Metronidazole
Newborn use only

2020

<table>
<tr><td>Alert</td><td>High risk medicine. There are few data from prospective trials on the safety and efficacy of metronidazole in newborn infants.</td></tr>
<tr><td>Indication</td><td>Anaerobic bacterial and protozoal infections including meningitis.
Necrotising enterocolitis.</td></tr>
<tr><td>Action</td><td>Bactericidal against anaerobic bacteria and an antiprotozoal agent.</td></tr>
<tr><td>Drug type</td><td>Antibacterial — nitromethylimidazole</td></tr>
<tr><td>Trade name</td><td>Metronidazole Sandoz IV Solution for infusion, DBL Metronidazole Intravenous Infusion, Metronidazole Intravenous Infusion (Baxter) Solution for infusion, Metronidazole-Claris Solution for infusion, Metronidazole Kabi solution fort Infusion.
Flagyl S oral Suspension</td></tr>
<tr><td>Presentation</td><td>500 mg/100 mL IV solution
200 mg/5 mL Oral Suspension</td></tr>
<tr><td>Dose</td><td>IV or Oral
<table>
<tr><th>Postmenstrual age/Corrected age*</th><th>Loading dose</th><th>Maintenance dose to commence</th><th>Maintenance</th></tr>
<tr><td>< 27 weeks</td><td>15 mg/kg</td><td>24 hours after loading</td><td>7.5 mg/kg 24 hourly</td></tr>
<tr><td>27^{+0}–33^{+6} weeks</td><td>15 mg/kg</td><td>12 hours after loading</td><td>7.5 mg/kg 12 hourly</td></tr>
<tr><td>34^{+0}–40^{+6} weeks</td><td>15 mg/kg</td><td>8 hours after loading</td><td>7.5 mg/kg 8 hourly</td></tr>
<tr><td>≥ 41^{+0} weeks</td><td>15 mg/kg</td><td>6 hours after loading</td><td>7.5 mg/kg 6 hourly</td></tr>
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* Also referred to as “current gestational age”</td></tr>
<tr><td>Dose adjustment</td><td></td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV, oral</td></tr>
<tr><td>Preparation</td><td>Use undiluted.</td></tr>
<tr><td>Administration</td><td>IV Infusion over 30 minutes.
Oral: Give 1 hour before feeds.</td></tr>
<tr><td>Monitoring</td><td>Full blood count if patient is on therapy > 1 week.
Liver and renal function tests.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to metronidazole or other nitroimidazoles.</td></tr>
<tr><td>Precautions</td><td>Patients with seizures or peripheral neuropathy, blood dyscrasias, renal or hepatic impairment – dose reduction may be required.</td></tr>
<tr><td>Drug interactions</td><td>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).</td></tr>
<tr><td>Adverse reactions</td><td>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.</td></tr>
<tr><td>Compatibility</td><td>Fluids: Glucose 5%, glucose 10% (not recommended due to high osmolarity of the resulting solution), sodium chloride 0.9%, glucose/sodium chloride fluids.
Y-site: Amino acid solution, aciclovir, dopamine, esmolol, fluconazole, labetalol, lipid emulsion, magnesium sulfate, methylprednisolone sodium succinate, midazolam, morphine sulfate, piperacillin-tazobactam (EDTA-free), remifentanil.</td></tr>
<tr><td>Incompatibility</td><td>Amphotericin, aztreonam, cefepime, ganciclovir</td></tr>
<tr><td>Stability</td><td>Once removed from original container, use as soon as practicable.</td></tr>
<tr><td>Storage</td><td>IV: Store below 25°C. Do NOT refrigerate.
Oral suspension: Store below 25°C. Protect from light.</td></tr>
<tr><td>Excipients</td><td>Injection: Citric acid, dibasic sodium phosphate, sodium chloride.</td></tr>
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	Suspension: Aluminium magnesium silicate, ethanol, methyl hydroxybenzoate, monobasic sodium phosphate, natural soluble lemon flavour, orange oil terpeneless, propyl hydroxybenzoate, sucrose.
Special comments	Metronidazole oral suspension is best absorbed on an empty stomach.
Evidence	**Efficacy and Safety** 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) **Pharmacokinetics** Metronidazole principally undergoes hepatic metabolism with clearance increasing with weight and post-menstrual age (PMA). Cohen-Wolkowiez 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)
Practice points	
References	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. Medicine. 2015;94(42). 2. Cohen-Wolkowiez M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. Antimicrob Agents Chemother 2012;56:1828–37. 3. Cohen-Wolkowiez M, Sampson M, Bloom BT, et al. Determining population and developmental pharmacokinetics of metronidazole using plasma and dried blood spot samples from premature infants. Pediatr Infect Dis J 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. Pediatrics. 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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