Amikacin

Newborn use only

2024

Alert	Amikacin and gentamicin are both AMINOGLYCOSIDE antibiotics and MUST NOT be prescribed together. The administration of antibiotics within 1 hour of the identification of sepsis is recommended. New South Wales Antimicrobial Stewardship category: Restricted after 72 hours. *Literature reports indicate that the antibiotic activity of some aminoglycosides may be impaired by beta-lactam antibiotics.[13] ANMF consensus: Where feasible, give at separate sites or separate the administration time of amikacin and beta-lactams (penicillin or cephalosporin).
Indication	Treatment of suspected or proven gram-negative infection resistant to other aminoglycosides.
Action	Bactericidal agent that acts by inhibiting protein synthesis in susceptible bacteria.
Drug type	Aminoglycoside
Trade name	DBL Amikacin, Amikacin SXP, Amikacin Wockhardt.
Presentation	500 mg/2 mL Excipients: Sodium citrate, sodium metabisulfite.
Dose	

Postmenstrual age/corrected gestational age	Postnatal age/days of life	Dose	Interval
≤29 weeks	0–7 days	14 mg/kg	48-hourly
	8–28 days	12 mg/kg	36-hourly
	≥29 days	12 mg/kg	24-hourly
30–34 weeks	0–7 days	12 mg/kg	36-hourly
	≥8 days	12 mg/kg	24-hourly
≥35 weeks	All	12 mg/kg	24-hourly

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]

Dose adjustment	Therapeutic hypothermia – Increase dose interval by 12 hours[1-3] ECMO – Renal impairment is the main determinant. Measure trough concentration before every dose. Renal impairment – Moderate to severe renal impairment - Increase dose interval by 12-24 hours. Perform trough concentrations (1 hour prior) before each dose. Wait for the result before administration of the dose. Adjust the dose/interval based on trough levels. Hepatic impairment – No dose adjustment is necessary.
Maximum dose	
Route	IV IM
Preparation	IV 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 Draw up 3 mL (75 mg) of this solution and add 12 mL of sodium chloride 0.9% to make a final volume of 15mL with a final concentration of 5 mg/mL. IM: < 1.5 kg: Add 1 mL (250 mg) of amikacin to 9 mL of sodium chloride 0.9% to make a 25 mg/mL solution. ≥ 1.5 kg: No dilution required.
Administration	IV infusion over 20-30 minutes. IM: May be given if IV route not available.
Monitoring	Therapeutic drug monitoring Routine therapeutic drug monitoring for ≤48 hours duration of therapy is not necessary unless renal function is impaired. For infants on continuing treatment >48 hours, perform trough (1 hour prior) and peak levels (30 minutes after the completion). Target peak levels 24–35 mg/L and troughs <5 mg/L.[2]

	If trough concentration ≥5 mg/L, withhold the dose, repeat trough concentrations before the subsequent dosing and discuss with infectious disease specialist/clinical microbiologist for either extended dosing interval or alternate antibiotic. Assess renal function.
Contraindications	Hypersensitivity to amikacin or other aminoglycosides. Myasthenia Gravis
Precautions	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.
Drug interactions	Diuretics may cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations. 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).
Overdose	In the newborn infant, exchange transfusion may be considered. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).[13]
Compatibility	Fluids: Glucose 5%, glucose 10%, glucose 20%, sodium chloride 0.9%, amino acid solutions. Y-site: Aciclovir, amiodarone, atenolol, atracurium, atropine, aztreonam, benzylpenicillin (penicillin g) buprenorphine, calcium chloride/gluconate, caspofungin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, cimetidine, clindamycin, dexamethasone, dexmedetomidine, digoxin, dobutamine, adrenaline (epinephrine), epoetin alfa, ertapenem, erythromycin, esmolol, fentanyl, filgrastim, fluconazole, foscarnet, furosemide (frusemide), gentamicin, hydrocortisone, isoprenaline, ketamine, labetalol, lidocaine (lignocaine), linezolid, magnesium sulfate, meropenem, methadone, methylprednisolone, metronidazole, 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. Y-site: Amphotericin, azathioprine, azithromycin, diazepam, diazoxide, fat emulsion (no specific information; fat emulsions should be considered incompatible until definitive evidence becomes available), folic acid, ganciclovir, heparin, hydralazine, ibuprofen, indomethacin, insulin, pentamidine, 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.
Evidence	**Background** Organ size and maturation as well as body composition and physiology change every day in neonates.

Both hepatic drug metabolism and renal elimination of drugs depend on postnatal age–driven maturation. Glomerular filtration rate (GFR) in full-term neonates is 35% of adult values. Term neonates show a rapid increase in GFR during the first 2 weeks of life and reach adult values by the end of the first year. Premature infants have similar maturational trends but may have a slower initial adjustment of GFR because nephrogenesis is not completed before 34 to 35 weeks of gestation. Both active tubular secretion and reabsorption are also immature at birth (20% to 30% of adult reference values) and reach adult values within a few years.[14] Key PD parameters used to link drug exposure and microbiological effects and guide dosing strategies include (1) area under the concentration versus time curve over a dose interval (eg,24 hours) to minimum inhibitory concentration ratio (AUC/MIC), (2) antibacterial peak concentration to MIC ratio (Cmax/MIC), and (3) number of hours or percentage of time for which the drug serum concentration remains above the MIC during a dose interval (%T >MIC). As only the unbound drug is pharmacology active, the prefix f can be added to represent the free fraction of a drug (eg, fT > MIC). Different antibiotics have different killing characteristics: β-lactam and glycopeptide antibiotics show time-dependent killing with T > MIC as the optimal predictor of efficacy, whereas aminoglycosides exhibit concentration-dependent killing where efficacy is characterized by Cmax/MIC.[14]

Amikacin is an aminoglycoside and is primarily renally eliminated. It is a concentration dependent antibiotic and so efficacy is measured by high peak concentrations relative to the MIC of the microorganism or to AUC/MIC ratio, whereas trough concentration is associated with toxicity (nephro- and ototoxicity).

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 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 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

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%.[8] Renal drug clearance was significantly lower in preterm neonates born SGA, infants on cyclo-oxygenase inhibitors and infants with perinatal asphyxia.[2,3,9] Labaune 2001 reported validation of an individualised dosing regimen for neonates in the first two days of life to target attainment of Cmax/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%.[10]

Two pharmacokinetic studies 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, in a retrospective study of comparing 2 dosing regimens, 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.[11] They reported 12% peak concentrations >35 mg/L and 2% trough concentrations >8mg/L. They reported ototoxicity rate of 6.6% with this regimen, with 50% of them had a supratherapeutic trough concentration.

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

Target peak and trough concentrations: The target thresholds for peak and trough concentrations vary in studies. There is no universally accepted definition for these thresholds. The acceptable trough level of 10 µg/mL has been accepted in neonates,[15] and the risk of ototoxicity was reported to increase at trough levels above 10 µg/mL.[16] Other studies targeted lower trough concentrations. Hughes et al targeted peak concentrations of 20-35 mg/L and trough concentration of ≤ 8mg/L.[11] Smits et al targeted >20 mg/L as peak and <5 mg/L as trough concentrations.[2] **ANMF consensus** is to target peak concentrations of 20-35 mg/L (up to 40 mg/L in serious or life-threatening infections) and trough concentrations up to 5 mg/L.

IV infusion duration: Amikacin is a concentration dependent antibiotic and more effective with faster achievement of peak concentrations. Smits, et al administered amikacin over 20 minutes with an aim to achieve peak concentration quicker. Tewari et al, in a RCT in neonates, amikacin was given over 30 minutes.[17] Sherwin et al administered amikacin over 30 minutes.[18]

Practice points

References

1. Cristea S, Smits A, Kulo A, Knibbe CAJ, van Weissenbruch M, Krekels EHJ, Allegaert K. Amikacin Pharmacokinetics To Optimize Dosing in Neonates with Perinatal Asphyxia Treated with Hypothermia. Antimicrob Agents Chemother. 2017;61.

2. Smits A, Kulo A, van den Anker J, Allegaert K. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. Expert Opin Drug Metab Toxicol. 2017;13:157-66.
3. Smits A, De Cock RF, Allegaert K, Vanhaesebrouck S, Danhof M, Knibbe CA. Prospective Evaluation of a Model-Based Dosing Regimen for Amikacin in Preterm and Term Neonates in Clinical Practice. Antimicrob Agents Chemother. 2015;59:6344-51.
4. Li JY, Chen SQ, Yan YY, Hu YY, Wei J, Wu QP, Lin ZL, Lin J. Identification and antimicrobial resistance of pathogens in neonatal septicemia in China-A meta-analysis. Int J Infect Dis. 2018;71:89-93.
5. Rao SC, Srinivasjois R, Moon K. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev. 2016;12:CD005091.
6. Sherwin CMT, Svahn S, Van Der Linden A, Broadbent RS, Medlicott NJ, Reith DM. Individualised dosing of amikacin in neonates: A pharmacokinetic/ pharmacodynamic analysis. European Journal of Clinical Pharmacology. 2009;65:705-13.
7. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982. J Antimicrob Chemother. 1984;13 Suppl A:9-22.
8. Allegaert K, Anderson BJ, van den Anker JN, Vanhaesebrouck S, de Zegher F. Renal drug clearance in preterm neonates: relation to prenatal growth. Ther Drug Monit. 2007;29:284-91.
9. Allegaert K. The impact of ibuprofen or indomethacin on renal drug clearance in neonates. J Matern Fetal Neonatal Med. 2009;22 Suppl 3:88-91.
10. Labaune JM, Bleyzac N, Maire P, Jelliffe RW, Boutroy MJ, Aulagner G, Putet G. Once-a-day individualized amikacin dosing for suspected infection at birth based on population pharmacokinetic models. Biol Neonate. 2001;80:142-7.
11. Hughes KM, Johnson PN, Anderson MP, Sekar KC, Welliver RC, Miller JL. Comparison of Amikacin Pharmacokinetics in Neonates Following Implementation of a New Dosage Protocol. J Pediatr Pharmacol Ther. 2017;22:33-40.
12. MerativeTM Micromedex® Complete IV Compatibility (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com/ (cited: April/19/2024)
13. DBL Amikacin injection. Pfizer Australia Pty Ltd. 1 February 2024. Accessed online via MIMS on 20 April 2024.
14. Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K, et al. Pharmacometric approaches to personalize use of primarily renally eliminated antibiotics in preterm and term neonates. The Journal of Clinical Pharmacology. 2016;56(8):909-35.
15. Engler D, Schellack N, Naude A, Gous A. A pilot study on the use of amikacin in neonates: Who should be monitored for ototoxicity? Southern African Journal of Infectious Diseases. 2015;30(3):114-8.
16. Endo A, Nemoto A, Hanawa K, Maebayashi Y, Hasebe Y, Kobayashi M, et al. Relationship between amikacin blood concentration and ototoxicity in low birth weight infants. Journal of Infection and Chemotherapy. 2019;25(1):17-21.
17. Tewari VV, Jain N. Monotherapy with amikacin or piperacillin-tazobactum empirically in neonates at risk for early-onset sepsis: a randomized controlled trial. Journal of tropical pediatrics. 2014;60(4):297-302.
18. Sherwin CM, Svahn S, Van Der Linden A, Broadbent RS, Medlicott NJ, Reith DM. Individualised dosing of amikacin in neonates: a pharmacokinetic/pharmacodynamic analysis. European journal of clinical pharmacology. 2009;65:705-13.

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