Population pharmacokinetics of intramuscular gentamicin administered to young infants with suspected severe sepsis in Kenya

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Aims To determine the population pharmacokinetics of intramuscular (i.m.) gentamicin in African infants with suspected severe sepsis.

Methods Samples were withdrawn 1 h after a single i.m. injection of 8 mg kg⁻¹ gentamicin and the next morning prior to any further dosing. Concentration–time data were analysed with the population pharmacokinetic package NONMEM. Data were fitted using a one-compartment model with a log-normal model for interindividual variability and an additive residual error model. The influence of a range of clinical characteristics was tested on the pharmacokinetics of intramuscular gentamicin and the effect of incorporating interindividual variability on bioavailability was examined.

Results The data set comprised 107 patients and 203 concentrations. Peak concentrations ranged from 3.0 mg L⁻¹ to 19.8 mg L⁻¹ (median 10.6 mg L⁻¹) and 'next day' samples from 0.3 mg L⁻¹ to 6.2 mg L⁻¹. The best models were clearance/bioavailability (CL) (L h⁻¹) = 0.0913 × weight (kg) × (age (days) + 1)/11^{0.130} and volume of distribution/bioavailability (V) = 2.02 × (1 + 0.277 × (weight - 3)). Therefore, an infant with the median weight of 3 kg and age 10 days would have a predicted CL of 0.274 L h⁻¹ and V of 2.02 L. Interindividual variability in CL was 40% and in V was 42%. This model required a term for covariance between CL and V. When variability in bioavailability was introduced as an alternative model, interindividual variability in CL was 22%, in V 18% and in relative bioavailability 36%.

Conclusions Intramuscular administration of 8 mg kg⁻¹ gentamicin daily to infants gives mean 1 h peak concentration of 10.6 mg L⁻¹ and a trough concentration of less than 2 mg L⁻¹. Wide variability in the peak concentration may reflect variable absorption rate or bioavailability.

Keywords: gentamicin, infants, intramuscular injection, pharmacokinetics

Introduction

There has been increasing interest in the use of high-dose, extended interval administration of gentamicin in adult patients [1] and this approach has been applied to a limited extent in children with doses ranging from 4 to 10 mg kg⁻¹ day⁻¹ [2]. It has been shown that infants,

especially neonates, have a higher volume of distribution per kg body weight and a lower clearance compared with older children and adults. Consequently, dosage intervals of 24 h, or longer, are necessary to achieve 'conventional' target peak concentrations of 5–12 mg L⁻¹ and trough concentrations below 2 mg L⁻¹ [3]. However, most of the available data relate to neonates given intravenous therapy and there is limited information on the drug pharmacokinetics and dosage requirements of infants who are treated with intramuscular (i.m.) gentamicin. In a recent trial of a once daily gentamicin dosing regimen for a developing country setting, a first dose of 8 mg kg⁻¹ was

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Received 3 September 2002, accepted 19 December 2002.

given intramuscularly to infants aged less than 90 days with clinically suspected severe infection [4]. The aim of the present study was to apply a population approach to analyse the concentration-time data generated from this study.

Methods

Protocol and patients

The original clinical study was conducted on the paediatric ward of Kilifi District Hospital in Kenya. In brief, all children less than 3 months of age admitted to the ward until January 2001 and less than 2 months of age from February 2001 were screened for enrolment in the study using a computerized questionnaire. In January 2001, on the basis of local bacteriological surveillance data (J. Berkley, unpublished), the local management guidelines were changed limiting the use of gentamicin as an empirical treatment to infants less than 2 months of age. Children were excluded if their weight was less than 1 kg, there was a primary diagnosis of tetanus, gentamicin had been administered previously, there were major life-threatening congenital malformations, there was a history of anuria for 24 h, or the creatinine clearance on admission was outside a defined acceptable range. The parents of children who remained eligible were given information about the study in their local language by a trained project assistant and consent was sought for enrolment. Approval for the study was obtained from the national Kenyan Ethical Committee and it ran from August 2000 to April 2001.

A gentamicin dose of 8 mg kg^{-1} was administered by intramuscular injection and a 'peak' sample was withdrawn 1 h after this dose. A second sample was withdrawn the following morning before the next dose of gentamicin, which was due at 09.00 h. Samples for gentamicin analysis were spun and serum separated and stored at -20°C prior to analysis by Fluorescence Polarization Immunoassay with the Abbott TDx FLx (Abbott Diagnostics, Abbott Park, IL, USA). Intra-assay coefficients of variation over the range of low (1 mg L^{-1}), medium (4 mg L^{-1}) and high (8 mg L^{-1}) quality control standards were 3.6, 1.4 and 1.0%, respectively, whereas the corresponding interassay coefficients of variation were 4.8, 2.0 and 1.6%, respectively. The limit of quantification was 0.27 mg L^{-1} .

The following data were recorded for each patient: identification number (ID); weight (kg); actual dose administered, date and time; concentration measurements, dates and times; creatinine concentration on admission; sex; white blood cell count; transfusion details; haemoglobin concentration; and postnatal age (days).

Data analysis

Data were analysed using NONMEM version V 1.1 [5] and FORTRAN compilation was performed using Visual Fortran Version 6.0 (DIGITAL™, Digital Equipment Corporation, Maynard, Massachusetts, USA). Post processing of NONMEM output was undertaken with the package Xpose (Version 3.007) [6], programmed in the statistics package SPLUS 2000 (Insightful Corporation Seattle, USA).

Preliminary analyses focused on the structural and variance models. A one-compartment model with a monoexponential decline and first order absorption (i.m. model) was compared with a bolus model with a monoexponential decline and a biexponential decline (i.v. model). The effect of using fixed estimates of absorption rate constant (i.m. model) was also examined. Inter-individual variability was assumed to have a log-normal structure, and residual error was modelled using additive, log-normal and combined error structures. Although bioavailability could not be determined because all doses were administered intramuscularly, the value of including a term for variability in bioavailability was investigated. The need for a full covariance matrix, which accounts for covariance between clearance and volume of distribution, was also examined. Initial analyses were performed using the First Order (FO) algorithm, subsequent analyses, including covariate modelling, were performed using the First Order Conditional Estimation (FOCE) algorithm.

The influence of clinical characteristics on the pharmacokinetic parameters was initially investigated by examining plots of empirical Bayes estimates of the individual parameter values against clinical characteristics and by generalized additive modelling (GAM) [6]. Covariates and combinations of covariates identified as potentially influencing the pharmacokinetic parameters were then tested formally in NONMEM. Linear relationships took the following general form:

$$\text{TVP}_k = \theta_1 \times [1 + \theta_2 \times (\text{covariate}_1 - \text{median})] \times [1 + \theta_3 \times (\text{covariate}_2 - \text{median})] + \dots$$

and nonlinear relationships took the following form: $\text{TVP}_k = \theta_1 \times (\text{covariate}_1 / \text{median})^{\theta_2} \times (\text{covariate}_2 / \text{median})^{\theta_3}$ where TVP_k are the typical values of the pharmacokinetic parameters clearance, volume of distribution and absorption rate constant, and θ_{1-n} are the parameters to be estimated. Mixtures of linear and nonlinear models were investigated where appropriate.

Models were compared statistically using a likelihood ratio test on the differences in the objective function value. Statistical significance was set at $P < 0.05$ (a reduction of >3.8 for one degree of freedom). Plots of residuals and weighted residuals, standard errors of parameter

estimates and changes in estimates of intersubject and residual variability were also considered.

Results

Patients and samples

The initial data set comprised 124 patients and 238 concentration measurements, 114 of which were 'peak' samples. This data set was modified by removal of 14 patients with missing creatinine concentrations, two patients with spurious results, and one patient with a single measurement below the limit of quantification. The final data set comprised 107 patients (39 female) and 203 concentration measurements (97 peaks and 106 'next day' samples). Details of the clinical characteristics of the patients are presented in Table 1 and the individual concentration measurements *vs.* time are illustrated in Figure 1. There was wide variability in the results, with peak concentrations ranging from 3.0 mg L⁻¹ to 19.8 mg L⁻¹ (median 10.6 mg L⁻¹) and 'next day' concentrations from 0.3 mg L⁻¹ to 6.2 mg L⁻¹. 'Peak' sample times ranged from 0.49 h to 2.9 h (median 1.05 h) and 'next day' samples from 8.35 to 32.85 h (median 16.87 h) after the dose. There was no relationship between low peak concentrations and any of the clinical characteristics.

Pharmacokinetic analysis

The basic model assumed a monoexponential elimination and intravenous (i.v.) bolus input with an additive residual error model. The fit of the data was not improved by using a biexponential decline or a combined residual error model. Rounding errors were obtained when a first order absorption model (i.m. model) was used. When the absorption rate was fixed, values below 3 h⁻¹ produced a poorer fit of the data, whereas values of 3 h⁻¹ and above produced no change in fit.

However, the objective function value fell by 109 when covariance was allowed between clearance/bioavailability (CL) and volume of distribution/bioavailability (V). A similar fall occurred when variability in bioavailability (F) was introduced as a separate parameter. This alternative approach led to partitioning of the vari-

ability between CL and F, rather than CL and V as seen with the original approach. The parameters of these models are presented in Table 2. The typical population estimate of CL was 0.268 L h⁻¹ and individual estimates ranged from 0.084 to 1.12 L h⁻¹ (median 0.267 L h⁻¹). V had a population estimate of 1.96 L and individual estimates ranged from 0.570 L to 8.17 L (median 1.92 L).

Plots of individual CL and V estimates obtained using the model that allowed covariance between CL and V indicated a strong, positive relationship between CL and weight and nonlinear relationships between CL and both age and creatinine concentration. Similar trends were observed in the plots of V against weight, age and serum creatinine concentration. The GAM analysis identified weight as the strongest predictor of both CL and V. Covariate models were then built within the population model using the FOCE method. Since all samples were measured within the first dosage interval and there was a maximum of two samples per patient, the FOCE approach achieved perfect agreement between the measured and individual predicted concentrations, which meant that residual error could not be characterized. Fixing this term to a negligible value resulted in little change to the objective function value or parameter estimates but allowed standard errors of the parameter estimates to be obtained.

The results of the covariate analysis are summarized in Table 3. The single factor with the strongest influence on CL was postnatal age when included as a nonlinear model, although improvements in fit were also seen with weight and creatinine concentration. For V, only a nonlinear relationship with age produced a significant reduction in the objective function value. When combinations of factors were examined, weight was found to influence both CL and V. The addition of a nonlinear relationship with age on CL proved beneficial and a further small improvement in fit was seen when creatinine concentra-

Table 1 Clinical and demographic characteristics of the 107 infants included in the study.

Characteristic	Median (range)
Postnatal age (days)	10 (0–99)
Weight (kg)	3.05 (1.24–6.72)
Creatinine (µmol L ⁻¹)	52 (17–173)
White blood cell count (x 10 ⁹ L ⁻¹)	11.3 (2.1–51.6)
Haemoglobin (g dL ⁻¹)	14.5 (4.2–21.5)

Figure 1 Plasma gentamicin concentrations following a single intramuscular dose of 8 mg kg⁻¹ to 107 infants.

Parameter	Model including covariance between CL and V Population estimate(RSE)	Model including interindividual variability in F Population estimate (RSE*)
CL (L h ⁻¹)	0.268 (5.7%)	0.268
V (L)	1.96 (4.8%)	1.96
IIV CL	59% (12%)	4%
IIV V	48% (14%)	ID
IIV F	NA	48%
Residual error (mg L ⁻¹)	0.0001 (fixed)	0.0001 (fixed)
Objective function value	458.0	458.0

*Covariance step failed. RSE, % relative standard error; IIV, interindividual variability; F, bioavailability; CL, clearance/bioavailability; V, volume of distribution/bioavailability; NA, not applicable; ID, indeterminate.

Table 2 Parameter estimates arising from the two basic models.

CL	V	OBJ
Basic model	Basic model	458.0
Age (linear)		439.9
Creatinine (nonlinear)		439.4
Weight (linear)		430.7
Age (nonlinear)		419.6
Age (nonlinear)	Weight (linear)	413.7
Weight (linear)	Weight (linear)	395.3
Weight (linear), creatinine (nonlinear)	Weight (linear)	384.7
Weight (linear), age (nonlinear)	Weight (linear)	375.7
Weight (linear), age (nonlinear), creatinine (nonlinear)	Weight (linear)	372.1
Weight (linear, no intercept), age (nonlinear)	Weight (linear)	375.8
Weight (linear, no intercept), age (nonlinear)	Weight (linear, no intercept)	381.0

OBJ, Objective function value; CL, clearance/bioavailability; V, volume of distribution/bioavailability.

Table 3 Summary of the covariate models tested (covariance model results).

tion was included in the model. However, as there was no obvious improvement in plots and interindividual variability in CL was unchanged, the simpler model was chosen. A direct linear relationship with no intercept was adequate to describe the relationship between CL and weight but an intercept improved the fit with V. The results obtained using the variable bioavailability approach were the same, except that covariance between CL and V could not be estimated, interindividual variability in CL was 22%, in volume 18% and in bioavailability 36%. Table 4 shows the parameter estimates of the best covariate model, Figure 2 shows the population predictions plotted against the measured concentrations for this model, and Figure 3 shows the population predicted steady-state profiles for infants at the minimum, maximum and median ages and weights.

Discussion

In this study, sparse gentamicin concentration-time data collected from a population of African infants were examined to determine factors that might influence the

variability in concentrations observed when doses of 8 mg kg⁻¹ were administered intramuscularly. Concentrations were measured after the first dose and typically involved two samples per patient, one taken at the time of the expected peak (1 h after the dose) and the other the next morning. Although the median peak concentration of 10.6 mg L⁻¹ was therapeutically appropriate, there was wide variability around this value and 9% of the measured peaks were below 6 mg L⁻¹. Since there was no obvious relationship between a low peak and any clinical characteristic, and trough concentrations below 2 mg L⁻¹ occur even at the lowest age and weight, the present regimen of 8 mg kg⁻¹ daily seems to be a reasonable starting dose.

The nature of the data introduced two problems to the analysis. First, the i.m. route of administration meant that it was not possible to determine the amount that reached the systemic circulation. Therefore, clearance and volume estimates obtained were scaled by the (unknown) bioavailability for each individual. Second, the single 'peak' sample provided no information on the rate of absorption. Initial attempts to fit a first order absorption

Table 4 Parameter estimates from the best covariate model (covariance model results shown).

<i>Model</i>	<i>Estimate(% RSE)</i>	<i>IIV (% RSE)</i>
<hr/>		
CL = $\theta_1 \times \text{wt} \times [(\text{age} + 1)/11]^{\theta_2 \star}$		
θ_1	0.0913 (4.2)	42 (12)
θ_2	0.130 (24)	
V = $\theta_3 \times [1 + \theta_4 \times (\text{wt}-3)]^\dagger$		
θ_3	2.02 (4.0)	40 (15)
θ_4	0.277 (11)	
Residual error (mg L ⁻¹)	0.0001 (Fixed)	

RSE, % relative standard error; IIV, interindividual variability expressed as a percentage coefficient of variation; CL, clearance/bioavailability; V, volume of distribution/bioavailability; wt, weight (kg); age, postnatal age (days). $\star$ 1 was added to the recorded and median ages to avoid 0 appearing in the model. CL for an infant of median age (10 days) is therefore 0.0913 L h⁻¹ kg⁻¹, i.e. 0.274 L h⁻¹ for a child of median weight (3 kg). $\dagger$ V is 2.02 L for a child weighing 3 kg and changes by 28% per kg body weight.

Figure 2 Population predicted *vs.* measured plasma gentamicin concentrations obtained using the best covariate model.

model to the data showed that the estimates of absorption rate constant (k_a) were poorly characterized, but indicated that absorption would be complete by 1 h. Only two of the 97 peak samples were obtained less than 1 h after the dose and 16 were taken at least 1.5 h after the dose. Difficulties in identifying absorption rates when samples are taken 1 h after an i.m. injection are supported by the observations of Paisley *et al.* [7], who found that peak concentrations occurred 15–30 min after i.m. injection in newborn infants. Furthermore, Hayani *et al.* [8] found no differences in 1 h post dose gentamicin concentrations between two groups of neonates given i.m. or i.v. therapy. Nevertheless, variability in absorption rate, caused particularly by delayed absorption due to poor muscle perfusion in the first week of life, may have contributed to the observed high variability in both CL and V.

Figure 3 Simulated plasma gentamicin concentration-time profiles for infants at the median, upper and lower limits of the age and weight range, given 8 mg kg⁻¹ daily. ---, Age 0, weight 1.2 kg; —, age 10 days, weight 3.0 kg; — · —, age 99 days, weight 6.7 kg.

Two modelling approaches were used in the analysis. The first assumed covariance between CL and V, whereas the second included a parameter for interpatient variability in bioavailability. The coefficient of variation of interpatient variability in bioavailability (48%) using the second approach was very similar to that in volume obtained using the first approach (49%), indicating that the partitioning of variability depended on the model chosen. Consequently, without intravenous data it is difficult to distinguish between variability due to bioavailability and variability due to clinical factors that influence both clearance and volume.

The GAM analysis identified weight as the most important factor influencing drug handling and this was confirmed in the population analysis. Simple linear relationships between both CL and V and weight were found, which are consistent with previous studies where weight was found to influence gentamicin clearance and volume of distribution in a paediatric population [3]. This study found no advantage in using a nonlinear relationship with weight, as has been advocated elsewhere [9–11].

Using both approaches, a nonlinear relationship between CL and age produced a further improvement in the fit of the model. Although weight and age were related (correlation coefficient 0.63), the patients ranged from newborn to 99 days old and it is likely that changes in renal function associated with maturity were responsible for this additional influence of age on CL. This finding is consistent with the observation that glomerular filtration rate increases over the first few weeks of life [12]. An additional factor that might have been useful, but was not available for this analysis, was postconceptual age. Premature infants have lower rates of glomerular filtration and this may have contributed to some of the lower clearances observed.

A nonlinear relationship between CL and creatinine concentration produced a reduction in the objective function value, which suggests that this biochemical indicator of renal function might be important. However, as there were no obvious improvements in diagnostic plots and no reduction in the estimates of interpatient variability in CL, the inclusion of creatinine cannot be justified in this analysis. This probably reflects the paucity of data from patients with renal impairment and the age range studied. Creatinine concentration in a neonate initially reflects the renal function of the mother and fluctuates widely over the first few days of life. Although 10 infants had creatinine concentrations above $100 \mu\text{mol L}^{-1}$, only three of them were more than 3 days old. The two patients with the highest creatinine concentrations (173 and $172 \mu\text{mol L}^{-1}$) were 1 and 5 days old, respectively.

Interindividual variability in CL fell from 59% in the basic model to 42% in the final model and individual variability in V from 48% to 40%. This small reduction in variability despite the addition of clinical characteristics to the model is disappointing and is reflected in the poor prediction of peak concentrations (Figure 2). As weight was the only factor that influenced V, and doses were based on weight, the wide variability in observed peak concentrations indicates that another factor or factors are likely to be involved.

When the individual CL and V estimates obtained with the second approach were corrected for relative bioavailability, they were identical to those estimated using 'covariance' modelling. Thus the only difference between the two approaches was in the way in which the variance was partitioned. Unfortunately, it is not possible from this analysis to define where the variability arises and why the standard dose of 8 mg kg^{-1} should give rise to such variability. Bioavailability is likely to differ between individuals, partly due to age-dependent variability in muscle mass and possibly also due to variability in administration technique. It should also be recognized that a slower absorption rate may be the explanation for the low peak concentration and apparent high volume of distribution observed in some patients. Thus, the concentration might have been higher in a later sample. Variability in absorption rate may also contribute to the observed variances in CL, V and relative bioavailability.

Individual estimates of CL and V in the present study are higher than those previously reported for similar patient groups, although most other studies focused on the neonatal period. A recent review reported gentamicin CL ranging from 0.02 to $0.12 \text{ L h}^{-1} \text{ kg}^{-1}$, with a mean of $0.057 \text{ L h}^{-1} \text{ kg}^{-1}$ [3]. The median (range) individual estimate of CL in the present study was 0.09 (0.03 – 0.23) $\text{L h}^{-1} \text{ kg}^{-1}$. Similar results were observed for volume

of distribution, for which published estimates ranged from 0.35 to 0.72 L kg^{-1} (mean 0.55 L kg^{-1}) [3] compared with a median (range) of 0.64 (0.28 – 2.35) L kg^{-1} in the present study. As most of the previous studies analysed data from i.v. administration, reduced bioavailability or variable absorption rate may account for the apparently higher estimates of CL and V observed. However, elimination half-life had a mean (SD) of 5.5 (2.2) h in the present study and was shorter than a typical mean of 8 – 9 h [3]. This suggests that the clearance may be higher, which could reflect differences in the characteristics of the patients. Many of the previous studies involved premature neonates, weighing less than 2 kg , and who were treated during the first 7 – 14 days of life. In contrast, 39% of the infants in the present study were more than 14 days old and 86% weighed more than 2 kg . It is reasonable to assume that these more mature infants had better renal function.

This study examined the pharmacokinetics of gentamicin in a group of African infants given a single dose of 8 mg kg^{-1} . Although this dose produced acceptable peak concentrations on average, a wide range of measurements was observed and the clinical characteristics recorded in the course of the study (postnatal age and weight) were able to explain only a small proportion of this variability. This may be due to unpredictability in the rate and extent of absorption following administration by the intramuscular route.

This work is published with the permission of the Director of Kenya Medical Research Institute (KEMRI). This study was supported by a Collaborative Research Initiative Grant from the Wellcome Trust (grant no. 057978/Z/99/Z), a Research Capability Strengthening Grant from WHO (TDR/MIM grant no. 980074) (both to G.O.K.) and a Wellcome Trust Fellowship (grant no. 050563) to M.E. We are grateful to Professor Kevin Marsh (Director, KEMRI-Wellcome Trust Collaborative Research Programme) and Dr Nobert Peshu (Director, KEMRI-Centre for Geographic Medicine Research-Coast) for their support.

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