Population pharmacokinetics of tobramycin

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1 Population pharmacokinetic parameters of tobramycin were determined in a heterogeneous group of 97 patients using serum samples drawn for the routine monitoring of tobramycin concentrations, following multiple dosing regimens.

2 To describe the accumulation kinetics of tobramycin a two-compartment pharmacokinetic model was required. The best fit to the data was obtained when drug clearance ($l\ h^{-1}$) was related linearly to creatinine clearance (proportionality constant: $0.059 \pm 0.002 \times CL_{cr}$ ($ml\ min^{-1}$)) and initial volume of distribution (l) was related linearly to body weight (proportionality constant: $0.327 \pm 0.014 \times$ body weight (kg)). The intersubject variability in these two parameters was 32% and 3%, respectively, whilst the residual or intrasubject variability amounted to 21% of the tobramycin concentration. The terminal half-life of tobramycin, $26.6 \pm 9.4\ h$, was appreciably shorter than previously reported.

3 The population pharmacokinetic model was validated against data obtained from 34 independent patients and the predicted and observed concentrations were found to be in good agreement. The population pharmacokinetic model was used to design *a priori* dosing recommendations for tobramycin.

Keywords tobramycin population pharmacokinetics therapeutic drug monitoring

Introduction

Aminoglycosides represent an important class of antimicrobial agents used primarily in patients with severe infections due to gram-negative bacteria. They are usually administered as intermittent bolus doses (or short infusions) and it appears that the achievement of a sufficiently high serum concentration within each dosage interval plays an important role with respect to their efficacy (Powell *et al.*, 1983; Moore *et al.*, 1984a,b; Gerber *et al.*, 1986). On the other hand the available data indicate that a continuous exposure to relatively high serum concentrations (reflected by high trough or average drug levels in each dosing interval) over a prolonged period of time increases the risk of the two severe side-effects, nephrotoxicity and ototoxicity (Mawer *et al.*, 1974; Smith *et al.*, 1986). Thus, for the

effective and safe use of aminoglycoside antibiotics it is important to achieve sufficiently high maximum serum concentrations and at the same time avoid prolonged continuous exposure to high drug serum levels.

Pharmacokinetic principles can be applied to achieve this goal. Population pharmacokinetic parameters, i.e. parameters that describe the average dose-concentration relationship and its between-patient variability in the patient population actually treated with the drug, represent, for two reasons, important information with respect to the effective use of pharmacokinetic principles for dosage optimization of tobramycin. Because of its narrow therapeutic index and the availability of a rapid assay, tobramycin is frequently monitored, particularly in patients with

Table 1 Patient demographic data

		Main study	Prospective study
Number of patients		97	34
Weight (kg)	mean	66.5	66.8
	median	66.8	66.5
	s.d.	12.5	10.9
	range	42–120	45–87
Age (years)	mean	50.6	57.8
	median	51.0	62.0
	s.d.	19.0	20.6
	range	16–85	17–85
Sex	male/female	52/45	22/12
Creatinine clearance (ml min ⁻¹)	mean	67.9	73.3
	median	65.0	63.3
	s.d.	33.0	34.4
	range	10–166	15–166

reduced renal function. Dosing guidelines are based on the pharmacokinetic parameters of the individual patient. However, frequently only one or two serum drug concentrations are available and consequently it is not possible to estimate an individual's pharmacokinetic parameters. In this situation Bayesian techniques, in which population pharmacokinetic parameters are sequentially updated by available serum measurements, have proven successful (Burton *et al.*, 1985). Apart from their use in Bayesian feedback, knowledge of population pharmacokinetics is useful in describing the average dose-concentration relationship and its intra- and interindividual variability. This information can be used to design an optimum *a priori* dosing regimen that should result in 'therapeutic' concentrations in the majority of patients and to evaluate the need for therapeutic drug monitoring.

It was the purpose of the present study to analyse routinely obtained serum tobramycin concentrations in a large number of patients with a view to estimating the population pharmacokinetic parameters of tobramycin and to determine an *a priori* dosing regimen in patients with various degrees of renal function impairment.

Methods

Patients

Data from 97 patients (45 female, 52 male) were included in the analysis (see Table 1). Blood

samples were taken in most cases for the routine monitoring of tobramycin concentrations. The dosing history and time of blood sampling were carefully recorded. The duration of therapy in individual patients ranged from 14 to 520 h. Three hundred and twenty-two tobramycin concentrations were available for the data analysis with between 1 and 9 per individual. The concentration data are shown in Figure 1. As can be seen there was a large number of patients with dosing over 10 days, allowing estimates of the accumulation characteristics. Drug concentrations were measured usually 2 and 6 h after the dose in patients with normal renal function, with additional measurements (12 and 24 h after the dose) in patients with impaired renal function. In eight patients the serum drug concentration was monitored up to 3 days after cessation of therapy (3–5 samples). The patients had an average age of 51 ± 19 years (range 16–85) and an average weight of 66 ± 12 kg (range 42–120). Creatinine clearance (estimated from serum creatinine) ranged from 10 to 160 ml min⁻¹ (average 67 ± 33). The formula used for the estimation of creatinine clearance (CL_{Cr}) was that proposed by Cockcroft & Gault (1976):

$$CL_{Cr} = \frac{(150 - \text{age}) \cdot \text{Body weight}}{C_{Cr}}$$

where C_{Cr} is the serum concentration of creatinine in $\mu\text{mol l}^{-1}$. Only patients with stable renal function were included in the study. For males 10% is added to and for females 10% is subtracted from the calculated value of CL_{Cr}.

Figure 1 Tobramycin concentration-time data from 97 patients used in the analysis.

Assay

For routine tobramycin monitoring, the serum drug concentrations were measured using an homogeneous enzyme immunoassay (EMIT®, Syva Corp., Palo Alto, CA). The within-assay and between-assay coefficients of variation for this method were 7.4% (at a concentration of 4 mg l⁻¹) and 3.6% (at a concentration of 6 mg l⁻¹), respectively (Francke *et al.*, 1981). In eight patients tobramycin serum concentrations were followed for up to 72 h after cessation of therapy. These serum samples were measured with a modified radioimmunoassay (Coat-A-Count®, Diagnostic Products Corp., Los Angeles, CA). In the modified method a 1:51 predilution of the serum samples rather than the 1:401 dilution as described in the manufacturer's instructions was used. The coefficient of variation of the RIA was 7.3% (at a concentration of 1 mg l⁻¹).

Data analysis

The analysis was performed with the NONMEM computer programme developed by Beal &

Sheiner (1979). The individual pharmacokinetic parameters are assumed to arise from a distribution (either normal or log normal) characterized by a population mean and interindividual variance. For example the clearance (CL) of the *j*th subject can be described by the following relationship

$$CL_j = \overline{CL} + \eta_{CLj} \quad (1)$$

where $\overline{CL}$ is the population mean and η_{CLj} is the difference between the population mean and the *j*th subject. η_{CL} is assumed to be a Gaussian random variable with mean zero and variance σ_{η}^2 . The concentration-time profile in the *j*th individual can be described by equation (2)

$$C_{ij}(t) = f(p_j, D_{ij}, t_{ij}) + \varepsilon_{ij} \quad (2)$$

where p_j are the pharmacokinetic parameters (such as clearance, volume etc) of the *j*th individual, t_{ij} is the time of the *i*th measurement, D_j is the dosing history of that individual and f is the pharmacokinetic model, for example a sum of exponentials. ε_{ij} represents the residual departure of the model from the observations

and contains contributions from intraindividual variability, assay error and model misspecification. As for the η s, ε is assumed to be a random Gaussian variable with a mean of zero and a variance σ_ε^2 .

Preliminary analysis revealed that the data were best fitted by a two-compartment model and that the probability distribution of the error terms η and ε was better described by log normal rather than normal distributions. Thus equations (1) and (2) are replaced by equations (3) and (4).

$$CL_j = \overline{CL} \cdot \exp(\eta_{CLj}) \quad (3)$$

$$C_{ij}(t) = f(p_j, D_{ij}, t_{ij}) \cdot \exp(\varepsilon_{ij}) \quad (4)$$

A recursive subroutine was written to describe serum concentrations during multiple dosing and the resulting equation was fitted to the 322 tobramycin concentrations using the NONMEM programme permitting the estimation of the population average of the pharmacokinetic parameters, intersubject variabilities in these parameters (variances of the η s) and the residual variance (σ_ε^2). In addition the programme NONMEM estimates the standard errors of these quantities and reports the value of the objective function, which can be used for hypothesis testing. Model comparison was made by testing the difference in log likelihood values against a chi-squared statistic ($P < 0.01$; Beal & Sheiner, 1979).

The four pharmacokinetic parameters used in the analysis were the clearance, initial volume of distribution (V_1) and the two transfer rate constants, k_{12} and k_{21} . In addition the dependence of these parameters on a number of covariates, such as creatinine clearance and body weight was tested.

Validation of the parameter estimates

To validate the pharmacokinetic model and the estimates of the population pharmacokinetic parameters another set of data which was not included in the original statistical analysis was evaluated. Data from 34 patients were used. The duration of therapy ranged from 1 to 21 days, with greater than 6 days therapy in 10 patients. Body weight ranged from 45 to 87 kg and the estimated creatinine clearance from 18 to 166 ml min⁻¹. The demographic data for this group of patients are compared to the original group in Table 1. Serum drug concentrations 2 and 6 h after the final dose were available for each patient. Based on the patient's creatinine clearance, body weight and dosing history a prediction of the tobramycin concentration was

made using the model and parameters described above. For each concentration a standardized prediction error (SPE – equation (5)) was calculated

$$SPE_{ij} = \frac{C_{ij} - f(p_j, D_{ij}, t_{ij})}{sd(C_{ij})} \quad (5)$$

where j refers to the patient, i to the time of the blood sample and sd is the predicted standard deviation defined in equation (6)

$$sd(C_{ij}) = \sqrt{\left[\frac{\partial f}{\partial \eta_{CL}} \right]^2 \sigma_{\eta_{CL}}^2 + \left[\frac{\partial f}{\partial \eta_V} \right]^2 \sigma_{\eta_V}^2 + f^2 \sigma_\varepsilon^2} \quad (6)$$

Under the assumption of a correct regression model and unbiased parameter estimates the SPE should have a mean value of zero and a variance of unity. A t -test was used to test whether the SPE was significantly different to zero and a bootstrap method (Efron & Gong, 1983) was used to calculate 95% confidence intervals for the variance of the SPE.

Results

As stated in the methods section a two-compartment model was clearly superior to a one-compartment model ($P < 0.001$) and correcting clearance for creatinine clearance (CL_{Cr}) viz.

$$CL = \Theta_1 \cdot CL_{Cr} \quad (7)$$

where Θ_1 is the parameter that is estimated, also resulted in a highly significant difference in the objective function ($P < 0.001$), and improvement of the goodness of fit as judged by the residual plots, interindividual variability in CL and the residual variability. The influence of body weight on V_1 was also significant ($P < 0.001$). Making V_1 dependent on either body weight raised to a power or lean body mass did not give any improvement over simple proportionality to body weight. There was a tendency for the proportionality constant between V_1 and body weight to depend on age in that it was larger for patients below the age of 21 years. However, since there were only five patients belonging to the young group the inclusion of age led to poorly determined parameter estimates. Therefore, it was eventually dropped from the analysis. Sex and age did not contribute significantly to any of the other pharmacokinetic parameters. The interindividual variability in

Table 2 Population pharmacokinetic parameters of tobramycin^{a,b}

Parameter	Population mean		Interindividual variability	
	Estimate	s.e.	Estimate	s.e.
CL ^c	0.059	0.002	32%	44%
k_{12} (h ⁻¹)	0.012	0.003	—	—
k_{21} (h ⁻¹)	0.027	0.021	—	—
V_1 (l kg ⁻¹)	0.327	0.014	3%	112%
σ_e ^d	21%	38%		

^a Estimates of variability expressed as coefficient of variation^b s.e. of variance components (var(CL), var(V), σ_e^2) taken as $\sqrt{\text{s.e. (estimate)}/\text{estimate}}$ expressed as a percentage^c Proportionality constant relating creatinine clearance (ml min⁻¹) to drug clearance (l h⁻¹)^d Residual intraindividual coefficient of variability of the serum concentration**Table 3** Mean and standard deviation of the standardized prediction error in 34 patients receiving tobramycin^a

	2 h		6 h	
	Mean (95% c.i.) ^b	s.d. (95% c.i.)	Mean (95% c.i.)	s.d. (95% c.i.)
Group I (n = 24)	0.16 (-0.22, 0.54)	0.88 (0.64, 1.08)	0.20 (-0.36, 0.76)	1.29 (0.76, 1.80)
Group II (n = 10)	0.53 (-0.17, 1.22)	0.91 (0.53, 1.22)	0.26 (-0.43, 0.94)	1.46 (0.58, 2.30)
Group I + II (n = 34)	0.27 (-0.06, 0.59)	0.91 (0.71, 1.08)	0.22 (-0.27, 0.71)	1.36 (0.86, 1.80)

^a Group I consists of those patients whose duration of therapy was less than 6 days; Group II duration of therapy greater than 6 days. *n* is the number of patients in each group.^b c.i. – confidence interval.

CL (after correction for creatinine clearance) was 32% (expressed as the coefficient of variation of the population average). The interindividual variability in V_1 was very small (with a large standard error) after correction for body weight. Including interindividual variability in k_{12} and k_{21} did not improve the fit and therefore these variances were removed from the final analysis. A summary of the results is shown in Table 2.

The two exponents had half-lives of 2.55 (s.e. – 0.12) and 26.6 h (s.e. – 9.4) (for an individual with a creatinine clearance of 100 ml min⁻¹) and the volume of distribution at steady state (for a 70 kg individual) was 32.9 L (s.e. – 1.0).

In the evaluation of the parameter estimates in the other group of 34 patients 2 h samples were analyzed separately from 6 h samples and patients were divided into two groups—those

with duration of therapy less than 6 days and those with durations greater than 6 days—to see whether the goodness of prediction was influenced by the time of blood sampling or duration of therapy. The results of this analysis are shown in Table 3. In all cases the SPE was unbiased (i.e. not significantly different from zero) and the variance of the SPE was not significantly different from unity.

Discussion

In most clinical settings the pharmacokinetics of tobramycin are described by a one-compartment model. Although such a model adequately predicts the serum concentration-time profile of the drug in most patients with normal renal function (disregarding a very short distribution phase) it does not account for accumulation of the drug in

tissues (which is believed to contribute to its toxicity) and fails to describe adequately the serum concentration-time profile in some patients on multiple dosing, in particular in the presence of renal function impairment (Vozech *et al.*, 1979; Evans *et al.*, 1980). Schentag *et al.* (1978) estimated the pharmacokinetic parameters of tobramycin associated with accumulation by fitting a two-compartment model to washout data obtained from patients after terminating a multiple dosage regimen. The parameters obtained by these authors were quite different from the present results in that the estimate of the terminal half-life was very much longer. The main difference between our study and the work of Schentag *et al.* (1978) is that in the present study the terminal half-life was determined predominantly by the accumulation in tobramycin concentrations after multiple dosing and not from washout data. In fact, the present report is, to our knowledge, the only study in which the accumulation half-life of an aminoglycoside antibiotic was determined directly from drug accumulation during multiple dosing. There are two main possibilities why the estimates of the terminal half-life determined under the two different experimental designs may show large differences. The degree of accumulation of tobramycin based on serum concentrations is, except in patients with severe renal failure, relatively small and consequently accurate estimation of the terminal half-life from these data may be difficult. On the other hand, in washout studies the serum drug concentrations are very low after the first 24 h ($< 0.05 \text{ mg l}^{-1}$) and it is conceivable that renal handling of the aminoglycoside antibiotics may be different at these extremely low serum concentrations compared with the concentrations achieved during a course of treatment. A saturable tubular reabsorption that is effective only at very low serum concentrations could, for example, result in a long lasting persistence of the serum concentrations in washout studies with a substantially shorter accumulation half-life determined under multiple dosing. There are indications in the literature that for some aminoglycosides nonlinear elimination processes are, in fact, present in the washout studies. A large discrepancy is observed between the estimates of the terminal half-life determined in the same subject from urinary data and the serum drug concentration-time course. Laskin *et al.* (1983) found in healthy subjects, in whom the elimination of gentamicin and netilmicin was followed over 1 week after multiple dosing, terminal half-lives of 94 and 155 h, respectively, based on the serum concentration measurements

compared with values of 58 and 46 h determined from the urinary excretion data. These authors suggest that nonlinear elimination processes become limiting at concentrations below 0.05 mg l^{-1} . Similar discrepancies can be noted in studies in patients performed by Kahlmeter *et al.* with gentamicin (1978a) and tobramycin (1978b). These findings contradict the notion that the extremely long half-life found in the washout studies is only due to slow release of the drug from tissues. Obviously, further work is needed to clarify these problems.

Several authors have tried to correlate volume of distribution to some function of body weight, such as lean body mass. Studies in morbidly obese patients show that there is some distribution of tobramycin into adipose tissues (Schwartz *et al.*, 1978; Bauer *et al.*, 1983) and consequently it is not surprising that in our studies lean body mass or other functions of body weight offered no definitive advantage over straight body weight to explain volume of distribution. We should like to point out, however, that in our study population (which was an unselected population of patients treated with tobramycin) only few patients were morbidly obese. It has been reported that younger patients require a higher loading dose on a mg kg^{-1} basis than older patients (King *et al.*, 1985), a trend seen in our studies. The reason for this age effect is not clear but it may reflect the different distribution of tissue masses as a function of age. The estimate of the intersubject variability in the volume of distribution was smaller than expected. However, the earliest blood sample was not taken until 2 h after the dose to avoid serum drug concentration measurements during the early distribution phase. We suspect that this might be the reason that there was little information in the data concerning the variability in V_1 . Most of the intersubject variability is accounted for by CL. The problem of distinguishing, in our data, between the variability in clearance and volume of distribution might have been aggravated by the fact that NONMEM uses a regression model which is linearized with respect to the η s to determine the interindividual variances (Beal & Sheiner, 1979). Therefore we have little faith in the actual estimate of the intersubject variability in the volume of distribution and believe that it is meaningful only in the context of the whole population pharmacokinetic model.

Because of the theoretical problems discussed above and the fact that population pharmacokinetic analysis is usually performed in an exploratory way it is important that the final model and the parameter estimates obtained in such

Table 4 Dosing recommendations for tobramycin

Creatinine clearance (ml min ⁻¹)	First 48 h		Maintenance	
	Dose ^a (% of loading dose)	Dosing interval (h)	Dose (mg)	Dosing interval (h)
> 100	100	8	120	8
75	80	8	90	8
50	93	12	90	12
30	60	12	54	12
20	80	24	70	24
15	67	24	54	24
10	60	24	35	24

^a A loading dose of 2.1 mg kg⁻¹ is used in each case with a conservative upper limit of 150 mg

studies are validated on a separate data set collected in another group of patients. This validation, using data in 34 patients has revealed that the prediction of both the average concentration and its variability are unbiased. Therefore it can be concluded that the model and population pharmacokinetic parameters determined in this study can be used satisfactorily to predict average concentrations and variability in patients receiving tobramycin therapy.

Derivation of a priori dosing regimens

The estimates of the population pharmacokinetic parameters allowed us to design *a priori* dosage recommendations for tobramycin. This was done by exploring the average concentration profile and its variability (intra- and inter-individual) under different dosing schemes with the help of computer simulations. The objective was to maintain sufficiently high maximum concentrations in the beginning of treatment before the dose can be individually adjusted on the basis of drug concentration measurements. Using conventional pharmacokinetic principles this is readily achieved. However the population analysis allowed us to determine not only the average response but also the fraction of the population that would likely meet our objectives. According to literature data a peak level above 5–6 mg l⁻¹ is associated with higher clinical efficacy (Moore *et al.*, 1984a,b). It was therefore decided to aim to achieve peak drug concentrations above 6 mg l⁻¹ in the majority of patients but maintain average concentrations, within a dosing interval (as a measure of accumulation potential), below 4 mg l⁻¹. The dosing recommendations are given in Table 4. Note that different dosage is recommended for

initial treatment and after 48 h. Using a loading dose of 2.1 mg kg⁻¹ (with a conservative upper limit of 150 mg in order not to overdose severely overweight patients) it is predicted that 72% of patients will achieve an initial concentration greater than 6 mg l⁻¹. After loading, the dosing regimen depends on renal function. Two examples are illustrated in Figures 2 and 3 (70 kg body weight is assumed in both cases). In the case of the subject with creatinine clearance 100 ml min⁻¹ (Figure 2) it is recommended that 150 mg be given every 8 h for 48 h by which time 82% of patients will have maximum concentrations in excess of 6 mg l⁻¹. In the other case (Figure 3) with a patient with a creatinine clearance of 10 ml min⁻¹ a loading dose of 150 mg is again given but the dosing interval is increased to 24 h and, to obtain a similar pattern to that shown in Figure 2, 90 mg is given at 24 h. Thus, based on the Monte Carlo simulations, a somewhat higher dose is needed than generally recommended (Sarubbi & Hull, 1978) to achieve sufficiently high peak drug concentrations in most patients. We believe that this recommendation is relatively safe in view of the fact that the risk of toxicity depends on duration of treatment (Mawer *et al.*, 1974; Smith *et al.*, 1986) and is therefore expected to be low during the first days of therapy. After the first 48 h, however, the dose should be reduced using serum drug concentration measurements to individually adjust dosage. The dosing rate is reduced (see Table 3 last column) to 120 mg every 8 h in the case of normal renal function, and to 35 mg every 24 h in the patient with a CL_{Cr} of 10 ml min⁻¹, resulting in 95% of patients having average concentrations below 4 mg l⁻¹. The reason for dose reduction after 48 h is the increased risk of excessive drug accumulation and

Figure 2 Predicted (± 1 s.d. i.e. approximate 68% prediction interval) tobramycin concentration-time profile for patients with creatinine clearances of 100 ml min^{-1} .

Figure 3 Predicted (± 1 s.d. i.e. approximate 68% prediction interval) tobramycin concentration-time profile for patients with creatinine clearances of 10 ml min^{-1} .

toxicity with prolonged treatment producing high average and trough concentrations. As can be seen in Figures 2 and 3, although relatively safe ($< 5\%$ of patients are expected to have average concentrations above 4 mg l^{-1}), the dosing regimen will fail to achieve the desired maximum concentration of 6 mg l^{-1} in a large proportion of patients (43% in Figure 2 and 98% in Figure 3). These results clearly show that individual dose adjustment based on serum drug concentration measurements is needed for safe

and effective therapy and that the dosing of tobramycin is difficult in patients with severely impaired renal function. On the other hand since toxicity and drug accumulation takes time, a relatively high dose can be administered initially which will guarantee effective concentrations in most patients. The period of 48 h during which the high dose is administered was chosen on the basis of our experience that within this time individual measurements of the serum drug concentration will be usually available, allowing

appropriate dose adjustment. Although trough concentrations are commonly used to avoid excessive accumulation of aminoglycoside antibiotics we believe that the average concentration (area under the serum concentration-time curve divided by the length of the dosing interval) is more meaningful in this situation (Barza *et al.*, 1978; Follath *et al.*, 1981; Wenk *et al.*, 1984). The main advantage of the average concentration compared with trough concentrations is that it reflects the accumulation potential independent of the length of the dosing interval. This is an important consideration in view of the fact that to achieve effective maximum concentrations in patients with impaired renal function (without excessive overdosing) different lengths of dosing interval have to be used depending on the patient's renal function (Table 4). The choice of the upper limit of 4 mg l^{-1} is somewhat arbitrary,

because very little quantitative information is available in the literature about the relationship between tobramycin toxicity and drug accumulation in the body. In a patient with normal renal function the average concentration at steady-state under the recommended dosage (Table 4, Figure 2) is expected to be 2.6 mg l^{-1} . The upper limit of 4 mg l^{-1} represents, therefore, a value that is associated with a 50% increase in drug accumulation compared with an average patient receiving an effective dosing regimen. It is also close to the average concentration in a patient with a trough concentration of 2 mg l^{-1} (and a peak of 6 mg l^{-1}) receiving tobramycin every 8 h (3.7 mg l^{-1}).

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