Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations

E. J. BEGG, H. C. ATKINSON, G. M. JEFFERY & N. W. TAYLOR

Department of Clinical Pharmacology, Christchurch Hospital, Christchurch, New Zealand

1 A prospective randomised trial was conducted to compare aminoglycoside dose prediction based on individually measured pharmacokinetic data, with dosage based on physician intuition.

2 After 2 days of therapy more patients in the pharmacokinetic group had achieved both peak ($6\text{--}10\text{ mg l}^{-1}$) and trough ($1\text{--}2\text{ mg l}^{-1}$) target plasma concentrations ($P = 0.007$), peaks alone ($P = 0.01$) and troughs alone ($P = 0.01$). Their mean (s.e. mean) peak concentration was $6.49 \pm 0.39\text{ mg l}^{-1}$ compared with $4.27 \pm 0.52\text{ mg l}^{-1}$ in the control group ($P = 0.001$), with trough concentrations of $1.44 \pm 0.22\text{ mg l}^{-1}$ and $0.94 \pm 0.21\text{ mg l}^{-1}$ respectively ($P = 0.054$).

3 After 5 days of therapy, peak and trough concentrations were still significantly higher in the pharmacokinetic group despite empirical dose adjustment ($P = 0.01$ and $P = 0.013$ respectively).

4 The mean (s.e. mean) daily dose of aminoglycoside was higher in the computer group ($312 \pm 17\text{ mg}$ vs $203 \pm 13\text{ mg}$, $P = 0.001$).

5 These findings suggest that dose estimation based on measured pharmacokinetic parameters is superior at achieving target plasma drug concentrations.

Keywords aminoglycoside gentamicin tobramycin individualised dosing pharmacokinetic

Introduction

The aminoglycoside antibiotics have a low therapeutic index and choice of dose regimen is critical. The aim is to achieve plasma concentrations of aminoglycoside which optimise efficacy but minimise toxicity. Adequate plasma concentrations early in the course of therapy appear to be particularly important. Moore *et al.* (1984a) showed that in 84 patients with gram-negative bacteraemia, there was only one death out of 41 patients (2.4%) who had peak plasma gentamicin or tobramycin concentrations of $> 5\text{ mg l}^{-1}$ or amikacin concentrations $> 20\text{ mg l}^{-1}$, measured at 24–48, compared with nine deaths out of 43 (20.9%) patients with lower peak concentrations ($P < 0.01$). A favourable outcome was also demonstrated in patients with gram-negative pneumonia who achieved maximum peak

concentrations of gentamicin or tobramycin of $> 7\text{ mg l}^{-1}$ or mean peak concentrations of $> 6\text{ mg l}^{-1}$ (Moore *et al.*, 1984b). Other studies support these findings and suggest that peak concentrations should not be $< 5\text{ mg l}^{-1}$, and preferably much higher (Noone *et al.*, 1974, Moore *et al.*, 1987).

The pharmacokinetics of the aminoglycosides are extremely variable, particularly in critically ill patients. Consequently doses are difficult to predict accurately, even in patients with normal creatinine clearance (Zaske *et al.*, 1980, 1982; Summer *et al.*, 1983). The common practice of basing maintenance doses on measured or estimated creatinine clearance may not be accurate enough. Some workers have therefore focused on dose prediction based on estimations of the

patient's own aminoglycoside clearance (CL) and volume of distribution (V). One such approach is the one-compartment pharmacokinetic model of Sawchuk *et al.* (1977). This utilises three post-distributional plasma concentrations after the initial dose to construct a regression line from which the CL and V can be calculated, and a dose regimen tailored to achieve any desired peak and trough concentrations. The accuracy of such an approach has already been supported (Burton *et al.*, 1985).

The aim of this prospective, randomised study was to compare the accuracy of dose prediction based on the one-compartment model with that of 'routine clinical practice', in a general hospital setting. Routine practice of attending physicians (i.e. physician intuition) was used because it was impossible to get agreement as to which was the preferred method of dose estimation which could be used in the control group. The specific end-points were achievement of peak plasma concentrations of 6–10 mg l⁻¹ and trough concentrations of 1–2 mg l⁻¹ measured at 2 and 5 days after the start of the aminoglycoside course.

Methods

Any hospital in-patient who was to receive either gentamicin or tobramycin was eligible for the study. Patients in the intensive care unit were excluded, since they formed the basis of a similar study with a different control group being conducted concurrently.

Each patient received a loading dose of 3 mg kg⁻¹ of gentamicin or tobramycin infused over 30 min. The patients were then randomised into either the individualised dosing group (the study group) or the control group, using a computer generated randomisation procedure.

Study group dose prediction

Three blood samples were drawn from the patient at intervals following the loading dose of aminoglycoside. In patients with an estimated creatinine clearance (CL_{cr}) using the Cockcroft and Gault formula (Cockcroft & Gault, 1976)

$$(\text{CL}_{\text{cr}}(\text{ml s}^{-1}) = \frac{[(140 - \text{age}) \times \text{weight}]/(48869 \times \text{serum creatinine})}{(\times 0.85 \text{ in females})})$$

of > 1.5 ml s⁻¹ samples were drawn at 1, 2, and 4 h following the start of the drug infusion. In those with estimated CL_{cr} between 0.5 and 1.5 ml s⁻¹ the sampling times were 1, 4, and 8 h, and in those with estimated CL_{cr} < 0.5 ml s⁻¹, 1, 5, and 12 h. The intervals were chosen to allow an

accurate estimation of the slope of the log-linear concentration-time curve. The exact times of each sample were recorded, and the samples were refrigerated and sent as a batch to the laboratory for analysis of aminoglycoside concentrations.

The dose and dose interval were calculated by computer using the method of Sawchuk *et al.* (1977) with a slight modification which involved reducing the slope of the plot of log plasma concentration against time by a factor of 0.75. This allows for the fact that some accumulation of drug results when doses are based on a one-compartment model owing to the presence of a 'deep compartment'. We have found empirically that the modified approach avoids excessive trough concentrations, and this is supported by others (Evans *et al.*, 1980). The programme was designed to give a predicted dose and dose interval to achieve a true peak concentration (i.e. at end of the infusion) of 8 mg l⁻¹ and a trough concentration of 1.5 mg l⁻¹. If the plasma concentration results were not available before the next dose was due (8 h after the loading dose in patients with normal estimated creatinine clearance or longer in proportion to impaired renal function) the next dose was estimated using a locally produced nomogram and given at the relevant time. Subsequent doses were given according to the computer dose predictions.

Control group dose prediction

The dose and dose interval were chosen by the attending medical team, with the aim of achieving peak plasma concentrations of between 6 and 10 mg l⁻¹ and trough concentrations of between 1 and 2 mg l⁻¹. The method of dose estimation was entirely up to the physicians concerned, although local policy supported the use of the Cockcroft and Gault formula (Cockcroft & Gault, 1976) to provide a yardstick for adjusting the dose interval in the presence of renal dysfunction.

Subsequent management

Peak (1 h after the start of the infusion) and trough (within 30 min of the next dose) concentrations were measured in both groups 2 and 5 days after starting the aminoglycoside course, and more often if clinically indicated. Doses were adjusted empirically in both groups.

Plasma aminoglycoside concentrations were measured using a fluorescence polarisation immunoassay (Abbott TDX®). The limit of detection was 0.1 mg l⁻¹, and the inter-assay coefficient of variation was 4.1% at 2.2 mg l⁻¹ and 2.6% at 6.1 mg l⁻¹.

End-points for data analysis

The number of patients meeting both peak and trough concentration criteria were compared, as were the numbers reaching peak and trough concentrations alone. The mean concentrations achieved in each group at 2 and 5 days were compared. In addition the following features of each group were compared: the mean daily dose the number of dose alterations, the change in creatinine clearance during the course of therapy, and the number of deaths. The pharmacokinetic values of the patients in the study group were also noted.

Statistics

The χ^2 test was used in all tests except for comparison of mean values for which Student's *t*-test was used.

Results

Fifty patients entered the study, 24 randomised to the study group and 26 to the control group. Of these, 22 in the study group and 23 in the control group had data which could be analysed. The remainder were withdrawn from the study because the aminoglycosides were discontinued prior to sampling of blood at 48 h. Not all of the patients had a complete set of data, because of altered management during the time course of the study, such as discontinuation of aminoglycosides between days 2 and 5, or because some samples were not taken, or were misplaced. The results in the tables indicate the numbers on which comparisons were based.

There were no major differences between the groups in their demographic features (Table 1).

In the study group eight patients had pyelonephritis/urinary tract infection, four patients had septicaemia, three had chest infections and seven had other infections. In the control group four had pyelonephritis/urinary tract infection, seven had septicaemia, eight had chest infections and four had other infections. Major pathogens in the study group included *E. coli* in six patients, *pseudomonas* in four and *staphylococci* in two, and in the control group, *E. coli* in two patients, *pseudomonas* in four and *staphylococci* in five. Isolated cases of other pathogens made up the remainder in each group.

After 2 days, peak plasma concentrations were $6.49 \pm 0.39 \text{ mg l}^{-1}$ (mean $\pm$ s.e. mean) in the study group compared with $4.27 \pm 0.52 \text{ mg l}^{-1}$ in the control group ($P = 0.001$). Trough concentrations were $1.44 \pm 0.22 \text{ mg l}^{-1}$ in the study group compared with $0.94 \pm 0.21 \text{ mg l}^{-1}$ in the control group ($P = 0.054$). Six patients in the study group and none in the control group satisfied both peak ($6\text{--}10 \text{ mg l}^{-1}$) and trough ($1\text{--}2 \text{ mg l}^{-1}$) concentration criteria ($P = 0.007$). Nine patients in the study group and only two in the control group satisfied the peak concentration criterion alone ($P = 0.01$), with exactly the same number (but some different patients) in each group satisfying the trough criterion ($P = 0.013$).

After 5 days, peak concentrations were $7.23 \pm 0.79 \text{ mg l}^{-1}$ (mean $\pm$ s.e. mean) in the study group compared with $5.03 \pm 0.46 \text{ mg l}^{-1}$ in the control group ($P = 0.01$). Trough concentrations were $1.76 \pm 0.28 \text{ mg l}^{-1}$ compared with $1.07 \pm 0.15 \text{ mg l}^{-1}$ ($P = 0.013$). There were no significant differences in the number of patients satisfying both peak and trough criteria, or each criterion alone.

The exact numbers attaining different concentration categories are shown in Table 2. The χ^2

Table 1 Comparability of groups

	Study group	Control group
Number entering study	24	26
Number with analysable data ¹	22	23
Age (mean $\pm$ s.d.)	60.3 ± 19.7	63.0 ± 15.8
Age range	22–84	22–96
Number on gentamicin	9	9
Number on tobramycin	13	14
Number with +ve cultures	17	19
Number on steroid drugs	3	9
Pretreatment GFR (ml min^{-1}) (mean $\pm$ s.d.)	73.5 ± 49.9	62.9 ± 29.8

¹For the remaining patients aminoglycoside therapy was discontinued before analysis of plasma concentrations.

Table 2 Number of patients with aminoglycoside concentrations in different concentration ranges

Concentrations	At 2 days		At 5 days	
	Study group	Control group	Study group	Control group
1) Peak concentrations (mg l ⁻¹)				
> 10	0	0	1	0
6-10	9	2	5	4
4-6	7	7	4	8
< 4	0	8	0	6
	16	17	10	16
2) Trough concentrations (mg l ⁻¹)				
2-4	2	3	4	2
1-2	9	2	4	2
0.5-1	5	6	2	6
< 0.5	0	5	0	2
	16	16	10	16

test was performed only on the number of patients who did or did not satisfy the target peak and trough concentration criteria.

The mean ($\pm$ s.e. mean) aminoglycoside dose per day was 312 ± 17 mg in the study group compared with 203 ± 13 mg in the control group ($P = 0.001$).

Although there was a trend towards fewer dose alterations in the study group, this did not quite reach significance ($P = 0.15$). Fourteen patients in the study group and nine in the control group had no dose alteration, while none in the study group and four in the control group had more than three alterations. The number of deaths in each group also did not reach significance although only one died in the study group compared with five in the control group ($P = 0.2$). There was no difference between the groups in terms of altered renal function from just prior to the start of treatment until the end of therapy ($P = 0.32$). Nine patients in the computer group and seven in the control group had no change in creatinine clearance, while nine in the computer group and six in the control group had a small but reversible decrease in creatinine clearance. The remainder in both groups had a small increase in creatinine clearance.

The pharmacokinetic parameters for the study group were a V of 15.43 ± 4.83 l (mean $\pm$ s.d.), a CL of 4.1 ± 2.06 l h⁻¹, and a $t_{1/2}$ of 3.33 ± 2.43 h.

Discussion

The results of this study indicate that aminoglycoside dose determination based on a measurement of the patient's own aminoglycoside clearance and volume of distribution allows target

plasma concentrations to be achieved more rapidly and reliably than dose estimation by physicians using other methods. Recent studies suggest that this may be associated with increased survival (Moore *et al.*, 1984a, 1984b, 1987; Noone *et al.*, 1974) and such a trend was suggested but not proven in this study. A minimum peak plasma concentration of 5 mg l⁻¹ seems to be important for favourable outcome (Moore *et al.*, 1984a, 1984b; Noone *et al.*, 1974) and the higher the peak above the minimum inhibitory concentration of the bacteria, the better (Moore *et al.*, 1987). It was therefore quite alarming that the mean peak concentration in the control group at 2 days was only 4.27 mg l⁻¹, with 95% confidence limits of ± 1.1 mg l⁻¹. Even after unconstrained empirical dose adjustment the mean peak concentration only rose to 5.03 mg l⁻¹ with confidence limits of ± 0.97 mg l⁻¹.

The mean dose per day in the study group for the entire period of treatment was over 50% higher than in the control group. This difference was closer to 100% if the mean initial maintenance dose suggested for the study group was compared with mean initial maintenance dose of the control group. This suggests that either physicians are choosing lower doses than necessary for fear of toxicity or that standard doses or nomogram doses are too low. The mortality associated with underdosing highlights the need to use a more accurate method of dose prediction such as that suggested in this study. Despite much higher doses in the computer group, there was little difference in the number of concentrations (peak or trough) which were above the 'therapeutic range' for gentamicin or tobramycin compared with the control group (10.7% vs 9.6%, see Table 2). Therefore an increase in toxicity

would not be expected. The incidence of deterioration in creatinine clearance was not significantly different between the two groups, though with the numbers involved this is not surprising. In no patient was there any permanent effect on renal function. The literature suggests that individualised dosing is associated with a lower incidence of nephrotoxicity compared with standard doses or physician intuition (Burton *et al.*, 1985). Therefore greater efficacy and lower toxicity are the likely consequences of dosing using measured pharmacokinetic values.

The fact that the mean peak concentration at 2 days (6.49 mg l^{-1}) was lower than the target concentration of 8 mg l^{-1} is not surprising since our target concentration was the theoretical true peak concentration at the end of the aminoglycoside infusion. The predicted 1 h concentration would be lower by a factor of $8e^{-kt}$, where k is the elimination rate constant, and t is time, in this case 0.5 h. For example, with the mean aminoglycoside half-life of 3.33 h in this study, a 1 h peak concentration of 6.84 mg l^{-1} would be

expected. This is very close to the actual mean value of 6.49 mg l^{-1} measured in this study. In addition the correction factor to allow for accumulation into a deep compartment would tend to decrease the actual peak compared with the predicted peak concentration during the early days of therapy.

An important question regarding the individualised method is its practicality. The availability of assays such as the fluorescence polarisation assay which enable plasma concentrations to be determined rapidly, and microcomputers which enable quick and accurate calculation, has meant that the technique is simple to use and practical for routine hospital use.

In summary, we have demonstrated that an individualised pharmacokinetic dosing technique based on the Sawchuk one-compartment model enables therapeutic concentrations of aminoglycosides to be achieved more accurately and more quickly than dosing based on physician intuition. Other studies suggest that this technique might improve both efficacy and toxicity.

References

- Burton, M. E., Vasko, M. R. & Brater, D. C. (1985). Comparison of dosing methods. *Clin. Pharmacokin.*, **10**, 1–37.
- Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatine clearance from serum creatinine. *Nephron*, **16**, 31.
- Evans, W. E., Taylor, R. H. & Feldman, S. (1980). A model for dosing gentamicin in children and adolescents that adjusts for tissue accumulation with continuous dosing. *Clin. Pharmacokin.*, **5**, 295–306.
- Moore, R. D., Smith, C. R. & Lietman, P. S. (1984a). The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *J. infect. Dis.*, **149**, 443–448.
- Moore, R. D., Smith, C. R. & Lietman, P. S. (1984b). Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am. J. Med.*, **77**, 657–662.
- Moore, R. D., Lietman, P. S. & Smith, C. R. (1987). Clinical response to aminoglycoside therapy: Importance of ratio of peak concentration to minimal inhibitory concentration. *J. infect. Dis.*, **155**, 93–99.
- Noone, P., Parsons, T. M. C., Pattison, J. R., Slack, R. C. B., Garfield-Davies, D. & Hughes, K. (1974). Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *Br. med. J.*, **1**, 477–481.
- Sawchuk, R. J., Zaske, D. E., Cipolle, R. J., Wargin, W. A. & Strate, R. G. (1977). Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin. Pharmac. Ther.*, **21**, 362–365.
- Summer, W. R., Michael, J. R. & Lipsky, J. J. (1983). Initial aminoglycoside levels in the critically ill. *Crit. Care Med.*, **11**, 948–950.
- Zaske, D. E., Cipolle, R. J. & Strate, R. G. (1980). Gentamicin dosage requirements: Wide interpatient variations in 242 surgery patients with normal renal function. *Surgery*, **87**, 164–169.
- Zaske, D. E., Cipolle, R. J., Rotschafer, J. C., Solem, L. D., Mosier, N. R. & Strate, R. G. (1982). Gentamicin pharmacokinetics in 1640 patients: Method for control of serum concentrations. *Antimicrobial Agents and Chemotherapy*, **21**, 407–411.

(Received 15 August 1988,
accepted 3 April 1989)