or soften plastic containers.

Title MCT Oil

Dose

Medium Chain Triglyceride Oil

Medium chain triglycerides (MCT) are lipid fractions of coconut oil consisting of triglycerides with chain lengths of 6 to 10 carbons. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

Pharmacology

Osmolality (mOsm/kg water): Not Available

Supplied: 1 quart glass bottles.

Ingredients: Medium chain triglycerides.

MCT Oil

Nutrient	per mL	per 15 mL (1 tbsp)	per 89 mL (3 fl oz)
Calories	7.7	115	685.3
Protein, g	0	0	0
Fat, g	0.94	14	44.5
Carbohydrate, g	0	0	0
Water, g	0	0	0
Linoleic Acid, g	0.367	5.5	32.63

Fatty Acid Distribution

Shorter than carbon 8

Caprylic C8:0 67%

Capric C10:0 23%

Longer than C10:0

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Use within 60 to 90 days after a bottle is opened. Do not store in plastic container. MCT may break or soften plastic containers.

1.110 Magnesium sulfate

Title Magnesium sulfate

Dose

Resuscitation (Pulseless Torsades)
25 to 50 mg/kg IV/intraosseous rapid infusion (over several minutes) [1] [2] [3] .

Hypomagnesemia
25 to 50 mg/kg IV infusion over 30 to 60 minutes; repeat dose as necessary [1] [4] [2] . For hypomagnesemia/torsades with pulses, an infusion time of 10 to 20 minutes is recommended [2] .

Daily Maintenance Requirements (Parenteral Nutrition)
0.25 to 0.5 mEq/kg/day IV [5] [6] .

Administration

Must be diluted prior to IV administration (10% to 20% solution (100 to 200 mg/mL)). Give by rapid infusion (over several minutes) for pulseless torsades, over 10 to 20 minutes for hypomagnesemia/torsades with pulses, and over 30 to 60 minutes for hypomagnesemia [7] [2] .

Uses

Treatment of torsades de pointes (polymorphic ventricular tachycardia associated with long QT interval) [1] [2] [8] .

Treatment and prevention of hypomagnesemia [7] [2] [6] .

Contraindications/Precautions

Contraindicated in patients with heart block or myocardial damage. Hypotension and bradycardia may occur with rapid infusion. Calcium chloride should be available to reverse magnesium toxicity. Use with caution in patients with renal impairment since magnesium sulfate is eliminated renally. Respiratory depression may occur from high magnesium levels. Contains aluminum which may be toxic, especially in premature neonates and patients with renal impairment [7] .

Pharmacology

Magnesium is a cation of the intracellular fluid that is necessary for the activity of many enzyme systems and plays an important role in neurochemical transmission and muscular excitability. Approximately 99% of total body magnesium is in the intracellular compartment (bone, 85%; soft tissue and liver, 14%) and only 1% is present in the extracellular fluid. Because of this, serum concentrations do not adequately reflect total body magnesium stores. Most of the filtered magnesium (95%) is reabsorbed by the kidney. Magnesium deficiency leads to varied structural and functional abnormalities [9] [7] .
Signs of hypomagnesemia include tetany, cardiac arrhythmia, decreased bone stability, apathy, and increased susceptibility to epileptic seizures. Magnesium deficiency is associated with hypocalcemia, hypokalemia, hypophosphatemia, decreased urinary magnesium and calcium levels, and decreased magnesium levels in cerebrospinal fluid, bone, muscle, and hematopoietic cells [11] [12] .

Adverse Effects

Flushing, sweating, hypothermia, and stupor may occur [7] .
Low calcium levels or bone problems, including osteopenia or fractures, may occur in developing baby or fetus following prolonged use (greater than 5 to 7 days) of magnesium sulfate for stopping pre-term labor in pregnant mothers [10] .

Monitoring

Monitor serum and urinary magnesium levels [9] [7] . Assess other electrolytes (calcium, potassium, phosphorus) and renal function periodically.

Special Considerations/Preparation

Supplied as 50% concentration in 2-, 10-, and 50-mL single dose vials containing 500 mg/mL of magnesium sulfate which provides 4.06 mEq each of magnesium and sulfate. Osmolarity is 4.06 mOsm/mL; pH range of 5.5 to 7 [7] [13] .

Solution Compatibility

D_5W, NS, LR, and Dex/AA solutions.

Solution Incompatibility

Fat emulsion.

Terminal Injection Site Compatibility

Acyclovir, amikacin, ampicillin, aztreonam, cefazolin, cefotaxime, cefoxitin, chloramphenicol, clindamycin, dobutamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, gentamicin, heparin sodium, hydrocortisone sodium succinate, insulin, linezolid, meropenem, metoclopramide, metronidazole, micafungin, milrinone, morphine, nafcillin, nicardipine, ondansetron, oxacillin, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Amiodarone, amphotericin B, calcium chloride, cefepime, pantoprazole, and sodium bicarbonate.

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- Product Information: magnesium sulfate IV injection, magnesium sulfate IV injection. Hospira,Inc, Lake Forest, IL, Feb1, 2006.

Title Magnesium sulfate

Dose

Resuscitation (Pulseless Torsades)
25 to 50 mg/kg IV/intraosseous rapid infusion (over several minutes) [1] [2] [3] .

Hypomagnesemia
25 to 50 mg/kg IV infusion over 30 to 60 minutes; repeat dose as necessary [1] [4] [2] .
For hypomagnesemia/torsades with pulses, an infusion time of 10 to 20 minutes is recommended [2] .

Daily Maintenance Requirements (Parenteral Nutrition)
0.25 to 0.5 mEq/kg/day IV [5] [6] .

Administration

Must be diluted prior to IV administration (10% to 20% solution (100 to 200 mg/mL)). Give by rapid infusion (over several minutes) for pulseless torsades, over 10 to 20

minutes for hypomagnesemia/torsades with pulses, and over 30 to 60 minutes for hypomagnesemia [7] [2] .

Uses

Treatment of torsades de pointes (polymorphic ventricular tachycardia associated with long QT interval) [1] [2] [8] .

Treatment and prevention of hypomagnesemia [7] [2] [6] .

Contraindications/Precautions

Contraindicated in patients with heart block or myocardial damage. Hypotension and bradycardia may occur with rapid infusion. Calcium chloride should be available to reverse magnesium toxicity. Use with caution in patients with renal impairment since magnesium sulfate is eliminated renally. Respiratory depression may occur from high magnesium levels. Contains aluminum which may be toxic, especially in premature neonates and patients with renal impairment [7] .

Pharmacology

Magnesium is a cation of the intracellular fluid that is necessary for the activity of many enzyme systems and plays an important role in neurochemical transmission and muscular excitability. Approximately 99% of total body magnesium is in the intracellular compartment (bone, 85%; soft tissue and liver, 14%) and only 1% is present in the extracellular fluid. Because of this, serum concentrations do not adequately reflect total body magnesium stores. Most of the filtered magnesium (95%) is reabsorbed by the kidney. Magnesium deficiency leads to varied structural and functional abnormalities [9] [7] .
Signs of hypomagnesemia include tetany, cardiac arrhythmia, decreased bone stability, apathy, and increased susceptibility to epileptic seizures. Magnesium deficiency is associated with hypocalcemia, hypokalemia, hypophosphatemia, decreased urinary magnesium and calcium levels, and decreased magnesium levels in cerebrospinal fluid, bone, muscle, and hematopoietic cells [11] [12] .

Adverse Effects

Flushing, sweating, hypothermia, and stupor may occur [7] .
Low calcium levels or bone problems, including osteopenia or fractures, may occur in developing baby or fetus following prolonged use (greater than 5 to 7 days) of magnesium sulfate for stopping pre-term labor in pregnant mothers [10] .

Monitoring

Monitor serum and urinary magnesium levels [9] [7] . Assess other electrolytes (calcium, potassium, phosphorus) and renal function periodically.

Special Considerations/Preparation

Supplied as 50% concentration in 2-, 10-, and 50-mL single dose vials containing 500 mg/mL of magnesium sulfate which provides 4.06 mEq each of magnesium and sulfate. Osmolarity is 4.06 mOsm/mL; pH range of 5.5 to 7 [7] [13] .

Solution Compatibility

D_5W, NS, LR, and Dex/AA solutions.

Solution Incompatibility

Fat emulsion.

Terminal Injection Site Compatibility

Acyclovir, amikacin, ampicillin, aztreonam, cefazolin, cefotaxime, cefoxitin, chloramphenicol, clindamycin, dobutamine, enalaprilat, erythromycin lactobionate, esmolol, famotidine, gentamicin, heparin sodium, hydrocortisone sodium succinate, insulin, linezolid, meropenem, metoclopramide, metronidazole, micafungin, milrinone, morphine, nafcillin, nicardipine, ondansetron, oxacillin, penicillin G potassium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Amiodarone, amphotericin B, calcium chloride, cefepime, pantoprazole, and sodium bicarbonate.

References

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- Hoshino K, Ogawa K, Hishitani T et al: Successful uses of magnesium sulfate for torsades de pointes in children with long QT syndrome. Pediatr Int 04/00/2006; 48(2): 112-117.

- Assadi F: Hypomagnesemia: an evidence-based approach to clinical cases. Iran J Kidney Dis Jan, 2010; 4(1): 13-19.

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- Haque A: On admission hypomagnesemia in critically ill children: Risk factors and outcome. Indian J Pediatr Dec, 2009; 76(12): 1227-1230.

- Juan D: Clinical review: the clinical importance of hypomagnesemia. Surgery May, 1982; 91(5): 510-517.

- Product Information: magnesium sulfate IV injection, magnesium sulfate IV injection. Hospira,Inc, Lake Forest, IL, Feb1, 2006.

1.111 Meropenem

Title Meropenem

Dose

Intra-abdominal and non-CNS infections
Less than 32 weeks GA and less than 14 days PNA: 20 mg/kg IV every 12 hours [1] [2] .
Less than 32 weeks GA and 14 days PNA and older: 20 mg/kg IV every 8 hours [1] [2] .
32 weeks GA and older, and less than 14 days PNA: 20 mg/kg IV every 8 hours [1] [2] .
32 weeks GA and older, and 14 days PNA and older: 30 mg/kg IV every 8 hours [1] [2] .
Consider concomitant use of an aminoglycoside antibiotic [1] .

Bacterial Meningitis
Data regarding appropriate dosing for CNS infections are lacking [2] . Consider 40 mg/kg/dose at the recommended age-specific dosing interval [3] [4]
Less than 32 weeks GA and less than 14 days PNA: every 12 hours [2] .
Less than 32 weeks GA and 14 days PNA and older: every 8 hours [2] .
32 weeks GA and older: every 8 hours [2] .

Administration

Administer as an IV infusion over 30 minutes at a concentration of 1 to 20 mg/mL [2] [5] .

Uses

Treatment of suspected or complicated intra-abdominal infections [1] , or other serious infections caused by susceptible Gram-negative organisms resistant to other antibiotics [6] [7] [8] . May be useful in treating neonates with meningitis, however, data are lacking.

Pediatric FDA Approved Indications
Treatment of complicated skin/skin structure infections due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, *S agalactiae*, viridans group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species in pediatric patients 3 months and older [9] .
Treatment of intra-abdominal infections [10] including complicated appendicitis and peritonitis caused by viridans group streptococci, *E. coli*, *Klebsiella pneumoniae*, *P aeruginosa*, *B fragilis*, *B thetaiotaomicron*, and *Peptostreptococcus* species in pediatric patients 3 months and older [9] . Meropenem is considered an appropriate single agent for pediatric patients with a complicated extra-biliary intra-abdominal infection [10]
Treatment of bacterial meningitis caused by *S pneumoniae*, *Haemophilus influenzae* , and *Neisseria meningitidis* in pediatric patients 3 months and older [9] .

Contraindications/Precautions

Contraindicated in patients with known hypersensitivity to carbapenems or previous anaphylactic reactions to beta-lactams. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams; these reactions are more likely to occur in those with a history of hypersensitivity to other beta-lactams or to multiple allergens. Before initiating therapy, obtain a detailed history of previous hypersensitivity reactions [9] .
Seizures and other CNS adverse events have been reported with meropenem therapy; these occurred mainly in patients with CNS disorders (eg, brain lesions or history of seizures) or patients with bacterial meningitis and/or compromised renal function [9] .

Pharmacology

Meropenem is a broad-spectrum carbapenem antibiotic that penetrates well into the CSF and most body tissues. It exhibits time-dependent killing of Gram-negative and Gram-positive pathogens, and the goal of therapy is to keep free drug concentrations above the MIC for at least 40% of the dosing interval. It is relatively stable to inactivation by human renal dehydropeptidase. Plasma protein binding is minimal. Clearance is directly related to renal function, and 70% of a dose is recovered intact in the urine. Hepatic function does not affect pharmacokinetics. Serum half-life of meropenem is 3 hours in preterm and 2 hours in full term neonates.

Adverse Effects

Diarrhea (4%), nausea/vomiting (1%) and rash (2%). May cause inflammation at the injection site. The use of carbapenem antibiotics can result in the development of cephalosporin resistance in *Enterobacter*, *Pseudomonas*, *Serratia*, *Proteus*, *Citrobacter*, and *Acinetobacter* species. The risks of pseudomembranous colitis and fungal infections are also increased.

Monitoring

Periodic CBC (for thrombocytosis and eosinophilia) and hepatic transaminases. Assess IV site for signs of inflammation.

Special Considerations/Preparation

Available (USA) as powder for injection in 500-mg, and 1000-mg vials. Reconstitute with 10 mL of compatible diluent (500 mg vial) or 20 ml (1000 mg vial). When reconstituted with sterile water for injection, stable for up to 2 hours at room temperature or up to 12 hours when refrigerated. When reconstituted with NS to a final concentration between 2.5 to 50 mg/mL, the solution is stable for up to 2 hours at room temperature or 18 hours when refrigerated. When reconstituted with D_5W to final concentration between 2.5 to 50 mg/mL, the solution is stable for up to 1 hour at room temperature or 8 hours when refrigerated. Solutions prepared in sterile water for injection or NS at concentrations of 1 to 20 mg/mL are stable in plastic syringes for up to 48 hours when refrigerated. Solutions prepared in D_5W at concentrations of 1 to 20 mg/mL are stable in plastic syringes for up to 6 hours when refrigerated. Solutions prepared for infusion in NS at concentrations of 1 to 20 mg/mL are stable in plastic IV bags for 4 hours at room temperature or 24 hours when refrigerated. Solutions prepared for infusion in D_5W at concentrations of 1 to 20 mg/mL are stable in plastic IV bags for 1 hour at room temperature or 4 hours when refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Aminophylline, atropine, caspofungin, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, fluconazole, furosemide, gentamicin, heparin, insulin, linezolid, metoclopramide, milrinone, morphine, norepinephrine, phenobarbital, potassium chloride, ranitidine, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, calcium gluconate, metronidazole, sodium bicarbonate, and zidovudine.

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10. Solomkin JS, Mazuski JE, Bradley JS et al: Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis Jan15, 2010; 50(2): 133-164.

Title Meropenem

Dose

Intra-abdominal and non-CNS infections

Less than 32 weeks GA and less than 14 days PNA: 20 mg/kg IV every 12 hours [1] [2] .

Less than 32 weeks GA and 14 days PNA and older: 20 mg/kg IV every 8 hours [1] [2] .

32 weeks GA and older, and less than 14 days PNA: 20 mg/kg IV every 8 hours [1] [2] .
32 weeks GA and older, and 14 days PNA and older: 30 mg/kg IV every 8 hours [1] [2] .
Consider concomitant use of an aminoglycoside antibiotic [1] .

Bacterial Meningitis
Data regarding appropriate dosing for CNS infections are lacking [2] . Consider 40 mg/kg/dose at the recommended age-specific dosing interval [3] [4]
Less than 32 weeks GA and less than 14 days PNA: every 12 hours [2] .
Less than 32 weeks GA and 14 days PNA and older: every 8 hours [2] .
32 weeks GA and older: every 8 hours [2] .

Administration

Administer as an IV infusion over 30 minutes at a concentration of 1 to 20 mg/mL [2] [5] .

Uses

Treatment of suspected or complicated intra-abdominal infections [1] , or other serious infections caused by susceptible Gram-negative organisms resistant to other antibiotics [6] [7] [8] . May be useful in treating neonates with meningitis, however, data are lacking.

Pediatric FDA Approved Indications
Treatment of complicated skin/skin structure infections due to *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, *S agalactiae*, viridans group streptococci, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and *Peptostreptococcus* species in pediatric patients 3 months and older [9] .
Treatment of intra-abdominal infections [10] including complicated appendicitis and peritonitis caused by viridans group streptococci, *E. coli*, *Klebsiella pneumoniae*, *P aeruginosa*, *B fragilis*, *B thetaiotaomicron*, and *Peptostreptococcus* species in pediatric patients 3 months and older [9] . Meropenem is considered an appropriate single agent for pediatric patients with a complicated extra-biliary intra-abdominal infection [10]
Treatment of bacterial meningitis caused by *S pneumoniae*, *Haemophilus influenzae* , and *Neisseria meningitidis* in pediatric patients 3 months and older [9] .

Contraindications/Precautions

Contraindicated in patients with known hypersensitivity to carbapenems or previous anaphylactic reactions to beta-lactams. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams; these reactions are more likely to occur in those with a history of hypersensitivity to other beta-lactams or to multiple allergens. Before initiating therapy, obtain a detailed history of previous hypersensitivity reactions [9] .
Seizures and other CNS adverse events have been reported with meropenem therapy; these occurred mainly in patients with CNS disorders (eg, brain lesions or history of seizures) or patients with bacterial meningitis and/or compromised renal function [9] .

Pharmacology

Meropenem is a broad-spectrum carbapenem antibiotic that penetrates well into the CSF and most body tissues. It exhibits time-dependent killing of Gram-negative and Gram-positive pathogens, and the goal of therapy is to keep free drug concentrations above the MIC for at least 40% of the dosing interval. It is relatively stable to inactivation by human renal dehydropeptidase. Plasma protein binding is minimal. Clearance is directly related to renal function, and 70% of a dose is recovered intact in the urine. Hepatic function does not affect pharmacokinetics. Serum half-life of meropenem is 3 hours in preterm and 2 hours in full term neonates.

Adverse Effects

Diarrhea (4%), nausea/vomiting (1%) and rash (2%). May cause inflammation at the injection site. The use of carbapenem antibiotics can result in the development of cephalosporin resistance in *Enterobacter*, *Pseudomonas*, *Serratia*, *Proteus*, *Citrobacter*, and *Acinetobacter* species. The risks of pseudomembranous colitis and fungal infections are also increased.

Monitoring

Periodic CBC (for thrombocytosis and eosinophilia) and hepatic transaminases. Assess IV site for signs of inflammation.

Special Considerations/Preparation

Available (USA) as powder for injection in 500-mg, and 1000-mg vials. Reconstitute with 10 mL of compatible diluent (500 mg vial) or 20 ml (1000 mg vial). When reconstituted with sterile water for injection, stable for up to 2 hours at room temperature or up to 12 hours when refrigerated. When reconstituted with NS to a final concentration between 2.5 to 50 mg/mL, the solution is stable for up to 2 hours at room temperature or 18 hours when refrigerated. When reconstituted with D_5W to final concentration between 2.5 to 50 mg/mL, the solution is stable for up to 1 hour at room temperature or 8 hours when refrigerated. Solutions prepared in sterile water for injection or NS at concentrations of 1 to 20 mg/mL are stable in plastic syringes for up to 48 hours when refrigerated. Solutions prepared in D_5W at concentrations of 1 to 20 mg/mL are stable in plastic syringes for up to 6 hours when refrigerated. Solutions prepared for infusion in NS at concentrations of 1 to 20 mg/mL are stable in plastic IV bags for 4 hours at room temperature or 24 hours when refrigerated. Solutions prepared for infusion in D_5W at concentrations of 1 to 20 mg/mL are stable in plastic IV bags for 1 hour at room temperature or 4 hours when refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Aminophylline, atropine, caspofungin, cimetidine, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, fluconazole, furosemide, gentamicin, heparin, insulin, linezolid, metoclopramide, milrinone, morphine, norepinephrine, phenobarbital, potassium chloride, ranitidine, and vancomycin.

Terminal Injection Site Incompatibility

Acyclovir, amphotericin B, calcium gluconate, metronidazole, sodium bicarbonate, and zidovudine.

References

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- Patel PR: Compatibility of meropenem with commonly used injectable drugs. *Am J Health-Syst Pharm* 1996;53:2853-55.
- Product Information: Merrem® meropenem for injection, AstraZeneca, 2009.
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2. Smith PB, Cohen-Wolkowiez M, Castro LM et al: Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J Oct, 2011; 30(10): 844-849.
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4. Bradley JS, Sauberan JB, Ambrose PG et al: Meropenem pharmacokinetics, pharmacodynamics, and Monte Carlo simulation in the neonate. Pediatr Infect Dis J Sep, 2008; 27(9): 794-799.
5. Product Information: MERREM(R) IV injection, meropenem IV injection. AstraZeneca, Wilmington, DE, Jul, 2009.
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8. Ondrusova A, Kalavsky E, Rudinsky B et al: Pseudomonas aeruginosa causing nosocomial meningitis in neonates and children: overview of 15 cases within 10 years. Neuro Endocrinol Lett Jun, 2007; 28 Suppl 2: 20-21.

9. Product Information: MERREM(R) intravenous injection, meropenem intravenous injection. AstraZeneca Pharmaceuticals LP (per FDA), Wilmington, DE, Mar, 2013.
10. Solomkin JS, Mazuski JE, Bradley JS et al: Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis Jan15, 2010; 50(2): 133-164.

1.112 Methadone

Title Methadone

Dose

Neonatal Abstinence Syndrome
Initial dose: 0.05 to 0.1 mg/kg per dose orally every 6 to 24 hours [1] [2] [3] [4] [5] . Adjust dose (in 10% to 20% increments) and weaning schedule based on signs and symptoms of withdrawal [2] [4] .

Uses

Treatment of neonatal abstinence syndrome [1] [2] [6] [3] [5] [4] [7] .

Contraindications/Precautions

Contraindicated in patients with a paralytic ileus [8] .

Black Box Warning According to the manufacturer's black box warning, deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, deaths appear to have occurred due to respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Respiratory depression is the chief hazard associated with methadone, and its peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed (in adults). Most cases involve (adult) patients being treated for pain with large, multiple daily doses, although cases have been reported in patients receiving doses used for maintenance treatment of opioid addiction. Special requirements for dispensing exist, and the oral solution must not be injected.

Pharmacology

Long-acting narcotic analgesic. Oral bioavailability is 50%, with peak plasma levels obtained in 2 to 4 hours. Metabolized extensively via hepatic N-demethylation. Highly protein bound (90% adults). Serum half-life ranges from 16 to 25 hours in neonates and is prolonged in patients with renal failure. Rifampin and phenytoin accelerate the metabolism of methadone and can precipitate withdrawal symptoms.

Adverse Effects

Respiratory depression in excessive doses. Ileus and delayed gastric emptying. In a single case report, QTc prolongation was noted in a term infant born to a mother receiving methadone maintenance therapy (50 mg/day). After birth, the infant's resting HR was 80 to 90 beats per minute and ECG showed a QTc of 510 msec. This resolved spontaneously over 5 days [9] .

Monitoring

Monitor respiratory and cardiac status closely. A 12-lead ECG should be obtained on methadone-exposed infants experiencing bradycardia or tachycardia [8] [9] . Assess for gastric residuals, abdominal distention, and loss of bowel sounds. For infants experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1] [6] .

Special Considerations/Preparation

Available as oral solutions in 1- and 2-mg/mL concentrations containing 8% alcohol, and a 10-mg/mL alcohol-free solution. May dilute 1 mL of the 10-mg/mL concentrated solution with 19 mL of sterile water to provide an oral dilution with a final concentration of 0.5 mg/mL. Stable for 24 hours refrigerated. Also available as 5- and 10-mg tablets.

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Atropine sulfate, dexamethasone, lorazepam, metoclopramide, midazolam, and phenobarbital.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Guo J, Greenberg M, Finer NN, Heldt GP: Methadone is a superior detoxification agent compared to tincture opium for treatment of neonatal narcotic abstinence syndrome (NAS). Abstract 4850.230, 2006 Pediatric Academic Societies Annual Meeting.
- Tobias JD, Schleien CL, Haun SE: Methadone as treatment for iatrogenic narcotic dependency in pediatric intensive care unit patients. *Crit Care Med* 1990;18:1292.
- Koren G, Maurice L: Pediatric uses of opioids. *Ped Clin North Am* 1989;36:1141.
- Rosen TS, Pippenger CE: Pharmacologic observations on the neonatal withdrawal syndrome. *J Pediatr* 1976;88:1044.
- Product Information, Roxane, 2007.

1. Hudak ML: Neonatal Drug Withdrawal. Pediatrics Feb, 2012; 129(2): e540-e560.
2. Burgos AE: Neonatal Abstinence Syndrome. Neoreviews 2009; 10(5): e222-e229.

3. Anand KJ: Pharmacological approaches to the management of pain in the neonatal intensive care unit. J Perinatol May, 2007; 27(Suppl 1): S4-S11.
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9. Hussain T: Maternal methadone may cause arrhythmias in neonates. Acta Paediatr May, 2007; 96(5): 768-769.

Uses, Compatibilities, and References updated 7/2009
Adverse Effects/Precautions, Monitoring and References updated 3/2009
Added 1/1995

Title Methadone

Dose

Neonatal Abstinence Syndrome
Initial dose: 0.05 to 0.1 mg/kg per dose orally every 6 to 24 hours [1] [2] [3] [4] [5] . Adjust dose (in 10% to 20% increments) and weaning schedule based on signs and symptoms of withdrawal [2] [4] .

Uses

Treatment of neonatal abstinence syndrome [1] [2] [6] [3] [5] [4] [7] .

Contraindications/Precautions

Contraindicated in patients with a paralytic ileus [8] .

Black Box Warning According to the manufacturer's black box warning, deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, deaths appear to have occurred due to respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Respiratory depression is the chief hazard associated with methadone, and its peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed (in adults). Most cases involve (adult) patients being treated for pain with large, multiple daily doses, although cases have been reported in patients receiving doses used for maintenance

treatment of opioid addiction. Special requirements for dispensing exist, and the oral solution must not be injected.

Pharmacology

Long-acting narcotic analgesic. Oral bioavailability is 50%, with peak plasma levels obtained in 2 to 4 hours. Metabolized extensively via hepatic N-demethylation. Highly protein bound (90% adults). Serum half-life ranges from 16 to 25 hours in neonates and is prolonged in patients with renal failure. Rifampin and phenytoin accelerate the metabolism of methadone and can precipitate withdrawal symptoms.

Adverse Effects

Respiratory depression in excessive doses. Ileus and delayed gastric emptying. In a single case report, QTc prolongation was noted in a term infant born to a mother receiving methadone maintenance therapy (50 mg/day). After birth, the infant's resting HR was 80 to 90 beats per minute and ECG showed a QTc of 510 msec. This resolved spontaneously over 5 days [9] .

Monitoring

Monitor respiratory and cardiac status closely. A 12-lead ECG should be obtained on methadone-exposed infants experiencing bradycardia or tachycardia [8] [9] . Assess for gastric residuals, abdominal distention, and loss of bowel sounds. For infants experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1] [6] .

Special Considerations/Preparation

Available as oral solutions in 1- and 2-mg/mL concentrations containing 8% alcohol, and a 10-mg/mL alcohol-free solution. May dilute 1 mL of the 10-mg/mL concentrated solution with 19 mL of sterile water to provide an oral dilution with a final concentration of 0.5 mg/mL. Stable for 24 hours refrigerated. Also available as 5- and 10-mg tablets.

Solution Compatibility

NS.

Terminal Injection Site Compatibility

Atropine sulfate, dexamethasone, lorazepam, metoclopramide, midazolam, and phenobarbital.

Terminal Injection Site Incompatibility

Phenytoin.

References

- Guo J, Greenberg M, Finer NN, Heldt GP: Methadone is a superior detoxification agent compared to tincture opium for treatment of neonatal narcotic abstinence syndrome (NAS). Abstract 4850.230, 2006 Pediatric Academic Societies Annual Meeting.
- Tobias JD, Schleien CL, Haun SE: Methadone as treatment for iatrogenic narcotic dependency in pediatric intensive care unit patients. *Crit Care Med* 1990;18:1292.
- Koren G, Maurice L: Pediatric uses of opioids. *Ped Clin North Am* 1989;36:1141.
- Rosen TS, Pippenger CE: Pharmacologic observations on the neonatal withdrawal syndrome. *J Pediatr* 1976;88:1044.
- Product Information, Roxane, 2007.

1. Hudak ML: Neonatal Drug Withdrawal. Pediatrics Feb, 2012; 129(2): e540-e560.
2. Burgos AE: Neonatal Abstinence Syndrome. Neoreviews 2009; 10(5): e222-e229.
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5. Wunsch MJ: A chart review comparing paregoric to methadone in the treatment of neonatal opioid withdrawal. J Addict Dis 2006; 25(3): 27-33.
6. Jansson LM: The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag Jan, 2009; 5(1): 47-55.
7. Calabrese JR: The neonatal narcotic abstinence syndrome: a brief review. Can J Psychiatry Dec, 1985; 30(8): 623-626.
8. Krantz MJ, Martin J, Stimmel B et al: QTc interval screening in methadone treatment. Ann Intern Med Mar17, 2009; 150(6): 387-95.
9. Hussain T: Maternal methadone may cause arrhythmias in neonates. Acta Paediatr May, 2007; 96(5): 768-769.

Uses, Compatibilities, and References updated 7/2009
Adverse Effects/Precautions, Monitoring and References updated 3/2009
Added 1/1995

1.113 Metoclopramide

Title Metoclopramide

Dose

0.033 to 0.1 mg/kg/dose orally or IV slow push every 8 hours.

Uses

To facilitate gastric emptying and gastrointestinal motility. May improve feeding intolerance. Use in gastroesophageal reflux patients is controversial.
(Also used to enhance lactation--10 mg every 8 hours.)

Black Box Warning Metoclopramide can cause tardive dyskinesia. The risk increases with duration of treatment and total cumulative dose. Discontinue drug in patients who develop signs or symptoms of tardive dyskinesia. Treatment with metoclopramide for longer than 12

weeks should be avoided except in rare cases where therapeutic benefit outweighs the risk of developing tardive dyskinesia.

Pharmacology

Derivative of procainamide. Exact mode of action is unknown; however, metoclopramide has both dopamine-receptor blocking activity and peripheral cholinergic effects. Well absorbed from gastrointestinal tract. Variable first-pass metabolism by liver. Significant fraction excreted unchanged in urine. Lipid-soluble, large volume of distribution. Serum half-life in adults is 4 hours; prolonged in patients with renal failure.

Adverse Effects

Intended for short-term use (several weeks). Dystonic reactions and extrapyramidal symptoms are seen frequently at higher doses and with prolonged use; children are more susceptible than adults.

Monitoring

Measure gastric residuals. Observe for increased irritability or vomiting.

Special Considerations/Preparation

Available as a 5-mg/mL injectable solution (osmolarity 280 mOsm/kg). **Protect from light.**A 0.1 mg/mL dilution may be made by adding 0.4 mL of the 5-mg/mL concentration to 19.6 mL of preservative-free NS. Dilution is stable for 24 hours at room temperature.

Oral preparation available in 1-mg/mL concentration. A 0.1 mg/mL oral dilution may be made by adding 1 mL of the 1-mg/mL concentration to 9 mL simple syrup. Stable for 4 weeks at room temperature.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, atropine, aztreonam, caffeine citrate, cimetidine, ciprofloxacin, clindamycin, dexamethasone, famotidine, fentanyl, fluconazole, heparin, hydrocortisone, lidocaine, linezolid, meropenem, methadone, midazolam, morphine, multivitamins, piperacillin/tazobactam, potassium chloride, potassium phosphate, prostaglandin E_1, quinupristin-dalfopristin, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, calcium gluconate, cefepime, chloramphenicol, erythromycin lactobionate, furosemide, penicillin G, propofol, and sodium bicarbonate.

References

- Meadow WL, Bui K, Strates E, et al: Metoclopramide promotes enteral feeding in preterm infants with feeding intolerance. *Dev Pharmacol Ther* 1989;13:38.
- Machida HM, Forbes DA, Gall DG, et al: Metoclopramide in gastroesophageal reflux of infancy. *J Pediatr* 1988;112:483.
- Ehrenkranz RA, Ackerman BA: Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics* 1986;78:614.
- Sankaran K, Yeboah E, Bingham WT, Ninan A: Use of metoclopramide in premature infants. *Dev Pharmacol Ther* 1982;5:114.
- Product Information, Baxter, 2004.

Title Metoclopramide

Dose

0.033 to 0.1 mg/kg/dose orally or IV slow push every 8 hours.

Uses

To facilitate gastric emptying and gastrointestinal motility. May improve feeding intolerance. Use in gastroesophageal reflux patients is controversial.
(Also used to enhance lactation--10 mg every 8 hours.)

Black Box Warning Metoclopramide can cause tardive dyskinesia. The risk increases with duration of treatment and total cumulative dose. Discontinue drug in patients who develop signs or symptoms of tardive dyskinesia. Treatment with metoclopramide for longer than 12 weeks should be avoided except in rare cases where therapeutic benefit outweighs the risk of developing tardive dyskinesia.

Pharmacology

Derivative of procainamide. Exact mode of action is unknown; however, metoclopramide has both dopamine-receptor blocking activity and peripheral cholinergic effects. Well absorbed from gastrointestinal tract. Variable first-pass metabolism by liver. Significant fraction excreted unchanged in urine. Lipid-soluble, large volume of distribution. Serum half-life in adults is 4 hours; prolonged in patients with renal failure.

Adverse Effects

Intended for short-term use (several weeks). Dystonic reactions and extrapyramidal symptoms are seen frequently at higher doses and with prolonged use; children are more susceptible than adults.

Monitoring

Measure gastric residuals. Observe for increased irritability or vomiting.

Special Considerations/Preparation

Available as a 5-mg/mL injectable solution (osmolarity 280 mOsm/kg). **Protect from light.**A 0.1 mg/mL dilution may be made by adding 0.4 mL of the 5-mg/mL concentration to 19.6 mL of preservative-free NS. Dilution is stable for 24 hours at room temperature.

Oral preparation available in 1-mg/mL concentration. A 0.1 mg/mL oral dilution may be made by adding 1 mL of the 1-mg/mL concentration to 9 mL simple syrup. Stable for 4 weeks at room temperature.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, atropine, aztreonam, caffeine citrate, cimetidine, ciprofloxacin, clindamycin, dexamethasone, famotidine, fentanyl, fluconazole, heparin, hydrocortisone, lidocaine, linezolid, meropenem, methadone, midazolam, morphine, multivitamins, piperacillin/tazobactam, potassium chloride, potassium phosphate, prostaglandin E_1, quinupristin-dalfopristin, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, calcium gluconate, cefepime, chloramphenicol, erythromycin lactobionate, furosemide, penicillin G, propofol, and sodium bicarbonate.

References

- Meadow WL, Bui K, Strates E, et al: Metoclopramide promotes enteral feeding in preterm infants with feeding intolerance. *Dev Pharmacol Ther* 1989;13:38.
- Machida HM, Forbes DA, Gall DG, et al: Metoclopramide in gastroesophageal reflux of infancy. *J Pediatr* 1988;112:483.
- Ehrenkranz RA, Ackerman BA: Metoclopramide effect on faltering milk production by mothers of premature infants. *Pediatrics* 1986;78:614.
- Sankaran K, Yeboah E, Bingham WT, Ninan A: Use of metoclopramide in premature infants. *Dev Pharmacol Ther* 1982;5:114.
- Product Information, Baxter, 2004.

1.114 MetroNIDAZOLE

Title MetroNIDAZOLE

Dose

Loading dose: 15 mg/kg orally or IV infusion by syringe pump over 60 minutes.
Maintenance dose: 7.5 mg/kg/dose orally or IV infusion over 60 minutes. Begin one dosing interval after initial dose.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	Postnatal (days)	Interval (hours)
≤29	0 to 28	48
	>28	24
30 to 36	0 to 14	24
	>14	12
37 to 44	0 to 7	24
	>7	12
≥45	ALL	8

Uses

Reserved for treatment of meningitis, ventriculitis, and endocarditis caused by *Bacteroides fragilis* and other anaerobes resistant to penicillin; treatment of serious intra-abdominal infections; and treatment of infections caused by *Trichomonas vaginalis.*Treatment of *C. difficile* colitis.

Black Box Warning According to the manufacturer's black box warning, metronidazole has been shown to be carcinogenic in mice and rats.

Pharmacology

Metronidazole is bactericidal for many anaerobic organisms. The drug exhibits concentration-dependent bactericidal activity with a post-antibiotic effect of greater than 3 hours. It is well absorbed after oral administration, with peak serum concentrations attained in 1 to 3 hours. Distribution in all tissues throughout the body is excellent. It is less than 20% protein bound. Hydroxylation in the liver occurs in term infants and premature infants exposed to antenatal betamethasone. Unchanged drug and the active metabolite are excreted renally. Elimination half-life is strongly related to gestational age, ranging from 22 to 109 hours.

Adverse Effects

Seizures and sensory polyneuropathy have been reported in a few adult patients receiving high doses over a prolonged period. Drug metabolites may cause brownish discoloration of the urine.

Monitoring

Measure CSF drug concentrations when treating CNS infections. Trough drug concentration should be greater than minimum inhibitory concentration for organism.

Special Considerations/Preparation

Available in 5 mg/mL concentration in 100 mL single-dose plastic ready-to-use solution containers. **Protect from light** until use and store at controlled room temperature. **Do not refrigerate**(crystals form, but redissolve on warming to room temperature). Osmolarity is 297 mOsm/L, pH is 4.5 to 7. Each container contains 13.5 mEq of sodium.

Supplied as 250-mg and 500-mg tablets for oral administration. Suspension may be prepared by crushing five 250-mg tablets (1250 mg), dissolving powder in 10 mL purified water, then adding cherry syrup to make a total volume of 83 mL. Final concentration is 15 mg/mL. **Protect from light.** Shake well. Suspension is stable for 30 days refrigerated.

Solution Compatibility

D_5W, and NS.

Solution Incompatibility

Manufacturer recommends that if metronidazole is used with a primary IV fluid system, the primary solution should be discontinued during metronidazole infusion.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, ampicillin, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, gentamicin, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin-tazobactam, prostaglandin E_1, remifentanil, and tobramycin.

Terminal Injection Site Incompatibility

Aztreonam and meropenem.

References

- Lamp KC, Freeman CD, Klutman NE, Lacy MK: Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999;36:353-373.
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- Allen LV, Errickson MA: Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, spironolactone in extemporaneously compounded oral liquids. *Am J Health Syst Pharm* 1996;53:2073-2078.
- Feder HM Jr: *Bacteroides fragilis* meningitis. *Rev Infect Dis* 1987;9:783.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p 76.
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- Jager-Roman E, Doyle PE, Baird-Lambert J, et al: Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982;100:651.
- Product Information, B Braun, 2004

Title MetroNIDAZOLE

Dose

Loading dose: 15 mg/kg orally or IV infusion by syringe pump over 60 minutes.
Maintenance dose: 7.5 mg/kg/dose orally or IV infusion over 60 minutes. Begin one dosing interval after initial dose.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	Postnatal (days)	Interval (hours)
≤29	0 to 28	48
	>28	24
30 to 36	0 to 14	24
	>14	12
37 to 44	0 to 7	24
	>7	12
≥45	ALL	8

Uses

Reserved for treatment of meningitis, ventriculitis, and endocarditis caused by *Bacteroides fragilis* and other anaerobes resistant to penicillin; treatment of serious intra-abdominal infections; and treatment of infections caused by *Trichomonas vaginalis.*Treatment of *C. difficile* colitis.

Black Box Warning According to the manufacturer's black box warning, metronidazole has been shown to be carcinogenic in mice and rats.

Pharmacology

Metronidazole is bactericidal for many anaerobic organisms. The drug exhibits concentration-dependent bactericidal activity with a post-antibiotic effect of greater than 3 hours. It is well absorbed after oral administration, with peak serum concentrations attained in 1 to 3 hours. Distribution in all tissues throughout the body is excellent. It is less than 20% protein bound. Hydroxylation in the liver occurs in term infants and premature infants exposed to antenatal betamethasone. Unchanged drug and the active metabolite are excreted renally. Elimination half-life is strongly related to gestational age, ranging from 22 to 109 hours.

Adverse Effects

Seizures and sensory polyneuropathy have been reported in a few adult patients receiving high doses over a prolonged period. Drug metabolites may cause brownish discoloration of the urine.

Monitoring

Measure CSF drug concentrations when treating CNS infections. Trough drug concentration should be greater than minimum inhibitory concentration for organism.

Special Considerations/Preparation

Available in 5 mg/mL concentration in 100 mL single-dose plastic ready-to-use solution containers. **Protect from light** until use and store at controlled room temperature. **Do not refrigerate**(crystals form, but redissolve on warming to room temperature). Osmolarity is 297 mOsm/L, pH is 4.5 to 7. Each container contains 13.5 mEq of sodium.

Supplied as 250-mg and 500-mg tablets for oral administration. Suspension may be prepared by crushing five 250-mg tablets (1250 mg), dissolving powder in 10 mL purified water, then adding cherry syrup to make a total volume of 83 mL. Final concentration is 15 mg/mL. **Protect from light.** Shake well. Suspension is stable for 30 days refrigerated.

Solution Compatibility

D_5W, and NS.

Solution Incompatibility

Manufacturer recommends that if metronidazole is used with a primary IV fluid system, the primary solution should be discontinued during metronidazole infusion.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amiodarone, ampicillin, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, gentamicin, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, netilmicin, nicardipine, penicillin G, piperacillin-tazobactam, prostaglandin E_1, remifentanil, and tobramycin.

Terminal Injection Site Incompatibility

Aztreonam and meropenem.

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- Lamp KC, Freeman CD, Klutman NE, Lacy MK: Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999;36:353-373.
- Wenisch C, Parschalk B, Hasenhundl M, et al: Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile* - associated diarrhea. *Clin Infect Dis* 1996;22:813.
- Allen LV, Errickson MA: Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, spironolactone in extemporaneously compounded oral liquids. *Am J Health Syst Pharm* 1996;53:2073-2078.
- Feder HM Jr: *Bacteroides fragilis* meningitis. *Rev Infect Dis* 1987;9:783.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p 76.
- Hall P, Kaye CM, McIntosh N, Steele J: Intravenous metronidazole in the newborn. *Arch Dis Child* 1983;58:529.
- Oldenburg B, Speck WT: Metronidazole. *Pediatr Clin North Am* 1983;30:71.
- Jager-Roman E, Doyle PE, Baird-Lambert J, et al: Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982;100:651.
- Product Information, B Braun, 2004

1.115 Micafungin

Title Micafungin

Dose

7 to 10 mg/kg/dose IV every 24 hours.
The higher dose should be used in the most immature neonates (less than 27 weeks gestation, less than 14 days PNA) and those with meningitis.

Administration

Administer by intermittent IV infusion over 1 hour at a concentration between 0.5 to 1.5 mg/mL. Existing IV line should be flushed with NS prior to administration.

Uses

Treatment of patients with fungal septicemia, peritonitis, and disseminated infections due to *Candida* species including *C. albicans*, azole-resistant *C. albicans*, and non-albicans species including *C. krusei*,*C. glabrata*,*C. tropicalis* and *C. parapsilosis*. There are case reports, but no controlled clinical trials, of patients treated for endocarditis and osteomyelitis due to *Candida*. Clinical studies are ongoing for use in neonatal hematogenous *Candida* meningoencephalitis (no data reported yet).

Pharmacology

Micafungin is a semisynthetic lipopeptide echinocandin antifungal agent with broad-spectrum fungicidal activity against many *Candida* species. It inhibits the synthesis of 1, 3-beta-D-glucan, an integral component of the fungal cell wall. The volume of distribution is relatively high in extremely premature infants, necessitating higher doses. Plasma protein binding is high, primarily to albumin, but it does not displace bilirubin. Pharmacokinetics are linear. Metabolism occurs primarily in the liver through both noncytochrome and cytochrome P450 pathways to 2 biologically inactive metabolites that are eliminated in the feces. Serum half-life ranges from 7 to 16 hours in neonates (mean 11 hours). Mutant strains of *Candida* with reduced susceptibility have been identified in some adult patients during treatment suggesting the potential development of drug resistance. Animal studies suggest tissue penetration to common sites of invasive fungal infections: liver, spleen, kidney, and lungs. No cerebrospinal fluid levels were detected but brain tissue levels were measurable.

Adverse Effects

Limited data in neonates. A case of elevated hepatic transaminases and total bilirubin was reported in a preterm infant exposed perinatally to HIV and hepatitis C infection. Micafungin (8 mg/kg per day) was discontinued after 16 days of treatment and laboratory values gradually declined. The most commonly reported adverse reactions in adults are diarrhea, vomiting, pyrexia, hypokalemia, thrombocytopenia, and histamine-mediated symptoms (including rash, pruritus, facial swelling, and vasodilatation). Rapid infusion rates may result in more frequent histamine-mediated reactions.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, BUN, hepatic transaminases, and creatinine (isolated renal dysfunction reported in adults).

Special Considerations/Preparation

Available in single-use lyophilized powder for injection in vials containing 50 and 100 mg. Add 5 mL of 0.9% sodium chloride injection (without bacteriostatic agent) to each 50 mg or 100 mg vial yielding approximately 10 mg or 20 mg per mL, respectively. Inspect reconstituted vials for particulate matter and discoloration prior to administration. Gently dissolve lyophilized powder by swirling the vial to avoid

excessive foaming. Do not shake. Protect from light. Reconstituted vials may be stored at room temperature for up to 24 hours before use.

Reconstituted drug should be further diluted in NS or D_5W to a final concentration between 0.5 to 1.5 mg/mL prior to administration. Diluted infusion should be protected from light and may be stored at room temperature for up to 24 hours before use. An existing IV line should be flushed with NS prior to administration.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Aminophylline, bumetanide, calcium chloride, calcium gluconate, dopamine, esmolol, furosemide, heparin, lidocaine, magnesium sulfate, milrinone, potassium chloride, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Albumin, amiodarone, dobutamine, epinephrine, insulin, midazolam, morphine, nicardipine, octreotide, phenytoin, rocuronium, and vecuronium.

References

- Benjamin DK Jr, Smith PB, Arrieta A, et al: Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther* 2010;87:93-99.
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- Steinbach WJ, Benjamin DK: New agents under development in children and neonates. *Curr Opin Infect Dis* 2005;18:484-489.
- Mohr J, Johnson M, Cooper T, et al: Current options in antifungal pharmacotherapy. *Pharmacotherapy* 2008;28:614-645.
- Product information, Astellas, 2008.

Title Micafungin

Dose

7 to 10 mg/kg/dose IV every 24 hours.
The higher dose should be used in the most immature neonates (less than 27 weeks gestation, less than 14 days PNA) and those with meningitis.

Administration

Administer by intermittent IV infusion over 1 hour at a concentration between 0.5 to 1.5 mg/mL. Existing IV line should be flushed with NS prior to administration.

Uses

Treatment of patients with fungal septicemia, peritonitis, and disseminated infections due to *Candida* species including *C. albicans*, azole-resistant *C. albicans*, and non-albicans species including *C. krusei*,*C. glabrata*,*C. tropicalis* and *C. parapsilosis*. There are case reports, but no controlled clinical trials, of patients treated for endocarditis and osteomyelitis due to *Candida*. Clinical studies are ongoing for use in neonatal hematogenous *Candida* meningoencephalitis (no data reported yet).

Pharmacology

Micafungin is a semisynthetic lipopeptide echinocandin antifungal agent with broad-spectrum fungicidal activity against many *Candida* species. It inhibits the synthesis of 1, 3-beta-D-glucan, an integral component of the fungal cell wall. The volume of distribution is relatively high in extremely premature infants, necessitating higher doses. Plasma protein binding is high, primarily to albumin, but it does not displace bilirubin. Pharmacokinetics are linear. Metabolism occurs primarily in the liver through both noncytochrome and cytochrome P450 pathways to 2 biologically inactive metabolites that are eliminated in the feces. Serum half-life ranges from 7 to 16 hours in neonates (mean 11 hours). Mutant strains of *Candida* with reduced susceptibility have been identified in some adult patients during treatment suggesting the potential development of drug resistance. Animal studies suggest tissue penetration to common sites of invasive fungal infections: liver, spleen, kidney, and lungs. No cerebrospinal fluid levels were detected but brain tissue levels were measurable.

Adverse Effects

Limited data in neonates. A case of elevated hepatic transaminases and total bilirubin was reported in a preterm infant exposed perinatally to HIV and hepatitis C infection. Micafungin (8 mg/kg per day) was discontinued after 16 days of treatment and laboratory values gradually declined. The most commonly reported adverse reactions in adults are diarrhea, vomiting, pyrexia, hypokalemia, thrombocytopenia, and histamine-mediated symptoms (including rash, pruritus, facial swelling, and vasodilatation). Rapid infusion rates may result in more frequent histamine-mediated reactions.

Monitoring

Assess IV site for signs of irritation. Periodic measurement of serum potassium, calcium, BUN, hepatic transaminases, and creatinine (isolated renal dysfunction reported in adults).

Special Considerations/Preparation

Available in single-use lyophilized powder for injection in vials containing 50 and 100 mg. Add 5 mL of 0.9% sodium chloride injection (without bacteriostatic agent) to each 50 mg or 100 mg vial yielding approximately 10 mg or 20 mg per mL, respectively. Inspect reconstituted vials for particulate matter and discoloration prior to administration. Gently dissolve lyophilized powder by swirling the vial to avoid excessive foaming. Do not shake. Protect from light. Reconstituted vials may be stored at room temperature for up to 24 hours before use.

Reconstituted drug should be further diluted in NS or D_5W to a final concentration between 0.5 to 1.5 mg/mL prior to administration. Diluted infusion should be protected from light and may be stored at room temperature for up to 24 hours before use. An existing IV line should be flushed with NS prior to administration.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Aminophylline, bumetanide, calcium chloride, calcium gluconate, dopamine, esmolol, furosemide, heparin, lidocaine, magnesium sulfate, milrinone, potassium chloride, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Albumin, amiodarone, dobutamine, epinephrine, insulin, midazolam, morphine, nicardipine, octreotide, phenytoin, rocuronium, and vecuronium.

References

- Benjamin DK Jr, Smith PB, Arrieta A, et al: Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther* 2010;87:93-99.
- Smith PB, Walsh TJ, Hope W, et al: Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J* 2009;28:412-415.
- King KY, Edwards MS and Word BM: Hepatitis associated with micafungin use in a preterm infant. *J Perinatol* 2009;29:320-322.
- Trusley C, Kupiec T, Trissel LA: Compatibility of micafungin injection with other drugs during simulated Y-site co-administration. *Int J Pharm Compounding* 2006;10:230-233.
- Heresi GP, Gerstmann DR, Reed MD, et at: The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr Infect Dis J* 2006;25:1110-1115.
- Groll AH, Mickiene D, Petraitis V, et al: Compartmental pharmacokinetics and tissue distribution of the antifungal echinocandin lipopeptide micafungin (FK463) in rabbits. *Antimicrob Agents Chemother* 2001;45:3322-3327.

- Hope WW, Mickiene D, Petraitis V, et al: The pharmacokinetics and pharmacodynamics of micafungin in experimental hematogenous Candida meningoencephalitis: Implications for echinocandin therapy in neonates. *J Infect Dis* 2008;197:163-171.
- Bliss JM, Wellington M, Gigliotti F: Antifungal pharmacotherapy for neonatal candidiasis. *Semin Perinatol* 2003;27:365-374.
- Steinbach WJ, Benjamin DK: New agents under development in children and neonates. *Curr Opin Infect Dis* 2005;18:484-489.
- Mohr J, Johnson M, Cooper T, et al: Current options in antifungal pharmacotherapy. *Pharmacotherapy* 2008;28:614-645.
- Product information, Astellas, 2008.

1.116 MicrolipidÂ®

Title MicrolipidÂ®

Dose

Microlipid is a 50% safflower oil fat emulsion with 4.5 calories/mL. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

Pharmacology

Osmolality (mOsm/kg water): Not available

Supplied: 48 three ounce bottles per case.

Ingredients: Safflower oil, water, polyglycerol esters of fatty acids, soy lecithin, xanthan gum, ascorbic acid.

Microlipid

Nutrient	per mL	per 15 mL (1 tbsp)	per 89 mL (3 fl oz)
Calories	4.5	67.5	400
Protein, g	0	0	0
Fat, g	0.5	7.5	44
Carbohydrate, g	0	0.04	0
Water, g	0.45	6.7	40
Linoleic Acid, g	0.4	5.9	35

Fatty Acid Distribution

Polyunsaturated 78%

Monounsaturated 12%

Saturated 10%

PUFA:SFA 8:1

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Shake well before opening. Opened product should be recapped, refrigerated, and discarded after 5 days. Store unopened bottles at room temperature. Protect from freezing.

Title MicrolipidÂ®

Dose

Microlipid is a 50% safflower oil fat emulsion with 4.5 calories/mL. Used to supplement orally, or added to tube feeding formulas. Mixes easily with enteral formulas.

Pharmacology

Osmolality (mOsm/kg water): Not available

Supplied: 48 three ounce bottles per case.

Ingredients: Safflower oil, water, polyglycerol esters of fatty acids, soy lecithin, xanthan gum, ascorbic acid.

	Microlipid		
Nutrient	**per mL**	**per 15 mL (1 tbsp)**	**per 89 mL (3 fl oz)**
Calories	4.5	67.5	400
Protein, g	0	0	0
Fat, g	0.5	7.5	44
Carbohydrate, g	0	0.04	0
Water, g	0.45	6.7	40
Linoleic Acid, g	0.4	5.9	35

Fatty Acid Distribution	
Polyunsaturated	78%
Monounsaturated	12%
Saturated	10%
PUFA:SFA	8:1

Special Considerations/Preparation

For oral use only. Do not give parenterally (IV). Shake well before opening. Opened product should be recapped, refrigerated, and discarded after 5 days. Store unopened bottles at room temperature. Protect from freezing.

1.117 Midazolam

Title Midazolam

Dose

Sedation:
IV: 0.05 to 0.15 mg/kg **over at least 5 minutes.** Repeat as required, usually every 2 to 4 hours. May also be given IM. Dosage requirements are decreased by concurrent use of narcotics.

Continuous IV infusion: 0.01 to 0.06 mg/kg per hour (10 to 60 mcg/kg/hour). Dosage may need to be increased after several days of therapy because of development of tolerance and/or increased clearance.

Intranasal: 0.2 to 0.3 mg/kg per dose using 5-mg/mL injectable form.

Sublingual: 0.2 mg/kg per dose using 5-mg/mL injectable form mixed with a small amount of flavored syrup.

Oral: 0.25 mg/kg per dose using Versed® oral syrup.

Anticonvulsant:
Loading dose: 0.15 mg/kg (150 mcg/kg) IV over at least 5 minutes, followed by
Maintenance infusion: 0.06 to 0.4 mg/kg per hour (1 to 7 mcg/kg per minute).

Uses

Sedative/hypnotic. Anesthesia induction. Treatment of refractory seizures.

Black Box Warning According to the manufacturer's black box warning, midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Doses should be titrated slowly. Midazolam should not be

given by rapid injection in the neonatal population, as severe hypotension and seizures have been reported.

Pharmacology

Relatively short-acting benzodiazepine with rapid onset of action. Sedative and anticonvulsant properties related to GABA accumulation and occupation of benzodiazepine receptor. Antianxiety properties related to increasing the glycine inhibitory neurotransmitter. Metabolized by hepatic CYP 3A4 to a less active hydroxylated metabolite, then glucuronidated before excretion in urine. Drug accumulation may occur with repeated doses, prolonged infusion therapy, or concurrent administration of cimetidine, erythromycin or fluconazole. Highly protein bound. Duration of action is 2 to 6 hours. Elimination half-life is approximately 4 to 6 hours in term neonates, and quite variable, up to 22 hours, in premature babies and those with impaired hepatic function. Bioavailability is approximately 36% with oral administration and 50% with sublingual and intranasal administration. Midazolam is water soluble in acidic solutions and becomes lipid soluble at physiologic pH.

Adverse Effects

Respiratory depression and hypotension are common when used in conjunction with narcotics, or following rapid bolus administration. Seizure-like myoclonus has been reported in 8% of premature infants receiving continuous infusions - this also may occur following rapid bolus administration and in patients with underlying CNS disorders. Nasal administration may be uncomfortable because of a burning sensation.

Monitoring

Follow respiratory status and blood pressure closely, especially when used concurrently with narcotics. Assess hepatic function. Observe for signs of withdrawal after discontinuation of prolonged therapy.

Special Considerations/Preparation

A preservative-free preparation is available as 1- and 5-mg/mL concentrations in 1-, 2-, and 5-mL vials. Also available in an injectable form as 1- and 5-mg/mL concentrations in 1-, 2-, 5-, and 10-mL vials which contain 1% (10 mg/mL) benzyl alcohol as a preservative. Stable for 24 hours when diluted with NS or D_5W to a concentration of 0.5 mg/mL; stable for 4 hours in LR [1] .

Oral syrup is available in a 2 mg/mL concentration. Store at room temperature [2] .

Injectable formulation is used for intranasal, buccal, or rectal administration [3] [4] [5] .

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions (midazolam 0.5 mg/mL or less; concentrations greater than 0.5 mg/mL incompatible) [6] [7] . Amikacin, aminophylline, amiodarone, atropine, calcium gluconate, cefazolin, cefotaxime, cimetidine, clindamycin, digoxin, dobutamine, dopamine, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, gentamicin, glycopyrrolate, heparin, imipenem/cilastatin, insulin, linezolid, lorazepam, methadone, metoclopramide, metronidazole, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, theophylline, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Fat emulsion. Albumin, ampicillin, bumetanide, cefepime, ceftazidime, dexamethasone, fosphenytoin, furosemide, hydrocortisone succinate, micafungin, nafcillin, and sodium bicarbonate.

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Title Midazolam

Dose

Sedation:
IV: 0.05 to 0.15 mg/kg **over at least 5 minutes.** Repeat as required, usually every 2 to 4 hours. May also be given IM. Dosage requirements are decreased by concurrent use of narcotics.

Continuous IV infusion: 0.01 to 0.06 mg/kg per hour (10 to 60 mcg/kg/hour). Dosage may need to be increased after several days of therapy because of development of tolerance and/or increased clearance.

Intranasal: 0.2 to 0.3 mg/kg per dose using 5-mg/mL injectable form.

Sublingual: 0.2 mg/kg per dose using 5-mg/mL injectable form mixed with a small amount of flavored syrup.

Oral: 0.25 mg/kg per dose using Versed® oral syrup.

Anticonvulsant:
Loading dose: 0.15 mg/kg (150 mcg/kg) IV over at least 5 minutes, followed by
Maintenance infusion: 0.06 to 0.4 mg/kg per hour (1 to 7 mcg/kg per minute).

Uses

Sedative/hypnotic. Anesthesia induction. Treatment of refractory seizures.

Black Box Warning According to the manufacturer's black box warning, midazolam has been associated with respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. Doses should be titrated slowly. Midazolam should not be given by rapid injection in the neonatal population, as severe hypotension and seizures have been reported.

Pharmacology

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benzodiazepine receptor. Antianxiety properties related to increasing the glycine inhibitory neurotransmitter. Metabolized by hepatic CYP 3A4 to a less active hydroxylated metabolite, then glucuronidated before excretion in urine. Drug accumulation may occur with repeated doses, prolonged infusion therapy, or concurrent administration of cimetidine, erythromycin or fluconazole. Highly protein bound. Duration of action is 2 to 6 hours. Elimination half-life is approximately 4 to 6 hours in term neonates, and quite variable, up to 22 hours, in premature babies and those with impaired hepatic function. Bioavailability is approximately 36% with oral administration and 50% with sublingual and intranasal administration. Midazolam is water soluble in acidic solutions and becomes lipid soluble at physiologic pH.

Adverse Effects

Respiratory depression and hypotension are common when used in conjunction with narcotics, or following rapid bolus administration. Seizure-like myoclonus has been reported in 8% of premature infants receiving continuous infusions - this also may occur following rapid bolus administration and in patients with underlying CNS disorders. Nasal administration may be uncomfortable because of a burning sensation.

Monitoring

Follow respiratory status and blood pressure closely, especially when used concurrently with narcotics. Assess hepatic function. Observe for signs of withdrawal after discontinuation of prolonged therapy.

Special Considerations/Preparation

A preservative-free preparation is available as 1- and 5-mg/mL concentrations in 1-, 2-, and 5-mL vials. Also available in an injectable form as 1- and 5-mg/mL concentrations in 1-, 2-, 5-, and 10-mL vials which contain 1% (10 mg/mL) benzyl alcohol as a preservative. Stable for 24 hours when diluted with NS or D_5W to a concentration of 0.5 mg/mL; stable for 4 hours in LR [1] .

Oral syrup is available in a 2 mg/mL concentration. Store at room temperature [2] .

Injectable formulation is used for intranasal, buccal, or rectal administration [3] [4] [5] .

Solution Compatibility

D_5W, NS, and sterile water for injection.

Terminal Injection Site Compatibility

Dex/AA solutions (midazolam 0.5 mg/mL or less; concentrations greater than 0.5 mg/mL incompatible) [6] [7] . Amikacin, aminophylline, amiodarone, atropine, calcium gluconate, cefazolin, cefotaxime, cimetidine, clindamycin, digoxin, dobutamine, dopamine, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, gentamicin, glycopyrrolate, heparin, imipenem/cilastatin, insulin, linezolid, lorazepam, methadone, metoclopramide, metronidazole, milrinone, morphine,

nicardipine, nitroglycerin, nitroprusside, pancuronium bromide, piperacillin, potassium chloride, propofol, ranitidine, remifentanil, theophylline, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Fat emulsion. Albumin, ampicillin, bumetanide, cefepime, ceftazidime, dexamethasone, fosphenytoin, furosemide, hydrocortisone succinate, micafungin, nafcillin, and sodium bicarbonate.

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1.118 Milrinone

Title Milrinone

Dose

Loading dose: 75 mcg/kg IV infused over 60 minutes, immediately followed by
Maintenance infusion: 0.5 to 0.75 mcg/kg per minute.
Note: Above doses are from studies of older infants and children.
Adjust infusion rate based upon hemodynamic and clinical response.

Premature infants less than 30 weeks GA:
Loading dose: 135 mcg/kg IV infused over 3 hours, immediately followed by
Maintenance infusion: 0.2 mcg/kg per minute.
(Preliminary data from pilot study referenced below.)

Uses

Short-term (less than 72 hours) treatment of acute low cardiac output after cardiac surgery or due to septic shock.

Based on results from a randomized, placebo-controlled clinical trial, milrinone was no more effective than placebo in preventing low systemic blood flow in preterm neonates less than 30 weeks GA. Neonates received milrinone (started before 6 hours of age) 0.75 mcg/kg/minute for the first 3 hours followed by 0.20 mcg/kg/minute until 18 hours of age. There was no difference in superior vena cava flow between the milrinone and placebo groups (Paradisis et al, 2009).

Pharmacology

Milrinone improves cardiac output by enhancing myocardial contractility, enhancing myocardial diastolic relaxation and decreasing vascular resistance. It acts via selective phosphodiesterase III inhibition that leads to increased intracellular cyclic AMP, increased myocardial intracellular calcium, and increased reuptake of calcium after systole. Vasodilatation is related to increased levels of cyclic GMP in vascular smooth muscle. Unlike catecholamines, myocardial oxygen consumption is not increased. Elimination is primarily via renal mechanisms. Half-life is quite variable, ranging from approximately 10 hours in ELBW neonates to approximately 3 hours in older and more mature infants.

Adverse Effects

Assure adequate vascular volume prior to initiating therapy. Blood pressure will likely fall 5% to 9% after the loading dose, but should gradually return to baseline by 24 hours. Heart rate increases of 5% to 10% are also common. Thrombocytopenia was

reported frequently in some studies and rarely in others. Arrhythmias occur occasionally.

Monitoring

Continuous monitoring of blood pressure, heart rate and rhythm. Assess signs of cardiac output. Carefully monitor fluid and electrolyte changes and renal function during therapy. Monitor platelet counts.

Special Considerations/Preparation

Available in 1-mg/mL solution for injection in 10-, 20-, and 50-mL single-dose vials. Dilute with compatible diluent prior to administration. **Maximum concentration for infusion is 200 mcg/mL.** Also available as premixed solution for injection (100-mL and 200-mL bags) in a concentration of 200 mcg/mL in 5% Dextrose (pH of 3.2 to 4).

Solution Compatibility

D_5W, NS, and LR.

Terminal Injection Site Compatibility

Dex/AA. Acyclovir, amikacin, aminophylline, amiodarone, ampicillin, atracurium, atropine, bumetanide, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, ceftazidime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, epinephrine, fentanyl, gentamicin, heparin, insulin, isoproterenol, lorazepam, meropenem, methylprednisolone, metronidazole, micafungin, midazolam, morphine, nicardipine, nitroglycerin, norepinephrine, oxacillin, pancuronium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, sodium bicarbonate, sodium nitroprusside, theophylline, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide, imipenem/cilastatin and procainamide.

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- Product Information: Primacor®, milrinone lactate in D_5W injection, Sanofi-Aventis, 2007.

Title Milrinone

Dose

Loading dose: 75 mcg/kg IV infused over 60 minutes, immediately followed by
Maintenance infusion: 0.5 to 0.75 mcg/kg per minute.
Note: Above doses are from studies of older infants and children.
Adjust infusion rate based upon hemodynamic and clinical response.

Premature infants less than 30 weeks GA:
Loading dose: 135 mcg/kg IV infused over 3 hours, immediately followed by
Maintenance infusion: 0.2 mcg/kg per minute.
(Preliminary data from pilot study referenced below.)

Uses

Short-term (less than 72 hours) treatment of acute low cardiac output after cardiac surgery or due to septic shock.

Based on results from a randomized, placebo-controlled clinical trial, milrinone was no more effective than placebo in preventing low systemic blood flow in preterm neonates less than 30 weeks GA. Neonates received milrinone (started before 6 hours of age) 0.75 mcg/kg/minute for the first 3 hours followed by 0.20 mcg/kg/minute until 18 hours of age. There was no difference in superior vena cava flow between the milrinone and placebo groups (Paradisis et al, 2009).

Pharmacology

Milrinone improves cardiac output by enhancing myocardial contractility, enhancing myocardial diastolic relaxation and decreasing vascular resistance. It acts via selective phosphodiesterase III inhibition that leads to increased intracellular cyclic AMP, increased myocardial intracellular calcium, and increased reuptake of calcium after systole. Vasodilatation is related to increased levels of cyclic GMP in vascular smooth muscle. Unlike catecholamines, myocardial oxygen consumption is not increased. Elimination is primarily via renal mechanisms. Half-life is quite variable, ranging from

approximately 10 hours in ELBW neonates to approximately 3 hours in older and more mature infants.

Adverse Effects

Assure adequate vascular volume prior to initiating therapy. Blood pressure will likely fall 5% to 9% after the loading dose, but should gradually return to baseline by 24 hours. Heart rate increases of 5% to 10% are also common. Thrombocytopenia was reported frequently in some studies and rarely in others. Arrhythmias occur occasionally.

Monitoring

Continuous monitoring of blood pressure, heart rate and rhythm. Assess signs of cardiac output. Carefully monitor fluid and electrolyte changes and renal function during therapy. Monitor platelet counts.

Special Considerations/Preparation

Available in 1-mg/mL solution for injection in 10-, 20-, and 50-mL single-dose vials. Dilute with compatible diluent prior to administration. **Maximum concentration for infusion is 200 mcg/mL.** Also available as premixed solution for injection (100-mL and 200-mL bags) in a concentration of 200 mcg/mL in 5% Dextrose (pH of 3.2 to 4).

Solution Compatibility

D_5W, NS, and LR.

Terminal Injection Site Compatibility

Dex/AA. Acyclovir, amikacin, aminophylline, amiodarone, ampicillin, atracurium, atropine, bumetanide, calcium chloride, calcium gluconate, cefazolin, cefepime, cefotaxime, ceftazidime, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, epinephrine, fentanyl, gentamicin, heparin, insulin, isoproterenol, lorazepam, meropenem, methylprednisolone, metronidazole, micafungin, midazolam, morphine, nicardipine, nitroglycerin, norepinephrine, oxacillin, pancuronium, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, sodium bicarbonate, sodium nitroprusside, theophylline, ticarcillin, ticarcillin/clavulanate, tobramycin, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Furosemide, imipenem/cilastatin and procainamide.

References

- Paradisis M, Evans N, Kluckow M, Osborn D: Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. *J Pediatr* 2009;154:189-195.

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- Lindsay CA, Barton P, Lawless S, et al: Pharmacokinetics and pharmacodynamics of milrinone in pediatric patients with septic shock. *J Pediatr* 1998;132:329-34.
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- Product Information: Primacor®, milrinone lactate in D_5W injection, Sanofi-Aventis, 2007.

1.119 Morphine

Title Morphine

Dose

0.05 to 0.2 mg/kg per dose IV over at least 5 minutes, IM, or subQ.
Repeat as required (usually every 4 hours).

Continuous infusion: Give a loading dose of 100 to 150 mcg/kg over 1 hour followed by 10 to 20 mcg/kg per hour.

Treatment of opioid dependence: Begin at most recent IV morphine dose equivalent. Taper 10% to 20% per day as tolerated. Oral dose is approximately 3 to 5 times IV dose.

Neonatal Abstinence Syndrome:
Initial dose: 0.03 to 0.1 mg/kg per dose orally every 3 to 4 hours. **Maximum dose 0.2 mg/kg** [1] [2] [3] . Wean dose by 10% to 20% every 2 to 3 days based on abstinence scoring. Use a 0.4-mg/mL dilution made from a concentrated oral morphine sulfate solution [4] [5] [3] .

Uses

Analgesia and sedation.
Treatment of opioid dependence and neonatal abstinence syndrome [1] [2] [4] [5] [3] .

Pharmacology

Morphine is a narcotic analgesic that stimulates brain opioid receptors. Increases venous capacitance, caused by release of histamine and central suppression of adrenergic tone. GI secretions and motility decreased. Increases smooth muscle tone. Morphine is converted in the liver to two glucuronide metabolites (morphine-6-glucuronide and morphine-3-glucuronide) that are renally excreted. Morphine-6-glucuronide (M6G) is a potent respiratory-depressant and analgesic. Morphine-3-glucuronide (M3G) is an antagonist to the effects of morphine and morphine-6-glucuronide. Morphine is 20% to 40% bioavailable when administered orally. Pharmacokinetics are widely variable. Elimination half-life is approximately 9 hours for morphine and 18 hours for morphine-6-glucuronide. Steady state concentrations of morphine are reached by 24 to 48 hours.

Adverse Effects

Naloxone should be readily available to reverse adverse effects. Marked respiratory depression (decreases the responsiveness of the respiratory center to CO_2 tension). Hypotension and bradycardia. Transient hypertonia. Ileus and delayed gastric emptying. Urine retention. Tolerance may develop after prolonged use; wean slowly. Seizures reported in two infants who received bolus plus infusion.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention and loss of bowel sounds. Consider urine retention if output is decreased. For infants experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1] [5] .

Special Considerations/Preparation

Injectable solutions are available in dosage strengths ranging from 0.5 to 50 mg/mL.

Oral morphine sulfate solutions are available in concentrations of 2 and 4 mg/mL.

A 0.4-mg/mL oral morphine dilution may be made by adding 1 mL of the 4-mg/mL injectable solution to 9 mL preservative-free normal saline. Stable for 7 days refrigerated. **Protect from light.**

Solution Compatibility

D_5W, $D_{10}W$, and NS.
For continuous infusions of morphine **containing heparin:** Use only NS; maximum morphine concentration 5 mg/mL.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alteplase, amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol,

cefazolin, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, furosemide, gentamicin, glycopyrrolate, heparin, hydrocortisone succinate, ibuprofen lysine, insulin, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, mezlocillin, midazolam, milrinone, nafcillin, nicardipine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Azithromycin, cefepime, micafungin, pentobarbital, and phenytoin.

References

- Langenfeld S, Birkenfeld L, Herkenrath P, et al: Therapy of the neonatal abstinence syndrome with tincture of opium or morphine drops. *Drug Alcohol Depend* 2005;77:31-36.
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4. Burgos AE: Neonatal Abstinence Syndrome. Neoreviews 2009; 10(5): e222-e229.
5. Jansson LM: The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag Jan, 2009; 5(1): 47-55.

Title Morphine

Dose

0.05 to 0.2 mg/kg per dose IV over at least 5 minutes, IM, or subQ.
Repeat as required (usually every 4 hours).

Continuous infusion: Give a loading dose of 100 to 150 mcg/kg over 1 hour followed by 10 to 20 mcg/kg per hour.

Treatment of opioid dependence: Begin at most recent IV morphine dose equivalent. Taper 10% to 20% per day as tolerated. Oral dose is approximately 3 to 5 times IV dose.

Neonatal Abstinence Syndrome:
Initial dose: 0.03 to 0.1 mg/kg per dose orally every 3 to 4 hours. **Maximum dose 0.2 mg/kg** [1] [2] [3] . Wean dose by 10% to 20% every 2 to 3 days based on abstinence scoring. Use a 0.4-mg/mL dilution made from a concentrated oral morphine sulfate solution [4] [5] [3] .

Uses

Analgesia and sedation.
Treatment of opioid dependence and neonatal abstinence syndrome [1] [2] [4] [5] [3] .

Pharmacology

Morphine is a narcotic analgesic that stimulates brain opioid receptors. Increases venous capacitance, caused by release of histamine and central suppression of adrenergic tone. GI secretions and motility decreased. Increases smooth muscle tone. Morphine is converted in the liver to two glucuronide metabolites (morphine-6-glucuronide and morphine-3-glucuronide) that are renally excreted. Morphine-6-glucuronide (M6G) is a potent respiratory-depressant and analgesic. Morphine-3-glucuronide (M3G) is an antagonist to the effects of morphine and morphine-6-glucuronide. Morphine is 20% to 40% bioavailable when administered orally. Pharmacokinetics are widely variable. Elimination half-life is approximately 9 hours for morphine and 18 hours for morphine-6-glucuronide. Steady state concentrations of morphine are reached by 24 to 48 hours.

Adverse Effects

Naloxone should be readily available to reverse adverse effects. Marked respiratory depression (decreases the responsiveness of the respiratory center to CO_2 tension). Hypotension and bradycardia. Transient hypertonia. Ileus and delayed gastric emptying. Urine retention. Tolerance may develop after prolonged use; wean slowly. Seizures reported in two infants who received bolus plus infusion.

Monitoring

Monitor respiratory and cardiovascular status closely. Observe for abdominal distention and loss of bowel sounds. Consider urine retention if output is decreased. For infants

experiencing neonatal abstinence syndrome, monitor and score signs of drug withdrawal using a published abstinence assessment tool such as the modified Neonatal Abstinence Scoring System (Finnegan) or the Lipsitz tool [1] [5] .

Special Considerations/Preparation

Injectable solutions are available in dosage strengths ranging from 0.5 to 50 mg/mL.

Oral morphine sulfate solutions are available in concentrations of 2 and 4 mg/mL.

A 0.4-mg/mL oral morphine dilution may be made by adding 1 mL of the 4-mg/mL injectable solution to 9 mL preservative-free normal saline. Stable for 7 days refrigerated. **Protect from light.**

Solution Compatibility

D_5W, $D_{10}W$, and NS.
For continuous infusions of morphine **containing heparin:** Use only NS; maximum morphine concentration 5 mg/mL.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alteplase, amikacin, aminophylline, amiodarone, ampicillin, atropine, aztreonam, bumetanide, caffeine citrate, calcium chloride, caspofungin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cefazolin, cimetidine, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, fluconazole, furosemide, gentamicin, glycopyrrolate, heparin, hydrocortisone succinate, ibuprofen lysine, insulin, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, metronidazole, mezlocillin, midazolam, milrinone, nafcillin, nicardipine, nitroglycerin, oxacillin, pancuronium bromide, penicillin G, phenobarbital, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, propranolol, ranitidine, remifentanil, sodium bicarbonate, sodium nitroprusside, ticarcillin/clavulanate, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Azithromycin, cefepime, micafungin, pentobarbital, and phenytoin.

References

- Langenfeld S, Birkenfeld L, Herkenrath P, et al: Therapy of the neonatal abstinence syndrome with tincture of opium or morphine drops. *Drug Alcohol Depend* 2005;77:31-36.
- Oei J, Lui K: Management of the newborn infant affected by maternal opiates and other drugs of dependency. *J Paediatr Child Health* 2007;43:9-18.
- Saarenmaa E, Neuvonen PJ, Rosenberg P, Fellman V: Morphine clearance and effects in newborn infants in relation to gestational age. *Clin Pharmacol Ther* 2000;68:160-166.

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3. Lainwala S, Brown ER, Weinschenk NP et al: A retrospective study of length of hospital stay in infants treated for neonatal abstinence syndrome with methadone versus oral morphine preparations. Adv Neonatal Care Oct, 2005; 5(5): 265-272.
4. Burgos AE: Neonatal Abstinence Syndrome. Neoreviews 2009; 10(5): e222-e229.
5. Jansson LM: The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag Jan, 2009; 5(1): 47-55.

1.120 Mupirocin

Title Mupirocin

Dose

Cutaneous infections: Apply small amounts topically to affected areas 3 times daily.

Decolonization: Apply small amounts to anterior nares twice daily for 5 to 7 days.

Uses

Topical use for skin infections caused by *Staphylococcus aureus, S epidermidis, S saprophyticus,* and *Streptococcus pyogenes.*
As part of multiple interventions for infection control during MRSA outbreaks in the NICU. Routine use for decolonization is not recommended.

Pharmacology

Topical antibacterial produced by fermentation of the organism *Pseudomonas fluorescens.*Inhibits protein synthesis by bonding to bacterial isoleucyl-transfer-RNA synthetase. Highly protein bound. Not absorbed into the systemic circulation after topical administration (older infants and children). Metabolized in the skin to an inactive compound and excreted.

Adverse Effects

Use only on the skin. No adverse effects reported from topical administration. Routine use may lead to selective bacterial resistance.

Monitoring

Assess affected area for continued infection.

Special Considerations/Preparation

Available in unit-dose packets and 15 and 30-g tubes as a 2% ointment and cream (20 mg/g).

References

- American Academy of Pediatrics. Staphylococcal Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics 2009: pp 613-615.
- Khoury J, Jones M, Grim A, et al: Eradication of methicillin-resistant *Staphylococcus aureus* from a neonatal intensive care unit by active surveillance and aggressive infection control measures. *Infect Control Hosp Epidemiol* 2005;26:616-621.
- Saiman L, Cronquist A, Wu F, et al: An outbreak of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:317-321.
- Zakrzewska-Bode A, Muytjens HL, Liem KD, Hoogkamp-Korstanje JAA: Mupirocin resistance in coagulase-negative staphylococci, after topical prophylaxis for the reduction of colonization of central venous catheters. *J Hosp Infect* 1995;31:189.
- Pappa KA: The clinical development of mupirocin. *J Am Acad Dermatol* 1990;22:873.
- Leyden JJ: Mupirocin: A new topical antibiotic. *Semin Dermatol* 1987;6:48.
- Davies EA, Emmerson AM, Hogg GM, et al: An outbreak of infection with a methicillin-resistant *Staphylococcus aureus* in a special care baby unit: Value of topical mupirocin and of traditional methods of infection control. *J Hosp Infect* 1987;10:120.
- Product Information, OrthoNeutrogena, 2006.

Title Mupirocin

Dose

Cutaneous infections: Apply small amounts topically to affected areas 3 times daily.

Decolonization: Apply small amounts to anterior nares twice daily for 5 to 7 days.

Uses

Topical use for skin infections caused by *Staphylococcus aureus*, *S epidermidis*, *S saprophyticus*, and *Streptococcus pyogenes.*
As part of multiple interventions for infection control during MRSA outbreaks in the NICU. Routine use for decolonization is not recommended.

Pharmacology

Topical antibacterial produced by fermentation of the organism *Pseudomonas fluorescens.*Inhibits protein synthesis by bonding to bacterial isoleucyl-transfer-RNA synthetase. Highly protein bound. Not absorbed into the systemic circulation after topical administration (older infants and children). Metabolized in the skin to an inactive compound and excreted.

Adverse Effects

Use only on the skin. No adverse effects reported from topical administration. Routine use may lead to selective bacterial resistance.

Monitoring

Assess affected area for continued infection.

Special Considerations/Preparation

Available in unit-dose packets and 15 and 30-g tubes as a 2% ointment and cream (20 mg/g).

References

- American Academy of Pediatrics. Staphylococcal Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics 2009: pp 613-615.
- Khoury J, Jones M, Grim A, et al: Eradication of methicillin-resistant *Staphylococcus aureus* from a neonatal intensive care unit by active surveillance and aggressive infection control measures. *Infect Control Hosp Epidemiol* 2005;26:616-621.
- Saiman L, Cronquist A, Wu F, et al: An outbreak of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2003;24:317-321.
- Zakrzewska-Bode A, Muytjens HL, Liem KD, Hoogkamp-Korstanje JAA: Mupirocin resistance in coagulase-negative staphylococci, after topical prophylaxis for the reduction of colonization of central venous catheters. *J Hosp Infect* 1995;31:189.
- Pappa KA: The clinical development of mupirocin. *J Am Acad Dermatol* 1990;22:873.
- Leyden JJ: Mupirocin: A new topical antibiotic. *Semin Dermatol* 1987;6:48.
- Davies EA, Emmerson AM, Hogg GM, et al: An outbreak of infection with a methicillin-resistant *Staphylococcus aureus* in a special care baby unit: Value of topical mupirocin and of traditional methods of infection control. *J Hosp Infect* 1987;10:120.
- Product Information, OrthoNeutrogena, 2006.

1.121 Nafcillin

Title Nafcillin

Dose

Usual dosage: 25 mg/kg/dose IV over 15 minutes.
Meningitis: 50 mg/kg/dose IV over 15 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of infections caused by penicillinase-producing staphylococci, particularly if evidence of renal dysfunction.

Contraindications/Precautions

Increase dosing interval in patients with hepatic dysfunction. Irritating to veins; watch for phlebitis.

Pharmacology

Inhibits synthesis of bacterial cell wall. Better penetration into CSF than methicillin. Excreted via hepatic clearance.

Adverse Effects

Cases of granulocytopenia have been reported.

Monitoring

Observe IV site for signs of phlebitis and extravasation. Assess CBC, renal and hepatic function weekly in patients receiving long-term therapy [1] [2] .

Special Considerations/Preparation

Available in 1 and 2-g vials. Reconstitute 1-g vial with 3.4 mL of sterile water for injection to provide a final volume of 4 mL and a concentration of 250 mg/mL. Also available in 1-g in 50-mL and 2-g in 100-mL frozen single-dose bags. Thaw bags at room temperature or under refrigeration. Do not force thaw by immersing into water baths or microwaving. pH of resulting solution 6 to 8.5. Thawed solution stable for 3 days at room temperature, 21 days refrigerator. Reconstituted solution stable for 3 days at room temperature, 7 days refrigerated. Osmolality was determined to be 709 mOsm/kg of water. For direct intravenous injection, dilute in 15 to 30 mL of NS.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, atropine, chloramphenicol, cimetidine, dexamethasone, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, heparin, lidocaine, magnesium sulfate, morphine, nicardipine, potassium chloride, propofol, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, gentamicin, hydrocortisone succinate, insulin, methylprednisolone, midazolam, netilmicin, and vancomycin.

References

- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Kitzing W, Nelson JD, Mohs E: Comparative toxicities of methicillin and nafcillin. *Am J Dis Child*1981;135:52.
- Banner W, Gooch WM, Burckart G, Korones SB: Pharmacokinetics of nafcillin in infants with low birth weights. *Antimicrob Agents Chemother* 1980;17:691.
- Product Information, Sandoz, 2004.

1. Product Information: nafcillin for injection, nafcillin for injection. Sandoz Inc, Broomfield, CO, 01/00/2004.
2. Nahata MC: Adverse effects of methicillin, nafcillin and oxacillin in pediatric patients. Dev Pharmacol Ther 1982; 4(3-4): 117-123.

Title Nafcillin

Dose

Usual dosage: 25 mg/kg/dose IV over 15 minutes.
Meningitis: 50 mg/kg/dose IV over 15 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of infections caused by penicillinase-producing staphylococci, particularly if evidence of renal dysfunction.

Contraindications/Precautions

Increase dosing interval in patients with hepatic dysfunction. Irritating to veins; watch for phlebitis.

Pharmacology

Inhibits synthesis of bacterial cell wall. Better penetration into CSF than methicillin. Excreted via hepatic clearance.

Adverse Effects

Cases of granulocytopenia have been reported.

Monitoring

Observe IV site for signs of phlebitis and extravasation. Assess CBC, renal and hepatic function weekly in patients receiving long-term therapy [1] [2] .

Special Considerations/Preparation

Available in 1 and 2-g vials. Reconstitute 1-g vial with 3.4 mL of sterile water for injection to provide a final volume of 4 mL and a concentration of 250 mg/mL. Also available in 1-g in 50-mL and 2-g in 100-mL frozen single-dose bags. Thaw bags at room temperature or under refrigeration. Do not force thaw by immersing into water baths or microwaving. pH of resulting solution 6 to 8.5. Thawed solution stable for 3 days at room temperature, 21 days refrigerator. Reconstituted solution stable for 3 days

at room temperature, 7 days refrigerated. Osmolality was determined to be 709 mOsm/kg of water. For direct intravenous injection, dilute in 15 to 30 mL of NS.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, atropine, chloramphenicol, cimetidine, dexamethasone, enalaprilat, esmolol, famotidine, fentanyl, fluconazole, heparin, lidocaine, magnesium sulfate, morphine, nicardipine, potassium chloride, propofol, sodium bicarbonate, tobramycin, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, aztreonam, gentamicin, hydrocortisone succinate, insulin, methylprednisolone, midazolam, netilmicin, and vancomycin.

References

- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Kitzing W, Nelson JD, Mohs E: Comparative toxicities of methicillin and nafcillin. *Am J Dis Child*1981;135:52.
- Banner W, Gooch WM, Burckart G, Korones SB: Pharmacokinetics of nafcillin in infants with low birth weights. *Antimicrob Agents Chemother* 1980;17:691.
- Product Information, Sandoz, 2004.

1. Product Information: nafcillin for injection, nafcillin for injection. Sandoz Inc, Broomfield, CO, 01/00/2004.
2. Nahata MC: Adverse effects of methicillin, nafcillin and oxacillin in pediatric patients. Dev Pharmacol Ther 1982; 4(3-4): 117-123.

1.122 Naloxone

Title Naloxone

Dose

Suggested dose: 0.1 mg/kg IV push.
Doses needed to reverse narcotic-induced depression may be as low as 0.01 mg/kg.
May give IM if adequate perfusion. Tracheal administration is not recommended.
There are no studies to support or refute the current dosing recommendations.

Uses

Narcotic antagonist. Adjuvant therapy to customary resuscitation efforts for narcotic-induced respiratory (CNS) depression. Naloxone is not recommended as part of the initial resuscitation of newborns with respiratory depression in the delivery room.

Before naloxone is given, providers should restore heart rate and color by supporting ventilation.

Pharmacology

Reverses respiratory depression by competing for CNS narcotic receptor sites. Onset of action is variable, but usually within minutes after IV administration, and approximately 1 hour after IM administration. Half-life in neonates is approximately 70 minutes. Metabolized by the liver and excreted in the urine. Increases circulating catecholamines.

Adverse Effects

No short-term toxicity observed. One case report of seizures secondary to acute opioid withdrawal after administration to an infant born to an opioid abuser. Long-term safety has not been investigated.

Monitoring

Assess respiratory effort and neurologic status.

Special Considerations/Preparation

Do not mix in an alkaline solution. Available in 0.4 mg/mL (1-mL fill in 2-mL Carpuject® cartridge) and 1-mg/mL concentrations. **Store at room temperature and protect from light.**

Solution Compatibility

NS and D_5W
No data are currently available on Dex/AA.

Terminal Injection Site Compatibility

Heparin, linezolid, and propofol.
No data are currently available on potassium chloride and other medications.

References

- The International Liaison Committee on Resuscitation: The International Liaison Committee on Resuscitation (ILCOR) Consensus on Science With Treatment Recommendations for Pediatric and Neonatal Patients: Neonatal Resuscitation. *Pediatrics* 2006(5). URL:http://www.pediatrics.org/cgi/content/full/117/5/e978 .
- Guinsburg R, Wyckoff MH. Naloxone during neonatal resuscitation: acknowledging the unknown. *Clin Perinatol* 2006;33:121-132.
- Herschel M, Khoshnood B, Lass N. Role of naloxone in newborn resuscitation. *Pediatrics* 2000;106:831-834.

- McGuire W, Fowlie PW. Naloxone for narcotic exposed newborn infants: systematic review. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F308-F311.
- Product Information, Hospira, 2005

Title Naloxone

Dose

Suggested dose: 0.1 mg/kg IV push.
Doses needed to reverse narcotic-induced depression may be as low as 0.01 mg/kg. May give IM if adequate perfusion. Tracheal administration is not recommended. There are no studies to support or refute the current dosing recommendations.

Uses

Narcotic antagonist. Adjuvant therapy to customary resuscitation efforts for narcotic-induced respiratory (CNS) depression. Naloxone is not recommended as part of the initial resuscitation of newborns with respiratory depression in the delivery room. Before naloxone is given, providers should restore heart rate and color by supporting ventilation.

Pharmacology

Reverses respiratory depression by competing for CNS narcotic receptor sites. Onset of action is variable, but usually within minutes after IV administration, and approximately 1 hour after IM administration. Half-life in neonates is approximately 70 minutes. Metabolized by the liver and excreted in the urine. Increases circulating catecholamines.

Adverse Effects

No short-term toxicity observed. One case report of seizures secondary to acute opioid withdrawal after administration to an infant born to an opioid abuser. Long-term safety has not been investigated.

Monitoring

Assess respiratory effort and neurologic status.

Special Considerations/Preparation

Do not mix in an alkaline solution. Available in 0.4 mg/mL (1-mL fill in 2-mL Carpuject® cartridge) and 1-mg/mL concentrations. **Store at room temperature and protect from light.**

Solution Compatibility

NS and D_5W
No data are currently available on Dex/AA.

Terminal Injection Site Compatibility

Heparin, linezolid, and propofol.
No data are currently available on potassium chloride and other medications.

References

- The International Liaison Committee on Resuscitation: The International Liaison Committee on Resuscitation (ILCOR) Consensus on Science With Treatment Recommendations for Pediatric and Neonatal Patients: Neonatal Resuscitation. *Pediatrics* 2006(5). URL:http://www.pediatrics.org/cgi/content/full/117/5/e978 .
- Guinsburg R, Wyckoff MH. Naloxone during neonatal resuscitation: acknowledging the unknown. *Clin Perinatol* 2006;33:121-132.
- Herschel M, Khoshnood B, Lass N. Role of naloxone in newborn resuscitation. *Pediatrics* 2000;106:831-834.
- McGuire W, Fowlie PW. Naloxone for narcotic exposed newborn infants: systematic review. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F308-F311.
- Product Information, Hospira, 2005

1.123 Neostigmine

Title Neostigmine

Dose

Myasthenia gravis: 0.1 mg IM (give 30 minutes before feeding).
1 mg orally (give 2 hours before feeding). Dose may have to be increased and should be titrated.

Reversal of neuromuscular blockade: 0.04 to 0.08 mg/kg IV, in addition to atropine 0.02 mg/kg.

Administration

Administer by slow IV push. Give with atropine or glycopyrrolate to prevent possible bradycardia, increased salivation, and hyperperistalsis [1] [1] [2] . For myasthenia gravis diagnosis, test dose is given IM [3] [4] .

Uses

Neonatal transient myasthenia gravis. Neonatal persistent (congenital) myasthenia gravis.

Pediatric FDA Approved Indications
Reversal of neuromuscular blocking agents [5] .

Contraindications/Precautions

Contraindicated in the presence of intestinal or urinary obstruction. Use cautiously in patients with bronchospasm, cardiac arrhythmia, hypotension, or bradycardia [2] .

Pharmacology

Reversible quaternary cholinesterase inhibitor which inhibits acetylcholinesterase at the neuromuscular junction, allowing accumulation of acetylcholine and thus restoring activity. In 1 study (n=27), ED50 (dose which produces 50% antagonism of neuromuscular blockade) was 13.1 mcg/kg in infants and 15.5 mcg/kg in children. Protein binding (serum albumin) of 15% to 25%. Volume of distribution of approximately 0.5 L/kg in infants and children. Undergoes hydrolysis by cholinesterase and also metabolized by microsomal enzymes in the liver to 3-hydroxy-phenyl-trimethyl ammonium. Renal excretion accounts for 50% of drug elimination. Half-life of approximately 30 to 60 minutes (shorter compared with adults) [2] [6] [7] . Reversal time dependent on neuromuscular blocker given and time of administration (given at presence of intense neuromuscular blockade or delayed until recovery (first twitch recovery of 1%, 10% or 25%)) [8] .

Adverse Effects

Adverse effects include muscle weakness, tremors, bradycardia, hypotension, respiratory depression, bronchospasm, diarrhea, and excessive salivation [2] .

Monitoring

Monitor respiratory and cardiovascular status closely. Monitor neuromuscular function recovery [2] .

Special Considerations/Preparation

Prostigmin®: Available as injectable solution in 10-mL multiple dose vials in concentrations of 1:1000 (1 mg/mL) and 1:2000 (0.5 mg/mL). **Protect from light** [2] .
Bloxiverz™: Available as injectable solution in 10-mL multiple dose vials in 1:2000 (0.5 mg/mL) and 1:1000 (1 mg/mL). **Protect from light** [5] .

Solution Compatibility

No data.

Terminal Injection Site Compatibility

Glycopyrrolate, heparin, hydrocortisone succinate, netilmicin, pentobarbital and potassium chloride.

References

- Goudsouzian NG, Crone RK, Todres ID: Recovery from pancuronium blockade in the neonatal intensive care unit. *Br J Anaesth* 1981;53:1303.
- Sarnat HB: Neuromuscular disorders in the neonatal period, in Korobken R, Guillemenault C (eds): *Advances in Perinatal Neurology*. New York: Spectrum Publications, 1979, p 153.

1. Buck ML: Use of nondepolarizing neuromuscular blocking agents in mechanically ventilated patients. Clin Pharm Jan, 1991; 10(1): 32-48.
2. Product Information: neostigmine methylsulfate IV, IM, subcutaneous injection solution, neostigmine methylsulfate IV, IM, subcutaneous injection solution. American Regent, Inc (Per DailyMed), Shirley, NY, Jan, 2009.
3. Saha A, Batra P, Vilhekar KY et al: Post-varicella myasthenia gravis. Singapore Med J Jun, 2007; 48(6): e177-e180.
4. Raksadawan N, Kankirawatana P, Balankura K et al: Childhood onset myasthenia gravis. J Med Assoc Thai Aug, 2002; 85 (Suppl 2): S769-S777.
5. Product Information: BLOXIVERZ(TM) intravenous injection, neostigmine methylsulfate intravenous injection. Eclat Pharmaceuticals (per FDA), Chesterfield, MO, May, 2013.
6. Aquilonius SM: Clinical pharmacokinetics of cholinesterase inhibitors. Clin Pharmacokinet May, 1986; 11(3): 236-249.
7. Fisher DM, Cronnelly R, Miller RD et al: The neuromuscular pharmacology of neostigmine in infants and children. Anesthesiology Sep, 1983; 59(3): 220-225.
8. Bevan JC, Collins L, Fowler C et al: Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children. Anesth Analg Aug, 1999; 89(2): 333-339.

Title Neostigmine

Dose

Myasthenia gravis: 0.1 mg IM (give 30 minutes before feeding).
1 mg orally (give 2 hours before feeding). Dose may have to be increased and should be titrated.

Reversal of neuromuscular blockade: 0.04 to 0.08 mg/kg IV, in addition to atropine 0.02 mg/kg.

Administration

Administer by slow IV push. Give with atropine or glycopyrrolate to prevent possible bradycardia, increased salivation, and hyperperistalsis [1] [1] [2] . For myasthenia gravis diagnosis, test dose is given IM [3] [4] .

Uses

Neonatal transient myasthenia gravis. Neonatal persistent (congenital) myasthenia gravis.

Pediatric FDA Approved Indications
Reversal of neuromuscular blocking agents [5] .

Contraindications/Precautions

Contraindicated in the presence of intestinal or urinary obstruction. Use cautiously in patients with bronchospasm, cardiac arrhythmia, hypotension, or bradycardia [2] .

Pharmacology

Reversible quaternary cholinesterase inhibitor which inhibits acetylcholinesterase at the neuromuscular junction, allowing accumulation of acetylcholine and thus restoring activity. In 1 study (n=27), ED50 (dose which produces 50% antagonism of neuromuscular blockade) was 13.1 mcg/kg in infants and 15.5 mcg/kg in children. Protein binding (serum albumin) of 15% to 25%. Volume of distribution of approximately 0.5 L/kg in infants and children. Undergoes hydrolysis by cholinesterase and also metabolized by microsomal enzymes in the liver to 3-hydroxy-phenyl-trimethyl ammonium. Renal excretion accounts for 50% of drug elimination. Half-life of approximately 30 to 60 minutes (shorter compared with adults) [2] [6] [7] . Reversal time dependent on neuromuscular blocker given and time of administration (given at presence of intense neuromuscular blockade or delayed until recovery (first twitch recovery of 1%, 10% or 25%)) [8] .

Adverse Effects

Adverse effects include muscle weakness, tremors, bradycardia, hypotension, respiratory depression, bronchospasm, diarrhea, and excessive salivation [2] .

Monitoring

Monitor respiratory and cardiovascular status closely. Monitor neuromuscular function recovery [2] .

Special Considerations/Preparation

Prostigmin®: Available as injectable solution in 10-mL multiple dose vials in concentrations of 1:1000 (1 mg/mL) and 1:2000 (0.5 mg/mL). **Protect from light** [2] . Bloxiverz™: Available as injectable solution in 10-mL multiple dose vials in 1:2000 (0.5 mg/mL) and 1:1000 (1 mg/mL). **Protect from light** [5] .

Solution Compatibility

No data.

Terminal Injection Site Compatibility

Glycopyrrolate, heparin, hydrocortisone succinate, netilmicin, pentobarbital and potassium chloride.

References

- Goudsouzian NG, Crone RK, Todres ID: Recovery from pancuronium blockade in the neonatal intensive care unit. *Br J Anaesth* 1981;53:1303.
- Sarnat HB: Neuromuscular disorders in the neonatal period, in Korobken R, Guillemenault C (eds): *Advances in Perinatal Neurology*. New York: Spectrum Publications, 1979, p 153.

1. Buck ML: Use of nondepolarizing neuromuscular blocking agents in mechanically ventilated patients. Clin Pharm Jan, 1991; 10(1): 32-48.

2. Product Information: neostigmine methylsulfate IV, IM, subcutaneous injection solution, neostigmine methylsulfate IV, IM, subcutaneous injection solution. American Regent, Inc (Per DailyMed), Shirley, NY, Jan, 2009.
3. Saha A, Batra P, Vilhekar KY et al: Post-varicella myasthenia gravis. Singapore Med J Jun, 2007; 48(6): e177-e180.
4. Raksadawan N, Kankirawatana P, Balankura K et al: Childhood onset myasthenia gravis. J Med Assoc Thai Aug, 2002; 85 (Suppl 2): S769-S777.
5. Product Information: BLOXIVERZ(TM) intravenous injection, neostigmine methylsulfate intravenous injection. Eclat Pharmaceuticals (per FDA), Chesterfield, MO, May, 2013.
6. Aquilonius SM: Clinical pharmacokinetics of cholinesterase inhibitors. Clin Pharmacokinet May, 1986; 11(3): 236-249.
7. Fisher DM, Cronnelly R, Miller RD et al: The neuromuscular pharmacology of neostigmine in infants and children. Anesthesiology Sep, 1983; 59(3): 220-225.
8. Bevan JC, Collins L, Fowler C et al: Early and late reversal of rocuronium and vecuronium with neostigmine in adults and children. Anesth Analg Aug, 1999; 89(2): 333-339.

1.124 Netilmicin

Title Netilmicin

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29*	0 to 7	5	48
	8 to 28	4	36
	≥29	4	24
30 to 34	0 to 7	4.5	36
	≥8	4	24
≥35	ALL	4	24

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Treatment of infections caused by aerobic gram-negative bacilli (e.g. *Pseudomonas*, *Klebsiella*, *E coli*). Usually used in combination with a β-lactam antibiotic.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of netilmicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity. The addition of other nephrotoxic and/or ototoxic medications (e.g. furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

Suggested Dosing Intervals

Level at 24 hours (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)

≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3	Measure level in 24 hours	

Special Considerations/Preparation

Available in a concentration of 100 mg/mL in 1.5 mL vials. A 10 mg/mL dilution may be made by adding 1 mL of this solution to 9 mL of sterile water for injection. Dilution is stable for 72 hours refrigerated. Do not freeze.**No longer available in the US.**

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Atropine, aztreonam, calcium gluconate, clindamycin, dexamethasone, heparin (concentrations ≤1 unit/mL), hydrocortisone succinate, iron dextran, isoproterenol, linezolid, metronidazole, norepinephrine, potassium chloride, procainamide, remifentanil, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Ampicillin, furosemide, heparin (concentrations >1 unit/mL), mezlocillin, nafcillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

References

- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA: Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-e118.
- Stolk LML, Degraeuwe PLJ, Nieman FHM, et al: Population pharmacokinetics and relationship between demographic and clinical variables and pharmacokinetics of gentamicin in neonates. *Ther Drug Monit* 2002;24:527-31.
- Avent ML, Kinney JS, Istre GR, Whitfield JM: Gentamicin and tobramycin in neonates: comparison of a new extended dosing regimen with a traditional multiple daily dosing regimen. *Am J Perinatol* 2002;8:413-19.
- Giapros VI, Andronikou S, Cholevas VI, Papadopoulou ZL: Renal function in premature infants during aminoglycoside therapy. *Pediatr Nephrol*1995;9:163.
- Daly JS, Dodge RA, Glew RH, et al: Effect of time and temperature on inactivation of aminoglycosides by ampicillin at neonatal dosages. *J Perinatol* 1997;17:42-45.

Title Netilmicin

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29*	0 to 7	5	48
	8 to 28	4	36
	≥29	4	24
30 to 34	0 to 7	4.5	36
	≥8	4	24
≥35	ALL	4	24

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Treatment of infections caused by aerobic gram-negative bacilli (e.g. *Pseudomonas*, *Klebsiella*, *E coli*). Usually used in combination with a β-lactam antibiotic.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of netilmicin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity.

The addition of other nephrotoxic and/or ototoxic medications (e.g. furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max} /MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

Suggested Dosing Intervals

Level at 24 hours (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3		Measure level in 24 hours

Special Considerations/Preparation

Available in a concentration of 100 mg/mL in 1.5 mL vials. A 10 mg/mL dilution may be made by adding 1 mL of this solution to 9 mL of sterile water for injection. Dilution is stable for 72 hours refrigerated. Do not freeze.**No longer available in the US.**

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Atropine, aztreonam, calcium gluconate, clindamycin, dexamethasone, heparin (concentrations ≤1 unit/mL), hydrocortisone succinate, iron

dextran, isoproterenol, linezolid, metronidazole, norepinephrine, potassium chloride, procainamide, remifentanil, sodium bicarbonate, and vitamin K_1.

Terminal Injection Site Incompatibility

Ampicillin, furosemide, heparin (concentrations >1 unit/mL), mezlocillin, nafcillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

References

- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA: Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-e118.
- Stolk LML, Degraeuwe PLJ, Nieman FHM, et al: Population pharmacokinetics and relationship between demographic and clinical variables and pharmacokinetics of gentamicin in neonates. *Ther Drug Monit* 2002;24:527-31.
- Avent ML, Kinney JS, Istre GR, Whitfield JM: Gentamicin and tobramycin in neonates: comparison of a new extended dosing regimen with a traditional multiple daily dosing regimen. *Am J Perinatol* 2002;8:413-19.
- Giapros VI, Andronikou S, Cholevas VI, Papadopoulou ZL: Renal function in premature infants during aminoglycoside therapy. *Pediatr Nephrol*1995;9:163.
- Daly JS, Dodge RA, Glew RH, et al: Effect of time and temperature on inactivation of aminoglycosides by ampicillin at neonatal dosages. *J Perinatol* 1997;17:42-45.

1.125 Nevirapine

Title Nevirapine

Dose

Prevention of Perinatal HIV Transmission:
Birth weight 1.5 to 2 kg: 8 mg/dose orally for 3 doses in the first week of life; give first dose within 48 hours of birth, second dose 48 hours after first dose, and third dose 96 hours after second dose [1] .
Birth weight greater than 2 kg: 12 mg/dose orally for 3 doses in the first week of life; give first dose within 48 hours of birth, second dose 48 hours after first dose, and third dose 96 hours after second dose [1] .
Nevirapine only used in combination with zidovudine prophylaxis. There are no recommendations for use of nevirapine in premature neonates due to lack of safety and dosing data [1] .

Administration

Can be given without regard to food [2] .

Uses

Prevention of maternal-fetal HIV transmission [1] . All neonates born to HIV-infected women should receive 6 weeks of zidovudine prophylaxis beginning as soon as possible after birth. Zidovudine alone is appropriate for infants born to women who received antepartum/intrapartum antiretroviral therapy with effective viral suppression.

Zidovudine plus 3 doses of nevirapine may be considered (in consultation with a pediatric HIV specialist) for infants born to women who received antepartum/intrapartum antiretroviral therapy but have suboptimal viral suppression near delivery. Zidovudine plus 3 doses of nevirapine is recommended for infants born to women who received only intrapartum antiretroviral therapy and for infants born to mothers who received no antepartum or intrapartum antiretroviral therapy [1] . In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamivudine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamivudine regimen was associated with increased toxicity (eg, neutropenia) [3] .

Black Box Warning According to the manufacturer's black box warning, severe, life-threatening, in some cases fatal, hepatotoxicity and skin reactions have been reported (in adults) [4] .

Pharmacology

Nevirapine is a non-nucleoside antiretroviral agent that inhibits HIV-1 replication by selectively interfering with viral reverse transcriptase without requiring intracellular metabolism. It also inactivates cell-free virions in the genital tract and breast milk. Synergistic antiviral activity occurs when administered with zidovudine. Nevirapine is rapidly absorbed after oral administration to pregnant women and is highly lipophilic, resulting in therapeutic concentrations being readily transferred across the placenta to the fetus. Serum half-life in neonates is approximately 30 to 44 hours [4] [5] . The 3-dose nevirapine regimen in neonates for prevention of perinatal HIV transmission provided serum concentrations above 100 ng/mL in all newborns through 10 days of life [6] . Nevirapine is extensively metabolized by, and an inducer of, hepatic CYP3A4 and CYP2B6 isoenzymes. Concomitant administration of phenobarbital or phenytoin (CYP3A inducers) may affect plasma concentrations [4] .

Adverse Effects

Limited data on toxicity; none reported in neonates.

Monitoring

CBC and differential before initiation of therapy, then periodically based on baseline values, gestational age, and the infant's clinical status, concomitant antiretrovirals and other medications, and maternal antiretroviral therapy. Serum chemistries and liver enzyme tests may be considered based on maternal antiretroviral regimen received during pregnancy [1] .

Special Considerations/Preparation

Available as an oral suspension in a concentration of 10 mg/mL. Store at room temperature. Shake suspension gently prior to administration [4] .

References

- Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission: Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Jul31, 2012. Available at: http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. National Institute of Health, Bethesda, MD, Aug11, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.

- Nielsen-Saines K, Watts DH, Veloso VG et al: Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med Jun21, 2012; 366(25): 2368-2379.

- Product Information: Viramune(R) oral tablets, suspension, nevirapine oral tablets, suspension. Boehringer Ingelheim Pharmaceuticals, Inc (per manufacturer), Ridgefield, CT, May, 2011.

- Mirochnick M, Fenton T, Gagnier P et al: Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. J Infect Dis 1998; 178(2): 368-374.

- Mirochnick M, Nielsen-Saines K, Pilotto JH et al: Nevirapine concentrations in newborns receiving an extended prophylactic regimen. J Acquir Immune Defic Syndr Mar1, 2008; 47(3): 334-337.

Title Nevirapine

Dose

Prevention of Perinatal HIV Transmission:
Birth weight 1.5 to 2 kg: 8 mg/dose orally for 3 doses in the first week of life; give first dose within 48 hours of birth, second dose 48 hours after first dose, and third dose 96 hours after second dose [1] .
Birth weight greater than 2 kg: 12 mg/dose orally for 3 doses in the first week of life; give first dose within 48 hours of birth, second dose 48 hours after first dose, and third dose 96 hours after second dose [1] .
Nevirapine only used in combination with zidovudine prophylaxis. There are no recommendations for use of nevirapine in premature neonates due to lack of safety and dosing data [1] .

Administration

Can be given without regard to food [2] .

Uses

Prevention of maternal-fetal HIV transmission [1] . All neonates born to HIV-infected women should receive 6 weeks of zidovudine prophylaxis beginning as soon as possible after birth. Zidovudine alone is appropriate for infants born to women who received antepartum/intrapartum antiretroviral therapy with effective viral suppression. Zidovudine plus 3 doses of nevirapine may be considered (in consultation with a pediatric HIV specialist) for infants born to women who received antepartum/intrapartum antiretroviral therapy but have suboptimal viral suppression near delivery. Zidovudine plus 3 doses of nevirapine is recommended for infants born to women who received only intrapartum antiretroviral therapy and for infants born to mothers who received no antepartum or intrapartum antiretroviral therapy [1] . In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamivudine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamivudine regimen was associated with increased toxicity (eg, neutropenia) [3] .

Black Box Warning According to the manufacturer's black box warning, severe, life-threatening, in some cases fatal, hepatotoxicity and skin reactions have been reported (in adults) [4] .

Pharmacology

Nevirapine is a non-nucleoside antiretroviral agent that inhibits HIV-1 replication by selectively interfering with viral reverse transcriptase without requiring intracellular metabolism. It also inactivates cell-free virions in the genital tract and breast milk. Synergistic antiviral activity occurs when administered with zidovudine. Nevirapine is rapidly absorbed after oral administration to pregnant women and is highly lipophilic, resulting in therapeutic concentrations being readily transferred across the placenta to the fetus. Serum half-life in neonates is approximately 30 to 44 hours [4] [5] . The 3-dose nevirapine regimen in neonates for prevention of perinatal HIV transmission provided serum concentrations above 100 ng/mL in all newborns through 10 days of life [6] . Nevirapine is extensively metabolized by, and an inducer of, hepatic CYP3A4 and CYP2B6 isoenzymes. Concomitant administration of phenobarbital or phenytoin (CYP3A inducers) may affect plasma concentrations [4] .

Adverse Effects

Limited data on toxicity; none reported in neonates.

Monitoring

CBC and differential before initiation of therapy, then periodically based on baseline values, gestational age, and the infant's clinical status, concomitant antiretrovirals and other medications, and maternal antiretroviral therapy. Serum chemistries and liver enzyme tests may be considered based on maternal antiretroviral regimen received during pregnancy [1] .

Special Considerations/Preparation

Available as an oral suspension in a concentration of 10 mg/mL. Store at room temperature. Shake suspension gently prior to administration [4] .

References

- Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission: Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. AIDSinfo, U.S. Department of Health and Human Services, Rockville, MD, Jul31, 2012. Available at: http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/.

- Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children: Guidelines for the use of antiretroviral agents in pediatric HIV infection. National Institute of Health, Bethesda, MD, Aug11, 2011. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf.

- Nielsen-Saines K, Watts DH, Veloso VG et al: Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. N Engl J Med Jun21, 2012; 366(25): 2368-2379.

- Product Information: Viramune(R) oral tablets, suspension, nevirapine oral tablets, suspension. Boehringer Ingelheim Pharmaceuticals, Inc (per manufacturer), Ridgefield, CT, May, 2011.

- Mirochnick M, Fenton T, Gagnier P et al: Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. J Infect Dis 1998; 178(2): 368-374.

- Mirochnick M, Nielsen-Saines K, Pilotto JH et al: Nevirapine concentrations in newborns receiving an extended prophylactic regimen. J Acquir Immune Defic Syndr Mar1, 2008; 47(3): 334-337.

1.126 NiCARdipine

Title NiCARdipine

Dose

Initial dose: 0.5 mcg/kg per minute continuous IV infusion.
Titrate dose to response. Blood pressure will begin to decrease within minutes of starting the infusion, reaching half of its ultimate decrease in approximately 45 minutes. Blood pressure equilibrium will not be achieved for approximately 50 hours (adult data).
Maintenance doses are usually 0.5 to 2 mcg/kg per minute.

Administration

Intravenous: Dilute prior to administration to a concentration of 0.1 mg/mL or use premixed solution (0.1 mg/mL; 200 mL). Administer by a central line or large peripheral vein [1] . There are literature reports of higher concentrations being used (0.5

mg/mL) in children without significant problems, except for superficial phlebitis [2] [3] .

Uses

Treatment of acute severe hypertension.

Contraindications/Precautions

Contraindicated in patients with advanced aortic stenosis [1] .

Pharmacology

Nicardipine is a dihydropyridine calcium channel blocker that significantly decreases systemic vascular resistance. Unlike other calcium channel blockers, it has limited effects on the myocardium. It is extensively metabolized by the liver, and is highly protein bound. Following infusion in adults, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (alpha half-life of 2.7 minutes), an intermediate phase (beta half-life of 44.8 minutes), and a slow terminal phase (gamma half-life of 14.4 hours) that can only be detected after long-term infusions. Experience in neonates is limited, and there are no reported pharmacokinetic data.

Adverse Effects

No adverse effects have been reported in neonates (small numbers). Hypotension and tachycardia are dose-dependent in adults. Headache, nausea, and vomiting were the other common effects reported.

Monitoring

Continuous monitoring of blood pressure, heart rate and rhythm during initiation of therapy, and frequently thereafter. Observe IV site for signs of irritation.

Special Considerations/Preparation

Available as 2.5-mg/mL solution for injection in 10-mL ampules. **Dilute prior to administration to a concentration of 0.1 mg/mL.** Dilution is stable at room temperature for 24 hours. Also available as premixed solution (0.1 mg/mL, 0.2 mg/mL; 200 mL) in dextrose or sodium chloride. Store ampuls and premixed solution at controlled room temperature in carton until ready to use. Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light.

Solution Compatibility

D_5W, NS, and D_5NS.

Solution Incompatibility

LR.

Terminal Injection Site Compatibility

No data available for Dex/AA solutions or fat emulsions.
Amikacin, aminophylline, aztreonam, calcium gluconate, cefazolin, ceftizoxime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin (concentrations of 1 unit/mL or less), hydrocortisone, lidocaine, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nitroglycerin, norepinephrine, penicillin G potassium, piperacillin, potassium chloride, potassium phosphate, ranitidine, sodium acetate, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefoperazone, ceftazidime, furosemide, heparin (concentrations greater than 1 unit/mL), micafungin, sodium bicarbonate and thiopental.

References

- McBride BF, White CM, Campbell M, Frey BM: Nicardipine to control neonatal hypertension during extracorporeal membrane oxygen support. *Ann Pharmacother* 2003;37:667-670.
- Tobias JD: Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001;8:3-6.
- Milou C, Debuche-Benouachkou V, Semama DS et al: Intravenous nicardipine as a first-line antihypertensive drug in neonates. *Intensive Care Med* 2000;26:956-958.
- Gouyon JB, Geneste B, Semama DS, et al: Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F126-127.

1. Product Information: CARDENE(R) IV Premixed Injection (0.1 mg/mL) IV injection, nicardipine HCL premixed injection (0.1 mg/mL) IV injection. EKR Therapeutics, Inc, Bedminster, NJ, Sep, 2010.
2. Flynn JT, Mottes TA, Brophy PD et al: Intravenous nicardipine for treatment of severe hypertension in children. J Pediatr Jul, 2001; 139(1): 38-43.
3. Michael J: Nicardipine for hypertensive emergencies in children with renal disease. Pediatr Nephrol Jan, 1998; 12(1): 40-42.

Title NiCARdipine

Dose

Initial dose: 0.5 mcg/kg per minute continuous IV infusion.
Titrate dose to response. Blood pressure will begin to decrease within minutes of starting the infusion, reaching half of its ultimate decrease in approximately 45 minutes. Blood pressure equilibrium will not be achieved for approximately 50 hours (adult data).
Maintenance doses are usually 0.5 to 2 mcg/kg per minute.

Administration

Intravenous: Dilute prior to administration to a concentration of 0.1 mg/mL or use premixed solution (0.1 mg/mL; 200 mL). Administer by a central line or large peripheral vein [1] . There are literature reports of higher concentrations being used (0.5 mg/mL) in children without significant problems, except for superficial phlebitis [2] [3] .

Uses

Treatment of acute severe hypertension.

Contraindications/Precautions

Contraindicated in patients with advanced aortic stenosis [1] .

Pharmacology

Nicardipine is a dihydropyridine calcium channel blocker that significantly decreases systemic vascular resistance. Unlike other calcium channel blockers, it has limited effects on the myocardium. It is extensively metabolized by the liver, and is highly protein bound. Following infusion in adults, nicardipine plasma concentrations decline tri-exponentially, with a rapid early distribution phase (alpha half-life of 2.7 minutes), an intermediate phase (beta half-life of 44.8 minutes), and a slow terminal phase (gamma half-life of 14.4 hours) that can only be detected after long-term infusions. Experience in neonates is limited, and there are no reported pharmacokinetic data.

Adverse Effects

No adverse effects have been reported in neonates (small numbers). Hypotension and tachycardia are dose-dependent in adults. Headache, nausea, and vomiting were the other common effects reported.

Monitoring

Continuous monitoring of blood pressure, heart rate and rhythm during initiation of therapy, and frequently thereafter. Observe IV site for signs of irritation.

Special Considerations/Preparation

Available as 2.5-mg/mL solution for injection in 10-mL ampules. **Dilute prior to administration to a concentration of 0.1 mg/mL.** Dilution is stable at room temperature for 24 hours. Also available as premixed solution (0.1 mg/mL, 0.2 mg/mL; 200 mL) in dextrose or sodium chloride. Store ampuls and premixed solution at controlled room temperature in carton until ready to use. Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided. Protect from light.

Solution Compatibility

D_5W, NS, and D_5NS.

Solution Incompatibility

LR.

Terminal Injection Site Compatibility

No data available for Dex/AA solutions or fat emulsions.
Amikacin, aminophylline, aztreonam, calcium gluconate, cefazolin, ceftizoxime, chloramphenicol, cimetidine, clindamycin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, esmolol, famotidine, fentanyl, gentamicin, heparin (concentrations of 1 unit/mL or less), hydrocortisone, lidocaine, linezolid, lorazepam, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nitroglycerin, norepinephrine, penicillin G potassium, piperacillin, potassium chloride, potassium phosphate, ranitidine, sodium acetate, sodium nitroprusside, tobramycin, trimethoprim/sulfamethoxazole, vancomycin, and vecuronium.

Terminal Injection Site Incompatibility

Ampicillin, cefepime, cefoperazone, ceftazidime, furosemide, heparin (concentrations greater than 1 unit/mL), micafungin, sodium bicarbonate and thiopental.

References

- McBride BF, White CM, Campbell M, Frey BM: Nicardipine to control neonatal hypertension during extracorporeal membrane oxygen support. *Ann Pharmacother* 2003;37:667-670.
- Tobias JD: Nicardipine to control mean arterial pressure after cardiothoracic surgery in infants and children. *Am J Ther* 2001;8:3-6.
- Milou C, Debuche-Benouachkou V, Semama DS et al: Intravenous nicardipine as a first-line antihypertensive drug in neonates. *Intensive Care Med* 2000;26:956-958.
- Gouyon JB, Geneste B, Semama DS, et al: Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997;76:F126-127.

1. Product Information: CARDENE(R) IV Premixed Injection (0.1 mg/mL) IV injection, nicardipine HCL premixed injection (0.1 mg/mL) IV injection. EKR Therapeutics, Inc, Bedminster, NJ, Sep, 2010.
2. Flynn JT, Mottes TA, Brophy PD et al: Intravenous nicardipine for treatment of severe hypertension in children. J Pediatr Jul, 2001; 139(1): 38-43.
3. Michael J: Nicardipine for hypertensive emergencies in children with renal disease. Pediatr Nephrol Jan, 1998; 12(1): 40-42.

1.127 Nitric Oxide

Title Nitric Oxide

Dose

Nitric oxide inhalation therapy (iNO) should be used only after mechanical ventilatory support has been optimized, including the use of surfactant. **Begin at 20 ppm.**
If within 4 hours PaO_2 increases to at least 60 torr, decrease to 5 ppm. Continue at 5 ppm and wean fiO_2 as tolerated. When fiO_2 is less than 0.6 and ventilatory support has

been decreased, wean iNO in 1 ppm increments at approximately 4 hour intervals as tolerated. Discontinue when stable on 1 ppm for 4 hours. The usual length of treatment is less than 4 days. Infants who cannot be weaned off after 4 days should undergo further diagnostic testing for other diseases.

Administration

Administer via an FDA/EMEA approved delivery system designed to accurately deliver NO uninterrupted into the ventilator system in parts-per-million concentrations that are constant throughout the respiratory cycle, while limiting NO_2 production (eg, INOvent™).

Uses

Treatment of term and near-term infants (greater than or equal to 34 weeks GA) with hypoxic respiratory failure (Oxygenation Index greater than 25) associated with clinical or echocardiographic evidence of pulmonary hypertension. It is usually not effective in infants with congenital diaphragmatic hernia.
Available evidence does not support the use in preterm infants less than 34 weeks GA [1] . The use of iNO in this population should be done under the auspices of a research protocol.

Contraindications/Precautions

Contraindicated in infants dependent on right-to-left cardiac blood flow.
Pulmonary edema has been reported in patients with preexisting left ventricular dysfunction.
Abrupt discontinuation may result in worsening oxygenation and increased pulmonary artery pressures. The risks of methemoglobinemia and elevated NO_2 levels increase significantly at doses greater than 20 ppm. Methemoglobin has very high affinity for oxygen and has a profound effect on oxygen content. Small increases in methemoglobin cause significant decreases in available oxygen content. Normal methemoglobin levels are less than 1%. In most neonatal studies, methemoglobinemia was defined as levels of 5% to 7%. Cyanosis develops at levels of 10%, although the patients generally remain asymptomatic. At methemoglobin levels approaching 30%, patients begin to experience respiratory distress, and cardiac, gastrointestinal, and neurologic symptoms. A methemoglobin level greater than 50% is usually lethal. Avoid concomitant use of acetaminophen, metoclopramide, sulfa drugs, topical anesthetics (EMLA, benzocaine, lidocaine, prilocaine). Congenital deficiencies in the methemoglobin reductase enzyme system occur but are rare. The environmental exposure limit set by the Occupational Safety and Health Administration is 25 ppm for NO and 5 ppm for NO_2.

Pharmacology

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that decreases extrapulmonary right-to-left shunting. It activates guanylate cyclase by binding to its heme component leading to production of cyclic GMP, with subsequent relaxation of pulmonary vascular smooth muscle. Oxygenation is also improved due to the redirecting of blood from poorly aerated to better aerated distal air spaces. In addition,

iNO appears to have both antioxidant and antiinflammatory activities. Systemically absorbed after inhalation. Metabolized to nitrate which is excreted in the urine.

Monitoring

Continuous monitoring of oxygenation, blood pressure and heart rate are mandatory. Measure blood methemoglobin concentration 4 hours after initiation of therapy and at 24 hour intervals thereafter. Monitoring of inspired gas must provide for continuous measurement of both NO and NO_2 concentrations, with a feedback mechanism that cuts off delivery if NO or NO_2 exceed acceptable limits.

Special Considerations/Preparation

Nitric oxide for inhalation is supplied in medical grade gas cylinders in 100 parts per million (ppm) and 800 ppm concentrations. Store vertically in well-ventilated areas at room temperature. All cylinders should be returned to the supplier for disposal. Hospital personnel should receive specific training in the administration of iNO.

References

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- Davidson D, Barefield ES, Kattwinkel J, et al: Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. *Pediatrics* 1999;104:231-36.
- The Neonatal Inhaled Nitric Oxide Study Group: Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med* 1997;336:597-604.
- Product Information, INO Therapeutics, 2009.

1. Askie LM, Ballard RA, Cutter GR et al: Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of Randomized Trials. Pediatrics Sep19, 2011; Epub: Epub.

Title Nitric Oxide

Dose

Nitric oxide inhalation therapy (iNO) should be used only after mechanical ventilatory support has been optimized, including the use of surfactant. **Begin at 20 ppm.**
If within 4 hours PaO_2 increases to at least 60 torr, decrease to 5 ppm. Continue at 5 ppm and wean fiO_2 as tolerated. When fiO_2 is less than 0.6 and ventilatory support has been decreased, wean iNO in 1 ppm increments at approximately 4 hour intervals as tolerated. Discontinue when stable on 1 ppm for 4 hours. The usual length of treatment is less than 4 days. Infants who cannot be weaned off after 4 days should undergo further diagnostic testing for other diseases.

Administration

Administer via an FDA/EMEA approved delivery system designed to accurately deliver NO uninterrupted into the ventilator system in parts-per-million concentrations that are constant throughout the respiratory cycle, while limiting NO_2 production (eg, INOvent™).

Uses

Treatment of term and near-term infants (greater than or equal to 34 weeks GA) with hypoxic respiratory failure (Oxygenation Index greater than 25) associated with clinical or echocardiographic evidence of pulmonary hypertension. It is usually not effective in infants with congenital diaphragmatic hernia.
Available evidence does not support the use in preterm infants less than 34 weeks GA [1] . The use of iNO in this population should be done under the auspices of a research protocol.

Contraindications/Precautions

Contraindicated in infants dependent on right-to-left cardiac blood flow.
Pulmonary edema has been reported in patients with preexisting left ventricular dysfunction.
Abrupt discontinuation may result in worsening oxygenation and increased pulmonary artery pressures. The risks of methemoglobinemia and elevated NO_2 levels increase significantly at doses greater than 20 ppm. Methemoglobin has very high affinity for oxygen and has a profound effect on oxygen content. Small increases in methemoglobin cause significant decreases in available oxygen content. Normal methemoglobin levels are less than 1%. In most neonatal studies, methemoglobinemia was defined as levels of 5% to 7%. Cyanosis develops at levels of 10%, although the patients generally remain asymptomatic. At methemoglobin levels approaching 30%, patients begin to experience respiratory distress, and cardiac, gastrointestinal, and neurologic symptoms. A methemoglobin level greater than 50% is usually lethal. Avoid concomitant use of acetaminophen, metoclopramide, sulfa drugs, topical anesthetics (EMLA, benzocaine, lidocaine, prilocaine). Congenital deficiencies in the

methemoglobin reductase enzyme system occur but are rare. The environmental exposure limit set by the Occupational Safety and Health Administration is 25 ppm for NO and 5 ppm for NO_2.

Pharmacology

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator that decreases extrapulmonary right-to-left shunting. It activates guanylate cyclase by binding to its heme component leading to production of cyclic GMP, with subsequent relaxation of pulmonary vascular smooth muscle. Oxygenation is also improved due to the redirecting of blood from poorly aerated to better aerated distal air spaces. In addition, iNO appears to have both antioxidant and antiinflammatory activities. Systemically absorbed after inhalation. Metabolized to nitrate which is excreted in the urine.

Monitoring

Continuous monitoring of oxygenation, blood pressure and heart rate are mandatory. Measure blood methemoglobin concentration 4 hours after initiation of therapy and at 24 hour intervals thereafter. Monitoring of inspired gas must provide for continuous measurement of both NO and NO_2 concentrations, with a feedback mechanism that cuts off delivery if NO or NO_2 exceed acceptable limits.

Special Considerations/Preparation

Nitric oxide for inhalation is supplied in medical grade gas cylinders in 100 parts per million (ppm) and 800 ppm concentrations. Store vertically in well-ventilated areas at room temperature. All cylinders should be returned to the supplier for disposal. Hospital personnel should receive specific training in the administration of iNO.

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- Product Information, INO Therapeutics, 2009.

1. Askie LM, Ballard RA, Cutter GR et al: Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of Randomized Trials. Pediatrics Sep19, 2011; Epub: Epub.

1.128 Nizatidine

Title Nizatidine

Dose

Oral: 2 to 5 mg/kg/dose orally every 12 hours.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Pharmacology

Inhibits gastric acid secretion by histamine H_2 -receptor antagonism. Peak serum concentration occurs 0.5 to 3 hours after oral administration and is not influenced by food. Bioavailability is quite variable. Greater than 90% eliminated in the urine within 12 hours with 60% excreted unchanged. Elimination half-life in neonates is 3 to 7 hours, and is prolonged in preterm infants and patients with renal insufficiency.

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for late-onset bacterial and fungal sepsis. Routine gastric acid suppression in neonates should be avoided. Limited data on nizatidine in neonatal patients. One case report of thrombocytopenia. No other adverse effects have been reported in infants or children. Elevations in hepatic enzymes and asymptomatic ventricular tachycardia have been reported in adults.

Monitoring

Gastric pH may be measured to assess efficacy.

Special Considerations/Preparation

Axid®alcohol-free oral solution (15 mg/mL) is supplied in 480 mL bottles. Store at room temperature.

References

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- Product information, Braintree Laboratories, Inc., 2005.

Title Nizatidine

Dose

Oral: 2 to 5 mg/kg/dose orally every 12 hours.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Pharmacology

Inhibits gastric acid secretion by histamine H_2 -receptor antagonism. Peak serum concentration occurs 0.5 to 3 hours after oral administration and is not influenced by food. Bioavailability is quite variable. Greater than 90% eliminated in the urine within 12 hours with 60% excreted unchanged. Elimination half-life in neonates is 3 to 7 hours, and is prolonged in preterm infants and patients with renal insufficiency.

Adverse Effects

The use of H2 blockers in preterm infants has been associated with an increased risk for late-onset bacterial and fungal sepsis. Routine gastric acid suppression in neonates

should be avoided. Limited data on nizatidine in neonatal patients. One case report of thrombocytopenia. No other adverse effects have been reported in infants or children. Elevations in hepatic enzymes and asymptomatic ventricular tachycardia have been reported in adults.

Monitoring

Gastric pH may be measured to assess efficacy.

Special Considerations/Preparation

Axid®alcohol-free oral solution (15 mg/mL) is supplied in 480 mL bottles. Store at room temperature.

References

- Graham PL, Begg MD, Larson E, et al: Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J* 2006;25:113-117.
- Saiman L, Ludington E, Pfaller M, et al: Risk factors for candidemia in neonatal intensive care unit patients. *Pediatr Infect Dis J* 2000;19:319-324.
- Orenstein SR, Gremse DA, Pantaleon CD, et at: Nizatidine for the treatment of pediatric gastroesophageal reflux symptoms: An open-label, multiple-dose, randomized, multicenter clinical trial in 210 children. *Clin Therapeutics* 2005;27:472-483.
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- Abdel-Rahman SM, Johnson FK, Manowitz N, et al: Single-dose pharmacokinetics of nizatidine (Axid®) in children. *J Clin Pharmacol*2002;42:1089-1096.
- Product information, Braintree Laboratories, Inc., 2005.

1.129 Norepinephrine

Title Norepinephrine

Dose

Septic Shock
Gestational age greater than 35 weeks: Initial dose, 0.2 to 0.5 mcg/kg/min by IV infusion; titrate every 30 minutes to target blood pressure. Usual Infusion rate 0.2 to 2 mcg/kg/min; higher rates may be required [1] .

Administration

Must be diluted before infusion and administered via central venous route [2] [1] [3] [4] at a concentration of 16 to 100 mcg/mL [5] [1] [3] . Avoid the catheter tie-in technique. Constantly watch the flow rate and never leave patient unattended [4] .

Uses

Septic shock. Norepinephrine and fluids are recommended for warm shock with low blood pressure that has not responded to fluid therapy, dopamine/dobutamine, and epinephrine [2] . A small observational study (n=22; gestational age greater than 35 weeks) suggested that norepinephrine be used for shock associated with hypotension and poor perfusion (cold shock) that has not responded to fluid therapy and dopamine/dobutamine. Norepinephrine was started via central venous catheter at 0.2 to 0.5 mcg/kg/min and titrated every 30 minutes to target mean blood pressure; maximum individual infusion rate was 7.1 mcg/kg/min. Mean values for systemic blood pressure (diastolic greater than systolic), heart rate, and urine output increased, while oxygen need and plasma lactate levels decreased. Three infants required extracorporeal membrane oxygenation due to persistent pulmonary hypertension. The mortality rate was 18% [1] .

Persistent pulmonary hypertension (PPHN) with circulatory failure. A small observational study (n=18; gestational age greater than 35 weeks) demonstrated that norepinephrine improved lung function in neonates with PPHN having low systemic blood pressure and reduced cardiac output despite fluid resuscitation. Norepinephrine was started via central venous catheter at 0.5 mcg/kg/min and titrated every 30 minutes to target systemic artery pressure (SAP); the maximum infusion rate was 1 mcg/kg/min. Mean SAP and mean pulmonary artery pressure (PAP) were both increased, with a concomitant decrease in the mean PAP/SAP ratio, resulting in increased pulmonary blood flow and cardiac output. In addition, median oxygen need was progressively reduced over time. No study patient required extracorporeal membrane oxygenation [3] .

Contraindications/Precautions

Contraindicated in hypotension due to blood volume deficits (except in emergency until blood can be administered), mesenteric or peripheral vascular thrombosis, during cyclopropane and halothane anesthesia, and in presence of profound hypoxia or hypercarbia [4] .

Contains sodium metabisulfite, which may cause allergic-type reactions (eg, anaphylactic symptoms; life-threatening or less severe asthmatic episodes) in certain susceptible people. Sensitivity is more common in asthmatic than nonasthmatic patients [4] .

Avoid abrupt withdrawal; taper infusion gradually, as indicated [4] .

Black Box Warning

To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with saline solution containing

phentolamine mesylate for injection USP, an adrenergic blocking agent. Phentolamine should be given as soon as possible after the extravasation is noted [4] .

Pharmacology

Norepinephrine, a sympathomimetic amine, has both alpha-adrenergic activity resulting in peripheral vasoconstriction, and beta-adrenergic activity leading to inotropic stimulation of the heart and coronary artery vasodilation [4] .

Monitoring

Monitor blood pressure every 2 minutes from start of administration until target blood pressure is obtained and every 5 minutes thereafter until infusion is discontinued. Observe for signs of extravasation. Assess for plasma volume depletion during prolonged treatment [4] . When used for septic shock, monitor hemodynamics and oxygen saturation using techniques appropriate for clinical status. Target heart rate and perfusion pressure appropriate for patient's gestational and postnatal age. For a full-term newborn, the target heart rate and perfusion pressure are 120 to 180 beats/min and 55 mmHg, respectively [2] [6] .

Special Considerations/Preparation

Available for IV infusion in 4-mL ampules containing 1 mg/mL. Protect ampules from light [4] .

Mix norepinephrine in dextrose solutions (dextrose 5% in water, dextrose 5% in saline) since dextrose-containing solutions protect against excessive oxidation and subsequent potency loss **Administration in saline alone is not recommended** [4] . Final concentration of 100 mcg/mL [1] [3]

Solution Compatibility

D_5W, D_5NS, NS, LR

Terminal Injection Site Compatibility

Norepinephrine 0.004 mg/mL:
Famotidine 0.2 mg/mL, vasopressin 0.2 units/mL, 20 units/10 mL, and 40 units/10 mL.

Norepinephrine 0.016 mg/mL:
Propofol 10 mg/mL, vasopressin 0.2 units/mL.

Norepinephrine 0.02 mg/mL:
Clonidine 0.018 mg/mL.

Norepinephrine 0.032 mg/mL:
Dobutamine 2 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.008 mg/mL.

Norepinephrine 0.064 mg/mL:
Dopamine 3.2 mg/mL, esmolol 40 mg/mL, labetalol 5 mg/mL, midazolam 1 mg/mL, milrinone 0.4 mg/mL, morphine 1 mg/mL.

Norepinephrine 0.1 mg/mL:
Dobutamine 10 mg/mL.

Norepinephrine 0.12 mg/mL:
Bivalirudin 5 mg/mL, cisatracurium 0.1, 2, and 5 mg/mL, dexmedetomidine 4 mcg/mL, diltiazem 1 mg/mL.

Norepinephrine 0.128 mg/mL:
Argatroban 1 mg/mL, caspofungin 0.5 and 0.7 mg/mL, daptomycin 10 mg/mL, diltiazem 1 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.02 mg/mL, ertapenem 20 mg/mL, fentanyl citrate 50 mcg/mL, granisetron 50 mcg/mL, heparin 100 units/mL, hydromorphone 1 mg/mL, labetalol 2 mg/mL, linezolid 2 mg/mL, lorazepam 0.5 mg/mL, methotrexate 15 mg/mL, metronidazole 5 mg/mL, micafungin 1.5 mg/mL, midazolam 2 mg/mL, milrinone 0.2 mg/mL, morphine 2 mg/mL, mycophenolate mofetil 6 mg/mL, nicardipine 1 mg/mL, nitroglycerin 0.4 mg/mL, octreotide acetate 5 mcg/mL, ondansetron 1 mg/mL, palonosetron 50 mcg/mL, pancuronium 0.1 mg/mL, piperacillin/tazobactam 40 and 5 mg/mL, ranitidine 1 mg/mL, tacrolimus 20 mcg/mL, vecuronium 1 mg/mL, voriconazole 4 mg/mL.

Norepinephrine 0.5 mg/mL:
Amikacin 20 mg/mL, atracurium 5 mg/mL, atropine 0.5 mg/mL, aztreonam 80 mg/mL, bumetanide 0.125 mg/mL, calcium chloride 50 mg/mL, calcium gluconate 50 mg/mL, cefazolin 220 mg/mL, cefotaxime 285 mg/mL, cefotetan 400 mg/mL, cefoxitin 450 mg/mL, ceftazidime 400 mg/mL, ceftriaxone 165 mg/mL, cefuroxime 125 mg/mL, chloramphenicol 333 mg/mL, cimetidine 24 mg/mL, clindamycin 48 mg/mL, cyanocobalamin 0.5 mg/mL, cyclosporine 2 mg/mL, dexamethasone 12 mg/mL, digoxin 0.125 mg/mL, diphenhydramine 25 mg/mL, dobutamine 6.25 and 10 mg/mL, dopamine 12.8 mg/mL, doxycycline 4 mg/mL, enalaprilat 0.625 mg/mL, ephedrine 12.5 mg/mL, epinephrine 0.5 mg/mL, epoetin alfa 5000 units/mL, erythromycin 20 mg/mL, esmolol 40 mg/mL, famotidine 5 mg/mL, fentanyl 25 mcg/mL, fluconazole 2 mg/mL, gentamicin 6.4 mg/mL, glycopyrrolate 0.1 mg/mL, heparin 160 units/mL, hydrocortisone 62.5 mg/mL, imipenem/cilastatin 5 mg/mL, isoproterenol 80 mcg/mL, ketorolac 15 mg/mL, labetalol 2.5 mg/mL, lidocaine 10 mg/mL, magnesium 250 mg/mL, mannitol 150 mg/mL (15%), methyldopate 25 mg/mL, methylprednisolone 125 mg/mL, metoclopramide 2.5 mg/mL, metoprolol 0.5 mg/mL, midazolam 2.5 mg/mL, morphine 4 mg/mL, nafcillin 250 mg/mL, nalbuphine 10 mg/mL, naloxone 16 mcg/mL, netilmicin 50 mg/mL, nitroglycerin 1.6 mg/mL, ondansetron 1 mg/mL, oxacillin 160 mg/mL, papaverine 15 mg/mL, penicillin G potassium 500,000 units/mL, penicillin G sodium 500,000 units/mL, phentolamine 5 mg/mL, phenylephrine 4 mg/mL, piperacillin 320 mg/mL, potassium chloride 1 mEq/mL, procainamide 250 mg/mL, prochlorperazine 2.5 mg/mL, propranolol 0.5 mg/mL, protamine 5 mg/mL, pyridoxine 50 mg/mL, ranitidine 2 mg/mL, succinylcholine 8 mg/mL, ticarcillin/clavulanate 195 mg/mL, tobramycin 6.4 mg/mL, vancomycin 20 mg/mL, vasopressin 4 units/mL, verapamil 1.25 mg/mL.

Norepinephrine 1 mg/mL:
Argatroban 1 mg/mL, dobutamine 10 mg/mL, epinephrine 0.5 and 1 mg/mL, heparin 1 unit/mL, hydrocortisone 0.01 mg/mL, meropenem 1 and 50 mg/mL, mycophenolate mofetil 5.9 mg/mL, potassium chloride 0.04 mEq/mL, propofol 10 mg/mL.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B conventional colloidal, amphotericin B lipid complex, azathioprine, diazepam, diazoxide, foscarnet, ganciclovir, indomethacin, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, sulfamethoxazole/trimethoprim.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 12/15/2012.

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Title Norepinephrine

Dose

Septic Shock
Gestational age greater than 35 weeks: Initial dose, 0.2 to 0.5 mcg/kg/min by IV

infusion; titrate every 30 minutes to target blood pressure. Usual Infusion rate 0.2 to 2 mcg/kg/min; higher rates may be required [1] .

Administration

Must be diluted before infusion and administered via central venous route [2] [1] [3] [4] at a concentration of 16 to 100 mcg/mL [5] [1] [3] . Avoid the catheter tie-in technique. Constantly watch the flow rate and never leave patient unattended [4] .

Uses

Septic shock. Norepinephrine and fluids are recommended for warm shock with low blood pressure that has not responded to fluid therapy, dopamine/dobutamine, and epinephrine [2] . A small observational study (n=22; gestational age greater than 35 weeks) suggested that norepinephrine be used for shock associated with hypotension and poor perfusion (cold shock) that has not responded to fluid therapy and dopamine/dobutamine. Norepinephrine was started via central venous catheter at 0.2 to 0.5 mcg/kg/min and titrated every 30 minutes to target mean blood pressure; maximum individual infusion rate was 7.1 mcg/kg/min. Mean values for systemic blood pressure (diastolic greater than systolic), heart rate, and urine output increased, while oxygen need and plasma lactate levels decreased. Three infants required extracorporeal membrane oxygenation due to persistent pulmonary hypertension. The mortality rate was 18% [1] .

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Contraindications/Precautions

Contraindicated in hypotension due to blood volume deficits (except in emergency until blood can be administered), mesenteric or peripheral vascular thrombosis, during cyclopropane and halothane anesthesia, and in presence of profound hypoxia or hypercarbia [4] .

Contains sodium metabisulfite, which may cause allergic-type reactions (eg, anaphylactic symptoms; life-threatening or less severe asthmatic episodes) in certain susceptible people. Sensitivity is more common in asthmatic than nonasthmatic patients [4] .

Avoid abrupt withdrawal; taper infusion gradually, as indicated [4] .

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To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with saline solution containing phentolamine mesylate for injection USP, an adrenergic blocking agent. Phentolamine should be given as soon as possible after the extravasation is noted [4] .

Pharmacology

Norepinephrine, a sympathomimetic amine, has both alpha-adrenergic activity resulting in peripheral vasoconstriction, and beta-adrenergic activity leading to inotropic stimulation of the heart and coronary artery vasodilation [4] .

Monitoring

Monitor blood pressure every 2 minutes from start of administration until target blood pressure is obtained and every 5 minutes thereafter until infusion is discontinued. Observe for signs of extravasation. Assess for plasma volume depletion during prolonged treatment [4] . When used for septic shock, monitor hemodynamics and oxygen saturation using techniques appropriate for clinical status. Target heart rate and perfusion pressure appropriate for patient's gestational and postnatal age. For a full-term newborn, the target heart rate and perfusion pressure are 120 to 180 beats/min and 55 mmHg, respectively [2] [6] .

Special Considerations/Preparation

Available for IV infusion in 4-mL ampules containing 1 mg/mL. Protect ampules from light [4] .

Mix norepinephrine in dextrose solutions (dextrose 5% in water, dextrose 5% in saline) since dextrose-containing solutions protect against excessive oxidation and subsequent potency loss **Administration in saline alone is not recommended** [4] . Final concentration of 100 mcg/mL [1] [3]

Solution Compatibility

D_5W, D_5NS, NS, LR

Terminal Injection Site Compatibility

Norepinephrine 0.004 mg/mL:
Famotidine 0.2 mg/mL, vasopressin 0.2 units/mL, 20 units/10 mL, and 40 units/10 mL.

Norepinephrine 0.016 mg/mL:
Propofol 10 mg/mL, vasopressin 0.2 units/mL.

Norepinephrine 0.02 mg/mL:
Clonidine 0.018 mg/mL.

Norepinephrine 0.032 mg/mL:
Dobutamine 2 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.008 mg/mL.

Norepinephrine 0.064 mg/mL:
Dopamine 3.2 mg/mL, esmolol 40 mg/mL, labetalol 5 mg/mL, midazolam 1 mg/mL, milrinone 0.4 mg/mL, morphine 1 mg/mL.

Norepinephrine 0.1 mg/mL:
Dobutamine 10 mg/mL.

Norepinephrine 0.12 mg/mL:
Bivalirudin 5 mg/mL, cisatracurium 0.1, 2, and 5 mg/mL, dexmedetomidine 4 mcg/mL, diltiazem 1 mg/mL.

Norepinephrine 0.128 mg/mL:
Argatroban 1 mg/mL, caspofungin 0.5 and 0.7 mg/mL, daptomycin 10 mg/mL, diltiazem 1 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, epinephrine 0.02 mg/mL, ertapenem 20 mg/mL, fentanyl citrate 50 mcg/mL, granisetron 50 mcg/mL, heparin 100 units/mL, hydromorphone 1 mg/mL, labetalol 2 mg/mL, linezolid 2 mg/mL, lorazepam 0.5 mg/mL, methotrexate 15 mg/mL, metronidazole 5 mg/mL, micafungin 1.5 mg/mL, midazolam 2 mg/mL, milrinone 0.2 mg/mL, morphine 2 mg/mL, mycophenolate mofetil 6 mg/mL, nicardipine 1 mg/mL, nitroglycerin 0.4 mg/mL, octreotide acetate 5 mcg/mL, ondansetron 1 mg/mL, palonosetron 50 mcg/mL, pancuronium 0.1 mg/mL, piperacillin/tazobactam 40 and 5 mg/mL, ranitidine 1 mg/mL, tacrolimus 20 mcg/mL, vecuronium 1 mg/mL, voriconazole 4 mg/mL.

Norepinephrine 0.5 mg/mL:
Amikacin 20 mg/mL, atracurium 5 mg/mL, atropine 0.5 mg/mL, aztreonam 80 mg/mL, bumetanide 0.125 mg/mL, calcium chloride 50 mg/mL, calcium gluconate 50 mg/mL, cefazolin 220 mg/mL, cefotaxime 285 mg/mL, cefotetan 400 mg/mL, cefoxitin 450 mg/mL, ceftazidime 400 mg/mL, ceftriaxone 165 mg/mL, cefuroxime 125 mg/mL, chloramphenicol 333 mg/mL, cimetidine 24 mg/mL, clindamycin 48 mg/mL, cyanocobalamin 0.5 mg/mL, cyclosporine 2 mg/mL, dexamethasone 12 mg/mL, digoxin 0.125 mg/mL, diphenhydramine 25 mg/mL, dobutamine 6.25 and 10 mg/mL, dopamine 12.8 mg/mL, doxycycline 4 mg/mL, enalaprilat 0.625 mg/mL, ephedrine 12.5 mg/mL, epinephrine 0.5 mg/mL, epoetin alfa 5000 units/mL, erythromycin 20 mg/mL, esmolol 40 mg/mL, famotidine 5 mg/mL, fentanyl 25 mcg/mL, fluconazole 2 mg/mL, gentamicin 6.4 mg/mL, glycopyrrolate 0.1 mg/mL, heparin 160 units/mL, hydrocortisone 62.5 mg/mL, imipenem/cilastatin 5 mg/mL, isoproterenol 80 mcg/mL, ketorolac 15 mg/mL, labetalol 2.5 mg/mL, lidocaine 10 mg/mL, magnesium 250 mg/mL, mannitol 150 mg/mL (15%), methyldopate 25 mg/mL, methylprednisolone 125 mg/mL, metoclopramide 2.5 mg/mL, metoprolol 0.5 mg/mL, midazolam 2.5 mg/mL, morphine 4 mg/mL, nafcillin 250 mg/mL, nalbuphine 10 mg/mL, naloxone 16 mcg/mL, netilmicin 50 mg/mL, nitroglycerin 1.6 mg/mL, ondansetron 1 mg/mL, oxacillin 160 mg/mL, papaverine 15 mg/mL, penicillin G potassium 500,000 units/mL, penicillin G sodium 500,000 units/mL, phentolamine 5 mg/mL, phenylephrine 4 mg/mL, piperacillin 320 mg/mL, potassium chloride 1 mEq/mL, procainamide 250 mg/mL, prochlorperazine 2.5 mg/mL, propranolol 0.5 mg/mL, protamine 5 mg/mL, pyridoxine 50 mg/mL, ranitidine 2 mg/mL, succinylcholine 8 mg/mL, ticarcillin/clavulanate 195

mg/mL, tobramycin 6.4 mg/mL, vancomycin 20 mg/mL, vasopressin 4 units/mL, verapamil 1.25 mg/mL.

Norepinephrine 1 mg/mL:
Argatroban 1 mg/mL, dobutamine 10 mg/mL, epinephrine 0.5 and 1 mg/mL, heparin 1 unit/mL, hydrocortisone 0.01 mg/mL, meropenem 1 and 50 mg/mL, mycophenolate mofetil 5.9 mg/mL, potassium chloride 0.04 mEq/mL, propofol 10 mg/mL.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B conventional colloidal, amphotericin B lipid complex, azathioprine, diazepam, diazoxide, foscarnet, ganciclovir, indomethacin, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, sulfamethoxazole/trimethoprim.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 12/15/2012.

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1.130 Nystatin

Title Nystatin

Dose

Topical: Apply ointment or cream to affected area every 6 hours.
Continue treatment for 3 days after symptoms have subsided.

Oral: 1 mL (preterm) to 2 mL (term) of 100,000-units/mL suspension divided and applied with swab to each side of mouth every 6 hours.
Continue treatment for 3 days after symptoms have subsided.

Prophylaxis: 1 mL of 100,000 units/mL suspension orally or instilled into stomach via oro/nasogastric tube 3 times per day.

Uses

Treatment of mucocutaneous candidal infections. Prophylaxis against invasive fungal infections in high risk VLBW infants.

Pharmacology

Polyene antifungal similar in structure to amphotericin B. May be fungicidal or fungistatic. Binds to the fungal cell membrane causing disruption of the cell structure. Not absorbed well from the GI tract, skin, or mucous membranes.

Adverse Effects

Possible skin rash caused by vehicle in ointment/cream.

Monitoring

Assess response to drug.

Special Considerations/Preparation

Topical ointment/cream: 100,000 units/g in 15- and 30-g tubes. Ointment dissolved in polyethylene and mineral-oil-gel base.

Topical powder: 100,000 units/g in 15- and 30-g plastic squeeze bottles.

Oral suspension: 100,000 units/mL in 5-, 60-, and 480-mL bottles. Shake well before applying to mouth. Appears to work best when not mixed with formula. Contains less than 1% alcohol, saccharin, and 50% sucrose.

References

- Ozturk MA, Gunes T, Koklu E, et al: Oral nystatin prophylaxis to prevent invasive candidiasis in neonatal intensive care unit. *Mycoses* 2006;49:484-492.
- Hoppe JE: Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Ped Inf Dis J* 1997;16:885-94.

- Faix RG, Kovarik SM, Shaw TR, Johnson RV: Mucocutaneous and invasive candidiasis among very low birth weight (*Pediatrics* 1989;83:101.
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- Product Information, Actavis, 2006.

Title Nystatin

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Continue treatment for 3 days after symptoms have subsided.

Oral: 1 mL (preterm) to 2 mL (term) of 100,000-units/mL suspension divided and applied with swab to each side of mouth every 6 hours.
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Pharmacology

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Adverse Effects

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Monitoring

Assess response to drug.

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Topical powder: 100,000 units/g in 15- and 30-g plastic squeeze bottles.

Oral suspension: 100,000 units/mL in 5-, 60-, and 480-mL bottles. Shake well before applying to mouth. Appears to work best when not mixed with formula. Contains less than 1% alcohol, saccharin, and 50% sucrose.

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- Ozturk MA, Gunes T, Koklu E, et al: Oral nystatin prophylaxis to prevent invasive candidiasis in neonatal intensive care unit. *Mycoses* 2006;49:484-492.
- Hoppe JE: Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Ped Inf Dis J* 1997;16:885-94.
- Faix RG, Kovarik SM, Shaw TR, Johnson RV: Mucocutaneous and invasive candidiasis among very low birth weight (*Pediatrics* 1989;83:101.
- Roberts RJ: *Drug Therapy in Infants.* Philadelphia: WB Saunders Co, 1984, p 81.
- Munz D, Powell KR, Pai CH: Treatment of candidal diaper dermatitis: A double-blind placebo-controlled comparison of topical nystatin with topical plus oral nystatin. *J Pediatr* 1982;101:1022.
- Product Information, Actavis, 2006.

1.131 Octreotide

Title Octreotide

Dose

Treatment of hyperinsulinemic hypoglycemia:
Initial dose: 1 mcg/kg/dose every 6 hours subQ or IV. Titrate upward to desired effect. Initial response should occur within 8 hours; tachyphylaxis may occur within several days.
Maximum dose: 10 mcg/kg/dose every 6 hours.

Treatment of chylothorax:
Begin at 1 mcg/kg/hour IV continuous infusion. Titrate upward as necessary based on reduction in chyle production; dosage increases of 1 mcg/kg/hour every 24 hours have been used. Infusion is decreased gradually over 2 to 7 days.
Maximum dose: 10 mcg/kg/hour.
Has also been used subQ or IV in divided doses.

Uses

Treatment of refractory hyperinsulinemic hypoglycemia.

Adjunctive treatment of congenital and postoperative chylothorax.

Pharmacology

Octreotide is a long-acting analog of the natural hormone somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. The elimination half-life of

octreotide from plasma is approximately 1.7 hours in adults compared with 1 to 3 minutes for the natural hormone. Excreted unchanged into the urine.

Adverse Effects

Vomiting, diarrhea, abdominal distention and steatorrhea may occur. Pulmonary hypertension has been reported in treated former premature infants with chronic lung disease. Necrotizing enterocolitis has been reported in term neonates receiving octreotide for the treatment of hyperinsulinemic hypoglycemia (6 cases) and chylothorax (2 cases). Hyperglycemia may occur in patients being treated for chylothorax.

Monitoring

Monitor blood glucose closely. Monitor for signs and symptoms of necrotizing enterocolitis.

Special Considerations/Preparation

Available in 1-mL single-dose ampules for injection containing 50-, 100-, or 500-mcg, and in 5-mL multiple-dose vials in concentrations of 200 and 1000 mcg/mL. pH 3.9 to 4.5. Osmolarity is 279 mOsm/kg. Refrigerate and protect from light. Do not warm artificially. After initial use, multiple dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

For subQ injection, use undiluted drug unless dose volume is not accurately measurable. For continuous IV administration, consider making a dilution of 10 to 25 mcg/mL using D_5W or NS.

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Do not add directly to Dex/AA bag because of the formation of glycosyl octreotide conjugate.

Terminal Injection Site Compatibility

Dex/AA and heparin.

Terminal Injection Site Incompatibility

Micafungin.

References

- Laje P, Halaby L, Adzick NS, Stanley CA: Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes* 2010;11:142-147.
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- Thornton PS, Alter CA, Katz LE, et al: Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123:637-643.
- Product Information, Novartis, 2005.

Title Octreotide

Dose

Treatment of hyperinsulinemic hypoglycemia:
Initial dose: 1 mcg/kg/dose every 6 hours subQ or IV. Titrate upward to desired effect. Initial response should occur within 8 hours; tachyphylaxis may occur within several days.
Maximum dose: 10 mcg/kg/dose every 6 hours.

Treatment of chylothorax:
Begin at 1 mcg/kg/hour IV continuous infusion. Titrate upward as necessary based on reduction in chyle production; dosage increases of 1 mcg/kg/hour every 24 hours have been used. Infusion is decreased gradually over 2 to 7 days.
Maximum dose: 10 mcg/kg/hour.
Has also been used subQ or IV in divided doses.

Uses

Treatment of refractory hyperinsulinemic hypoglycemia.

Adjunctive treatment of congenital and postoperative chylothorax.

Pharmacology

Octreotide is a long-acting analog of the natural hormone somatostatin. It is an even more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Like somatostatin, it also suppresses LH response to GnRH, decreases splanchnic blood flow, and inhibits release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide. After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. The elimination half-life of octreotide from plasma is approximately 1.7 hours in adults compared with 1 to 3 minutes for the natural hormone. Excreted unchanged into the urine.

Adverse Effects

Vomiting, diarrhea, abdominal distention and steatorrhea may occur. Pulmonary hypertension has been reported in treated former premature infants with chronic lung disease. Necrotizing enterocolitis has been reported in term neonates receiving octreotide for the treatment of hyperinsulinemic hypoglycemia (6 cases) and chylothorax (2 cases). Hyperglycemia may occur in patients being treated for chylothorax.

Monitoring

Monitor blood glucose closely. Monitor for signs and symptoms of necrotizing enterocolitis.

Special Considerations/Preparation

Available in 1-mL single-dose ampules for injection containing 50-, 100-, or 500-mcg, and in 5-mL multiple-dose vials in concentrations of 200 and 1000 mcg/mL. pH 3.9 to 4.5. Osmolarity is 279 mOsm/kg. Refrigerate and protect from light. Do not warm artificially. After initial use, multiple dose vials should be discarded within 14 days. Ampuls should be opened just prior to administration and the unused portion discarded.

For subQ injection, use undiluted drug unless dose volume is not accurately measurable. For continuous IV administration, consider making a dilution of 10 to 25 mcg/mL using D_5W or NS.

Solution Compatibility

D_5W and NS.

Solution Incompatibility

Do not add directly to Dex/AA bag because of the formation of glycosyl octreotide conjugate.

Terminal Injection Site Compatibility

Dex/AA and heparin.

Terminal Injection Site Incompatibility

Micafungin.

References

- Laje P, Halaby L, Adzick NS, Stanley CA: Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr Diabetes* 2010;11:142-147.
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- Moreira-Pinto J, Rocha P, Osorio A, et al: Octreotide in the treatment of neonatal postoperative chylothorax: Report of three cases and literature review. *Pediatr Surg Int* 2010;Sept 7 [Epub ahead of print].
- Bulbul A, Okan F, Nuhoglu A: Idiopathic congenital chylothorax presented with severe hydrops and treated with octreotide in term newborn. *J Matern Fetal Neonatal Med* 2009;22:1197-1200.
- Paget-Brown A, Kattwinkel J, Rodgers BM, Michalsky MP: The use of octreotide to treat congenital chylothorax. *J Pediatr Surg* 2006;41:845-847.
- Sahin Y, Aydin D: Congenital chylothorax treated with octreotide. *Indian J Pediatr* 2005;72:885-888.
- Young S, Dalgleish S, Eccleston A, et al: Severe congenital chylothorax treated with octreotide. *J Perinatol* 2004;24:200-202.
- de Lonlay P, Touati G, Robert J-J, Saudubray J-M: Persistent hyperinsulinemic hypoglycaemia. *Semin Neonatol* 2002;7:95-100.
- Schwitzgebel VM, Gitelman SE: Neonatal hyperinsulinism. *Clin Perinatol* 1998;25:1015-38.
- Cheung Y-F, Leung MP, Yip M-M: Octreotide for treatment of postoperative chylothorax. *J Pediatr* 2001;139:157-59.
- Thornton PS, Alter CA, Katz LE, et al: Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr* 1993;123:637-643.
- Product Information, Novartis, 2005.

1.132 Omeprazole

Title Omeprazole

Dose

0.5 to 1.5 mg/kg/dose orally once daily.

Uses

Short-term (less than 8 weeks) treatment of documented reflux esophagitis or duodenal ulcer refractory to conventional therapy.

Contraindications/Precautions

Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year) of proton pump inhibitors. Concomitant use of drugs that cause hypomagnesemia may increase the risk. Monitoring is recommended during therapy. In some cases, hypomagnesemia was not reversed with magnesium supplementation and

discontinuation of the proton pump inhibitor was necessary.
An increased risk of *Clostridium difficile*-associated diarrhea (CDAD) has been associated with proton pump inhibitor (PPI) use [1] [2] . Although not reported in neonates to date, a higher risk of CDAD was seen in children who received PPI therapy. In a retrospective, single-center, observational, case-control study of children (1 year of age and older) having protracted diarrhea and stool analysis for *C. difficile*, 68 cases of CDAD were identified and then randomly matched to 68 control subjects who tested*C. difficile* negative. The use of PPI therapy was significantly higher in the patients with CDAD (22%; n=15) compared to the control group (6%; n=4), resulting in an odds ratio of 4.5 (95% CI, 1.4 to 14.4; p=0.006) [2] .

Pharmacology

Omeprazole inhibits gastric acid secretion by inhibition of hydrogen-potassium ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Onset of action is within one hour of administration, maximal effect is at approximately 2 hours. Inhibition of acid secretion is about 50% of maximum at 24 hours and the duration of action is approximately 72 hours.

Adverse Effects

Hypergastrinemia and mild transaminase elevations are the only adverse effects reported in children who received omeprazole for extended periods of time. Available data are limited to small studies of infants and children.

Monitoring

Observe for symptomatic improvement within 3 days. Consider intraesophageal pH monitoring to assess for efficacy (pH greater than 4.0). Measure AST and ALT if duration of therapy is greater than 8 weeks. Hypomagnesemia has been reported with prolonged administration (in most cases, greater than 1 year). Monitor magnesium levels prior to initiation of therapy and periodically during therapy in patients expected to be on long-term therapy or patients receiving concomitant drugs such as digoxin or those that may cause hypomagnesemia.

Special Considerations/Preparation

Zegerid® (omeprazole/sodium bicarbonate) is supplied as a 20-mg powder for suspension packet. A 2-mg/mL concentration can be prepared by reconstituting up to a total volume of 10 mL with water. The appropriate dose can be administered through a nasogastric or orogastric tube. The suspension should be flushed through the tube with water or normal saline. Studies regarding stability of this product for partial doses have been conducted. A suspension made from six 20-mg packets mixed to a final volume of 60 mL (final concentration, 2 mg/mL) was stable under refrigeration for at least 45 days. In another study, suspensions of 0.6 to 4 mg/mL were stable under refrigeration for up to 28 days; suspensions of 1 to 4 mg/mL were stable at room temperature for 7 days, with a yellow color change.

Prilosec® is supplied as 2.5-mg and 10-mg unit dose packets for delayed-release oral suspension (omeprazole magnesium) and as delayed-release capsules containing 10, 20, or 40-mg omeprazole as enteric-coated granules.

To prepare the delayed-release suspension, empty the 2.5 mg packet into a container containing 5 mL of water (or the 10 mg packet into a container containing 15 mL of water). Stir and leave 2 to 3 minutes to thicken. Stir and administer appropriate patient-specific dose within 30 minutes. For nasogastric or gastric tube administration, add 5 mL of water to a catheter-tipped syringe then add contents of 2.5 mg packet (or add 15 mL of water to syringe for adding 10 mg packet). Shake syringe immediately and leave 2 to 3 minutes to thicken. Shake syringe and inject patient-specific dose through the tube within 30 minutes. Flush tube with an appropriate amount of water.

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Title Omeprazole

Dose

0.5 to 1.5 mg/kg/dose orally once daily.

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Zegerid® (omeprazole/sodium bicarbonate) is supplied as a 20-mg powder for suspension packet. A 2-mg/mL concentration can be prepared by reconstituting up to a total volume of 10 mL with water. The appropriate dose can be administered through a nasogastric or orogastric tube. The suspension should be flushed through the tube with water or normal saline. Studies regarding stability of this product for partial doses have been conducted. A suspension made from six 20-mg packets mixed to a final volume of 60 mL (final concentration, 2 mg/mL) was stable under refrigeration for at least 45 days. In another study, suspensions of 0.6 to 4 mg/mL were stable under refrigeration for up to 28 days; suspensions of 1 to 4 mg/mL were stable at room temperature for 7 days, with a yellow color change.

Prilosec® is supplied as 2.5-mg and 10-mg unit dose packets for delayed-release oral suspension (omeprazole magnesium) and as delayed-release capsules containing 10, 20, or 40-mg omeprazole as enteric-coated granules.

To prepare the delayed-release suspension, empty the 2.5 mg packet into a container containing 5 mL of water (or the 10 mg packet into a container containing 15 mL of water). Stir and leave 2 to 3 minutes to thicken. Stir and administer appropriate patient-specific dose within 30 minutes. For nasogastric or gastric tube administration, add 5 mL of water to a catheter-tipped syringe then add contents of 2.5 mg packet (or add 15 mL of water to syringe for adding 10 mg packet). Shake syringe immediately and leave 2 to 3 minutes to thicken. Shake syringe and inject patient-specific dose through the tube within 30 minutes. Flush tube with an appropriate amount of water.

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1.133 Oseltamivir

Title Oseltamivir

Dose

Influenza, Treatment:
Postmenstrual age less than 38 weeks: 1 mg/kg/dose orally twice daily for 5 days [1] . Longer treatment may be necessary for patients who remain severely ill after 5 days of treatment [2] .
Postmenstrual age 38 to 40 weeks: 1.5 mg/kg/dose orally twice daily for 5 days [1] . Longer treatment may be necessary for patients who remain severely ill after 5 days of treatment [2] .
Postmenstrual age greater than 40 weeks: 3 mg/kg/dose orally twice daily for 5 days [1] . Longer treatment may be necessary for patients who remain severely ill after 5 days of treatment [2] .

Administration

May be given with or without food. Food may increase tolerability in some patients [3] .

Uses

Treatment of confirmed or suspected influenza virus for patients who have severe, complicated, or progressive illness, or who are hospitalized [1] [2] . Treatment should not wait for laboratory confirmation of influenza, but instead be initiated as soon as possible after the onset of symptoms [1] [2] , including patients seeking medical attention more than 48 hours after onset of symptoms. The duration of therapy is 5 days [1] [2] , but a longer treatment duration may be considered in patients who remain severely ill after 5 days of treatment. Unless an alternative diagnosis is made, a full treatment course should be completed by patients with suspected influenza regardless of negative initial test results [2] .

Oseltamivir has been used in term and preterm infants in the NICU setting for treatment and prophylaxis of influenza A virus (H1N1) with no reported safety concerns [4] [5] .

Contraindications/Precautions

Anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme, have been reported [3] .

Pharmacology

Oseltamivir phosphate, through its active form oseltamivir carboxylate, inhibits influenza virus neuraminidase which affects viral particle release. Oseltamivir exhibits activity against influenza A and influenza B viruses. Bioavailability is approximately 75%. Food has no effect on absorption. Minimal protein binding (3% for oseltamivir carboxylate). Extensively metabolized in the liver to oseltamivir carboxylate by esterases. Primarily eliminated in the kidneys (greater than 90%). Clearance is faster in younger pediatric patients compared with adults. Elimination half-life ranges from 1 to 3 hours [3] . There are very limited pharmacokinetic data in neonates or preterm infants, but it appears preterm infants would require a lower dose than term infants [6] [7] .

Adverse Effects

Most common adverse events reported in pediatric patients are nausea and vomiting [3] . Mild rash and gastrointestinal signs, and transient rise in transaminases have been reported in neonates receiving oseltamivir; no abnormal neurologic manifestations were reported.

Monitoring

Closely monitor patients with influenza for neurologic symptoms or abnormal behavior [3] .

Special Considerations/Preparation

Available as 30-mg, 45-mg, and 75-mg capsules and oral suspension (6 mg/mL when reconstituted) [3] .

Oral Suspension
In July 2011, the manufacturer changed the commercially available suspension concentration from 12 mg/mL to 6 mg/mL. There were no quality issues with the 12 mg/mL product; therefore, the 12 mg/mL suspension may remain in the marketplace and in state or national stockpiles until such supplies expire. The 12 mg/mL concentration will no longer be marketed after current supplies run out [8] .
To reconstitute oral suspension, add 55 mL of water to bottle and shake well for 15 seconds. The oral suspension has a concentration of 6 mg/mL after reconstitution. Stable for 17 days refrigerated or 10 days if stored at room temperature [3] .
Oseltamivir oral suspension contains 2 g of sorbitol per 75 mg dose, which exceeds the

maximum daily sorbitol limit in patients with hereditary fructose intolerance, and may cause dyspepsia and diarrhea in these patients [3] .

Emergency Compounding

During shortage of commercially manufactured oseltamivir (Tamiflu®) oral suspension, the suspension can be compounded using oseltamivir 75 mg capsules. The compounded suspension yields a 6 mg/mL concentration (same as commercially available 6 mg/mL suspension) and total volume adequate for 1 patient for a 5-day course of treatment or a 10-day course of prophylaxis. The compounded suspension is only to be used in emergency situations, and should not be used for convenience or when the commercially manufactured suspension is available [3] .

- **Directions for Compounding**

- Determine dose and total volume required for compounding. For a dose of 15 mg or less, total volume is 37.5 mL; for 30 mg, total volume is 75 mL; for 45 mg, total volume is 100 mL; for 60 mg, total volume is 125 mL; for 75 mg, total volume is 150 mL. If the dose is between these doses, default to the next greater dose and volume.

- Determine number of capsules, volume of water, and volume of vehicle required. Place specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (2.5 mL for 3 capsules; 5 mL for 6 capsules; 7 mL for 8 capsules; 8 mL for 10 capsules; 10 mL for 12 capsules).

- Transfer contents of required number of oseltamivir 75 mg capsules into the PET or glass bottle and gently swirl for at least 2 minutes; slowly add the specified volume of vehicle (cherry syrup, Ora-Sweet(R) sugar-free, or simple syrup: 34.5 mL for 3 capsules (total volume, 37.5 mL); 69 mL for 6 capsules (total volume, 75 mL); 91 mL for 8 capsules (total volume, 100 mL); 115 mL for 10 capsules (total volume, 125 mL); 137 mL for 12 capsules (total volume, 150 mL).

- Close the bottle and shake well for 30 seconds to dissolve active drug; stable for 35 days when refrigerated (2 to 8 degrees C) or for 5 days at room temperature.

References

- Committee on Infectious Diseases : Recommendations for Prevention and Control of Influenza in Children, 2013-2014. Pediatrics Sep2, 2013; Epub: Epub-.

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- Product Information: TAMIFLU(R) oral capsules, oral suspension, oseltamivir phosphate oral capsules, oral suspension. Genentech, Inc. (per FDA), South San Francisco, CA, 12/2012.

- Rocha G, Pissarra S, Silva G et al: Experience with oseltamivir in term and preterm newborns. J Pediatr Infect Dis 2010; 5(4): 327-331.

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Administration

May be given with or without food. Food may increase tolerability in some patients [3] .

Uses

Treatment of confirmed or suspected influenza virus for patients who have severe, complicated, or progressive illness, or who are hospitalized [1] [2] . Treatment should not wait for laboratory confirmation of influenza, but instead be initiated as soon as possible after the onset of symptoms [1] [2] , including patients seeking medical attention more than 48 hours after onset of symptoms. The duration of therapy is 5 days [1] [2] , but a longer treatment duration may be considered in patients who remain severely ill after 5 days of treatment. Unless an alternative diagnosis is made, a full treatment course should be completed by patients with suspected influenza regardless of negative initial test results [2] .
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Contraindications/Precautions

Anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme, have been reported [3] .

Pharmacology

Oseltamivir phosphate, through its active form oseltamivir carboxylate, inhibits influenza virus neuraminidase which affects viral particle release. Oseltamivir exhibits activity against influenza A and influenza B viruses. Bioavailability is approximately 75%. Food has no effect on absorption. Minimal protein binding (3% for oseltamivir carboxylate). Extensively metabolized in the liver to oseltamivir carboxylate by esterases. Primarily eliminated in the kidneys (greater than 90%). Clearance is faster in younger pediatric patients compared with adults. Elimination half-life ranges from 1 to 3 hours [3] . There are very limited pharmacokinetic data in neonates or preterm infants, but it appears preterm infants would require a lower dose than term infants [6] [7] .

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Most common adverse events reported in pediatric patients are nausea and vomiting [3] . Mild rash and gastrointestinal signs, and transient rise in transaminases have been reported in neonates receiving oseltamivir; no abnormal neurologic manifestations were reported.

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Oseltamivir oral suspension contains 2 g of sorbitol per 75 mg dose, which exceeds the maximum daily sorbitol limit in patients with hereditary fructose intolerance, and may cause dyspepsia and diarrhea in these patients [3] .

Emergency Compounding
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available 6 mg/mL suspension) and total volume adequate for 1 patient for a 5-day course of treatment or a 10-day course of prophylaxis. The compounded suspension is only to be used in emergency situations, and should not be used for convenience or when the commercially manufactured suspension is available [3] .

- **Directions for Compounding**

- Determine dose and total volume required for compounding. For a dose of 15 mg or less, total volume is 37.5 mL; for 30 mg, total volume is 75 mL; for 45 mg, total volume is 100 mL; for 60 mg, total volume is 125 mL; for 75 mg, total volume is 150 mL. If the dose is between these doses, default to the next greater dose and volume.

- Determine number of capsules, volume of water, and volume of vehicle required. Place specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (2.5 mL for 3 capsules; 5 mL for 6 capsules; 7 mL for 8 capsules; 8 mL for 10 capsules; 10 mL for 12 capsules).

- Transfer contents of required number of oseltamivir 75 mg capsules into the PET or glass bottle and gently swirl for at least 2 minutes; slowly add the specified volume of vehicle (cherry syrup, Ora-Sweet(R) sugar-free, or simple syrup: 34.5 mL for 3 capsules (total volume, 37.5 mL); 69 mL for 6 capsules (total volume, 75 mL); 91 mL for 8 capsules (total volume, 100 mL); 115 mL for 10 capsules (total volume, 125 mL); 137 mL for 12 capsules (total volume, 150 mL).

- Close the bottle and shake well for 30 seconds to dissolve active drug; stable for 35 days when refrigerated (2 to 8 degrees C) or for 5 days at room temperature.

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- Committee on Infectious Diseases : Recommendations for Prevention and Control of Influenza in Children, 2013-2014. Pediatrics Sep2, 2013; Epub: Epub-.

- Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. Centers for Disease Control and Prevention (CDC), Atlanta, GA, Nov09, 2012. Available at: http://www.cdc.gov/flu/pdf/professionals/antivirals/antiviral-summary-clinicians.pdf.

- Product Information: TAMIFLU(R) oral capsules, oral suspension, oseltamivir phosphate oral capsules, oral suspension. Genentech, Inc. (per FDA), South San Francisco, CA, 12/2012.

- Rocha G, Pissarra S, Silva G et al: Experience with oseltamivir in term and preterm newborns. J Pediatr Infect Dis 2010; 5(4): 327-331.

- Pannaraj PS: Oseltamivir treatment and prophylaxis in a neonatal intensive care unit during a 2009 H1N1 influenza outbreak. J Perinatol Jul, 2011; 31(7): 487-493.

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- Acosta EP, Jester P, Gal P et al: Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis Aug15, 2010; 202(4): 563-566.

- U.S. Food and Drug Administration: FDA Drug Safety Communication: Important safety changes to the influenza drug Tamiflu (oseltamivir phosphate) for oral suspension. U.S. Food and Drug Administration, Silver Spring, MD, Jul11, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm261686.htm.

1.134 Oxacillin

Title Oxacillin

Dose

Usual dosage: 25 mg/kg/dose IV over at least 10 minutes.
Meningitis: 50 mg/kg/dose IV over at least 10 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Administration

Intravenous: Administer IV push over 10 minutes at a **concentration not exceeding 100 mg/mL**. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 15 to 60 minutes.

Uses

Treatment of infections caused by penicillinase-producing staphylococci.

Pharmacology

Inhibits synthesis of bacterial cell wall. Rapidly excreted renally unchanged. Poor CSF penetration. Good penetration of pleural, pericardial, and synovial fluids.

Adverse Effects

Interstitial nephritis associated with hematuria, albuminuria, and casts in urine. Bone marrow depression. Elevated AST and ALT. Hypersensitivity in the form of a rash. Tolerant strains of staphylococci have been reported.

Monitoring

Periodic CBC and urinalysis. AST, ALT. Irritating to veins--watch for phlebitis. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder injection in 250-mg, 500-mg, 1-g, 2-g, and 10-g vials. Reconstitute 250 mg vial with 5 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution is stable for 4 days at room temperature, 7 days refrigerated. Dilute further using sterile water or NS to a concentration less than or equal to 40 mg/mL. Dilution stable for 4 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, cefotaxime, cefoxitin, chloramphenicol, dopamine, famotidine, fluconazole, heparin, hydrocortisone succinate, magnesium sulfate, milrinone, morphine, potassium chloride, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, caffeine citrate, gentamicin, netilmicin, sodium bicarbonate, and tobramycin.

References

- Maraqa NF, Gomez MM, Rathore MH, Alvarez AM: Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis* 2002;34:50-54.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Nahata MC, Debolt SL, Powell DA: Adverse effects of methicillin, nafcillin, and oxacillin in pediatric patients. *Dev Pharmacol Ther* 1982;4:117.
- Axline SG, Yaffe SJ, Simon HJ: Clinical pharmacology of antimicrobials in premature infants: II. Ampicillin, methicillin, oxacillin, neomycin, and colistin. *Pediatrics* 1967;39:97.
- Product Information, Sandoz, 2005.

Title Oxacillin

Dose

Usual dosage: 25 mg/kg/dose IV over at least 10 minutes.
Meningitis: 50 mg/kg/dose IV over at least 10 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Administration

Intravenous: Administer IV push over 10 minutes at a **concentration not exceeding 100 mg/mL**. For intermittent IV infusion, dilute to a concentration of 10 to 40 mg/mL and infuse over 15 to 60 minutes.

Uses

Treatment of infections caused by penicillinase-producing staphylococci.

Pharmacology

Inhibits synthesis of bacterial cell wall. Rapidly excreted renally unchanged. Poor CSF penetration. Good penetration of pleural, pericardial, and synovial fluids.

Adverse Effects

Interstitial nephritis associated with hematuria, albuminuria, and casts in urine. Bone marrow depression. Elevated AST and ALT. Hypersensitivity in the form of a rash. Tolerant strains of staphylococci have been reported.

Monitoring

Periodic CBC and urinalysis. AST, ALT. Irritating to veins--watch for phlebitis. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder injection in 250-mg, 500-mg, 1-g, 2-g, and 10-g vials. Reconstitute 250 mg vial with 5 mL of sterile water for injection to make a concentration of 50 mg/mL. Reconstituted solution is stable for 4 days at room temperature, 7 days refrigerated. Dilute further using sterile water or NS to a concentration less than or equal to 40 mg/mL. Dilution stable for 4 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, cefotaxime, cefoxitin, chloramphenicol, dopamine, famotidine, fluconazole, heparin, hydrocortisone succinate, magnesium sulfate, milrinone, morphine, potassium chloride, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, caffeine citrate, gentamicin, netilmicin, sodium bicarbonate, and tobramycin.

References

- Maraqa NF, Gomez MM, Rathore MH, Alvarez AM: Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. *Clin Infect Dis* 2002;34:50-54.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
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- Product Information, Sandoz, 2005.

1.135 PENTobarbital

Title PENTobarbital

Dose

2 to 6 mg/kg IV slow push.

Uses

Sedative/hypnotic, for short-term use.

Pharmacology

Short-acting barbiturate. Pentobarbital has no analgesic effects. Serum half-life is dose-dependent (15 to 50 hours in adults) and unknown in neonates. Metabolized by hepatic microsomal enzyme system.

Adverse Effects

Respiratory depression. Tolerance, dependence, and cardiovascular depression occur with continued use. Enhances metabolism of phenytoin, sodium valproate, and corticosteroids by microsomal enzyme induction.

Monitoring

Monitor respiratory status and blood pressure closely.
Serum concentration for sedation: 0.5 to 3 mcg/mL.

Special Considerations/Preparation

Available as a 50-mg/mL solution in 20 mL and 50 mL multidose vials. Solution contains propylene glycol 40%, and alcohol 10%. Irritating to veins; pH is 9.5.
A 5-mg/mL dilution may be made by adding 1 mL of the 50-mg/mL solution to 9 mL of preservative-free normal saline. Use immediately.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Acyclovir, amikacin, aminophylline, atropine, calcium chloride, chloramphenicol, erythromycin lactobionate, hyaluronidase, insulin, lidocaine, linezolid, neostigmine, and propofol.

Terminal Injection Site Incompatibility

Fat emulsion. Cimetidine, fentanyl, hydrocortisone succinate, midazolam, morphine, pancuronium bromide, penicillin G, phenytoin, ranitidine, and vancomycin. No data are currently available on heparin and potassium chloride.

References

- Strain JD, Harvey LA, Foley LC, Campbell JB: Intravenously administered pentobarbital sodium for sedation in pediatric CT. *Radiology* 1986;161:105-108.
- Product Information, Ovation, 2005.

Title PENTobarbital

Dose

2 to 6 mg/kg IV slow push.

Uses

Sedative/hypnotic, for short-term use.

Pharmacology

Short-acting barbiturate. Pentobarbital has no analgesic effects. Serum half-life is dose-dependent (15 to 50 hours in adults) and unknown in neonates. Metabolized by hepatic microsomal enzyme system.

Adverse Effects

Respiratory depression. Tolerance, dependence, and cardiovascular depression occur with continued use. Enhances metabolism of phenytoin, sodium valproate, and corticosteroids by microsomal enzyme induction.

Monitoring

Monitor respiratory status and blood pressure closely.
Serum concentration for sedation: 0.5 to 3 mcg/mL.

Special Considerations/Preparation

Available as a 50-mg/mL solution in 20 mL and 50 mL multidose vials. Solution contains propylene glycol 40%, and alcohol 10%. Irritating to veins; pH is 9.5.
A 5-mg/mL dilution may be made by adding 1 mL of the 50-mg/mL solution to 9 mL of preservative-free normal saline. Use immediately.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Acyclovir, amikacin, aminophylline, atropine, calcium chloride, chloramphenicol, erythromycin lactobionate, hyaluronidase, insulin, lidocaine, linezolid, neostigmine, and propofol.

Terminal Injection Site Incompatibility

Fat emulsion. Cimetidine, fentanyl, hydrocortisone succinate, midazolam, morphine, pancuronium bromide, penicillin G, phenytoin, ranitidine, and vancomycin. No data are currently available on heparin and potassium chloride.

References

- Strain JD, Harvey LA, Foley LC, Campbell JB: Intravenously administered pentobarbital sodium for sedation in pediatric CT. *Radiology* 1986;161:105-108.
- Product Information, Ovation, 2005.

1.136 PHENobarbital

Title PHENobarbital

Dose

Anticonvulsant:
Loading dose: 20 mg/kg IV, given slowly over 10 to 15 minutes.
Refractory seizures: Additional 5-mg/kg doses, up to a total of 40 mg/kg.
Maintenance: 3 to 4 mg/kg **per day** beginning 12 to 24 hours after the load.
Frequency/Route: Daily (every 12 hours probably unnecessary). IV slow push (most rapid control of seizures), IM, orally, or rectally.

Neonatal Abstinence Syndrome:
Loading dose: 16 mg/kg orally on day 1.
Maintenance: 1 to 4 mg/kg/dose orally every 12 hours.
Based on abstinence scoring, weaning can be achieved by decreasing dose 20% every other day.

Administration **Intravenous:** Administer by slow IV bolus infusion over 10 to 15 minutes (**2 mg/kg/min; 30 mg/minute maximum**) [1] [2] . Phenobarbital sodium can be diluted to 10 mg/mL in normal saline prior to administration [3] .
Oral: The intravenous formulation of phenobarbital, diluted to 10 mg/mL, has been used orally. An extemporaneous phenobarbital suspension can also be used to avoid alcohol content in the phenobarbital oral and IV solution (See Special Considerations/Preparation) [4] .

Uses

Anticonvulsant. May improve outcomes in severely asphyxiated infants (40 mg/kg IV infusion over 1 hour, prior to onset of seizures).

Treatment of neonatal abstinence syndrome in nonopiate- or polydrug-exposed infants.

May enhance bile excretion in patients with cholestasis before ^{99}Tc-IDA scanning.

Contraindications/Precautions

Contraindicated in patients with manifest or latent porphyria, marked liver function impairment, or respiratory disease with dyspnea or obstruction.

Pharmacology

Phenobarbital limits the spread of seizure activity, possibly by increasing inhibitory neurotransmission. Approximately 30% protein bound. Primarily metabolized by liver, then excreted in the urine as p-hydroxyphenobarbital (no anticonvulsant activity). Serum half-life in neonates is 40 to 200 hours.

Adverse Effects

Sedation at serum concentrations above 40 mcg/mL. Respiratory depression at concentrations above 60 mcg/mL. Irritating to veins - pH is approximately 10 and osmolality is approximately 15,000 mOsm/kg H_2O.

Monitoring

Phenobarbital monotherapy will control seizures in 43% to 85% of affected neonates - adding a second drug (phenytoin or lorazepam) is often needed. Therapeutic serum concentration is 15 to 40 mcg/mL. Drug accumulation may occur using recommended maintenance dose during the first two weeks of life. Altered (usually increased) serum concentrations may occur in patients also receiving phenytoin or valproate. Observe IV site for signs of extravasation and phlebitis. In infants with neonatal abstinence syndrome, serum concentrations of 20 to 30 mcg/mL are associated with adequate symptom control.

Special Considerations/Preparation

Injectable solution available in concentrations of 60-, 65-, and 130-mg/mL, all containing 10% (100 mg/mL) alcohol and 67.8% propylene glycol. Phenobarbital sodium, diluted to 10 mg/mL in normal saline, was stable for 4 weeks under refrigeration [3] .
Oral solution is available in 20 mg/5 mL concentration; contains 13.5 % alcohol.
To avoid alcohol content of the oral solution, an extemporaneous phenobarbital suspension can be compounded by crushing ten (10) 60-mg tablets (600 mg total) into a fine powder. Mix 30 mL of Ora-Plus with 30 mL of either Ora-Sweet or Ora-Sweet SF. Add 15 mL to phenobarbital powder and triturate. Transfer suspension to 2-ounce amber plastic bottle and fill to final volume of 60 mL with Ora-Plus/Ora-Sweet mixture. Label "shake well before use"; suspension stable for 115 days at room temperature [4] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Amikacin, aminophylline, caffeine citrate, calcium chloride, calcium gluconate, enalaprilat, fentanyl, fosphenytoin, heparin, ibuprofen lysine, linezolid, meropenem, methadone, morphine, propofol, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Fat emulsion. Hydralazine, hydrocortisone succinate, insulin, methadone, pancuronium, ranitidine, and vancomycin. No data available on potassium chloride.

References

- Burgos AE, Burke Jr. BL: Neonatal abstinence syndrome. *NeoReviews* 2009;10:e222-e229.
- Cober MP, Johnson CE: Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007;64:644-646.
- Volpe JJ: *Neurology of the Newborn,* ed 4. Philadelphia: WB Saunders Co, 2001, p 203-204.
- Hall RT, Hall FK, Daily SK: High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: A randomized, prospective study with three-year follow-up. *J Pediatr* 1998;132:345-348.
- Nahata MC, Hipple TF, Strausbaugh SD: Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1986;43:384-385.
- Finnegan LP, Michael H, Leifer B, Desai S: An evaluation of neonatal abstinence treatment modalities. *NIDA Res Monogr* 1984;49:282-288.
- Finnegan LP, Mitros TF, Hopkins LE: Management of neonatal narcotic abstinence utilizing a phenobarbital loading dose method. *NIDA Res Monogr* 1979;27:247-253.
- Product Information, PAI, 2010.
- Product Information, Hospira, 2004.

1. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
2. Abend NS: Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol Jun, 2008; 38(6): 377-390.
3. Nahata MC: Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection. Am J Hosp Pharm Feb, 1986; 43(2): 384-385.
4. Cober MP: Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. Am J Health Syst Pharm Mar15, 2007; 64(6): 644-646.

Title PHENobarbital

Dose

Anticonvulsant:
Loading dose: 20 mg/kg IV, given slowly over 10 to 15 minutes.
Refractory seizures: Additional 5-mg/kg doses, up to a total of 40 mg/kg.
Maintenance: 3 to 4 mg/kg **per day** beginning 12 to 24 hours after the load.
Frequency/Route: Daily (every 12 hours probably unnecessary). IV slow push (most rapid control of seizures), IM, orally, or rectally.

Neonatal Abstinence Syndrome:
Loading dose: 16 mg/kg orally on day 1.
Maintenance: 1 to 4 mg/kg/dose orally every 12 hours.
Based on abstinence scoring, weaning can be achieved by decreasing dose 20% every other day.

Administration **Intravenous:** Administer by slow IV bolus infusion over 10 to 15 minutes (**2 mg/kg/min; 30 mg/minute maximum**) [1] [2] . Phenobarbital sodium can be diluted to 10

mg/mL in normal saline prior to administration [3] .

Oral: The intravenous formulation of phenobarbital, diluted to 10 mg/mL, has been used orally. An extemporaneous phenobarbital suspension can also be used to avoid alcohol content in the phenobarbital oral and IV solution (See Special Considerations/Preparation) [4] .

Uses

Anticonvulsant. May improve outcomes in severely asphyxiated infants (40 mg/kg IV infusion over 1 hour, prior to onset of seizures).

Treatment of neonatal abstinence syndrome in nonopiate- or polydrug-exposed infants.

May enhance bile excretion in patients with cholestasis before ^{99}Tc-IDA scanning.

Contraindications/Precautions

Contraindicated in patients with manifest or latent porphyria, marked liver function impairment, or respiratory disease with dyspnea or obstruction.

Pharmacology

Phenobarbital limits the spread of seizure activity, possibly by increasing inhibitory neurotransmission. Approximately 30% protein bound. Primarily metabolized by liver, then excreted in the urine as p-hydroxyphenobarbital (no anticonvulsant activity). Serum half-life in neonates is 40 to 200 hours.

Adverse Effects

Sedation at serum concentrations above 40 mcg/mL. Respiratory depression at concentrations above 60 mcg/mL. Irritating to veins - pH is approximately 10 and osmolality is approximately 15,000 mOsm/kg H_2O.

Monitoring

Phenobarbital monotherapy will control seizures in 43% to 85% of affected neonates - adding a second drug (phenytoin or lorazepam) is often needed. Therapeutic serum concentration is 15 to 40 mcg/mL. Drug accumulation may occur using recommended maintenance dose during the first two weeks of life. Altered (usually increased) serum concentrations may occur in patients also receiving phenytoin or valproate. Observe IV site for signs of extravasation and phlebitis. In infants with neonatal abstinence syndrome, serum concentrations of 20 to 30 mcg/mL are associated with adequate symptom control.

Special Considerations/Preparation

Injectable solution available in concentrations of 60-, 65-, and 130-mg/mL, all containing 10% (100 mg/mL) alcohol and 67.8% propylene glycol. Phenobarbital sodium, diluted to 10 mg/mL in normal saline, was stable for 4 weeks under

refrigeration [3] .
Oral solution is available in 20 mg/5 mL concentration; contains 13.5 % alcohol.
To avoid alcohol content of the oral solution, an extemporaneous phenobarbital suspension can be compounded by crushing ten (10) 60-mg tablets (600 mg total) into a fine powder. Mix 30 mL of Ora-Plus with 30 mL of either Ora-Sweet or Ora-Sweet SF. Add 15 mL to phenobarbital powder and triturate. Transfer suspension to 2-ounce amber plastic bottle and fill to final volume of 60 mL with Ora-Plus/Ora-Sweet mixture. Label "shake well before use"; suspension stable for 115 days at room temperature [4] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA Solutions. Amikacin, aminophylline, caffeine citrate, calcium chloride, calcium gluconate, enalaprilat, fentanyl, fosphenytoin, heparin, ibuprofen lysine, linezolid, meropenem, methadone, morphine, propofol, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Fat emulsion. Hydralazine, hydrocortisone succinate, insulin, methadone, pancuronium, ranitidine, and vancomycin. No data available on potassium chloride.

References

- Burgos AE, Burke Jr. BL: Neonatal abstinence syndrome. *NeoReviews* 2009;10:e222-e229.
- Cober MP, Johnson CE: Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. *Am J Health-Syst Pharm* 2007;64:644-646.
- Volpe JJ: *Neurology of the Newborn,* ed 4. Philadelphia: WB Saunders Co, 2001, p 203-204.
- Hall RT, Hall FK, Daily SK: High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: A randomized, prospective study with three-year follow-up. *J Pediatr* 1998;132:345-348.
- Nahata MC, Hipple TF, Strausbaugh SD: Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection. *Am J Hosp Pharm* 1986;43:384-385.
- Finnegan LP, Michael H, Leifer B, Desai S: An evaluation of neonatal abstinence treatment modalities. *NIDA Res Monogr* 1984;49:282-288.
- Finnegan LP, Mitros TF, Hopkins LE: Management of neonatal narcotic abstinence utilizing a phenobarbital loading dose method. *NIDA Res Monogr* 1979;27:247-253.
- Product Information, PAI, 2010.
- Product Information, Hospira, 2004.

1. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
2. Abend NS: Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol Jun, 2008; 38(6): 377-390.

3. Nahata MC: Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection. Am J Hosp Pharm Feb, 1986; 43(2): 384-385.
4. Cober MP: Stability of an extemporaneously prepared alcohol-free phenobarbital suspension. Am J Health Syst Pharm Mar15, 2007; 64(6): 644-646.

1.137 Palivizumab

Title Palivizumab

Dose

15 mg/kg per dose IM, preferably in the anterolateral aspect of the thigh.
Repeat monthly during RSV season.

Uses

Immunoprophylaxis against severe RSV lower respiratory tract infections in high risk infants:
• up to 24 months of age, hemodynamically significant acyanotic and cyanotic congenital heart disease (maximum 5 doses),
• less than 24 months of age, chronic lung disease of prematurity (CLD) who have required medical therapy for CLD within 6 months before the start of the RSV season (maximum 5 doses),
• up to 12 months of age, born at 28 weeks gestation or earlier (maximum 5 doses),
• up to 6 months of age, born at 29 to 31 weeks, 6 days gestation (maximum 5 doses),
• less than 3 months of age, born between 32 to 34 weeks, 6 days gestation with at least 1 risk factor and born 3 months before or during RSV season (maximum 3 doses or stop therapy at 3 months of age),
• infants born before 35 weeks of gestation with congenital abnormalities of the airway or a neuromuscular disease that compromises handling of respiratory secretions (maximum 5 doses during first year of life).

Risk factors include child care attendance or a sibling less than 5 years of age.

Once an infant qualifies for initiation of prophylaxis, it should continue throughout the RSV season, with the exception of infants 32 to less than 35 weeks gestation.
Palivizumab is not effective for treatment of established RSV disease.

Contraindications/Precautions Anaphylaxis, anaphylactic shock, and other acute hypersensitivity reactions, some severe and/or fatal, have been reported on initial exposure or re-exposure to palivizumab; permanently discontinue if a severe hypersensitivity reaction occurs. Do not administer to patients who have had a previous significant hypersensitivity reaction to palivizumab [1] .

Pharmacology

Synagis ® is a humanized monoclonal antibody produced by recombinant DNA technology. This composite of human (95%) and murine (5%) antibody sequences inhibits RSV replication. The mean half-life of Synagis ®is approximately 20 days. Adequate antibody titers are maintained in most infants for one month following a 15-

mg/kg dose. Due to a faster metabolic rate, some hospitalized very low birth weight infants (less than 500 g) may not maintain optimal RSV titers for the entire initial month until after the second dose. Palivizumab does not interfere with the response to other vaccines and as such, they can be administered concurrently.

Adverse Effects

In clinical trials, fever and rash occurred slightly more frequently in palivizumab recipients (27% and 12%, respectively) compared with those who received placebo (25% and 10%, respectively) [1] .

Monitoring

Observe injection site for induration and swelling.

Special Considerations/Preparation

Synagis® is supplied as 50-mg and 100-mg single-dose vials in ready-to-use, **NO RECONSTITUTION required**, liquid solution. Do not add any diluent to the liquid solution and use one dose per vial. Do not re-enter vial after initial withdrawal and discard any unused portions. Administer as soon as possible after withdrawal from the vial. **Do not FREEZE or SHAKE**.

The liquid solution should be stored **refrigerated between 2 to 8 degrees C (36 to 46 degrees F).** Synagis®contains no preservatives, thimerosal, or other mercury salts. Rubber stopper on top of vials does not contain latex [1] .

References

- American Academy of Pediatrics. Respiratory Syncytial Virus (RSV) Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics 2009:562-569.
- Meissner HC, Long SS, Committee on Infectious Diseases and Committee on Fetus and Newborn: Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Policy Statement and Technical Report. *Pediatrics* 2003;122:1442-46 and 1447-52.
- Romero JR: Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: results from four years of palivizumab usage. *Pediatr Infect Dis J* 2003;22:S46-54.
- The Impact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531-537.
- Groothuis JR: Safety and tolerance of palivizumab administration in a large northern hemisphere trial. *Pediatr Infect Dis J* 2001;20:628-629.
- Wu S-Y, Bonaparte J, Pyati S: Palivizumab use in very premature infants in the neonatal intensive care unit. *Pediatrics* 2004;114:e554-e556.
- Product Information, MedImmune, 2012.

1. Product Information: Synagis(R) intramuscular injection, palivizumab intramuscular injection. MedImmune, LLC (per FDA), Gaithersburg, MD, Apr, 2012.

Title Palivizumab

Dose

15 mg/kg per dose IM, preferably in the anterolateral aspect of the thigh.
Repeat monthly during RSV season.

Uses

Immunoprophylaxis against severe RSV lower respiratory tract infections in high risk infants:
• up to 24 months of age, hemodynamically significant acyanotic and cyanotic congenital heart disease (maximum 5 doses),
• less than 24 months of age, chronic lung disease of prematurity (CLD) who have required medical therapy for CLD within 6 months before the start of the RSV season (maximum 5 doses),
• up to 12 months of age, born at 28 weeks gestation or earlier (maximum 5 doses),
• up to 6 months of age, born at 29 to 31 weeks, 6 days gestation (maximum 5 doses),
• less than 3 months of age, born between 32 to 34 weeks, 6 days gestation with at least 1 risk factor and born 3 months before or during RSV season (maximum 3 doses or stop therapy at 3 months of age),
• infants born before 35 weeks of gestation with congenital abnormalities of the airway or a neuromuscular disease that compromises handling of respiratory secretions (maximum 5 doses during first year of life).

Risk factors include child care attendance or a sibling less than 5 years of age.

Once an infant qualifies for initiation of prophylaxis, it should continue throughout the RSV season, with the exception of infants 32 to less than 35 weeks gestation.
Palivizumab is not effective for treatment of established RSV disease.

Contraindications/Precautions Anaphylaxis, anaphylactic shock, and other acute hypersensitivity reactions, some severe and/or fatal, have been reported on initial exposure or re-exposure to palivizumab; permanently discontinue if a severe hypersensitivity reaction occurs. Do not administer to patients who have had a previous significant hypersensitivity reaction to palivizumab [1] .

Pharmacology

Synagis ® is a humanized monoclonal antibody produced by recombinant DNA technology. This composite of human (95%) and murine (5%) antibody sequences inhibits RSV replication. The mean half-life of Synagis ®is approximately 20 days. Adequate antibody titers are maintained in most infants for one month following a 15-mg/kg dose. Due to a faster metabolic rate, some hospitalized very low birth weight infants (less than 500 g) may not maintain optimal RSV titers for the entire initial month until after the second dose. Palivizumab does not interfere with the response to other vaccines and as such, they can be administered concurrently.

Adverse Effects

In clinical trials, fever and rash occurred slightly more frequently in palivizumab recipients (27% and 12%, respectively) compared with those who received placebo (25% and 10%, respectively) [1] .

Monitoring

Observe injection site for induration and swelling.

Special Considerations/Preparation

Synagis® is supplied as 50-mg and 100-mg single-dose vials in ready-to-use, **NO RECONSTITUTION required**, liquid solution. Do not add any diluent to the liquid solution and use one dose per vial. Do not re-enter vial after initial withdrawal and discard any unused portions. Administer as soon as possible after withdrawal from the vial. **Do not FREEZE or SHAKE**.

The liquid solution should be stored **refrigerated between 2 to 8 degrees C (36 to 46 degrees F).** Synagis®contains no preservatives, thimerosal, or other mercury salts. Rubber stopper on top of vials does not contain latex [1] .

References

- American Academy of Pediatrics. Respiratory Syncytial Virus (RSV) Infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics 2009:562-569.
- Meissner HC, Long SS, Committee on Infectious Diseases and Committee on Fetus and Newborn: Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Policy Statement and Technical Report. *Pediatrics* 2003;122:1442-46 and 1447-52.
- Romero JR: Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: results from four years of palivizumab usage. *Pediatr Infect Dis J* 2003;22:S46-54.
- The Impact-RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531-537.
- Groothuis JR: Safety and tolerance of palivizumab administration in a large northern hemisphere trial. *Pediatr Infect Dis J* 2001;20:628-629.
- Wu S-Y, Bonaparte J, Pyati S: Palivizumab use in very premature infants in the neonatal intensive care unit. *Pediatrics* 2004;114:e554-e556.
- Product Information, MedImmune, 2012.

1. Product Information: Synagis(R) intramuscular injection, palivizumab intramuscular injection. MedImmune, LLC (per FDA), Gaithersburg, MD, Apr, 2012.

1.138 Pancuronium

Title Pancuronium

Dose

0.1 mg/kg (0.04 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Black Box Warning According to the manufacturer's black box warning, pancuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors and also causes sympathetic stimulation. Partially hydroxylated by the liver, 40% excreted unchanged in urine. Onset of action is 1 to 2 minutes; duration varies with dose and age. Reversed by neostigmine and atropine.
Factors affecting duration of neuromuscular blockade:
Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, renal failure, cardiovascular disease, younger age, aminoglycosides, hypermagnesemia, and hypokalemia.
Antagonism: Alkalosis, epinephrine, and hyperkalemia.
Sensation remains intact; analgesia should be used for painful procedures.

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. Tachycardia and blood pressure changes (both hypotension and hypertension) occur frequently. Increased salivation.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

Special Considerations/Preparation

Available in concentrations of 1 mg/mL (10-mL vials) and 2 mg/mL (2-mL and 5-mL vials). Products contain 1% (10 mg/mL) benzyl alcohol. Product maintains full clinical potency for 6 months if kept at room temperature or 36 months when refrigerated. Stable for 48 hours when further diluted in compatible solution.

Solution Compatibility

D_5W, NS, and Lactated Ringer's.

Terminal Injection Site Compatibility

Dex/AA. Aminophylline, caffeine citrate, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, lorazepam, midazolam, milrinone, morphine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Pentobarbital and phenobarbital.

References

- Bhutani VK, Abbasi S, Sivieri EM: Continuous skeletal muscle paralysis: Effect on neonatal pulmonary mechanics. *Pediatrics* 1988;81:419.
- Costarino AT, Polin RA: Neuromuscular relaxants in the neonate. *Clin Perinatol* 1987;14:965.
- Cabal LA, Siassi B, Artal R, et al: Cardiovascular and catecholamine changes after administration of pancuronium in distressed neonates. *Pediatrics* 1985;75:284.
- Product Information, Sicor, 2003.

Title Pancuronium

Dose

0.1 mg/kg (0.04 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Black Box Warning According to the manufacturer's black box warning, pancuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors and also causes sympathetic stimulation. Partially hydroxylated by the liver, 40% excreted unchanged in urine. Onset of action is 1 to 2 minutes; duration varies with dose and age. Reversed by neostigmine and atropine.
Factors affecting duration of neuromuscular blockade:
Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, renal failure, cardiovascular disease, younger age, aminoglycosides, hypermagnesemia, and hypokalemia.
Antagonism: Alkalosis, epinephrine, and hyperkalemia.
Sensation remains intact; analgesia should be used for painful procedures.

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. Tachycardia and blood pressure changes (both hypotension and hypertension) occur frequently. Increased salivation.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

Special Considerations/Preparation

Available in concentrations of 1 mg/mL (10-mL vials) and 2 mg/mL (2-mL and 5-mL vials). Products contain 1% (10 mg/mL) benzyl alcohol. Product maintains full clinical potency for 6 months if kept at room temperature or 36 months when refrigerated. Stable for 48 hours when further diluted in compatible solution.

Solution Compatibility

D_5W, NS, and Lactated Ringer's.

Terminal Injection Site Compatibility

Dex/AA. Aminophylline, caffeine citrate, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, lorazepam, midazolam, milrinone, morphine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Pentobarbital and phenobarbital.

References

- Bhutani VK, Abbasi S, Sivieri EM: Continuous skeletal muscle paralysis: Effect on neonatal pulmonary mechanics. *Pediatrics* 1988;81:419.
- Costarino AT, Polin RA: Neuromuscular relaxants in the neonate. *Clin Perinatol* 1987;14:965.
- Cabal LA, Siassi B, Artal R, et al: Cardiovascular and catecholamine changes after administration of pancuronium in distressed neonates. *Pediatrics* 1985;75:284.
- Product Information, Sicor, 2003.

1.139 Papaverine

Title Papaverine

Dose

30 mg per 250 mL of arterial catheter infusion solution.

Administration

Administer via intra-arterial catheter in infusion solution of NS or ½ NS with heparin (1 unit/mL).

Uses

Prolongation of peripheral arterial catheter patency.

Pharmacology

Papaverine directly relaxes the tonus of various smooth muscle, especially when it has been spasmodically contracted. It relaxes the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral and pulmonary arteries. Vasodilation may be related to its ability to inhibit cyclic nucleotide phosphodiesterase, thus increasing levels of intracellular cyclic AMP. During administration, the muscle cell is not paralyzed and still responds to drugs and other stimuli causing contraction. Possibly because of its direct vasodilating action on cerebral blood vessels, papaverine increases cerebral blood flow and decreases cerebral vascular resistance in healthy subjects; oxygen consumption is unaltered. Papaverine is metabolized in the liver and excreted in the urine in an inactive form.

Adverse Effects

Use with caution in VLBW infants in the first days after birth due to potential of developing or extending an intracranial hemorrhage. Chronic hepatitis, as evidenced by an increase in serum bilirubin and serum glutamic transaminase, has been reported in three adults following long-term papaverine therapy. One patient had jaundice, and another had abnormal liver function on biopsy.

Special Considerations/Preparation

Supplied as 30-mg/mL solution for injection in 2-mL preservative-free vials and 10-mL multiple dose vials containing 0.5% chlorobutanol as a preservative. Vials also contain edetate disodium 0.005%.

Solution Compatibility

NS, 0.45 NS, both with 1 unit/mL heparin.

Solution Incompatibility

Lactated Ringer's (precipitate forms).

Terminal Injection Site Compatibility

Phentolamine.

References

- Griffin MP, Siadaty MS: Papaverine prolongs patency of peripheral arterial catheters in neonates. *J Pediatr* 2005;146:62-65.
- Heulitt MJ, Farrington EA, O'Shea TM, et al: Double-blind randomized controlled trial of papaverine-containing solutions to prevent failure of arterial catheters in pediatric patients. *Crit Care Med* 1993;21:825-829.
- Product Information, Parenta Pharmaceuticals, Inc., 2006.

Title Papaverine

Dose

30 mg per 250 mL of arterial catheter infusion solution.

Administration

Administer via intra-arterial catheter in infusion solution of NS or ½ NS with heparin (1 unit/mL).

Uses

Prolongation of peripheral arterial catheter patency.

Pharmacology

Papaverine directly relaxes the tonus of various smooth muscle, especially when it has been spasmodically contracted. It relaxes the smooth musculature of the larger blood vessels, especially coronary, systemic peripheral and pulmonary arteries. Vasodilation may be related to its ability to inhibit cyclic nucleotide phosphodiesterase, thus increasing levels of intracellular cyclic AMP. During administration, the muscle cell is not paralyzed and still responds to drugs and other stimuli causing contraction. Possibly because of its direct vasodilating action on cerebral blood vessels, papaverine increases cerebral blood flow and decreases cerebral vascular resistance in healthy subjects; oxygen consumption is unaltered. Papaverine is metabolized in the liver and excreted in the urine in an inactive form.

Adverse Effects

Use with caution in VLBW infants in the first days after birth due to potential of developing or extending an intracranial hemorrhage. Chronic hepatitis, as evidenced by an increase in serum bilirubin and serum glutamic transaminase, has been reported in three adults following long-term papaverine therapy. One patient had jaundice, and another had abnormal liver function on biopsy.

Special Considerations/Preparation

Supplied as 30-mg/mL solution for injection in 2-mL preservative-free vials and 10-mL multiple dose vials containing 0.5% chlorobutanol as a preservative. Vials also contain edetate disodium 0.005%.

Solution Compatibility

NS, 0.45 NS, both with 1 unit/mL heparin.

Solution Incompatibility

Lactated Ringer's (precipitate forms).

Terminal Injection Site Compatibility

Phentolamine.

References

- Griffin MP, Siadaty MS: Papaverine prolongs patency of peripheral arterial catheters in neonates. *J Pediatr* 2005;146:62-65.
- Heulitt MJ, Farrington EA, O'Shea TM, et al: Double-blind randomized controlled trial of papaverine-containing solutions to prevent failure of arterial catheters in pediatric patients. *Crit Care Med* 1993;21:825-829.
- Product Information, Parenta Pharmaceuticals, Inc., 2006.

1.140 Penicillin G

Title Penicillin G

Dose

»Use only aqueous crystalline penicillin G for IV administration«

Bacteremia: 25,000 to 50,000 units/kg/dose IV infusion over 15 minutes, or IM.

Meningitis: 75,000 to 100,000 units/kg/dose IV infusion over 30 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8

≥45	ALL	6

Group B Streptococcal Meningitis:
Experts recommend using higher doses for the treatment of GBS meningitis [1] [2] [3] :
7 days and younger:250,000 to 450,000 units/kg/day IV divided every 8 hours.
8 days and older:450,000 to 500,000 units/kg/day IV divided every 6 hours.
Ampicillin plus an aminoglycoside is recommended as initial therapy [2] . Penicillin G monotherapy is recommended once the diagnosis of GBS meningitis has been established and CSF is sterile; antibiotic therapy should be continued for at least 2 weeks [2] [3] .

Congenital Syphilis: 50,000 units/kg/dose IV over 15 minutes, given every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days.

Uses

Treatment of serious infections (bacteremia and meningitis) due to susceptible strains of streptococci (non enterococcal).

Treatment of congenital syphilis. For congenital syphilis, aqueous crystalline penicillin G is recommended in infants with proven or highly probable disease and:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test of body fluid(s)

Also recommended in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery

Pharmacology

Inhibits synthesis of bacterial cell wall. Excreted unchanged in the urine. CSF penetration is poor, except in inflamed meninges. Concentrates in joint fluid and urine.

Adverse Effects

Cardiac arrest has been reported in patients who received high doses infused rapidly. Significant CNS toxicity has been reported in adults with renal failure who developed

CSF concentrations greater than 10 mcg/mL. Bone marrow depression, granulocytopenia, and hepatitis are rare. Hypersensitivity has not been seen in neonates.

Monitoring

Follow serum sodium and potassium when using high doses and in patients with renal failure. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Aqueous penicillin G is available as powder for injection in two salt forms: penicillin G potassium and penicillin G sodium. Penicillin G potassium contains 1.68 mEq (65.6 mg) potassium per 1 million units, and 0.3 mEq (6.8 mg) sodium per 1 million units. Penicillin G sodium contains 2 mEq (46 mg) sodium per 1 million units. Reconstitute the 5-million unit vial with 8 mL sterile water for injection to make a final concentration of 500,000 units/mL. Reconstituted solution good for 7 days refrigerated. A 100,000 unit/mL dilution may be made by adding 10 mL of reconstituted solution to 40 mL sterile water for injection. Dilution stable for 7 days refrigerated. Penicillin G sodium reconstituted solution stable for 3 days in refrigerator.
Penicillin G potassium is also available as a premixed frozen iso-osmotic solution containing 1, 2 or 3 million units in 50 mL.

Note: Penicillin G is also known as benzylpenicillin. Do not confuse with benzathine penicillin which is used only for IM injection. 1 million units is the equivalent of 600 mg.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, cefotaxime, cefoxitin, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, esmolol, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nicardipine, potassium chloride, prostaglandin E_1, ranitidine and sodium bicarbonate.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B, metoclopramide, netilmicin, pentobarbital, phenytoin, and tobramycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.

- American Academy of Pediatrics. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: pp 644-646.
- Stoll BJ: Congenital syphilis: evaluation and management of neonates born to mothers with reactive serologic tests for syphilis. *Pediatr Infect Dis J* 1994;13:845.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p45.
- Pyati SP, Pildes RS, Jacobs NM, et al: Penicillin in infants weighing two kilograms or less with early onset group B streptococcal disease. *N Engl J Med* 1983;308:1383.
- McCracken GH Jr, Ginsburg C, Chrane DF, et al: Clinical pharmacology of penicillin in newborn infants. *J Pediatr* 1973;82:692.
- Product Information, Sandoz, 2009.
- Product Information, Sandoz, 2007.

1. Committee on Infectious Diseases, American Academy of Pediatrics , Pickering LK, Baker CJ et al: Red Book(R): 2009 Report of the Committee on Infectious Diseases, 28th ed., 28th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.
2. Heath PT: Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed May, 2003; 88(3): F173-F178.
3. Kimberlin DW: Meningitis in the neonate. Curr Treat Options Neurol May, 2002; 4(3): 239-248.

Title Penicillin G

Dose

»Use only aqueous crystalline penicillin G for IV administration«

Bacteremia: 25,000 to 50,000 units/kg/dose IV infusion over 15 minutes, or IM.

Meningitis: 75,000 to 100,000 units/kg/dose IV infusion over 30 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12

	>7	8
≥45	ALL	6

Group B Streptococcal Meningitis:
Experts recommend using higher doses for the treatment of GBS meningitis [1] [2] [3] :
7 days and younger:250,000 to 450,000 units/kg/day IV divided every 8 hours.
8 days and older:450,000 to 500,000 units/kg/day IV divided every 6 hours.
Ampicillin plus an aminoglycoside is recommended as initial therapy [2] . Penicillin G monotherapy is recommended once the diagnosis of GBS meningitis has been established and CSF is sterile; antibiotic therapy should be continued for at least 2 weeks [2] [3] .

Congenital Syphilis: 50,000 units/kg/dose IV over 15 minutes, given every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days.

Uses

Treatment of serious infections (bacteremia and meningitis) due to susceptible strains of streptococci (non enterococcal).

Treatment of congenital syphilis. For congenital syphilis, aqueous crystalline penicillin G is recommended in infants with proven or highly probable disease and:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test of body fluid(s)

Also recommended in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery

Pharmacology

Inhibits synthesis of bacterial cell wall. Excreted unchanged in the urine. CSF penetration is poor, except in inflamed meninges. Concentrates in joint fluid and urine.

Adverse Effects

Cardiac arrest has been reported in patients who received high doses infused rapidly. Significant CNS toxicity has been reported in adults with renal failure who developed CSF concentrations greater than 10 mcg/mL. Bone marrow depression, granulocytopenia, and hepatitis are rare. Hypersensitivity has not been seen in neonates.

Monitoring

Follow serum sodium and potassium when using high doses and in patients with renal failure. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Aqueous penicillin G is available as powder for injection in two salt forms: penicillin G potassium and penicillin G sodium. Penicillin G potassium contains 1.68 mEq (65.6 mg) potassium per 1 million units, and 0.3 mEq (6.8 mg) sodium per 1 million units. Penicillin G sodium contains 2 mEq (46 mg) sodium per 1 million units. Reconstitute the 5-million unit vial with 8 mL sterile water for injection to make a final concentration of 500,000 units/mL. Reconstituted solution good for 7 days refrigerated. A 100,000 unit/mL dilution may be made by adding 10 mL of reconstituted solution to 40 mL sterile water for injection. Dilution stable for 7 days refrigerated. Penicillin G sodium reconstituted solution stable for 3 days in refrigerator.
Penicillin G potassium is also available as a premixed frozen iso-osmotic solution containing 1, 2 or 3 million units in 50 mL.

Note: Penicillin G is also known as benzylpenicillin. Do not confuse with benzathine penicillin which is used only for IM injection. 1 million units is the equivalent of 600 mg.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, amikacin, amiodarone, caffeine citrate, calcium chloride, calcium gluconate, cefotaxime, cefoxitin, chloramphenicol, cimetidine, clindamycin, dopamine, enalaprilat, erythromycin lactobionate, esmolol, fluconazole, furosemide, gentamicin, heparin, hydrocortisone succinate, lidocaine, magnesium sulfate, metronidazole, morphine, nicardipine, potassium chloride, prostaglandin E_1, ranitidine and sodium bicarbonate.

Terminal Injection Site Incompatibility

Aminophylline, amphotericin B, metoclopramide, netilmicin, pentobarbital, phenytoin, and tobramycin.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- American Academy of Pediatrics. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report of the Committee on Infectious Diseases.* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009: pp 644-646.
- Stoll BJ: Congenital syphilis: evaluation and management of neonates born to mothers with reactive serologic tests for syphilis. *Pediatr Infect Dis J* 1994;13:845.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Roberts RJ: *Drug Therapy in Infants.*Philadelphia: WB Saunders Co, 1984, p45.
- Pyati SP, Pildes RS, Jacobs NM, et al: Penicillin in infants weighing two kilograms or less with early onset group B streptococcal disease. *N Engl J Med* 1983;308:1383.
- McCracken GH Jr, Ginsburg C, Chrane DF, et al: Clinical pharmacology of penicillin in newborn infants. *J Pediatr* 1973;82:692.
- Product Information, Sandoz, 2009.
- Product Information, Sandoz, 2007.

1. Committee on Infectious Diseases, American Academy of Pediatrics , Pickering LK, Baker CJ et al: Red Book(R): 2009 Report of the Committee on Infectious Diseases, 28th ed., 28th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.
2. Heath PT: Neonatal meningitis. Arch Dis Child Fetal Neonatal Ed May, 2003; 88(3): F173-F178.
3. Kimberlin DW: Meningitis in the neonate. Curr Treat Options Neurol May, 2002; 4(3): 239-248.

1.141 Penicillin G benzathine

Title Penicillin G benzathine

Dose

Congenital Syphilis: 50,000 units/kg/dose IM as a single dose.

Administration

For IM injection only. Avoid injection into or near an artery or nerve. Administer by deep IM injection in the midlateral aspect of the thigh. Rotate injection site for repeated administration. Needle may be blocked if injection is not made at a slow, steady rate due to high concentration of suspended material in the product.

Uses

Treatment of congenital syphilis in infants during the first month of life. Recommended as an alternative to aqueous crystalline penicillin G or procaine penicillin G in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;

- mother was treated with erythromycin or another non-penicillin regimen; OR

- mother received treatment less than 4 weeks before delivery.

Also recommended in infants whose mother was adequately treated during pregnancy (and treatment given greater than 4 weeks before delivery) and mother has no evidence of reinfection or relapse. Close serologic testing may be used instead of treatment in infants whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis and remained stable or low for late syphilis.
For infants whose mother's treatment was adequate before pregnancy and nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL less than 1:2; RPR less than 1:4), no treatment is required; however, it may be considered if follow-up is not assured.

Black Box Warning

According to the manufacturer's black box warning, inadvertent intravenous administration of penicillin G benzathine (to be given IM only) has been associated with cardiorespiratory arrest and death.

Pharmacology

Inhibits synthesis of bacterial cell wall. Dissolves slowly at site of injection with hydrolysis to penicillin G. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged.

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. The Jarisch-Hersheimer reaction (fever, chills, myalgia, headache, tachycardia, hyperventilation, mild hypotension) may occur after initiation of therapy in patients with syphilis. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh.

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Product Information: Bicillin® L-A, penicillin G benzathine injection, suspension, King Pharmaceuticals, 2009.

Title Penicillin G benzathine

Dose

Congenital Syphilis: 50,000 units/kg/dose IM as a single dose.

Administration

For IM injection only. Avoid injection into or near an artery or nerve. Administer by deep IM injection in the midlateral aspect of the thigh. Rotate injection site for repeated administration. Needle may be blocked if injection is not made at a slow, steady rate due to high concentration of suspended material in the product.

Uses

Treatment of congenital syphilis in infants during the first month of life. Recommended as an alternative to aqueous crystalline penicillin G or procaine penicillin G in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery.

Also recommended in infants whose mother was adequately treated during pregnancy (and treatment given greater than 4 weeks before delivery) and mother has no evidence of reinfection or relapse. Close serologic testing may be used instead of treatment in infants whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis and remained stable or low for late syphilis.
For infants whose mother's treatment was adequate before pregnancy and nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL less than 1:2; RPR less than 1:4), no treatment is required; however, it may be considered if follow-up is not assured.

Black Box Warning

According to the manufacturer's black box warning, inadvertent intravenous administration of penicillin G benzathine (to be given IM only) has been associated with cardiorespiratory arrest and death.

Pharmacology

Inhibits synthesis of bacterial cell wall. Dissolves slowly at site of injection with hydrolysis to penicillin G. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged.

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. The Jarisch-Hersheimer reaction (fever, chills, myalgia, headache, tachycardia, hyperventilation, mild hypotension) may occur after initiation of therapy in patients with syphilis. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh.

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Product Information: Bicillin® L-A, penicillin G benzathine injection, suspension, King Pharmaceuticals, 2009.

1.142 Penicillin G procaine

Title Penicillin G procaine

Dose

Congenital Syphilis: 50,000 units/kg/dose IM once daily for 10 days.

Administration

For IM injection only. Avoid injection into or near an artery or nerve. Administer by deep IM injection in the midlateral aspect of the thigh. Rotate injection site for repeated administration. Needle may be blocked if injection is not made at a slow, steady rate due to high concentration of suspended material in the product.

Uses

Treatment of congenital syphilis in infants during the first month of life. For congenital syphilis, procaine penicillin G is recommended as an alternative to aqueous crystalline penicillin G in infants with proven or highly probable disease and:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test of body fluid(s).

Also recommended as an alternative to aqueous crystalline penicillin G in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery.

Pharmacology

Inhibits synthesis of bacterial cell wall. Equimolecular compound of procaine and penicillin G in a suspension. Dissolves slowly at site of injection, with maximum blood level at approximately 4 hours, declining slowly over a period of 15 to 20 hours. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged. Approximately 60% to 90% of a dose is excreted in the urine within 24 to 36 hours.

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh. Prolonged therapy may lead to an increased risk of neutropenia and serum sickness-like reactions.

Monitoring

Periodic monitoring of CBC and renal function is recommended.

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Product Information: Penicillin G procaine injectable suspension, King Pharmaceuticals, 2006.

Title Penicillin G procaine

Dose

Congenital Syphilis: 50,000 units/kg/dose IM once daily for 10 days.

Administration

For IM injection only. Avoid injection into or near an artery or nerve. Administer by deep IM injection in the midlateral aspect of the thigh. Rotate injection site for repeated administration. Needle may be blocked if injection is not made at a slow, steady rate due to high concentration of suspended material in the product.

Uses

Treatment of congenital syphilis in infants during the first month of life. For congenital syphilis, procaine penicillin G is recommended as an alternative to aqueous crystalline penicillin G in infants with proven or highly probable disease and:

- an abnormal physical examination consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer; OR
- a positive darkfield test of body fluid(s).

Also recommended as an alternative to aqueous crystalline penicillin G in infants who have a normal physical examination and a serum quantitative nontreponemal titer the same or less than fourfold the maternal titer and the:

- mother was not treated, inadequately treated, or has no documentation of having received treatment;
- mother was treated with erythromycin or another non-penicillin regimen; OR
- mother received treatment less than 4 weeks before delivery.

Pharmacology

Inhibits synthesis of bacterial cell wall. Equimolecular compound of procaine and penicillin G in a suspension. Dissolves slowly at site of injection, with maximum blood level at approximately 4 hours, declining slowly over a period of 15 to 20 hours. Distributes widely into body tissues. Highest concentration in the kidneys, with smaller amounts in the liver, skin, and intestines. Approximately 60% bound to serum protein. Excreted rapidly by tubular excretion. In young infants and patients with renal impairment, excretion is prolonged. Approximately 60% to 90% of a dose is excreted in the urine within 24 to 36 hours.

Adverse Effects

Serious and potentially fatal hypersensitivity reactions have occurred. Avoid intravenous or intra-arterial administration, or injection into or near a nerve; severe neurovascular damage (transverse myelitis with permanent paralysis, gangrene requiring amputation, and necrosis and sloughing at or around injection site) has

occurred, especially in infants. Quadriceps femoris fibrosis and atrophy have occurred following repeated intramuscular administration into the anterolateral thigh. Prolonged therapy may lead to an increased risk of neutropenia and serum sickness-like reactions.

Monitoring

Periodic monitoring of CBC and renal function is recommended.

Special Considerations/Preparation

Available in a concentration of 600,000 units/mL in 1-, 2-, and 4-mL syringes. **Store in refrigerator. Do not freeze.**.

References

- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR-12):1-110.
- Product Information: Penicillin G procaine injectable suspension, King Pharmaceuticals, 2006.

1.143 Phentolamine

Title Phentolamine

Dose

Inject a 0.5-mg/mL solution of phentolamine subcutaneously into the affected area. Usual amount needed is 1 to 5 mL, depending on the size of the infiltrate. May be repeated if necessary.

Uses

Prevention of dermal necrosis and sloughing caused by extravasation of vasoconstrictive agents, eg, dopamine.

Pharmacology

Alpha-adrenergic blocking agent that produces peripheral vasodilation, thereby reversing ischemia produced by vasopressor infiltration. The effect should be seen almost immediately. Biological half-life when injected subcutaneously is less than 20 minutes.

Adverse Effects

Hypotension could potentially occur if a very large dose is administered. Consider using topical 2% nitroglycerin ointment if affected extremity is significantly swollen.

Monitoring

Assess affected area for reversal of ischemia. Monitor blood pressure.

Special Considerations/Preparation

Available in 5-mg vial as a lyophilized powder.
To prepare:
1) Reconstitute one vial with 1 mL of normal saline.
2) Dilute to a concentration of 0.5 mg/mL with 9 mL normal saline. Use immediately.
Do not use if solution is discolored or contains particulate contamination.

Terminal Injection Site Compatibility

Amiodarone, dobutamine, and papaverine.

References

- Subhani M, Sridhar S, DeCristofaro JD: Phentolamine use in a neonate for the prevention of dermal necrosis caused by dopamine: A case report. *J Perinatol* 2001;21:324-326.
- Denkler KA, Cohen BE: Reversal of dopamine extravasation injury with topical nitroglycerin ointment. *Plast Reconstr Surg* 1989;84:811.
- Siwy BK, Sadove AM: Acute management of dopamine infiltration injury with Regitine. *Plast Reconstr Surg* 1987;80:610.
- Product Information, Bedford, 1999

Title Phentolamine

Dose

Inject a 0.5-mg/mL solution of phentolamine subcutaneously into the affected area. Usual amount needed is 1 to 5 mL, depending on the size of the infiltrate. May be repeated if necessary.

Uses

Prevention of dermal necrosis and sloughing caused by extravasation of vasoconstrictive agents, eg, dopamine.

Pharmacology

Alpha-adrenergic blocking agent that produces peripheral vasodilation, thereby reversing ischemia produced by vasopressor infiltration. The effect should be seen almost immediately. Biological half-life when injected subcutaneously is less than 20 minutes.

Adverse Effects

Hypotension could potentially occur if a very large dose is administered. Consider using topical 2% nitroglycerin ointment if affected extremity is significantly swollen.

Monitoring

Assess affected area for reversal of ischemia. Monitor blood pressure.

Special Considerations/Preparation

Available in 5-mg vial as a lyophilized powder.
To prepare:
1) Reconstitute one vial with 1 mL of normal saline.
2) Dilute to a concentration of 0.5 mg/mL with 9 mL normal saline. Use immediately.
Do not use if solution is discolored or contains particulate contamination.

Terminal Injection Site Compatibility

Amiodarone, dobutamine, and papaverine.

References

- Subhani M, Sridhar S, DeCristofaro JD: Phentolamine use in a neonate for the prevention of dermal necrosis caused by dopamine: A case report. *J Perinatol* 2001;21:324-326.
- Denkler KA, Cohen BE: Reversal of dopamine extravasation injury with topical nitroglycerin ointment. *Plast Reconstr Surg* 1989;84:811.
- Siwy BK, Sadove AM: Acute management of dopamine infiltration injury with Regitine. *Plast Reconstr Surg* 1987;80:610.
- Product Information, Bedford, 1999

1.144 Phenylephrine (Ophthalmic)

Title Phenylephrine (Ophthalmic)

Dose

1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 2.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis for diagnostic and therapeutic ophthalmic procedures.

Pharmacology

Alpha-adrenergic. Mydriasis begins within 5 minutes of instillation and lasts for 60 minutes. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

Adverse Effects

May cause decreased pulmonary compliance, tidal volume, and peak air flow in babies with BPD. Do not use in patients receiving beta-blocker medications (e.g. propranolol). The use of 10% solutions has caused systemic hypertension and tachycardia in infants.

Monitoring

Monitor heart rate and oxygen saturation in babies with BPD.

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.12%, 2.5%, and 10% concentrations in 2 to 15 mL quantities. Do not use solution that becomes discolored or contains precipitate. Refer to specific product or manufacturer's recommendation for storage.

A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 8-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

References

- Wallace DK, Steinkuller PG: Ocular medications in children. *Clin Pediatr* 1998;37:645-652.
- Laws DE, Morton C, Weindling M, Clark D: Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol* 1996;80:425-428.
- McGregor MLK: Adrenergic agonists, in Mauger TF, Craig EL (eds): *Havener's Ocular Pharmacology,* ed 6. St. Louis: Mosby-YearBook, 1994, pp 70-72.
- Mirmanesh SJ, Abbasi S, Bhutani VK: Alpha-adrenergic bronchoprovocation in neonates with bronchopulmonary dysplasia. *J Pediatr* 1992;121:622-625.
- Isenberg S, Everett S: Cardiovascular effects of mydriatics in low-birth-weight infants. *J Pediatr* 1984;105:111-112
- Caputo AR, Schnitzer RE, Lindquist TD, Sun S: Dilation in neonates: a protocol. *Pediatrics* 1982;69:77-80.
- Borromeo-McGrall V, Bordiuk JM, Keitel H: Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. *Pediatrics* 1973;51:1032-1036.
- Product Information, Alcon, 2005.

Title Phenylephrine (Ophthalmic)

Dose

1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 2.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis for diagnostic and therapeutic ophthalmic procedures.

Pharmacology

Alpha-adrenergic. Mydriasis begins within 5 minutes of instillation and lasts for 60 minutes. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

Adverse Effects

May cause decreased pulmonary compliance, tidal volume, and peak air flow in babies with BPD. Do not use in patients receiving beta-blocker medications (e.g. propranolol). The use of 10% solutions has caused systemic hypertension and tachycardia in infants.

Monitoring

Monitor heart rate and oxygen saturation in babies with BPD.

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.12%, 2.5%, and 10% concentrations in 2 to 15 mL quantities. Do not use solution that becomes discolored or contains precipitate. Refer to specific product or manufacturer's recommendation for storage.

A preparation containing cyclopentolate 0.2% and phenylephrine 1% (Cyclomydril®) is commercially available in 2- and 8-mL Drop-tainers.
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

References

- Wallace DK, Steinkuller PG: Ocular medications in children. *Clin Pediatr* 1998;37:645-652.
- Laws DE, Morton C, Weindling M, Clark D: Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol* 1996;80:425-428.
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- Product Information, Alcon, 2005.

1.145 Phenytoin

Title Phenytoin

Dose

Loading dose: 15 to 20 mg/kg IV infusion over at least 30 minutes.
Maintenance dose: 4 to 8 mg/kg every 24 hours IV slow push, or orally.
(Up to 8 mg/kg per dose every 8 to 12 hours after 1 week of age).
Maximum rate of infusion 0.5 mg/kg per minute. Flush IV with saline before and after administration. **Phenytoin is highly unstable in any IV solution. Avoid using in central lines because of the risk of precipitation. IM route not acceptable; drug crystallizes in muscle.**Oral absorption is erratic.

Uses

Anticonvulsant often used to treat seizures refractory to phenobarbital.

Black Box Warning

The rate of intravenous phenytoin administration should not exceed 1 to 3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous phenytoin. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [1] .

Pharmacology

Hepatic metabolism capacity is limited; saturation may occur within therapeutic range. Pharmacokinetics are dose-dependent. Elimination rate is increased during first few weeks of life. Serum half-life is 18 to 60 hours. 85% to 90% protein bound. Bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [6] [7] [8] [5] [9] .

Adverse Effects

Extravasation causes tissue inflammation and necrosis due to high pH and osmolality. Propylene glycol content of the intravenous formulation has been associated with seizures and may potentiate the cardiovascular effects of phenytoin. Purple glove syndrome can occur with IV use (even without extravasation). Hypotension and cardiac arrhythmias have been reported. High serum concentrations are associated with seizures. Dose related adverse events include nystagmus (total level 15 to 25 mg/L) and ataxia and mental status changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Hypersensitivity reactions have been reported in infants. Long-term effects of phenytoin include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Cutaneous side effects include maculopapular exanthema, drug-induced lupus, and pigmentary alterations. Phenytoin interacts with carbamazepine, cimetidine,

corticosteroids, digoxin, furosemide, phenobarbital, and valproate [1] [3] [4] .
Use with caution in infants and children with hyperbilirubinemia: bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [5] .

Serious and sometimes fatal skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, have been reported with phenytoin therapy. Onset of symptoms is typically within 28 days, but can occur later. Limited data suggests that a particular human leukocyte antigen (HLA) allele, HLA-B*1502, found in patients of Asian ancestry may be a risk factor for the development of SJS/TEN in patients taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502 [1] .

Monitoring

Monitor electrocardiogram, blood pressure, and respiratory function continuously during infusion, and for 15 minutes to 1 hour after infusion [1] [2] . Observe IV site for extravasation. Follow serum concentration closely: therapeutic range is 6 to 15 mcg/mL in the first weeks, then 10 to 20 mcg/mL due to changes in protein binding. Obtain initial trough level 48 hours after IV loading dose.

Special Considerations/Preparation

Injectable solution available in a concentration of 50 mg/mL. Contains 40% propylene glycol and 10% alcohol (100 mg/mL) [1] .
Oral suspension available in a concentration of 25 mg/mL [10] .

Solution Compatibility

NS only.

Solution Incompatibility

D_5W and $D_{10}W$.

Terminal Injection Site Compatibility

Esmolol, famotidine, and fluconazole.

Terminal Injection Site Incompatibility

Dex/AA solutions, fat emulsion. Amikacin, cefepime, ceftazidime, chloramphenicol, clindamycin, dobutamine, enalaprilat, fentanyl, heparin, hyaluronidase, hydrocortisone succinate, insulin, lidocaine, linezolid, methadone, micafungin, morphine, nitroglycerin, pentobarbital, potassium chloride, procainamide, propofol, sodium bicarbonate, and vitamin K_1.

References

- Volpe JJ: *Neurology of the Newborn,* ed 4. Philadelphia: WB Saunders Co, 2001, p 204-205.
- Wheless JW: Pediatric use of intravenous and intramuscular phenytoin: lessons learned. *J Child Neurol* 1998;13(Suppl 1): S11-14.

1. Product Information: Dilantin(R) intravenous injection solution, phenytoin sodium intravenous injection solution. Pfizer (Per FDA), New York, NY, Oct, 2011.
2. Meek PD, Davis SN, Collins DM et al: Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. Panel on Nonemergency Use of Parenteral Phenytoin Products. Arch Intern Med Dec13, 1999; 159(22): 2639-2644.
3. Scheinfeld N: Impact of phenytoin therapy on the skin and skin disease. Expert Opin Drug Saf Nov, 2004; 3(6): 655-665.
4. Wheless JW: Pediatric use of intravenous and intramuscular phenytoin: lessons learned. J Child Neurol Oct, 1998; 13 Suppl 1: S11-S14.
5. Battino D: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet Nov, 1995; 29(5): 341-369.
6. De Negri M: Treatment of status epilepticus in children. Paediatr Drugs 2001; 3(6): 411-420.
7. Stowe CD, Lee KR, Storgion SA et al: Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. J Clin Pharmacol Dec, 2000; 40(12 Pt 2): 1452-1461.
8. Bourgeois BF: Pharmacokinetic properties of current antiepileptic drugs: what improvements are needed?Neurology 2000; 55(11 Suppl 3): S11-S16.
9. Albani M: Phenytoin in infancy and childhood. Adv Neurol 1983; 34: 457-464.
10. Product Information: DILANTIN-125(R) oral suspension, phenytoin oral suspension. Parke-Davis, New York, NY, Apr, 2009.

Title Phenytoin

Dose

Loading dose: 15 to 20 mg/kg IV infusion over at least 30 minutes.
Maintenance dose: 4 to 8 mg/kg every 24 hours IV slow push, or orally.
(Up to 8 mg/kg per dose every 8 to 12 hours after 1 week of age).
Maximum rate of infusion 0.5 mg/kg per minute. Flush IV with saline before and after administration. **Phenytoin is highly unstable in any IV solution. Avoid using in central lines because of the risk of precipitation. IM route not acceptable; drug crystallizes in muscle.**Oral absorption is erratic.

Uses

Anticonvulsant often used to treat seizures refractory to phenobarbital.

Black Box Warning

The rate of intravenous phenytoin administration should not exceed 1 to 3 mg/kg/min (or 50 mg per minute, whichever is slower) in pediatric patients because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous phenytoin. Although the risk of

cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed [1] .

Pharmacology

Hepatic metabolism capacity is limited; saturation may occur within therapeutic range. Pharmacokinetics are dose-dependent. Elimination rate is increased during first few weeks of life. Serum half-life is 18 to 60 hours. 85% to 90% protein bound. Bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [6] [7] [8] [5] [9] .

Adverse Effects

Extravasation causes tissue inflammation and necrosis due to high pH and osmolality. Propylene glycol content of the intravenous formulation has been associated with seizures and may potentiate the cardiovascular effects of phenytoin. Purple glove syndrome can occur with IV use (even without extravasation). Hypotension and cardiac arrhythmias have been reported. High serum concentrations are associated with seizures. Dose related adverse events include nystagmus (total level 15 to 25 mg/L) and ataxia and mental status changes (total level greater than 30 mg/L). Movement disorders (bradykinesia and choreoathetosis) may also occur rarely. Hypersensitivity reactions have been reported in infants. Long-term effects of phenytoin include gingival hyperplasia, coarsening of the facies, hirsutism, hyperglycemia, and hypoinsulinemia. Cutaneous side effects include maculopapular exanthema, drug-induced lupus, and pigmentary alterations. Phenytoin interacts with carbamazepine, cimetidine, corticosteroids, digoxin, furosemide, phenobarbital, and valproate [1] [3] [4] .
Use with caution in infants and children with hyperbilirubinemia: bilirubin displaces phenytoin from protein-binding sites, resulting in increased serum free phenytoin concentration [5] .

Serious and sometimes fatal skin reactions, including Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis, have been reported with phenytoin therapy. Onset of symptoms is typically within 28 days, but can occur later. Limited data suggests that a particular human leukocyte antigen (HLA) allele, HLA-B*1502, found in patients of Asian ancestry may be a risk factor for the development of SJS/TEN in patients taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502 [1] .

Monitoring

Monitor electrocardiogram, blood pressure, and respiratory function continuously during infusion, and for 15 minutes to 1 hour after infusion [1] [2] . Observe IV site for extravasation. Follow serum concentration closely: therapeutic range is 6 to 15 mcg/mL in the first weeks, then 10 to 20 mcg/mL due to changes in protein binding. Obtain initial trough level 48 hours after IV loading dose.

Special Considerations/Preparation

Injectable solution available in a concentration of 50 mg/mL. Contains 40% propylene glycol and 10% alcohol (100 mg/mL) [1] .
Oral suspension available in a concentration of 25 mg/mL [10] .

Solution Compatibility

NS only.

Solution Incompatibility

D_5W and $D_{10}W$.

Terminal Injection Site Compatibility

Esmolol, famotidine, and fluconazole.

Terminal Injection Site Incompatibility

Dex/AA solutions, fat emulsion. Amikacin, cefepime, ceftazidime, chloramphenicol, clindamycin, dobutamine, enalaprilat, fentanyl, heparin, hyaluronidase, hydrocortisone succinate, insulin, lidocaine, linezolid, methadone, micafungin, morphine, nitroglycerin, pentobarbital, potassium chloride, procainamide, propofol, sodium bicarbonate, and vitamin K_1.

References

- Volpe JJ: *Neurology of the Newborn,* ed 4. Philadelphia: WB Saunders Co, 2001, p 204-205.
- Wheless JW: Pediatric use of intravenous and intramuscular phenytoin: lessons learned. *J Child Neurol* 1998;13(Suppl 1): S11-14.

1. Product Information: Dilantin(R) intravenous injection solution, phenytoin sodium intravenous injection solution. Pfizer (Per FDA), New York, NY, Oct, 2011.
2. Meek PD, Davis SN, Collins DM et al: Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. Panel on Nonemergency Use of Parenteral Phenytoin Products. Arch Intern Med Dec13, 1999; 159(22): 2639-2644.
3. Scheinfeld N: Impact of phenytoin therapy on the skin and skin disease. Expert Opin Drug Saf Nov, 2004; 3(6): 655-665.
4. Wheless JW: Pediatric use of intravenous and intramuscular phenytoin: lessons learned. J Child Neurol Oct, 1998; 13 Suppl 1: S11-S14.
5. Battino D: Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part II. Phenytoin, carbamazepine, sulthiame, lamotrigine, vigabatrin, oxcarbazepine and felbamate. Clin Pharmacokinet Nov, 1995; 29(5): 341-369.
6. De Negri M: Treatment of status epilepticus in children. Paediatr Drugs 2001; 3(6): 411-420.
7. Stowe CD, Lee KR, Storgion SA et al: Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. J Clin Pharmacol Dec, 2000; 40(12 Pt 2): 1452-1461.

8. Bourgeois BF: Pharmacokinetic properties of current antiepileptic drugs: what improvements are needed?Neurology 2000; 55(11 Suppl 3): S11-S16.
9. Albani M: Phenytoin in infancy and childhood. Adv Neurol 1983; 34: 457-464.
10. Product Information: DILANTIN-125(R) oral suspension, phenytoin oral suspension. Parke-Davis, New York, NY, Apr, 2009.

1.146 Piperacillin

Title Piperacillin

Dose

50 to 100 mg/kg/dose IV infusion by syringe pump over 30 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Semisynthetic penicillin with increased activity against *Pseudomonas aeruginosa*and many strains of *Klebsiella, Serratia, E coli, Enterobacter, Citrobacter*, and *Proteus.*Also effective against group B *Streptococcus*.

Pharmacology

Piperacillin is a potent, broad-spectrum, semi-synthetic, ureidopenicillin possessing high activity against gram-negative bacteria. Inactivation by beta-lactamase-producing bacteria. Synergistic with aminoglycosides. Good penetration into bone; CSF penetration similar to that of other penicillins. Serum half-life depends on gestational age and postnatal age. Primarily excreted renally unchanged.

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine.

Monitoring

Desired peak serum concentration is approximately 150 mcg/mL.
Desired trough concentration ranges from 15 to 50 mcg/mL (available as bioassay).
Peak serum concentration is lower with IM administration. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection in 2-g, 3-g, 4-g, and 40-g vials. Reconstitute 2-g vial with 10 mL of sterile water for injection to make a final concentration of 200 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 2 days refrigerated. A 50 mg/mL dilution may be made by adding 2.5 mL of reconstituted solution to 7.5 mL sterile water for injection. Dilution stable for 2 days refrigerated.

IM Administration : Use 400 mg/mL concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, aztreonam, clindamycin, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, nicardipine, potassium chloride, propofol, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, gentamicin, netilmicin, fluconazole, tobramycin, and vancomycin.

References

- Kacet N, Roussel-Delvallez M, Gremillet C, et al: Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J* 1992;11:365.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Reed MD, Myers CM, Yamashita TS, Blumer JL: Developmental pharmacology and therapeutics of piperacillin in gram-negative infections. *Dev Pharmacol Ther* 1986;9:102.
- Placzek M, Whitelaw A, Want S, et al: Piperacillin in early neonatal infection. *Arch Dis Child* 1983;58:1006-1009.
- Product Information, Abraxis Pharmaceutical Products, 2006.

Title Piperacillin

Dose

50 to 100 mg/kg/dose IV infusion by syringe pump over 30 minutes, or IM.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Semisynthetic penicillin with increased activity against *Pseudomonas aeruginosa*and many strains of *Klebsiella, Serratia, E coli, Enterobacter, Citrobacter,* and *Proteus.*Also effective against group B *Streptococcus*.

Pharmacology

Piperacillin is a potent, broad-spectrum, semi-synthetic, ureidopenicillin possessing high activity against gram-negative bacteria. Inactivation by beta-lactamase-producing bacteria. Synergistic with aminoglycosides. Good penetration into bone; CSF penetration similar to that of other penicillins. Serum half-life depends on gestational age and postnatal age. Primarily excreted renally unchanged.

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine.

Monitoring

Desired peak serum concentration is approximately 150 mcg/mL.
Desired trough concentration ranges from 15 to 50 mcg/mL (available as bioassay).

Peak serum concentration is lower with IM administration. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection in 2-g, 3-g, 4-g, and 40-g vials. Reconstitute 2-g vial with 10 mL of sterile water for injection to make a final concentration of 200 mg/mL. Reconstituted solution stable for 24 hours at room temperature, 2 days refrigerated. A 50 mg/mL dilution may be made by adding 2.5 mL of reconstituted solution to 7.5 mL sterile water for injection. Dilution stable for 2 days refrigerated.

IM Administration : Use 400 mg/mL concentration.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, aminophylline, aztreonam, clindamycin, enalaprilat, esmolol, famotidine, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, midazolam, milrinone, morphine, nicardipine, potassium chloride, propofol, ranitidine, remifentanil, and zidovudine.

Terminal Injection Site Incompatibility

Amikacin, amiodarone, gentamicin, netilmicin, fluconazole, tobramycin, and vancomycin.

References

- Kacet N, Roussel-Delvallez M, Gremillet C, et al: Pharmacokinetic study of piperacillin in newborns relating to gestational and postnatal age. *Pediatr Infect Dis J* 1992;11:365.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Reed MD, Myers CM, Yamashita TS, Blumer JL: Developmental pharmacology and therapeutics of piperacillin in gram-negative infections. *Dev Pharmacol Ther* 1986;9:102.
- Placzek M, Whitelaw A, Want S, et al: Piperacillin in early neonatal infection. *Arch Dis Child* 1983;58:1006-1009.
- Product Information, Abraxis Pharmaceutical Products, 2006.

1.147 Piperacillin\Tazobactam

Title Piperacillin/Tazobactam

Dose

50 to 100 mg/kg/dose (as piperacillin component) IV infusion.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	8

Administration

Infuse IV over at least 30 minutes at a final concentration of 10 to 40 mg/mL (piperacillin component). **Maximum concentration 80 mg/mL**.

Uses

Treatment of non-CNS infections, caused by susceptible beta-lactamase producing bacteria, including many strains of *E. coli*, *Enterobacter*, *Klebsiella*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas spp.*,and*Staph. aureus.* Also effective against group *B Streptococcus.*

Pharmacology

Zosyn® combines the extended-spectrum antibiotic piperacillin with the beta-lactamase inhibitor tazobactam in a 8:1 ratio. Piperacillin is primarily eliminated unchanged by renal mechanisms, whereas tazobactam undergoes significant hepatic metabolism. The mean half-life of piperacillin and tazobactam in neonates is approximately 1.5 hours. CNS penetration is modest (limited data).

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine.

Monitoring

Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection (containing EDTA and sodium citrate) in 2.25-g, 3.375-g, and 4.5-g single-dose vials. These vials are intended for one-time, single-dose use, and the final concentration when diluted as directed by the manufacturer (5 mL per 1 g piperacillin) is not available. The entire contents of the single-dose vial should be withdrawn and further diluted to 10 to 40 mg/mL with a compatible solution prior to withdrawing the desired patient-specific dose. The 40.5 g pharmacy bulk vial, when reconstituted as directed by the manufacturer, has a known final concentration of 200 mg/mL. The desired dose should be further diluted to 10 to 40 mg/mL with a compatible solution prior to administration. **Maximum concentration 80 mg/mL.** Reconstituted solution stable for 24 hours at room temperature, 48 hours refrigerated. pH 4.5 to 6.8. Each 2.25-g, 3.375-g, and 4.5-g vial contains 5.58, 8.38, and 11.17 mEq (128, 192, 256 mg) of sodium, respectively.

Also available in Galaxy® containers (containing EDTA and sodium citrate) as 2.25 g/50 mL, 3.375 g/50 mL, and 4.5 g/100 mL.

Solution Compatibility

D_5W, $D_{10}W$, NS and LR.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Aminophylline, aztreonam, bumetanide, calcium gluconate, cefepime, cimetidine, clindamycin, dexamethasone, dopamine, enalaprilat, esmolol, fluconazole, furosemide, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amikacin, amiodarone, amphotericin B, azithromycin, caspofungin, dobutamine, famotidine, ganciclovir, gentamicin, netilmicin, tobramycin, and vancomycin.

References

- Pillay T, Pillay DG, Adhikari M, Sturn AW: Piperacillin/tazobactam in the treatment of *Klebsiella pneumoniae* infections in neonates. *Am J Perinatol*1998;15:47-51.
- Reed MD, Goldfarb J, Yamashita TS, Blumer JL: Single dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother*1994;38:2817-26.
- Schoonover L, Occhipinti D, Rodvold K, et al: Piperacillin/tazobactam: A new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother*1995;29:501-14.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Product Information, Wyeth, 2009.

Title Piperacillin/Tazobactam

Dose

50 to 100 mg/kg/dose (as piperacillin component) IV infusion.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	8

Administration

Infuse IV over at least 30 minutes at a final concentration of 10 to 40 mg/mL (piperacillin component). **Maximum concentration 80 mg/mL**.

Uses

Treatment of non-CNS infections, caused by susceptible beta-lactamase producing bacteria, including many strains of *E. coli*, *Enterobacter*, *Klebsiella*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas spp.*,and*Staph. aureus.* Also effective against group *B Streptococcus.*

Pharmacology

Zosyn® combines the extended-spectrum antibiotic piperacillin with the beta-lactamase inhibitor tazobactam in a 8:1 ratio. Piperacillin is primarily eliminated unchanged by renal mechanisms, whereas tazobactam undergoes significant hepatic metabolism. The mean half-life of piperacillin and tazobactam in neonates is approximately 1.5 hours. CNS penetration is modest (limited data).

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine.

Monitoring

Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection (containing EDTA and sodium citrate) in 2.25-g, 3.375-g, and 4.5-g single-dose vials. These vials are intended for one-time, single-dose use, and the final concentration when diluted as directed by the manufacturer (5 mL per 1 g piperacillin) is not available. The entire contents of the single-dose vial should be withdrawn and further diluted to 10 to 40 mg/mL with a compatible solution prior to withdrawing the desired patient-specific dose. The 40.5 g pharmacy bulk vial, when reconstituted as directed by the manufacturer, has a known final concentration of 200 mg/mL. The desired dose should be further diluted to 10 to 40 mg/mL with a compatible solution prior to administration. **Maximum concentration 80 mg/mL.** Reconstituted solution stable for 24 hours at room temperature, 48 hours refrigerated. pH 4.5 to 6.8. Each 2.25-g, 3.375-g, and 4.5-g vial contains 5.58, 8.38, and 11.17 mEq (128, 192, 256 mg) of sodium, respectively.

Also available in Galaxy® containers (containing EDTA and sodium citrate) as 2.25 g/50 mL, 3.375 g/50 mL, and 4.5 g/100 mL.

Solution Compatibility

D_5W, $D_{10}W$, NS and LR.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Aminophylline, aztreonam, bumetanide, calcium gluconate, cefepime, cimetidine, clindamycin, dexamethasone, dopamine, enalaprilat, esmolol, fluconazole, furosemide, heparin, hydrocortisone succinate, linezolid, lorazepam, magnesium sulfate, metoclopramide, metronidazole, milrinone, morphine, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, trimethoprim/sulfamethoxazole, and zidovudine.

Terminal Injection Site Incompatibility

Acyclovir, amikacin, amiodarone, amphotericin B, azithromycin, caspofungin, dobutamine, famotidine, ganciclovir, gentamicin, netilmicin, tobramycin, and vancomycin.

References

- Pillay T, Pillay DG, Adhikari M, Sturn AW: Piperacillin/tazobactam in the treatment of *Klebsiella pneumoniae* infections in neonates. *Am J Perinatol*1998;15:47-51.

- Reed MD, Goldfarb J, Yamashita TS, Blumer JL: Single dose pharmacokinetics of piperacillin and tazobactam in infants and children. *Antimicrob Agents Chemother*1994;38:2817-26.
- Schoonover L, Occhipinti D, Rodvold K, et al: Piperacillin/tazobactam: A new beta-lactam/beta-lactamase inhibitor combination. *Ann Pharmacother*1995;29:501-14.
- Prober CG, Stevenson DK, Benitz WE: The use of antibiotics in neonates weighing less than 1200 grams. *Pediatr Infect Dis J* 1990;9:111.
- Product Information, Wyeth, 2009.

1.148 Pneumococcal 13-Valent Conjugate Vaccine (PCV13)

Title Pneumococcal 13-Valent Conjugate Vaccine (PCV13)

Dose

0.5 mL IM; the usual vaccination schedule of pneumococcal 13-valent conjugate vaccine (PCV13) consists of 4 doses given at 2 months (as young as 6 weeks of age is acceptable), 4 months, 6 months, and 12 to 15 months of age [1] . The recommended dosing interval is 4 to 8 weeks [2] .

Administration

Shake vigorously prior to use. Vaccine should appear as a homogeneous white suspension; do not use if it cannot be resuspended. Do not mix with other vaccines. Administer IM in the anterolateral thigh. Do not inject IV, subQ, or intradermally. When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel.

Uses

Immunoprophylaxis against invasive disease caused by *S. pneumoniae* due to the 13 serotypes contained in the vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and for prevention of otitis media caused by the 7 serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) in children 6 weeks to less than 59 months of age.

Contraindications/Precautions

Contraindicated in patients with a serious allergic reaction (eg, anaphylaxis) after a previous pneumococcal vaccine dose, or any diphtheria toxoid-containing vaccine. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine.

Pharmacology

PCV13 contains the original 7 pneumococcal capsular polysaccharides found in PCV7 and 6 additional pneumococcal serotypes (1, 3, 5, 6A, 7F, and 19A), which have been attributed to 64% of invasive pneumococcal disease now occurring in US children younger than 5 years of age (the 7 original serotypes account for 83% of the disease in

the US). PCV13 is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to diphtheria CRM197 protein. The increased antigenic load of PCV13 did not interfere with immune responses against other vaccines given concurrently nor did it increase vaccine reactogenicity during clinical trials. Each dose contains 0.125 mg aluminum as aluminum phosphate adjuvant.

Adverse Effects

Local injection site reactions (eg, erythema, induration, and tenderness) are common (greater than 20%) after each injection. Systemic reactions (eg, fever, irritability, decreased appetite, or decreased/increased sleep) are common (greater than 20%). Rare anaphylactic reactions (eg, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported.

Monitoring

Observe injection site for erythema, induration (common), palpable nodule (uncommon), or sterile abscess (rare).

Special Considerations/Preparation

Prevnar 13™ is supplied in 0.5-mL single-dose, latex-free, pre-filled syringes. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). Do not freeze; discard if frozen.

References

- Advisory Committee on Immunization Practices: ACIP Recommendations. Most recent updates available on the National Immunization Program website: http://www.cdc.gov/vaccines/pubs/acip-list.htm.
- American Academy of Pediatrics (AAP): Policy statement recommendations for the prevention of streptococcus pneumonia infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics* 2010; 126: published online May 24, 2010.
- Bryant KA, Block SL, Baker SA, et al: Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010; 125:866-875.
- Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(RR-02):1-60.
- Centers for Disease Control and Prevention: Prevention of pneumococcal disease among infants and children - Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59(RR-11):1-19.
- Centers for Disease Control and Prevention: Invasive pneumococcal disease in young children before licensure of 13-valent pneumococcal conjugate vaccine-United States, 2007. *MMWR* 2010; 59(9):253-257.
- Esposito S, Tansey S, Thompson A, et al: Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine compared to 7-valent pneumococcal. *Clin Vaccine Immunol* 2010 April 28 [Epub ahead of print].

- Product information: Prevnar 13™ pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein), Wyeth Pharmaceuticals, 2011.
- Yeh SH, Gurtman A, Hurley DC, et al: Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in infants and toddlers. *Pediatrics* 2010;16:e493-e505.

1. Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.
2. Product Information: PREVNAR 13 intramuscular injection suspension, pneumococcal 13 valent conjugate vaccine diphtheria CRM197 protein intramuscular injection suspension. Wyeth Pharmaceuticals Inc. (per manufacturer), Philadelphia, PA, Jan, 2013.

Title Pneumococcal 13-Valent Conjugate Vaccine (PCV13)

Dose

0.5 mL IM; the usual vaccination schedule of pneumococcal 13-valent conjugate vaccine (PCV13) consists of 4 doses given at 2 months (as young as 6 weeks of age is acceptable), 4 months, 6 months, and 12 to 15 months of age [1] . The recommended dosing interval is 4 to 8 weeks [2] .

Administration

Shake vigorously prior to use. Vaccine should appear as a homogeneous white suspension; do not use if it cannot be resuspended. Do not mix with other vaccines. Administer IM in the anterolateral thigh. Do not inject IV, subQ, or intradermally. When giving multiple vaccines, use a separate syringe for each and give at different sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel.

Uses

Immunoprophylaxis against invasive disease caused by *S. pneumoniae* due to the 13 serotypes contained in the vaccine (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and for prevention of otitis media caused by the 7 serotypes contained in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F) in children 6 weeks to less than 59 months of age.

Contraindications/Precautions

Contraindicated in patients with a serious allergic reaction (eg, anaphylaxis) after a previous pneumococcal vaccine dose, or any diphtheria toxoid-containing vaccine. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have a suboptimal response to the vaccine.

Pharmacology

PCV13 contains the original 7 pneumococcal capsular polysaccharides found in PCV7 and 6 additional pneumococcal serotypes (1, 3, 5, 6A, 7F, and 19A), which have been attributed to 64% of invasive pneumococcal disease now occurring in US children younger than 5 years of age (the 7 original serotypes account for 83% of the disease in the US). PCV13 is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to diphtheria CRM197 protein. The increased antigenic load of PCV13 did not interfere with immune responses against other vaccines given concurrently nor did it increase vaccine reactogenicity during clinical trials. Each dose contains 0.125 mg aluminum as aluminum phosphate adjuvant.

Adverse Effects

Local injection site reactions (eg, erythema, induration, and tenderness) are common (greater than 20%) after each injection. Systemic reactions (eg, fever, irritability, decreased appetite, or decreased/increased sleep) are common (greater than 20%). Rare anaphylactic reactions (eg, hives, swelling of the mouth, hypotension, breathing difficulty, and shock) have been reported.

Monitoring

Observe injection site for erythema, induration (common), palpable nodule (uncommon), or sterile abscess (rare).

Special Considerations/Preparation

Prevnar 13™ is supplied in 0.5-mL single-dose, latex-free, pre-filled syringes. Store refrigerated at 2 to 8 degrees C (36 to 46 degrees F). Do not freeze; discard if frozen.

References

- Advisory Committee on Immunization Practices: ACIP Recommendations. Most recent updates available on the National Immunization Program website: http://www.cdc.gov/vaccines/pubs/acip-list.htm.
- American Academy of Pediatrics (AAP): Policy statement recommendations for the prevention of streptococcus pneumonia infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). *Pediatrics* 2010; 126: published online May 24, 2010.
- Bryant KA, Block SL, Baker SA, et al: Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010; 125:866-875.
- Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2011; 60(RR-02):1-60.
- Centers for Disease Control and Prevention: Prevention of pneumococcal disease among infants and children - Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - Advisory Committee on Immunization Practices (ACIP). *MMWR* 2010; 59(RR-11):1-19.
- Centers for Disease Control and Prevention: Invasive pneumococcal disease in young children before licensure of 13-valent pneumococcal conjugate vaccine-United States, 2007. *MMWR* 2010; 59(9):253-257.

- Esposito S, Tansey S, Thompson A, et al: Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine compared to 7-valent pneumococcal. *Clin Vaccine Immunol* 2010 April 28 [Epub ahead of print].
- Product information: Prevnar 13™ pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein), Wyeth Pharmaceuticals, 2011.
- Yeh SH, Gurtman A, Hurley DC, et al: Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in infants and toddlers. *Pediatrics* 2010;16:e493-e505.

1. Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.
2. Product Information: PREVNAR 13 intramuscular injection suspension, pneumococcal 13 valent conjugate vaccine diphtheria CRM197 protein intramuscular injection suspension. Wyeth Pharmaceuticals Inc. (per manufacturer), Philadelphia, PA, Jan, 2013.

1.149 Poliovirus Vaccine Enhanced-Inactivated

Title Poliovirus Vaccine Enhanced-Inactivated

Dose

0.5 mL IM or subQ x 4 doses at 2, 4, 6 to 18 months of age, and at 4 to 6 years of age. First dose may be given at 6 weeks of age if needed [1] . Immunize premature infants according to their postnatal age.

Administration

Administer IM or subQ in mid-lateral thigh. When giving multiple vaccines, use a separate syringe for each and give at separate sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] .

Uses

Immunoprophylaxis against poliomyelitis caused by poliovirus types 1, 2 and 3 in infants 6 weeks or older, children, and adults [3] [2] .
Inactivated poliovirus vaccine is now the only poliovirus vaccine available; live, attenuated oral poliovirus vaccine (OPV) is no longer available in the US and is only recommended for use in special circumstances (eg, control of outbreaks) [3] [2] .

Contraindications/Precautions **Contraindicated** in patients with anaphylaxis or shock within 24 hours after dose, or to any component of the vaccine which includes neomycin, streptomycin, polymyxin B, formaldehyde, and 2-phenoxyethanol. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [4] [2] .

Pharmacology

Sterile suspension of types 1, 2, and 3 poliovirus inactivated with formaldehyde. The vaccine produced using a microcarrier culture technique of monkey kidney cells has enhanced potency. Contains traces of streptomycin, neomycin, and polymyxin B [2] .

Adverse Effects

Local injection site reactions (erythema (3.2%), induration (1%) or tenderness (13%)), fever (102 degrees F or greater (39 degrees C or greater); 38% when given concurrently with DTP), irritability, and tiredness were observed during clinical studies. Guillain-Barre syndrome and deaths have occurred in temporal association after vaccination of infants with IPV, although no causal relationships have been established [2] .

Monitoring

No specific monitoring required.

Special Considerations/Preparation

IPOL® (Sanofi Pasteur) is a clear, colorless suspension, available in 0.5 mL single-dose syringes and multidose vial. Do not use if the vaccine is turbid or discolored. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze** [2] .

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: IPOL(R) injection, poliovirus vaccine inactivated injection. Aventis Pasteur Inc, Swiftwater, PA, Apr1, 2005.

- American Academy of Pediatrics Committee on Infectious Diseases : Poliovirus. Pediatrics Oct, 2011; 128(4): 805-808.

- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

Title Poliovirus Vaccine Enhanced-Inactivated

Dose

0.5 mL IM or subQ x 4 doses at 2, 4, 6 to 18 months of age, and at 4 to 6 years of age. First dose may be given at 6 weeks of age if needed [1] . Immunize premature infants according to their postnatal age.

Administration

Administer IM or subQ in mid-lateral thigh. When giving multiple vaccines, use a separate syringe for each and give at separate sites. Care should be taken to draw back on the plunger of the syringe before injection to be certain the needle is not in a blood vessel [2] .

Uses

Immunoprophylaxis against poliomyelitis caused by poliovirus types 1, 2 and 3 in infants 6 weeks or older, children, and adults [3] [2] .
Inactivated poliovirus vaccine is now the only poliovirus vaccine available; live, attenuated oral poliovirus vaccine (OPV) is no longer available in the US and is only recommended for use in special circumstances (eg, control of outbreaks) [3] [2] .

Contraindications/Precautions

Contraindicated in patients with anaphylaxis or shock within 24 hours after dose, or to any component of the vaccine which includes neomycin, streptomycin, polymyxin B, formaldehyde, and 2-phenoxyethanol. Vaccination should be deferred in patients with moderate or severe acute illness, with or without fever. Immunocompromised patients may have suboptimal response to vaccine [4] [2] .

Pharmacology

Sterile suspension of types 1, 2, and 3 poliovirus inactivated with formaldehyde. The vaccine produced using a microcarrier culture technique of monkey kidney cells has enhanced potency. Contains traces of streptomycin, neomycin, and polymyxin B [2] .

Adverse Effects

Local injection site reactions (erythema (3.2%), induration (1%) or tenderness (13%)), fever (102 degrees F or greater (39 degrees C or greater); 38% when given concurrently with DTP), irritability, and tiredness were observed during clinical studies. Guillain-Barre syndrome and deaths have occurred in temporal association after vaccination of infants with IPV, although no causal relationships have been established [2] .

Monitoring

No specific monitoring required.

Special Considerations/Preparation

IPOL® (Sanofi Pasteur) is a clear, colorless suspension, available in 0.5 mL single-dose syringes and multidose vial. Do not use if the vaccine is turbid or discolored. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F). **Do not freeze** [2] .

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Product Information: IPOL(R) injection, poliovirus vaccine inactivated injection. Aventis Pasteur Inc, Swiftwater, PA, Apr1, 2005.
- American Academy of Pediatrics Committee on Infectious Diseases : Poliovirus. Pediatrics Oct, 2011; 128(4): 805-808.
- Centers for Disease Control and Prevention (CDC) : General recommendations on immunization --- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jan28, 2011; 60(2): 1-64.

1.150 Poly-Vi-SolÂ® MVI Drops

Title Poly-Vi-SolÂ® MVI Drops

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician.

Poly-Vi-Sol® Multivitamin Drops

Nutrient amt	w/o Iron	with Iron
Vitamins		
A, IU	1500	1500
D, IU	400	400
C, mg	35	35
E, IU	5	5
Thiamine B 1 , mg	0.5	0.5
Riboflavin B 2 , mg	0.6	0.6
Niacin, mg	8	8
B 6 , mg	0.4	0.4
B 12 , mcg	2	0
Minerals		
Iron, mg	0	10

Title Poly-Vi-SolÂ® MVI Drops

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician.

Poly-Vi-Sol® Multivitamin Drops

Nutrient amt	w/o Iron	with Iron
Vitamins		
A, IU	1500	1500
D, IU	400	400
C, mg	35	35
E, IU	5	5
Thiamine B 1 , mg	0.5	0.5
Riboflavin B 2 , mg	0.6	0.6
Niacin, mg	8	8
B 6 , mg	0.4	0.4
B 12 , mcg	2	0
Minerals		
Iron, mg	0	10

1.151 Poractant alfa

Title Poractant alfa

Dose

Initial dose is 2.5 mL/kg per dose intratracheally, divided into 2 aliquots followed by up to two subsequent doses of 1.25 mL/kg per dose administered at 12-hour intervals if needed [1] .

Administration

For Endotracheal Tube Instillation Using a 5-French end-hole Catheter
Clear the trachea of secretions. Shorten a 5F end-hole catheter to 8 cm so the tip of the catheter will protrude just beyond end of ET tube above infant's carina. Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle. **Do not filter or shake**. Attach shortened catheter to syringe. Fill catheter with surfactant. Discard excess through catheter so only total dose to be given

remains in syringe [1] .
Infant's ventilator settings should be changed to a rate of 40 to 60 breaths/min, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain oxygen saturation at greater than 92% immediately before administration. Keep infant in the neutral position and briefly disconnect the endotracheal tube from the ventilator and instill the first aliquot (1.25 mL/kg). Infant should be positioned so that either right or left side is dependent for the aliquot. After administration of the aliquot, the dosing catheter is removed from the ET tube and the infant is ventilated for at least 1 minute until stable. Reposition the infant so that the other side is dependent and administer the remaining aliquot with the same procedure [1] .

For Endotracheal Tube Instillation Using the Second Lumen of a Dual Lumen Endotracheal Tube
Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle. **Do not filter or shake**. Do not attach a 5 F end-hole catheter. Keep the infant in a neutral position and administer as a single dose through the proximal end of the secondary lumen of the endotracheal tube. Administer dose over 1 minute without interrupting mechanical ventilation [1] .

Uses

Treatment of respiratory distress syndrome (RDS) in premature infants [1] .

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Curosurf® is a modified porcine-derived minced lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Each mL of surfactant contains 80 mg of total phospholipids (54 mg of phosphatidylcholine of which 30.5 mg dipalmitoyl phosphatidylcholine) and 1 mg of protein including 0.3 mg of SP-B [1] .

Adverse Effects

Transient episodes of reflux of bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation have been reported during administration [1] .

Monitoring

Monitor clinical and laboratory tests frequently for appropriate oxygen therapy and ventilatory support [1] .

Special Considerations/Preparation

Available in 1.5 mL (120 mg phospholipid) and 3 mL (240 mg phospholipid) vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Curosurf® for discoloration; normal color is creamy white. If settling occurs during storage, gently turn vial upside-down in order to uniformly suspend. **Do not shake.**Used vials with residual drug should be discarded. Unopened vials that have

been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

References

- Collaborative European Multicenter Study Group: Surfactant replacement therapy for severe neonatal respiratory distress syndrome: A international randomized clinical trial. *Pediatrics* 1988;82:683-691.
- Bevilacqua G, Parmigiani S, Robertson B: Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomized trial. *J Perinat Med*1996;24:609-620.
- Egberts J, de Winter JP, Sedin G, et al: Comparison of prophylaxis and rescue treatment with Curosurf® in neonates less than 30 weeks' gestation: A randomized trial. *Pediatrics* 1993;92:768-774.
- Halliday HL, Tarnow-Mordi WO, Corcoran JD, et al: Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf® 4 trials). *Arch Dis Child* 1993;69:276-280.

1. Product Information: CUROSURF(R) intratracheal suspension, poractant alfa intratracheal suspension. Dey, Napa, CA, 03/00/2002.

Title Poractant alfa

Dose

Initial dose is 2.5 mL/kg per dose intratracheally, divided into 2 aliquots followed by up to two subsequent doses of 1.25 mL/kg per dose administered at 12-hour intervals if needed [1] .

Administration

For Endotracheal Tube Instillation Using a 5-French end-hole Catheter
Clear the trachea of secretions. Shorten a 5F end-hole catheter to 8 cm so the tip of the catheter will protrude just beyond end of ET tube above infant's carina. Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle. **Do not filter or shake**. Attach shortened catheter to syringe. Fill catheter with surfactant. Discard excess through catheter so only total dose to be given remains in syringe [1] .
Infant's ventilator settings should be changed to a rate of 40 to 60 breaths/min, inspiratory time 0.5 second, and supplemental oxygen sufficient to maintain oxygen saturation at greater than 92% immediately before administration. Keep infant in the neutral position and briefly disconnect the endotracheal tube from the ventilator and instill the first aliquot (1.25 mL/kg). Infant should be positioned so that either right or left side is dependent for the aliquot. After administration of the aliquot, the dosing catheter is removed from the ET tube and the infant is ventilated for at least 1 minute until stable. Reposition the infant so that the other side is dependent and administer the remaining aliquot with the same procedure [1] .

For Endotracheal Tube Instillation Using the Second Lumen of a Dual Lumen Endotracheal Tube

Slowly withdraw entire contents of vial into a plastic syringe through a large (greater than 20 gauge) needle. **Do not filter or shake**. Do not attach a 5 F end-hole catheter. Keep the infant in a neutral position and administer as a single dose through the proximal end of the secondary lumen of the endotracheal tube. Administer dose over 1 minute without interrupting mechanical ventilation [1] .

Uses

Treatment of respiratory distress syndrome (RDS) in premature infants [1] .

Pharmacology

Pulmonary lung surfactants are essential for effective ventilation by modifying alveolar surface tension thereby stabilizing the alveoli. Curosurf® is a modified porcine-derived minced lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins B and C. Each mL of surfactant contains 80 mg of total phospholipids (54 mg of phosphatidylcholine of which 30.5 mg dipalmitoyl phosphatidylcholine) and 1 mg of protein including 0.3 mg of SP-B [1] .

Adverse Effects

Transient episodes of reflux of bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation have been reported during administration [1] .

Monitoring

Monitor clinical and laboratory tests frequently for appropriate oxygen therapy and ventilatory support [1] .

Special Considerations/Preparation

Available in 1.5 mL (120 mg phospholipid) and 3 mL (240 mg phospholipid) vials. Refrigerate at 2 to 8 degrees C (36 to 46 degrees F) and protect from light. Inspect Curosurf® for discoloration; normal color is creamy white. If settling occurs during storage, gently turn vial upside-down in order to uniformly suspend. **Do not shake.**Used vials with residual drug should be discarded. Unopened vials that have been warmed to room temperature one time may be refrigerated within 24 hours and stored for future use. Should not be warmed and returned to the refrigerator more than once [1] .

References

- Collaborative European Multicenter Study Group: Surfactant replacement therapy for severe neonatal respiratory distress syndrome: A international randomized clinical trial. *Pediatrics* 1988;82:683-691.
- Bevilacqua G, Parmigiani S, Robertson B: Prophylaxis of respiratory distress syndrome by treatment with modified porcine surfactant at birth: a multicentre prospective randomized trial. *J Perinat Med*1996;24:609-620.

- Egberts J, de Winter JP, Sedin G, et al: Comparison of prophylaxis and rescue treatment with Curosurf® in neonates less than 30 weeks' gestation: A randomized trial. *Pediatrics* 1993;92:768-774.
- Halliday HL, Tarnow-Mordi WO, Corcoran JD, et al: Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf® 4 trials). *Arch Dis Child* 1993;69:276-280.

1. Product Information: CUROSURF(R) intratracheal suspension, poractant alfa intratracheal suspension. Dey, Napa, CA, 03/00/2002.

1.152 Potassium chloride

Title Potassium chloride

Dose

Initial oral replacement therapy: 0.5 to 1 mEq/kg per day divided and administered with feedings (small, more frequent aliquots preferred). Adjust dosage based on monitoring of serum potassium concentrations.

1 g KCl = 13.4 mEq K^+1 mEq K^+= 74.6 mg KCl

Acute treatment of symptomatic hypokalemia: Begin with 0.5 to 1 mEq/kg IV over 1 hour, then reassess.
Maximum concentration: 40 mEq/L for peripheral, 80 mEq/L for central venous infusions.

Uses

Treatment of hypokalemia.

Contraindications/Precautions

Contraindicated in patients with renal failure. Rapid IV infusions, especially concentrated solutions through central lines, may cause arrhythmias including heart block and cardiac arrest. Peripheral IV administration of concentrated potassium solutions is associated with thrombophlebitis and pain at the injection site; central line should be used for concentrated solutions. Other signs of potassium toxicity include paresthesia of the extremities, weakness, and mental confusion [1] [2] .

Pharmacology

Potassium is the major intracellular cation. Hypokalemia in critically ill neonates is usually the result of diuretic (furosemide, thiazides) therapy or diarrhea. Other causes include congenital adrenal hyperplasia and renal disorders. Alkalosis, as well as insulin infusions, will lower serum potassium concentrations by driving the ion intracellularly. Symptoms of hypokalemia include neuromuscular weakness and paralysis, ileus, urine retention, and EKG changes (ST segment depression, low-voltage T wave, and appearance of U wave). Hypokalemia increases digitalis toxicity. Oral potassium preparations are completely absorbed.

Adverse Effects

GI irritation is common--most commonly diarrhea, vomiting, and bleeding-- minimized by dividing oral doses and administering with feedings. Use with caution (if at all) in patients receiving potassium-sparing diuretics, e.g. spironolactone [1] [2] .

Monitoring

Continuous EKG monitoring is mandatory if administering by the IV route, especially for central infusions. Observe IV site closely for signs of extravasation when using concentrated solutions. Monitor serum potassium concentration. Assess for GI intolerance.

Special Considerations/Preparation

Potassium chloride for injection is supplied as 2-mEq/mL solution. **Always dilute before administration.** Hyperosmolar - 4355 mOsm/kg determined by freezing-point depression. pH ranges from 4 to 8 depending on buffering. Various oral solutions are available, with concentrations ranging from 10 to 40 mEq per 15 mL. Other oral forms available include powder packets, tablets, and sustained-release capsules.

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, and phenytoin.

References

- Satlin LM, Schwartz GJ: Disorders of potassium metabolism, in Ichikawa I (ed): *Pediatric Textbook of Fluids and Electrolytes*. Baltimore: Williams & Wilkins, 1990, p 227.
- Morgan BC: Rapidly infused potassium chloride therapy in a child. *JAMA* 1981;245:2446.
- DeFronzo RA, Bia M: Intravenous potassium chloride therapy. *JAMA* 1981;245:2446.

1. Product Information: KLOR-CON(R) powder for oral solution, potassium chloride powder for oral solution. Upsher-Smith, Maple Grove, MN, Aug, 2009.
2. Product Information: potassium chloride injection, potassium chloride injection. Hospira,Inc., Lake Forest, IL, 04/00/2004.

Title Potassium chloride

Dose

Initial oral replacement therapy: 0.5 to 1 mEq/kg per day divided and administered with feedings (small, more frequent aliquots preferred). Adjust dosage based on monitoring of serum potassium concentrations.

1 g KCl = 13.4 mEq K^+1 mEq K^+= 74.6 mg KCl

Acute treatment of symptomatic hypokalemia: Begin with 0.5 to 1 mEq/kg IV over 1 hour, then reassess.
Maximum concentration: 40 mEq/L for peripheral, 80 mEq/L for central venous infusions.

Uses

Treatment of hypokalemia.

Contraindications/Precautions

Contraindicated in patients with renal failure. Rapid IV infusions, especially concentrated solutions through central lines, may cause arrhythmias including heart block and cardiac arrest. Peripheral IV administration of concentrated potassium solutions is associated with thrombophlebitis and pain at the injection site; central line should be used for concentrated solutions. Other signs of potassium toxicity include paresthesia of the extremities, weakness, and mental confusion [1] [2] .

Pharmacology

Potassium is the major intracellular cation. Hypokalemia in critically ill neonates is usually the result of diuretic (furosemide, thiazides) therapy or diarrhea. Other causes include congenital adrenal hyperplasia and renal disorders. Alkalosis, as well as insulin infusions, will lower serum potassium concentrations by driving the ion intracellularly. Symptoms of hypokalemia include neuromuscular weakness and paralysis, ileus, urine retention, and EKG changes (ST segment depression, low-voltage T wave, and appearance of U wave). Hypokalemia increases digitalis toxicity. Oral potassium preparations are completely absorbed.

Adverse Effects

GI irritation is common--most commonly diarrhea, vomiting, and bleeding-- minimized by dividing oral doses and administering with feedings. Use with caution (if at all) in patients receiving potassium-sparing diuretics, e.g. spironolactone [1] [2] .

Monitoring

Continuous EKG monitoring is mandatory if administering by the IV route, especially for central infusions. Observe IV site closely for signs of extravasation when using concentrated solutions. Monitor serum potassium concentration. Assess for GI intolerance.

Special Considerations/Preparation

Potassium chloride for injection is supplied as 2-mEq/mL solution. **Always dilute before administration.** Hyperosmolar - 4355 mOsm/kg determined by freezing-point depression. pH ranges from 4 to 8 depending on buffering. Various oral solutions are available, with concentrations ranging from 10 to 40 mEq per 15 mL. Other oral forms available include powder packets, tablets, and sustained-release capsules.

Solution Compatibility

Most standard IV solutions.

Terminal Injection Site Compatibility

Most drugs.

Terminal Injection Site Incompatibility

Amphotericin B, diazepam, and phenytoin.

References

- Satlin LM, Schwartz GJ: Disorders of potassium metabolism, in Ichikawa I (ed): *Pediatric Textbook of Fluids and Electrolytes*. Baltimore: Williams & Wilkins, 1990, p 227.
- Morgan BC: Rapidly infused potassium chloride therapy in a child. *JAMA* 1981;245:2446.
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1. Product Information: KLOR-CON(R) powder for oral solution, potassium chloride powder for oral solution. Upsher-Smith, Maple Grove, MN, Aug, 2009.
2. Product Information: potassium chloride injection, potassium chloride injection. Hospira,Inc., Lake Forest, IL, 04/00/2004.

1.153 Procainamide

Title Procainamide

Dose

Initial bolus dose: 7 to 10 mg/kg IV.

Maintenance IV infusion: 20 to 80 mcg/kg per minute. Premature neonates should receive the lowest dose.

Administration

Intravenous/Intraosseous: Administer loading dose over 30 to 60 minutes at a concentration of 20 mg/mL. For continuous infusion, administer at a concentration of 2 to 4 mg/mL [1] [2] [3] .

Uses

Acute treatment of supraventricular tachycardia (SVT) refractory to vagal maneuvers and adenosine. Acute treatment of ventricular tachycardia unresponsive to cardioversion and adenosine. Ectopic tachycardia, junctional ectopic tachycardia, and atrial flutter. Consider obtaining expert consultation before use.

Contraindications/Precautions

Contraindicated in patients with complete heart block and torsades de pointes [3] .

Black Box Warning The use of procainamide hydrochloride as well as other antiarrhythmic agents should be reserved for patients with life-threatening ventricular arrhythmias. The prolonged administration of procainamide often leads to the development of a positive ANA test, with or without symptoms of a lupus erythematosus-like syndrome. Agranulocytosis, bone marrow depression, neutropenia, hypoplastic anemia, and thrombocytopenia in patients receiving procainamide hydrochloride have been reported (in adults), some of which were fatal. Discontinue procainamide if hematologic disorders are identified [3] .

Pharmacology

Procainamide is a class IA antiarrhythmic agent that increases the effective refractory period of the atria and the ventricles of the heart. Onset of action occurs within minutes of starting the loading dose. Half-life is approximately 5 hours in the term neonate, and longer in preterms. Metabolized primarily (60%) in the liver to N-acetylprocainamide (NAPA), an active metabolite. The rate of acetylation is primarily genetically determined in adults and children. Preterm neonates have a higher NAPA:procainamide ratio than term infants presumably due to delayed excretion of NAPA. Renal function is a significant determinant of procainamide clearance [4] [3] [10] .

Adverse Effects

Severe hypotension with rapid infusion, bradycardia, A-V block, and ventricular fibrillation have been reported in adult patients. Normal procainamide concentrations widen the QRS complex due to slowing of conduction in the Purkinje system and ventricular muscle. The drug should be discontinued if the QRS duration increases by more than 35 to 50 percent to avoid serious toxicity. Adverse effects are reversible with discontinuation of drug [7] [8] [9] .

Monitoring

Continuous monitoring of the EKG, blood pressure and heart rate [1] [3] . Measure procainamide and N-acetyl procainamide (NAPA) concentrations at 2, 12, and 24 hours after starting the loading dose infusion [4] .
Therapeutic concentrations:
Procainamide: 4 to 10 mcg/mL, NAPA 6 to 20 mcg/mL [4] [5] [6] .
Sum of procainamide and NAPA: 10 to 30 mcg/mL [4] .
Increasing frequency of toxicity associated with procainamide levels greater than 10 mcg/mL [3] .

Special Considerations/Preparation

Available in 10-mL vials providing 100 mg/mL or 2-mL vials providing 500 mg/mL. Store at room temperature. **Do not freeze.**

Dilute initial bolus dose to a final concentration of 20 mg/mL prior to administration. Maintenance infusion should be diluted to 2 to 4 mg/mL in compatible solution before administration [3] .

Solution Compatibility

D_5W (conflicting data), 0.45% NaCl, and NS.

Solution Incompatibility

D_5W (conflicting data).

Terminal Injection Site Compatibility

Amiodarone, dobutamine, famotidine, flumazenil, heparin, hydrocortisone, lidocaine, netilmicin, ranitidine, remifentanil, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Esmolol, milrinone, and phenytoin.

References

- Wong KK, Potts JE, Ethridge SP, Sanatani S: Medications used to manage supraventricular tachycardia in the infant: a North American survey. *Pediatr Cardiol* 2006;27:199-203.
- Sianipar A, Parkin JE and Sunderland B: Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994;46:951-955.
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- Raymond GG, Reed MT, Teagarden JR, et al: Stability of procainamide hydrochloride in neutralized 5% dextrose injection. *Am J Hosp Pharm* 1988;45:2513-2517.

1. Kleinman ME, Chameides L, Schexnayder SM et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14: pediatric advanced life support. Circulation Nov02, 2010; 122(18 Suppl.3): S876-S908.
2. Bouhouch R, El Houari T, Fellat I et al: Pharmacological therapy in children with nodal reentry tachycardia: when, how and how long to treat the affected patients. Curr Pharm Des 2008; 14(8): 766-769.
3. Product Information: procainamide hcl injection, procainamide hcl injection. Hospira,Inc, Lake Forest, IL, Jan1, 2004.
4. Moffett BS, Cannon BC, Friedman RA et al: Therapeutic levels of intravenous procainamide in neonates: a retrospective assessment. Pharmacotherapy Dec, 2006; 26(12): 1687-1693.

5. Mandapati R, Byrum CJ, Kavey RE et al: Procainamide for rate control of postsurgical junctional tachycardia. Pediatr Cardiol Mar, 2000; 21(2): 123-128.
6. Walsh EP, Saul JP, Sholler GF et al: Evaluation of a staged treatment protocol for rapid automatic junctional tachycardia after operation for congenital heart disease. J Am Coll Cardiol Apr, 1997; 29(5): 1046-1053.
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9. Luedtke SA: Pharmacologic management of supraventricular tachycardias in children. Part 2: Atrial flutter, atrial fibrillation, and junctional and atrial ectopic tachycardia. Ann Pharmacother Nov, 1997; 31(11): 1347-1359.
10. Singh S, Gelband H, Mehta AV et al: Procainamide elimination kinetics in pediatric patients. Clin Pharmacol Ther Nov, 1982; 32(5): 607-611.

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Increasing frequency of toxicity associated with procainamide levels greater than 10 mcg/mL [3] .

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Solution Compatibility

D_5W (conflicting data), 0.45% NaCl, and NS.

Solution Incompatibility

D_5W (conflicting data).

Terminal Injection Site Compatibility

Amiodarone, dobutamine, famotidine, flumazenil, heparin, hydrocortisone, lidocaine, netilmicin, ranitidine, remifentanil, and sodium nitroprusside.

Terminal Injection Site Incompatibility

Esmolol, milrinone, and phenytoin.

References

- Wong KK, Potts JE, Ethridge SP, Sanatani S: Medications used to manage supraventricular tachycardia in the infant: a North American survey. *Pediatr Cardiol* 2006;27:199-203.
- Sianipar A, Parkin JE and Sunderland B: Chemical incompatibility between procainamide hydrochloride and glucose following intravenous admixture. *J Pharm Pharmacol* 1994;46:951-955.
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1. Kleinman ME, Chameides L, Schexnayder SM et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14: pediatric advanced life support. Circulation Nov02, 2010; 122(18 Suppl.3): S876-S908.
2. Bouhouch R, El Houari T, Fellat I et al: Pharmacological therapy in children with nodal reentry tachycardia: when, how and how long to treat the affected patients. Curr Pharm Des 2008; 14(8): 766-769.
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1.154 Prolact+ H(2) MFÂ® Human Milk Fortifier

Title Prolact+ H(2) MFÂ® Human Milk Fortifier

Table

Prolact+ H(2)MF® human milk fortifier

Nutrient per 100 mL	Prolact+4	Prolact+6	Prolact+8	Prolact+10
Energy, kcal	141	141	141	141
Protein, g	6	6	6	6
Fat, g	9	9	9	9
Carbohydrate, g	9.1	9.1	9.1	9.1
Minerals				
Calcium, mg	588	400	306	250
Phosphorus, mg	348	236	181	147
Magnesium, mg	25.6	18.1	14.4	12.1
Iron, mg	0.5	0.5	0.5	0.5
Zinc, mg	2.7	1.9	1.5	1.3
Manganese, mcg	less than 60	less than 60	less than 60	less than 60
Copper, mcg	304	224	184	160
Sodium, mg	185	132	105	89
Potassium, mg	172	134	115	103
Chloride, mg	193	147	124	110
Vitamins				
Vitamin A, IU	298	298	298	298
Vitamin D, IU	130	130	130	130
Vitamin E, IU	2	2	2	2
Vitamin K, mcg	less than 1	less than 1	less than 1	less than 1
Thiamin B1, mcg	20	20	20	20

Riboflavin B2, mcg	75	75	75	75
Niacin, mcg	262	262	262	262
Folic acid, mcg	27	27	27	27
Pantothenic acid, mcg	374	374	374	374
Biotin, mcg	0.9	0.9	0.9	0.9
Vitamin C, mg	less than 1	less than 1	less than 1	less than 1

Prolact+4 H(2)MF® formulated to meet target of 4 Cal/fl oz.
Fortifies breast milk up to 2.3 g of protein in 100 mL of nutrition.

Prolact+6 H(2)MF® formulated to meet target of 6 Cal/fl oz.
Fortifies breast milk up to 2.8 g of protein in 100 mL of nutrition.

Prolact+8 H(2)MF® formulated to meet target of 8 Cal/fl oz.
Fortifies breast milk up to 3.2 g of protein in 100 mL of nutrition.

Prolact+10 H(2)MF® formulated to meet target of 10 Cal/fl oz.
Fortifies breast milk up to 3.7 g of protein in 100 mL of nutrition.

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Prolact+ H(2)MF® human milk fortifier

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Calcium, mg	588	400	306	250
Phosphorus, mg	348	236	181	147
Magnesium, mg	25.6	18.1	14.4	12.1

Iron, mg	0.5	0.5	0.5	0.5
Zinc, mg	2.7	1.9	1.5	1.3
Manganese, mcg	less than 60	less than 60	less than 60	less than 60
Copper, mcg	304	224	184	160
Sodium, mg	185	132	105	89
Potassium, mg	172	134	115	103
Chloride, mg	193	147	124	110
Vitamins				
Vitamin A, IU	298	298	298	298
Vitamin D, IU	130	130	130	130
Vitamin E, IU	2	2	2	2
Vitamin K, mcg	less than 1	less than 1	less than 1	less than 1
Thiamin B1, mcg	20	20	20	20
Riboflavin B2, mcg	75	75	75	75
Niacin, mcg	262	262	262	262
Folic acid, mcg	27	27	27	27
Pantothenic acid, mcg	374	374	374	374
Biotin, mcg	0.9	0.9	0.9	0.9
Vitamin C, mg	less than 1	less than 1	less than 1	less than 1

Prolact+4 H(2)MF® formulated to meet target of 4 Cal/fl oz.
Fortifies breast milk up to 2.3 g of protein in 100 mL of nutrition.

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1.155 Propranolol

Title Propranolol

Dose

Hypertension and Tachyarrhythmias
Starting oral dose: 0.25 mg/kg per dose every 6 hours.
Increase as needed to maximum of 3.5 mg/kg per dose every 6 hours.

Starting IV dose: 0.01 mg/kg every 6 hours over 10 minutes.
Increase as needed to maximum of 0.15 mg/kg per dose every 6 hours.
Effective dosage requirements will vary significantly.

Infantile Hemangiomas
Usual maintenance doses have been 2 to 3 mg/kg/day orally in 3 divided doses. Initial doses of 2 mg/kg/day orally in 3 divided doses have been used while some authors recommend starting at 0.3 to 1 mg/kg/day to assess tolerability and then increasing to 2 mg/kg/day incrementally over several days. Therapy should continue until full involution of the lesion has occurred or until 1 year of age. Recurrences have been reported with early discontinuation of therapy. Tapering periods have ranged from 2 weeks to 1 month.

Administration For infants receiving propranolol, regular, frequent food intake (every 3 to 4 hours) is an important consideration with regards to risks for hypoglycemia.

Uses

Treatment of tachyarrhythmias and hypertension. Preferred therapy for SVT if associated with Wolff-Parkinson-White syndrome. Palliation of tetralogy of Fallot and hypertrophic obstructive cardiomyopathy. Adjunctive treatment of neonatal thyrotoxicosis. Treatment of infantile hemangiomas in cases of ulceration, impairment of vital function (ocular compromise or airway obstruction), or risk of permanent disfigurement.

Contraindications/Precautions

Contraindicated in patients with cardiogenic shock, sinus bradycardia greater than first degree block, reactive airway disease, or diminished myocardial contractility.

Pharmacology

Propranolol is the most widely used nonselective β-adrenergic-receptor blocking agent. Peak serum concentration is reached approximately 2 hours after an oral dose. Propranolol undergoes significant first-pass hepatic metabolism, resulting in 30% to 40% bioavailability. Protein binding is 70% in neonates. Serum half-life is prolonged in patients with liver disease. Elimination is by renal excretion of metabolites.

Potential molecular mechanisms of action for propranolol in the treatment of infantile hemangioma include vasoconstriction (reduction of blood flow to the hemangioma), inhibition of angiogenesis (decreased expression of vascular endothelial growth factor and inhibition of tubulogenesis of endothelial cells), and induction of apoptosis in endothelial cells.

Adverse Effects

Adverse effects are related to beta-receptor blockade: Bradycardia, bronchospasm, and hypoglycemia are most frequently reported. Hypotension occurs in patients with underlying myocardial dysfunction. A withdrawal syndrome (nervousness, tachycardia, sweating, hypertension) has been associated with sudden cessation of the drug. Asymptomatic and symptomatic hypoglycemia, requiring hospitalization, have been reported in infants receiving propranolol for the treatment of infantile hemangioma. Infants less than 3 months of age are at increased risk.

Monitoring

Continuous ECG monitoring should be done during acute treatment of arrhythmias and during IV therapy. Measure systemic blood pressure frequently. Monitor vital signs and measure blood glucose during initiation of treatment and after dosage changes. Assess for increased airway resistance.

Special Considerations/Preparation

Oral solution is available in concentrations of 4 mg/mL and 8 mg/mL (contains 0.6% alcohol). Injectable form is available in 1-mL vials containing 1 mg.
Make a 0.1 mg/mL dilution by adding 1 vial to 9 mL preservative-free normal saline.
Protect from light. Store at room temperature.

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Alteplase, dobutamine, heparin, hydrocortisone succinate, linezolid, milrinone, morphine, potassium chloride, and propofol.

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- Drolet BA, Frommelt PC, Chamlin SL, et al; Initiation and use of propranolol for infantile hemangioma: Report of a consensus conference. *Pediatrics* 2012;131:128-140.
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References

- Drolet BA, Frommelt PC, Chamlin SL, et al; Initiation and use of propranolol for infantile hemangioma: Report of a consensus conference. *Pediatrics* 2012;131:128-140.
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- Pickoff AS, Zies L, Ferrer PL, et al: High-dose propranolol therapy in the management of supraventricular tachycardia. *J Pediatr* 1979;94:144.
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- Product Information, Roxane, 2007.

1.156 Protamine

Title Protamine

Dose

Intravenous
Time since last heparin dose in minutes and protamine dose:
Less than 30 min: 1 mg per 100 units heparin received [1] .
30 to 60 min: 0.5 to 0.75 mg per 100 units heparin received [1] .
60 to 120 min: 0.375 to 0.5 mg per 100 units heparin received [1] .
Greater than 120 min: 0.25 to 0.375 mg per 100 units heparin received [1] .

Maximum dose: 50 mg

Administration

Administer intravenously. Recommended to be given undiluted, but if necessary, may further dilute in D_5W or NS. Infusion rate of a 10 mg/mL solution (undiluted) should not exceed 5 mg/min [1] [2] .

Uses

Heparin antagonist [1] [2] .

Black Box Warning Hypotension, cardiovascular collapse, pulmonary edema, pulmonary vasoconstriction, and pulmonary hypertension may occur [2] [3] . Cases of life-threatening pulmonary hypertension and severe hemorrhagic pulmonary edema have been reported in infants after protamine administration [4] . Risk factors for severe protamine adverse reactions include high doses, rapid administration, repeated doses, previous exposure to protamine or protamine-containing drugs (eg, NPH insulin, protamine zinc insulin, and certain beta blockers), known hypersensitivity reactions to fish, severe left ventricular dysfunction, and abnormal preoperative pulmonary hemodynamics. Vasopressors and resuscitation equipment should be available. Should not be used for bleeding occurring without prior heparin use [2] .

Pharmacology

Anticoagulant when given alone. Combines ionically with heparin to form a stable complex devoid of anticoagulant activity. Rapid action after IV use (5 minutes) [2] .

Adverse Effects

Excessive doses can cause serious bleeding problems. Hypotension, bradycardia, dyspnea, and transitory flushing have been reported in adults [2] .

Monitoring

Monitor vital signs, clotting functions, and blood pressure continuously. Observe for bleeding.

Special Considerations/Preparation

Available as a 10-mg/mL concentration (preservative-free) in 5- and 25-mL vials. Store at room temperature Can be diluted in D_5W or NS if necessary [2] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Cimetidine and ranitidine.

Terminal Injection Site Incompatibility

Most cephalosporins and penicillins.

References

- Monagle P, Chan AK, Goldenberg NA et al: Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest Feb, 2012; 141(2 suppl): e737S-e801S.

- Product Information: protamine sulfate IV injection, protamine sulfate IV injection. APP Pharmaceuticals LLC, Schaumburg, IL, Jan1, 2008.

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- Boigner H, Lechner E, Brock H et al: Life threatening cardiopulmonary failure in an infant following protamine reversal of heparin after cardiopulmonary bypass. Paediatr Anaesth Nov, 2001; 11(6): 729-732.

Title Protamine

Dose

Intravenous
Time since last heparin dose in minutes and protamine dose:
Less than 30 min: 1 mg per 100 units heparin received [1] .
30 to 60 min: 0.5 to 0.75 mg per 100 units heparin received [1] .
60 to 120 min: 0.375 to 0.5 mg per 100 units heparin received [1] .
Greater than 120 min: 0.25 to 0.375 mg per 100 units heparin received [1] .

Maximum dose: 50 mg

Administration

Administer intravenously. Recommended to be given undiluted, but if necessary, may further dilute in D_5W or NS. Infusion rate of a 10 mg/mL solution (undiluted) should not exceed 5 mg/min [1] [2] .

Uses

Heparin antagonist [1] [2] .

Black Box Warning Hypotension, cardiovascular collapse, pulmonary edema, pulmonary vasoconstriction, and pulmonary hypertension may occur [2] [3] . Cases of life-threatening pulmonary hypertension and severe hemorrhagic pulmonary edema have been reported in infants after protamine administration [4] . Risk factors for severe protamine adverse reactions include high doses, rapid administration, repeated doses, previous exposure to protamine or protamine-containing drugs (eg, NPH insulin, protamine zinc insulin, and certain beta blockers), known hypersensitivity reactions to fish, severe left ventricular dysfunction, and abnormal preoperative pulmonary hemodynamics. Vasopressors and resuscitation equipment should be available. Should not be used for bleeding occurring without prior heparin use [2] .

Pharmacology

Anticoagulant when given alone. Combines ionically with heparin to form a stable complex devoid of anticoagulant activity. Rapid action after IV use (5 minutes) [2] .

Adverse Effects

Excessive doses can cause serious bleeding problems. Hypotension, bradycardia, dyspnea, and transitory flushing have been reported in adults [2] .

Monitoring

Monitor vital signs, clotting functions, and blood pressure continuously. Observe for bleeding.

Special Considerations/Preparation

Available as a 10-mg/mL concentration (preservative-free) in 5- and 25-mL vials. Store at room temperature Can be diluted in D_5W or NS if necessary [2] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Cimetidine and ranitidine.

Terminal Injection Site Incompatibility

Most cephalosporins and penicillins.

References

- Monagle P, Chan AK, Goldenberg NA et al: Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest Feb, 2012; 141(2 suppl): e737S-e801S.

- Product Information: protamine sulfate IV injection, protamine sulfate IV injection. APP Pharmaceuticals LLC, Schaumburg, IL, Jan1, 2008.

- Malviya S: Monitoring and management of anticoagulation in children requiring extracorporeal circulation. Semin Thromb Hemost 1997; 23(6): 563-567.

- Boigner H, Lechner E, Brock H et al: Life threatening cardiopulmonary failure in an infant following protamine reversal of heparin after cardiopulmonary bypass. Paediatr Anaesth Nov, 2001; 11(6): 729-732.

1.157 Protein C Concentrate (Human)

Title Protein C Concentrate (Human)

Dose

Prevention and Treatment of Venous Thrombosis and Purpura Fulminans associated with Protein C Deficiency:
Acute Episode/Short-Term Prophylaxis:
Initial dose: 100 to 120 international units/kg IV, followed by 60 to 80 international units/kg IV every 6 hours for next 3 doses [1] .
Maintenance dose: 45 to 60 international units/kg IV every 6 or 12 hours [1] .

Dose regimen should be adjusted to maintain a target peak protein C activity of 100%. After resolution of acute episode, maintain trough protein C activity level above 25% for duration of treatment. Continue treatment until desired anticoagulation is achieved [1] .

Long-Term Prophylaxis: 45 to 60 international units/kg IV every 12 hours. Maintain trough protein C activity level above 25% [1] .

Administration

Administer by IV infusion at a **maximum rate of 0.2 mL/kg/minute** [1] .

Uses

Treatment of patients with severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. Also indicated as a

replacement therapy [1] [2] [3] [4] .
For patients beginning warfarin therapy (vitamin K antagonist therapy), continue protein C until stable anticoagulation is achieved. Begin warfarin therapy at a low dose and titrate up to desired anticoagulation.

Pharmacology

Protein C, a precursor of a vitamin K-dependent anticoagulant glycoprotein, is activated by the thrombin/thrombomodulin-complex on the endothelial cell surface resulting in subsequent potent anticoagulant effects. Once activated, protein C inactivates the activated forms of factors V and VIII with subsequent reduction in thrombin formation. Other effects include profibrinolytic effects. The pharmacokinetic profile in children has not been studied extensively. One pharmacokinetic analysis determined a half-life of 4.2 to 8.3 hours and a recovery of about 44% after infusion in children. Limited data also suggests a faster clearance and larger volume of distribution in young children which may lead to significantly reduced C_{max} and therefore, reduced systemic exposure compared to older subjects [1] [3] .

Adverse Effects

Patients receiving protein C and initiating oral anticoagulant therapy are at increased risk for warfarin-induced skin necrosis. Most serious and common adverse events reported were hypersensitivity or allergic reactions and lightheadedness. Made from human blood. Bleeding episodes were reported in clinical studies. Product contains small amount of heparin. Patients with renal impairment may experience sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1] .

Monitoring

Measure plasma level of protein C before and during treatment. During acute thrombotic events, measure protein C activity immediately before the next dose until the patient is stabilized; dose regimen should be adjusted to maintain a target peak protein C activity of 100% (1 international unit/mL). After stabilization, maintain trough protein C activity level above 25% (0.25 international units/mL). Monitor coagulation parameters (including platelet count) during therapy. Closely monitor patients with renal impairment for sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1] [3] .

Special Considerations/Preparation

Available in single-dose vials that contain nominally 500 (blue color bar) or 1000 (green color bar) international units human protein C. Vials should be brought to room temperature and reconstituted with 5 mL and 10 mL of sterile water for injection, respectively, to provide a concentration of 100 international units/mL. Should be used within 3 hours of reconstitution. A filter needle should be used to withdraw dose from vial. When reconstituted, contains the following excipients: human albumin 8 mg/mL, trisodium citrate dihydrate 4.4 mg/mL, and sodium chloride 8.8 mg/mL. **Store unopened vials at 2 to 8 degrees C and protect from light. Avoid freezing** [1] .

References

- Product Information: CEPROTIN(TM) lyophilized powder for solution for IV injection, protein c concentrate (human) lyophilized powder for solution for IV injection. Baxter Healthcare Corporation (per manufacturer), Westlake Village, CA, May, 2010.

- Tcheng WY, Dovat S, Gurel Z et al: Severe congenital protein C deficiency: description of a new mutation and prophylactic protein C therapy and in vivo pharmacokinetics. J Pediatr Hematol Oncol Feb, 2008; 30(2): 166-171.

- Knoebl PN: Severe congenital protein C deficiency: the use of protein C concentrates (human) as replacement therapy for life-threatening blood-clotting complications. Biologics Jun, 2008; 2(2): 285-296.

- Dreyfus M, Masterson M, David M et al: Replacement therapy with a monoclonal antibody purified protein C concentrate in newborns with severe congenital protein C deficiency. Semin Thromb Hemost 1995; 21(4): 371-381.

Title Protein C Concentrate (Human)

Dose

Prevention and Treatment of Venous Thrombosis and Purpura Fulminans associated with Protein C Deficiency:
Acute Episode/Short-Term Prophylaxis:
Initial dose: 100 to 120 international units/kg IV, followed by 60 to 80 international units/kg IV every 6 hours for next 3 doses [1] .
Maintenance dose: 45 to 60 international units/kg IV every 6 or 12 hours [1] .

Dose regimen should be adjusted to maintain a target peak protein C activity of 100%. After resolution of acute episode, maintain trough protein C activity level above 25% for duration of treatment. Continue treatment until desired anticoagulation is achieved [1] .

Long-Term Prophylaxis: 45 to 60 international units/kg IV every 12 hours. Maintain trough protein C activity level above 25% [1] .

Administration

Administer by IV infusion at a **maximum rate of 0.2 mL/kg/minute** [1] .

Uses

Treatment of patients with severe congenital protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. Also indicated as a replacement therapy [1] [2] [3] [4] .
For patients beginning warfarin therapy (vitamin K antagonist therapy), continue protein C until stable anticoagulation is achieved. Begin warfarin therapy at a low dose and titrate up to desired anticoagulation.

Pharmacology

Protein C, a precursor of a vitamin K-dependent anticoagulant glycoprotein, is activated by the thrombin/thrombomodulin-complex on the endothelial cell surface resulting in subsequent potent anticoagulant effects. Once activated, protein C inactivates the activated forms of factors V and VIII with subsequent reduction in thrombin formation. Other effects include profibrinolytic effects. The pharmacokinetic profile in children has not been studied extensively. One pharmacokinetic analysis determined a half-life of 4.2 to 8.3 hours and a recovery of about 44% after infusion in children. Limited data also suggests a faster clearance and larger volume of distribution in young children which may lead to significantly reduced C_{max} and therefore, reduced systemic exposure compared to older subjects [1] [3] .

Adverse Effects

Patients receiving protein C and initiating oral anticoagulant therapy are at increased risk for warfarin-induced skin necrosis. Most serious and common adverse events reported were hypersensitivity or allergic reactions and lightheadedness. Made from human blood. Bleeding episodes were reported in clinical studies. Product contains small amount of heparin. Patients with renal impairment may experience sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1] .

Monitoring

Measure plasma level of protein C before and during treatment. During acute thrombotic events, measure protein C activity immediately before the next dose until the patient is stabilized; dose regimen should be adjusted to maintain a target peak protein C activity of 100% (1 international unit/mL). After stabilization, maintain trough protein C activity level above 25% (0.25 international units/mL). Monitor coagulation parameters (including platelet count) during therapy. Closely monitor patients with renal impairment for sodium overload (contains greater than 200 mg of sodium in maximum daily dose) [1] [3] .

Special Considerations/Preparation

Available in single-dose vials that contain nominally 500 (blue color bar) or 1000 (green color bar) international units human protein C. Vials should be brought to room temperature and reconstituted with 5 mL and 10 mL of sterile water for injection, respectively, to provide a concentration of 100 international units/mL. Should be used within 3 hours of reconstitution. A filter needle should be used to withdraw dose from vial. When reconstituted, contains the following excipients: human albumin 8 mg/mL, trisodium citrate dihydrate 4.4 mg/mL, and sodium chloride 8.8 mg/mL. **Store unopened vials at 2 to 8 degrees C and protect from light. Avoid freezing** [1] .

References

- Product Information: CEPROTIN(TM) lyophilized powder for solution for IV injection, protein c concentrate (human) lyophilized powder for solution for IV injection. Baxter Healthcare Corporation (per manufacturer), Westlake Village, CA, May, 2010.

- Tcheng WY, Dovat S, Gurel Z et al: Severe congenital protein C deficiency: description of a new mutation and prophylactic protein C therapy and in vivo pharmacokinetics. J Pediatr Hematol Oncol Feb, 2008; 30(2): 166-171.

- Knoebl PN: Severe congenital protein C deficiency: the use of protein C concentrates (human) as replacement therapy for life-threatening blood-clotting complications. Biologics Jun, 2008; 2(2): 285-296.

- Dreyfus M, Masterson M, David M et al: Replacement therapy with a monoclonal antibody purified protein C concentrate in newborns with severe congenital protein C deficiency. Semin Thromb Hemost 1995; 21(4): 371-381.

1.158 Pyridoxine

Title Pyridoxine

Dose

Pyridoxine-Dependent Seizures
Initial diagnostic dose: 50 to 100 mg IV push, or IM [1] [2] [3] .

Maintenance dose: 50 to 100 mg orally every 24 hours [3] . High doses may be required during periods of intercurrent illness.

Uses

Diagnosis and treatment of pyridoxine-dependent seizures. The test dose of pyridoxine to confirm diagnosis of PDS is not well established. The consensus is that diagnosis of PDS is confirmed when high doses of pyridoxine achieve complete seizure control that has been resistant to traditional antiepileptics. Pyridoxine and antiepileptics are then withdrawn, followed by a reoccurrence of clinical seizures that are, again, successfully treated with pyridoxine monotherapy [4] [5] [1] [2] [3] .

Pharmacology

Pyridoxine is a coenzyme in amino acid and carbohydrate metabolism required for the conversion of tryptophan to both niacin and neurotransmitter serotonin and conversion of dopa to dopamine. It is also required for the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Pyridoxine-dependent seizures are a result of defective binding of pyridoxine in the formation of GABA. They typically present in the neonatal period or early infancy; however, seizures can occur for the first time at up to 3 years of age. In addition to seizures, presentation may include hypothermia, jitteriness, encephalopathy, abdominal distension, and vomiting. Administration of pharmacologic doses of pyridoxine will correct this GABA deficiency [7] [6] [1] [9] .

Adverse Effects

There have been reports of prolonged depression of neurologic and respiratory function, as well as depression of cerebral electrical activity when given either orally or IV.

Cardiorespiratory monitoring is recommended and ventilator support may be necessary with initial administration of pyridoxine. When given IV, there have been reports of bradycardia, apnea, and hypotension. Pyridoxine injection contains aluminum that may be toxic with prolonged IV administration in patients with renal impairment or in premature infants (immature kidney function) [6] [8] [3] .

Monitoring

When possible, initial administration of pyridoxine should be accompanied by EEG monitoring. Monitor for cardiorespiratory depression [6] [5] [1] . Monitor for signs of peripheral neuropathy with long-term use [3] . A pyridoxine level than less 20 nanomoles/L is indicative of deficiency [7]

Special Considerations/Preparation

Injectable form available in concentration of 100 mg/mL (1 mL in 2-mL vial). May use injectable form orally; mix in simple syrup if desired. **Protect from light** [8] .

Solution Incompatibility

Alkaline solutions. No data are currently available on Dex/AA.

Terminal Injection Site Incompatibility

Iron salts and oxidizing agents. No data are currently available on heparin and potassium chloride.

References

- Gospe SM: Pyridoxine-dependent seizures: findings from recent studies pose new questions. Pediatr Neurol Mar, 2002; 26(3): 181-185.
- Baxter P: Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child Nov, 1999; 81(5): 431-433.
- Gospe SM: Current perspectives on pyridoxine-dependent seizures. J Pediatr Jun, 1998; 132(6): 919-923.
- Basura GJ, Hagland SP, Wiltse AM et al: Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur J Pediatr Jun, 2009; 168(6): 697-704.
- Been JV, Bok LA, Andriessen P et al: Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child Dec, 2005; 90(12): 1293-1296.
- Koul R: Pyridoxine-dependent seizures: 10-year follow-up of eight cases. Neurol India Jul, 2009; 57(4): 460-463.

- Kleinman RE: Pediatric Nutrition Handbook, 6th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.

- Product Information: pyridoxine HCl IM, IV injection, pyridoxine HCl IM, IV injection. APP Pharmaceuticals, LLC (per Manufacturer), Schaumburg, IL, Apr, 2008.

- Baxter P, Griffiths P, Kelly T et al: Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Dev Med Child Neurol Nov, 1996; 38(11): 998-1006.

Title Pyridoxine

Dose

Pyridoxine-Dependent Seizures
Initial diagnostic dose: 50 to 100 mg IV push, or IM [1] [2] [3] .

Maintenance dose: 50 to 100 mg orally every 24 hours [3] . High doses may be required during periods of intercurrent illness.

Uses

Diagnosis and treatment of pyridoxine-dependent seizures. The test dose of pyridoxine to confirm diagnosis of PDS is not well established. The consensus is that diagnosis of PDS is confirmed when high doses of pyridoxine achieve complete seizure control that has been resistant to traditional antiepileptics. Pyridoxine and antiepileptics are then withdrawn, followed by a reoccurrence of clinical seizures that are, again, successfully treated with pyridoxine monotherapy [4] [5] [1] [2] [3] .

Pharmacology

Pyridoxine is a coenzyme in amino acid and carbohydrate metabolism required for the conversion of tryptophan to both niacin and neurotransmitter serotonin and conversion of dopa to dopamine. It is also required for the synthesis of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Pyridoxine-dependent seizures are a result of defective binding of pyridoxine in the formation of GABA. They typically present in the neonatal period or early infancy; however, seizures can occur for the first time at up to 3 years of age. In addition to seizures, presentation may include hypothermia, jitteriness, encephalopathy, abdominal distension, and vomiting. Administration of pharmacologic doses of pyridoxine will correct this GABA deficiency [7] [6] [1] [9] .

Adverse Effects

There have been reports of prolonged depression of neurologic and respiratory function, as well as depression of cerebral electrical activity when given either orally or IV. Cardiorespiratory monitoring is recommended and ventilator support may be necessary with initial administration of pyridoxine. When given IV, there have been reports of bradycardia, apnea, and hypotension. Pyridoxine injection contains aluminum that may

be toxic with prolonged IV administration in patients with renal impairment or in premature infants (immature kidney function) [6] [8] [3] .

Monitoring

When possible, initial administration of pyridoxine should be accompanied by EEG monitoring. Monitor for cardiorespiratory depression [6] [5] [1] . Monitor for signs of peripheral neuropathy with long-term use [3] . A pyridoxine level than less 20 nanomoles/L is indicative of deficiency [7]

Special Considerations/Preparation

Injectable form available in concentration of 100 mg/mL (1 mL in 2-mL vial). May use injectable form orally; mix in simple syrup if desired. **Protect from light** [8] .

Solution Incompatibility

Alkaline solutions. No data are currently available on Dex/AA.

Terminal Injection Site Incompatibility

Iron salts and oxidizing agents. No data are currently available on heparin and potassium chloride.

References

- Gospe SM: Pyridoxine-dependent seizures: findings from recent studies pose new questions. Pediatr Neurol Mar, 2002; 26(3): 181-185.
- Baxter P: Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child Nov, 1999; 81(5): 431-433.
- Gospe SM: Current perspectives on pyridoxine-dependent seizures. J Pediatr Jun, 1998; 132(6): 919-923.
- Basura GJ, Hagland SP, Wiltse AM et al: Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur J Pediatr Jun, 2009; 168(6): 697-704.
- Been JV, Bok LA, Andriessen P et al: Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child Dec, 2005; 90(12): 1293-1296.
- Koul R: Pyridoxine-dependent seizures: 10-year follow-up of eight cases. Neurol India Jul, 2009; 57(4): 460-463.
- Kleinman RE: Pediatric Nutrition Handbook, 6th ed. ed. American Academy of Pediatrics, Elk Grove Village, IL, 2009.

- Product Information: pyridoxine HCl IM, IV injection, pyridoxine HCl IM, IV injection. APP Pharmaceuticals, LLC (per Manufacturer), Schaumburg, IL, Apr, 2008.

- Baxter P, Griffiths P, Kelly T et al: Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Dev Med Child Neurol Nov, 1996; 38(11): 998-1006.

1.159 Quinupristin\Dalfopristin

Title Quinupristin/Dalfopristin

Dose

7.5 mg/kg/dose every 12 hours by IV infusion over 60 minutes.
Administration via a central catheter is recommended.

Uses

Limited to treatment of infections caused by gram positive organisms resistant to other antibiotics, eg, methicillin-resistant *Staph. aureus* and vancomycin-resistant *Enterococcus faecium* (not *E faecalis*).

Pharmacology

No data are available for infants. Synercid® is a parenteral antimicrobial agent which consists of two streptogramin antibiotics (quinupristin and dalfopristin in a 30:70 ratio) that inhibit bacterial protein synthesis by binding to separate sites on the bacterial ribosome. Serum half-life of quinupristin in adults ranges from 1 to 3 hours, and of dalfopristin ranges from 5 to 9 hours. Seventy-five percent is excreted via the biliary route.

Adverse Effects

Myalgias and arthralgias occur frequently in adults with hepatic or renal failure. Elevations in serum bilirubin and transaminases are common. Diarrhea and rash occur infrequently.

Monitoring

Periodic measurement of serum bilirubin and transaminases. Assess peripheral IV site for signs of inflammation.

Special Considerations/Preparation

Synercid® is supplied as a lyophilized powder in single-dose, 10-mL vials containing 500 mg or 600 mg. Store refrigerated. Reconstitute 500-mg and 600-mg vials by adding 5 mL or 6 mL of Sterile Water for Injection or D_5W, respectively, resulting in a concentration of 100 mg/mL. Reconstituted solution should be diluted within 30 minutes. Before administration, dilute with D_5W to a concentration of 2 mg/mL. A concentration up to 5 mg/mL may be used for central lines. Concentrations less than 1

mg/mL may be used if venous irritation occurs following peripheral administration. Diluted solution is stable for 5 hours at room temperature, or 54 hours if stored under refrigeration. **Do not freeze**.

Solution Compatibility

D_5W.

Solution Incompatibility

NS.

Terminal Injection Site Compatibility

Aztreonam, fluconazole, metoclopramide, and potassium chloride.

References

- Loeffler AM, Drew RH, Perfect JR, et al: Safety and efficacy of quinupristin/dalfopristin for treatment of invasive Gram-positive infections in pediatric patients. *Pediatr Infect Dis J* 2002;21:950-56.
- Gray JW, Darbyshire PJ, Beath SV, et al: Experience with quinupristin/dalfopristin in treating infections with vancomycin-resistant *Enterococcus faecium* in children. *Pediatr Infect Dis J* 2000;19:234-238.
- Lamb HM, Figgitt DP, Faulds D: Quinupristin/Dalfopristin: A review of its use in the management of serious gram-positive infections. *Drugs* 1999;58:1061-1097.
- Product Information, Monarch Pharmaceuticals, 2010.

Title Quinupristin/Dalfopristin

Dose

7.5 mg/kg/dose every 12 hours by IV infusion over 60 minutes.
Administration via a central catheter is recommended.

Uses

Limited to treatment of infections caused by gram positive organisms resistant to other antibiotics, eg, methicillin-resistant *Staph. aureus* and vancomycin-resistant *Enterococcus faecium* (not *E faecalis*).

Pharmacology

No data are available for infants. Synercid® is a parenteral antimicrobial agent which consists of two streptogramin antibiotics (quinupristin and dalfopristin in a 30:70 ratio) that inhibit bacterial protein synthesis by binding to separate sites on the bacterial ribosome. Serum half-life of quinupristin in adults ranges from 1 to 3 hours, and of dalfopristin ranges from 5 to 9 hours. Seventy-five percent is excreted via the biliary route.

Adverse Effects

Myalgias and arthralgias occur frequently in adults with hepatic or renal failure. Elevations in serum bilirubin and transaminases are common. Diarrhea and rash occur infrequently.

Monitoring

Periodic measurement of serum bilirubin and transaminases. Assess peripheral IV site for signs of inflammation.

Special Considerations/Preparation

Synercid® is supplied as a lyophilized powder in single-dose, 10-mL vials containing 500 mg or 600 mg. Store refrigerated. Reconstitute 500-mg and 600-mg vials by adding 5 mL or 6 mL of Sterile Water for Injection or D_5W, respectively, resulting in a concentration of 100 mg/mL. Reconstituted solution should be diluted within 30 minutes. Before administration, dilute with D_5W to a concentration of 2 mg/mL. A concentration up to 5 mg/mL may be used for central lines. Concentrations less than 1 mg/mL may be used if venous irritation occurs following peripheral administration. Diluted solution is stable for 5 hours at room temperature, or 54 hours if stored under refrigeration. **Do not freeze**.

Solution Compatibility

D_5W.

Solution Incompatibility

NS.

Terminal Injection Site Compatibility

Aztreonam, fluconazole, metoclopramide, and potassium chloride.

References

- Loeffler AM, Drew RH, Perfect JR, et al: Safety and efficacy of quinupristin/dalfopristin for treatment of invasive Gram-positive infections in pediatric patients. *Pediatr Infect Dis J* 2002;21:950-56.
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1.160 Ranitidine

Title Ranitidine

Dose

Oral: 2 mg/kg/dose every 8 hours.
IV:Term: 1.5 mg/kg/dose every 8 hours slow push.
Preterm:0.5 mg/kg/dose every 12 hours slow push.
Continuous IV infusion: 0.0625 mg/kg/hour; dose range, 0.04 to 0.1 mg/kg/hour.

Uses

Prevention and treatment of stress ulcers and GI hemorrhage aggravated by gastric acid secretion.

Contraindications/Precautions

The use of H2-blockers in preterm infants has been associated with facilitating *Candida* species colonization [1] , and an increased risk for late-onset bacterial and fungal sepsis [2] [1] . In a prospective, multicenter, observational study comparing VLBW neonates receiving ranitidine (n=91) to those not receiving ranitidine (n=183), neonates receiving ranitidine had an increased rate of infection (37.4% versus 9.8%; OR 5.5; 95% CI, 2.9 to 10.4), increased risk for NEC (9.8% versus 1.6%; OR 6.6; 95% CI, 1.7 to 25), and increased mortality (9.9% versus 1.6%) [3] . In a retrospective, case-control study, H2-blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [4] . Routine gastric acid suppression should be avoided, particularly in preterm neonates [5] .

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Peak serum concentration occurs 1 to 3 hours after oral administration and is not influenced by food. Bioavailability is quite variable. Hepatic biotransformation predominates after oral absorption, with 30% excreted unchanged in the urine. In contrast, 70% of an IV dose is excreted unchanged in the urine. Elimination half-life in neonates is 3 to 7 hours, and is prolonged in preterm infants and patients with renal or hepatic insufficiency.

Adverse Effects

Ranitidine is generally well tolerated by infants, children and adults, and has a low incidence of adverse effects, including rash, headache, fatigue, irritability, dizziness, nausea, constipation, and diarrhea, that are usually mild. Elevations in hepatic enzymes, leukopenia, and bradycardia have been reported in adults [6] [7] .

Monitoring

Gastric pH may be measured to assess efficacy.

Special Considerations/Preparation

Available as a 1 mg/mL preservative-free solution for injection in 50 mL single-dose plastic containers, and a 25 mg/mL injectable solution in 2- and 6-mL vials. A 2 mg/mL dilution may be made by adding 0.8 mL of the 25 mg/mL concentration to 9.2 mL preservative-free sterile water or normal saline for injection. Stable for 48 hours at room temperature. May be given orally; absorption is equivalent to that of the oral solution.

Manufacturer's oral solution (15 mg/mL) contains 7.5% alcohol.

Also available as 150- and 300-mg tablets. May prepare oral solution by crushing a 150-mg tablet and dissolving in 30 mL of sterile water to yield a final concentration of 5 mg/mL. Stable for 28 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, acetazolamide, amikacin, aminophylline, ampicillin, atropine, aztreonam, cefazolin, cefepime, cefoxitin, ceftazidime, chloramphenicol, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine, erythromycin lactobionate, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, midazolam, milrinone, morphine, nicardipine, nitroprusside, pancuronium bromide, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, protamine, remifentanil, tobramycin, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, pentobarbital, and phenobarbital.

References

- Wells TG, Heulitt MJ, Taylor BJ et al: Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998;38:402-407.
- Kuusela A-L: Long term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F151-F153.
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4. Guillet R, Stoll BJ, Cotten CM et al: Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 02/00/2006; 117(2): e137-e142.
5. Pulsifer-Anderson E: National Institues of Health recommends the routine use of H2 blockers in preterm infants be carefully evaluated. Neonatal Netw May, 2006; 25(3): 223-224.
6. Product Information: ZANTAC(R) oral tablets, efferdose(R) oral tablets, oral syrup, ranitidine hydrochloride oral tablets, efferdose(R) oral tablets, oral syrup. GlaxoSmithKline, Research Triangle Park, NC, Feb, 2009.
7. Product Information: ZANTAC(R) IV, IM injection, IV premixed injection, ranitidine hydrochloride IV, IM injection, IV premixed injection. GlaxoSmithkline, Research Triangle Park, NC, Feb, 2009.

Title Ranitidine

Dose

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blocker use in VLBW infants was associated with an increased incidence of NEC (OR 1.7; 95% CI, 1.34 to 2.19) [4] . Routine gastric acid suppression should be avoided, particularly in preterm neonates [5] .

Pharmacology

Inhibits gastric acid secretion by histamine H_2-receptor antagonism. Peak serum concentration occurs 1 to 3 hours after oral administration and is not influenced by food. Bioavailability is quite variable. Hepatic biotransformation predominates after oral absorption, with 30% excreted unchanged in the urine. In contrast, 70% of an IV dose is excreted unchanged in the urine. Elimination half-life in neonates is 3 to 7 hours, and is prolonged in preterm infants and patients with renal or hepatic insufficiency.

Adverse Effects

Ranitidine is generally well tolerated by infants, children and adults, and has a low incidence of adverse effects, including rash, headache, fatigue, irritability, dizziness, nausea, constipation, and diarrhea, that are usually mild. Elevations in hepatic enzymes, leukopenia, and bradycardia have been reported in adults [6] [7] .

Monitoring

Gastric pH may be measured to assess efficacy.

Special Considerations/Preparation

Available as a 1 mg/mL preservative-free solution for injection in 50 mL single-dose plastic containers, and a 25 mg/mL injectable solution in 2- and 6-mL vials. A 2 mg/mL dilution may be made by adding 0.8 mL of the 25 mg/mL concentration to 9.2 mL preservative-free sterile water or normal saline for injection. Stable for 48 hours at room temperature. May be given orally; absorption is equivalent to that of the oral solution.

Manufacturer's oral solution (15 mg/mL) contains 7.5% alcohol.

Also available as 150- and 300-mg tablets. May prepare oral solution by crushing a 150-mg tablet and dissolving in 30 mL of sterile water to yield a final concentration of 5 mg/mL. Stable for 28 days refrigerated.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, acetazolamide, amikacin, aminophylline, ampicillin, atropine, aztreonam, cefazolin, cefepime, cefoxitin, ceftazidime, chloramphenicol, clindamycin, dexamethasone, digoxin, dobutamine, dopamine, enalaprilat, epinephrine,

erythromycin lactobionate, fentanyl, fluconazole, flumazenil, furosemide, gentamicin, glycopyrrolate, heparin, insulin, isoproterenol, lidocaine, linezolid, lorazepam, meropenem, metoclopramide, midazolam, milrinone, morphine, nicardipine, nitroprusside, pancuronium bromide, penicillin G, piperacillin, piperacillin/tazobactam, potassium chloride, propofol, protamine, remifentanil, tobramycin, vancomycin, vecuronium, vitamin K_1, and zidovudine.

Terminal Injection Site Incompatibility

Amphotericin B, pentobarbital, and phenobarbital.

References

- Wells TG, Heulitt MJ, Taylor BJ et al: Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998;38:402-407.
- Kuusela A-L: Long term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 1998;78:F151-F153.
- Cothran DS, Borowitz SM, Sutphen JL, et al: Alteration of normal gastric flora in neonates receiving ranitidine. *J Perinatol* 1997;17:383-388.
- Goyal A, Treem WR, Hyams FS: Severe upper gastrointestinal bleeding in healthy full-term neonates. *Am J Gastroenterol* 1994;89:613-616.
- Kelly EJ, Chatfield SL, Brownlee KG, et al: The effect of intravenous ranitidine on the intragastric pH of preterm infants receiving dexamethasone. *Arch Dis Child* 1993;69:37.
- Fontana M, Massironi E, Rossi A, et al: Ranitidine pharmacokinetics in newborn infants. *Arch Dis Child* 1993;68:602.
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1. Saiman L, Ludington E, Pfaller M et al: Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. Pediatr Infect Dis J Apr, 2000; 19(4): 319-324.
2. Graham PL, Begg MD, Larson E et al: Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. Pediatr Infect Dis J Feb, 2006; 25(2): 113-117.
3. Terrin G, Passariello A, De Curtis M et al: Ranitidine is Associated With Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns. Pediatrics Dec12, 2011; Epub: Epub.
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6. Product Information: ZANTAC(R) oral tablets, efferdose(R) oral tablets, oral syrup, ranitidine hydrochloride oral tablets, efferdose(R) oral tablets, oral syrup. GlaxoSmithKline, Research Triangle Park, NC, Feb, 2009.
7. Product Information: ZANTAC(R) IV, IM injection, IV premixed injection, ranitidine hydrochloride IV, IM injection, IV premixed injection. GlaxoSmithkline, Research Triangle Park, NC, Feb, 2009.

1.161 Remifentanil

Title Remifentanil

Dose

Endotracheal Intubation
Remifentanil alone
Preterm, 29 to 32 weeks gestation: 2 mcg/kg IV bolus over 60 seconds; dose may be repeated [1] .
Concomitant with midazolam
Preterm, 28 to 34 weeks gestation: 1 mcg/kg IV bolus [2] over 60 seconds [1] .

Maintenance of General Anesthesia; Adjunct
Reduction of other anesthetics (thiopental, propofol, isoflurane, and midazolam) doses by up to 75% may be necessary [3] .
Full-term neonate weighing at least 2500 g:
Maintenance rate: 0.4 mcg/kg/min IV, titrated up to 1 mcg/kg/min IV in increments of up to 50% or reduced by 25% to 50% decrements every 2 to 5 minutes for desired effect; plus nitrous oxide [3] .
Supplemental bolus: 1 mcg/kg IV every 2 to 5 minutes if needed. Smaller bolus doses may be necessary in those receiving supplementation with potent inhalation agents or neuraxial anesthesia, those with significant co-morbidities or undergoing significant fluid shifts, or those who have not been pretreated with atropine [3] .

Mechanical Ventilation: Adjunct
Full-term: initial rate, 0.15 mcg/kg/min IV, followed by incremental increases of 0.05 mcg/kg/min as needed up to a **maximum 0.5 mcg/kg/min**; use with midazolam [4] .

Administration

Must be administered only in a monitored anesthesia care setting.
IV administration only. Administer continuous infusions only by an infusion device. Injection should be made into IV tubing at or close to the venous cannula. All IV tubing should be cleared at the time of discontinuation of infusion. Do not administered blood in the same IV tubing. Bolus administration should be used only during the maintenance of general anesthesia. Administer single doses over 30 to 60 seconds in non-intubated patients. Administration of bolus doses simultaneously with a continuous infusion is not recommended in spontaneously breathing patients [3] .

Uses

Premature neonates: Numerous preliminary studies in preterm infants (25 weeks or more gestation) demonstrated efficacy and safety of remifentanil for **induction to**

intubate (including for INtubation SURfactant Extubation) [1] [2] , during **mechanical ventilation** [5] [6] [7] , or for a procedure in patients on mechanical ventilation [8] . Remifentanil was the sole agent (no other analgesia or sedative) used in two studies [5] [1] , whereas all other studies used midazolam concomitantly. One of the major advantages with remifentanil was early extubation. Both remifentanil and morphine provided good quality sedation and analgesia during ventilation, but remifentanil was superior to morphine for induction to intubate and times to awakening and extubation in preterm neonates with respiratory failure due to respiratory distress syndrome (n=20) [6] [2] . Remifentanil provided good conditions for **intubation** and immediate extubation after surfactant administration in preterm neonates (29 to 32 weeks gestation; n=21) [1] . The longest duration of remifentanil infusion was 5.9+/-5.7 days, with extubation time of 36+/-12 minutes after discontinuing the infusion, in 48 preterm infants with respiratory distress disease requiring mechanical ventilation [5] .
During mechanical ventilation, initial rates in preterm infants (25 to 36 weeks gestation) were 0.075 to 0.5 mcg/kg/min and titrated up to 0.94 mcg/kg/min. At the time of extubation, the rates were reduced by 50%, then discontinued after 30 minutes [5] [6] [7] . Doses as high as 3 to 5 mcg/kg/min, based on respiratory changes and spontaneous movements, have been used in ventilated premature infants (n=6) when undergoing laser therapy for retinopathy of prematurity. Remifentanil was discontinued at the end of laser therapy [8] .

Full-term neonates: A double-blind, randomized, controlled, pilot study (n=23) demonstrated median extubation times of 80 minutes and 782.5 minutes (p=0.005) in neonates administered remifentanil/midazolam and fentanyl/midazolam, respectively, in mechanically ventilated neonates and infants. Infants in the remifentanil group (n=11) were a mean of 1.6+/- 2.1 postnatal days (1 to 8 days) and a gestational age of at least 36 weeks. Both remifentanil/midazolam and fentanyl/midazolam provided adequate sedation and analgesia. The dose of midazolam was 0.83 mcg/kg/min, followed by incremental increases of 0.833 mcg/kg/min as needed up to a maximum of 6.67 mcg/kg/min. The mean remifentanil dose was 0.23 +/- 0.08 mcg/kg/min [4] .

Pediatric FDA Approved Indications
Analgesic agent used as an adjunct for maintenance of general anesthesia [3] .

Contraindications/Precautions

Contraindicated for epidural or intrathecal administration (formulation contains glycine) and with hypersensitivity to fentanyl analogs [3] .

Do not use in diagnostic or therapeutic procedures outside the monitored anesthesia care setting. Apnea and respiratory depression may occur with remifentanil; decreasing the infusion rate or temporarily discontinuing the infusion may be necessary if respiratory depression occurs. Bradycardia and hypotension have been reported. Muscle rigidity, particularly chest wall rigidity, may occur with remifentanil; decrease in infusion rate or temporary discontinuation of infusion may be necessary. Life-threatening cases may require neuromuscular blocking agent or naloxone. Chest wall rigidity is more likely to occur when bolus doses are administered concurrently with continuous infusion; simultaneous use is not recommended in patients with spontaneous ventilation. Use as sole agent for maintenance of general anesthesia is not recommended as loss of consciousness is not certain and may increase the risk of

apnea, muscle rigidity, and tachycardia. Due to rapid offset of effect, adequate analgesia should be provided prior to discontinuation of remifentanil. Due to concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of remifentanil [3] .
Avoid use for conscious sedation (ie, sedation score of 3) in neonates due to their inability to respond to verbal commands to breathe deeply [9] .

Pharmacology

Remifentanil hydrochloride is a mu-opioid agonist exhibiting analgesic effects with a rapid onset and a short duration of action. Unlike fentanyl, duration of action does not increase with prolonged administration. Effects are antagonized by opioid antagonists (eg, naloxone). Pharmacokinetics fit a 3-compartment model, with a central Vd of 100 mL/kg and a steady-state Vd of 350 mL/kg. Rapid and slow distribution half-life are 1 and 6 minutes, respectively. Approximately 70% protein bound, the majority to alpha-1-acid-glycoprotein. Unlike other opioid analgesics, remifentanil contains an ester linkage in its structure and is susceptible to rapid hydrolysis in tissues and blood by nonspecific esterases (to essentially inactive metabolites). It is not a substrate for pseudocholinesterase; therefore, normal duration of action is expected in patients with atypical cholinesterase. The lung and liver are not significant contributors in the metabolism of remifentanil. Total body clearance generally correlates with total body weight, except in severely obese patients, when clearance correlates better with ideal body weight. Terminal elimination half-life is 10 to 20 minutes, however, the effective biological half-life is 3 to 10 minutes. Renal or hepatic impairment do not affect the pharmacokinetics [3] .

The half-life of remifentanil was similar in all anesthetized pediatric patients (n=42) undergoing elective surgery or diagnostic procedures; however, infants up to the age of 2 years experienced higher clearance rates compared with older children. Clearance rates were 90 mL/kg/min in 5 days to 8 weeks of age infants, 92 mL/kg/min in children older than 2 months to younger than 2 years, 76 mL/kg/min in children 2 to 6 years of age, and 46 to 59.7 mL/kg/min in 7 to younger than 18 years. Corresponding Vd were 452.8 mL/kg (significantly different from other groups), 307.9 mL/kg, 240.1 mL/kg, and 223 to 248.9 mL/kg, respectively. [10] [3] .

Adverse Effects

In controlled studies in pediatric patients up to 12 years of age receiving remifentanil as an analgesic agent for use in the maintenance of general anesthesia (n=342), adverse events reported during the recovery and follow-up phases included nausea (8% and 6%), vomiting (12% and 16%), rhonchi (3% and 0%), shivering (3% and 0%), and postoperative complication (2% and 1%) [3] .
Volume expansion (4 versus 5 patients) and vasoactive amines (3 versus 6) were required with remifentanil and morphine infusions, respectively, in 20 ventilated premature neonates with respiratory distress syndrome [6] . Chest wall rigidity was not observed in any preterm neonates during studies (n=95) [5] [8] [2] [1] .

Monitoring

Vital signs, especially oxygen saturation, should be continuously monitored for evidence of apnea or respiratory depression during administration and following the discontinuation of infusion. Monitor for skeletal muscle rigidity, including chest wall rigidity and an inability to adequately ventilate [3] .

Special Considerations/Preparation

Ultiva(R): Available in 3-mL, 5-mL, and 10-mL vials containing 1 mg, 2 mg, and 5 mg, respectively, of remifentanil lyophilized powder for solution. Store between 2 and 25 degrees C (36 and 77 degrees F) [3] .

Reconstitute with 1 mL of diluent per mg of remifentanil. Shake well to dissolve (reconstituted solution contains approximately 1 mg of activity per 1 mL). The reconstituted solution should then be diluted to a final concentration of 20, 25, 50, or 250 mcg/mL prior to administration. Stable for 24 hours at room temperature after reconstitution and further dilution. A final concentration of 20 or 25 mcg/mL for pediatric patients 1 year or older is recommended [3] .

Solution Compatibility

D_5W, D_5LR, D_5NS, NS, 0.45% sodium chloride, sterile water for injection.

Terminal Injection Site Compatibility

Remifentanil 0.025 mg/mL:
Acyclovir 7 mg/mL, amikacin 5 mg/mL, aminophylline 2.5 mg/mL, ampicillin 20 mg/mL, ampicillin/sulbactam 20/10 mg/mL, aztreonam 40 mg/mL, bumetanide 40 mcg/mL, calcium gluconate 40 mg/mL, cefazolin 20 mg/mL, cefotaxime 20 mg/mL, cefotetan 20 mg/mL, cefoxitin 20 mg/mL, ceftriaxone 20 mg/mL, cefuroxime 30 mg/mL, cimetidine 12 mg/mL, ciprofloxacin 1 mg/mL, cisatracurium 2 mg/mL, clindamycin 10 mg/mL, dexamethasone 2 mg/mL, digoxin 0.25 mg/mL, diphenhydramine 2 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, doxycycline hyclate 1 mg/mL, enalaprilat 0.1 mg/mL, epinephrine 50 mcg/mL, esmolol 10 mg/mL, famotidine 2 mg/mL, fentanyl 12.5 mcg/mL, fluconazole 2 mg/mL, ganciclovir 20 mg/mL, gentamicin 5 mg/mL, haloperidol 0.2 mg/mL, heparin 100 units/mL, hydrocortisone 1 mg/mL, hydromorphone 0.5 mg/mL, imipenem/cilastatin 10 mg/mL, isoproterenol 20 mcg/mL, ketorolac 15 mg/mL, lidocaine 8 mg/mL, lorazepam 0.5 mg/mL, magnesium 100 mg/mL, mannitol 150 mg/mL, methylprednisolone 5 mg/mL, metoclopramide 5 mg/mL, metronidazole 5 mg/mL, midazolam 1 mg/mL, morphine 1 mg/mL, nalbuphine 10 mg/mL, netilmicin 5 mg/mL, nitroglycerin 0.4 mg/mL, norepinephrine 0.12 mg/mL, ondansetron 1 mg/mL, phenylephrine 1 mg/mL, piperacillin 40 mg/mL, piperacillin/tazobactam 40/5 mg/mL, potassium chloride 0.1 mEq/mL, procainamide 10 mg/mL, ranitidine 2 mg/mL, sodium bicarbonate 1 mEq/mL (8.4%), sulfamethoxazole/trimethoprim 4/0. 8 mg/mL, ticarcillin/clavulanate 31 mg/mL, tobramycin 5 mg/mL, vancomycin 10 mg/mL, zidovudine 4 mg/mL.

Remifentanil 0.12 mg/mL:
Heparin 417 units/mL, insulin 1 unit/mL, magnesium 8 mg/mL, midazolam 1 mg/mL, potassium chloride 0.1 mEq/mL.

Remifentanil 0.2 mg/mL:
Cefepime 120 mg/mL, ceftazidime 120 mg/mL.

Remifentanil 0.25 mg/mL:
Acyclovir 7 mg/mL, amikacin 5 mg/mL, aminocaproic acid 20 mg/mL, aminophylline 2.5 mg/mL, ampicillin 20 mg/mL, ampicillin/sulbactam 20/10 mg/mL, anidulafungin 0.5 mg/mL, argatroban 1 mg/mL, azithromycin 2 mg/mL, aztreonam 40 mg/mL, bivalirudin 5 mg/mL, bumetanide 40 mcg/mL, calcium gluconate 40 mg/mL, caspofungin 0.5 mg/mL, cefazolin 20 mg/mL, cefotaxime 20 mg/mL, cefotetan 20 mg/mL, cefoxitin 20 mg/mL, ceftriaxone 20 mg/mL, cefuroxime 30 mg/mL, cimetidine 12 mg/mL, ciprofloxacin 1 mg/mL, cisatracurium 2 mg/mL, clindamycin 10 mg/mL, dexamethasone 2 mg/mL, dexmedetomidine 4 mcg/mL, digoxin 0.25 mg/mL, diltiazem 5 mg/mL, diphenhydramine 2 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, doxycycline hyclate 1 mg/mL, enalaprilat 0.1 mg/mL, epinephrine 50 mcg/mL, ertapenem 20 mg/mL, esmolol 10 mg/mL, famotidine 2 mg/mL, fentanyl 12.5 mcg/mL, fluconazole 2 mg/mL, foscarnet 24 mg/mL, ganciclovir 20 mg/mL, gentamicin 5 mg/mL, granisetron 50 mcg/mL, haloperidol 0.2 mg/mL, heparin 100 units/mL, hydrocortisone 1 mg/mL, hydromorphone 0.5 mg/mL, imipenem/cilastatin 10 mg/mL, isoproterenol 20 mcg/mL, ketorolac 15 mg/mL, levofloxacin 5 mg/mL, lidocaine 8 mg/mL, lorazepam 0.5 mg/mL, magnesium 100 mg/mL, mannitol 150 mg/mL, methotrexate 15 mg/mL, methylprednisolone 5 mg/mL, metoclopramide 5 mg/mL, metronidazole 5 mg/mL, midazolam 1 mg/mL, milrinone 0.2 mg/mL, morphine 1 mg/mL, mycophenolate 6 mg/mL, nalbuphine 10 mg/mL, netilmicin 5 mg/mL, nicardipine 0.1 mg/mL, nitroglycerin 0.4 mg/mL, norepinephrine 0.12 mg/mL, octreotide 5 mcg/mL, ondansetron 1 mg/mL, palonosetron 50 mcg/mL, pancuronium 0.1 mg/mL, phenylephrine 1 mg/mL, piperacillin 40 mg/mL, piperacillin/tazobactam 40/5 mg/mL, potassium chloride 0.1 mEq/mL, procainamide 10 mg/mL, ranitidine 2 mg/mL, rocuronium 1 mg/mL, sodium bicarbonate 1 mEq/mL (8.4%), sulfamethoxazole/trimethoprim 4/0. 8 mg/mL, tacrolimus 20 mcg/mL, ticarcillin/clavulanate 31 mg/mL, tobramycin 5 mg/mL, vancomycin 10 mg/mL, vasopressin 1 unit/mL, vecuronium 1 mg/mL, voriconazole 4 mg/mL, zidovudine 4 mg/mL.

Remifentanil 0.5 mg/mL:
Linezolid 2 mg/mL.

Terminal Injection Site Incompatibility

Amphotericin B cholesteryl, amphotericin B lipid complex, daptomycin, pantoprazole.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 06/15/2012.

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Title Remifentanil

Dose

Endotracheal Intubation
Remifentanil alone
Preterm, 29 to 32 weeks gestation: 2 mcg/kg IV bolus over 60 seconds; dose may be repeated [1] .
Concomitant with midazolam
Preterm, 28 to 34 weeks gestation: 1 mcg/kg IV bolus [2] over 60 seconds [1] .

Maintenance of General Anesthesia; Adjunct
Reduction of other anesthetics (thiopental, propofol, isoflurane, and midazolam) doses by up to 75% may be necessary [3] .
Full-term neonate weighing at least 2500 g:
Maintenance rate: 0.4 mcg/kg/min IV, titrated up to 1 mcg/kg/min IV in increments of

up to 50% or reduced by 25% to 50% decrements every 2 to 5 minutes for desired effect; plus nitrous oxide [3] .
Supplemental bolus: 1 mcg/kg IV every 2 to 5 minutes if needed. Smaller bolus doses may be necessary in those receiving supplementation with potent inhalation agents or neuraxial anesthesia, those with significant co-morbidities or undergoing significant fluid shifts, or those who have not been pretreated with atropine [3] .

Mechanical Ventilation: Adjunct
Full-term: initial rate, 0.15 mcg/kg/min IV, followed by incremental increases of 0.05 mcg/kg/min as needed up to a **maximum 0.5 mcg/kg/min**; use with midazolam [4] .

Administration

Must be administered only in a monitored anesthesia care setting.
IV administration only. Administer continuous infusions only by an infusion device. Injection should be made into IV tubing at or close to the venous cannula. All IV tubing should be cleared at the time of discontinuation of infusion. Do not administered blood in the same IV tubing. Bolus administration should be used only during the maintenance of general anesthesia. Administer single doses over 30 to 60 seconds in non-intubated patients. Administration of bolus doses simultaneously with a continuous infusion is not recommended in spontaneously breathing patients [3] .

Uses

Premature neonates: Numerous preliminary studies in preterm infants (25 weeks or more gestation) demonstrated efficacy and safety of remifentanil for **induction to intubate** (including for INtubation SURfactant Extubation) [1] [2] , during **mechanical ventilation** [5] [6] [7] , or for a procedure in patients on mechanical ventilation [8] . Remifentanil was the sole agent (no other analgesia or sedative) used in two studies [5] [1] , whereas all other studies used midazolam concomitantly. One of the major advantages with remifentanil was early extubation. Both remifentanil and morphine provided good quality sedation and analgesia during ventilation, but remifentanil was superior to morphine for induction to intubate and times to awakening and extubation in preterm neonates with respiratory failure due to respiratory distress syndrome (n=20) [6] [2] . Remifentanil provided good conditions for **intubation** and immediate extubation after surfactant administration in preterm neonates (29 to 32 weeks gestation; n=21) [1] . The longest duration of remifentanil infusion was 5.9+/-5.7 days, with extubation time of 36+/-12 minutes after discontinuing the infusion, in 48 preterm infants with respiratory distress disease requiring mechanical ventilation [5] .
During mechanical ventilation, initial rates in preterm infants (25 to 36 weeks gestation) were 0.075 to 0.5 mcg/kg/min and titrated up to 0.94 mcg/kg/min. At the time of extubation, the rates were reduced by 50%, then discontinued after 30 minutes [5] [6] [7] . Doses as high as 3 to 5 mcg/kg/min, based on respiratory changes and spontaneous movements, have been used in ventilated premature infants (n=6) when undergoing laser therapy for retinopathy of prematurity. Remifentanil was discontinued at the end of laser therapy [8] .

Full-term neonates: A double-blind, randomized, controlled, pilot study (n=23) demonstrated median extubation times of 80 minutes and 782.5 minutes (p=0.005) in neonates administered remifentanil/midazolam and fentanyl/midazolam, respectively,

in mechanically ventilated neonates and infants. Infants in the remifentanil group (n=11) were a mean of 1.6+/- 2.1 postnatal days (1 to 8 days) and a gestational age of at least 36 weeks. Both remifentanil/midazolam and fentanyl/midazolam provided adequate sedation and analgesia. The dose of midazolam was 0.83 mcg/kg/min, followed by incremental increases of 0.833 mcg/kg/min as needed up to a maximum of 6.67 mcg/kg/min. The mean remifentanil dose was 0.23 +/- 0.08 mcg/kg/min [4] .

Pediatric FDA Approved Indications
Analgesic agent used as an adjunct for maintenance of general anesthesia [3] .

Contraindications/Precautions

Contraindicated for epidural or intrathecal administration (formulation contains glycine) and with hypersensitivity to fentanyl analogs [3] .

Do not use in diagnostic or therapeutic procedures outside the monitored anesthesia care setting. Apnea and respiratory depression may occur with remifentanil; decreasing the infusion rate or temporarily discontinuing the infusion may be necessary if respiratory depression occurs. Bradycardia and hypotension have been reported. Muscle rigidity, particularly chest wall rigidity, may occur with remifentanil; decrease in infusion rate or temporary discontinuation of infusion may be necessary. Life-threatening cases may require neuromuscular blocking agent or naloxone. Chest wall rigidity is more likely to occur when bolus doses are administered concurrently with continuous infusion; simultaneous use is not recommended in patients with spontaneous ventilation. Use as sole agent for maintenance of general anesthesia is not recommended as loss of consciousness is not certain and may increase the risk of apnea, muscle rigidity, and tachycardia. Due to rapid offset of effect, adequate analgesia should be provided prior to discontinuation of remifentanil. Due to concomitant anesthetics, respiratory depression may occur up to 30 minutes after discontinuation of remifentanil [3] .
Avoid use for conscious sedation (ie, sedation score of 3) in neonates due to their inability to respond to verbal commands to breathe deeply [9] .

Pharmacology

Remifentanil hydrochloride is a mu-opioid agonist exhibiting analgesic effects with a rapid onset and a short duration of action. Unlike fentanyl, duration of action does not increase with prolonged administration. Effects are antagonized by opioid antagonists (eg, naloxone). Pharmacokinetics fit a 3-compartment model, with a central Vd of 100 mL/kg and a steady-state Vd of 350 mL/kg. Rapid and slow distribution half-life are 1 and 6 minutes, respectively. Approximately 70% protein bound, the majority to alpha-1-acid-glycoprotein. Unlike other opioid analgesics, remifentanil contains an ester linkage in its structure and is susceptible to rapid hydrolysis in tissues and blood by nonspecific esterases (to essentially inactive metabolites). It is not a substrate for pseudocholinesterase; therefore, normal duration of action is expected in patients with atypical cholinesterase. The lung and liver are not significant contributors in the metabolism of remifentanil. Total body clearance generally correlates with total body weight, except in severely obese patients, when clearance correlates better with ideal body weight. Terminal elimination half-life is 10 to 20 minutes, however, the effective

biological half-life is 3 to 10 minutes. Renal or hepatic impairment do not affect the pharmacokinetics [3] .

The half-life of remifentanil was similar in all anesthetized pediatric patients (n=42) undergoing elective surgery or diagnostic procedures; however, infants up to the age of 2 years experienced higher clearance rates compared with older children. Clearance rates were 90 mL/kg/min in 5 days to 8 weeks of age infants, 92 mL/kg/min in children older than 2 months to younger than 2 years, 76 mL/kg/min in children 2 to 6 years of age, and 46 to 59.7 mL/kg/min in 7 to younger than 18 years. Corresponding Vd were 452.8 mL/kg (significantly different from other groups), 307.9 mL/kg, 240.1 mL/kg, and 223 to 248.9 mL/kg, respectively. [10] [3] .

Adverse Effects

In controlled studies in pediatric patients up to 12 years of age receiving remifentanil as an analgesic agent for use in the maintenance of general anesthesia (n=342), adverse events reported during the recovery and follow-up phases included nausea (8% and 6%), vomiting (12% and 16%), rhonchi (3% and 0%), shivering (3% and 0%), and postoperative complication (2% and 1%) [3] .
Volume expansion (4 versus 5 patients) and vasoactive amines (3 versus 6) were required with remifentanil and morphine infusions, respectively, in 20 ventilated premature neonates with respiratory distress syndrome [6] . Chest wall rigidity was not observed in any preterm neonates during studies (n=95) [5] [8] [2] [1] .

Monitoring

Vital signs, especially oxygen saturation, should be continuously monitored for evidence of apnea or respiratory depression during administration and following the discontinuation of infusion. Monitor for skeletal muscle rigidity, including chest wall rigidity and an inability to adequately ventilate [3] .

Special Considerations/Preparation

Ultiva(R): Available in 3-mL, 5-mL, and 10-mL vials containing 1 mg, 2 mg, and 5 mg, respectively, of remifentanil lyophilized powder for solution. Store between 2 and 25 degrees C (36 and 77 degrees F) [3] .

Reconstitute with 1 mL of diluent per mg of remifentanil. Shake well to dissolve (reconstituted solution contains approximately 1 mg of activity per 1 mL). The reconstituted solution should then be diluted to a final concentration of 20, 25, 50, or 250 mcg/mL prior to administration. Stable for 24 hours at room temperature after reconstitution and further dilution. A final concentration of 20 or 25 mcg/mL for pediatric patients 1 year or older is recommended [3] .

Solution Compatibility

D_5W, D_5LR, D_5NS, NS, 0.45% sodium chloride, sterile water for injection.

Terminal Injection Site Compatibility

Remifentanil 0.025 mg/mL:
Acyclovir 7 mg/mL, amikacin 5 mg/mL, aminophylline 2.5 mg/mL, ampicillin 20 mg/mL, ampicillin/sulbactam 20/10 mg/mL, aztreonam 40 mg/mL, bumetanide 40 mcg/mL, calcium gluconate 40 mg/mL, cefazolin 20 mg/mL, cefotaxime 20 mg/mL, cefotetan 20 mg/mL, cefoxitin 20 mg/mL, ceftriaxone 20 mg/mL, cefuroxime 30 mg/mL, cimetidine 12 mg/mL, ciprofloxacin 1 mg/mL, cisatracurium 2 mg/mL, clindamycin 10 mg/mL, dexamethasone 2 mg/mL, digoxin 0.25 mg/mL, diphenhydramine 2 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, doxycycline hyclate 1 mg/mL, enalaprilat 0.1 mg/mL, epinephrine 50 mcg/mL, esmolol 10 mg/mL, famotidine 2 mg/mL, fentanyl 12.5 mcg/mL, fluconazole 2 mg/mL, ganciclovir 20 mg/mL, gentamicin 5 mg/mL, haloperidol 0.2 mg/mL, heparin 100 units/mL, hydrocortisone 1 mg/mL, hydromorphone 0.5 mg/mL, imipenem/cilastatin 10 mg/mL, isoproterenol 20 mcg/mL, ketorolac 15 mg/mL, lidocaine 8 mg/mL, lorazepam 0.5 mg/mL, magnesium 100 mg/mL, mannitol 150 mg/mL, methylprednisolone 5 mg/mL, metoclopramide 5 mg/mL, metronidazole 5 mg/mL, midazolam 1 mg/mL, morphine 1 mg/mL, nalbuphine 10 mg/mL, netilmicin 5 mg/mL, nitroglycerin 0.4 mg/mL, norepinephrine 0.12 mg/mL, ondansetron 1 mg/mL, phenylephrine 1 mg/mL, piperacillin 40 mg/mL, piperacillin/tazobactam 40/5 mg/mL, potassium chloride 0.1 mEq/mL, procainamide 10 mg/mL, ranitidine 2 mg/mL, sodium bicarbonate 1 mEq/mL (8.4%), sulfamethoxazole/trimethoprim 4/0. 8 mg/mL, ticarcillin/clavulanate 31 mg/mL, tobramycin 5 mg/mL, vancomycin 10 mg/mL, zidovudine 4 mg/mL.

Remifentanil 0.12 mg/mL:
Heparin 417 units/mL, insulin 1 unit/mL, magnesium 8 mg/mL, midazolam 1 mg/mL, potassium chloride 0.1 mEq/mL.

Remifentanil 0.2 mg/mL:
Cefepime 120 mg/mL, ceftazidime 120 mg/mL.

Remifentanil 0.25 mg/mL:
Acyclovir 7 mg/mL, amikacin 5 mg/mL, aminocaproic acid 20 mg/mL, aminophylline 2.5 mg/mL, ampicillin 20 mg/mL, ampicillin/sulbactam 20/10 mg/mL, anidulafungin 0.5 mg/mL, argatroban 1 mg/mL, azithromycin 2 mg/mL, aztreonam 40 mg/mL, bivalirudin 5 mg/mL, bumetanide 40 mcg/mL, calcium gluconate 40 mg/mL, caspofungin 0.5 mg/mL, cefazolin 20 mg/mL, cefotaxime 20 mg/mL, cefotetan 20 mg/mL, cefoxitin 20 mg/mL, ceftriaxone 20 mg/mL, cefuroxime 30 mg/mL, cimetidine 12 mg/mL, ciprofloxacin 1 mg/mL, cisatracurium 2 mg/mL, clindamycin 10 mg/mL, dexamethasone 2 mg/mL, dexmedetomidine 4 mcg/mL, digoxin 0.25 mg/mL, diltiazem 5 mg/mL, diphenhydramine 2 mg/mL, dobutamine 4 mg/mL, dopamine 3.2 mg/mL, doxycycline hyclate 1 mg/mL, enalaprilat 0.1 mg/mL, epinephrine 50 mcg/mL, ertapenem 20 mg/mL, esmolol 10 mg/mL, famotidine 2 mg/mL, fentanyl 12.5 mcg/mL, fluconazole 2 mg/mL, foscarnet 24 mg/mL, ganciclovir 20 mg/mL, gentamicin 5 mg/mL, granisetron 50 mcg/mL, haloperidol 0.2 mg/mL, heparin 100 units/mL, hydrocortisone 1 mg/mL, hydromorphone 0.5 mg/mL, imipenem/cilastatin 10 mg/mL, isoproterenol 20 mcg/mL, ketorolac 15 mg/mL, levofloxacin 5 mg/mL, lidocaine 8 mg/mL, lorazepam 0.5 mg/mL, magnesium 100 mg/mL, mannitol 150 mg/mL, methotrexate 15 mg/mL, methylprednisolone 5 mg/mL, metoclopramide 5 mg/mL, metronidazole 5 mg/mL, midazolam 1 mg/mL, milrinone 0.2 mg/mL, morphine 1 mg/mL, mycophenolate 6 mg/mL, nalbuphine 10 mg/mL, netilmicin 5 mg/mL, nicardipine 0.1 mg/mL, nitroglycerin 0.4 mg/mL, norepinephrine 0.12 mg/mL,

octreotide 5 mcg/mL, ondansetron 1 mg/mL, palonosetron 50 mcg/mL, pancuronium 0.1 mg/mL, phenylephrine 1 mg/mL, piperacillin 40 mg/mL, piperacillin/tazobactam 40/5 mg/mL, potassium chloride 0.1 mEq/mL, procainamide 10 mg/mL, ranitidine 2 mg/mL, rocuronium 1 mg/mL, sodium bicarbonate 1 mEq/mL (8.4%), sulfamethoxazole/trimethoprim 4/0. 8 mg/mL, tacrolimus 20 mcg/mL, ticarcillin/clavulanate 31 mg/mL, tobramycin 5 mg/mL, vancomycin 10 mg/mL, vasopressin 1 unit/mL, vecuronium 1 mg/mL, voriconazole 4 mg/mL, zidovudine 4 mg/mL.

Remifentanil 0.5 mg/mL:
Linezolid 2 mg/mL.

Terminal Injection Site Incompatibility

Amphotericin B cholesteryl, amphotericin B lipid complex, daptomycin, pantoprazole.

Compatibility information refers to physical compatibility and is derived from Trissel's™ 2 Clinical Pharmaceutics Database. The determination of compatibility is based on concentrations for administration recommended herein. Drug compatibility is dependent on multiple factors (eg, drug concentrations, diluents, storage conditions). This list should not be viewed as all-inclusive and should not replace sound clinical judgment. The user is referred to Trissel's™ 2 for more complete details.
Trissel's™ 2 Clinical Pharmaceutics Database, version updated on 06/15/2012.

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1.162 Rifampin

Title Rifampin

Dose

Oral: 10 to 20 mg/kg/dose every 24 hours. May administer with feedings.
IV:5 to 10 mg/kg/dose every 12 hours [1] [2] [3] , given via syringe pump over 30 minutes.
Do not administer IM or subQ.

Prophylaxis for high-risk contacts of invasive meningococcal disease: 5 mg/kg per dose orally every 12 hours, for 2 days.

Prophylaxis for high-risk contacts of invasive H influenzae type b disease: 10 mg/kg per dose orally every 24 hours, for 4 days.

Uses

Used in combination with vancomycin or aminoglycosides for treatment of persistent staphylococcal infections [1] [2] [3] . Prophylaxis against infections caused by *N meningitidis* and *H influenzae* type b .

Pharmacology

Rifampin is a semisynthetic antibiotic with a wide spectrum of antibacterial activity against staphylococci, most streptococci, *H influenzae*, *Neisseria* species, *Legionella*, *Listeria*, some *Bacteroides*species, Mycobacterium tuberculosis, and certain atypical mycobacterium. Enterococci and aerobic gram-negative bacilli are generally resistant. Not used as monotherapy because resistance may develop during therapy. Inhibits transcription of DNA to RNA by binding to the beta subunit of bacterial RNA-polymerase. Well absorbed orally. Rapidly deacetylated to desacetylrifampin (active metabolite) and undergoes enterohepatic circulation. Nearly all of the rifampin excreted into the bile is deacetylated within 6 hours. Serum half-life ranges from 1 to 3 hours.

Adverse Effects

Causes orange/red discoloration of body secretions (eg, sweat, urine, tears, sputum). Extravasation may cause local irritation and inflammation. Rifampin in a potent inducer

of several cytochrome P450 enzymes. If administered concomitantly, the following drugs may have decreased pharmacologic effects due to increased metabolism: aminophylline, amiodarone, cimetidine, corticosteroids, digoxin, enalapril, fluconazole, midazolam, morphine, phenobarbital, phenytoin, propranolol, and zidovudine.

Monitoring

Monitor hepatic transaminases and bilirubin. Periodic CBC for thrombocytopenia. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as a lyophilized powder for injection in 600-mg vials. Reconstitute with 10 mL of sterile water for injection to make a final concentration of 60 mg/mL. Reconstituted solution is stable for 24 hours at room temperature. Further dilution is required - maximum concentration for infusion is 6 mg/mL.
A 3 mg/mL dilution may be made by adding 0.5 mL of reconstituted solution to 9.5 mL of NS or D_5W. Dilution made with NS is stable for 24 hours at room temperature. Dilution made with D_5 W is stable for 4 hours at room temperature. Do not use if solution precipitates.

A neonatal suspension may be prepared by mixing 5 mL (300 mg) of the reconstituted IV solution with 25 mL of simple syrup to make a final concentration of 10 mg/mL. Shake well before use. Suspension is stable for 4 weeks at room temperature or refrigerated. Also available in 150- and 300-mg capsules. Preparation of oral suspension using capsules yields variable dosage bioavailability.

Solution Compatibility

D_5W and NS. No data available on Dex/AA or fat emulsion.

Terminal Injection Site Compatibility

No data available.

Terminal Injection Site Incompatibility Diltiazem.

References

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3. Tan TQ, Mason EO, Ou C-N et al: Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia.Antimicrob Agents Chemother 1993; 37(11): 2401-6.

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Dose

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Prophylaxis for high-risk contacts of invasive H influenzae type b disease: 10 mg/kg per dose orally every 24 hours, for 4 days.

Uses

Used in combination with vancomycin or aminoglycosides for treatment of persistent staphylococcal infections [1] [2] [3] . Prophylaxis against infections caused by *N meningitidis* and *H influenzae* type b .

Pharmacology

Rifampin is a semisynthetic antibiotic with a wide spectrum of antibacterial activity against staphylococci, most streptococci, *H influenzae*, *Neisseria* species, *Legionella*, *Listeria*, some *Bacteroides*species, Mycobacterium tuberculosis, and certain atypical mycobacterium. Enterococci and aerobic gram-negative bacilli are generally resistant. Not used as monotherapy because resistance may develop during therapy. Inhibits transcription of DNA to RNA by binding to the beta subunit of bacterial RNA-polymerase. Well absorbed orally. Rapidly deacetylated to desacetylrifampin (active metabolite) and undergoes enterohepatic circulation. Nearly all of the rifampin excreted into the bile is deacetylated within 6 hours. Serum half-life ranges from 1 to 3 hours.

Adverse Effects

Causes orange/red discoloration of body secretions (eg, sweat, urine, tears, sputum). Extravasation may cause local irritation and inflammation. Rifampin in a potent inducer of several cytochrome P450 enzymes. If administered concomitantly, the following drugs may have decreased pharmacologic effects due to increased metabolism: aminophylline, amiodarone, cimetidine, corticosteroids, digoxin, enalapril, fluconazole, midazolam, morphine, phenobarbital, phenytoin, propranolol, and zidovudine.

Monitoring

Monitor hepatic transaminases and bilirubin. Periodic CBC for thrombocytopenia. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as a lyophilized powder for injection in 600-mg vials. Reconstitute with 10 mL of sterile water for injection to make a final concentration of 60 mg/mL. Reconstituted solution is stable for 24 hours at room temperature. Further dilution is required - maximum concentration for infusion is 6 mg/mL.
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Solution Compatibility

D_5W and NS. No data available on Dex/AA or fat emulsion.

Terminal Injection Site Compatibility

No data available.

Terminal Injection Site Incompatibility Diltiazem.

References

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1.163 Rocuronium

Title Rocuronium

Dose

0.3 to 0.6 mg/kg per dose IV push over 5 to 10 seconds. Do not give IM.
Must be accompanied by adequate analgesia and/or sedation.

Uses

Skeletal muscle relaxation/paralysis in infants requiring endotracheal intubation.

Pharmacology

Rocuronium is an amino steroid nondepolarizing neuromuscular blocking agent that is an analog of vecuronium with 10% to 15% of its potency. It has a rapid to intermediate onset depending on dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium. Plasma levels of rocuronium follow a three compartment open model following intravenous administration. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Onset of clinical effect usually occurs within 2 minutes and the duration ranges from 20 minutes to 2 hours. Larger doses (0.9 to 1.2 mg/kg) lead to more rapid onset and longer duration of clinical effect. It can have differential effects on various muscle groups (eg, laryngeal vs adductor pollicis vs diaphragm). The onset of laryngeal adductor paralysis is significantly slower with rocuronium compared with succinylcholine. Despite this difference, rocuronium has the fastest onset of any currently available nondepolarizing muscle relaxant. Average half-life in newborns is 1.1 hours. Rocuronium is approximately 30% protein bound, and is primarily excreted by the liver. There are no known metabolites.

Adverse Effects

The use of rocuronium in infants has only been studied in patients under halothane anesthesia. The overall analysis of ECG data in pediatric patients indicates that the concomitant use of rocuronium with general anesthetic agents can prolong the QTc interval. Most pediatric patients anesthetized with halothane who did not receive atropine for induction experienced a transient increase (30% or greater) in heart rate after intubation, whereas only 1 of 19 infants anesthetized with halothane and fentanyl who received atropine for induction experienced this magnitude of change. Aminoglycosides, vancomycin, and hypermagnesemia may enhance neuromuscular blockade. Propofol has no effect. Phenytoin may diminish neuromuscular blockade. Respiratory and metabolic acidosis prolong the recovery time, respiratory alkalosis shortens it. Rocuronium may be associated with increased pulmonary vascular

resistance, so caution is appropriate in patients with pulmonary hypertension. Extravasations cause local tissue irritation. The package insert statement that rocuronium is not recommended for rapid sequence intubations in pediatric patients is due to the lack of studies.

Monitoring

Assess vital signs frequently and blood pressure continuously if possible.

Special Considerations/Preparation

Zemuron® for intravenous injection is available in 5 mL and 10 mL multiple-dose vials containing 10 mg/mL. Each mL contains 10 mg rocuronium bromide and 2 mg sodium acetate. The solution is clear, colorless to yellow/orange, and is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide. Store refrigerated, 2 to 8 degrees C (36 to 46 degrees F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25 degrees C/77 degrees F), use within 60 days. Use opened vials within 30 days.
To prepare a 1 mg/mL solution, dilute 1 mL of the 10 mg/mL solution up to a final volume of 10 mL with NS. Dilution stable for 24 hours.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Milrinone.

Terminal Injection Site Incompatibility

Micafungin.

References

- Perry JJ, Lee JS, Sillberg VAH, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD002788. DOI:10.1002/14651858.CD002788.pub2.
- Rapp H-J, Altenmueller CA, Waschke C: Neuromuscular recovery following rocuronium bromide single dose in infants. *Pediatr Anesthes* 2004; 14:329-355.
- Eikermann M, Hunkemoller I, Peine L, et al: Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children. *Br J Anesthaes* 2002;89:277-281.
- Sparr HJ, Beaufort TM, Fuchs-Buder T: Newer neuromuscular blocking agents: how do they compare with established agents. *Drugs* 2001;61:919-942.
- Product information, Schering, 2008.

Title Rocuronium

Dose

0.3 to 0.6 mg/kg per dose IV push over 5 to 10 seconds. Do not give IM.
Must be accompanied by adequate analgesia and/or sedation.

Uses

Skeletal muscle relaxation/paralysis in infants requiring endotracheal intubation.

Pharmacology

Rocuronium is an amino steroid nondepolarizing neuromuscular blocking agent that is an analog of vecuronium with 10% to 15% of its potency. It has a rapid to intermediate onset depending on dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium. Plasma levels of rocuronium follow a three compartment open model following intravenous administration. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Onset of clinical effect usually occurs within 2 minutes and the duration ranges from 20 minutes to 2 hours. Larger doses (0.9 to 1.2 mg/kg) lead to more rapid onset and longer duration of clinical effect. It can have differential effects on various muscle groups (eg, laryngeal vs adductor pollicis vs diaphragm). The onset of laryngeal adductor paralysis is significantly slower with rocuronium compared with succinylcholine. Despite this difference, rocuronium has the fastest onset of any currently available nondepolarizing muscle relaxant. Average half-life in newborns is 1.1 hours. Rocuronium is approximately 30% protein bound, and is primarily excreted by the liver. There are no known metabolites.

Adverse Effects

The use of rocuronium in infants has only been studied in patients under halothane anesthesia. The overall analysis of ECG data in pediatric patients indicates that the concomitant use of rocuronium with general anesthetic agents can prolong the QTc interval. Most pediatric patients anesthetized with halothane who did not receive atropine for induction experienced a transient increase (30% or greater) in heart rate after intubation, whereas only 1 of 19 infants anesthetized with halothane and fentanyl who received atropine for induction experienced this magnitude of change. Aminoglycosides, vancomycin, and hypermagnesemia may enhance neuromuscular blockade. Propofol has no effect. Phenytoin may diminish neuromuscular blockade. Respiratory and metabolic acidosis prolong the recovery time, respiratory alkalosis shortens it. Rocuronium may be associated with increased pulmonary vascular resistance, so caution is appropriate in patients with pulmonary hypertension. Extravasations cause local tissue irritation. The package insert statement that rocuronium is not recommended for rapid sequence intubations in pediatric patients is due to the lack of studies.

Monitoring

Assess vital signs frequently and blood pressure continuously if possible.

Special Considerations/Preparation

Zemuron® for intravenous injection is available in 5 mL and 10 mL multiple-dose vials containing 10 mg/mL. Each mL contains 10 mg rocuronium bromide and 2 mg sodium acetate. The solution is clear, colorless to yellow/orange, and is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide. Store refrigerated, 2 to 8 degrees C (36 to 46 degrees F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25 degrees C/77 degrees F), use within 60 days. Use opened vials within 30 days.
To prepare a 1 mg/mL solution, dilute 1 mL of the 10 mg/mL solution up to a final volume of 10 mL with NS. Dilution stable for 24 hours.

Solution Compatibility

D_5W, Lactated Ringer's, and NS.

Terminal Injection Site Compatibility

Milrinone.

Terminal Injection Site Incompatibility

Micafungin.

References

- Perry JJ, Lee JS, Sillberg VAH, Wells GA. Rocuronium versus succinylcholine for rapid sequence induction intubation. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD002788. DOI:10.1002/14651858.CD002788.pub2.
- Rapp H-J, Altenmueller CA, Waschke C: Neuromuscular recovery following rocuronium bromide single dose in infants. *Pediatr Anesthes* 2004; 14:329-355.
- Eikermann M, Hunkemoller I, Peine L, et al: Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children. *Br J Anesthaes* 2002;89:277-281.
- Sparr HJ, Beaufort TM, Fuchs-Buder T: Newer neuromuscular blocking agents: how do they compare with established agents. *Drugs* 2001;61:919-942.
- Product information, Schering, 2008.

1.164 Rotavirus Vaccine (RotaTeqÂ®)

Title Rotavirus Vaccine (RotaTeqÂ®)

Dose

2 mL per dose orally [1] .
The RotaTeq® vaccine is a 3-dose series with at least 4 weeks between each dose. The recommended vaccination schedule is 2 months of age **(minimum age 6 weeks and maximum age 14 weeks 6 days)**, 4 months of age, and 6 months of age **(maximum age 8 months)**. Vaccination should not be initiated for infants 15 weeks, 0 days of age and older [2] [3] .

Administration

FOR ORAL USE ONLY. NOT FOR INJECTION [1] .
1) Tear open the pouch and remove the dosing tube.
2) Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.
3) Puncture the dispensing tip by screwing cap clockwise until it becomes tight, then remove the cap by turning it counterclockwise.
4) Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty [1] .

If the infant spits out or regurgitates most of the vaccine dose, a single replacement dose is NOT recommended, since this was not studied in clinical trials [3] . There are no restrictions on the infant's liquid consumption (including breast milk) before or after vaccination [1] .

If an infant is exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Uses

Pediatric FDA Approved Indications
Immunoprophylaxis against rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 in children 6 weeks to 24 weeks of age [1] [3] .

Contraindications/Precautions

Contraindicated in infants with Severe Combined Immunodeficiency Syndrome (SCID); vaccine-acquired rotavirus disease, severe diarrhea and prolonged shedding of vaccine virus have been reported in these patients [1] [6] . Also **contraindicated** in infants with a history of intussusception [1] .

Vaccination should be deferred in infants with acute moderate to severe gastroenteritis, and infants with moderate to severe acute illness [3] . Due to an increased risk of infection, if an infant has been exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Pharmacology

RotaTeq® is a bovine-based pentavalent vaccine containing 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express 1 of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell-culture media, and trace amounts of fetal bovine serum. There are no preservatives or thimerosal [1] .

Fecal shedding of vaccine virus occurred in 32 (8.9%) of 360 subjects after dose 1, 0 (0%) of 249 subjects after dose 2, and 1 (0.3%) of 385 subjects after dose 3. In phase III studies, shedding was observed as early as 1 day and as late as 15 days after a dose. The potential for transmission of vaccine virus was not assessed through epidemiologic studies [1] .

RotaTeq® may be coadministered with other routine childhood vaccines (DTaP, Hib, IPV, hepatitis B, and pneumococcal conjugate); immune response to any of the vaccine antigens was not altered in clinical trials. It has 98% efficacy for prevention of severe illness and 74% for prevention of rotavirus-induced diarrheal episodes [1] [3] .

Adverse Effects

Over 47 million doses of RotaTeq® vaccine have been distributed from the time of US Food and Drug Administration approval in February 2006 through April 2012. During this time, there were 584 confirmed cases of intussusception reported through the Vaccine Adverse Event Reporting System (VAERS). Analysis of these events revealed a persistent clustering of events during days 3 to 6 after administration of the first dose. The estimated excess risk of intussusception was 0.74, 0.21, and -0.16 events per 100,000 vaccinated infants during the 3 to 6 day window after doses 1, 2 and 3, respectively; the overall excess risk from all 3 doses was estimated at approximately 0.79. Thirty-three excess events per year are expected in the US when the rotavirus vaccine program is fully mature [7] .

According to the US Vaccine Adverse Event Reporting System (VAERS), although clinical trial data reported higher (though not statistically significant) Kawasaki disease rates with RotaTeq®, analyses of postmarketing reports (1990 through 2007) of Kawasaki disease did not show an elevated risk with RotaTeq® or other US-licensed vaccines [8] .

Transmission of vaccine virus strains from vaccinees to non-vaccinated contacts has been reported. In clinical studies, vaccine virus shedding was noted from 1 day to 15 days after a dose. Caution is advised when administering vaccine to patients with close contact to individuals with immunodeficiencies (malignancies, primary immunodeficiency, immunocompromised, or receiving immunosuppressive therapy) [1] .

Special Considerations/Preparation

RotaTeq® is supplied as a suspension for oral use in individually pouched single-dose tubes. Each dosage tube contains 2 mL. It is a pale yellow clear liquid that may have a pink tint. **Store and transport refrigerated. Protect from light.** Administer as soon as possible after removing from refrigeration. Discard in approved biological waste containers [1] .

References

- Product Information: RotaTeq oral solution, Rotavirus Vaccine, Live, Oral, Pentavalent oral solution. Merck (per manufacturer), Whitehouse Station, NJ, Jul, 2011.

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Cortese MM: Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Feb6, 2009; 58(RR-2): 1-25.

- Product Information: SIMPONI(R) solution for subcutaneous injection, golimumab solution for subcutaneous injection. Janssen Biotech, Inc. (per Manufacturer), Horsham, PA, Sep, 2011.

- Product Information: REMICADE(R) intravenous injection lyophilized concentrate, infliximab intravenous injection lyophilized concentrate. Janssen Biotech, Inc. (per manufacturer), Horsham, PA, Oct, 2011.

- Patel NC, Hertel PM, Estes MK et al: Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med Jan28, 2010; 362(4): 314-319.

- Haber P, Patel M, Pan Y et al: Intussusception After Rotavirus Vaccines Reported to US VAERS, 2006-2012. Pediatrics Jun, 2013; 131(6): 1042-1049.

- Hua W, Izurieta HS, Slade B et al: Kawasaki Disease After Vaccination: Reports to the Vaccine Adverse Event Reporting System 1990-2007. Pediatr Infect Dis J Sep12, 2009; epub: epub.

Title Rotavirus Vaccine (RotaTeqÂ®)

Dose

2 mL per dose orally [1] .
The RotaTeq® vaccine is a 3-dose series with at least 4 weeks between each dose. The recommended vaccination schedule is 2 months of age **(minimum age 6 weeks and maximum age 14 weeks 6 days)**, 4 months of age, and 6 months of age **(maximum age 8 months)**. Vaccination should not be initiated for infants 15 weeks, 0 days of age and older [2] [3] .

Administration

FOR ORAL USE ONLY. NOT FOR INJECTION [1] .
1) Tear open the pouch and remove the dosing tube.
2) Clear the fluid from the dispensing tip by holding tube vertically and tapping cap.
3) Puncture the dispensing tip by screwing cap clockwise until it becomes tight, then remove the cap by turning it counterclockwise.
4) Administer dose by gently squeezing liquid into infant's mouth toward the inner cheek until dosing tube is empty [1] .

If the infant spits out or regurgitates most of the vaccine dose, a single replacement dose is NOT recommended, since this was not studied in clinical trials [3] . There are no restrictions on the infant's liquid consumption (including breast milk) before or after vaccination [1] .

If an infant is exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Uses

Pediatric FDA Approved Indications
Immunoprophylaxis against rotavirus gastroenteritis caused by serotypes G1, G2, G3, and G4 in children 6 weeks to 24 weeks of age [1] [3] .

Contraindications/Precautions

Contraindicated in infants with Severe Combined Immunodeficiency Syndrome (SCID); vaccine-acquired rotavirus disease, severe diarrhea and prolonged shedding of vaccine virus have been reported in these patients [1] [6] . Also **contraindicated** in infants with a history of intussusception [1] .

Vaccination should be deferred in infants with acute moderate to severe gastroenteritis, and infants with moderate to severe acute illness [3] . Due to an increased risk of infection, if an infant has been exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Pharmacology

RotaTeq® is a bovine-based pentavalent vaccine containing 5 live reassortant rotaviruses. The rotavirus parent strains of the reassortants were isolated from human and bovine hosts. Four reassortant rotaviruses express 1 of the outer capsid proteins (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. The reassortants are suspended in a buffered stabilizer solution. Each vaccine dose contains sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell-culture media, and trace amounts of fetal bovine serum. There are no preservatives or thimerosal [1] .

Fecal shedding of vaccine virus occurred in 32 (8.9%) of 360 subjects after dose 1, 0 (0%) of 249 subjects after dose 2, and 1 (0.3%) of 385 subjects after dose 3. In phase III studies, shedding was observed as early as 1 day and as late as 15 days after a dose. The potential for transmission of vaccine virus was not assessed through epidemiologic studies [1] .

RotaTeq® may be coadministered with other routine childhood vaccines (DTaP, Hib, IPV, hepatitis B, and pneumococcal conjugate); immune response to any of the vaccine antigens was not altered in clinical trials. It has 98% efficacy for prevention of severe illness and 74% for prevention of rotavirus-induced diarrheal episodes [1] [3] .

Adverse Effects

Over 47 million doses of RotaTeq® vaccine have been distributed from the time of US Food and Drug Administration approval in February 2006 through April 2012. During this time, there were 584 confirmed cases of intussusception reported through the Vaccine Adverse Event Reporting System (VAERS). Analysis of these events revealed a persistent clustering of events during days 3 to 6 after administration of the first dose. The estimated excess risk of intussusception was 0.74, 0.21, and -0.16 events per 100,000 vaccinated infants during the 3 to 6 day window after doses 1, 2 and 3, respectively; the overall excess risk from all 3 doses was estimated at approximately 0.79. Thirty-three excess events per year are expected in the US when the rotavirus vaccine program is fully mature [7] .

According to the US Vaccine Adverse Event Reporting System (VAERS), although clinical trial data reported higher (though not statistically significant) Kawasaki disease rates with RotaTeq®, analyses of postmarketing reports (1990 through 2007) of Kawasaki disease did not show an elevated risk with RotaTeq® or other US-licensed vaccines [8] .

Transmission of vaccine virus strains from vaccinees to non-vaccinated contacts has been reported. In clinical studies, vaccine virus shedding was noted from 1 day to 15 days after a dose. Caution is advised when administering vaccine to patients with close contact to individuals with immunodeficiencies (malignancies, primary immunodeficiency, immunocompromised, or receiving immunosuppressive therapy) [1] .

Special Considerations/Preparation

RotaTeq® is supplied as a suspension for oral use in individually pouched single-dose tubes. Each dosage tube contains 2 mL. It is a pale yellow clear liquid that may have a pink tint. **Store and transport refrigerated. Protect from light.** Administer as soon as possible after removing from refrigeration. Discard in approved biological waste containers [1] .

References

- Product Information: RotaTeq oral solution, Rotavirus Vaccine, Live, Oral, Pentavalent oral solution. Merck (per manufacturer), Whitehouse Station, NJ, Jul, 2011.

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Cortese MM: Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Feb6, 2009; 58(RR-2): 1-25.

- Product Information: SIMPONI(R) solution for subcutaneous injection, golimumab solution for subcutaneous injection. Janssen Biotech, Inc. (per Manufacturer), Horsham, PA, Sep, 2011.

- Product Information: REMICADE(R) intravenous injection lyophilized concentrate, infliximab intravenous injection lyophilized concentrate. Janssen Biotech, Inc. (per manufacturer), Horsham, PA, Oct, 2011.

- Patel NC, Hertel PM, Estes MK et al: Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. N Engl J Med Jan28, 2010; 362(4): 314-319.

- Haber P, Patel M, Pan Y et al: Intussusception After Rotavirus Vaccines Reported to US VAERS, 2006-2012. Pediatrics Jun, 2013; 131(6): 1042-1049.

- Hua W, Izurieta HS, Slade B et al: Kawasaki Disease After Vaccination: Reports to the Vaccine Adverse Event Reporting System 1990-2007. Pediatr Infect Dis J Sep12, 2009; epub: epub.

1.165 Rotavirus Vaccine (RotarixÂ®)

Title Rotavirus Vaccine (RotarixÂ®)

Dose

1 mL per dose.
FOR ORAL USE ONLY. NOT FOR INJECTION.
The Rotarix® vaccine is a 2-dose series with at least 4 weeks between each dose. The recommended vaccination schedule is 2 months of age **(minimum age 6 weeks and maximum age 14 weeks 6 days)** and 4 months of age (**maximum age 8 months**). Vaccination should not be initiated for infants 15 weeks, 0 days of age and older [1] [2] .

Administration

1) Connect transfer adapter onto vial of lyophilized vaccine.
2) Shake the oral applicator containing the liquid diluent (white, turbid suspension).
3) Connect the oral applicator to the transfer adapter.
4) Push plunger of oral applicator to transfer diluent into vial (suspension will appear white and turbid).
5) Withdraw the entire mixture back into the oral applicator.
6) Twist and remove the oral applicator from the transfer adapter.
7) With infant seated in a reclining position, administer orally the entire contents of the oral applicator (on the inside of the cheek).
Refer to package insert for illustrations [3] .

If the infant spits out or regurgitates most of the vaccine dose, a single replacement dose is NOT recommended, since this was not studied in clinical trials [2] . There are no restrictions on the infant's liquid consumption (including breast milk) before or after vaccination.

If an infant is exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Uses

Immunoprophylaxis against rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9) [3] [2] [6] [7] .

Contraindications/Precautions

Vaccination **contraindicated** in infants with a history of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant for intussusception, in infants with a history of intussusception, and in infants with a history of Severe Combined Immunodeficiency Disease (SCID). Infants with severe latex allergy (anaphylaxis) should not receive Rotarix® (oral applicator contains latex rubber). Vaccination should be deferred in infants with acute moderate to severe gastroenteritis, and infants with moderate to severe acute illness [3] .
In a safety and efficacy study (n=63,225 infants), no increased risk of intussusception was observed in infants receiving Rotarix® when compared with placebo. There were 6 cases of intussusception reported in the Rotarix® infants versus 7 cases in the placebo infants within 31 days after any dose [3] [2] [7] . In a postmarketing observational study in Mexico, cases of intussusception with a temporal relationship to vaccination (within 31 days) were reported, with a cluster of cases occurring in the first 7 days post-vaccination. It is unclear if the risk of intussusception seen in infants in Mexico is applicable to infants in the United States [8] .

Shedding of rotavirus in the stool occurs after vaccination, with peak excretion approximately on day 7 after dose 1; transmission of vaccine virus to healthy seronegative contacts was demonstrated in 1 clinical trial; consider benefit to risk when deciding to vaccinate infants with immunodeficient close contacts; handwashing is recommended after diaper changes to help prevent spreading of vaccine virus [8] .

Due to an increased risk of infection, if an infant has been exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Pharmacology

Rotarix® is a human-derived rotavirus vaccine from the 89-12 strain, which belongs to G1P[8] type. The lyophilized vaccine contains amino acids, dextran, Dulbecco's Modified Eagle Medium, sorbitol, and sucrose. The liquid diluent contains calcium carbonate (to protect the vaccine during passage through the stomach and prevent inactivation), sterile water, and xanthan [3] .
Fecal shedding after vaccination was reported in approximately 26% of vaccinated infants, in two studies. Peak excretion occurred around day 7 after the first dose. Transmission of virus was not evaluated, and the potential for transmission of vaccine virus is not known.
Approximately 80% of Rotarix® recipients will be seroconverted one to two months after a 2-dose series [3] .
Rotarix® may be coadministered with other routine childhood vaccines (DTaP, Hib, IPV, hepatitis B, and pneumococcal conjugate); immune response to any of the vaccine antigens was not altered in clinical trials [2] .

Adverse Effects

Kawasaki disease was reported in 18 (0.035%) recipients of Rotarix® and 9 (0.021%) placebo recipients from 16 completed or ongoing clinical trials. Of the 27 cases, 5 occurred following Rotarix® in clinical trials that were either not placebo-controlled or 1:1 randomized. Three of the 27 cases (2 cases Rotarix®, 1 case placebo) were reported within 30 days post-vaccination. Kawasaki disease was reported in 17 Rotarix® recipients and 9 placebo recipients (relative risk, 1.71; 95% confidence interval, 0.71 to 4.38) in placebo-controlled trials. Among recipients of Rotarix®, the time of onset after study dose ranged from 3 days to 19 months [3] .

Special Considerations/Preparation

Rotarix® is supplied as a vial of lyophilized vaccine, a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution. The vaccine contains no preservatives. Oral applicator contains latex rubber. Lyophilized vials should be refrigerated and protected from light, and the diluent can be stored at room temperature.
Do not freeze, and discard vaccine if frozen.
Reconstituted vaccine may be stored refrigerated or at room temperature, and vaccine should be administered within 24 hours of reconstitution. Discard if not used within 24 hours.
Do not mix with other vaccines or solutions [3] .

References

- Centers for Disease Control and Prevention : Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older — United States, 2013. MMWR Morb Mortal Wkly Rep Jan28, 2013; 62(Suppl 1): 1-19.

- Cortese MM: Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Feb6, 2009; 58(RR-2): 1-25.

- Product Information: ROTARIX oral suspension, rotavirus vaccine, live, oral suspension. GlaxoSmithKline, Research Triangle Park, NC, 2011.

- Product Information: SIMPONI(R) solution for subcutaneous injection, golimumab solution for subcutaneous injection. Janssen Biotech, Inc. (per Manufacturer), Horsham, PA, Sep, 2011.

- Product Information: REMICADE(R) intravenous injection lyophilized concentrate, infliximab intravenous injection lyophilized concentrate. Janssen Biotech, Inc. (per manufacturer), Horsham, PA, Oct, 2011.

- Vesikari T, Karvonen A, Prymula R et al: Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet Nov24, 2007; 370(9601): 1757-1763.

- Ruiz-Palacios GM, Perez-Schael I, Velazquez FR et al: Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med Jan5, 2006; 354(1): 11-22.

• Product Information: ROTARIX(R) oral suspension, rotavirus vaccine live oral suspension. GlaxoSmithKline (per FDA), Research Triangle Park, NC, Sep, 2012.

Title Rotavirus Vaccine (RotarixÂ®)

Dose

1 mL per dose.
FOR ORAL USE ONLY. NOT FOR INJECTION.
The Rotarix® vaccine is a 2-dose series with at least 4 weeks between each dose. The recommended vaccination schedule is 2 months of age **(minimum age 6 weeks and maximum age 14 weeks 6 days)** and 4 months of age (**maximum age 8 months**). Vaccination should not be initiated for infants 15 weeks, 0 days of age and older [1] [2] .

Administration

1) Connect transfer adapter onto vial of lyophilized vaccine.
2) Shake the oral applicator containing the liquid diluent (white, turbid suspension).
3) Connect the oral applicator to the transfer adapter.
4) Push plunger of oral applicator to transfer diluent into vial (suspension will appear white and turbid).
5) Withdraw the entire mixture back into the oral applicator.
6) Twist and remove the oral applicator from the transfer adapter.
7) With infant seated in a reclining position, administer orally the entire contents of the oral applicator (on the inside of the cheek).
Refer to package insert for illustrations [3] .

If the infant spits out or regurgitates most of the vaccine dose, a single replacement dose is NOT recommended, since this was not studied in clinical trials [2] . There are no restrictions on the infant's liquid consumption (including breast milk) before or after vaccination.

If an infant is exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Uses

Immunoprophylaxis against rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9) [3] [2] [6] [7] .

Contraindications/Precautions

Vaccination **contraindicated** in infants with a history of uncorrected congenital malformation of the gastrointestinal tract that would predispose the infant for intussusception, in infants with a history of intussusception, and in infants with a history of Severe Combined Immunodeficiency Disease (SCID). Infants with severe latex allergy (anaphylaxis) should not receive Rotarix® (oral applicator contains latex rubber). Vaccination should be deferred in infants with acute moderate to severe

gastroenteritis, and infants with moderate to severe acute illness [3] .
In a safety and efficacy study (n=63,225 infants), no increased risk of intussusception was observed in infants receiving Rotarix® when compared with placebo. There were 6 cases of intussusception reported in the Rotarix® infants versus 7 cases in the placebo infants within 31 days after any dose [3] [2] [7] . In a postmarketing observational study in Mexico, cases of intussusception with a temporal relationship to vaccination (within 31 days) were reported, with a cluster of cases occurring in the first 7 days post-vaccination. It is unclear if the risk of intussusception seen in infants in Mexico is applicable to infants in the United States [8] .

Shedding of rotavirus in the stool occurs after vaccination, with peak excretion approximately on day 7 after dose 1; transmission of vaccine virus to healthy seronegative contacts was demonstrated in 1 clinical trial; consider benefit to risk when deciding to vaccinate infants with immunodeficient close contacts; handwashing is recommended after diaper changes to help prevent spreading of vaccine virus [8] .

Due to an increased risk of infection, if an infant has been exposed to IgG antibody (ie, golimumab, infliximab) in utero, administration of live vaccines, such as rotavirus vaccine, is not recommended until 6 months after the mother's last injection in pregnancy [4] [5] .

Pharmacology

Rotarix® is a human-derived rotavirus vaccine from the 89-12 strain, which belongs to G1P[8] type. The lyophilized vaccine contains amino acids, dextran, Dulbecco's Modified Eagle Medium, sorbitol, and sucrose. The liquid diluent contains calcium carbonate (to protect the vaccine during passage through the stomach and prevent inactivation), sterile water, and xanthan [3] .
Fecal shedding after vaccination was reported in approximately 26% of vaccinated infants, in two studies. Peak excretion occurred around day 7 after the first dose. Transmission of virus was not evaluated, and the potential for transmission of vaccine virus is not known.
Approximately 80% of Rotarix® recipients will be seroconverted one to two months after a 2-dose series [3] .
Rotarix® may be coadministered with other routine childhood vaccines (DTaP, Hib, IPV, hepatitis B, and pneumococcal conjugate); immune response to any of the vaccine antigens was not altered in clinical trials [2] .

Adverse Effects

Kawasaki disease was reported in 18 (0.035%) recipients of Rotarix® and 9 (0.021%) placebo recipients from 16 completed or ongoing clinical trials. Of the 27 cases, 5 occurred following Rotarix® in clinical trials that were either not placebo-controlled or 1:1 randomized. Three of the 27 cases (2 cases Rotarix®, 1 case placebo) were reported within 30 days post-vaccination. Kawasaki disease was reported in 17 Rotarix® recipients and 9 placebo recipients (relative risk, 1.71; 95% confidence interval, 0.71 to 4.38) in placebo-controlled trials. Among recipients of Rotarix®, the time of onset after study dose ranged from 3 days to 19 months [3] .

Special Considerations/Preparation

Rotarix® is supplied as a vial of lyophilized vaccine, a prefilled oral applicator of liquid diluent (1 mL) with a plunger stopper, and a transfer adapter for reconstitution. The vaccine contains no preservatives. Oral applicator contains latex rubber. Lyophilized vials should be refrigerated and protected from light, and the diluent can be stored at room temperature.
Do not freeze, and discard vaccine if frozen.
Reconstituted vaccine may be stored refrigerated or at room temperature, and vaccine should be administered within 24 hours of reconstitution. Discard if not used within 24 hours.
Do not mix with other vaccines or solutions [3] .

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- Product Information: SIMPONI(R) solution for subcutaneous injection, golimumab solution for subcutaneous injection. Janssen Biotech, Inc. (per Manufacturer), Horsham, PA, Sep, 2011.

- Product Information: REMICADE(R) intravenous injection lyophilized concentrate, infliximab intravenous injection lyophilized concentrate. Janssen Biotech, Inc. (per manufacturer), Horsham, PA, Oct, 2011.

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- Product Information: ROTARIX(R) oral suspension, rotavirus vaccine live oral suspension. GlaxoSmithKline (per FDA), Research Triangle Park, NC, Sep, 2012.

1.166 Sildenafil

Title Sildenafil

Dose

IV: Administer a loading dose of 0.4 mg/kg over 3 hours, followed by a continuous infusion of 1.6 mg/kg/day (0.067 mg/kg/hour). These data are based on a dose-escalation trial (n=36) and not an efficacy trial [1] .

Oral: 0.5 to 2 mg/kg/dose every 6 to 12 hours [2] [3] .
Some authors have successfully used doses of 3 mg/kg/dose orally every 6 hours in term and post-term neonates [4] .
Pharmacokinetics of sildenafil in neonates are highly variable [5] . Careful dose titration while monitoring oxygenation and blood pressure is required.

Uses

Limited to treatment of patients with persistent pulmonary hypertension (PPHN) refractory to inhaled nitric oxide (iNO) and other conventional therapies, those who are persistently unable to be weaned off of inhaled nitric oxide, or in situations where nitric oxide and high frequency ventilation are not available. According to an intervention review of the use of sildenafil in neonates with PPHN, sildenafil was associated with a significant reduction in mortality with a number need to treat to benefit of 3. All studies included in the review were in resource-limited settings [6] . In a prospective, randomized trial (n=65), oral sildenafil was more effective than magnesium sulfate in a setting without iNO or high frequency ventilation based on time to adequate effect, duration of mechanical ventilation, and use of inotropic support [2] .
Sildenafil has been reported to improve pulmonary blood flow in patients with severe Ebstein's anomaly [7] .
A retrospective study (n=7) reported reductions in pulmonary hypertension, and improved respiratory status and oxygenation in neonates with congenital diaphragmatic hernia (CDH) with pulmonary hypertension refractory to inhaled nitric oxide [8] .
Another report from a single center documented increasing use of sildenafil in neonates with CDH and pulmonary hypertension between the years 2000 and 2006 (from 0% to 45%, respectively) despite limited evidence to support its use. No outcomes data were available [9] .

Pharmacology

Sildenafil is a selective phosphodiesterase type-5 (PDE5) inhibitor. This inhibition leads to accumulation of cyclic GMP in pulmonary smooth muscle cells, causing pulmonary vascular relaxation. It may also potentiate the effect of inhaled nitric oxide.
Pharmacokinetics in neonates receiving sildenafil, both intravenously and orally, are highly variable [12] [5] . Oral absorption is rapid in adults with approximately 40% bioavailability; peak concentrations are reached in 30 to 120 minutes. Protein binding is 94%. It is metabolized primarily by hepatic CYP3A4 to an active metabolite (N-desmethyl sildenafil) that also has PDE5 inhibitory activity [13] . The terminal half-life of sildenafil in neonates on Day 1 of life is estimated to be 56 hours, and that of the metabolite 10 hours. This compares to adult data where both sildenafil and the metabolite have terminal half-lives of 4 hours. Clearance increases rapidly (triples) in the first week of life, likely related to both maturation and improvements in patient hemodynamics. Patients with significant hepatic or renal dysfunction have reduced clearance. Significant increases in sildenafil concentrations may occur when used concomitantly with drugs that are CYP3A4 inhibitors: eg, fluconazole, erythromycin, amlodipine, and cimetidine [13] .

Adverse Effects

Use in neonates should be restricted and considered experimental. Data in neonates remain limited. The most concerning short-term adverse effects are worsening oxygenation and systemic hypotension [1] . There is one case report of bleeding after circumcision in a neonate receiving chronic therapy [10] . Use with caution in infants with sepsis. Sildenafil causes transient impairment of color discrimination in adults, and there is concern that it could increase the risk of severe retinopathy of prematurity if used in extremely premature infants. In a study of neonates receiving sildenafil for at least weeks (n=22), positive ocular findings were reported in 4 patients, none of which were considered drug-related [11] .

Monitoring

Continuous monitoring of blood pressure and oxygenation [1] .

Special Considerations/Preparation

Oral Revatio® is supplied as 20-mg tablets and an oral suspension [14] . Viagra® is supplied as 25-mg, 50-mg, and 100-mg tablets.
Revatio® oral suspension must be constituted by the pharmacist prior to dispensing to the patient. To prepare the oral solution, shake the Revatio® bottle to loosen the powder. Remove the cap and add 60 mL of water. Shake the closed bottle for a minimum of 30 seconds. Open the bottle and add an additional 30 mL of water and shake the closed bottle for another 30 seconds. The prepared solution contains sildenafil 10 mg per 1 mL. Once reconstituted, the oral solution should be stored below 30 degrees C (86 degrees F) or in the refrigerator for up to 30 days. Do not freeze [14] .
The Revatio® oral suspension is supplied as an off-white powder for constitution, forming a white to off-white grape flavored solution, which when constituted with water as directed contains 10 mg/mL of sildenafil. Available in glass bottles containing approximately 112 mL of solution after constitution; a press-in bottle adaptor and oral syringe are supplied with each bottle. The inactive ingredients of sildenafil oral solution include sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous and grape flavor [14] .
Intravenous Revatio® is supplied as a single-use vial containing 10 mg (12.5 mL) of sildenafil, equivalent to 0.8 mg sildenafil per mL. Each mL of solution also contains 50.5 mg dextrose and water for injection [13] .

To prepare an oral 2.5-mg/mL suspension (150 mL), thoroughly crush fifteen (15) 25-mg tablets into a fine powder and add a 1:1 mixture of Ora-Sweet® and Ora-Plus® or methylcellulose 1% and Simple Syrup, NF to make a final concentration of 2.5 mg/mL. Suspension is stable for 91 days in plastic bottles at 4 and 25 degrees C [15] . This extemporaneous suspension was made using the Viagra® (sildenafil) dosage form.

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- Product Information: REVATIO(R) IV injection, oral tablets, sildenafil IV injection, oral tablets. Pfizer Labs, New York, NY, Nov, 2010.

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1.167 SimilacÂ® Human Milk Fortifier

Title SimilacÂ® Human Milk Fortifier

Table

Similac® Human Milk Fortifier

Nutrient	per 1 pk	per 4 pks
Energy, Cal	3.5	14.4
Protein, g	0.25	1
Fat, g	0.09	0.36
Linoleic acid, mg	-	-
Carbohydrate, g	0.45	1.8
Minerals		
Calcium, mg (mEq)	29.25 (1.46)	117 (5.84)
Phosphorus, mg (mEq)	16.8 (0.54)	67 (2.16)
Magnesium, mg	1.75	7
Iron, mg	0.08*	0.35*
Zinc, mg	0.26	1
Manganese, mcg	1.8	7.2
Copper, mcg	42.5	170
Iodine, mcg	-	-
Selenium, mcg	-	-
Sodium, mg (mEq)	3.75 (0.16)	15 (0.65)

Potassium, mg (mEq)	15.75 (0.4)	63 (1.61)
Chloride, mg (mEq)	9.5 (0.27)	38 (1.07)
Vitamins		
Vitamin A, IU	155	620
Vitamin D, IU	30	120
Vitamin E, IU	0.8	3.2
Vitamin K, mcg	2.07	8.3
Thiamine (B 1), mcg	58.3	233
Riboflavin (B 2), mcg	104	417
Vitamin B 6 , mcg	53	211
Vitamin B 12 , mcg	0.16	0.64
Niacin, mcg	893	3570
Folic acid (Folacin), mcg	5.75	23
Pantothenic acid, mcg	375	1500
Biotin, mcg	6.6	26
Vitamin C (Ascorbic acid), mg	6.3	25
Choline, mg	0.5	2
Inositol, mg	0.96	3.9
Renal Solute Load , mOsm	2.8	11.2

* Additional iron should be supplied from other sources.

Precautions: Nutritionally incomplete. Tolerance to enteral feedings should be confirmed by offering small volumes of unfortified human milk. Once enteral feeding is well established, Similac Human Milk Fortifier can be added.

Title SimilacÂ® Human Milk Fortifier

Table

Similac® Human Milk Fortifier

Nutrient	**per 1 pk**	**per 4 pks**
Energy, Cal	3.5	14.4
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Fat, g	0.09	0.36
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Calcium, mg (mEq)	29.25 (1.46)	117 (5.84)
Phosphorus, mg (mEq)	16.8 (0.54)	67 (2.16)
Magnesium, mg	1.75	7
Iron, mg	0.08*	0.35*
Zinc, mg	0.26	1
Manganese, mcg	1.8	7.2
Copper, mcg	42.5	170
Iodine, mcg	-	-
Selenium, mcg	-	-
Sodium, mg (mEq)	3.75 (0.16)	15 (0.65)
Potassium, mg (mEq)	15.75 (0.4)	63 (1.61)
Chloride, mg (mEq)	9.5 (0.27)	38 (1.07)
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Precautions: Nutritionally incomplete. Tolerance to enteral feedings should be confirmed by offering small volumes of unfortified human milk. Once enteral feeding is well established, Similac Human Milk Fortifier can be added.

1.168 Sodium Bicarbonate

Title Sodium Bicarbonate

Dose

Dosage based on base deficit:
HCO_3 needed (mEq) = HCO_3 deficit (mEq/L) x (0.3 x body wt [kg])
Administer half of calculated dose, then assess need for remainder.

Usual dosage: 1 to 2 mEq/kg IV over at least 30 minutes.

Administration

Intravenous: Administer slow IV push. According to the manufacturer, for infants less than 2 years of age, the administration rate should not exceed 10 mL/minute. The recommended concentration for IV administration in neonates is the 4.2% strength (0.5 mEq/mL) [1] [2] . Can also be administered by continuous IV infusion.
Can also be administered by the intraosseous route or orally.

Uses

Treatment of normal anion gap metabolic acidosis caused by renal or gastrointestinal losses.

Sodium bicarbonate is not a recommended therapy in neonatal resuscitation guidelines. Administration during brief CPR may be detrimental. Administration during prolonged resuscitation remains controversial; use only after adequate ventilation is established and there is no response to other therapies.

Pharmacology

When bicarbonate is administered, buffering of hydrogen ions occurs, leading to increased production of carbon dioxide and water. Animal studies of resuscitation demonstrate poor coronary perfusion leads to carbon dioxide accumulation within the myocardium, leading to decreased myocardial contractility.

Adverse Effects

Bicarbonate administered during inadequate ventilation increases PCO_2, thereby decreasing pH. Rapid infusion of hypertonic solution is linked to intracranial hemorrhage in neonates and infants. Extravasation may cause local tissue necrosis at IV site. Fluid overload, hypocalcemia, hypokalemia, and hypernatremia may occur. Aggressive therapy may result in metabolic alkalosis (associated with muscle twitching, irritability, and tetany) [3] [2] [4] .

Monitoring

Monitor ABGs, acid/base status, and serum calcium and potassium [2] .

Special Considerations/Preparation

Supplied by many manufacturers in multiple concentrations: 4% (0.48 mEq/mL), 4.2% (0.5 mEq/mL; 1 mOsmol/mL), 5% (0.6 mEq/mL; 1.19 mOsmol/mL), 7.5% (0.9 mEq/mL; 1.79 mOsmol/mL) and 8.4% (1 mEq/mL; 2 mOsmol/mL). Maximum concentration used in neonates is 4.2% (0.5 mEq/mL). May dilute with sterile water for injection. Do not infuse with calcium or phosphate containing solutions; precipitation will occur.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, amphotericin B, atropine, aztreonam, cefepime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, esmolol, famotidine, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, insulin, lidocaine, linezolid, milrinone, morphine, nafcillin, netilmicin, penicillin G, phenobarbital, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Dex/AA. Amiodarone, ampicillin, calcium chloride, cefotaxime, dobutamine, dopamine, epinephrine, glycopyrrolate, imipenem/cilastatin, isoproterenol, magnesium sulfate, meropenem, methadone, metoclopramide, midazolam, nicardipine, norepinephrine, oxacillin, phenytoin, and ticarcillin/clavulanate.

References

- Aschner JL, Poland RL: Sodium bicarbonate: basically useless therapy. *Pediatrics* 2008;122:831-835.
- van Alfen-van der Velden AA, Hopman JC, Klaessens JH, et al: Effects of rapid versus slow infusion of sodium bicarbonate on cerebral hemodynamics and oxygenation in preterm infants. *Biol Neonate* 2006;90:122-127.
- Lokesh L, Kumar P, Murki S, Narang A. A randomized controlled trial of sodium bicarbonate in neonatal resuscitation - effect on immediate outcome. *Resuscitation* 2004;60:219-23.
- Murki M, Kumar P, Lingappa L, Narang A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life. *Journal of Perinatology* 2004;24:696-9.
- Ammari AN, Schulze KF: Uses and abuses of sodium bicarbonate in the neonatal intensive care unit. *Curr Opin Pediatr* 2002;14:151-156.
- Wyckoff MH, Perlman J, Niermeyer S: Medications during resuscitation - what is the evidence? *Semin Neonatol* 2001;6:251-259.
- Howell JH: Sodium bicarbonate in the perinatal setting--revisited. *Clin Perinatol* 1987;14:807.
- Product Information, Hospira, 2004.

1. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
2. Product Information: sodium bicarbonate IV injection, sodium bicarbonate IV injection. Hospira,Inc, Lake Forest, IL, Jan1, 2006.
3. Andrade OV: Metabolic acidosis in childhood: why, when and how to treat. J Pediatr (Rio J) May, 2007; 83(2 Suppl): S11-S21.
4. Forsythe SM: Sodium bicarbonate for the treatment of lactic acidosis. Chest 2000; 117(1): 260-267.

Title Sodium Bicarbonate

Dose

Dosage based on base deficit:
HCO_3 needed (mEq) = HCO_3 deficit (mEq/L) x (0.3 x body wt [kg])
Administer half of calculated dose, then assess need for remainder.

Usual dosage: 1 to 2 mEq/kg IV over at least 30 minutes.

Administration

Intravenous: Administer slow IV push. According to the manufacturer, for infants less than 2 years of age, the administration rate should not exceed 10 mL/minute. The recommended concentration for IV administration in neonates is the 4.2% strength (0.5 mEq/mL) [1] [2] . Can also be administered by continuous IV infusion.
Can also be administered by the intraosseous route or orally.

Uses

Treatment of normal anion gap metabolic acidosis caused by renal or gastrointestinal losses.

Sodium bicarbonate is not a recommended therapy in neonatal resuscitation guidelines. Administration during brief CPR may be detrimental. Administration during prolonged resuscitation remains controversial; use only after adequate ventilation is established and there is no response to other therapies.

Pharmacology

When bicarbonate is administered, buffering of hydrogen ions occurs, leading to increased production of carbon dioxide and water. Animal studies of resuscitation demonstrate poor coronary perfusion leads to carbon dioxide accumulation within the myocardium, leading to decreased myocardial contractility.

Adverse Effects

Bicarbonate administered during inadequate ventilation increases PCO_2, thereby decreasing pH. Rapid infusion of hypertonic solution is linked to intracranial hemorrhage in neonates and infants. Extravasation may cause local tissue necrosis at IV site. Fluid overload, hypocalcemia, hypokalemia, and hypernatremia may occur. Aggressive therapy may result in metabolic alkalosis (associated with muscle twitching, irritability, and tetany) [3] [2] [4] .

Monitoring

Monitor ABGs, acid/base status, and serum calcium and potassium [2] .

Special Considerations/Preparation

Supplied by many manufacturers in multiple concentrations: 4% (0.48 mEq/mL), 4.2% (0.5 mEq/mL; 1 mOsmol/mL), 5% (0.6 mEq/mL; 1.19 mOsmol/mL), 7.5% (0.9 mEq/mL; 1.79 mOsmol/mL) and 8.4% (1 mEq/mL; 2 mOsmol/mL). Maximum

concentration used in neonates is 4.2% (0.5 mEq/mL). May dilute with sterile water for injection. Do not infuse with calcium or phosphate containing solutions; precipitation will occur.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Acyclovir, amikacin, aminophylline, amphotericin B, atropine, aztreonam, cefepime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, erythromycin lactobionate, esmolol, famotidine, furosemide, heparin, hydrocortisone succinate, ibuprofen lysine, indomethacin, insulin, lidocaine, linezolid, milrinone, morphine, nafcillin, netilmicin, penicillin G, phenobarbital, piperacillin/tazobactam, potassium chloride, propofol, remifentanil, vancomycin, and vitamin K_1.

Terminal Injection Site Incompatibility

Dex/AA. Amiodarone, ampicillin, calcium chloride, cefotaxime, dobutamine, dopamine, epinephrine, glycopyrrolate, imipenem/cilastatin, isoproterenol, magnesium sulfate, meropenem, methadone, metoclopramide, midazolam, nicardipine, norepinephrine, oxacillin, phenytoin, and ticarcillin/clavulanate.

References

- Aschner JL, Poland RL: Sodium bicarbonate: basically useless therapy. *Pediatrics* 2008;122:831-835.
- van Alfen-van der Velden AA, Hopman JC, Klaessens JH, et al: Effects of rapid versus slow infusion of sodium bicarbonate on cerebral hemodynamics and oxygenation in preterm infants. *Biol Neonate* 2006;90:122-127.
- Lokesh L, Kumar P, Murki S, Narang A. A randomized controlled trial of sodium bicarbonate in neonatal resuscitation - effect on immediate outcome. *Resuscitation* 2004;60:219-23.
- Murki M, Kumar P, Lingappa L, Narang A. Effect of a single dose of sodium bicarbonate given during neonatal resuscitation at birth on the acid-base status on first day of life. *Journal of Perinatology* 2004;24:696-9.
- Ammari AN, Schulze KF: Uses and abuses of sodium bicarbonate in the neonatal intensive care unit. *Curr Opin Pediatr* 2002;14:151-156.
- Wyckoff MH, Perlman J, Niermeyer S: Medications during resuscitation - what is the evidence? *Semin Neonatol* 2001;6:251-259.
- Howell JH: Sodium bicarbonate in the perinatal setting--revisited. *Clin Perinatol* 1987;14:807.
- Product Information, Hospira, 2004.

1. Hegenbarth MA: Preparing for pediatric emergencies: drugs to consider. Pediatrics Feb, 2008; 121(2): 433-443.
2. Product Information: sodium bicarbonate IV injection, sodium bicarbonate IV injection. Hospira,Inc, Lake Forest, IL, Jan1, 2006.

3. Andrade OV: Metabolic acidosis in childhood: why, when and how to treat. J Pediatr (Rio J) May, 2007; 83(2 Suppl): S11-S21.
4. Forsythe SM: Sodium bicarbonate for the treatment of lactic acidosis. Chest 2000; 117(1): 260-267.

1.169 Sodium Chloride (0.9%)

Title Sodium Chloride (0.9%)

Dose

Resuscitation (volume expansion):10 mL/kg IV over 5 to 10 minutes. Consider a second dose of 10 mL/kg if there is no significant improvement after the first dose. Normal saline is the recommended volume expander. Lactated Ringer's is an acceptable alternative [1] .

Administration

For resuscitation (volume expansion), give over 5 to 10 minutes. Consider a longer duration of administration in preterm neonates less than 30 weeks GA [1] .

Uses

Resuscitation. Volume expanders should be considered in neonates with clinically apparent hypovolemia, but should not be used in the absence of evidence of acute blood loss. Normal saline (sodium chloride 0.9%) is the preferred isotonic crystalloid solution, and Lactated Ringer's is an acceptable alternative. In babies with severe fetal anemia, O Rh-negative packed red blood cells should be considered as part of volume expansion [1] .

Contraindications/Precautions

Large fluid volumes can decrease cardiac output in hypoxic infants. Avoid rapid administration of volume expanders due to the risk for intracranial hemorrhage. Rapid administration of packed red blood cells may precipitate heart failure [1] .

Monitoring

Monitor heart rate, blood pressure.

References

- Kattwinkel J: Neonatal Resuscitation Textbook, 6th ed ed. American Heart Association; American Academy of Pediatrics, Elk Grove Village, IL, 2011.

Title Sodium Chloride (0.9%)

Dose

Resuscitation (volume expansion):10 mL/kg IV over 5 to 10 minutes. Consider a second dose of 10 mL/kg if there is no significant improvement after the first dose.

Normal saline is the recommended volume expander. Lactated Ringer's is an acceptable alternative [1] .

Administration

For resuscitation (volume expansion), give over 5 to 10 minutes. Consider a longer duration of administration in preterm neonates less than 30 weeks GA [1] .

Uses

Resuscitation. Volume expanders should be considered in neonates with clinically apparent hypovolemia, but should not be used in the absence of evidence of acute blood loss. Normal saline (sodium chloride 0.9%) is the preferred isotonic crystalloid solution, and Lactated Ringer's is an acceptable alternative. In babies with severe fetal anemia, O Rh-negative packed red blood cells should be considered as part of volume expansion [1] .

Contraindications/Precautions

Large fluid volumes can decrease cardiac output in hypoxic infants. Avoid rapid administration of volume expanders due to the risk for intracranial hemorrhage. Rapid administration of packed red blood cells may precipitate heart failure [1] .

Monitoring

Monitor heart rate, blood pressure.

References

- Kattwinkel J: Neonatal Resuscitation Textbook, 6th ed ed. American Heart Association; American Academy of Pediatrics, Elk Grove Village, IL, 2011.

1.170 Sodium Glycerophosphate

Title Sodium Glycerophosphate

Dose

Phosphate Supplement:1 to 1.5 mmol/kg/day, individualized to needs of patient [1] .

Administration

Must not be administered undiluted. Administer over no less than 8 hours [1] .

Uses

Phosphate supplementation: After administration of sodium glycerophosphate 1.5 mmol/kg/day, mean increases in plasma phosphorus concentrations were 0.53+/-0.08 mmol/L at 12 hours, 0.72 +/-0.3 mmol/L at 36 hours, and 0.9+/-0.3 mmol/L at 60 hours (p less than 0.0001 for all values) from a baseline of less than 0.5 mmol/L in a

retrospective report of very low birthweight neonates with hypophosphatemia receiving parenteral nutrition (n=19; mean gestational age 28+/-3 weeks). All patients had been receiving parenteral nutrition solutions with inorganic calcium and phosphorus salts at the limit of solubility when hypophosphatemia resulted. The switch to sodium glycerophosphate as the sole phosphorus source not only increased the amount of phosphorus that could be administered each day, but also allowed an increase in the amount of calcium infused to 1.5 mmol/kg/day. By 60 hours, all patients had achieved a plasma phosphorus concentration of 1.5 mmol/L or greater [2] .

Pediatric FDA Approved Indications
Because of the critical shortage of phosphate injection in the United States market, an alternative imported formulation of Glycophos™ has been made available; however, it is not approved by the US Food and Drug Administration [3] .

Contraindications/Precautions

Contraindicated in patients with dehydration, hypernatremia, hyperphosphatemia, severe renal insufficiency, or shock [1] .

Product contains 2 mEq/mL of sodium. Use with caution in patients with renal impairment [1] .
Barcodes on the Glycophos™ product will not be recognized by scanning systems used in the US and should not be used. The product should be manually input into the system. Alternate procedures should be put in place to assure that the correct drug product is being prepared and administered to the patient [3] .

Pharmacology

Sodium glycerophosphate is an organic phosphate, which is different from the inorganic phosphate products usually used in the US [3] . Organic phosphates tend to be more compatible with calcium, such that solutions of calcium and phosphate may exist at higher concentrations without precipitation and, at higher pH (greater than 6), organic phosphate is less likely to precipitate [3] . It is used as an IV nutritional supplement when plasma phosphate concentrations are low. Bioavailability is dependant on hydrolysis of the phosphate group from the glycerophosphate molecule, which occurs most efficiently at plasma concentrations of greater than 0.7 mmol/L. Normal serum alkaline phosphatase is capable of hydrolyzing approximately 12 to 15 mmol of sodium glycerophosphate each day. Pharmacokinetic data not available for infants [1] .

Adverse Effects

No adverse effects of sodium glycerophosphate have been reported [2] [1] .

Monitoring

Regularly monitor phosphate status [1] .

Special Considerations/Preparation

Glycophos™ (sodium glycerophosphate) is a preservative-free concentrated solution (pH 7.4) containing 2 mEq/mL of sodium and 1 mmol/mL of phosphate in a 20-mL single-dose plastic vial [3] . Do not store above 25 degrees C. Do not freeze. Discard vial after use [1] .
Note: Glycophos™ contains **1 mmol/mL** of organic phosphate. Sodium and potassium phosphate products typically used in the US are **3 mmol/mL** of inorganic phosphate [3] .

Solution Compatibility

Up to 10 mL of Glycophos™ and 10 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of D_5W [1] .
Up to 20 mL of Glycophos™ and 20 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{20}W$ [1] .
Up to 60 mL of Glycophos™ and 24 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{50}W$ [1] .
As a reference only (these products are not available in the US), up to 120 mL of Glycophos™ and 48 mmol of calcium (as $CaCl_2$) may be added to the following amino acid solutions (1000 mL) [1] :

- Vamin 14 (Ca 5 mmol/L; pH 5.4 to 5.8; amino acids 8.5%; nitrogen 13.5 g/L)
- Vamin 14 (pH 5.4 to 5.8, amino acids 8.5%; nitrogen 13.5 g/L) electrolyte free
- Vamin 18 (pH 5.4 to 5.8; amino acids 11.4%; nitrogen 18 g/L) electrolyte free
- Vaminolact (pH 5.2; amino acids 6.53%; nitrogen 9.3 g/L)More complete information on the composition of these products is available [4] [5] .

References

- Product Information: GLYCOPHOS(TM) intravenous injection, sodium glycerophosphate anhydrous intravenous injection. Fresenius Kabi USA, LLC (per DailyMed), Lake Zurich, IL, May, 2013.
- Costello I: Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. Arch Dis Child Fetal Neonatal Ed Jul, 1995; 73(1): F44-F45.
- Fresenius Kabi USA, LLC: Dear Healthcare Professional letter for Glycophos(TM) (sodium glycolate). U.S. Food and Drug Administration, Silver Spring, MD, May29, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM354277.pdf.
- Product Information: VAMIN(R) VAMIN(R) 14, VAMIN(R) 14 Electrolyte Free and VAMIN(R) 18 Electrolyte Free intravenous injection solution, amino acids intravenous injection solution. Fresenius Kabi Australia Pty Limited (per Manufacturer), Pymble, Australia, Mar, 2010.
- Product Information: VAMINOLACT intravenous injection solution, amino acid intravenous injection solution. Fresenius Kabi New Zealand Limited (per manufacturer), Auckland, New Zealand, Mar, 2010.

Title Sodium Glycerophosphate

Dose

Phosphate Supplement:1 to 1.5 mmol/kg/day, individualized to needs of patient [1] .

Administration

Must not be administered undiluted. Administer over no less than 8 hours [1] .

Uses

Phosphate supplementation: After administration of sodium glycerophosphate 1.5 mmol/kg/day, mean increases in plasma phosphorus concentrations were 0.53+/-0.08 mmol/L at 12 hours, 0.72 +/-0.3 mmol/L at 36 hours, and 0.9+/-0.3 mmol/L at 60 hours (p less than 0.0001 for all values) from a baseline of less than 0.5 mmol/L in a retrospective report of very low birthweight neonates with hypophosphatemia receiving parenteral nutrition (n=19; mean gestational age 28+/-3 weeks). All patients had been receiving parenteral nutrition solutions with inorganic calcium and phosphorus salts at the limit of solubility when hypophosphatemia resulted. The switch to sodium glycerophosphate as the sole phosphorus source not only increased the amount of phosphorus that could be administered each day, but also allowed an increase in the amount of calcium infused to 1.5 mmol/kg/day. By 60 hours, all patients had achieved a plasma phosphorus concentration of 1.5 mmol/L or greater [2] .

Pediatric FDA Approved Indications
Because of the critical shortage of phosphate injection in the United States market, an alternative imported formulation of Glycophos™ has been made available; however, it is not approved by the US Food and Drug Administration [3] .

Contraindications/Precautions

Contraindicated in patients with dehydration, hypernatremia, hyperphosphatemia, severe renal insufficiency, or shock [1] .

Product contains 2 mEq/mL of sodium. Use with caution in patients with renal impairment [1] .
Barcodes on the Glycophos™ product will not be recognized by scanning systems used in the US and should not be used. The product should be manually input into the system. Alternate procedures should be put in place to assure that the correct drug product is being prepared and administered to the patient [3] .

Pharmacology

Sodium glycerophosphate is an organic phosphate, which is different from the inorganic phosphate products usually used in the US [3] . Organic phosphates tend to be more compatible with calcium, such that solutions of calcium and phosphate may exist at higher concentrations without precipitation and, at higher pH (greater than 6), organic phosphate is less likely to precipitate [3] . It is used as an IV nutritional supplement when plasma phosphate concentrations are low. Bioavailability is

dependant on hydrolysis of the phosphate group from the glycerophosphate molecule, which occurs most efficiently at plasma concentrations of greater than 0.7 mmol/L. Normal serum alkaline phosphatase is capable of hydrolyzing approximately 12 to 15 mmol of sodium glycerophosphate each day. Pharmacokinetic data not available for infants [1] .

Adverse Effects

No adverse effects of sodium glycerophosphate have been reported [2] [1] .

Monitoring

Regularly monitor phosphate status [1] .

Special Considerations/Preparation

Glycophos™ (sodium glycerophosphate) is a preservative-free concentrated solution (pH 7.4) containing 2 mEq/mL of sodium and 1 mmol/mL of phosphate in a 20-mL single-dose plastic vial [3] . Do not store above 25 degrees C. Do not freeze. Discard vial after use [1] .
Note: Glycophos™ contains **1 mmol/mL** of organic phosphate. Sodium and potassium phosphate products typically used in the US are **3 mmol/mL** of inorganic phosphate [3] .

Solution Compatibility

Up to 10 mL of Glycophos™ and 10 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of D_5W [1] .
Up to 20 mL of Glycophos™ and 20 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{20}W$ [1] .
Up to 60 mL of Glycophos™ and 24 mmol of calcium (as $CaCl_2$) may be added to 1000 mL of $D_{50}W$ [1] .
As a reference only (these products are not available in the US), up to 120 mL of Glycophos™ and 48 mmol of calcium (as $CaCl_2$) may be added to the following amino acid solutions (1000 mL) [1] :

- Vamin 14 (Ca 5 mmol/L; pH 5.4 to 5.8; amino acids 8.5%; nitrogen 13.5 g/L)
- Vamin 14 (pH 5.4 to 5.8, amino acids 8.5%; nitrogen 13.5 g/L) electrolyte free
- Vamin 18 (pH 5.4 to 5.8; amino acids 11.4%; nitrogen 18 g/L) electrolyte free
- Vaminolact (pH 5.2; amino acids 6.53%; nitrogen 9.3 g/L)More complete information on the composition of these products is available [4] [5] .

References

- Product Information: GLYCOPHOS(TM) intravenous injection, sodium glycerophosphate anhydrous intravenous injection. Fresenius Kabi USA, LLC (per DailyMed), Lake Zurich, IL, May, 2013.

- Costello I: Sodium glycerophosphate in the treatment of neonatal hypophosphataemia. Arch Dis Child Fetal Neonatal Ed Jul, 1995; 73(1): F44-F45.

- Fresenius Kabi USA, LLC: Dear Healthcare Professional letter for Glycophos(TM) (sodium glycolate). U.S. Food and Drug Administration, Silver Spring, MD, May29, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM354277.pdf.

- Product Information: VAMIN(R) VAMIN(R) 14, VAMIN(R) 14 Electrolyte Free and VAMIN(R) 18 Electrolyte Free intravenous injection solution, amino acids intravenous injection solution. Fresenius Kabi Australia Pty Limited (per Manufacturer), Pymble, Australia, Mar, 2010.

- Product Information: VAMINOLACT intravenous injection solution, amino acid intravenous injection solution. Fresenius Kabi New Zealand Limited (per manufacturer), Auckland, New Zealand, Mar, 2010.

1.171 Sodium Nitroprusside

Title Sodium Nitroprusside

Dose

Initial Dose: 0.25 to 0.5 mcg/kg/minute continuous IV infusion.
Titrate dose upward every 20 minutes until desired response is attained.
Usual **maintenance dose** is less than 2 mcg/kg per minute.
For hypertensive crisis, may use up to 10 mcg/kg per minute, but for no longer than 10 minutes.
Sodium thiosulfate has been coadministered with sodium nitroprusside to accelerate the metabolism of cyanide; however, this has not been extensively studied.

Administration

Administer as a continuous IV infusion at a concentration of 50 to 200 mcg/mL (0.05 to 0.2 mg/mL). Use a large vein for IV. Protect infusion from light during administration (not necessary to cover tubing).

Uses

Acute treatment of hypertensive emergencies. Acute afterload reduction in patients with refractory congestive heart failure.

Black Box Warning According to the manufacturer's black box warning, nitroprusside is not suitable for direct injection; the reconstituted solution must be further diluted in sterile 5% dextrose injection before infusion. Nitroprusside can cause precipitous decreases in blood pressure; monitor blood pressure continuously while patient is on therapy. Monitor acid-base balance and venous oxygen concentration while on therapy as these tests may indicate cyanide toxicity. Infusion at the maximum dose rate (10 mcg/kg/minute) should never last more than 10 minutes.

Pharmacology

Direct-acting nonselective (arterial and venous) vasodilator. Immediately interacts with RBC oxyhemoglobin, dissociating and forming methemoglobin with release of cyanide and nitric oxide. Rapid onset of action with a serum half-life of 3 to 4 minutes in adults. Further metabolized to thiocyanate in the liver and kidney. Thiocyanate is renally eliminated with a half-life of 4 to 7 days.

Adverse Effects

Severe hypotension and tachycardia. Cyanide toxicity may occur with prolonged treatment (greater than 3 days) and high (greater than 3 mcg/kg per minute) doses. Use with caution in liver and renal failure patients due to possible impairment of the metabolism of cyanide to thiocyanate. Extravasation can cause tissue sloughing and necrosis.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is mandatory. Daily measurement of RBC cyanide (should be less than 200 ng/mL) and serum thiocyanate (should be less than 50 mcg/mL) concentrations. Assess frequently for development of metabolic acidosis. Daily assessment of renal and hepatic function. Monitor IV site closely.

Special Considerations/Preparation

Available as powder for injection in 2 mL single-dose 50 mg vials. Reconstitute contents of vial with 2 to 3 mL of D_5W or NS. **Do not administer reconstituted drug directly from vial.**Dilute entire vial contents to a final concentration of 50 to 200 mcg/mL (0.05 to 0.2 mg/mL) in D_5W or NS. Use within 24 hours of preparation. **Protect from light** with aluminum foil or other opaque material. Blue, green or deep red discoloration indicates nitroprusside inactivation. Slight brownish discoloration is common and not significant.

Solution Compatibility

D_5W, NS, and LR only.

Terminal Injection Site Compatibility

Caffeine citrate, calcium chloride, cimetidine, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, heparin, indomethacin, insulin, isoproterenol, lidocaine, magnesium, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium, potassium chloride, procainamide, propofol, prostaglandin E_1, ranitidine, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone.

References

- Seto W, Trope A, Carfrae L, et al: Visual compatibility of sodium nitroprusside with other injectable medications given to pediatric patients. *Am J Health-Syst Pharm* 2001;58:1422-6.
- Friederich JA, Butterworth JF: Sodium nitroprusside: Twenty years and counting. *Anesth Analg* 1995;81:152.
- Benitz WE, Malachowski N, Cohen RS, et al: Use of sodium nitroprusside in neonates: Efficacy and safety. *J Pediatr* 1985;106:102.
- Roberts RJ: *Drug Therapy in Infants* Philadelphia: WB Saunders Co, 1984, p 184.
- Dillon TR, Janos GG, Meyer RA, et al: Vasodilator therapy for congestive heart failure. *J Pediatr* 1980;96:623.
- Product Information, Hospira, 2004.

Title Sodium Nitroprusside

Dose

Initial Dose: 0.25 to 0.5 mcg/kg/minute continuous IV infusion.
Titrate dose upward every 20 minutes until desired response is attained.
Usual **maintenance dose** is less than 2 mcg/kg per minute.
For hypertensive crisis, may use up to 10 mcg/kg per minute, but for no longer than 10 minutes.
Sodium thiosulfate has been coadministered with sodium nitroprusside to accelerate the metabolism of cyanide; however, this has not been extensively studied.

Administration

Administer as a continuous IV infusion at a concentration of 50 to 200 mcg/mL (0.05 to 0.2 mg/mL). Use a large vein for IV. Protect infusion from light during administration (not necessary to cover tubing).

Uses

Acute treatment of hypertensive emergencies. Acute afterload reduction in patients with refractory congestive heart failure.

Black Box Warning According to the manufacturer's black box warning, nitroprusside is not suitable for direct injection; the reconstituted solution must be further diluted in sterile 5% dextrose injection before infusion. Nitroprusside can cause precipitous decreases in blood pressure; monitor blood pressure continuously while patient is on therapy. Monitor acid-base balance and venous oxygen concentration while on therapy as these tests may indicate cyanide toxicity. Infusion at the maximum dose rate (10 mcg/kg/minute) should never last more than 10 minutes.

Pharmacology

Direct-acting nonselective (arterial and venous) vasodilator. Immediately interacts with RBC oxyhemoglobin, dissociating and forming methemoglobin with release of cyanide and nitric oxide. Rapid onset of action with a serum half-life of 3 to 4 minutes in adults. Further metabolized to thiocyanate in the liver and kidney. Thiocyanate is renally eliminated with a half-life of 4 to 7 days.

Adverse Effects

Severe hypotension and tachycardia. Cyanide toxicity may occur with prolonged treatment (greater than 3 days) and high (greater than 3 mcg/kg per minute) doses. Use with caution in liver and renal failure patients due to possible impairment of the metabolism of cyanide to thiocyanate. Extravasation can cause tissue sloughing and necrosis.

Monitoring

Continuous heart rate and intra-arterial blood pressure monitoring is mandatory. Daily measurement of RBC cyanide (should be less than 200 ng/mL) and serum thiocyanate (should be less than 50 mcg/mL) concentrations. Assess frequently for development of metabolic acidosis. Daily assessment of renal and hepatic function. Monitor IV site closely.

Special Considerations/Preparation

Available as powder for injection in 2 mL single-dose 50 mg vials. Reconstitute contents of vial with 2 to 3 mL of D_5W or NS. **Do not administer reconstituted drug directly from vial.**Dilute entire vial contents to a final concentration of 50 to 200 mcg/mL (0.05 to 0.2 mg/mL) in D_5W or NS. Use within 24 hours of preparation. **Protect from light** with aluminum foil or other opaque material. Blue, green or deep red discoloration indicates nitroprusside inactivation. Slight brownish discoloration is common and not significant.

Solution Compatibility

D_5W, NS, and LR only.

Terminal Injection Site Compatibility

Caffeine citrate, calcium chloride, cimetidine, dobutamine, dopamine, enalaprilat, epinephrine, esmolol, famotidine, furosemide, heparin, indomethacin, insulin, isoproterenol, lidocaine, magnesium, micafungin, midazolam, milrinone, morphine, nicardipine, nitroglycerin, pancuronium, potassium chloride, procainamide, propofol, prostaglandin E_1, ranitidine, and vecuronium.

Terminal Injection Site Incompatibility

Amiodarone.

References

- Seto W, Trope A, Carfrae L, et al: Visual compatibility of sodium nitroprusside with other injectable medications given to pediatric patients. *Am J Health-Syst Pharm* 2001;58:1422-6.
- Friederich JA, Butterworth JF: Sodium nitroprusside: Twenty years and counting. *Anesth Analg* 1995;81:152.

- Benitz WE, Malachowski N, Cohen RS, et al: Use of sodium nitroprusside in neonates: Efficacy and safety. *J Pediatr* 1985;106:102.
- Roberts RJ: *Drug Therapy in Infants* Philadelphia: WB Saunders Co, 1984, p 184.
- Dillon TR, Janos GG, Meyer RA, et al: Vasodilator therapy for congestive heart failure. *J Pediatr* 1980;96:623.
- Product Information, Hospira, 2004.

1.172 Sodium phenylacetate\Sodium benzoate

Title Sodium phenylacetate/Sodium benzoate

Dose

Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known CPS, OTC, or NAGS Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known ASS or ASL Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis [4] .

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Administration

Must be administered through a central line. For loading and maintenance doses, dilute sodium phenylacetate/sodium benzoate and arginine in 25 to 35 mL/kg of $D_{10}W$ prior to administration [1] [4] .

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Arginine hydrochloride should be used concomitantly with sodium phenylacetate/sodium benzoate. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [1] [2] [5] [3] [4] . Caloric supplementation, dietary protein restriction, and other ammonia lowering therapies should also be considered during acute hyperammonemic episodes [1] .

Contraindications/Precautions

Caution advised for use in patients with congestive heart failure, severe renal impairment, or other clinical conditions involving sodium retention with edema; product contains 30.5 mg of sodium per mL. Extravasation may lead to tissue necrosis; administration through central line required [1] .

Pharmacology

The use of sodium phenylacetate and sodium benzoate provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Phenylacetate is conjugated with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is excreted by the kidney and results in removal of 2 moles of waste nitrogen for each mole of phenylacetate administered. Benzoate is conjugated with glycine to form hippurate. Hippurate is excreted by the kidney and results in removal of 1 mole of waste nitrogen for each mole of benzoate administered [1] [5] [3] .

Adverse Effects

The most common adverse effects include vomiting (9%), hyperglycemia (7%), and hypokalemia (7%). Vomiting and lethargy can occur with higher than recommended doses. Hypotension seen more frequently in patients 30 days of age and less. Potentially life-threatening toxicity can occur with doses greater than 750 mg/kg per day [1] [3] .

Monitoring

Measure plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor blood glucose, electrolytes (especially potassium), and acid-base status closely during the acute phase (eg, every 4 hours). Toxicity due to ammonia scavenging drugs presents as ketoacidosis. An anion gap that is greater than 15 mEq/L or has increased by greater than 6 mEq/L from baseline may indicate drug accumulation. Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal. Assess AST and ALT levels [1] [3] [4] . Evaluate neurological status, Glasgow Coma Scale, respiratory status, CT or MRI or fundoscopic evidence of cerebral edema, and/or of gray matter and white matter damage to assess patient response to treatment. Monitor infusion site closely during infusion for signs of extravasation [1] .

Special Considerations/Preparation

Sodium phenylacetate/sodium benzoate (Ammunol®) is available as a 10%/10% solution in a single-use glass vial containing 50 mL. Contains 30.5 mg of sodium per mL.
During the admixture process, the Millex® Durapore GV 33 mm Sterile Syringe Filter (0.22 micrometer) provided by the manufacturer must be used when injecting Ammunol® into the 10% dextrose IV bag [1] .

Solution Compatibility

$D_{10}W$ and arginine hydrochloride 10%.

References

- Product Information: AMMONUL(R) IV injection, sodium phenylacetate and sodium benzoate IV injection. Ucyclyd Pharma, Inc (per FDA), Scottsdale, AZ, Jun, 2011.
- Enns GM, Berry SA, Berry GT et al: Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med May31, 2007; 356(22): 2282-2292.
- Summar M: Current strategies for the management of neonatal urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S30-S39.
- Urea Cycle Disorders Conference group : Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S1-S5.
- Batshaw ML: Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr Jan, 2001; 138(1 Suppl): S46-S54.

Title Sodium phenylacetate/Sodium benzoate

Dose

Pending Definitive Diagnosis of Urea Cycle Enzyme Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known CPS, OTC, or NAGS Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 200 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Known ASS or ASL Deficiency:
Loading dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in

combination with arginine hydrochloride 600 mg/kg as an IV infusion over 90 to 120 minutes [1] [2] [3] [4] .
Maintenance dose: Sodium phenylacetate 250 mg/kg and sodium benzoate 250 mg/kg in combination with arginine hydrochloride 600 mg/kg as an IV infusion over 24 hours [1] [2] [3] [4] .

Repeating the loading dose within 24 hours of the initial loading dose should be considered only for patients with a severe disorder receiving dialysis [4] .

CPS = carbamyl phosphate synthetase; OTC = ornithine transcarbamylase; NAGS = N-acetyl glutamate synthase; ASS = argininosuccinic acid synthetase; ASL = argininosuccinic acid lyase

Administration

Must be administered through a central line. For loading and maintenance doses, dilute sodium phenylacetate/sodium benzoate and arginine in 25 to 35 mL/kg of $D_{10}W$ prior to administration [1] [4] .

Uses

Adjunctive treatment of acute hyperammonemia in neonates with urea cycle disorders. Arginine hydrochloride should be used concomitantly with sodium phenylacetate/sodium benzoate. Hemodialysis is the primary treatment of acute hyperammonemia during the early management period [1] [2] [5] [3] [4] . Caloric supplementation, dietary protein restriction, and other ammonia lowering therapies should also be considered during acute hyperammonemic episodes [1] .

Contraindications/Precautions

Caution advised for use in patients with congestive heart failure, severe renal impairment, or other clinical conditions involving sodium retention with edema; product contains 30.5 mg of sodium per mL. Extravasation may lead to tissue necrosis; administration through central line required [1] .

Pharmacology

The use of sodium phenylacetate and sodium benzoate provides an alternative pathway for waste nitrogen excretion in patients with urea cycle disorders, attenuating the risk for ammonia- and glutamine-induced neurotoxicity. Phenylacetate is conjugated with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is excreted by the kidney and results in removal of 2 moles of waste nitrogen for each mole of phenylacetate administered. Benzoate is conjugated with glycine to form hippurate. Hippurate is excreted by the kidney and results in removal of 1 mole of waste nitrogen for each mole of benzoate administered [1] [5] [3] .

Adverse Effects

The most common adverse effects include vomiting (9%), hyperglycemia (7%), and hypokalemia (7%). Vomiting and lethargy can occur with higher than recommended doses. Hypotension seen more frequently in patients 30 days of age and less. Potentially life-threatening toxicity can occur with doses greater than 750 mg/kg per day [1] [3] .

Monitoring

Measure plasma ammonia levels every hour during dialysis until levels stabilize to less than 200 to 300 micromoles/L. Capillary blood should not be used for monitoring ammonia levels. Monitor blood glucose, electrolytes (especially potassium), and acid-base status closely during the acute phase (eg, every 4 hours). Toxicity due to ammonia scavenging drugs presents as ketoacidosis. An anion gap that is greater than 15 mEq/L or has increased by greater than 6 mEq/L from baseline may indicate drug accumulation. Monitor amino acids daily to assess the effectiveness of citrulline/arginine replacement and glutamine removal. Assess AST and ALT levels [1] [3] [4] . Evaluate neurological status, Glasgow Coma Scale, respiratory status, CT or MRI or fundoscopic evidence of cerebral edema, and/or of gray matter and white matter damage to assess patient response to treatment. Monitor infusion site closely during infusion for signs of extravasation [1] .

Special Considerations/Preparation

Sodium phenylacetate/sodium benzoate (Ammunol®) is available as a 10%/10% solution in a single-use glass vial containing 50 mL. Contains 30.5 mg of sodium per mL.
During the admixture process, the Millex® Durapore GV 33 mm Sterile Syringe Filter (0.22 micrometer) provided by the manufacturer must be used when injecting Ammunol® into the 10% dextrose IV bag [1] .

Solution Compatibility

$D_{10}W$ and arginine hydrochloride 10%.

References

- Product Information: AMMONUL(R) IV injection, sodium phenylacetate and sodium benzoate IV injection. Ucyclyd Pharma, Inc (per FDA), Scottsdale, AZ, Jun, 2011.
- Enns GM, Berry SA, Berry GT et al: Survival after treatment with phenylacetate and benzoate for urea-cycle disorders. N Engl J Med May31, 2007; 356(22): 2282-2292.
- Summar M: Current strategies for the management of neonatal urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S30-S39.
- Urea Cycle Disorders Conference group : Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr Jan, 2001; 138(1 Suppl): S1-S5.
- Batshaw ML: Alternative pathway therapy for urea cycle disorders: twenty years later. J Pediatr Jan, 2001; 138(1 Suppl): S46-S54.

1.173 Sotalol

Title Sotalol

Dose

Initial dose: 1 mg/kg/dose orally every 12 hours.
Gradually increase as needed every 3 to 5 days until stable rhythm is maintained.
Maximum dose: 4 mg/kg/dose orally every 12 hours.

Uses

Treatment of refractory ventricular and supraventricular tachyarrhythmias.

Contraindications/Precautions

Contraindicated in patients with sinus bradycardia (less than 50 beats/minute during waking hours), sick sinus syndrome or second and third degree AV block (unless functioning pacemaker present), congenital or acquired long QT syndromes, baseline QT interval greater than 450 msec, cardiogenic shock, uncontrolled heart failure, hypokalemia (less than 4 mEq/L), creatinine clearance less than 40 mL/minute, and bronchial asthma [1] .

Black Box Warning According to the manufacturer's black box warning, to minimize the risk of induced arrhythmia, patients initiated or re-initiated on sotalol should receive continuous cardiac monitoring for a minimum of three days on maintenance doses and renal function assessment [1] .

Pharmacology

Sotalol is an antiarrhythmic agent that combines Class II beta-blocking properties with Class III prolongation of cardiac action potential duration. Betapace® is a racemic mixture of *d*- and *l*-sotalol. Oral bioavailability is good, but absorption is decreased by 20% to 30% by food, especially milk. Sotalol does not bind to plasma proteins, is not metabolized, and is renally excreted as unchanged drug. Limited pharmacokinetic data in infants show a half-life of 8 hours, increasing significantly in elderly patients and those with renal dysfunction.

Adverse Effects

Proarrhythmic effects occur in 10% of pediatric patients: sinoatrial block, A-V block, torsades de pointes and ventricular ectopic activity. These effects usually occur in the first few days of treatment. Prolongation of the QT interval is dose-dependent. Other adverse effects include fatigue, dyspnea, and hypotension.

Monitoring

Frequent EKG during initiation of therapy.

Special Considerations/Preparation

Oral formulation supplied in 80-mg, 120-mg, 160-mg, and 240-mg tablets.
A 5 mg/mL oral suspension may be made as follows: crush 5 (five) 120-mg tablets and add to 120 mL of OraPlus®:OraSweet® (1:1) or 1% methylcellulose:Simple Syrup NF (1:9) in a 6-ounce amber plastic bottle. Shake to adequately suspend. Stable for 90 days at room temperature or refrigerated [1] [2] .

References

- Saul JP, Schaffer MS, Karpawich PP, et al: Single dose pharmacokinetics of sotalol in a pediatric population with supraventricular and/or ventricular tachyarrhythmia. *J Clin Pharmacol* 2001;41:35-43.
- Pfammatter JP, Paul T, Lehmann C, Kallfelz HC: Efficacy and proarrhythmia of oral sotalol in pediatric patients. *J Am Coll Cardiol* 1995;26:1002.
- Tanel RE, Walsh EP, Lulu JA, and Saul JP: Sotalol for refractory arrhythmias in pediatric and young adult patients: Initial efficacy and long-term outcome. *Am Heart J* 1995;130:791.
- Hohnloser SH, Woosley RL: Sotalol. *N Engl J Med* 1994;331:31.
- Nappi JM, McCollam PL: Sotalol: A breakthrough antiarrhythmic? *Ann Pharmacother* 1993;27:1359.
- Maragnes P, Tipple M, Fournier A: Effectiveness of oral sotalol for treatment of pediatric arrhythmias. *Am J Cardiol* 1992;69:751.
- Product Information, Berlex, 2004.

1. Product Information: BETAPACE AF(R) oral tablets, sotalol hcl oral tablets. Bayer Healthcare Pharmaceuticals,Inc, Wayne, NJ, Apr1, 2007.
2. Nahata MC: Stability of sotalol in two liquid formulations at two temperatures. Ann Pharmacother Apr, 2003; 37(4): 506-509.

Title Sotalol

Dose

Initial dose: 1 mg/kg/dose orally every 12 hours.
Gradually increase as needed every 3 to 5 days until stable rhythm is maintained.
Maximum dose: 4 mg/kg/dose orally every 12 hours.

Uses

Treatment of refractory ventricular and supraventricular tachyarrhythmias.

Contraindications/Precautions

Contraindicated in patients with sinus bradycardia (less than 50 beats/minute during waking hours), sick sinus syndrome or second and third degree AV block (unless functioning pacemaker present), congenital or acquired long QT syndromes, baseline QT interval greater than 450 msec, cardiogenic shock, uncontrolled heart failure, hypokalemia (less than 4 mEq/L), creatinine clearance less than 40 mL/minute, and bronchial asthma [1] .

Black Box Warning According to the manufacturer's black box warning, to minimize the risk of induced arrhythmia, patients initiated or re-initiated on sotalol should receive continuous

cardiac monitoring for a minimum of three days on maintenance doses and renal function assessment [1] .

Pharmacology

Sotalol is an antiarrhythmic agent that combines Class II beta-blocking properties with Class III prolongation of cardiac action potential duration. Betapace® is a racemic mixture of *d*- and *l*-sotalol. Oral bioavailability is good, but absorption is decreased by 20% to 30% by food, especially milk. Sotalol does not bind to plasma proteins, is not metabolized, and is renally excreted as unchanged drug. Limited pharmacokinetic data in infants show a half-life of 8 hours, increasing significantly in elderly patients and those with renal dysfunction.

Adverse Effects

Proarrhythmic effects occur in 10% of pediatric patients: sinoatrial block, A-V block, torsades de pointes and ventricular ectopic activity. These effects usually occur in the first few days of treatment. Prolongation of the QT interval is dose-dependent. Other adverse effects include fatigue, dyspnea, and hypotension.

Monitoring

Frequent EKG during initiation of therapy.

Special Considerations/Preparation

Oral formulation supplied in 80-mg, 120-mg, 160-mg, and 240-mg tablets.
A 5 mg/mL oral suspension may be made as follows: crush 5 (five) 120-mg tablets and add to 120 mL of OraPlus®:OraSweet® (1:1) or 1% methylcellulose:Simple Syrup NF (1:9) in a 6-ounce amber plastic bottle. Shake to adequately suspend. Stable for 90 days at room temperature or refrigerated [1] [2] .

References

- Saul JP, Schaffer MS, Karpawich PP, et al: Single dose pharmacokinetics of sotalol in a pediatric population with supraventricular and/or ventricular tachyarrhythmia. *J Clin Pharmacol* 2001;41:35-43.
- Pfammatter JP, Paul T, Lehmann C, Kallfelz HC: Efficacy and proarrhythmia of oral sotalol in pediatric patients. *J Am Coll Cardiol* 1995;26:1002.
- Tanel RE, Walsh EP, Lulu JA, and Saul JP: Sotalol for refractory arrhythmias in pediatric and young adult patients: Initial efficacy and long-term outcome. *Am Heart J* 1995;130:791.
- Hohnloser SH, Woosley RL: Sotalol. *N Engl J Med* 1994;331:31.
- Nappi JM, McCollam PL: Sotalol: A breakthrough antiarrhythmic? *Ann Pharmacother* 1993;27:1359.
- Maragnes P, Tipple M, Fournier A: Effectiveness of oral sotalol for treatment of pediatric arrhythmias. *Am J Cardiol* 1992;69:751.
- Product Information, Berlex, 2004.

1. Product Information: BETAPACE AF(R) oral tablets, sotalol hcl oral tablets. Bayer Healthcare Pharmaceuticals,Inc, Wayne, NJ, Apr1, 2007.
2. Nahata MC: Stability of sotalol in two liquid formulations at two temperatures. Ann Pharmacother Apr, 2003; 37(4): 506-509.

1.174 Spironolactone

Title Spironolactone

Dose

1 to 3 mg/kg/dose orally every 24 hours.

Uses

Used in combination with other diuretics in the treatment of congestive heart failure and BPD (situations of increased aldosterone secretion).

Contraindications/Precautions

Contraindicated with concomitant use of eplerenone, and in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hyperkalemia, or Addison's disease or other conditions associated with hyperkalemia [1] .
Concomitant use of spironolactone and potassium-sparing diuretics, potassium-containing salt substitutes, potassium supplements, ACE inhibitors, angiotensin II antagonists, aldosterone blockers, NSAIDs, or heparin or low molecular weight heparin increases the risk of severe hyperkalemia. Potassium supplementation and potassium rich diets are not recommended with spironolactone use. Dizziness and somnolence have been reported [1] .

Black Box Warning According to the manufacturer's black box warning, spironolactone has been shown to be a tumorigen in chronic animal toxicity studies.

Pharmacology

Competitive antagonist of mineralocorticoids (eg, aldosterone). Metabolized to canrenone and 7-a-thiomethylspironolactone, active metabolites with extended elimination half-lives. Decreases excretion of potassium. Highly protein bound. Increases excretion of calcium, magnesium, sodium, and chloride (small effect). Serum half-life with long term use is 13 to 24 hours. Addition of spironolactone to thiazide diuretic therapy in patients with BPD may yield little, if any, additional benefit.

Adverse Effects

Rashes, vomiting, diarrhea, paresthesias. Dose-dependent androgenic effects in females. Gynecomastia in males. Headaches, nausea, and drowsiness. Use with caution in patients with impaired renal function. May cause false positive ELISA screening tests for congenital adrenal hyperplasia.

Monitoring

Follow serum potassium closely during long-term therapy. Also, measuring urinary potassium is a useful indicator of effectiveness.

Special Considerations/Preparation

Available in 25-mg, 50-mg, and 100-mg tablets.
A 2.5- or 5-mg/mL oral suspension can be made by crushing five or ten 25-mg spironolactone tablets, respectively, and suspending the powder in 50 mL of simple syrup. Suspensions are stable for 1 month refrigerated.

To prepare 25 mg/mL oral suspension, grind one hundred twenty (120) 25-mg tablets to a fine powder in a mortar. Add 40 mL of vehicle* and mix to a uniform paste. Then add the vehicle in geometric portions and mix after each addition. Transfer contents of the mortar to the calibrated bottle and add enough vehicle to bring the total volume to 120 mL. Protect from light. Shake well. Suspension is stable for 60 days refrigerated or at room temperature (at 5 and 25 degrees C).
*Vehicles: 1:1 mixture of Ora-Sweet® and Oral-Plus®; 1:1 mixture of Ora-Sweet SF® and Oral-Plus®; or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup).

References

- Allen LV Jr, Erickson MA III: Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. *Am J Health-Syst Pharm* 1996;53:2073-2078.
- Brion LP, Primhak RA, Ambrosio-Perz I: Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease (Cochrane Review). In: *The Cochrane Library* Issue 1, 2003. Oxford: Update Software.
- Hoffman DJ, Gerdes JS, Abbasi S: Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled randomized trial. *J Perinatol* 2000;20:41-45.
- Karim A: Spironolactone: Disposition, metabolism, pharmacodynamics, and bioavailability. *Drug Metab Rev* 1978;8:151.
- Loggie JMH, Kleinman LI, Van Maanen EF: Renal function and diuretic therapy in infants and children. Part II. *J Pediatr* 1975;86:657.
- Mathur LK, Wickman A: Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989;46:2040.
- Overdiek HW, Hermens WA, Merkus FW: New insights into the pharmacokinetics of spironolactone. *Clin Pharmacol Ther* 1985;38:469.
- Terai I, Yamano K, Ichihara N, et al: Influence of spironolactone on neonatal screening for congenital adrenal hyperplasia. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F179.
- Product Information, Actavis, 2006.

1. Product Information: Aldactone(R) oral tablets, spironolactone oral tablets. G.D. Searle (per FDA), New York, NY, Jun, 2013.

Title Spironolactone

Dose

1 to 3 mg/kg/dose orally every 24 hours.

Uses

Used in combination with other diuretics in the treatment of congestive heart failure and BPD (situations of increased aldosterone secretion).

Contraindications/Precautions

Contraindicated with concomitant use of eplerenone, and in patients with anuria, acute renal insufficiency, significant impairment of renal excretory function, hyperkalemia, or Addison's disease or other conditions associated with hyperkalemia [1] .
Concomitant use of spironolactone and potassium-sparing diuretics, potassium-containing salt substitutes, potassium supplements, ACE inhibitors, angiotensin II antagonists, aldosterone blockers, NSAIDs, or heparin or low molecular weight heparin increases the risk of severe hyperkalemia. Potassium supplementation and potassium rich diets are not recommended with spironolactone use. Dizziness and somnolence have been reported [1] .

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Pharmacology

Competitive antagonist of mineralocorticoids (eg, aldosterone). Metabolized to canrenone and 7-a-thiomethylspironolactone, active metabolites with extended elimination half-lives. Decreases excretion of potassium. Highly protein bound. Increases excretion of calcium, magnesium, sodium, and chloride (small effect). Serum half-life with long term use is 13 to 24 hours. Addition of spironolactone to thiazide diuretic therapy in patients with BPD may yield little, if any, additional benefit.

Adverse Effects

Rashes, vomiting, diarrhea, paresthesias. Dose-dependent androgenic effects in females. Gynecomastia in males. Headaches, nausea, and drowsiness. Use with caution in patients with impaired renal function. May cause false positive ELISA screening tests for congenital adrenal hyperplasia.

Monitoring

Follow serum potassium closely during long-term therapy. Also, measuring urinary potassium is a useful indicator of effectiveness.

Special Considerations/Preparation

Available in 25-mg, 50-mg, and 100-mg tablets.
A 2.5- or 5-mg/mL oral suspension can be made by crushing five or ten 25-mg spironolactone tablets, respectively, and suspending the powder in 50 mL of simple syrup. Suspensions are stable for 1 month refrigerated.

To prepare 25 mg/mL oral suspension, grind one hundred twenty (120) 25-mg tablets to a fine powder in a mortar. Add 40 mL of vehicle* and mix to a uniform paste. Then add the vehicle in geometric portions and mix after each addition. Transfer contents of the mortar to the calibrated bottle and add enough vehicle to bring the total volume to 120 mL. Protect from light. Shake well. Suspension is stable for 60 days refrigerated or at room temperature (at 5 and 25 degrees C).
*Vehicles: 1:1 mixture of Ora-Sweet® and Oral-Plus®; 1:1 mixture of Ora-Sweet SF® and Oral-Plus®; or cherry syrup (cherry syrup concentrate diluted 1:4 with simple syrup).

References

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- Brion LP, Primhak RA, Ambrosio-Perz I: Diuretics acting on the distal renal tubule for preterm infants with (or developing) chronic lung disease (Cochrane Review). In: *The Cochrane Library* Issue 1, 2003. Oxford: Update Software.
- Hoffman DJ, Gerdes JS, Abbasi S: Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled randomized trial. *J Perinatol* 2000;20:41-45.
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- Loggie JMH, Kleinman LI, Van Maanen EF: Renal function and diuretic therapy in infants and children. Part II. *J Pediatr* 1975;86:657.
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- Terai I, Yamano K, Ichihara N, et al: Influence of spironolactone on neonatal screening for congenital adrenal hyperplasia. *Arch Dis Child Fetal Neonatal Ed* 1999;81:F179.
- Product Information, Actavis, 2006.

1. Product Information: Aldactone(R) oral tablets, spironolactone oral tablets. G.D. Searle (per FDA), New York, NY, Jun, 2013.

1.175 Succinylcholine

Title Succinylcholine

Dose

Skeletal Muscle Relaxation/Paralysis
Intravenous
1 to 2 mg/kg IV immediately prior to intubation [1] [2] [3] [4] [5] [6] [7] [8] . Repeat doses of 1 mg/kg up to a maximum total dose of 4 mg/kg have been used if muscle relaxation was not attained by 1 to 3 minutes after administration [4] [5] .
Must be accompanied by adequate analgesia or sedation [1] .

Intramuscular
2 to 4 mg/kg may be given via the IM route only if IV route not accessible [1] [3] [9] .

Administration

May administer undiluted as an IV bolus or further dilute in compatible solution to a concentration of 1 to 2 mg/mL [1] .

Uses

Skeletal muscle relaxation/paralysis for neonates requiring rapid sequence intubation or non-emergent endotracheal intubation [2] [3] [9] [10] [4] [4] [11] [5] [6] [7] .
Premedication is recommended in neonates for all non-emergent intubations if time permits. Premedication regimens for endotracheal intubation typically include a skeletal muscle relaxant in combination with an analgesic (an opioid) and/or sedative and a vagolytic agent (usually atropine) [2] [3] [10] [8] [6] . Use of a muscle relaxant without an analgesic agent is not recommended [3] . Premedication has been shown to decrease the time to successful intubation and decrease the occurrence of adverse effects (ie, increased intracranial pressure, hypertension, decreased heart rate and oxygenation) in neonates [4] [11] [5] [8] [7] . Use of succinylcholine has resulted in fewer intubation attempts and more successful intubations compared with no succinylcholine in clinical studies in neonates [10] .

Pediatric FDA Approved Indications
Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation [1] .

Contraindications/Precautions

Contraindicated in the acute phase of injury after multiple trauma, major burns, extensive denervation of skeletal muscle, or upper motor neuron injury; may result in severe hyperkalemia, and possible onset of cardiac arrest. Also **contraindicated** in patients with a personal or family history of malignant hyperthermia and in patients with skeletal muscle myopathies [1] .

Serious anaphylactic reactions, including fatal cases, have been reported. Bradycardia and possible asystole may occur; higher risk with second dose; incidence and severity increased in pediatric patients compared with adults; premedication regimen that includes atropine may protect against bradyarrhythmias induced by succinylcholine. Hyperkalemia may occur. Serious cardiac arrhythmias or cardiac arrest due to hyperkalemia may occur in patients with massive digitalis toxicity or patients with electrolyte abnormalities. Increased risk of severe hyperkalemia in patients with subarachnoid hemorrhage or chronic abdominal infection, or conditions causing degeneration of central and peripheral nervous systems [1] .
Risk of prolonged neuromuscular blockade in patients with reduced plasma cholinesterase activity, such as those with genetic abnormalities of plasma cholinesterase (eg, heterozygous or homozygous for atypical plasma cholinesterase gene) or conditions associated with pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Neuromuscular blockade may also be prolonged in patients with hypokalemia or hypocalcemia. Prolonged administration may result in a block resembling a nondepolarizing block (Phase II block). Risk of tachyphylaxis with repeated use [1] .

Malignant hyperthermia has been reported rarely in children who have received succinylcholine [14] [15] ; increased risk with coadministration of volatile anesthetics; monitoring recommended [1] .
Intracranial pressure increase (transient) may occur. Increased intraocular pressure has been reported in patients with narrow angle glaucoma or penetrating eye injury.
Intragastric pressure increase may occur, resulting in regurgitation and possible aspiration of stomach contents. Initial muscle fasciculations may cause additional trauma in patients with fractures or muscle spasm [1] . Muscle fasciculations have been rarely reported in children [14] .

Black Box Warning

Acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death have been rarely reported in seemingly healthy children (usually, but not exclusively, males, and most frequently 8 years of age or younger) who were subsequently found to have undiagnosed skeletal muscle myopathy (most frequently Duchenne's muscular dystrophy) after administration of succinylcholine chloride [12] [13] . This syndrome often presents as peaked T-waves and sudden cardiac arrest within minutes after the administration of the drug. Treatment for hyperkalemia should be immediately instituted for infants or children who appear healthy but develop cardiac arrest, not felt to be due to inadequate ventilation, oxygenation, or anesthetic overdose after administration of succinylcholine chloride. Routine resuscitative measures are likely to be unsuccessful; extraordinary and prolonged resuscitative efforts may be required. If there are signs present for malignant hyperthermia, appropriate treatment should be instituted concurrently. It is recommended that succinylcholine chloride use in children be restricted to emergency intubation or instances where immediate securing of the airway is necessary [1] .

Pharmacology

Succinylcholine is an ultra short-acting depolarizing-type, skeletal muscle relaxant. Has no effect on pain threshold, consciousness, or cerebration. Onset of paralysis after IV administration is 30 to 60 seconds with a duration of action of 4 to 6 minutes [16] [17] . Onset of action after IM administration is 2 to 4 minutes with a duration of action of 19 to 23 minutes [1] [18] . Rapidly hydrolyzed by plasma cholinesterase to succinylmonocholine (which possesses clinically insignificant depolarizing muscle relaxant properties) and then more slowly to succinic acid and choline. Approximately 10% of the drug is eliminated in the urine as unchanged drug [1] .

Adverse Effects

Hypertension, hypotension, prolonged respiratory depression or apnea, jaw rigidity, postoperative muscle pain, excessive salivation, and rash have been reported [1] .

Monitoring

Monitor oxygen saturation, heart rate, and blood pressure continuously [3] .
Closely monitor ECG for peaked T-waves, an early sign of potential cardiac arrest secondary to acute rhabdomyolysis with hyperkalemia. Monitor temperature and

expired carbon dioxide continuously for early recognition of malignant hyperthermia [1] .

Special Considerations/Preparation

Available in 100 mg/mL single-use vials and 20 mg/mL multi-dose vials. Store in refrigerator. Multidose vials are stable for up to 14 days if stored at room temperature. May be further diluted in compatible solution to a concentration of 1 to 2 mg/mL. Diluted solutions should be used within 24 hours of preparation [1] [19] .

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, D_5 1/2 NS, NS, 1/2 NS, and LR.

Terminal Injection Site Compatibility

Succinylcholine diluted to 2 mg/mL:
Acyclovir (7 mg/mL), amphotericin B lipid complex (1 mg/mL), argatroban (1 mg/mL), azithromycin (2 mg/mL), bivalirudin (5 mg/mL), caspofungin (0.5 mg/mL), daptomycin (10 mg/mL), dexmedetomidine (4 mcg/mL), diltiazem (5 mg/mL), ertapenem (20 mg/mL), granisetron (0.05 mg/mL), levofloxacin (5 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), methotrexate (15 mg/mL), metronidazole (5 mg/mL), milrinone (0.2 mg/mL), mycophenolate (6 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (0.05 mg/mL), pantoprazole (0.4 mg/mL), piperacillin/tazobactam (40 mg/mL piperacillin), quinupristin/dalfopristin (5 mg/mL), tacrolimus (0.02 mg/mL), vecuronium (1 mg/mL), and voriconazole (4 mg/mL).

Succinylcholine diluted to 8 mg/mL:
Amikacin (20 mg/mL), aminophylline (12.5 mg/mL), ampicillin (80 mg/mL in NS only), ampicillin/sulbactam (80 mg/mL in NS only), atropine (0.5 mg/mL), aztreonam (80 mg/mL), bumetanide (0.125 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefazolin (220 mg/mL), cefotaxime (285 mg/mL), cefotetan (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftriaxone (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol (333 mg/mL), cimetidine (24 mg/mL), clindamycin (48 mg/mL), cyclosporine (2 mg/mL), dexamethasone (12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine (25 mg/mL), dobutamine (6.25 mg/mL), dopamine (12.8 mg/mL), enalaprilat (0.625 mg/mL), epinephrine (0.008 or 0.5 mg/mL), epoetin (5000 units/mL), erythromycin (20 mg/mL), esmolol (40 mg/mL), famotidine (5 mg/mL), fentanyl (25 mcg/mL), fluconazole (2 mg/mL), furosemide (5 mg/mL), gentamicin (6.4 mg/mL), heparin (1 unit/mL or 160 units/mL), hydralazine (10 mg/mL in NS only), hydrocortisone (62.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (50 units/mL in NS only), isoproterenol (0.08 mg/mL), labetalol (2.5 mg/mL), lidocaine (10 mg/mL), magnesium sulfate (250 mg/mL), methylprednisolone (125 mg/mL), metoclopramide (2.5 mg/mL), metoprolol (0.5 mg/mL), midazolam (2.5 mg/mL), morphine (4 mg/mL), naloxone (16 mcg/mL), nitroprusside sodium (0.8 mg/mL), ondansetron (1 mg/mL), papaverine (15 mg/mL), phentolamine (5 mg/mL), phytonadione (5 mg/mL), piperacillin (320 mg/mL), potassium chloride (1 mEq/mL), procainamide (250 mg/mL), propranolol (0.5 mg/mL), protamine (5 mg/mL), pyridoxine (50 mg/mL), ranitidine (2 mg/mL), theophylline (4 mg/mL),

ticarcillin/clavulanate (195 mg/mL ticarcillin), tobramycin (6.4 mg/mL), vancomycin (20 mg/mL), vasopressin (4 units/mL), and verapamil (1.25 mg/mL).

Undiluted Succinylcholine 20 mg/mL:
Heparin (1 unit/mL), hydrocortisone (0.1 mg/mL), potassium chloride (0.04 mEq/mL), and propofol (10 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B, azathioprine, diazepam, diazoxide, ganciclovir, indomethacin, nafcillin, oxacillin, penicillin G potassium, penicillin G sodium, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, and trimethoprim/sulfamethoxazole.

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- Product Information: QUELICIN(TM) intravenous injection solution, intramuscular injection solution, succinylcholine chloride intravenous injection solution, intramuscular injection solution. Hospira, Inc. (per DailyMed), Lake Forest, IL, Sep, 2010.

Title Succinylcholine

Dose

Skeletal Muscle Relaxation/Paralysis
Intravenous
1 to 2 mg/kg IV immediately prior to intubation [1] [2] [3] [4] [5] [6] [7] [8] . Repeat doses of 1 mg/kg up to a maximum total dose of 4 mg/kg have been used if muscle relaxation was not attained by 1 to 3 minutes after administration [4] [5] .
Must be accompanied by adequate analgesia or sedation [1] .

Intramuscular
2 to 4 mg/kg may be given via the IM route only if IV route not accessible [1] [3] [9] .

Administration

May administer undiluted as an IV bolus or further dilute in compatible solution to a concentration of 1 to 2 mg/mL [1] .

Uses

Skeletal muscle relaxation/paralysis for neonates requiring rapid sequence intubation or non-emergent endotracheal intubation [2] [3] [9] [10] [4] [4] [11] [5] [6] [7] .

Premedication is recommended in neonates for all non-emergent intubations if time permits. Premedication regimens for endotracheal intubation typically include a skeletal muscle relaxant in combination with an analgesic (an opioid) and/or sedative and a vagolytic agent (usually atropine) [2] [3] [10] [8] [6] . Use of a muscle relaxant without an analgesic agent is not recommended [3] . Premedication has been shown to decrease the time to successful intubation and decrease the occurrence of adverse effects (ie, increased intracranial pressure, hypertension, decreased heart rate and oxygenation) in neonates [4] [11] [5] [8] [7] . Use of succinylcholine has resulted in fewer intubation attempts and more successful intubations compared with no succinylcholine in clinical studies in neonates [10] .

Pediatric FDA Approved Indications
Adjunct to general anesthesia, to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation [1] .

Contraindications/Precautions

Contraindicated in the acute phase of injury after multiple trauma, major burns, extensive denervation of skeletal muscle, or upper motor neuron injury; may result in severe hyperkalemia, and possible onset of cardiac arrest. Also **contraindicated** in patients with a personal or family history of malignant hyperthermia and in patients with skeletal muscle myopathies [1] .

Serious anaphylactic reactions, including fatal cases, have been reported. Bradycardia and possible asystole may occur; higher risk with second dose; incidence and severity increased in pediatric patients compared with adults; premedication regimen that includes atropine may protect against bradyarrhythmias induced by succinylcholine.
Hyperkalemia may occur. Serious cardiac arrhythmias or cardiac arrest due to hyperkalemia may occur in patients with massive digitalis toxicity or patients with electrolyte abnormalities. Increased risk of severe hyperkalemia in patients with subarachnoid hemorrhage or chronic abdominal infection, or conditions causing degeneration of central and peripheral nervous systems [1] .
Risk of prolonged neuromuscular blockade in patients with reduced plasma cholinesterase activity, such as those with genetic abnormalities of plasma cholinesterase (eg, heterozygous or homozygous for atypical plasma cholinesterase gene) or conditions associated with pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Neuromuscular blockade may also be prolonged in patients with hypokalemia or hypocalcemia. Prolonged administration may result in a block resembling a nondepolarizing block (Phase II block). Risk of tachyphylaxis with repeated use [1] .
Malignant hyperthermia has been reported rarely in children who have received succinylcholine [14] [15] ; increased risk with coadministration of volatile anesthetics; monitoring recommended [1] .
Intracranial pressure increase (transient) may occur. Increased intraocular pressure has been reported in patients with narrow angle glaucoma or penetrating eye injury.
Intragastric pressure increase may occur, resulting in regurgitation and possible aspiration of stomach contents. Initial muscle fasciculations may cause additional trauma in patients with fractures or muscle spasm [1] . Muscle fasciculations have been rarely reported in children [14] .

Black Box Warning

Acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death have been rarely reported in seemingly healthy children (usually, but not exclusively, males, and most frequently 8 years of age or younger) who were subsequently found to have undiagnosed skeletal muscle myopathy (most frequently Duchenne's muscular dystrophy) after administration of succinylcholine chloride [12] [13] . This syndrome often presents as peaked T-waves and sudden cardiac arrest within minutes after the administration of the drug. Treatment for hyperkalemia should be immediately instituted for infants or children who appear healthy but develop cardiac arrest, not felt to be due to inadequate ventilation, oxygenation, or anesthetic overdose after administration of succinylcholine chloride. Routine resuscitative measures are likely to be unsuccessful; extraordinary and prolonged resuscitative efforts may be required. If there are signs present for malignant hyperthermia, appropriate treatment should be instituted concurrently. It is recommended that succinylcholine chloride use in children be restricted to emergency intubation or instances where immediate securing of the airway is necessary [1] .

Pharmacology

Succinylcholine is an ultra short-acting depolarizing-type, skeletal muscle relaxant. Has no effect on pain threshold, consciousness, or cerebration. Onset of paralysis after IV administration is 30 to 60 seconds with a duration of action of 4 to 6 minutes [16] [17] . Onset of action after IM administration is 2 to 4 minutes with a duration of action of 19 to 23 minutes [1] [18] . Rapidly hydrolyzed by plasma cholinesterase to succinylmonocholine (which possesses clinically insignificant depolarizing muscle relaxant properties) and then more slowly to succinic acid and choline. Approximately 10% of the drug is eliminated in the urine as unchanged drug [1] .

Adverse Effects

Hypertension, hypotension, prolonged respiratory depression or apnea, jaw rigidity, postoperative muscle pain, excessive salivation, and rash have been reported [1] .

Monitoring

Monitor oxygen saturation, heart rate, and blood pressure continuously [3] .
Closely monitor ECG for peaked T-waves, an early sign of potential cardiac arrest secondary to acute rhabdomyolysis with hyperkalemia. Monitor temperature and expired carbon dioxide continuously for early recognition of malignant hyperthermia [1] .

Special Considerations/Preparation

Available in 100 mg/mL single-use vials and 20 mg/mL multi-dose vials. Store in refrigerator. Multidose vials are stable for up to 14 days if stored at room temperature. May be further diluted in compatible solution to a concentration of 1 to 2 mg/mL. Diluted solutions should be used within 24 hours of preparation [1] [19] .

Solution Compatibility

D_5W, $D_{10}W$, D_5LR, D_5NS, D_5 1/2 NS, NS, 1/2 NS, and LR.

Terminal Injection Site Compatibility

Succinylcholine diluted to 2 mg/mL:
Acyclovir (7 mg/mL), amphotericin B lipid complex (1 mg/mL), argatroban (1 mg/mL), azithromycin (2 mg/mL), bivalirudin (5 mg/mL), caspofungin (0.5 mg/mL), daptomycin (10 mg/mL), dexmedetomidine (4 mcg/mL), diltiazem (5 mg/mL), ertapenem (20 mg/mL), granisetron (0.05 mg/mL), levofloxacin (5 mg/mL), linezolid (2 mg/mL), lorazepam (0.5 mg/mL), methotrexate (15 mg/mL), metronidazole (5 mg/mL), milrinone (0.2 mg/mL), mycophenolate (6 mg/mL), octreotide (5 mcg/mL), ondansetron (1 mg/mL), palonosetron (0.05 mg/mL), pantoprazole (0.4 mg/mL), piperacillin/tazobactam (40 mg/mL piperacillin), quinupristin/dalfopristin (5 mg/mL), tacrolimus (0.02 mg/mL), vecuronium (1 mg/mL), and voriconazole (4 mg/mL).

Succinylcholine diluted to 8 mg/mL:
Amikacin (20 mg/mL), aminophylline (12.5 mg/mL), ampicillin (80 mg/mL in NS only), ampicillin/sulbactam (80 mg/mL in NS only), atropine (0.5 mg/mL), aztreonam (80 mg/mL), bumetanide (0.125 mg/mL), calcium chloride (50 mg/mL), calcium gluconate (50 mg/mL), cefazolin (220 mg/mL), cefotaxime (285 mg/mL), cefotetan (400 mg/mL), cefoxitin (450 mg/mL), ceftazidime (400 mg/mL), ceftriaxone (165 mg/mL), cefuroxime (125 mg/mL), chloramphenicol (333 mg/mL), cimetidine (24 mg/mL), clindamycin (48 mg/mL), cyclosporine (2 mg/mL), dexamethasone (12 mg/mL), digoxin (0.125 mg/mL), diphenhydramine (25 mg/mL), dobutamine (6.25 mg/mL), dopamine (12.8 mg/mL), enalaprilat (0.625 mg/mL), epinephrine (0.008 or 0.5 mg/mL), epoetin (5000 units/mL), erythromycin (20 mg/mL), esmolol (40 mg/mL), famotidine (5 mg/mL), fentanyl (25 mcg/mL), fluconazole (2 mg/mL), furosemide (5 mg/mL), gentamicin (6.4 mg/mL), heparin (1 unit/mL or 160 units/mL), hydralazine (10 mg/mL in NS only), hydrocortisone (62.5 mg/mL), imipenem/cilastatin (5 mg/mL), insulin (50 units/mL in NS only), isoproterenol (0.08 mg/mL), labetalol (2.5 mg/mL), lidocaine (10 mg/mL), magnesium sulfate (250 mg/mL), methylprednisolone (125 mg/mL), metoclopramide (2.5 mg/mL), metoprolol (0.5 mg/mL), midazolam (2.5 mg/mL), morphine (4 mg/mL), naloxone (16 mcg/mL), nitroprusside sodium (0.8 mg/mL), ondansetron (1 mg/mL), papaverine (15 mg/mL), phentolamine (5 mg/mL), phytonadione (5 mg/mL), piperacillin (320 mg/mL), potassium chloride (1 mEq/mL), procainamide (250 mg/mL), propranolol (0.5 mg/mL), protamine (5 mg/mL), pyridoxine (50 mg/mL), ranitidine (2 mg/mL), theophylline (4 mg/mL), ticarcillin/clavulanate (195 mg/mL ticarcillin), tobramycin (6.4 mg/mL), vancomycin (20 mg/mL), vasopressin (4 units/mL), and verapamil (1.25 mg/mL).

Undiluted Succinylcholine 20 mg/mL:
Heparin (1 unit/mL), hydrocortisone (0.1 mg/mL), potassium chloride (0.04 mEq/mL), and propofol (10 mg/mL).

Terminal Injection Site Incompatibility

Amphotericin B, azathioprine, diazepam, diazoxide, ganciclovir, indomethacin, nafcillin, oxacillin, penicillin G potassium, penicillin G sodium, pentobarbital, phenobarbital, phenytoin, sodium bicarbonate, and trimethoprim/sulfamethoxazole.

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1.176 Sucrose

Title Sucrose

Dose

Preterm infants: 0.5 to 1 mL of 12% to 24% sucrose solution.
Term infants: 2 mL of 12% to 24% sucrose solution.
Administer sucrose solution directly to the tongue 2 minutes prior to the painful procedure. For patients able to suck, a pacifier should be offered immediately after sucrose administration.
Alternatively, a pacifier dipped in sucrose solution can be offered 2 minutes prior to the procedure.

Uses

Mild analgesia and behavioral comforting.

Pharmacology

Sucrose administration provides a calming effect and reduces acute procedural pain in both preterm and term infants. The potential mechanism of these effects includes activation of the endogenous opioid system through taste receptors on the tip of the tongue. The time to maximal effect is approximately 2 minutes and the duration of effect is approximately 5 to 10 minutes. The beneficial effects of sucrose can be improved by nonnutritive sucking.

Adverse Effects

Sucrose 24% has an osmolarity of approximately 1000 mOsm/L. The adverse effects of repeated doses in premature infants are unknown.

Monitoring

Assess for signs of pain and discomfort.

Special Considerations/Preparation

Sweet-Ease®, a 24% sucrose and water solution, is aseptically packaged in an 15 ml cup with a peel off lid that is suitable for dipping a pacifier or for administration via a dropper.

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- Product Information, Sweetease® website: http://www.healthcare.philips.com/main/products/mother_and_child_care/post_natal_care/well_baby/calming_and_soothing/sweetease/indes.wpd

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1.177 Surfactant (Natural, animal-derived)

Title Surfactant (Natural, animal-derived)

Dose

See specific products (beractant, calfactant, or poractant alfa) for dosing and administration information.

Uses

Prophylaxis of infants at high risk for RDS (those less than 29 weeks gestation).
Rescue treatment of infants with moderate to severe RDS.
Treatment of mature infants with respiratory failure due to meconium aspiration syndrome, pneumonia, or persistent pulmonary hypertension.

Pharmacology

In infants with RDS, exogenous surfactant therapy reverses atelectasis and increases FRC, with rapid improvements in oxygenation. All preparations reduce mortality from RDS. Natural surfactants are more effective than synthetics in reducing pulmonary air leak. There are no significant differences between preparations in chronic lung disease or other long term outcomes. All commercially available preparations contain surfactant apoprotein C (SP-C), none contain SP-A. The lung-mince extracts Survanta® and Curosurf® contain less than 10% of the SP-B contained in the lung-wash extract Infasurf®.

Adverse Effects

Administration of exogenous surfactants should be restricted to highly supervised clinical settings, with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Reflux of exogenous surfactant up the ET tube and falls in oxygenation occur frequently. If the infant becomes dusky or agitated, heart rate slows, oxygen saturation falls more than 15%, or surfactant backs up in the ET tube, dosing should be slowed or halted. If necessary, ventilator settings and/or FiO_2 should be turned up. Pulmonary hemorrhage occurs in 2% to 4% of treated infants, primarily the smallest patients with untreated PDA. This may be due to hemorrhagic pulmonary edema caused by the rapid fall in pulmonary vascular resistance and resulting increased pulmonary blood flow.

Monitoring

Assess ET tube patency and position. Oxygen saturation, EKG, and blood pressure should be monitored continuously during dosing. Assess for impairment of gas exchange caused by blockage of the airway. After dosing, frequent assessments of oxygenation and ventilation should be performed to prevent postdose hyperoxia, hypocarbia, and overventilation.

References

- **Review Articles**
- Engle WA and the Committee on Fetus and Newborn: Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. *Pediatrics* 2008;121:419-432.
- Suresh GK, Soll RF: Current surfactant use in premature infants.*Clin Perinatol* 2001;28:671-694.
- Rodriguez RJ, Martin RJ: Exogenous surfactant therapy in newborns. *Resp Care Clin North Am* 1999;5:595-616.
- Kattwinkel J: Surfactant: Evolving issues. *Clin Perinatol* 1998; 25:17-32.
- Morley CJ: Systematic review of prophylactic vs rescue surfactant. *Arch Dis Child* 1997;77:F70-F74.
- Halliday HL: Natural vs synthetic surfactants in neonatal respiratory distress syndrome. *Drugs* 1996;51:226-237.
- **Selected References for Non-RDS Indications**
- Lotze A, Mitchell BR, Bulas DI, et al: Multicenter study of surfactant (Beractant) use in the treatment of term infants with severe respiratory failure. *J Pediatr* 1998;132:40.
- Findlay RD, Taeusch HW, Walther FJ: Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* 1996;97:48.

Title Surfactant (Natural, animal-derived)

Dose

See specific products (beractant, calfactant, or poractant alfa) for dosing and administration information.

Uses

Prophylaxis of infants at high risk for RDS (those less than 29 weeks gestation).
Rescue treatment of infants with moderate to severe RDS.
Treatment of mature infants with respiratory failure due to meconium aspiration syndrome, pneumonia, or persistent pulmonary hypertension.

Pharmacology

In infants with RDS, exogenous surfactant therapy reverses atelectasis and increases FRC, with rapid improvements in oxygenation. All preparations reduce mortality from RDS. Natural surfactants are more effective than synthetics in reducing pulmonary air leak. There are no significant differences between preparations in chronic lung disease or other long term outcomes. All commercially available preparations contain surfactant apoprotein C (SP-C), none contain SP-A. The lung-mince extracts Survanta® and Curosurf® contain less than 10% of the SP-B contained in the lung-wash extract Infasurf®.

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Assess ET tube patency and position. Oxygen saturation, EKG, and blood pressure should be monitored continuously during dosing. Assess for impairment of gas exchange caused by blockage of the airway. After dosing, frequent assessments of oxygenation and ventilation should be performed to prevent postdose hyperoxia, hypocarbia, and overventilation.

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- Findlay RD, Taeusch HW, Walther FJ: Surfactant replacement therapy for meconium aspiration syndrome. *Pediatrics* 1996;97:48.

1.178 THAM acetate

Title THAM acetate

Dose

1 to 2 mmol/kg (3.3 to 6.6 mL/kg) per dose IV.
Infuse in a large vein over at least 30 minutes.
Dose (of the 0.3 M solution) may be calculated from the following formula:

Dose (mL) = Weight (kg) x Base deficit (mEq/L)

Maximum dose in neonates with normal renal function is approximately 5 to 7 mmol/kg per 24 hours. Clinical studies support only short-term use.

Uses

Treatment of metabolic acidosis, primarily in mechanically ventilated patients with significant hypercarbia or hypernatremia. **Do not use in patients who are anuric or uremic.**THAM is not indicated for treatment of metabolic acidosis caused by bicarbonate deficiency.

Contraindications/Precautions

Most reports of toxicity in neonates (hypoglycemia, hyperkalemia, liver necrosis) were related to rapid umbilical venous infusion of high doses of THAM base solutions that were more alkaline and hypertonic than the THAM acetate solution currently available from Abbott (pH 8.6; osmolarity 380 mOsm/L). **Irritating to veins**.

Pharmacology

THAM (Tris-Hydroxymethyl Aminomethane) is a proton acceptor that generates NH_3^+ and HCO_3- without generating CO_2. The protonated R-NH_3^+ is eliminated by the kidneys. Unlike bicarbonate, THAM does not require an open system for CO_2 elimination in order to exert its buffering effect.

Monitoring

Observe IV site closely for signs of extravasation. Follow blood-gas results to assess therapeutic efficacy. Follow urine output. Monitor for respiratory depression, hypoglycemia, and hyperkalemia when using several doses.

Special Considerations/Preparation

Supplied as a 0.3-M solution (1 mmol = 3.3 mL) in a 500-mL single-dose container with no bacteriostatic agent. Intended for single-dose use and unused portion should be discarded.

Solution Compatibility No data are currently available on solutions and additives.

References

- Holmdahl MH, Wiklund L, Wetterberg T, et al: The place of THAM in the management of acidemia in clinical practice. *Acta Anaethesiol Scand* 2000;44:524-527.
- Nahas GG, Sutin KM, Fermon C, et al: Guidelines for the treatment of acidemia with THAM. *Drugs*1998;55:191-224. (Errata published 1998;55:517).
- Baum JD, Robertson NRC: Immediate effects of alkaline infusion in infants with respiratory distress syndrome. *J Pediatr* 1975;87:255.
- Strauss J: Tris (hydroxymethyl amino-methane [THAM]): A pediatric evaluation. *Pediatrics* 1968;41:667.
- Gupta JM, Dahlenburg GW, Davis JW: Changes in blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. *Arch Dis Child* 1967;42:416-427.
- Product Information, Hospira, 2006.

Title THAM acetate

Dose

1 to 2 mmol/kg (3.3 to 6.6 mL/kg) per dose IV.
Infuse in a large vein over at least 30 minutes.
Dose (of the 0.3 M solution) may be calculated from the following formula:

Dose (mL) = Weight (kg) x Base deficit (mEq/L)

Maximum dose in neonates with normal renal function is approximately 5 to 7 mmol/kg per 24 hours. Clinical studies support only short-term use.

Uses

Treatment of metabolic acidosis, primarily in mechanically ventilated patients with significant hypercarbia or hypernatremia. **Do not use in patients who are anuric or uremic.**THAM is not indicated for treatment of metabolic acidosis caused by bicarbonate deficiency.

Contraindications/Precautions

Most reports of toxicity in neonates (hypoglycemia, hyperkalemia, liver necrosis) were related to rapid umbilical venous infusion of high doses of THAM base solutions that were more alkaline and hypertonic than the THAM acetate solution currently available from Abbott (pH 8.6; osmolarity 380 mOsm/L). **Irritating to veins**.

Pharmacology

THAM (Tris-Hydroxymethyl Aminomethane) is a proton acceptor that generates NH_3^+ and HCO_3- without generating CO_2. The protonated R-NH_3^+ is eliminated by the kidneys. Unlike bicarbonate, THAM does not require an open system for CO_2 elimination in order to exert its buffering effect.

Monitoring

Observe IV site closely for signs of extravasation. Follow blood-gas results to assess therapeutic efficacy. Follow urine output. Monitor for respiratory depression, hypoglycemia, and hyperkalemia when using several doses.

Special Considerations/Preparation

Supplied as a 0.3-M solution (1 mmol = 3.3 mL) in a 500-mL single-dose container with no bacteriostatic agent. Intended for single-dose use and unused portion should be discarded.

Solution Compatibility No data are currently available on solutions and additives.

References

- Holmdahl MH, Wiklund L, Wetterberg T, et al: The place of THAM in the management of acidemia in clinical practice. *Acta Anaethesiol Scand* 2000;44:524-527.
- Nahas GG, Sutin KM, Fermon C, et al: Guidelines for the treatment of acidemia with THAM. *Drugs*1998;55:191-224. (Errata published 1998;55:517).

- Baum JD, Robertson NRC: Immediate effects of alkaline infusion in infants with respiratory distress syndrome. *J Pediatr* 1975;87:255.
- Strauss J: Tris (hydroxymethyl amino-methane [THAM]): A pediatric evaluation. *Pediatrics* 1968;41:667.
- Gupta JM, Dahlenburg GW, Davis JW: Changes in blood gas tensions following administration of amine buffer THAM to infants with respiratory distress syndrome. *Arch Dis Child* 1967;42:416-427.
- Product Information, Hospira, 2006.

1.179 Ticarcillin\Clavulanate

Title Ticarcillin/Clavulanate

Dose

75 to 100 mg/kg/dose IV infusion by syringe pump over 30 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of non-CNS infections, caused by susceptible β-lactamase producing bacteria, including many strains of*E. coli*, *Enterobacter*, *Klebsiella*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas spp.*,and*Staph. aureus*.

Contraindications/Precautions

Seizures may occur when administered at very high doses and in the presence of renal impairment. Sodium content should be considered when treating patients requiring salt restrictions (4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate).

Pharmacology

Timentin® combines the extended-spectrum antibiotic ticarcillin with the β-lactamase inhibitor clavulanic acid in a 30:1 ratio. Ticarcillin is primarily eliminated unchanged by renal mechanisms, whereas clavulanate undergoes significant hepatic metabolism. As a result the mean half-life of ticarcillin in neonates is 4.2 hours compared to a mean half-life of 2 hours for clavulanate. CNS penetration is modest (limited data).

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine. Hypernatremia may be exacerbated in ELBW patients.

Monitoring

Serum concentrations are not routinely monitored. Assess renal function prior to therapy. Measure serum sodium concentrations and hepatic transaminases periodically. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection in 3.1-g vials. Reconstitute vial by adding 13 mL of sterile water for injection. Dilute further with a compatible solution to a concentration between 10 and 100 mg/mL. Dilutions are stable for 24 hours at room temperature, 3 days refrigerated (D_5W), and 7 days refrigerated (NS and LR). Frozen dilutions stable for 7 days for D_5W and 30 days for NS and LR.
Contains 4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aztreonam, cefepime, famotidine, fluconazole, heparin, insulin, milrinone, morphine, propofol, remifentanil, and theophylline.

Terminal Injection Site Incompatibility

Amikacin, azithromycin, gentamicin, netilmicin, sodium bicarbonate, tobramycin, and vancomycin.

References

- Rubino CM, Gal P, Ransom JL: A review of the pharmacokinetic and pharmacodynamic characteristics of β-lactam/β-lactamase inhibitor combination antibiotics in premature infants. *Pediatr Infect Dis J* 1998;17:1200-1210.
- Reed MD: A reassessment of ticarcillin/clavulanic acid dose recommendations for infants, children, and adults. *Pediatr Infect Dis J* 1998;17:1195-1199.

- Product Information, GlaxoSmithKline, 2007.

Title Ticarcillin/Clavulanate

Dose

75 to 100 mg/kg/dose IV infusion by syringe pump over 30 minutes.

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	PostNatal (days)	Interval (hours)
≤29	0 to 28	12
	>28	8
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Uses

Treatment of non-CNS infections, caused by susceptible β-lactamase producing bacteria, including many strains of*E. coli*, *Enterobacter*, *Klebsiella*, *Haemophilus influenzae*, *Proteus mirabilis*, *Pseudomonas spp.*,and*Staph. aureus*.

Contraindications/Precautions

Seizures may occur when administered at very high doses and in the presence of renal impairment. Sodium content should be considered when treating patients requiring salt restrictions (4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate).

Pharmacology

Timentin® combines the extended-spectrum antibiotic ticarcillin with the β-lactamase inhibitor clavulanic acid in a 30:1 ratio. Ticarcillin is primarily eliminated unchanged by renal mechanisms, whereas clavulanate undergoes significant hepatic metabolism. As a result the mean half-life of ticarcillin in neonates is 4.2 hours compared to a mean half-life of 2 hours for clavulanate. CNS penetration is modest (limited data).

Adverse Effects

Eosinophilia. Hyperbilirubinemia. Elevations in ALT, AST, BUN, and serum creatinine. Hypernatremia may be exacerbated in ELBW patients.

Monitoring

Serum concentrations are not routinely monitored. Assess renal function prior to therapy. Measure serum sodium concentrations and hepatic transaminases periodically. Observe IV site for signs of extravasation.

Special Considerations/Preparation

Available as powder for injection in 3.1-g vials. Reconstitute vial by adding 13 mL of sterile water for injection. Dilute further with a compatible solution to a concentration between 10 and 100 mg/mL. Dilutions are stable for 24 hours at room temperature, 3 days refrigerated (D_5W), and 7 days refrigerated (NS and LR). Frozen dilutions stable for 7 days for D_5W and 30 days for NS and LR.
Contains 4.5 mEq (103.6 mg) of sodium per gram of ticarcillin/clavulanate.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Aztreonam, cefepime, famotidine, fluconazole, heparin, insulin, milrinone, morphine, propofol, remifentanil, and theophylline.

Terminal Injection Site Incompatibility

Amikacin, azithromycin, gentamicin, netilmicin, sodium bicarbonate, tobramycin, and vancomycin.

References

- Rubino CM, Gal P, Ransom JL: A review of the pharmacokinetic and pharmacodynamic characteristics of β-lactam/β-lactamase inhibitor combination antibiotics in premature infants. *Pediatr Infect Dis J* 1998;17:1200-1210.
- Reed MD: A reassessment of ticarcillin/clavulanic acid dose recommendations for infants, children, and adults. *Pediatr Infect Dis J* 1998;17:1195-1199.
- Product Information, GlaxoSmithKline, 2007.

1.180 Tobramycin

Title Tobramycin

Dose

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual

Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
≤29*	0 to 7	5	48
	8 to 28	4	36
	≥29	4	24
30 to 34	0 to 7	4.5	36
	≥8	4	24
≥35	ALL	4	24

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Treatment of infections caused by aerobic gram-negative bacilli (eg, *Pseudomonas*, *Klebsiella*, *E coli*). Usually used in combination with a β-lactam antibiotic.

Black Box Warning Aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of tobramycin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

Adverse Effects

Transient and reversible renal tubular dysfunction may occur, resulting in increased urinary losses of sodium, calcium, and magnesium. Vestibular and auditory ototoxicity may occur. The addition of other nephrotoxic and/or ototoxic medications (e.g. furosemide, vancomycin) may increase these adverse effects. Increased neuromuscular blockade (i.e. neuromuscular weakness and respiratory failure) may occur when used with pancuronium or other neuromuscular blocking agents and in patients with hypermagnesemia.

Monitoring

Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

Therapeutic serum concentrations:
Peak: 5 to 12 mcg/mL (or C_{max}/MIC ratio greater than 8:1)
Trough: 0.5 to 1 mcg/mL

Suggested Dosing Intervals

Level at 24 hours (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3		Measure level in 24 hours

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, alprostadil, amiodarone, aztreonam, calcium gluconate, cefoxitin, ceftazidime, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, furosemide, insulin, heparin (concentrations less than or equal to 1 unit/mL), linezolid, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nicardipine, ranitidine, remifentanil, theophylline, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, azithromycin, cefepime, imipenem/cilastatin, indomethacin, heparin (concentrations greater than 1 unit/mL), mezlocillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

References

- Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA: Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004;114:e111-e118.
- Avent ML, Kinney JS, Istre GR, Whitfield JM: Gentamicin and tobramycin in neonates: comparison of a new extended dosing regimen with a traditional multiple daily dosing regimen. *Am J Perinatol* 2002;8:413-19.
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- Giapros VI, Andronikou S, Cholevas VI, Papadopoulou ZL: Renal function in premature infants during aminoglycoside therapy. *Pediatr Nephrol*1995;9:163.
- Daly JS, Dodge RA, Glew RH, et al: Effect of time and temperature on inactivation of aminoglycosides by ampicillin at neonatal dosages. *J Perinatol* 1997;17:42-45.
- Williams BS, Ransom JL, Gal P, et al: Gentamicin pharmacokinetics in neonates with patent ductus arteriosus. *Crit Care Med* 1997;25:273-275.
- Product Information, Hospira, 2005.

Title Tobramycin

Dose

Antibiotic Dosing Chart:

Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Chart

* or significant asphyxia, PDA, or treatment with indomethacin

PMA (weeks)	Postnatal (days)	Dose (mg/kg)	Interval (hours)
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30 to 34	0 to 7	4.5	36
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≥35	ALL	4	24

Administration

Give as an IV infusion by syringe pump over 30 minutes. Administer as a separate infusion from penicillin-containing compounds. IM injection is associated with variable absorption, especially in the very small infant.

Uses

Treatment of infections caused by aerobic gram-negative bacilli (eg, *Pseudomonas*, *Klebsiella*, *E coli*). Usually used in combination with a β-lactam antibiotic.

Black Box Warning Aminoglycoside therapy has been associated with potential neurotoxicity, ototoxicity, and nephrotoxicity. Patients with impaired renal function, dehydration, and those who receive high dosage or prolonged therapy are at an increased risk of toxicity. Discontinue therapy or adjust dose if there is evidence of ototoxicity or nephrotoxicity. Aminoglycoside ototoxicity is usually irreversible.

Pharmacology

Dosing recommendations are based on: (1) Higher peak concentrations increase concentration-dependent bacterial killing; (2) There is a post-antibiotic effect on bacterial killing, especially when treating concurrently with a β-lactam antibiotic; (3) There may be less toxicity with less frequent dosing, due to less renal drug accumulation. Volume of distribution is increased and clearance is decreased in patients with PDA. Serum half-life is prolonged in premature and asphyxiated newborns. Inactivation of tobramycin by penicillin-containing compounds appears to be a time-, temperature-, and concentration-dependent process. This is probably clinically significant only when penicillin-containing compounds are mixed in IV solutions or when the blood is at room temperature for several hours before the assay is performed.

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Measure serum concentrations when treating for more than 48 hours. Obtain peak concentration 30 minutes after end of infusion, and trough concentration just prior to

the next dose. When treating patients with serious infections or significantly changing fluid or renal status consider measuring the serum concentration 24 hours after a dose, and use the chart below for the suggested dosing interval. Blood samples obtained to monitor serum drug concentrations should be spun and refrigerated or frozen as soon as possible.

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Peak: 5 to 12 mcg/mL (or C_{max}/MIC ratio greater than 8:1)
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Level at 24 hours (mcg/mL)	Half-life (hours)	Suggested Dosing Interval (hours)
≤1	~ 8	24
1.1 to 2.3	~ 12	36
2.4 to 3.2	~ 15	48
≥3.3		Measure level in 24 hours

Special Considerations/Preparation

Pediatric injectable solution available in a concentration of 10 mg/mL.

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions, fat emulsion. Acyclovir, alprostadil, amiodarone, aztreonam, calcium gluconate, cefoxitin, ceftazidime, clindamycin, dopamine, enalaprilat, esmolol, fluconazole, furosemide, insulin, heparin (concentrations less than or equal to 1 unit/mL), linezolid, magnesium sulfate, metronidazole, midazolam, milrinone, morphine, nafcillin, nicardipine, ranitidine, remifentanil, theophylline, and zidovudine.

Terminal Injection Site Incompatibility

Ampicillin, azithromycin, cefepime, imipenem/cilastatin, indomethacin, heparin (concentrations greater than 1 unit/mL), mezlocillin, oxacillin, penicillin G, propofol, and ticarcillin/clavulanate.

References

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- Avent ML, Kinney JS, Istre GR, Whitfield JM: Gentamicin and tobramycin in neonates: comparison of a new extended dosing regimen with a traditional multiple daily dosing regimen. *Am J Perinatol* 2002;8:413-19.
- de Hoog M, Schoemaker RC, Mouton JW, van den Anker JN: Tobramycin population pharmacokinetics in neonates. *Clin Pharmacol Ther* 1997;62:392-399.
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- Product Information, Hospira, 2005.

1.181 Topiramate

Title Topiramate

Dose

Prevention of Hypoxic-ischemic Encephalopathy (HIE), Adjunct to Hypothermia
Efficacy trials have not been published [1] [2] .

Administration

Sprinkle Capsules: May be opened and the sprinkles mixed with water to be administered via orogastric tube [1] [3] . Use mixture immediately. Do not store opened capsules for future use [3] .

Uses

Adjunct for neuroprotection against hypoxic-ischemic encephalopathy (HIE): Topiramate has been safely used, in concert with deep or mild hypothermia, for HIE in full-term newborns (n=27). An initial dose of 5 mg/kg (by orogastric tube) was started at initiation of hypothermia, followed by doses of either 5 mg/kg or 3 mg/kg given on days 2 and 3 [1] . A larger safety and efficacy trial (Neonatal Neuroprotection of Asphyxiated Tuscan Infants (NeoNATI)), which evaluates neurologic outcomes from combined treatment with hypothermia and topiramate versus hypothermia alone, is currently recruiting patients (proposed n=64). The dose being used in this trial is 10 mg/kg/dose for 3 doses [2] .

Seizure disorders: The addition of topiramate controlled or reduced acute seizure activity in 4 of 6 term infants having a variety of seizure syndromes refractory to phenobarbital or phenobarbital + phenytoin in a retrospective review of use in term newborns (n=6). At follow-up (5 to 11.5 months), 5 of 6 patients were seizure-free on topiramate monotherapy. Of these 5 patients, 4 received topiramate 10 mg/kg/day; the remaining patient received 3 mg/kg/day [4] .

Pediatric FDA Approved Indications
Topamax®: Indicated for partial-onset or primary generalized tonic-clonic seizures in patients 2 years or older (initial monotherapy) and ages 2 years or older (adjunctive therapy). Indicated for seizures associated with Lennox-Gastaut syndrome in patients 2 years or older [3] .
Trokendi XR™: Indicated for partial-onset or primary generalized tonic-clonic seizures in patients 10 years or older (initial monotherapy) and 6 years or older (adjunctive therapy). Indicated for seizures associated with Lennox-Gastaut syndrome in patients 6 years or older (adjunctive therapy) [5] .

Contraindications/Precautions

Acute myopia, associated with secondary angle-closure glaucoma, has been reported with topiramate, generally within the first month of use. Hyperthermia and decreased sweating have been reported, especially in pediatric patients. Metabolic acidosis has been reported, with an increased risk in patients with conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or certain drugs). In patients with or without a history of seizures, topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. Hyperammonemia with or without encephalopathy may occur with topiramate with or without concomitant valproic acid [3] .

Pharmacology

The exact mechanism of action of topiramate is unknown; however, 4 properties that may contribute to antiepileptic and antimigraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid (GABA) activity at some subtypes of the GABA-A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV [3] . Neuroprotective effects appear to be related to AMPA and kainate receptor inhibition, blockade of sodium channels, high-voltage activated calcium currents, carbonic anhydrase isoenzymes, and mitochondrial permeability transition pore (MPTP) [2] .
Topiramate serum concentrations and pharmacokinetics varied, based upon the level of hypothermia and use of concomitant phenobarbital in 13 full-term newborns with hypoxic-ischemic encephalopathy who received either deep hypothermia (DH; n=5) or mild hypothermia (MH; n=8) and either topiramate monotherapy (n=6) or with concomitant phenobarbital (n=7). All patients received a topiramate dose of 5 mg/kg every 24 hours for 3 days, starting with the initiation of hypothermia. Serum concentrations were lower in patients who received both MH and phenobarbital (NS). The coefficient of variability was greater in the DH group than the MH group (p=0.005), likely due to more irregular absorption and elimination. In those patients who attained virtual steady state (n=9), lower AUC, lower average serum concentration, and a longer half-life were seen in the DH compared to the MH group (318.1+/-101.6 vs 366.2+/-48.1 mg/L/hr, 13.25+/-4.2 vs 15.26+/-2 mg/L, and 48.82+/-4.6 vs 29.03+/-23.8 hours, respectively; all NS). Patients who received concomitant phenobarbital had lower minimum serum concentrations than those on topiramate monotherapy (8.7+/-2.9 vs 11.67+/-0.9 mg/L; p=0.032), with lower maximum and average serum concentrations, lower AUC, shorter half-life, and higher clearance (15.38+/-5.3 vs

19.87+/-1.9 mg/L, 12.6+/-3.7 vs 15.66+/-1.6 mg/L, 302.4+/-89.7 vs 375.8+/-37.4 mg/L/hr, 26.46+/-17.7 vs 42.88+/-19.1 hours, 17.92+/-6.2 vs 13.42+/-1.4 mL/kg/hr, respectively; all NS). Serum concentrations within the reference range of 5 to 20 mg/L were achieved in most patients [6] .

Adverse Effects

When used for neuroprotection in concert with hypothermia for hypoxic-ischemic encephalopathy (n=27), mild and reversible acidosis was seen in patients receiving deep hypothermia (DH); metabolic acidosis was not seen with mild hypothermia (MH). In addition, short course topiramate did not cause acid-base imbalance, nephrolithiasis, or ophthalmological concerns [1] .
When used for seizure disorders, 3 of 6 term infants had a weight of less than the 5th percentile, however, these patients also had poor oromotor control [4] .

Monitoring

Monitor for hyperthermia and decreased sweating, especially in hot weather. Measure serum bicarbonate levels at baseline and periodically during treatment. Seizures or increased seizure frequency should be monitored in patients with or without a history of epilepsy if rapid withdrawal of topiramate therapy is required. Examination of ammonia levels is recommended in any patient experiencing unexplained lethargy, vomiting, or changes in mental status, which may be indicative of hyperammonemia with or without encephalopathy [3] .

Special Considerations/Preparation

Oral Sprinkle Capsules: Available as 15-mg and 25-mg sprinkle capsules. Store at or below 25 degrees C (77 degrees F); protect from moisture [3] .

References

- Filippi L, Poggi C, la Marca G et al: Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J Pediatr Sep, 2010; 157(3): 361-366.

- Filippi L, Fiorini P, Daniotti M et al: Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI). BMC Pediatr Sep5, 2012; 12: 144-.

- Product Information: TOPAMAX(R) oral tablets capsules, topiramate oral tablets capsules. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, Oct, 2012.

- Glass HC: Topiramate for the treatment of neonatal seizures. Pediatr Neurol Jun, 2011; 44(6): 439-442.

- Product Information: Trokendi XR(TM) oral extended-release capsules, topiramate oral extended-release capsules. Supernus Pharmaceuticals (per manufacturer), Rockville, MD, Aug, 2013.

- Filippi L, la Marca G, Fiorini P et al: Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia Nov, 2009; 50(11): 2355-2361.

Title Topiramate

Dose

Prevention of Hypoxic-ischemic Encephalopathy (HIE), Adjunct to Hypothermia
Efficacy trials have not been published [1] [2] .

Administration

Sprinkle Capsules: May be opened and the sprinkles mixed with water to be administered via orogastric tube [1] [3] . Use mixture immediately. Do not store opened capsules for future use [3] .

Uses

Adjunct for neuroprotection against hypoxic-ischemic encephalopathy (HIE): Topiramate has been safely used, in concert with deep or mild hypothermia, for HIE in full-term newborns (n=27). An initial dose of 5 mg/kg (by orogastric tube) was started at initiation of hypothermia, followed by doses of either 5 mg/kg or 3 mg/kg given on days 2 and 3 [1] . A larger safety and efficacy trial (Neonatal Neuroprotection of Asphyxiated Tuscan Infants (NeoNATI)), which evaluates neurologic outcomes from combined treatment with hypothermia and topiramate versus hypothermia alone, is currently recruiting patients (proposed n=64). The dose being used in this trial is 10 mg/kg/dose for 3 doses [2] .

Seizure disorders: The addition of topiramate controlled or reduced acute seizure activity in 4 of 6 term infants having a variety of seizure syndromes refractory to phenobarbital or phenobarbital + phenytoin in a retrospective review of use in term newborns (n=6). At follow-up (5 to 11.5 months), 5 of 6 patients were seizure-free on topiramate monotherapy. Of these 5 patients, 4 received topiramate 10 mg/kg/day; the remaining patient received 3 mg/kg/day [4] .

Pediatric FDA Approved Indications
Topamax®: Indicated for partial-onset or primary generalized tonic-clonic seizures in patients 2 years or older (initial monotherapy) and ages 2 years or older (adjunctive therapy). Indicated for seizures associated with Lennox-Gastaut syndrome in patients 2 years or older [3] .
Trokendi XR™: Indicated for partial-onset or primary generalized tonic-clonic seizures in patients 10 years or older (initial monotherapy) and 6 years or older (adjunctive therapy). Indicated for seizures associated with Lennox-Gastaut syndrome in patients 6 years or older (adjunctive therapy) [5] .

Contraindications/Precautions

Acute myopia, associated with secondary angle-closure glaucoma, has been reported with topiramate, generally within the first month of use. Hyperthermia and decreased

sweating have been reported, especially in pediatric patients. Metabolic acidosis has been reported, with an increased risk in patients with conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or certain drugs). In patients with or without a history of seizures, topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. Hyperammonemia with or without encephalopathy may occur with topiramate with or without concomitant valproic acid [3] .

Pharmacology

The exact mechanism of action of topiramate is unknown; however, 4 properties that may contribute to antiepileptic and antimigraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid (GABA) activity at some subtypes of the GABA-A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV [3] . Neuroprotective effects appear to be related to AMPA and kainate receptor inhibition, blockade of sodium channels, high-voltage activated calcium currents, carbonic anhydrase isoenzymes, and mitochondrial permeability transition pore (MPTP) [2] .
Topiramate serum concentrations and pharmacokinetics varied, based upon the level of hypothermia and use of concomitant phenobarbital in 13 full-term newborns with hypoxic-ischemic encephalopathy who received either deep hypothermia (DH; n=5) or mild hypothermia (MH; n=8) and either topiramate monotherapy (n=6) or with concomitant phenobarbital (n=7). All patients received a topiramate dose of 5 mg/kg every 24 hours for 3 days, starting with the initiation of hypothermia. Serum concentrations were lower in patients who received both MH and phenobarbital (NS). The coefficient of variability was greater in the DH group than the MH group (p=0.005), likely due to more irregular absorption and elimination. In those patients who attained virtual steady state (n=9), lower AUC, lower average serum concentration, and a longer half-life were seen in the DH compared to the MH group (318.1+/-101.6 vs 366.2+/-48.1 mg/L/hr, 13.25+/-4.2 vs 15.26+/-2 mg/L, and 48.82+/-4.6 vs 29.03+/-23.8 hours, respectively; all NS). Patients who received concomitant phenobarbital had lower minimum serum concentrations than those on topiramate monotherapy (8.7+/-2.9 vs 11.67+/-0.9 mg/L; p=0.032), with lower maximum and average serum concentrations, lower AUC, shorter half-life, and higher clearance (15.38+/-5.3 vs 19.87+/-1.9 mg/L, 12.6+/-3.7 vs 15.66+/-1.6 mg/L, 302.4+/-89.7 vs 375.8+/-37.4 mg/L/hr, 26.46+/-17.7 vs 42.88+/-19.1 hours, 17.92+/-6.2 vs 13.42+/-1.4 mL/kg/hr, respectively; all NS). Serum concentrations within the reference range of 5 to 20 mg/L were achieved in most patients [6] .

Adverse Effects

When used for neuroprotection in concert with hypothermia for hypoxic-ischemic encephalopathy (n=27), mild and reversible acidosis was seen in patients receiving deep hypothermia (DH); metabolic acidosis was not seen with mild hypothermia (MH). In addition, short course topiramate did not cause acid-base imbalance, nephrolithiasis, or ophthalmological concerns [1] .
When used for seizure disorders, 3 of 6 term infants had a weight of less than the 5th percentile, however, these patients also had poor oromotor control [4] .

Monitoring

Monitor for hyperthermia and decreased sweating, especially in hot weather. Measure serum bicarbonate levels at baseline and periodically during treatment. Seizures or increased seizure frequency should be monitored in patients with or without a history of epilepsy if rapid withdrawal of topiramate therapy is required. Examination of ammonia levels is recommended in any patient experiencing unexplained lethargy, vomiting, or changes in mental status, which may be indicative of hyperammonemia with or without encephalopathy [3] .

Special Considerations/Preparation

Oral Sprinkle Capsules: Available as 15-mg and 25-mg sprinkle capsules. Store at or below 25 degrees C (77 degrees F); protect from moisture [3] .

References

- Filippi L, Poggi C, la Marca G et al: Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J Pediatr Sep, 2010; 157(3): 361-366.
- Filippi L, Fiorini P, Daniotti M et al: Safety and efficacy of topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia (NeoNATI). BMC Pediatr Sep5, 2012; 12: 144-.
- Product Information: TOPAMAX(R) oral tablets capsules, topiramate oral tablets capsules. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, Oct, 2012.
- Glass HC: Topiramate for the treatment of neonatal seizures. Pediatr Neurol Jun, 2011; 44(6): 439-442.
- Product Information: Trokendi XR(TM) oral extended-release capsules, topiramate oral extended-release capsules. Supernus Pharmaceuticals (per manufacturer), Rockville, MD, Aug, 2013.
- Filippi L, la Marca G, Fiorini P et al: Topiramate concentrations in neonates treated with prolonged whole body hypothermia for hypoxic ischemic encephalopathy. Epilepsia Nov, 2009; 50(11): 2355-2361.

1.182 Tri-Vi-SolÂ® MVI Drops

Title Tri-Vi-SolÂ® MVI Drops

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician.

Tri-Vi-Sol® Multivitamin Drops

Nutrient amt	w/o Iron	with Iron
Vitamins		
A, IU	1500	1500
D, IU	400	400
C, mg	35	35
E, IU	0	0
Thiamine B 1 , mg	0	0
Riboflavin B 2 , mg	0	0
Niacin, mg	0	0
B 6 , mg	0	0
B 12 , mcg	0	0
Minerals		
Iron, mg	0	10

Title Tri-Vi-SolÂ® MVI Drops

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician.

Tri-Vi-Sol® Multivitamin Drops

Nutrient amt	w/o Iron	with Iron
Vitamins		
A, IU	1500	1500
D, IU	400	400
C, mg	35	35
E, IU	0	0
Thiamine B 1 , mg	0	0

Riboflavin B 2 , mg	0	0
Niacin, mg	0	0
B 6 , mg	0	0
B 12 , mcg	0	0
Minerals		
Iron, mg	0	10

1.183 Tropicamide (Ophthalmic)

Title Tropicamide (Ophthalmic)

Dose

1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 0.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.

Pharmacology

Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Mydriasis begins within 5 minutes of instillation; cycloplegia occurs in 20 to 40 minutes. Recovery of accommodation occurs in 6 hours. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

Adverse Effects

Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth, restlessness, decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.

Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.5%, and 1% concentrations in 2-, 3-, and 15-mL dropper bottles. Store away from heat. **Do not refrigerate.**
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

References

- Wallace DK, Steinkuller PG: Ocular medications in children. *Clin Pediatr* 1998;37:645-652.
- Laws DE, Morton C, Weindling M, Clark D: Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol* 1996;80:425-428.
- McGregor MLK: Anticholinergic agents, in Mauger TF, Craig EL (eds): *Havener's Ocular Pharmacology,* ed 6. St. Louis: Mosby-YearBook, 1994, pp 148-155.
- Caputo AR, Schnitzer RE, Lindquist TD, Sun S: Dilation in neonates: a protocol. *Pediatrics* 1982;69:77-80.
- Product Information, Alcon, 2004.

Title Tropicamide (Ophthalmic)

Dose

1 drop instilled in the eye at least 10 minutes prior to funduscopic procedures.
Use **only** the 0.5% ophthalmic solution in neonates.
Apply pressure to the lacrimal sac during and for 2 minutes after instillation to minimize systemic absorption.

Uses

Induction of mydriasis and cycloplegia for diagnostic and therapeutic ophthalmic procedures.

Pharmacology

Anticholinergic drug that produces pupillary dilation by inhibiting the sphincter pupillae muscle, and paralysis of accommodation. Mydriasis begins within 5 minutes of instillation; cycloplegia occurs in 20 to 40 minutes. Recovery of accommodation occurs in 6 hours. Without lacrimal sac occlusion, approximately 80% of each drop may pass through the nasolacrimal system and be available for rapid systemic absorption by the nasal mucosa.

Adverse Effects

Feedings should be withheld for 4 hours following procedure. Systemic effects are those of anticholinergic drugs: Fever, tachycardia, vasodilatation, dry mouth,

restlessness, decreased gastrointestinal motility, and urinary retention. The use of solutions with concentrations of 1% or greater have caused systemic toxicity in infants.

Monitoring

Monitor heart rate and assess for signs of ileus prior to feeding.

Special Considerations/Preparation

Supplied as ophthalmic solution in 0.5%, and 1% concentrations in 2-, 3-, and 15-mL dropper bottles. Store away from heat. **Do not refrigerate.**
A combination eye drop solution ("Caputo drops") may be prepared in a 15-mL bottle with 3.75 mL of cyclopentolate 2%, 7.5 mL of tropicamide 1%, and 3.75 mL of phenylephrine 10%. The final solution contains cyclopentolate 0.5%, tropicamide 0.5%, and phenylephrine 2.5%.
Use within 24 hours, as the solution contains no preservatives.

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- Wallace DK, Steinkuller PG: Ocular medications in children. *Clin Pediatr* 1998;37:645-652.
- Laws DE, Morton C, Weindling M, Clark D: Systemic effects of screening for retinopathy of prematurity. *Br J Ophthalmol* 1996;80:425-428.
- McGregor MLK: Anticholinergic agents, in Mauger TF, Craig EL (eds): *Havener's Ocular Pharmacology,* ed 6. St. Louis: Mosby-YearBook, 1994, pp 148-155.
- Caputo AR, Schnitzer RE, Lindquist TD, Sun S: Dilation in neonates: a protocol. *Pediatrics* 1982;69:77-80.
- Product Information, Alcon, 2004.

1.184 Ursodiol

Title Ursodiol

Dose

10 to 15 mg/kg/dose orally every 12 hours.

Uses

Treatment of cholestasis associated with parenteral nutrition, biliary atresia, and cystic fibrosis. Also used to dissolve cholesterol gallstones.

Contraindications/Precautions

Contraindicated in patients with complete biliary obstruction [1] [2] .

Pharmacology

Ursodiol is a hydrophilic bile acid that decreases both the secretion of cholesterol from the liver and its intestinal absorption. It is well absorbed orally. After conjugation with

taurine or glycine, it then enters the enterohepatic circulation where it is excreted into the bile and intestine. It is hydrolyzed back to the unconjugated form or converted to lithocholic acid which is excreted in the feces. Serum half-life is 3 to 4 days in adults. Dissolution of gallstones may take several months. Aluminum-containing antacids bind ursodiol and inhibit absorption.

Adverse Effects

Nausea/vomiting, abdominal pain, constipation, and flatulence.

Monitoring

Hepatic transaminases and direct bilirubin concentration.

Special Considerations/Preparation

Available in 300-mg capsules. A liquid suspension may be made by opening ten (10) 300-mg capsules into a glass mortar. Mix this powder with 10 mL of glycerin and stir until smooth. Add 60 mL of Ora-Plus® to the mixture and stir. Transfer the contents of the mortar to a glass amber bottle and shake well. Add a small amount of Orange Syrup to the mortar and rinse. Pour the remaining contents into the amber glass bottle, then add enough simple syrup to make the final volume 120 mL, with a final concentration of 25-mg/mL. Shake vigorously. Mixture is stable for 60 days stored at room temperature or refrigerated.

References

- Chen C-Y, Tsao P-N, Chen H-L, et al: Ursodeoxycholic acid (UDCA) therapy in very-low-birth-weight infants with parenteral nutrition-associated cholestasis. *J Pediatr* 2004;145:317-321.
- Levine A, Maayan A, Shamir R, et al: Parenteral nutrition-associated cholestasis in preterm neonates: Evaluation of ursodeoxycholic acid treatment. *J Pediatr Endocrinol Metab*1999;12:549-553.
- Balisteri WF: Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. *J Pediatr Gastroenterol Nutr* 1997;24:573-89.
- Teitelbaum DH: Parenteral nutrition-associated cholestasis. *Curr Opin Pediatr* 1997;9:270-75.
- Mallett MS Hagan RL, Peters DA: Stability of ursodiol 25mg/mL in an extemporaneously prepared oral liquid. *Am J Health-Syst Pharm* 1997;54:1401.
- Spagnuolo MI, Iorio R, Vegnente A, Guarino A: Ursodeoxycholic acid for treatment of cholestasis in children. *Gastroenterol*1996;111:716-719.
- Ward A, Brogden RN, Heel RC, et al: Ursodeoxycholic acid: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1984;27:95.

1. Product Information: URSO Forte(R) oral tablets, ursodiol oral tablets. Aptalis Pharma US, Inc. (per FDA), Bridgewater, NJ, Jun, 2013.
2. Product Information: URSO 250(R) oral tablets, ursodiol oral tablets. Aptalis Pharma US, Inc. (per FDA), Bridgewater, NJ, Jun, 2013.

Title Ursodiol

Dose

10 to 15 mg/kg/dose orally every 12 hours.

Uses

Treatment of cholestasis associated with parenteral nutrition, biliary atresia, and cystic fibrosis. Also used to dissolve cholesterol gallstones.

Contraindications/Precautions

Contraindicated in patients with complete biliary obstruction [1] [2] .

Pharmacology

Ursodiol is a hydrophilic bile acid that decreases both the secretion of cholesterol from the liver and its intestinal absorption. It is well absorbed orally. After conjugation with taurine or glycine, it then enters the enterohepatic circulation where it is excreted into the bile and intestine. It is hydrolyzed back to the unconjugated form or converted to lithocholic acid which is excreted in the feces. Serum half-life is 3 to 4 days in adults. Dissolution of gallstones may take several months. Aluminum-containing antacids bind ursodiol and inhibit absorption.

Adverse Effects

Nausea/vomiting, abdominal pain, constipation, and flatulence.

Monitoring

Hepatic transaminases and direct bilirubin concentration.

Special Considerations/Preparation

Available in 300-mg capsules. A liquid suspension may be made by opening ten (10) 300-mg capsules into a glass mortar. Mix this powder with 10 mL of glycerin and stir until smooth. Add 60 mL of Ora-Plus® to the mixture and stir. Transfer the contents of the mortar to a glass amber bottle and shake well. Add a small amount of Orange Syrup to the mortar and rinse. Pour the remaining contents into the amber glass bottle, then add enough simple syrup to make the final volume 120 mL, with a final concentration of 25-mg/mL. Shake vigorously. Mixture is stable for 60 days stored at room temperature or refrigerated.

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1. Product Information: URSO Forte(R) oral tablets, ursodiol oral tablets. Aptalis Pharma US, Inc. (per FDA), Bridgewater, NJ, Jun, 2013.
2. Product Information: URSO 250(R) oral tablets, ursodiol oral tablets. Aptalis Pharma US, Inc. (per FDA), Bridgewater, NJ, Jun, 2013.

1.185 ValGANciclovir

Title ValGANciclovir

Dose

16 mg/kg per dose orally every 12 hours.
Treat for a minimum of 6 weeks; longer-term treatment may be appropriate.
Note: Dosing applies only to pharmaceutical grade valganciclovir. Data are not available for extemporaneous formulations.

Dose Adjustment for Hematologic Toxicity: If absolute neutrophil count (ANC) less than 500 cells/mm^3, hold drug until ANC greater than 750 cells/mm^3. If the ANC falls again to less than 750 cells/mm^3, reduce the dosage by 50%. If ANC again falls to less than 500 cells/mm^3, discontinue the drug.

Uses

Treatment of infants with symptomatic congenital CMV infections.

Contraindications/Precautions

Should not be administered if absolute neutrophil count (ANC) is less than 500 cells/mcL, the platelet count is less than 25,000/mcL, or if the hemoglobin is less than 8 g/dL. Neutropenia and anemia occur frequently (greater than 10%). Renal failure may occur, especially in patients receiving concurrent nephrotoxic drugs or in patients with dehydration. Adequate hydration should be maintained during therapy.

Black Box Warning According to the manufacturer's black box warning, the clinical toxicity of valganciclovir, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia. Animal data indicate that ganciclovir is mutagenic, teratogenic, and carcinogenic. [1] .

Pharmacology

Valganciclovir is a prodrug of ganciclovir that is rapidly converted to ganciclovir after oral administration by liver and intestinal esterases. Bioavailability is 40% to 60%, and may be improved by administering with food. Excreted entirely by the kidneys as unchanged drug. Elimination half-life in infants is 3 hours. Dosing adjustments may be required for infants with renal impairment.

Monitoring

CBC, including differential, and platelet counts should be monitor frequently, especially in patients with a history of leukopenia resulting from ganciclovir or other nucleoside analogue use, and in those with neutrophil counts less than 1000 cells/mcL at the beginning of treatment. Increase monitoring for cytopenias if therapy with oral ganciclovir is changed to valganciclovir due to increased plasma concentrations of ganciclovir after valganciclovir administration. Monitor renal function during therapy.

Special Considerations/Preparation

Valcyte® is supplied as a white to slightly yellow powder for constitution, forming a colorless to brownish yellow tutti-frutti flavored solution, which when constituted with water as directed contains 50 mg/mL valganciclovir free base. Available in glass bottles containing approximately 100 mL of solution after constitution. The inactive ingredients of Valcyte for oral solution are sodium benzoate, fumaric acid, povidone K-30, sodium saccharin, mannitol and tutti-frutti flavoring.
Valcyte® for oral solution must be constituted by the pharmacist prior to dispensing to the patient. Avoid direct contact of the powder for oral solution and the reconstituted oral solution with the skin or mucous membranes. To prepare the oral solution measure 91 mL of purified water in a graduated cylinder. Shake the Valcyte® bottle to loosen the powder. Remove the cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL. Store constituted oral solution under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) for no longer than 49 days. **Do not freeze**.

References

- Gandhi RS, Fernandez-Alvarez JR, Rabe H: Management of congenital cytomegalovirus infection: An evidence-based approach. *Acta Paediatrica* 2010;99:509-515.
- Kimberlin DW, Acosta EP, Sanchez PJ, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis* 2008; 197:836-45.
- Marshall BC, Koch WC: Antivirals for cytomegalovirus infection in neonates and infants. *Pediatr Drugs* 2009;11:309-321.
- Michaels MG: Treatment of congenital cytomegalovirus: where are we now? *Expert Rev Anti Infect Ther* 2007;5:441-448.
- Product Information: Valcyte®, valganciclovir hydrochloride tablets and oral solution, Roche, 2010.

1. Product Information: VALCYTE(R) oral solution, oral tablets, valganciclovir hydrochloride oral solution, oral tablets. Genentech USA, Inc, South San Francisco, CA, Aug, 2010.

Title ValGANciclovir

Dose

16 mg/kg per dose orally every 12 hours.
Treat for a minimum of 6 weeks; longer-term treatment may be appropriate.
Note: Dosing applies only to pharmaceutical grade valganciclovir. Data are not available for extemporaneous formulations.

Dose Adjustment for Hematologic Toxicity: If absolute neutrophil count (ANC) less than 500 cells/mm^3, hold drug until ANC greater than 750 cells/mm^3. If the ANC falls again to less than 750 cells/mm^3, reduce the dosage by 50%. If ANC again falls to less than 500 cells/mm^3, discontinue the drug.

Uses

Treatment of infants with symptomatic congenital CMV infections.

Contraindications/Precautions

Should not be administered if absolute neutrophil count (ANC) is less than 500 cells/mcL, the platelet count is less than 25,000/mcL, or if the hemoglobin is less than 8 g/dL. Neutropenia and anemia occur frequently (greater than 10%). Renal failure may occur, especially in patients receiving concurrent nephrotoxic drugs or in patients with dehydration. Adequate hydration should be maintained during therapy.

Black Box Warning According to the manufacturer's black box warning, the clinical toxicity of valganciclovir, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia. Animal data indicate that ganciclovir is mutagenic, teratogenic, and carcinogenic. [1] .

Pharmacology

Valganciclovir is a prodrug of ganciclovir that is rapidly converted to ganciclovir after oral administration by liver and intestinal esterases. Bioavailability is 40% to 60%, and may be improved by administering with food. Excreted entirely by the kidneys as unchanged drug. Elimination half-life in infants is 3 hours. Dosing adjustments may be required for infants with renal impairment.

Monitoring

CBC, including differential, and platelet counts should be monitor frequently, especially in patients with a history of leukopenia resulting from ganciclovir or other nucleoside analogue use, and in those with neutrophil counts less than 1000 cells/mcL at the beginning of treatment. Increase monitoring for cytopenias if therapy with oral

ganciclovir is changed to valganciclovir due to increased plasma concentrations of ganciclovir after valganciclovir administration. Monitor renal function during therapy.

Special Considerations/Preparation

Valcyte® is supplied as a white to slightly yellow powder for constitution, forming a colorless to brownish yellow tutti-frutti flavored solution, which when constituted with water as directed contains 50 mg/mL valganciclovir free base. Available in glass bottles containing approximately 100 mL of solution after constitution. The inactive ingredients of Valcyte for oral solution are sodium benzoate, fumaric acid, povidone K-30, sodium saccharin, mannitol and tutti-frutti flavoring.
Valcyte® for oral solution must be constituted by the pharmacist prior to dispensing to the patient. Avoid direct contact of the powder for oral solution and the reconstituted oral solution with the skin or mucous membranes. To prepare the oral solution measure 91 mL of purified water in a graduated cylinder. Shake the Valcyte® bottle to loosen the powder. Remove the cap and add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute. Add the remainder of water and shake the closed bottle well for about 1 minute. This prepared solution contains 50 mg of valganciclovir free base per 1 mL. Store constituted oral solution under refrigeration at 2 to 8 degrees C (36 to 46 degrees F) for no longer than 49 days. **Do not freeze**.

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- Product Information: Valcyte®, valganciclovir hydrochloride tablets and oral solution, Roche, 2010.

1. Product Information: VALCYTE(R) oral solution, oral tablets, valganciclovir hydrochloride oral solution, oral tablets. Genentech USA, Inc, South San Francisco, CA, Aug, 2010.

1.186 Vancomycin

Title Vancomycin

Dose

Meningitis: 15 mg/kg/dose IV
Bacteremia: 10 mg/kg/dose IV

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual

Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	Postnatal (days)	Interval (hours)
≤29	0 to 14	18
	>14	12
30 to 36	0 to 14	12
	>14	8
37 to 44	0 to 7	12
	>7	8
≥45	ALL	6

Administration

IV infusion by syringe pump over 60 minutes.

Uses

Drug of choice for serious infections caused by methicillin-resistant staphylococci (eg, *S aureus*and *S epidermidis*) and penicillin-resistant pneumococci.

Pharmacology

Vancomycin is bactericidal for most gram-positive bacteria, but bacteriostatic for enterococci. It interferes with cell wall synthesis, inhibits RNA synthesis, and alters plasma membrane function. Killing activity is primarily a time-dependent process, not concentration-dependent. MICs for sensitive organisms are less than or equal to 1 mcg/mL. Diffusion into the lung and bone is variable. CSF concentrations in premature infants ranged from 26 to 68% of serum concentrations. Protein binding is as high as 50% in adults. Elimination is primarily by glomerular filtration, with a small amount of hepatic metabolism.

Adverse Effects

Nephrotoxicity and ototoxicity: Enhanced by aminoglycoside therapy.
Rash and hypotension (red man syndrome): Appears rapidly and resolves within minutes to hours. Lengthening infusion time usually eliminates risk for subsequent doses.
Neutropenia: Reported after prolonged administration (more than 3 weeks).
Phlebitis: May be minimized by slow infusion and dilution of the drug.

Monitoring

To minimize the risk of ototoxicity, auditory function monitoring should be considered in patients receiving concomitant ototoxic drugs [1] . Monitor renal function for nephrotoxicity. Periodic monitoring of white blood cell count should be done to screen for neutropenia in patients on prolonged therapy with vancomycin or those who are receiving concomitant drugs that may cause neutropenia. Monitor for infusion-related events, including hypotension and red man syndrome [2] .

Assessment of serum vancomycin trough concentrations is recommended for monitoring efficacy. Troughs should be obtained just prior to the next dose under steady state conditions (approximately just before the fourth dose) and then repeated as clinically necessary. Trough concentrations (not peak) are the most accurate measure to monitor for efficacy. Monitoring of peak concentrations is not recommended in most cases since vancomycin has been found to be a concentration-independent antibiotic and peak concentrations may be affected by multi-compartment pharmacokinetic properties [3] [1] . Due to the variability in pharmacokinetic parameters, peak and trough concentrations have been recommended to provide more individualized dosing in neonates [4] If peak concentrations are measured, draw 60 minutes after end of infusion.

Data are lacking for correlating pharmacokinetic/pharmacodynamic properties of vancomycin with its clinical efficacy in the neonatal population [5] . The following recommendations are based primarily on adult data. Based on pharmacodynamic properties of vancomycin and their presumed similarity among different age groups, these recommendations may be applicable to neonates [6] .

Recommended trough concentration range for native valve endocarditis (non-MRSA) is 10 to 15 mcg/mL [7] .

Recommended trough concentration range for bacterial meningitis is 15 to 20 mcg/mL [8] .
Many experts recommend a trough of 15 to 20 mcg/mL when treating MRSA bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, complicated skin and soft-tissue infections, or bone/joint infections [3] [1] . A suggested AUC/MIC ratio greater than 400 provides near maximal bactericidal activity and may be an alternative monitoring parameter for efficacy when treating MRSA [9] [10] .
Recommended trough concentration range for less severe infections is 10 to 15 mcg/mL [1] .

For treatment of MRSA, vancomycin doses necessary to achieve trough concentrations of 15 to 20 mcg/mL or an AUC/MIC ratio greater than 400, particularly when treating infections with an MIC greater than 1 mcg/mL, may increase the risk for nephrotoxicity [9] . Additionally, an MIC greater than 1 mcg/mL has been associated with an increased likelihood of treatment failure in adult patients with MRSA [11] [12] [13] . In a recent report from a US institution, the modal vancomycin MIC was 1.5 mcg/mL for invasive community-acquired MRSA isolates in pediatric patients [14] . In a retrospective study of pediatric patients (n=22, including 8 preterm infants) receiving vancomycin therapy for MRSA bloodstream infection, 50% of patients were considered treatment failures (mortality, persistent bacteremia for greater than 7 days or infection recurrence within

30 days of therapy). There was no difference in the number of patients with MICs greater than 1 mcg/mL or in the time to troughs greater than 15 mcg/mL between treatment failures and non-failures. Prematurity and PVL-positive isolates were the only significant factors associated with treatment failure [15] .
Methicillin-resistant *Staphylococcus aureus* isolates with a vancomycin MIC greater than 2 mcg/mL (eg, vancomycin-intermediate or vancomycin-resistant *S. aureus* [VISA or VRSA]) require alternative therapy [3] .
For shunt infections, consider monitoring CSF vancomycin levels during therapy to assess drug concentrations (goal: trough, 5 to 10 mcg/mL) and potential drug accumulation [16] [17] [18] .

Special Considerations/Preparation

Available as powder for injection in 500-mg and 1-g vials. Reconstitute 500-mg and 1-g vial with 10 mL and 20 mL of sterile water for injection, respectively, to make a final concentration of 50 mg/mL. Reconstituted solution stable for 4 days refrigerated. Dilute prior to administration using D_5W or NS to a maximum concentration of 5 mg/mL (concentrations up to 10 mg/mL may also be used in fluid restricted patients) [2] .

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alprostadil, amikacin, ampicillin, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium gluconate, caspofungin, cimetidine, enalaprilat, esmolol, famotidine, fluconazole, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, insulin, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, dexamethasone, heparin (concentrations greater than 1 unit/mL), mezlocillin, nafcillin, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, ticarcillin, and ticarcillin/clavulanate.

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Title Vancomycin

Dose

Meningitis: 15 mg/kg/dose IV
Bacteremia: 10 mg/kg/dose IV

Antibiotic Dosing Chart:
Renal function and drug elimination are most strongly correlated with Postmenstrual Age (PMA; equivalent to Gestational Age plus Postnatal Age). PMA is the primary determinant of dosing interval, with Postnatal Age as the secondary qualifier.

Dosing Interval Chart

PMA (weeks)	Postnatal (days)	Interval (hours)
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Administration

IV infusion by syringe pump over 60 minutes.

Uses

Drug of choice for serious infections caused by methicillin-resistant staphylococci (eg, *S aureus*and *S epidermidis*) and penicillin-resistant pneumococci.

Pharmacology

Vancomycin is bactericidal for most gram-positive bacteria, but bacteriostatic for enterococci. It interferes with cell wall synthesis, inhibits RNA synthesis, and alters plasma membrane function. Killing activity is primarily a time-dependent process, not concentration-dependent. MICs for sensitive organisms are less than or equal to 1 mcg/mL. Diffusion into the lung and bone is variable. CSF concentrations in premature infants ranged from 26 to 68% of serum concentrations. Protein binding is as high as 50% in adults. Elimination is primarily by glomerular filtration, with a small amount of hepatic metabolism.

Adverse Effects

Nephrotoxicity and ototoxicity: Enhanced by aminoglycoside therapy.
Rash and hypotension (red man syndrome): Appears rapidly and resolves within minutes to hours. Lengthening infusion time usually eliminates risk for subsequent doses.
Neutropenia: Reported after prolonged administration (more than 3 weeks).
Phlebitis: May be minimized by slow infusion and dilution of the drug.

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For shunt infections, consider monitoring CSF vancomycin levels during therapy to assess drug concentrations (goal: trough, 5 to 10 mcg/mL) and potential drug accumulation [16] [17] [18] .

Special Considerations/Preparation

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Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, alprostadil, amikacin, ampicillin, aminophylline, amiodarone, aztreonam, caffeine citrate, calcium gluconate, caspofungin, cimetidine,

enalaprilat, esmolol, famotidine, fluconazole, heparin (concentrations of 1 unit/mL or less), hydrocortisone succinate, insulin, linezolid, lorazepam, magnesium sulfate, meropenem, midazolam, milrinone, morphine, nicardipine, pancuronium bromide, potassium chloride, propofol, ranitidine, remifentanil, sodium bicarbonate, vecuronium, and zidovudine.

Terminal Injection Site Incompatibility

Cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, dexamethasone, heparin (concentrations greater than 1 unit/mL), mezlocillin, nafcillin, pentobarbital, phenobarbital, piperacillin, piperacillin/tazobactam, ticarcillin, and ticarcillin/clavulanate.

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1.187 Varicella-zoster Immune Globulin

Title Varicella-zoster Immune Globulin

Dose

Prevention or Attenuation of Varicella Infection
Administer a single dose as soon as possible, **ideally within 96 hours of exposure,** for greatest effectiveness [1] . May be administered up to 10 days following exposure [2] [3] . Administer a second full dose if additional exposures occur more than 3 weeks following initial dose [2] [4] [1] .
2 kg or less: Single dose of 62.5 international units (one-half vial) IM [1] .
Greater than 2 kg: Single dose of 125 international units (one vial) IM [1] .

Administration

Administer by **IM injection only,** into the anterolateral aspects of the upper thigh. To avoid sciatic nerve injury, do not use the gluteal region for injection [1] .

Uses

Post-exposure prophylaxis of varicella. The decision to administer varicella zoster immune globulin depends 3 factors: 1) lack of evidence of immunity, 2) whether exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the general population. The following neonatal patients should receive varicella zoster immune globulin following exposure [2] [4] :

- Immunocompromised patients
- Neonates whose mothers have signs and symptoms of varicella from 5 days before to 2 days after delivery
- Premature infants, exposed anytime during entire period for which they require hospital care for their prematurity, born at 28 weeks of gestation or greater whose mothers do not have evidence of immunity
- Premature infants, exposed anytime during entire period for which they require hospital care for their prematurity, born at less than 28 weeks of gestation or who weigh 1000 g or less at birth, regardless of maternal immunity

Varicella zoster immune globulin is not recommended for healthy, full-term infants who are exposed postnatally, even if their mothers have no history of varicella infection [4] .

Any patient who received varicella zoster immune globulin to prevent varicella infection should receive varicella vaccine, unless contraindicated, at the recommended age [4] .

Pediatric FDA Approved Indications
Indicated for post-exposure prophylaxis of varicella in high-risk individuals. High-risk groups include [1] :

- Premature infants
- Newborns of mothers having varicella shortly before or after delivery
- Infants less than 1 year old
- Immunocompromised patients
- Pregnant females

Contraindications/Precautions

Contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity to avoid a possible anaphylactoid reaction [1] .

In patients with severe thrombocytopenia or any coagulation disorder that would contraindicate IM injection, only administer if the expected benefits outweigh the potential risks. Thrombotic events may occur; those at risk include those with multiple cardiovascular risk factors, impaired cardiac output, coagulation disorders, prolong period of immobilization, and/or know-suspected hyperviscosity [1] .

Pharmacology

Sterile preparation of purified human IgG prepared from plasma donated by healthy, screened donors with high titers of antibodies to the varicella zoster virus (VZV), the causative agent of chickenpox. Provides passive immunization for non-immune individuals exposed to VZV, thereby reducing the severity of varicella infection. In volunteers, the mean peak concentration of varicella antibodies occurs within 5 days of administration. [1] .

Adverse Effects

The most common adverse effects observed in clinical trials and patients are injection site pain (2%) and headache (2%). Less common adverse effects include chills, fatigue, rash, and nausea [1] .

Special Considerations/Preparation

Available as a kit with a glass vial containing approximately 125 international units of freeze-dried varicella zoster virus antibodies and a single dose vial of sterile diluent. Store under refrigeration and do not freeze; Do not use solution that has been frozen. Do not use after expiration date. May store reconstituted solution for up to 12 hours under refrigeration prior to use. Partially used vials, including the diluent, should be discarded [1] . As this product is available only through investigational new drug application expanded access protocol, obtain through FFF Enterprises by calling 1-800-843-7477 or by contacting online at http://www.fffenterprises.com [3] .

References

- Product Information: VARIZIG(R) intramuscular injection powder, varicella zoster immune globulin (human) intramuscular injection powder. Cangene Corporation (per FDA), Winnipeg, ON, Dec, 2012.

- Centers for Disease Control and Prevention (CDC) : Updated recommendations for use of VariZIG - United States, 2013. MMWR Morb Mortal Wkly Rep Jul19, 2013; 62(28): 574-576.

- Centers for Disease Control and Prevention (CDC) : FDA approval of an extended period for administering VariZIG for postexposure prophylaxis of varicella. MMWR Morb Mortal Wkly Rep Mar30, 2012; 61(12): 212-212.

- Marin M, Guris D, Chaves SS et al: Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jun22, 2007; 56(RR-4): 1-40.

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Dose

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Administration

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Indicated for post-exposure prophylaxis of varicella in high-risk individuals. High-risk groups include [1] :

- Premature infants
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Contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity to avoid a possible anaphylactoid reaction [1] .

In patients with severe thrombocytopenia or any coagulation disorder that would contraindicate IM injection, only administer if the expected benefits outweigh the potential risks. Thrombotic events may occur; those at risk include those with multiple cardiovascular risk factors, impaired cardiac output, coagulation disorders, prolong period of immobilization, and/or know-suspected hyperviscosity [1] .

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Available as a kit with a glass vial containing approximately 125 international units of freeze-dried varicella zoster virus antibodies and a single dose vial of sterile diluent. Store under refrigeration and do not freeze; Do not use solution that has been frozen. Do not use after expiration date. May store reconstituted solution for up to 12 hours under refrigeration prior to use. Partially used vials, including the diluent, should be discarded [1] . As this product is available only through investigational new drug application expanded access protocol, obtain through FFF Enterprises by calling 1-800-843-7477 or by contacting online at http://www.fffenterprises.com [3] .

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- Product Information: VARIZIG(R) intramuscular injection powder, varicella zoster immune globulin (human) intramuscular injection powder. Cangene Corporation (per FDA), Winnipeg, ON, Dec, 2012.

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- Marin M, Guris D, Chaves SS et al: Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep Jun22, 2007; 56(RR-4): 1-40.

1.188 Vecuronium

Title Vecuronium

Dose

0.1 mg/kg (0.03 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Black Box Warning According to the manufacturer's black box warning, vecuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors. Sympathetic stimulation is minimal. Vecuronium is metabolized rapidly in the liver to 3-desacetyl-vecuronium, which is 50% to 70% active, and is excreted renally. Newborns, particularly premature infants, are especially sensitive to vecuronium; this sensitivity diminishes with age. Onset of action is 1 to 2 minutes; duration of effect is prolonged with higher doses and in premature infants. Skeletal relaxation/paralysis is reversed by neostigmine and atropine.
Factors affecting duration of neuromuscular blockade:
Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, cardiovascular disease, aminoglycosides, hypokalemia, hypermagnesemia, renal failure, and younger age.

Antagonism: Alkalosis, epinephrine, and hyperkalemia.
Sensation remains intact; analgesia should be used for painful procedures.

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. When used alone, cardiovascular side effects are minimal; however, decreases in heart rate and blood pressure have been observed when used concurrently with narcotics.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

Special Considerations/Preparation

Available as powder for injection in 10-mg and 20-mg vials. Reconstitute 10 mg-vial with 10 mL of compatible solution (1 mg/mL). After reconstitution- 24 hrs stability in refrigerator. Single use only, discard unused portion. After dilution, use within 24 hours after admixing.
A 0.4-mg/mL dilution may be made by diluting 1 mL of 1-mg/mL concentration with 1.5 mL of preservative-free normal saline. Dilution is stable for 24 hours in refrigerator.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, aminophylline, amiodarone, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, linezolid, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Diazepam, furosemide, ibuprofen lysine, and micafungin.

References

- Martin LD, Bratton SL, O'Rourke P: Clinical uses and controversies of neuromuscular blocking agents in infants and children. *Crit Care Med* 1999;27:1358-1368.
- Segredo V, Matthay MA, Sharma ML, et al: Prolonged neuromuscular blockage after long-term administration of vecuronium in two critically ill patients. *Anesthesiology* 1990;72:566.
- Bhutani VK, Abbasi S, Sivieri EM: Continuous skeletal muscle paralysis: Effect on neonatal pulmonary mechanics. *Pediatrics* 1988;81:419.

- Gravlee GP, Ramsey FM, Roy RC, et al: Rapid administration of a narcotic and neuromuscular blocker: A hemodynamic comparison of fentanyl, sufentanil, pancuronium, and vecuronium. *Anesth Analg* 1988;67:39.
- Meretoja OA, Wirtavuori K, Neuvonen PJ: Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. *Anesth Analg* 1988;67:21.
- Costarino AT, Polin RA: Neuromuscular relaxants in the neonate. *Clin Perinatol* 1987;14:965.
- Product Information, Bedford Laboratories, 2007

Title Vecuronium

Dose

0.1 mg/kg (0.03 to 0.15 mg/kg) IV push, as needed for paralysis. Usual dosing interval is 1 to 2 hours. Adjust dose as needed based on duration of paralysis.

Uses

Skeletal muscle relaxation/paralysis in infants requiring mechanical ventilation. Proposed desirable effects are improved oxygenation/ ventilation, reduced barotrauma, and reduced fluctuations in cerebral blood flow.

Black Box Warning According to the manufacturer's black box warning, vecuronium should be administered by adequately trained individuals familiar with its actions, characteristics, and hazards.

Pharmacology

Nondepolarizing muscle-relaxant that competitively antagonizes autonomic cholinergic receptors. Sympathetic stimulation is minimal. Vecuronium is metabolized rapidly in the liver to 3-desacetyl-vecuronium, which is 50% to 70% active, and is excreted renally. Newborns, particularly premature infants, are especially sensitive to vecuronium; this sensitivity diminishes with age. Onset of action is 1 to 2 minutes; duration of effect is prolonged with higher doses and in premature infants. Skeletal relaxation/paralysis is reversed by neostigmine and atropine.
Factors affecting duration of neuromuscular blockade:
Potentiation: Acidosis, hypothermia, neuromuscular disease, hepatic disease, cardiovascular disease, aminoglycosides, hypokalemia, hypermagnesemia, renal failure, and younger age.
Antagonism: Alkalosis, epinephrine, and hyperkalemia.
Sensation remains intact; analgesia should be used for painful procedures.

Adverse Effects

Hypoxemia may occur because of inadequate mechanical ventilation and deterioration in pulmonary mechanics. When used alone, cardiovascular side effects are minimal; however, decreases in heart rate and blood pressure have been observed when used concurrently with narcotics.

Monitoring

Monitor vital signs frequently, blood pressure continuously. Use some form of eye lubrication.

Special Considerations/Preparation

Available as powder for injection in 10-mg and 20-mg vials. Reconstitute 10 mg-vial with 10 mL of compatible solution (1 mg/mL). After reconstitution- 24 hrs stability in refrigerator. Single use only, discard unused portion. After dilution, use within 24 hours after admixing.
A 0.4-mg/mL dilution may be made by diluting 1 mL of 1-mg/mL concentration with 1.5 mL of preservative-free normal saline. Dilution is stable for 24 hours in refrigerator.

Solution Compatibility

D_5W, LR, and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Alprostadil, aminophylline, amiodarone, cefazolin, cimetidine, dobutamine, dopamine, epinephrine, esmolol, fentanyl, fluconazole, gentamicin, heparin, hydrocortisone succinate, isoproterenol, linezolid, lorazepam, midazolam, milrinone, morphine, nicardipine, nitroglycerin, nitroprusside, propofol, ranitidine, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Diazepam, furosemide, ibuprofen lysine, and micafungin.

References

- Martin LD, Bratton SL, O'Rourke P: Clinical uses and controversies of neuromuscular blocking agents in infants and children. *Crit Care Med* 1999;27:1358-1368.
- Segredo V, Matthay MA, Sharma ML, et al: Prolonged neuromuscular blockage after long-term administration of vecuronium in two critically ill patients. *Anesthesiology* 1990;72:566.
- Bhutani VK, Abbasi S, Sivieri EM: Continuous skeletal muscle paralysis: Effect on neonatal pulmonary mechanics. *Pediatrics* 1988;81:419.
- Gravlee GP, Ramsey FM, Roy RC, et al: Rapid administration of a narcotic and neuromuscular blocker: A hemodynamic comparison of fentanyl, sufentanil, pancuronium, and vecuronium. *Anesth Analg* 1988;67:39.
- Meretoja OA, Wirtavuori K, Neuvonen PJ: Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. *Anesth Analg* 1988;67:21.
- Costarino AT, Polin RA: Neuromuscular relaxants in the neonate. *Clin Perinatol* 1987;14:965.
- Product Information, Bedford Laboratories, 2007

1.189 Vi-DaylinÂ® MVI Drops

Title Vi-DaylinÂ® MVI Drops

Table

Vi-Daylin® Multivitamin Drops

Vitamins	**Nutrient amount per 0.6 mL**
A, IU	5000
D, IU	400
C, mg	50
Thiamine B 1 , mg	1.5
Riboflavin B 2 , mg	1.2
Niacin, mg	10
B 6 , mg	0.5
Minerals	
Iron, mg	0

Title Vi-DaylinÂ® MVI Drops

Table

Vi-Daylin® Multivitamin Drops

Vitamins	**Nutrient amount per 0.6 mL**
A, IU	5000
D, IU	400
C, mg	50
Thiamine B 1 , mg	1.5
Riboflavin B 2 , mg	1.2
Niacin, mg	10
B 6 , mg	0.5
Minerals	

Iron, mg	0

1.190 Vi-SolÂ® Multivitamin Products

Title Vi-SolÂ® Multivitamin Products

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician. Percentages of the Reference Daily Intakes (%RDIs) listed in the table below are for infants.

Vi-Sol® Products

	Tri-Vi-Sol ® Multivitamin Drops	**Tri-Vi-Sol ® Multivitamin with Iron Drops**	**Poly-Vi-Sol ® Multivitamin Drops**	**Poly-Vi-Sol ® Multivitamin with Iron Drops**
	Amt (%RDI)	**Amt (%RDI)**	**Amt (%RDI)**	**Amt (%RDI)**
Vitamins				
A (IU)	1500 (100)	1500 (100)	1500 (100)	1500 (100)
D (IU)	400 (100)	400 (100)	400 (100)	400 (100)
C (mg)	35 (100)	35 (100)	35 (100)	35 (100)
E (IU)			5 (100)	5 (100)
Thiamine (B 1) (mg)			0.5 (100)	0.5 (100)
Riboflavin (B 2) (mg)			0.6 (100)	0.6 (100)
Niacin (mg)			8 (100)	8 (100)
B 6 (mg)			0.4 (100)	0.4 (100)
B 12 (mcg)			2 (100)	*0
Minerals				
Iron (mg)		10 (67)		10 (67)

*Iron product contains no vitamin B12 due to instability with iron and vitamin C concentrations.

Title Vi-SolÂ® Multivitamin Products

Dose

1 dropperful (1 mL) every 24 hours, or as directed by physician. Percentages of the Reference Daily Intakes (%RDIs) listed in the table below are for infants.

Vi-Sol® Products

	Tri-Vi-Sol ® Multivitamin Drops	**Tri-Vi-Sol ® Multivitamin with Iron Drops**	**Poly-Vi-Sol ® Multivitamin Drops**	**Poly-Vi-Sol ® Multivitamin with Iron Drops**
	Amt (%RDI)	**Amt (%RDI)**	**Amt (%RDI)**	**Amt (%RDI)**
Vitamins				
A (IU)	1500 (100)	1500 (100)	1500 (100)	1500 (100)
D (IU)	400 (100)	400 (100)	400 (100)	400 (100)
C (mg)	35 (100)	35 (100)	35 (100)	35 (100)
E (IU)			5 (100)	5 (100)
Thiamine (B 1) (mg)			0.5 (100)	0.5 (100)
Riboflavin (B 2) (mg)			0.6 (100)	0.6 (100)
Niacin (mg)			8 (100)	8 (100)
B 6 (mg)			0.4 (100)	0.4 (100)
B 12 (mcg)			2 (100)	*0
Minerals				
Iron (mg)		10 (67)		10 (67)

*Iron product contains no vitamin B12 due to instability with iron and vitamin C concentrations.

1.191 Vitamin A

Title Vitamin A

Dose

Vitamin A Deficiency - VLBW and ELBW Neonates: 5000 units IM 3 times weekly for 4 weeks [1] .

Administration

Do not administer IV. Administer IM using a 29-g needle and insulin syringe [2] .

Uses

To reduce the risk of chronic lung disease in high risk premature neonates with Vitamin A deficiency [3] [4] [1] [5] . In the NICHD-sponsored trial, 14 infants needed to be treated to prevent 1 case of chronic lung disease [1] . In a follow-up study of this trial, there were no significant differences in neurodevelopmental outcomes or mortality at 18 to 22 months corrected age between infants receiving vitamin A and controls; however, the original trial was not adequately powered to confirm these follow-up endpoints [6] ..

Pharmacology

The pulmonary histopathologic changes of BPD and Vitamin A deficiency are remarkably similar. Vitamin A is the generic name for a group of fat soluble compounds which have the biological activity of the primary alcohol, retinol. Retinol metabolites exhibit potent and site-specific effects on gene expression and on lung growth and development. Retinol is supplied in the diet as retinyl esters [5] .

Adverse Effects

See monitoring section. Concomitant vitamin A (particularly larger doses) and glucocorticoids (particularly dexamethasone) should be used cautiously as significant, short-term increases in plasma concentrations of retinol and retinol binding protein can occur [7] [8] [9] . Preterm neonates from these studies were not receiving the high doses of vitamin A recommended while receiving dexamethasone therapy.

Monitoring

Assess regularly for signs of toxicity: full fontanel, lethargy, irritability, hepatomegaly, edema, mucocutaneous lesions, and bony tenderness. Consider measuring plasma retinol concentrations if available, especially if patient is also receiving glucocorticoid therapy. Desired concentrations are approximately 30 to 60 mcg/dL [5] . Concentrations less than 20 mcg/dL indicate deficiency, while those greater than 100 mcg/dL are potentially toxic [5] .

Special Considerations/Preparation

Available as Aquasol A® Parenteral (water-miscible vitamin A palmitate) 50,000 units per mL, equivalent to 15 mg retinol per mL, in 2-mL vials. **Protect from light.**Store refrigerated at 36 to 46 degrees F (2 to 8 degrees C). Do not freeze [2] .

References

- Tyson JE, Wright LL, Oh W et al: Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med Jun24, 1999; 340(25): 1962-1968.

- Product Information: AQUASOL A(R) PARENTERAL intramuscular injection, vitamin a palmitate intramuscular injection. Mayne Pharma (USA) Inc., Paramus, NJ, 04/00/2005.

- Darlow BA: Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. Cochrane Database Syst Rev Oct5, 2011; 2011(10): 1-.

- Laughon MM: Prevention of chronic lung disease. Semin Fetal Neonatal Med Dec, 2009; 14(6): 374-382.

- Shenai JP: Vitamin A supplementation in very low birth weight neonates: rationale and evidence. Pediatrics Dec, 1999; 104(6): 1369-1374.

- Ambalavanan N, Tyson JE, Kennedy KA et al: Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months. Pediatrics Mar, 2005; 115(3): e249-e254.

- Atkinson SA: Special nutritional needs of infants for prevention of and recovery from bronchopulmonary dysplasia. J Nutr Mar, 2001; 131(3): 942S-946S.

- Shenai JP: Vitamin A status and postnatal dexamethasone treatment in bronchopulmonary dysplasia. Pediatrics Sep, 2000; 106(3): 547-553.

- Georgieff MK, Mammel MC, Mills MM et al: Effect of postnatal steroid administration on serum vitamin A concentrations in newborn infants with respiratory compromise. J Pediatr Feb, 1989; 114(2): 301-304.

Title Vitamin A

Dose

Vitamin A Deficiency - VLBW and ELBW Neonates: 5000 units IM 3 times weekly for 4 weeks [1] .

Administration

Do not administer IV. Administer IM using a 29-g needle and insulin syringe [2] .

Uses

To reduce the risk of chronic lung disease in high risk premature neonates with Vitamin A deficiency [3] [4] [1] [5] . In the NICHD-sponsored trial, 14 infants needed to be treated to prevent 1 case of chronic lung disease [1] . In a follow-up study of this trial, there were no significant differences in neurodevelopmental outcomes or mortality at 18 to 22 months corrected age between infants receiving vitamin A and controls; however, the original trial was not adequately powered to confirm these follow-up endpoints [6] ..

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1.192 Vitamin D

Title Vitamin D

Dose

Supplementation: 400 units per day orally [1] .
Treatment of vitamin D deficiency: 1000 units per day orally.

Uses

Prevention and treatment of vitamin D deficiency. For breastfed infants, the AAP recommends that supplementation should begin within the first few days of life, regardless of whether the infant is exclusively breastfed or supplemented with infant formula. Exclusively formula-fed infants receiving at least 1000 mL/day of formula receive adequate amounts of vitamin D without supplementation. Recent data indicate that administration of high doses of vitamin D (4000 to 6400 units daily) to breastfeeding mothers is capable of raising 25(OH)-D levels in the infant to levels similar to those seen with infant supplementation without causing hypervitaminosis D in the mother.

Pharmacology

The main source of vitamin D is vitamin D_3, which is synthesized in the skin through exposure to ultraviolet B (UV-B) radiation. UV-B in the range of 290 to 315 nm initiates the synthesis of vitamin D_3 by converting 7-dehydrocholesterol into previtamin D_3, which is further converted to vitamin D_3. Vitamin D_3 binds to vitamin D-binding protein and is transported to the liver for 25-hydroxylation to 25(OH)-D (calcidiol). Calcidiol undergoes further hydroxylation in the kidney and other tissues to calcitriol (1,25-dihydroxyvitamin D) (1,25-OH_2-D), the active form of vitamin D. Calcitriol stimulates the intestinal absorption of calcium and phosphorous, renal reabsorption of filtered calcium, and mobilization of calcium and phosphorous from bone. As a supplement, vitamin D_3 has been shown to be more effective in raising 25(OH)-D levels when compared with vitamin D_2.

Adverse Effects

Signs of vitamin D toxicity include hypercalcemia, azotemia, vomiting, and nephrocalcinosis. A 25(OH)-D concentration greater than 250 nmol/L may be associated with a risk for vitamin D intoxication.

Monitoring

Signs of vitamin D deficiency include symptomatic hypocalcemia (including seizures), growth failure, irritability, lethargy, and increased susceptibility for respiratory infections. A 25-hydroxyvitamin D (25(OH)-D) concentration of less than 50 nmol/L is thought to be indicative of vitamin D deficiency in infants [1] [2] [3] .

Special Considerations/Preparation

Vitamin D supplements are available as vitamin D_2 (ergocalciferol; plant derived) and vitamin D_3 (cholecalciferol; animal derived).
Drisdol® (ergocalciferol oral solution) contains 200 units (5 mcg) vitamin D_2 per drop. The inactive ingredient is propylene glycol.
Baby D drops™ (cholecalciferol liquid vitamin supplement) is supplied as 400 units vitamin D_3 per drop. The inactive ingredient is purified palm-kernel oil.
Bio-D-Mulsion™ (cholecalciferol; emulsified vitamin D_3) is supplied as 400 units per drop. Inactive ingredients include water, sesame oil and acacia.
Just D (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. The inactive ingredient is corn oil.
Enfamil® D-Vi-Sol™ (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. Inactive ingredients include glycerin, water, polysorbate 80, citric acid, sodium citrate, sodium hydroxide, artificial flavor and artificial caramel color.

The vitamin D_3 content of Vi-Daylin® and Vi-Sol® products is 400 units per mL.
The vitamin D_3 content of AquADEKs™ drops is 400 units per mL.

References

- American Academy of Pediatrics Committee on Nutrition: Vitamins. In: *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, Il: American Academy of Pediatrics 2009: pp 458, 464-466.
- Wagner CL, Greer FR and the Section on Breastfeeding and Committee on Nutrition: Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142-1152.
- Misra M, Pacaud D, Petryk A et al: Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. *Pediatrics* 2008;122:398-417.

1. Institute of Medicine : Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press, Washington, DC, 2011.
2. Hall WB: Vitamin d deficiency in cystic fibrosis. Int J Endocrinol 2010; 2010: 218691.
3. Greer FR: Defining vitamin D deficiency in children: beyond 25-OH vitamin D serum concentrations. Pediatrics Nov, 2009; 124(5): 1471-1473.

Title Vitamin D

Dose

Supplementation: 400 units per day orally [1] .
Treatment of vitamin D deficiency: 1000 units per day orally.

Uses

Prevention and treatment of vitamin D deficiency. For breastfed infants, the AAP recommends that supplementation should begin within the first few days of life, regardless of whether the infant is exclusively breastfed or supplemented with infant formula. Exclusively formula-fed infants receiving at least 1000 mL/day of formula receive adequate amounts of vitamin D without supplementation. Recent data indicate that administration of high doses of vitamin D (4000 to 6400 units daily) to breastfeeding mothers is capable of raising 25(OH)-D levels in the infant to levels similar to those seen with infant supplementation without causing hypervitaminosis D in the mother.

Pharmacology

The main source of vitamin D is vitamin D_3, which is synthesized in the skin through exposure to ultraviolet B (UV-B) radiation. UV-B in the range of 290 to 315 nm initiates the synthesis of vitamin D_3 by converting 7-dehydrocholesterol into previtamin D_3, which is further converted to vitamin D_3. Vitamin D_3 binds to vitamin D-binding protein and is transported to the liver for 25-hydroxylation to 25(OH)-D (calcidiol). Calcidiol undergoes further hydroxylation in the kidney and other tissues to calcitriol (1,25-dihydroxyvitamin D) (1,25-OH_2-D), the active form of vitamin D. Calcitriol stimulates the intestinal absorption of calcium and phosphorous, renal reabsorption of filtered calcium, and mobilization of calcium and phosphorous from bone. As a supplement, vitamin D_3 has been shown to be more effective in raising 25(OH)-D levels when compared with vitamin D_2.

Adverse Effects

Signs of vitamin D toxicity include hypercalcemia, azotemia, vomiting, and nephrocalcinosis. A 25(OH)-D concentration greater than 250 nmol/L may be associated with a risk for vitamin D intoxication.

Monitoring

Signs of vitamin D deficiency include symptomatic hypocalcemia (including seizures), growth failure, irritability, lethargy, and increased susceptibility for respiratory infections. A 25-hydroxyvitamin D (25(OH)-D) concentration of less than 50 nmol/L is thought to be indicative of vitamin D deficiency in infants [1] [2] [3] .

Special Considerations/Preparation

Vitamin D supplements are available as vitamin D_2 (ergocalciferol; plant derived) and vitamin D_3 (cholecalciferol; animal derived).
Drisdol® (ergocalciferol oral solution) contains 200 units (5 mcg) vitamin D_2 per drop. The inactive ingredient is propylene glycol.
Baby D drops™ (cholecalciferol liquid vitamin supplement) is supplied as 400 units

vitamin D_3 per drop. The inactive ingredient is purified palm-kernel oil.
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Just D (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. The inactive ingredient is corn oil.
Enfamil® D-Vi-Sol™ (cholecalciferol) is supplied as 400 units vitamin D_3 per mL. Inactive ingredients include glycerin, water, polysorbate 80, citric acid, sodium citrate, sodium hydroxide, artificial flavor and artificial caramel color.

The vitamin D_3 content of Vi-Daylin® and Vi-Sol® products is 400 units per mL.
The vitamin D_3 content of AquADEKs™ drops is 400 units per mL.

References

- American Academy of Pediatrics Committee on Nutrition: Vitamins. In: *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, Il: American Academy of Pediatrics 2009: pp 458, 464-466.
- Wagner CL, Greer FR and the Section on Breastfeeding and Committee on Nutrition: Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142-1152.
- Misra M, Pacaud D, Petryk A et al: Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. *Pediatrics* 2008;122:398-417.

1. Institute of Medicine : Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press, Washington, DC, 2011.
2. Hall WB: Vitamin d deficiency in cystic fibrosis. Int J Endocrinol 2010; 2010: 218691.
3. Greer FR: Defining vitamin D deficiency in children: beyond 25-OH vitamin D serum concentrations. Pediatrics Nov, 2009; 124(5): 1471-1473.

1.193 Vitamin E

Title Vitamin E

Dose

5 to 25 units per day orally. Dilute with feedings. Do not administer simultaneously with iron; iron absorption is impaired.

Uses

Prevention of vitamin E deficiency. May be indicated in babies receiving erythropoietin and high iron dosages. Higher doses used to reduce oxidant-induced injury (ROP, BPD, IVH) remain controversial.

Pharmacology

Alpha-tocopherol is the most active antioxidant of the group of tocopherols known as vitamin E. The amount required by the body is primarily dependent upon the dietary intake of fat, especially polyunsaturated fatty acids (PUFA). Human milk and currently available infant formulas contain adequate vitamin E and have appropriate E:PUFA

ratios to prevent hemolytic anemia. Infants receiving supplemental iron amounts above 2 mg/kg/day may also require additional vitamin E. Oral absorption of vitamin E is dependent upon hydrolysis that requires bile salts and pancreatic esterases. This can be quite variable in very immature infants and those with fat malabsorption. Free tocopherol is absorbed in the small intestine, taken via chylomicrons into the gastrointestinal lymphatics, then carried via low-density lipoproteins to be incorporated into cell membranes. Significant tissue accumulation may occur with pharmacologic doses.

Adverse Effects

Feeding intolerance may occur due to hyperosmolarity of preparation. Pharmacologic doses of alpha tocopherol have been associated with increased rates of sepsis (antioxidant effect of drug) and NEC (osmolarity of oral formulation).

Monitoring

Assess feeding tolerance. Signs of vitamin E deficiency include hemolytic anemia and thrombocytosis. Physiologic serum vitamin E concentrations are between 0.8 and 3.5 mg/dL.

Special Considerations/Preparation

Available as liquid drops: Aquavit E® (Hospira), 15 units (equivalent to 15 mg) per 0.3 mL. Also contains polysorbate 80, propylene glycol, sorbitol, saccharin, and artificial flavor. Hyperosmolar (3620 mOsm/kg H_2O). Store at controlled room temperature.

References

- Gross SJ: Vitamin E. In Tsang RC, Lucas A, Uauy R, Zlotkin S (eds): *Nutritional Needs of the Preterm Infant: Scientific Basis and Practical Guidelines*. Pauling, New York: Caduceus Medical Publishers, 1993, pp 101-109.
- Roberts RJ, Knight ME: Pharmacology of vitamin E in the newborn. *Clin Perinatol* 1987;14:843-855.
- Raju TNK, Langenberg P, Bhutani V, Quinn GE: Vitamin E prophylaxis to reduce retinopathy of prematurity: A reappraisal of published trials. *J Pediatr* 1997;131:844-850.

Title Vitamin E

Dose

5 to 25 units per day orally. Dilute with feedings. Do not administer simultaneously with iron; iron absorption is impaired.

Uses

Prevention of vitamin E deficiency. May be indicated in babies receiving erythropoietin and high iron dosages. Higher doses used to reduce oxidant-induced injury (ROP, BPD, IVH) remain controversial.

Pharmacology

Alpha-tocopherol is the most active antioxidant of the group of tocopherols known as vitamin E. The amount required by the body is primarily dependent upon the dietary intake of fat, especially polyunsaturated fatty acids (PUFA). Human milk and currently available infant formulas contain adequate vitamin E and have appropriate E:PUFA ratios to prevent hemolytic anemia. Infants receiving supplemental iron amounts above 2 mg/kg/day may also require additional vitamin E. Oral absorption of vitamin E is dependent upon hydrolysis that requires bile salts and pancreatic esterases. This can be quite variable in very immature infants and those with fat malabsorption. Free tocopherol is absorbed in the small intestine, taken via chylomicrons into the gastrointestinal lymphatics, then carried via low-density lipoproteins to be incorporated into cell membranes. Significant tissue accumulation may occur with pharmacologic doses.

Adverse Effects

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Assess feeding tolerance. Signs of vitamin E deficiency include hemolytic anemia and thrombocytosis. Physiologic serum vitamin E concentrations are between 0.8 and 3.5 mg/dL.

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1.194 Vitamin K1

Title Vitamin K1

Dose

Recommended Prophylaxis: 0.5 to 1 mg IM at birth.
Preterm infants less than 32 weeks of gestation:
Birthweight greater than 1000 grams: 0.5 mg IM.
Birthweight less than 1000 grams: 0.3 mg/kg IM.

Alternate strategy for healthy, term, exclusively breast-fed infants:
1 to 2 mg orally at birth, at 1 to 2 weeks of age, and at 4 weeks of age.

Oral prophylaxis is contraindicated in infants who are premature, ill, on antibiotics, have cholestasis, or have diarrhea. There has been an increased number of cases of hemorrhagic disease of the newborn in countries that have changed to oral prophylaxis, primarily in patients who received only a single oral dose.

Also: Maternal daily intake of 5 mg/day of phylloquinone significantly increases Vitamin K concentrations in breast milk and infant plasma.

Treatment of severe hemorrhagic disease: 1 to 10 mg IV slow push.

Administration

For IV administration, give very slowly, not exceeding 1 mg per minute, with physician present.

Uses

Prophylaxis and therapy of hemorrhagic disease of the newborn. Treatment of hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K_1.

Black Box Warning Fatalities have occurred during and immediately after IV and IM administration, even when precautions have been taken to dilute phytonadione and to avoid rapid infusion for the IV route. These reactions typically resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. IV/IM routes should be restricted to when subQ route is not feasible. IM administration, however, is recommended for use in newborns as a single dose.

Pharmacology

Vitamin K_1 (phytonadione) promotes formation of the following clotting factors in the liver: active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). Vitamin K_1 does **not** counteract the anticoagulant action of heparin.

Adverse Effects

Severe reactions, including death, have been reported with IV administration in adults. These reactions are extremely rare, and have resembled anaphylaxis and included shock and cardiac/respiratory arrest.

With IV administration, give very slowly, not exceeding 1 mg per minute, with physician present. Pain and swelling may occur at IM injection site. Efficacy of treatment with vitamin K_1 is decreased in patients with liver disease. The risk of childhood cancer is not increased by IM administration of vitamin K_1.

Monitoring

Check prothrombin time when treating clotting abnormalities. A minimum of 2 to 4 hours is needed for measurable improvement.

Special Considerations/Preparation

Available as a 2 mg/mL aqueous dispersion in 0.5-mL ampules and 10 mg/mL aqueous dispersion in 1-mL ampules and 2.5- and 5-mL vials. Contains 0.9% (9 mg/mL) benzyl alcohol as a preservative. **Protect from light.**
An extemporaneous oral suspension can be made by triturating six 5-mg tablets in a mortar. While mixing, add 5 mL purified water, USP and 5 mL 1% methylcellulose. Transfer to a graduate and qs to 30 mL with 70% sorbitol solution. Final concentration is 1 mg/mL and suspension is stable for 3 days refrigerated. Shake well before using.
***** Efficacy associated with the use of this preparation orally is uncertain. *****

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, ampicillin, chloramphenicol, cimetidine, epinephrine, famotidine, heparin, hydrocortisone succinate, netilmicin, potassium chloride, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Dobutamine and phenytoin.

References

- American Academy of Pediatrics Committee on Nutrition: Vitamins. In: *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, Il: American Academy of Pediatrics 2009: pp 93, 468-471.
- Nahata MC, Pai VB, Hipple TF, eds. *Pediatric Drug Formulations* . 5th ed. Cincinnati, OH: Harvey Whitney Books Company; 2004:219.
- Costakos DT, Greer FR, Love LA, et al: Vitamin K prophylaxis for premature infants: 1 mg versus 0.5 mg. *Am J Perinatol* 2003;20:485-90.
- American Academy of Pediatrics, Committee on Fetus and Newborn: Controversies concerning vitamin K and the newborn. *Pediatrics* 2003;112:191-92.
- Kumar D, Greer FR, Super DM, et al: Vitamin K status of premature infants: implications for current recommendations. *Pediatrics* 2001;108:1117-1122.
- Fiore LD, Scola MA, Cantillon CE, Brophy MT: Anaphylactoid reactions to Vitamin K. *J Thromb Thrombolysis* 2001;11:175-188.

- Zipursky AL: Prevention of vitamin K deficiency bleeding in newborns. *Br J Haematol*1999;104:430-437.
- Greer FR: Vitamin K deficiency and hemorrhage in infancy. *Clin Perinatol* 1995;22:759.
- Greer FR, Marshall SP, Foley AL, Suttie JW: Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997;99:88.
- Product Information, Hospira, 2004.
- Product Information, Aton Pharma, 2007.

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Birthweight greater than 1000 grams: 0.5 mg IM.
Birthweight less than 1000 grams: 0.3 mg/kg IM.

Alternate strategy for healthy, term, exclusively breast-fed infants:
1 to 2 mg orally at birth, at 1 to 2 weeks of age, and at 4 weeks of age.

Oral prophylaxis is contraindicated in infants who are premature, ill, on antibiotics, have cholestasis, or have diarrhea. There has been an increased number of cases of hemorrhagic disease of the newborn in countries that have changed to oral prophylaxis, primarily in patients who received only a single oral dose.

Also: Maternal daily intake of 5 mg/day of phylloquinone significantly increases Vitamin K concentrations in breast milk and infant plasma.

Treatment of severe hemorrhagic disease: 1 to 10 mg IV slow push.

Administration

For IV administration, give very slowly, not exceeding 1 mg per minute, with physician present.

Uses

Prophylaxis and therapy of hemorrhagic disease of the newborn. Treatment of hypoprothrombinemia secondary to factors limiting absorption or synthesis of vitamin K_1.

Black Box Warning Fatalities have occurred during and immediately after IV and IM administration, even when precautions have been taken to dilute phytonadione and to avoid rapid infusion for the IV route. These reactions typically resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. IV/IM routes should be restricted to when subQ route is not feasible. IM administration, however, is recommended for use in newborns as a single dose.

Pharmacology

Vitamin K_1 (phytonadione) promotes formation of the following clotting factors in the liver: active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). Vitamin K_1 does **not** counteract the anticoagulant action of heparin.

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With IV administration, give very slowly, not exceeding 1 mg per minute, with physician present. Pain and swelling may occur at IM injection site. Efficacy of treatment with vitamin K_1 is decreased in patients with liver disease. The risk of childhood cancer is not increased by IM administration of vitamin K_1.

Monitoring

Check prothrombin time when treating clotting abnormalities. A minimum of 2 to 4 hours is needed for measurable improvement.

Special Considerations/Preparation

Available as a 2 mg/mL aqueous dispersion in 0.5-mL ampules and 10 mg/mL aqueous dispersion in 1-mL ampules and 2.5- and 5-mL vials. Contains 0.9% (9 mg/mL) benzyl alcohol as a preservative. **Protect from light.**
An extemporaneous oral suspension can be made by triturating six 5-mg tablets in a mortar. While mixing, add 5 mL purified water, USP and 5 mL 1% methylcellulose. Transfer to a graduate and qs to 30 mL with 70% sorbitol solution. Final concentration is 1 mg/mL and suspension is stable for 3 days refrigerated. Shake well before using.
***** Efficacy associated with the use of this preparation orally is uncertain. *****

Solution Compatibility

D_5W, $D_{10}W$, and NS.

Terminal Injection Site Compatibility

Dex/AA. Amikacin, ampicillin, chloramphenicol, cimetidine, epinephrine, famotidine, heparin, hydrocortisone succinate, netilmicin, potassium chloride, ranitidine, and sodium bicarbonate.

Terminal Injection Site Incompatibility

Dobutamine and phenytoin.

References

- American Academy of Pediatrics Committee on Nutrition: Vitamins. In: *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, Il: American Academy of Pediatrics 2009: pp 93, 468-471.
- Nahata MC, Pai VB, Hipple TF, eds. *Pediatric Drug Formulations* . 5th ed. Cincinnati, OH: Harvey Whitney Books Company; 2004:219.
- Costakos DT, Greer FR, Love LA, et al: Vitamin K prophylaxis for premature infants: 1 mg versus 0.5 mg. *Am J Perinatol* 2003;20:485-90.
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- Kumar D, Greer FR, Super DM, et al: Vitamin K status of premature infants: implications for current recommendations. *Pediatrics* 2001;108:1117-1122.
- Fiore LD, Scola MA, Cantillon CE, Brophy MT: Anaphylactoid reactions to Vitamin K. *J Thromb Thrombolysis* 2001;11:175-188.
- Zipursky AL: Prevention of vitamin K deficiency bleeding in newborns. *Br J Haematol*1999;104:430-437.
- Greer FR: Vitamin K deficiency and hemorrhage in infancy. *Clin Perinatol* 1995;22:759.
- Greer FR, Marshall SP, Foley AL, Suttie JW: Improving the vitamin K status of breastfeeding infants with maternal vitamin K supplements. *Pediatrics* 1997;99:88.
- Product Information, Hospira, 2004.
- Product Information, Aton Pharma, 2007.

1.195 Zidovudine

Title Zidovudine

Dose

Prevention of Perinatal HIV Transmission:
Oral
35 weeks gestation and older: 4 mg/kg/dose orally every 12 hours [1] .
30 weeks to less than 35 weeks gestation: 2 mg/kg/dose orally every 12 hours, then 3 mg/kg every 12 hours at 15 days postnatal age [1] [2] .
Less than 30 weeks gestation: 2 mg/kg/dose orally every 12 hours, then 3 mg/kg every 12 hours after 4 weeks postnatal age [1] [2] .
Start therapy as soon as possible after birth, preferably within 6 to 12 hours of birth; prophylaxis should be continued through 6 weeks of age. Neonates born to HIV-infected women who have not received antepartum antiretroviral therapy should also receive 3 doses of nevirapine; at birth, 48 hours later, and 96 hours after the second dose [1] .

Intravenous
35 weeks gestation and older:3 mg/kg/dose IV every 12 hours if unable to tolerate oral [1] .
30 weeks to less than 35 weeks gestation: 1.5 mg/kg/dose IV every 12 hours, then 2.3 mg/kg every 12 hours at 15 days postnatal age [1] [2] .
Less than 30 weeks gestation: 1.5 mg/kg/dose IV every 12 hours, then 2.3 mg/kg every 12 hours after 4 weeks postnatal age [1] [2] .
Start therapy as soon as possible after birth, preferably within 6 to 12 hours of birth; prophylaxis should be continued through 6 weeks of age. Neonates born to HIV-infected women who have not received antepartum antiretroviral therapy should also

receive 3 doses of nevirapine; at birth, 48 hours later, and 96 hours after the second dose [1] .

Administration

Oral: Can be given without regard to food [3] .
Intravenous: Administer IV at a constant rate over 1 hour at a **concentration not greater than 4 mg/mL**. Rapid infusion or bolus injection should be avoided. **Should not be given intramuscularly** [4] .

Uses

Prevention of maternal-fetal HIV transmission [1] [5] . HIV-infected women with HIV RNA of 400 copies/mL or greater should receive IV zidovudine during labor and delivery. Intravenous zidovudine is not required in women with an HIV RNA of less than 400 copies/mL. The IV formulation is preferred in women requiring zidovudine in the intrapartum period; however, the oral formulation can be considered when IV administration is not a possibility. All neonates born to HIV-infected women should receive 6 weeks of zidovudine prophylaxis beginning as soon as possible after birth. Zidovudine alone is appropriate for infants born to women who received antepartum/intrapartum antiretroviral therapy with effective viral suppression. Zidovudine plus 3 doses of nevirapine may be considered (in consultation with a pediatric HIV specialist) for infants born to women who received antepartum/intrapartum antiretroviral therapy but have suboptimal viral suppression near delivery. Zidovudine plus 3 doses of nevirapine is recommended for infants born to women who received only intrapartum antiretroviral therapy and for infants born to mothers who received no antepartum or intrapartum antiretroviral therapy [1] . .
In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamivudine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamivudine regimen was associated with increased toxicity (eg, neutropenia) [6] .

Treatment of HIV-infected infants with combination antiretroviral therapy should be done in consultation with a pediatric infectious disease expert.

Black Box Warning According to the manufacturer's black box warning, zidovudine has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (in adults) [7] .

Pharmacology

Zidovudine is a nucleoside analog that inhibits HIV replication by interfering with viral reverse transcriptase. It is converted intracellularly in several steps to a triphosphate derivative, metabolized via hepatic glucuronidation, then renally excreted. Protein binding is approximately 25%. Zidovudine distributes into cells by passive diffusion and is relatively lipophilic. The CSF: plasma ratio is 0.24. The relationship between

serum concentration and clinical efficacy is unclear. The oral syrup is well-absorbed, but only 65% bioavailable due to significant first-pass metabolism. The serum half-life in term newborns is 3 hours, declining to 2 hours after 2 weeks of age. In preterm infants less than 33 weeks gestation, half-life during the first two weeks of life ranges from 5 to 10 hours, decreasing to 2 to 6 hours afterward [7] [2] [9] .

Adverse Effects

Anemia and neutropenia occur frequently, and are associated with serum concentrations greater than 3 micromol/L [2] . Mild cases usually respond to a reduction in dose . Severe cases may require cessation of treatment and/or transfusion. Bone marrow toxicity may be increased by concomitant administration of acyclovir, ganciclovir, and sulfamethoxazole/trimethoprim. Transient lactic acidemia is common in infants exposed to in utero highly active antiretroviral therapy or neonatal zidovudine [8] . Concomitant treatment with fluconazole or methadone significantly reduces zidovudine metabolism - dosing interval should be prolonged.

Monitoring

CBC and differential before initiation of therapy, then periodically based on baseline values, gestational age, and the infant's clinical status, concomitant antiretrovirals and other medications, and maternal antiretroviral therapy. Serum chemistries and liver enzyme tests may be considered based on maternal antiretroviral regimen received during pregnancy [1] .

Special Considerations/Preparation

Available as a syrup for oral use in a concentration of 10 mg/mL [7] .

The IV form is supplied in a concentration of 10 mg/mL in a 20 mL single-use vial. **Dilute in D5W before IV administration to a concentration not exceeding 4 mg/mL.**A dilution of 4 mg/mL may be prepared by adding 4 mL of the 10-mg/mL concentration to 6 mL D_5W. After dilution, the drug is stable for 24 hours at room temperature or 48 hours if refrigerated. Protect from light [10] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amphotericin B, aztreonam, cefepime, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, erythromycin lactobionate, fluconazole, gentamicin, heparin, imipenem, linezolid, lorazepam, metoclopramide, morphine, nafcillin, oxacillin, piperacillin, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanil, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Blood products and albumin solutions. Meropenem.

References

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- Connor EM, Sperling RS, Gelber R et al: Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine therapy.N Engl J Med 1994; 331(18): 1173-80.

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- Product Information: RETROVIR(R) IV infusion, zidovudine IV infusion. ViiV Healthcare (per manufacturer), Research Triangle Park, NC, Sep, 2010.

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Dose

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mg/kg every 12 hours at 15 days postnatal age [1] [2] .
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Intravenous
35 weeks gestation and older:3 mg/kg/dose IV every 12 hours if unable to tolerate oral [1] .
30 weeks to less than 35 weeks gestation: 1.5 mg/kg/dose IV every 12 hours, then 2.3 mg/kg every 12 hours at 15 days postnatal age [1] [2] .
Less than 30 weeks gestation: 1.5 mg/kg/dose IV every 12 hours, then 2.3 mg/kg every 12 hours after 4 weeks postnatal age [1] [2] .
Start therapy as soon as possible after birth, preferably within 6 to 12 hours of birth; prophylaxis should be continued through 6 weeks of age. Neonates born to HIV-infected women who have not received antepartum antiretroviral therapy should also receive 3 doses of nevirapine; at birth, 48 hours later, and 96 hours after the second dose [1] .

Administration

Oral: Can be given without regard to food [3] .
Intravenous: Administer IV at a constant rate over 1 hour at a **concentration not greater than 4 mg/mL**. Rapid infusion or bolus injection should be avoided. **Should not be given intramuscularly** [4] .

Uses

Prevention of maternal-fetal HIV transmission [1] [5] . HIV-infected women with HIV RNA of 400 copies/mL or greater should receive IV zidovudine during labor and delivery. Intravenous zidovudine is not required in women with an HIV RNA of less than 400 copies/mL. The IV formulation is preferred in women requiring zidovudine in the intrapartum period; however, the oral formulation can be considered when IV administration is not a possibility. All neonates born to HIV-infected women should receive 6 weeks of zidovudine prophylaxis beginning as soon as possible after birth. Zidovudine alone is appropriate for infants born to women who received antepartum/intrapartum antiretroviral therapy with effective viral suppression. Zidovudine plus 3 doses of nevirapine may be considered (in consultation with a pediatric HIV specialist) for infants born to women who received antepartum/intrapartum antiretroviral therapy but have suboptimal viral suppression near delivery. Zidovudine plus 3 doses of nevirapine is recommended for infants born to women who received only intrapartum antiretroviral therapy and for infants born to mothers who received no antepartum or intrapartum antiretroviral therapy [1] . .
In a phase III randomized trial (n=1684), the combination of 6 weeks of zidovudine plus 3 doses of nevirapine or the combination of 6 weeks of zidovudine plus nelfinavir and lamivudine for 2 weeks was associated with a lower intrapartum transmission rate when compared with zidovudine alone in infants born to women who received no

antenatal antiretroviral therapy (2.2% versus 2.5% versus 4.9%, respectively). The zidovudine/nelfinavir/lamivudine regimen was associated with increased toxicity (eg, neutropenia) [6] .

Treatment of HIV-infected infants with combination antiretroviral therapy should be done in consultation with a pediatric infectious disease expert.

Black Box Warning According to the manufacturer's black box warning, zidovudine has been associated with hematologic toxicity, including neutropenia and severe anemia, particularly in patients with advanced HIV disease. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (in adults) [7] .

Pharmacology

Zidovudine is a nucleoside analog that inhibits HIV replication by interfering with viral reverse transcriptase. It is converted intracellularly in several steps to a triphosphate derivative, metabolized via hepatic glucuronidation, then renally excreted. Protein binding is approximately 25%. Zidovudine distributes into cells by passive diffusion and is relatively lipophilic. The CSF: plasma ratio is 0.24. The relationship between serum concentration and clinical efficacy is unclear. The oral syrup is well-absorbed, but only 65% bioavailable due to significant first-pass metabolism. The serum half-life in term newborns is 3 hours, declining to 2 hours after 2 weeks of age. In preterm infants less than 33 weeks gestation, half-life during the first two weeks of life ranges from 5 to 10 hours, decreasing to 2 to 6 hours afterward [7] [2] [9] .

Adverse Effects

Anemia and neutropenia occur frequently, and are associated with serum concentrations greater than 3 micromol/L [2] . Mild cases usually respond to a reduction in dose . Severe cases may require cessation of treatment and/or transfusion. Bone marrow toxicity may be increased by concomitant administration of acyclovir, ganciclovir, and sulfamethoxazole/trimethoprim. Transient lactic acidemia is common in infants exposed to in utero highly active antiretroviral therapy or neonatal zidovudine [8] . Concomitant treatment with fluconazole or methadone significantly reduces zidovudine metabolism - dosing interval should be prolonged.

Monitoring

CBC and differential before initiation of therapy, then periodically based on baseline values, gestational age, and the infant's clinical status, concomitant antiretrovirals and other medications, and maternal antiretroviral therapy. Serum chemistries and liver enzyme tests may be considered based on maternal antiretroviral regimen received during pregnancy [1] .

Special Considerations/Preparation

Available as a syrup for oral use in a concentration of 10 mg/mL [7] .

The IV form is supplied in a concentration of 10 mg/mL in a 20 mL single-use vial. **Dilute in D5W before IV administration to a concentration not exceeding 4 mg/mL.**A dilution of 4 mg/mL may be prepared by adding 4 mL of the 10-mg/mL concentration to 6 mL D_5W. After dilution, the drug is stable for 24 hours at room temperature or 48 hours if refrigerated. Protect from light [10] .

Solution Compatibility

D_5W and NS.

Terminal Injection Site Compatibility

Dex/AA solutions. Acyclovir, amikacin, amphotericin B, aztreonam, cefepime, ceftazidime, ceftriaxone, cimetidine, clindamycin, dexamethasone, dobutamine, dopamine, erythromycin lactobionate, fluconazole, gentamicin, heparin, imipenem, linezolid, lorazepam, metoclopramide, morphine, nafcillin, oxacillin, piperacillin, piperacillin-tazobactam, potassium chloride, ranitidine, remifentanil, tobramycin, trimethoprim-sulfamethoxazole, and vancomycin.

Terminal Injection Site Incompatibility

Blood products and albumin solutions. Meropenem.

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