

Metronidazole

Newborn Use Only

2016

Alert	There are few data from prospective trials on the safety and efficacy of metronidazole in newborn infants.		
Indication	Treatment of anaerobic bacterial (including meningitis) and protozoal infections. Treatment of necrotising enterocolitis.		
Action	Metronidazole is bactericidal against anaerobic bacteria and an antiprotozoal agent.		
Drug Type	Antibacterial — nitroimidazole		
Trade Name	Flagyl, Metronidazole Sandoz IV Solution for infusion, DBL Metronidazole Intravenous Infusion, Metronidazole Intravenous Infusion (Baxter) Solution for infusion, Metronidazole-Claris Solution for infusion Flagyl S Suspension		
Presentation	500 mg/100 mL IV solution 200 mg/5 mL Oral Suspension		
Dosage/Interval	IV or PO		
	Postmenstrual age/Corrected age	Loading dose	Maintenance
	< 27 weeks	15 mg/kg	7.5 mg/kg 24 hourly
	27 ⁺⁰ –33 ⁺⁶ weeks	15 mg/kg	7.5 mg/kg 12 hourly
	34 ⁺⁰ –40 ⁺⁶ weeks	15 mg/kg	7.5 mg/kg 8 hourly
	≥ 41 ⁺⁰ weeks	15 mg/kg	7.5 mg/kg 6 hourly
Maximum daily dose			
Route	IV or PO		
Preparation/Dilution	IV: Use undiluted.		
Administration	IV Infusion: Over 30 minutes with a syringe pump. Oral: Give 1 hour before feeds preferably .		
Monitoring	Full blood count if patient is on therapy > 1 week. Liver and renal function tests.		
Contraindications	Hypersensitivity to metronidazole or other nitroimidazoles.		
Precautions	Patients with seizures or peripheral neuropathy, blood dyscrasias, renal or hepatic impairment – dose reduction may be required.		
Drug Interactions	Co-administration with phenobarbital (phenobarbitone) and phenytoin may reduce metronidazole concentrations and increase phenytoin concentrations. Monitor anticonvulsant concentrations. Concurrent use with QT-prolonging drugs may result in increase of QT interval resulting in arrhythmias (torsades de pointes).		
Adverse Reactions	More common: GI upset, stomatitis and candida overgrowth. Drug metabolite may cause brownish discolouration of urine. Rare: Convulsive seizures and peripheral neuropathy characterised mainly by numbness or paraesthesia of an extremity have been reported in adults. May cause reversible leucopenia and/or thrombocytopenia.		
Compatibility	Fluids: Glucose 5%, glucose 10%, sodium chloride 0.9% Drugs via Y-site: Amino acid solution, aciclovir, dopamine, esmolol, fluconazole, labetalol, lipid emulsion, magnesium sulfate, methylprednisolone sodium succinate, midazolam, morphine sulfate, piperacillin-tazobactam (EDTA-free), remifentanyl		
Incompatibility	Amphotericin, aztreonam, cefepime, ganciclovir		
Stability	Once removed from original container, use as soon as practicable		
Storage	IV: Store below 25°C. Do NOT refrigerate. Oral suspension: Store below 25°C. Protect from light.		
Special Comments	Metronidazole oral suspension is best absorbed on an empty stomach.		

Evidence summary	<p>Efficacy and Safety</p> <p>There is a lack of data from prospective trials on the safety and efficacy of metronidazole in newborn infants. A retrospective study reported broad-spectrum antibiotics plus metronidazole may not prevent the deterioration of NEC in full-term and near-term infants.¹ (LOE III-3 GOR D)</p> <p>Pharmacokinetics</p> <p>Metronidazole principally undergoes hepatic metabolism with clearance increasing with weight and post-menstrual age (PMA). Cohen-Wolkowicz et al evaluated the pharmacokinetics of metronidazole in 32 infants born at ≤ 32 weeks' gestation and less than 120 days old. The study correlated metronidazole clearance with PMA and developed a PK model using nonlinear mixed-effect modeling (NONMEM). Monte Carlo simulations were performed and the study gives dosing recommendations based on PMA separated into < 34 weeks, 34 weeks to 40 weeks, and > 40 weeks.^{2,3} Suyagh et al evaluated the pharmacokinetics of 32 infants born at ≤ 37 weeks gestation and less than 55 days old. A 1-compartment model was developed using NONMEM. Monte Carlo simulations were performed and dose recommendations are given based on PMA separated into < 26 weeks, 26–27 weeks, 28–33 weeks, and ≥ 34 weeks.⁴ (LOE IV GOR C)</p>
References	<ol style="list-style-type: none"> 1. Luo LJ, Li X, Yang KD, Lu JY, Li LQ. Broad-spectrum antibiotic plus metronidazole may not prevent the deterioration of necrotizing enterocolitis from stage II to III in full-term and near-term infants: A propensity score-matched cohort study. <i>Medicine</i>. 2015;94(42). 2. Cohen-Wolkowicz M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. <i>Antimicrob Agents Chemother</i> 2012;56:1828–37. 3. Cohen-Wolkowicz M, Sampson M, Bloom BT, et al. Determining population and developmental pharmacokinetics of metronidazole using plasma and dried blood spot samples from premature infants. <i>Pediatr Infect Dis J</i> 2013;32:956–61. 4. Suyagh M, Collier PS, Millership JS, Iheagwaram G, Millar M, Halliday HL, McElnay JC. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. <i>Pediatrics</i>. 2011 Feb 1;127(2):e367-74.1. 5. MIMS Product Information (2014) DBL Metronidazole Intravenous Infusion, Hospira 6. Australian Injectable Drugs Handbook, 6th Edition 2016. 7. Micromedex. Metronidazole monograph, accessed on 10/10/2016 8. MIMS Product Information (2016) Flagyl S Suspension, Sanofi-Aventis

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