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A suggested approach to once-daily aminoglycoside dosing

EVAN J. BEGG, MURRAY L. BARCLAY & STEPHEN B. DUFFULL
Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand

1 Once-daily aminoglycoside dosing has many advantages and has been widely advocated. However, existing guidelines for methods of administration and monitoring are non-specific and may lead to excessive dosing.
2 The traditional approach of aiming for target peak and trough concentrations is not appropriate for once-daily dosing.
3 A method is proposed which uses a target area under the concentration-time curve (AUC) for the aminoglycoside based on the 24 h AUC that would result with conventional dosing. This method requires measurement of two drug concentrations, one approximately 0.5 h after the end of the infusion and another at a later time (6–22 h) depending on renal function.
4 A simpler, graphical method is also proposed for patients with normal renal function, which requires the measurement of a single concentration at a time between 6 and 14 h.
5 Both methods are likely to be safer than existing guidelines.

Keywords aminoglycosides once-daily dosing

Introduction

The potential advantages of once-daily aminoglycoside dosing have received recent attention [1–3]. Therapeutic advantages over conventional dosing include a probable lower incidence of toxicity, and at least equal efficacy. Practical advantages include straightforward dosage calculation, guaranteed high peak serum concentrations, decreased personnel time, fewer assays for therapeutic monitoring and lower consumable costs [1].

Many believe the time has come for the introduction of once-daily dosing into clinical practice, at least for some patient groups [1, 2]. Unfortunately no one has described exactly how this should be done and the adoption of the loose guidelines that have been offered may lead to excessive dosing in some patients.

The purpose of this article is to offer an approach to the actual dosing strategy, discussed under five headings.

i) Patient selection
ii) Starting dose
iii) Monitoring
iv) Dose revision
v) Dosing in patients with renal dysfunction

Patient selection

Until more studies are available in different patient groups, it is recommended that once-daily dosing should not be applied to:

a) the paediatric population
b) patients with bacterial endocarditis
c) patients with calculated creatinine clearance $CL_{Cr} < 0.35$ ml s^{-1}

Starting dose

The exact starting dose has not been defined clearly although approximately 5 mg kg^{-1} day^{-1} of gentamicin, tobramycin or netilmicin has been suggested. In 29 clinical trials of once-daily dosing *vs* conventional dosing, the mean once-daily doses were 5.4 mg kg^{-1} day^{-1} for netilmicin (n = 14), 4.25 mg kg^{-1} day^{-1} for gentamicin (n = 2) and 4.4 mg kg^{-1} day^{-1} for tobramycin (n = 4) [4]. Unfortunately, pharmacokinetic individualisation, the currently accepted optimal method of aminoglycoside dosing, was not used in these trials.

Correspondence: Dr E. J. Begg, Department of Clinical Pharmacology, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand

Pharmacokinetic individualisation involves the measurement of between 1 and 4 serum drug concentrations after a starting dose, and determination of the subsequent dose and dose interval by the Sawchuk & Zaske [5] or a Bayesian approach [6]. A peak concentration of 6–10 mg l^{-1} and a trough concentration of < 2 mg l^{-1} are usually targeted. These methods, which aim for peak concentrations of 6–10 mg l^{-1} and trough concentrations of < 2 mg l^{-1}, lead to higher mean daily doses than associated with non-individualised approaches. Using pharmacokinetic individualisation, Konrad *et al.* [7] found that the average total daily dose of netilmicin in patients with normal renal function was 7.8 mg kg^{-1} day^{-1} and recommended a starting dose of once-daily therapy of 7.0 mg kg^{-1} day^{-1}. Retrospective analysis of over 100 patients with normal renal function in our hospital produced similar figures for the average daily dose achieved with pharmacokinetic individualisation, i.e. 7.0 mg kg^{-1} day^{-1} in females and 6.7 mg kg^{-1} day^{-1} in males.

Potential starting doses, from 4.0 to 7.0 mg kg^{-1} day^{-1}, cannot be distinguished on the basis of clinical studies. Since there is more clinical experience with once-daily dosing using doses near the lower end of this range, it is suggested that 5 mg kg^{-1} day^{-1} is a convenient starting point for further clinical evaluation. Those who wish to use doses of up to 7.0 mg kg^{-1} day^{-1} should feel free to do so based on current information, at least in patients with normal renal function. Since aminoglycosides distribute only minimally into adipose tissue, the dosage should be based on the patient's lean body weight, or total body weight if this is lower.

Monitoring

Conventional target peak concentrations (i.e. 6–10 mg l^{-1}) do not apply to once-daily dosing. Furthermore, there are various reasons why monitoring trough concentrations is inappropriate; i) the time until dose adjustment can be made is unnecessarily prolonged, ii) currently accepted upper limits of trough concentrations at 24 h are too high, iii) predicted concentrations at 24 h are below the limit of current assay sensitivity.

The use of a 24 h trough measurement does not allow dose alteration until the third dose, 48 h after the first dose. It would be preferable to individualise the second dose. This can be achieved with drug concentration monitoring at a time well before the second dose is due.

A variety of authors have recommended or implied that trough concentrations of less than 2 mg l^{-1} are acceptable when using once-daily dosing [3, 7, 10, 11]. Others have said that 2 mg l^{-1} is too high and have suggested an upper limit of 1 mg l^{-1} for a 24 h trough concentration [9, 12]. We contend that both of these limits are far too high based on the area under the concentration-time curve (AUC) which would accompany such trough concentrations (see Figure 1). Patients with normal aminoglycoside pharmacokinetics would not be expected to have a trough concentration exceeding 0.05 mg l^{-1} at 24 h.

Predicted trough concentrations are too low to be detected by conventional aminoglycoside assay technology (Abbott TDx, fluorescence polarization immunoassay, limit of sensitivity 0.27 mg l^{-1}; Syva EMIT enzyme immunoassay, limit of sensitivity 0.25 mg l^{-1}). The UK National External Quality Assurance programme indicates that accuracy of assays for concentrations below 1 mg l^{-1} is poor [9].

Trough concentrations at 24 h are also limited because they reflect the gamma phase of elimination (slow release of drug from tissues) rather than the beta phase (which largely reflects renal function).

For all of these reasons, measurement of a trough concentration is not appropriate for once-daily dosing. Some authors have recognised the problems of measuring trough concentrations at 24 h and have suggested measuring concentrations at 8–12 h [9, 13] and 18 h [2]. However, pharmacokinetically-based reference concentrations to enable dose individualisation were not given for these time points.

It can also be argued that measurement of peak concentrations is superfluous with a once-daily dosing regimen [7]. The raison d'être of monitoring peaks has been to ensure that these concentrations are sufficiently above the MIC of the organism, and concentrations above 5 or 6 mg l^{-1} have been associated with better clinical outcome [14]. However, administration of the entire daily dose as a single dose ensures that this endpoint is always achieved (a peak of 17–25 mg l^{-1} would be expected after a dose, based on a volume of distribution (V) for the aminoglycosides of 0.2–0.3 l kg^{-1}).

Although peak and trough concentrations, as used currently, are not appropriate for once-daily dosing,

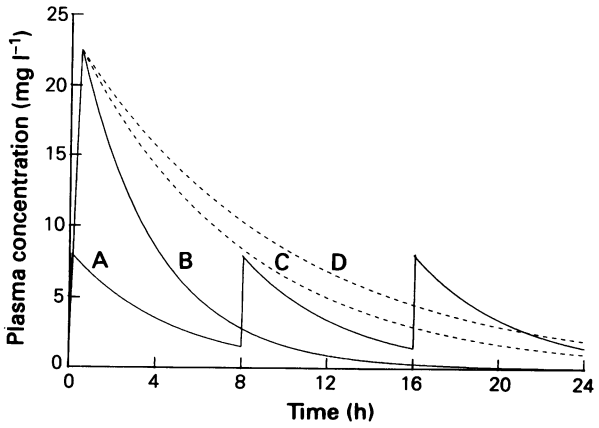

Figure 1 Aminoglycoside concentration *vs* time curves for different dosage regimens. A) dosing every 8 h to achieve a peak concentration of 8 mg l^{-1} and trough concentration of 1.5 mg l^{-1}, and B) once-daily dosing (same total daily dose) to give the same AUC. The two dashed lines (C and D) show once-daily dosing concentration-time curves when trough concentrations of 1 mg l^{-1} and 2 mg l^{-1} are obtained. For curves C and D, the AUC is 1.8- and 2.3-fold higher, respectively, than that of curves A and B.

some method of monitoring plasma concentrations is still necessary to avoid untoward drug accumulation and toxicity. A logical approach is to aim for a target area under the aminoglycoside serum concentration-time curve (AUC). For a chosen dose, the target AUC could be defined as the AUC that would be expected in a patient with mean population values of V (e.g. 0.25 l kg^{-1}) and half-life of elimination (e.g. 2.5 h) (see Table 1). This AUC will be identical to that which occurs when the same total daily dose is administered with conventional dosing although the shape of the concentration-time profiles will be very different (Figure 1).

A method is proposed for assessing the 24 h AUC with acceptable accuracy, within the constraints of practicality, after a single dose of 5–7 mg kg^{-1} day^{-1}. A second simpler method is also proposed for patients with normal renal function.

The AUC method

Measurement of two aminoglycoside concentrations, 0.5 h after the end of the infusion and at a time at least 2.5 half-lives later, but not greater than 5 half-lives (see Appendix 2), enables a 24 h AUC to be calculated. These times ensure that the portion of the AUC that is extrapolated is not excessive and that the concentrations are measurable within existing assay sensitivity. The range of times for the second sample allows flexibility in terms of sampling and assay measurement. The calculated AUC is compared with the target AUC. Relevant calculations can be performed using a hand held calculator, or a simple computer program, assuming a one-compartment model [15] (see Appendix 1).

A simple, graphical method for patients with normal renal function

A simpler approach would allow wider applicability. Accepting that monitoring of the peak concentration is less important for once-daily dosing than for conventional dosing, the main aim of monitoring aminoglycoside concentrations is to avoid overdosing and potential toxicity. A concentration-time curve has been constructed, below which drug accumulation would be unlikely, and above which a decrease in dose is recommended (Figure 2). This curve is based on the maximum AUC (119 mg l^{-1} h) which would have been permitted using the conventional aminoglycoside regimen, i.e. that which would occur with a peak of 10 mg l^{-1} and a trough of 2 mg l^{-1}. This AUC is still substantially smaller than those that would occur with trough concentrations approaching 1 or 2 mg l^{-1} with once-daily dosing (compare Figure 1 and Figure 2).

If a patient's drug concentration falls below this curve then an excessive AUC will be unlikely. A single blood sample can be drawn at a time between 6 and 14 h and the concentration compared with the concentration at the same time point on the graph. Others have independently proposed a very similar graphical method [16].

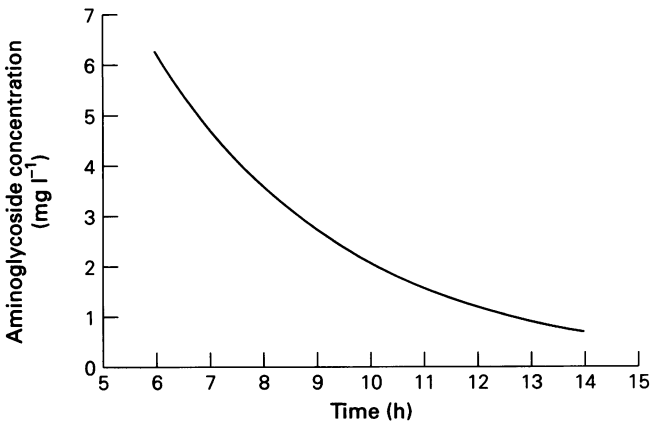

Figure 2 Aminoglycoside concentration *vs* time curve for once-daily dosing in patients with normal renal function. The line represents the concentration-time profile associated with the maximum AUC that would be achieved using the conventional dosing regimen (i.e. peak concentrations of 10 mg l^{-1}, and trough concentrations of 2 mg l^{-1}). Serum aminoglycoside concentrations measured between 6 and 14 h after a single daily dose should be below the line.

Note that there is no line below which dosing can be considered inadequate. Achieving an adequate initial peak concentration is the critical feature in aminoglycoside dosing and as previously mentioned, this will always occur with single doses of 5–7 mg kg^{-1}.

Dose revision

Using either of the above methods, there is time for feedback of concentrations to occur and for dose readjustment to be made prior to the second dose.

a) *Dose adjustment using the AUC method* (Appendix 2)

A simple linear dose adjustment can be made using the target and measured AUCs.

$$\text{i.e. second dose} = \frac{\text{target AUC}}{\text{measured AUC}} \times \text{first dose}$$

b) *Dose adjustment using the graph*

No dose alteration is necessary if concentrations are under the given line between 6 and 14 h. If, however, the concentration is above the line, then a proportional decrease in dose is recommended.

Dosing in patients with renal dysfunction

The AUC method lends itself to dosing in renal dysfunction. The simple, graphical method is not appropriate for this patient group as it is based on the assumption of normal aminoglycoside clearance.

In renal dysfunction, aminoglycoside clearance will be impaired and thus the shape of the concentration-time profile will be different. In order to achieve the same AUC as in patients with normal renal function, a lower dose will be necessary every 24 h. The starting dose should therefore be decreased in proportion to the degree of impairment of renal function. A lower peak concentration will result but the AUC will be the same due to greater retention of aminoglycoside.

A peak of 10 mg l^{-1} was chosen as the lowest peak for which once-daily aminoglycoside dosing remains appropriate. This is the peak which would be expected with a CL_{Cr} of around 0.35 ml s^{-1}, based on a V of 0.25 l kg^{-1} and a target AUC of 101 mg l^{-1} h. The concentration-time profile in moderate to severe renal dysfunction will thus approach the profile seen with conventional therapy aiming for peaks of 6–10 mg l^{-1}.

The higher AUC of 101 mg l^{-1} h, which is associated with a dose of 7 mg kg^{-1} in patients with normal renal function, was chosen for use in renal impairment to achieve the highest peak serum concentration possible in association with the lower range of doses. The AUC method does however allow for dosing to any target AUC. It should be noted that using this method trough concentrations will be below 1 mg l^{-1}, even with CL_{Cr} as low as 0.35 ml s^{-1}.

It is possible, and perhaps desirable, to use larger doses over a longer dose interval than 24 h in patients with moderate to severe renal dysfunction (e.g. < 0.7 ml s^{-1}) to be consistent with the high peak and low trough strategy. The calculated 24 h dose could be increased by 50% for a dose interval of 36 h, or by 100% for a dose interval of 48 h. However, intervals longer than 24 h have not been assessed in clinical trials.

A second antibiotic is almost always given with aminoglycosides, and this may be even more important if the dose interval is prolonged beyond 24 h. For patients with CL_{Cr} < 0.35 ml s^{-1} we suggest seeking specialist advice if considering the use of an aminoglycoside.

Conclusion

There is increasing support for the introduction of once-daily dosing of aminoglycosides. Non-specific guidelines have been available for dosing and monitoring but therapy based on these could result in overdose and toxicity. There is a need for a simple, safe and practical method of dosing. Two such methods are proposed.

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Appendix 1 – Calculation of a patient's 24 h AUC

1 Calculate the rate constant of elimination (k):

$$k = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$$

2 Calculate the concentration at the end of the infusion (C_{end}), i.e. the theoretical maximum concentration:

$$C_{end} = \frac{C_1}{e^{-k\,(t_1 - t_{end})}}$$

3 Calculate the predicted minimum concentration (C_{24}):

$$C_{24} = C_2 \cdot e^{-k\,(24 - t_2)}$$

4 Calculate the AUC over the 24 h dose interval AUC(0,24), assuming a half-hour infusion:

$$\text{AUC}(0,24) = \text{AUC}(\text{end}, 24) + \text{AUC}_{\text{infusion}}$$

$$\text{AUC}(0,24) = \frac{C_{end} - C_{24}}{k} + 0.065 \times \frac{C_{end} - C_{24}}{k}$$

Abbreviations

k = rate constant of elimination
t_1 = time at which the first concentration was measured, after the start of the infusion
t_2 = time at which the second concentration was measured, after the start of the infusion
t_{end} = time at the end of the infusion (usually 0.5 h)
C_1 = concentration measured at t_1
C_2 = concentration measured at t_2
C_{end} = concentration at the end of the infusion (usually at 0.5 h) – theoretical maximum concentration
C_{24} = predicted concentration at 24 h – theoretical minimum concentration
AUC(0,24) = AUC over the entire 24 h dose interval
AUC(end,24) = AUC from the end of the infusion to 24 h
$\text{AUC}_{\text{infusion}}$ = AUC during the infusion phase – approximates to 6.5% of the AUC(0,24)

Appendix 2 – Once daily dosing using the AUC method

1 The patient's dose and calculated creatinine clearance (CL_{Cr}) should be based on the lean body weight, or total body weight if lower.

lean body weight (males) = 50 kg + 0.9 kg for each cm above 150 cm in height

lean body weight (females) = 45 kg + 0.9 kg for each cm above 150 cm in height

2 Calculate CL_{Cr}

$$CL_{Cr} = \frac{(140 - \text{age}) * \text{wt}}{50{,}000 * [\text{Cr}]}\ (\text{ml s}^{-1})$$

$\times$ 0.85 if female

3 Choose starting dose (mg kg^{-1}) (Table 1)

Table 1

CL_{Cr} (ml s^{-1})	*Starting dose (mg kg^{-1})*	*Target AUC*	*Time of second sample*
> 1.1	5, 6, 7	72, 86, 101	6–14 h
0.9–1.1	5, 6	86, 101	8–16 h
0.7–0.9	5	101	10–18 h
0.5–0.7	4	101	12–20 h
0.35–0.5	3	101	14–22 h
< 0.35	seek specialist advice		

4 Administer the dose as an infusion over 30 min, recording the exact times of starting and finishing the infusion.

5 Take a blood sample approximately half an hour after the end of the infusion recording the exact time of sampling.

6 Take a second blood sample within the time interval indicated in Table 1.

7 Calculate the patient's aminoglycoside AUC (see Appendix 1).

8 Compare the patient's AUC with the target AUC for that dose (see Table 1).

9 Calculate the second dose:

$$\text{Dose 2} = \frac{\text{AUC}_{\text{target}}}{\text{AUC}_{\text{observed}}} \times \text{Dose 1}$$

10 Administer the second dose as an infusion over 30 min, 24 h after the first dose.

11 Monitor as above every 48 h or according to the patient's clinical condition.

