Amikacin

Newborn use only

2019

<table>
<tr><td>Alert</td><td>Amikacin and gentamicin are both AMINOGLYCOSIDE antibiotics and MUST NOT be prescribed at the same time.
The Antimicrobial Stewardship Team has listed this drug under the following category: Restricted.</td></tr>
<tr><td>Indication</td><td>Treatment of suspected or proven gram-negative infection resistant to other aminoglycosides.
Used in combination with a beta-lactam antibiotic for sepsis in the newborn.</td></tr>
<tr><td>Action</td><td>Bactericidal agent that acts by inhibiting protein synthesis in susceptible bacteria.</td></tr>
<tr><td>Drug Type</td><td>Aminoglycoside</td></tr>
<tr><td>Trade Name</td><td>DBL Amikacin, Amikacin SXP, Amikacin Wockhardt.</td></tr>
<tr><td>Presentation</td><td>500 mg/2 mL
Excipients: Sodium citrate, sodium metabisulfite.</td></tr>
<tr><td>Dosage/Interval</td><td>
<table>
<tr><th>Postmenstrual age/corrected gestational age</th><th>Postnatal age</th><th>Dose</th><th>Interval</th></tr>
<tr><td>≤29 weeks</td><td>0–7 days</td><td>14 mg/kg</td><td>48-hourly</td></tr>
<tr><td></td><td>8–28 days</td><td>12 mg/kg</td><td>36-hourly</td></tr>
<tr><td></td><td>≥29 days</td><td>12 mg/kg</td><td>24-hourly</td></tr>
<tr><td>30–34 weeks</td><td>0–7 days</td><td>12 mg/kg</td><td>36-hourly</td></tr>
<tr><td></td><td>≥8 days</td><td>12 mg/kg</td><td>24-hourly</td></tr>
<tr><td>≥35 weeks</td><td>All</td><td>12 mg/kg</td><td>24-hourly</td></tr>
</table>
Infants with perinatal asphyxia and on therapeutic hypothermia: Increase dose interval by 12 hours [1-3].
Infants treated with cyclo-oxygenase inhibitors (indomethacin or ibuprofen): Increase dose interval by 12 hours [1-3]</td></tr>
<tr><td>Maximum daily dose</td><td></td></tr>
<tr><td>Route</td><td>Intravenous infusion
Intramuscular injection</td></tr>
<tr><td>Preparation/Dilution</td><td>Two-step dilution:
Step 1: Add 1 mL (250 mg) of amikacin to 9 mL of sodium chloride 0.9% to make a 25 mg/mL solution.
Step 2: FURTHER DILUTE 1 mL (25 mg) of this solution to 9 mL of sodium chloride 0.9% to make 2.5 mg/mL solution.</td></tr>
<tr><td>Administration</td><td>IV infusion over 60 minutes using the proximal IV port.
IM: May be given if IV route not available.</td></tr>
<tr><td>Monitoring</td><td>Routine therapeutic drug monitoring for ≤48 hours duration of therapy is not necessary unless renal function is impaired.
For infants on continuing treatment, perform early trough and peak levels (prior to and 1 hour after the second amikacin dose). Target peak levels 24–35 mg/L and troughs <5 mg/L [2].
Assess renal function.</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to amikacin or other aminoglycosides.
Myasthenia Gravis[13]</td></tr>
<tr><td>Precautions</td><td>Treatment with amikacin for more than 14 days has not been established as being safe.
CAUTION in patients with pre-existing renal impairment, auditory or vestibular impairment, hypocalcaemia, depressed neuromuscular transmission.
Gastrointestinal: Amikacin has been associated with Clostridium difficile diarrhoea; discontinue use if suspected.
Immunological: Allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic reactions, may occur in patients with sulfite sensitivity as preparation contains sodium metabisulfite.
Neurological: Use caution in patients with parkinsonism; muscle weakness may be aggravated.</td></tr>
<tr><td>Drug Interactions</td><td>Diuretics may cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations.</td></tr>
</table>

	Neurotoxic and/or nephrotoxic agents: Avoid concurrent or sequential use of other neurotoxic and/or nephrotoxic antibiotics, including other aminoglycosides, polymyxin B, colistin, cisplatin, vancomycin, amphotericin B, clindamycin and cephalosporins. Anaesthetics/neuromuscular blocking agents or medications with neuromuscular blocking activity: succinylcholine, tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics, opioid analgesics and massive transfusions with citrate anticoagulated blood may increase neuromuscular blockade. Treatment with anticholinesterase agents or calcium salts may help to reverse the blockade. Penicillins: Aminoglycosides are inactivated by solutions containing penicillins. Ensure line is adequately flushed between antibiotics.
Adverse Reactions	Serious reactions include neuromuscular blockade with subsequent respiratory paralysis, ototoxicity and nephrotoxicity (see evidence review).
Compatibility	Fluids: Glucose 5%, glucose 10%, glucose 20%, sodium chloride 0.9%, amino acid solutions. Aciclovir, amiodarone, atenolol, atracurium, atropine, aztreonam, buprenorphine, calcium chloride/gluconate, caspofungin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, dexmedetomidine, digoxin, dobutamine, adrenaline (epinephrine), epoetin alfa, erythromycin, esmolol, fentanyl, filgrastim, fluconazole, foscarnet, furosemide (frusemide), gentamicin, isoprenaline, ketamine, labetalol, lidocaine (lignocaine), linezolid, magnesium sulfate, methadone, methylprednisolone, midazolam, milrinone, morphine, glyceryl trinitrate, noradrenaline (norepinephrine), octreotide, ondansetron, pancuronium, pethidine, phenobarbital (phenobarbitone), piperacillin, piperacillin-tazobactam, potassium chloride, procainamide, propranolol, protamine, pyridoxine, ranitidine, remifentanil, rocuronium, sodium acetate, sodium bicarbonate, succinylcholine, vancomycin, vasopressin, vecuronium, warfarin, zidovudine
Incompatibility	Fluids: No information Penicillins and cephalosporins, amphotericin, azathioprine, azithromycin, diazepam, diazoxide, folic acid, ganciclovir, heparin, hydralazine, ibuprofen, indomethacin, insulin, pentamidine, pentobarbital (pentobarbitone), phenytoin, potassium chloride, propofol, sulfamethoxazole-trimethoprim, teicoplanin
Stability	Administer immediately, discard unused portion. The diluted solution is stable for 24-hours at room temperature.
Storage	Store below 25°C.
Special Comments	
Evidence summary	**Efficacy:** Increasing organism resistance is being reported in infants with neonatal infection requiring tailoring of antibiotic regimens. A recent systematic review identifying organism and antimicrobial resistance of pathogens in neonatal septicaemia in China reported over 50% of the Gram-negative isolates, including *Escherichia* and *Klebsiella*, were resistant to third-generation cephalosporins. Most of the Gram-positive and Gram-negative bacteria isolated were sensitive to aminoglycosides, especially amikacin (<20% resistance) [4]. The most recent Cochrane review on one dose per day compared to multiple doses per day for gentamicin in neonates found insufficient evidence from the currently available RCTs to conclude whether a 'once a day' or a 'multiple doses a day' regimen of gentamicin is superior in treating proven neonatal sepsis. However, a 'once a day' gentamicin regimen was superior to a 'multiple doses a day' regimen in achieving higher peak concentrations while avoiding toxic trough concentrations [5]. Sherwin 2009, in a cohort study, reported a peak/MIC ratio of <8 predicted treatment failure [6]. **Safety**: Toxicity is thought to be related to the Area Under the time versus concentration Curve (AUC), reflected by the trough concentration [2]. For amikacin, historical data (prospective clinical trials 1975–1982) suggest an incidence of cochlear, vestibular and renal toxicity of 13.9%, 2.8%, and 9.4% in adults [7]. This high incidence may relate to the practice of using multiple doses per day regimens. Although short-term renal toxicity in human neonates has been reported, there is consistently a lower rate of ototoxicity and nephrotoxicity in neonates when

compared to adults [2]. The most recent Cochrane review on one dose per day compared to multiple doses per day for gentamicin in neonates found (pooled, all dosing regimens) the incidence of ototoxicity was 1.4% (n = 3/214) with no cases (n = 0/348) of nephrotoxicity (increased creatinine or decreased creatinine clearance) [5]. Limited reports have not identified a link between amikacin pharmacokinetics and ototoxicity in neonates [2]. However, extrapolated from other populations, to avoid adaptive resistance and toxicity, it is recommended higher doses should be combined with extended interval dosing [2].

Pharmacokinetics/pharmacodynamics: Sherwin 2009, in a cohort study, reported a peak/MIC ratio of <8 predicted treatment failure [6]. Allegaert 2007 reported weight explained 47.3% of drug clearance; post menstrual age 25.2%; co-administration of a nonselective cyclo-oxygenase inhibitor 3.5%; renal function 7.6% and being born SGA, 1.7%. Renal drug clearance was significantly lower in preterm neonates born SGA [8], infants on cyclo-oxygenase inhibitors [2, 3, 9] and infants with perinatal asphyxia [2]. Labaune 2001 [10] reported validation of an individualised dosing regimen for neonates in the first two days of life to target attainment of C_{max}/MIC ratio >10 using a simplified once-a-day regimen with target peak serum concentrations obtained in 62‑80% of patients after the first dose and in 80‑100% after the second dose, and trough concentrations were obtained in 100%.

Two recent pharmacokinetic studies have reported attainment of therapeutic peak and trough levels for modelled amikacin regimens [2, 11]. The regimens had similar rates of attainment of target concentrations with the regimen assessed by Hughes et al [11] considered the preferable regimen for ease of implementation by the ANMF group (Table 1).

Hughes 2017 [11] targeted peak concentrations 20 to 35 mg/L with sub- and supra-therapeutic peak concentrations were defined as <20 mg/L and >35 mg/L, respectively; and supra-therapeutic trough concentrations >8 mg/L using the regimen in table 1. They reported 12% peak concentrations >35 mg/L and 2% trough concentrations >8mg/L.

Table 1

–Postmenstrual age	Postnatal age	Dose
≤29 weeks	0–7 days	14 mg/kg, q48h
	8–28 days	12 mg/kg, q36h
	≥29 days	12 mg/kg, q24h
30–34 weeks	0–7 days	12 mg/kg, q36h
	≥8 days	12 mg/kg, q24h
≥35 weeks	All	12 mg/kg, q24h

Smits 2017 [2, 3] targeted trough concentrations of 1.5–3 mg/L and peak concentrations of 24–35 mg/L. They reported 98% of peak concentrations in target zone >20 mg/L (90% 24–35 mg/L) and 90% of troughs in target zone <5 mg/L (53% <3 mg/L) using the regimen in Table 2. Cristea 2017 retrospectively quantified the impact of perinatal asphyxia treated with therapeutic hypothermia on amikacin clearance in neonates and reported amikacin clearance decreased by 40.6%. A 12-hour increase in the dosing interval while keeping the amikacin dose (milligram per kilogram) unchanged, had a minimal impact on the peak concentrations but improved the attained trough concentrations [1]. Smits 2015 reported attainment of therapeutic targets when dose intervals were increased by 10 hours for infants on ibuprofen [3].

Table 2

Current body weight (g)	Postnatal age <14 days	Postnatal age ≥14 days
<800	16 mg/kg, q48h	20 mg/kg, q42h
800–1199	16 mg/kg, q42h	20 mg/kg, q36h
1200–1999	15 mg/kg, q36h	18 mg/kg, q30h
2000–2799	15mg/kg, q36h	18 mg/kg, q24h
≥2800	15mg/kg, q30h	18 mg/kg, q20h

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Authors Contribution

Original author/s	David Osborn, Rajesh Maheshwari, Srinivas Bolisetty
Evidence Review - original	David Osborn
Expert review	Tony Lai, Brendan McMullan, Alison Kesson
Nursing Review	Eszter Jozsa
Pharmacy Review	Cindy Chen, Jing Xiao, Michelle Jenkins
ANMF Group contributors	Nilkant Phad, Himanshu Popat
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty