

What do I need to know about aminoglycoside antibiotics?

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ABSTRACT

The aminoglycosides are broad-spectrum, bactericidal antibiotics that are commonly prescribed for children, primarily for infections caused by Gram-negative pathogens. The aminoglycosides include gentamicin, amikacin, tobramycin, neomycin, and streptomycin. Gentamicin is the most commonly used antibiotic in UK neonatal units. Aminoglycosides are polar drugs, with poor gastrointestinal absorption, so intravenous or intramuscular administration is needed. They are excreted renally. Aminoglycosides are concentration-dependent antibiotics, meaning that the ratio of the peak concentration to the minimum inhibitory concentration of the pathogen is the pharmacokinetic-pharmacodynamic index best linked to their antimicrobial activity and clinical efficacy. However, due to their narrow therapeutic index, the patient's renal function should be monitored to avoid toxicity, and therapeutic drug monitoring is often required. Here we provide a review of aminoglycosides, with a particular focus on gentamicin, considering their pharmacokinetics and pharmacodynamics, and also practical issues associated with prescribing these drugs in a paediatric clinical setting.

Aminoglycosides are a closely related group of bactericidal antimicrobials all containing an aminocyclitol ring to which amino sugars are attached by glycosidic linkages. They are derived from Gram-positive bacteria of the genus *Streptomyces* (eg, tobramycin) and *Micromonospora* (eg, gentamicin).¹

INDICATIONS AND MODE OF ACTION

Aminoglycoside antibiotics have been used in clinical practice since the 1940s² and include gentamicin, amikacin, tobramycin, neomycin and streptomycin. The aminoglycosides are broad-spectrum antimicrobials that are effective against both Gram-negative aerobic bacteria and staphylococci. Gentamicin is the most

widely prescribed aminoglycoside in the UK and the most commonly used antibiotic in neonatal units. It is often used first line when treating serious bacterial infections in neonates, commonly as empirical therapy in combination with another antibiotic, such as penicillin. In paediatrics, gentamicin is used for a variety of indications, including septicaemia, meningitis and other central nervous system infections, biliary tract infections, acute pyelonephritis and endocarditis.³ In cystic fibrosis, it can also be used for respiratory infections caused by *Pseudomonas aeruginosa*, and this is the most common indication for tobramycin.³ If the infection is caused by Gram-negative bacteria that are resistant to gentamicin, amikacin may be appropriate instead.³ Neomycin cannot be administered parenterally due to its toxicity but can be used as, for example, topical therapy (eg, in the eye before ophthalmic surgery¹) or orally prior to abdominal surgery involving the gastrointestinal tract.³ Streptomycin is used almost solely for tuberculosis.

Aminoglycosides are hydrophilic drugs, meaning they cannot easily penetrate the hydrophobic bacterial cell membrane. To do so, an electron transport system (from the cell's respiratory cycle) is needed, which is why aminoglycosides are only effective against aerobic bacteria.² Once in the cytosol, they exhibit bactericidal activity by interrupting protein synthesis, binding irreversibly to the 16S ribosomal RNA receptor on the 30S subunit of the bacterial ribosome.²

PHARMACOKINETICS

All aminoglycoside antibiotics exhibit similar pharmacokinetic (PK) profiles;⁴ however, there is significant variability in the PK between patients, especially in the neonatal population.

As aminoglycosides are polar drugs, they are not lipophilic and hence are very



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poorly absorbed from the healthy gastrointestinal tract. They therefore need to be administered intramuscularly or, more commonly, by the intravenous route. Aminoglycosides exhibit low plasma protein binding (<10%)⁴ and distribute mainly into the extracellular water due to their hydrophilic nature. Their apparent volume of distribution (V_d) (which describes how well a drug distributes into body tissue) is thus low, that is, in the range of 0.2–0.3 L/kg in adults;⁴ however, due to a higher proportion of total body water in neonates, V_d is increased in this population.⁵ V_d is also increased in conditions such as sepsis, severe burns and febrile neutropenia.⁴ Aminoglycosides are excreted renally as intact compounds.¹ Elimination half-lives are approximately 2–3 hours in adults,⁴ but are prolonged in young children, especially neonates, due to their immature renal function. Nephron development starts in utero (around week 9 of gestation⁵), which is why the maturation of the glomerular filtration rate, and therefore renal function, correlates better with postmenstrual age (ie, gestational plus postnatal age (PNA)) than postnatal (chronological) age. After birth, during the first days of life, the renal and intrarenal blood flows increase dramatically, resulting in rapidly improved renal function. After the first week of life, renal function increases more gradually, reaching adult levels at approximately 12 months of age.⁵ As renal function and therefore elimination of aminoglycosides depend both on gestational age and PNA, both factors should be considered when determining dosing regimens in neonates.

PHARMACODYNAMICS

Aminoglycosides are concentration-dependent antibiotics, meaning that the ratio of the peak concentration (C_{max}) to the minimum inhibitory concentration (MIC) of the pathogen is the pharmacokinetic–pharmacodynamic (PK–PD) index that is best linked to their antimicrobial activity and clinical efficacy.⁶ A C_{max} /MIC ratio of 8–12 has been demonstrated necessary to achieve a clinical response in most cases (based on adult clinical data).⁶ However, since the immune system is immature in neonates, and in light of increasing resistance among Gram-negative microorganisms, a higher PD target may be justifiable in this population.⁷ Further research is needed to define an appropriate evidence-based target. Importantly, aminoglycoside therapy will often be started empirically when the causative pathogen (and its MIC) is still unknown; therefore, MIC distributions from reference laboratories (eg, EUCAST, the committee established to harmonise clinical antimicrobial breakpoints in Europe) will typically be used instead.

Aminoglycosides have a narrow therapeutic index, and their use may result in toxicity (namely ototoxicity and nephrotoxicity); thus for courses >2–3 days in duration, their serum concentration must be monitored to ensure efficacy and avoid excessive predose

(trough) concentrations. While nephrotoxicity is usually only transient, ototoxicity may be irreversible. Although immature renal function in neonates could potentially contribute to a higher risk of aminoglycoside-induced toxicity, the rates of toxicity actually appear to be significantly lower in this population⁸ compared with adults. Nevertheless, renal function should be monitored before and during the administration of these drugs, and concomitant use of loop diuretics (eg, furosemide), nephrotoxic agents and ototoxic drugs (such as cisplatin) should be avoided where clinically feasible.⁸ If other nephrotoxic drugs are coadministered, the respective dose times should be separated as far as possible. The m.1555A>G mutation in human mitochondrial DNA⁸ has been shown to explain a proportion of aminoglycoside-related ototoxicity. Testing patients for this mutation could be useful in children with conditions such as cystic fibrosis, where prolonged or repeated courses of these antibiotics may be necessary. However, the attributable risks associated with this mutation have not yet been clarified, and importantly other mitochondrial DNA mutations can contribute to deafness following aminoglycoside therapy.

A rare but important contraindication to aminoglycoside therapy is myasthenia gravis because these antibiotics can impair neuromuscular transmission (to a clinically significant degree).³ Aminoglycosides can also enhance the effects of muscle relaxants and anticholinesterases, and can potentially cause a reversible, dose-related myasthenia-like syndrome. Other potential adverse reactions include drug-induced hypersensitivity, hypomagnesaemia with long treatment courses, seizures and encephalopathy (very rare).

PRACTICAL ISSUES/PITFALLS IN PRESCRIBING

Both once-daily and multiple-daily (formerly considered ‘standard dose’) dosing regimens of aminoglycosides are routinely used. The once-daily regimens use a higher single dose compared with the relatively smaller individual doses in multiple-daily regimens. Table 1 summarises their respective advantages and disadvantages. The British National Formulary for Children (BNFC)³ recommends an extended interval dosing regimen (ie, initial dose intervals of 24 or 36 hours) in neonates, adjusted according to serum concentration, which should be monitored frequently. Generally, the dosing interval should also be extended if the predose concentration exceeds the accepted threshold; for example, 2 mg/L for multiple-daily dosing and extended interval dosing in neonates, or 1 mg/L in children receiving gentamicin once daily.³

Due to the complicated changes in the maturation of neonatal renal function with both increasing gestational age and PNA, the dosing regimen should ideally be based on both factors; this approach is used in some centres, although the current BNFC recommendation is to prescribe the dose according to the

Table 1 Comparison of once-daily and multiple-daily dosing regimens of aminoglycosides in paediatric patients

	Advantages	Disadvantages
Once-daily dosing	<ul style="list-style-type: none"> ▶ Higher peak concentrations lead to more rapid and higher (initial) bacterial kill ▶ Toxicity is not increased because aminoglycoside uptake in the kidney and ear is saturable ▶ Higher peaks prolong 'postantibiotic' effect (continued suppression of bacterial growth after drug administration stops and serum concentrations are below the minimum inhibitory concentration) ▶ Lower predose concentrations reduce toxicity⁹ ▶ Longer 'drug-free' periods help reduce/reverse adaptive resistance (form of resistance developing after initial exposure of bacteria to aminoglycoside)¹⁰ 	<ul style="list-style-type: none"> ▶ If drug clearance is high, 'no-drug' (untreated) periods between doses could result in clinically significant bacterial regrowth¹⁰ ▶ Standard once-daily doses, high doses should be avoided in children over 1 month of age with creatinine clearance <20 mL/min/1.73 m²
Multiple-daily dosing	<ul style="list-style-type: none"> ▶ More appropriate for burns patients (burns covering >20% of total body surface area) due to excess fluid loss and other complicating factors, and for children with endocarditis³ 	<ul style="list-style-type: none"> ▶ Not appropriate for patients with reduced renal function (creatinine clearance <20 mL/min/1.73 m²), or neonates, due to insufficient time between doses to clear the drug³ ▶ More time-consuming and costly in clinical practice

PNA only (eg, every 36 hours for PNA <7 days or every 24 hours if PNA >7 days, respectively, in the case of gentamicin).³

Significant variability in the dosing and monitoring of aminoglycosides in UK neonatal units has previously been shown: gentamicin trough (predose) concentrations were most commonly taken just before the third dose (in 40% of participating units) and before the second dose in approximately 25% of cases.¹¹ The BNFC recommends measuring aminoglycoside serum concentration following three or four doses after treatment initiation (when renal function in the child is normal and they are on a multiple-daily dosing regimen).³ However, if renal function is impaired, the trough concentration should be checked earlier and more frequently. When gentamicin is given multiple times a day, concentrations at 1 hour post dose (ie, 'peak' concentrations) should also be checked (BNFC recommends a peak of 3–5 mg/L for endocarditis).³

For centres using electronic prescribing, an issue to be aware of is that there is typically no checkbox for the collection and measurement of a predose serum drug concentration; therefore, alternative strategies are required to ensure medical and nursing staff are aware of the need to measure levels before administering the next dose when required. The UK National Patient Safety Agency highlighted ongoing issues with gentamicin use in neonates, including administering the drug at incorrect times, inaccuracies with prescriptions and also problems with therapeutic drug monitoring (TDM), and they subsequently recommended implementation of standardised neonatal care bundles to support safe prescribing.¹²

PK-PD modelling could be used to individualise treatment in the future, especially in neonates, where the between-patient variability is high.¹³ Model-based TDM software could also be used to facilitate the collection of gentamicin TDM samples at any time in the

Learning points

- ▶ Aminoglycosides are effective against Gram-negative bacteria and some Gram-positives including staphylococci.
- ▶ Usually they are administered using once-daily dosing regimens, except when renal function is impaired, in the treatment of endocarditis or in patients with severe burns.
- ▶ An extended interval dosing regimen is used in the neonatal population to account for the immature renal function (the BNFC-recommended dosing interval is 36 hours for neonates in their first week of life, reducing to 24 hours thereafter).
- ▶ Aminoglycoside predose (trough) concentrations need to be monitored to avoid toxicity.
- ▶ In addition, peak concentrations (1 hour post dose) should be measured in multiple-daily dose regimens in order to ensure therapeutic concentrations are achieved.
- ▶ Coadministration with loop diuretics (eg, furosemide), nephrotoxic agents or ototoxic drugs (eg, cisplatin) should be avoided.
- ▶ Individualised dosing based on pharmacokinetic-pharmacodynamic modelling could be used in the future, particularly in neonates, but at present this is mainly used in research-active centres and is not yet routine practice.

dosing interval (ie, with routine blood tests or blood gases),¹⁴ thereby reducing the burden on hospital staff, patients and parents; however, while a topic of ongoing research, this facility is not yet available in routine National Health Service care. A detailed review of model-based dosing and TDM is beyond the scope of this paper, but it is important that PK models used for TDM software should be externally

Test your knowledge

1. Aminoglycosides are effective against anaerobic bacteria
 - A. Yes
 - B. No
2. Aminoglycosides are usually given three times daily for which of the following indications?
 - A. Early-onset neonatal sepsis
 - B. Infective endocarditis
 - C. Urinary tract infections
3. Predose gentamicin concentrations need to be monitored to prevent excessive concentrations, which could lead to
 - A. Reversible ototoxicity
 - B. Irreversible ototoxicity
 - C. Nephrotoxicity
 - D. A and C
 - E. B and C
4. When prescribing aminoglycosides for children who are obese, which body weight descriptor should be used for calculating the dose?
 - A. Ideal body weight
 - B. Total body weight

The answers are after the references.

validated whenever possible and need to be regularly reviewed by suitable experts.

CONTROVERSIES AROUND THE DRUGS

Aminoglycosides are not new drugs, and bacteria have developed resistance by different mechanisms including aminoglycoside-modifying enzymes, efflux pumps and target binding site modification.² In this era of increasing antimicrobial resistance, new aminoglycoside derivatives are being developed but are not yet ready to be used in clinical practice.

"STOP DOING THIS"

Aminoglycosides distribute mainly into lean tissue; therefore, dosing in patients who are obese should be based on ideal body weight (IBW), not total body weight, and serum concentrations should be closely monitored.³ There are several approaches for calculating IBW,¹⁵ but the most commonly used approach, the McLaren method, assumes that the weight-to-height ratio is constant for a certain age; therefore, IBW can simply be read off a growth chart. However, the optimal approach to drug dosing in children who are obese is yet to be defined.

CONCLUSIONS

Aminoglycosides are effective broad-spectrum antibiotics and are among the most commonly prescribed

antibiotics on neonatal units. However, they can have toxic effects; therefore, both serum concentrations and renal function should be monitored. In neonates, dosing should ideally be based on both gestational and chronological age, although this is not currently recommended as routine practice in the UK.

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Answers to the multiple choice questions

1. (B); 2. (B); 3. (E); 4. (A).



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