Title: What do I need to know about aminoglycoside antibiotics?

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The 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* (e.g. tobramycin) and the genus *Micromonospora* (e.g. gentamicin) [1].

Indications and mode of action

Aminoglycoside antibiotics have been used in clinical practice since the 1940s [2] 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 on 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 a penicillin. In paediatrics, gentamicin is used for a variety of indications, including septicaemia, meningitis and other central nervous system (CNS) 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 (e.g. in the eye before ophthalmic surgery [1]) 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 ribonucleic acid (rRNA) 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 very 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 (Vd) (which describes how well a drug distributes into body tissue, instead of plasma) is thus low, i.e. 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, Vd is increased in this population[5]. Vd 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 gestation [5]), which is why the maturation of the glomerular filtration rate (GFR), and therefore renal function, correlates better with postmenstrual age (i.e. gestational plus postnatal age) than postnatal (chronological) age. After birth, during the first days of life, the renal and intra-renal 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 depends both on gestational and postnatal ages, 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 (e.g. 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 oto- and nephrotoxicity), thus for courses greater than 2-3 days in duration, their serum concentration must be monitored to ensure efficacy and avoid excessive pre-dose (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 population [8], when compared to adults. Nevertheless, renal function should be monitored before and during the administration of these drugs, and concomitant use of loop diuretics (e.g. furosemide), nephrotoxic agents, and ototoxic drugs (such as cisplatin) should be avoided where clinically feasible [8]. If other nephrotoxic drugs are co-administered, the respective dose times should be separated as far as possible. The m.1555A>G mutation in human mitochondrial DNA [8] 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 myasthaenia 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 in comparison to 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 (i.e. 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 pre-dose concentration exceeds the accepted threshold; e.g. 2 mg/L for multiple-daily dosing and extended-interval dosing in neonates , or 1 mg/L in children receiving gentamicin once daily [3].

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

	Advantages	**Disadvantages**
Once-daily dosing	• Higher peak concentrations lead to more rapid and higher (initial) bacterial kill.	• If drug clearance is high, "no-drug" (untreated) periods between doses could result in

	• Toxicity is not increased because aminoglycoside uptake in the kidney and ear is saturable. • Higher peaks prolong ''post-antibiotic'' effect (continued suppression of bacterial growth after drug administration stops and serum concentrations are below the MIC). • Lower pre-dose concentrations reduce toxicity [9] • Longer "drug-free" periods help reduce/reverse adaptive resistance (form of resistance developing after initial exposure of bacteria to aminoglycoside) [10]	clinically significant bacterial regrowth [10] • Standard once-daily doses, high-doses should be avoided in children over 1 month of age with creatinine clearance <20 mL/minute/1.73 m^2
Multiple-daily dosing	• More appropriate for burns patients (burns covering >20% of total body surface area) due to excess fluid loss and other complicating factors,	• Not appropriate for patients with reduced renal function (creatinine clearance <20 mL/minute/1.73m^2), or neonates, due to insufficient

	and children with endocarditis [3].	time between doses to clear the drug [3] • More time-consuming and costly in clinical practice

Due to the complicated changes in the maturation of neonatal renal function with both increasing gestational and postnatal age (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 dose according to the postnatal age only (e.g. every 36h for PNA <7 days or every 24h 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 (pre-dose) 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 3 or 4 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 (i.e. “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 pre-dose 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 (NPSA) highlighted ongoing issues with gentamicin use in neonates, including administering the drug at incorrect times, inaccuracies with prescriptions, and also problems with TDM, and they subsequently recommended implementation of standardised neonatal care bundles to support safe prescribing [12].

Pharmacokinetic-pharmacodynamic 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 dosing interval (i.e. with routine blood tests or blood gases) [14], therefore reducing the burden on hospital staff, patients, and parents; however, while a topic of ongoing research, this facility is not yet available in routine NHS 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 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 the clinic.

"Stop doing this"

Aminoglycosides distribute mainly into lean tissue, therefore dosing in obese patients 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 weight-to-height ratio is constant for a certain age, therefore IBW can be simply read off a growth chart. However, the optimal approach to drug dosing in obese children 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 routine practice in the UK.

Learning point box

1. Aminoglycosides are effective against Gram-negative bacteria, and some Gram-positives including staphylococci.
2. 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.
3. An extended-interval dosing regimen is used in the neonatal population to account for the immature renal function (BNFC-recommended dosing interval is 36 hours for neonates in their first week of life, reducing to 24 hours thereafter).
4. Aminoglycoside pre-dose (trough) concentrations need to be monitored to avoid toxicity.
5. In addition peak concentrations (one hour post-dose) in multiple daily dose regimens should be measured in order to ensure therapeutic concentrations are achieved.
6. Co-administration with loop diuretics (e.g. furosemide), nephrotoxic agents, or ototoxic drugs (e.g. cisplatin) should be avoided.
7. 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.

MCQs

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. Pre-dose 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 obese children, which body weight descriptor should be used for calculating the dose
    a. **Ideal body weight**
    b. Total body weight

Contributorship statement

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Competing interest

None.

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