Aminoglycoside administration in paediatrics: a literature search comparing international practices of intravenous injection or intravenous infusion

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INTRODUCTION

Aminoglycosides are a class of broad-spectrum, bactericidal antibiotics of which amikacin, gentamicin and tobramycin are the most commonly prescribed. These antibiotics are frequently prescribed for children, usually for infections, which are caused by aerobic Gram-negative pathogens. [1]

Aminoglycosides are very poorly absorbed from the gastrointestinal tract, due to their lack of lipophilicity. Therefore, they must be administered parenterally. They are also concentration dependent, which means that the ratio between the peak concentrations (C_{max}) to the pathogen's minimum inhibitory concentration (MIC) is the pharmacokinetic-pharmacodynamic index, which is a marker for antimicrobial activity and effectiveness. To achieve an effective clinical response, a C_{max}/MIC ratio between 8 and 12 has been advised, although this is based on adult data.[1] Aminoglycosides have a narrow therapeutic margin, so therapeutic drug monitoring must be used to monitor for toxicity. High serum levels may result in ototoxicity and nephrotoxicity.[1]

Aminoglycosides are administered as once-daily or multiple-daily (previously known as 'standard dose') regimes. Once-daily regimens deliver a higher individual dose than multiple-daily doses. There are advantages and disadvantages of both methods, which have not been discussed in detail within this article.

Aminoglycoside use can result in rare cases of ototoxicity, even at normal serum levels. There is some evidence that suggests an association between mitochondrial mutations (particularly the m.1555A>G mutation, corresponding to a change of the *MT-RNR1* gene), leading to an increased risk of ototoxicity.[2] Within the UK, this occurrence is estimated at 1 in 500 patients. Currently, neonatal testing for the genetic variant is available through point of care testing for neonates with sepsis; however this is not commissioned nationally in the UK.[2]

Methods of administering intravenous medications include intermittent/or continuous intravenous infusions, or via slow

Key messages

- The suggested methods of aminoglycoside administration in paediatrics vary within the UK and internationally; however, there is more experience with intravenous infusion administration of aminoglycosides than for intravenous injection.
- There is no definitive guidance available suggesting what method of administration is most appropriate for gentamicin, amikacin or tobramycin in paediatric patients.
- Further studies are required to compare administration via intravenous injection and intravenous infusion, as well as pharmacodynamics changes, for example, the effects on time above the minimum inhibitory concentration when giving aminoglycosides via intravenous injection and how this affects both the clinical outcome and the incidence of adverse effects.
- There are multiple small studies/case reports highlighting the efficacy and safety of giving gentamicin one time per day via intravenous injection. Further research regarding the cost-saving and time-saving benefits would further the discussion and help to clarify optimal practice.

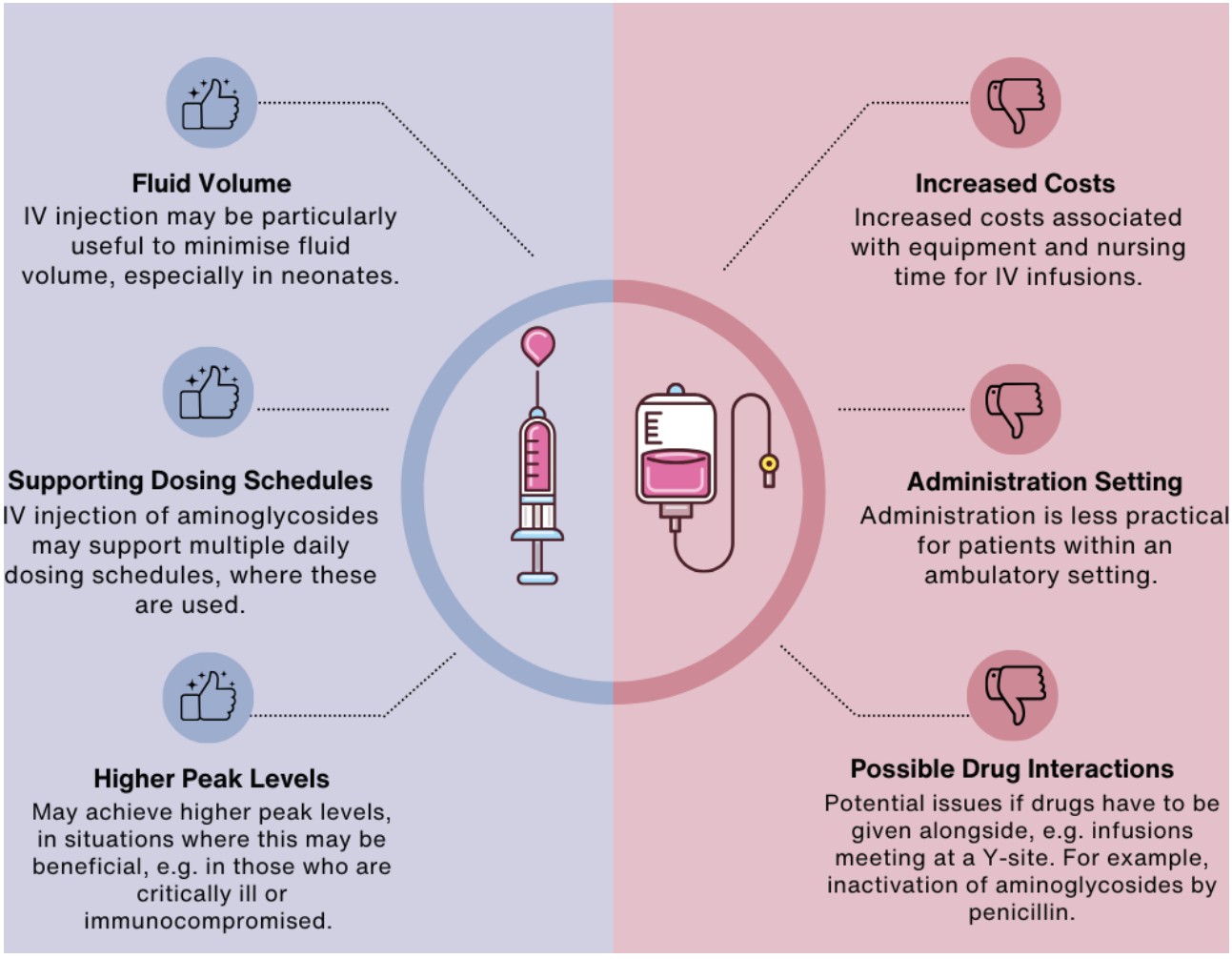

Figure 1 Examples of the advantages and disadvantages of IV injections and IV infusions.

intravenous injection (previously known as a bolus injection) (figure 1). Intravenous injection has the benefit of short administration time and minimal volume. This is particularly useful for patients who may be fluid restricted. The administration time may provide advantages due to the prompt time-to-first-dose, or a higher peak concentration.[3] Theoretical added benefits, include cost-savings, reduced nursing time and avoidance of drug incompatibilities, for example, the inactivation of aminoglycosides by β-lactam antibiotics.[4]

Despite these potential benefits, a review by *Spencer et al* states that aminoglycosides are not usually recommended for intravenous injection, due to the concerns that elevated peak levels after rapid administration may be a controllable risk factor for toxicity. However, this review acknowledges that intravenous injection of gentamicin and tobramycin has been reported frequently in the literature.[3]

AIM

The aim of this medicines update is to review the current practices and published evidence regarding the administration of aminoglycosides in paediatrics, via intravenous infusion or intravenous injection (specifically amikacin, gentamicin and tobramycin). This review will focus on current practices across the UK as well as the USA, New Zealand and Australia.

RESEARCH METHODS

A literature search of Medline and Embase databases was conducted between the dates of 15 July 2022 and 14 August 2023, as well as personal communications with specialist paediatric pharmacists in other UK health boards and internationally, to identify established local practices.

GENTAMICIN

When comparing the two routes of administration, intravenous infusions have been associated with both subtherapeutic and excessive trough concentrations of gentamicin.[5] As shown in online supplemental appendix 1, intravenous infusion over 30 min to 2 hours (in 50–200 mL) is recommended in the USA. Conversely, in the UK, licensed product information recommends infusing over a maximum of 20 min to 30 min, in a limited fluid volume (100 mL) or a slow intravenous injection over 3 min.[6 7]

A literature search revealed only two studies conducted in paediatrics, the vast majority of the papers found were focused on adult patients.[8 9] Initial studies conducted by

the manufacturer mostly evaluated two routes of administration, intravenous infusion (30–60 min) and intramuscular injection. A review of multiple studies in adults showed gentamicin has been safely administered as an intravenous injection over 3–5 min.[3]

Robinson and Nahata retrospectively investigated intravenous injection (2–3 min) of gentamicin in paediatric patients (n=123; neonates n=11, age 31 days to 1 year n=71, 13 months to 12 years n=26, 12 years to adult n=15) at a single centre. Patients received a median of nine doses; with 42% receiving doses every 8 hours, 32% receiving doses every 24 hours, and the remainder at other intervals ranging from every 12 to 36 hours. The results did not show a significant elevation in peak serum gentamicin concentrations or renal function changes. In the neonatal population, no changes in auditory function were noted. Auditory data were not available for the older population. No other adverse effects were mentioned.[8]

Bromiker *et al* conducted a study in Israel to evaluate auditory and renal function in 30 infants (gestation age: 38.9±2.1 weeks, birth weight: 3057g±516g) who were treated with rapid intravenous gentamicin injection over 1 min at a dose of 2.5 mg/kg two times per day for 72 hours. Auditory evaluation was based on transient evoked otoacoustic emissions (TEOAEs) and behavioural observation audiometry. Initial auditory tests (n=25) produced normal findings bilaterally except for one patient whom normal TEOAE results were obtained from only one ear. Follow-up TEOAE examination of 24 out of 30 infants at 5 weeks or more after completion of therapy found normal results bilaterally in 23 infants, and one infant had a normal unilateral response. Data were not found to suggest intravenous injection caused an increase in adverse effects compared with intravenous infusion.[9]

Loewenthal and Dobson reported experiences in the use of gentamicin and tobramycin in an outpatient setting, between November 1995 and October 2010. These were administered as an intravenous injection over 3–5 min to children and adults aged 3–84 years, as 5593 doses (tobramycin n=3652 and gentamicin n=1941). One case of vestibular toxicity and hearing loss was reported in a middle-aged woman, with complex medical problems, 16 hours after the last dose of tobramycin.[10]

AMIKACIN

Usually amikacin is given via intravenous infusion (see online supplemental appendix 1); however, there are some indications for which intravenous injection is preferred, especially within the UK. One study conducted in adults (n=5) evaluated the administration of amikacin 7.5 mg/kg over 2 min; however, this resulted in potentially toxic peak serum concentrations (68–122 µg/mL).[3] A literature search identified two studies of amikacin in paediatrics; however, none used an intravenous injection method.[11 12]

Manufacturers of amikacin differ in their administration guidance. Pfizer confirmed that intravenous injection of amikacin in neonates and children ≤12 weeks would be outside of the product's license.[13]

Online supplemental appendix 1 summarises some of the international practices with regards to administering aminoglycosides. The Australasian Neonatal Medicines Formulary recommends preterm and term neonates should be given amikacin via intravenous infusion over 60 min.[14] American literature sources advise intravenous infusion over 30–60 min, or over 1–2 hours in infants, and do not recommend intravenous injection. However, these sources acknowledge that this practice is used. This is in contrast to UK sources, such as the British National Formulary for Children (BNFC), which recommend administering amikacin as an intravenous injection over 3–5 min, or via a slow intravenous infusion over 30–60 min, for the majority of indications.[15]

TOBRAMYCIN

The BNFC recommended tobramycin is given by slow intravenous injection over 3–5 min or by intravenous, infusion over 20–60 min (see online supplemental appendix 1). The NHS Injectable Medicines Guide (Medusa) recommends that the intravenous injection is restricted for multiple-dose regimens, while once-daily high-dose regimens should be given by intravenous infusion.[16] Tobramycin once-daily dosing has become common practice within the UK but is an unlicensed method of administration.[17 18]

The manufacturers state for paediatric patients, the dose should be infused over 20–60 min and it can be given as a direct intravenous injection. However, when given as an IV injection, serum levels may exceed 12 microgram/mL for a short period of time. While this is listed as a caution, slow intravenous injection is still a licensed method of administration.[17]

American literature sources do not recommend intravenous injection, despite acknowledging that this practice is used. The rationale for this is that infusion periods of less than 20 min may result in peak serum tobramycin concentrations exceeding 12 µg/mL.[18] There are concerns that these elevated peak levels after rapid administration may cause toxicity, such as ototoxicity.[3] The Australasian Neonatal Medicines Formulary also recommends that tobramycin 5 mg/kg/dose 24–48 hourly should be given as an intravenous infusion over 20–60 min (see online supplemental appendix 1).

The TOPIC study compared once-daily versus three-time daily regimens of tobramycin intravenous infusion in children (n=125) and adults (n=94) with cystic fibrosis. The pharmacokinetic modelling from this study showed equivalent efficacy for once-daily tobramycin, compared with, what was at the time, the conventional three-time daily treatment. A smaller rise in N-acetyl-β-D glucosaminidase in children in the once-daily group, compared with the three-time daily group suggests that the once-daily regimen may be less nephrotoxic than three-time daily regimen in children. As this safety and efficacy data were obtained following intravenous infusion, rather than

intravenous injection, this may explain the preference for the intravenous infusion method. There are limitations to this study, as toxic effects may be cumulative and could also contribute to the findings. None of the patients developed ototoxic effects.[19]

SUMMARY

There are multiple small studies or case reports highlighting the efficacy and safety of intravenous injection of gentamicin in paediatrics, especially for multiple daily dose regimens. Both methods of administration (intravenous injection and intravenous infusion) are licensed for gentamicin.[7] Therefore, as both methods of administration seem acceptable, intravenous injection may provide cost and time-saving benefits. Further investigation of the cost benefits would be needed; however, this is outside the scope of this review.

More quality research is needed to support the administration of tobramycin and amikacin via intravenous injection, although online supplemental appendix 1 shows that this practice is used within the UK and internationally.

Test your knowledge

MCQs

1. In what situation would it be beneficial to give a medicine via an intravenous infusion:
   a. For patients who are fluid restricted, for example, heart failure
   b. In an outpatient setting
   c. For medicines with a multiple daily dose schedule
   d. Where there are concerns regarding the rapid administration of a medicine
2. What bacteria are aminoglycosides most effective against?
   a. Gram-positive anaerobic bacteria
   b. Gram-negative aerobic bacteria
   c. Gram-positive aerobic bacteria
   d. Gram-negative anaerobic bacteria
3. Currently, which aminoglycoside has the most published data to support intravenous injection in paediatrics?
   a. Tobramycin
   b. Streptomycin
   c. Gentamicin
   d. Amikacin
4. What is the best marker of aminoglycoside antimicrobial activity and clinical effectiveness?
   a. C_{max}
   b. MIC
   c. C_{max}/MIC
   d. Trough level
5. What gene is responsible for rare cases of ototoxicity with aminoglycosides?
   a. MT-RNR4
   b. MT-RNR1
   c. MT-RNR2
   d. MT-RNR6

Answers to the quiz are at the end of the references.

Correction notice This paper has been corrected since it was first published. There was an error in figure 1.

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Answer to the multiple choice questions

1. d
2. b
3. c
4. c
5. b