Journal of Antimicrobial Chemotherapy (2007) **59**, 681–689
doi:10.1093/jac/dkl561
Advance Access publication 8 March 2007

JAC

Population pharmacokinetics of a single daily intramuscular dose of gentamicin in children with severe malnutrition

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Received 2 August 2006; returned 6 October 2006; revised 1 November 2006; accepted 3 January 2007

***Objectives*: The World Health Organization recommends that all children admitted with severe malnutrition should routinely receive parenteral ampicillin and gentamicin; despite this, mortality remains high. Since this population group is at risk of altered volume of distribution, we aimed to study the population pharmacokinetics of once daily gentamicin (7.5 mg/kg) in children with severe malnutrition and to evaluate clinical factors affecting pharmacokinetic parameters.**

***Methods*: Thirty-four children aged 0.5–10 years were studied. One hundred and thirty-two gentamicin concentrations (median of four per patient), drawn 0.4–24.6 h after administration of the intramuscular dose, were analysed. The data were fitted by a two-compartment model using the population package NONMEM®.**

***Results*: Gentamicin was rapidly absorbed and all concentrations measured within the first 2 h after administration were >8 mg/L (indicating that satisfactory peak concentrations were achieved). Ninety-eight percent of samples measured more than 20 h after the dose were <1 mg/L. The best model included weight, and it was found that high base deficit, high creatinine concentration and low temperature (all markers of hypovolaemic shock) reduced clearance (CL/*F*). Weight influenced volume of the central (V1/*F*) and peripheral (V2/*F*) compartments, and high base deficit reduced V2/*F* and intercompartmental CL (Q/*F*). Interindividual variability in CL was 26%, in V1/*F* 33% and in V2/*F* and *Q*/*F* was 52%. Individual estimates of CL/*F* ranged from 0.02 to 0.16 (median 0.10) L/h/kg and those of Vss/*F* from 0.26 to 1.31 (median 0.67) L/kg. Initial half-lives had a median of 1.4 h and elimination half-lives and a median of 14.9 h. Excessive concentrations were observed in one patient who had signs of renal impairment and shock.**

***Conclusions*: Although a daily dose of 7.5 mg/kg achieves satisfactory gentamicin concentrations in the majority of patients, patients with renal impairment and shock may be at risk of accumulation with 24 hourly dosing. Further studies of gentamicin pharmacokinetics in this group are now needed to inform future international guideline recommendations.**

Keywords: antimicrobial therapy, population pharmacokinetics, kwashiorkor, marasmus, Africa, parenteral

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Introduction

Globally, severe malnutrition is a common cause of paediatric admission to hospital in less well-developed countries. Children with severe malnutrition are more susceptible to infection; proven invasive bacterial disease is a common complication, particularly among those dying.[1,2,32] From the limited number of studies detailing the spectrum of infecting pathogens, both Gram-positive and Gram-negative organisms appear to be important.[3–6] Principal isolates include *Streptococcus pneumoniae*, *Escherichia coli* and non-typhoid salmonellae, *Haemophilus influenzae* and *Staphylococcus aureus*.[7] Consequently, the WHO recommends that all children admitted with severe malnutrition should routinely receive parenteral ampicillin and gentamicin.[1] Examination of in-house data has shown that confirmed bacteraemia occurs in 12% of all severe malnutrition admissions and complicates 26% of case fatalities: 52% of these deaths occurring within 48 h of admission. This high fatality is striking given that *in vitro* antibiotic susceptibility testing indicates that up to 85%[7] of organisms are fully susceptible to the antimicrobial regimen recommended by WHO,[1] which is prescribed on admission to all cases of severe malnutrition.[7] A previous study examining susceptibility patterns among Gram-negative bacilli reported lower levels of isolates fully susceptible to gentamicin (76%); however, in cases with malnutrition, gentamicin resistance was not found to be associated with mortality.[8] These deaths, on adequate treatment, call for an evaluation of the additional risk factors associated with in-hospital death, including an in-depth assessment of the pharmacokinetics of gentamicin in this patient group.

Gentamicin, an aminoglycoside, remains the mainstay of treatment for Gram-negative sepsis, as it is cheap and widely available. It demonstrates a concentration-dependent bactericidal activity against a broad spectrum of Gram-negative bacilli, aerobic and facultative anaerobes and also has *in vitro* activity against *Haemophilus* spp. and methicillin-susceptible *S. aureus*, especially when used as part of a combination therapy.[9] The use of 'once daily' dosing of gentamicin is increasingly favoured as it results in high peak concentrations (increasing antibacterial efficacy) and the prolonged drug-free interval reduces the risk of drug toxicity. The volume of distribution is the most important parameter determining the peak concentration and is closely related to the extracellular fluid volume because of the low level of protein binding and high solubility in water.[9] The volume of distribution is increased in oedematous states, burns (or extensive skin desquamation) and with capillary leak in severe infection. Children with severe malnutrition may have all three complications: oedema, wide spread dermatosis and shock due to bacterial infection. The high fatality of children on treatment warrants further studies examining the pharmacokinetics of once daily gentamicin dosing.

Materials and methods

Patients and protocol

The study was undertaken at the KEMRI Centre for Geographic Medicine Research (Coast) at Kilifi District Hospital, Kenya. Parental consent was obtained for all subjects. The KEMRI scientific steering and national ethics research committees approved the study. The aim was to examine the pharmacokinetics of intramuscular gentamicin in children admitted with severe malnutrition who were routinely managed according to the WHO guidelines, including the provision of nutritional support and empirical antibiotic therapy.

Children over 6 months of age whose parents gave consent to enter the study and who had one of the following anthropometric criteria for severe malnutrition were eligible for inclusion in the study: weight for height percentile $<70\%$; bilateral oedema (of kwashiorkor) or mid-upper arm circumference (MUAC) <11.0 cm (if >12 months of age). Additional indicators of severe malnutrition, including visible severe wasting and typical hair and skin changes, were used when anthropometric criteria were not available. Children admitted with a plasma creatinine concentration >160 μmol/L (twice the upper limit of normal for children more than 1 year old) were excluded from the study.

Children were treated according to the standard WHO management guidelines for severe malnutrition,[10,11] which includes resuscitation procedures where appropriate, the judicious use of intravenous (iv) fluids, nasogastric feeding and vitamin and mineral supplementation. Antimicrobial treatment included intramuscular gentamicin (7.5 mg/kg once daily) for 7 days and iv ampicillin (50 mg/kg four times daily) for 48 h. At this stage, a decision was made to change to oral amoxicillin (15 mg/kg three times daily) if the child was clinically improving and blood cultures were negative. If the child had deteriorated, iv chloramphenicol (25 mg/kg three times daily) was added for 5 days. In addition, all children were treated with mebendazole (100 mg twice daily) for 3 days. A single batch of gentamicin, obtained from a national supplier (MEDS, Nairobi, Kenya) with appropriate quality control certification, was used for this study. The doses were prepared and administered by a member of the study team.

Gentamicin sampling and analysis

Patients were randomized on admission, using a computer-generated randomization list, into three groups for gentamicin sampling: Group A children had samples taken after the first dose of gentamicin (day 1); Group B children on day 3; and Group C children on day 5. In order to maximize the information and at the same time to minimize the blood sampling frequency per child, within each group, patients were allocated to one of three sampling schedules: Subgroup 1 at 0, 0.5, 8 and 24 h; Subgroup 2 at 0, 2, 12 and 24 h; and Subgroup 3 at 0, 4, 16 and 24 h. At each time point, a sample of 0.5 mL of venous blood was collected into a lithium heparin tube, spun, plasma removed and stored in Cryovials at -20°C for later batch processing.

Plasma gentamicin concentrations were determined using the Abbott *TDxFLx*® fluorescence polarization immunoassay (Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA). The target (range) concentrations for low (L), medium (M) and high (H) quality control (QC) samples were 1.0 (0.85–1.15), 4.0 (3.60–4.40) and 8.0 (7.20–8.80) mg/L, respectively. The nominal concentrations for the gentamicin calibrators were 0, 0.5, 1.5, 3.0, 6.0 and 10.0 mg/L. The manufacturer supplied the samples for calibration and QC samples. The method is reported to have a sensitivity of 0.27 mg/L and concentrations >10 mg/L were diluted before analysis. The assay coefficients of variation were 6.8% ($n = 6$), 6.3% ($n = 7$) and 4.7% ($n = 5$) for the LQC, MQC and HQC, respectively.

Data analysis

Details of clinical features, blood sampling times, results and gentamicin dosage history and concentration measurements, including all dosage and sampling times, were entered into an Excel® spreadsheet. Pharmacokinetic parameter estimates were obtained using NONMEM® (Version V, GloboMax LLC, Hanover, MD, USA), with a Visual FORTRAN Version 6.0 compiler (DIGITAL™, Digital Equipment Corporation, Maynard, MA, USA). Further analyses of the NONMEM output results were conducted using Xpose (Version 3.1)[12] and SPLUS6® (Insightful Corporation, Seattle, WA, USA).

Data were analysed using both one- and two-compartment models with the First Order Conditional Estimation with Interaction algorithm. Interindividual variability was assumed to be log-normally distributed and residual error was initially examined using a combined (additive and proportional) error structure. Individual estimates of clearance/bioavailability (CL/*F*), volume of distribution/*F*, etc. and individual predicted concentrations were also obtained.

The potential influence of clinical characteristics on the pharmacokinetics of gentamicin was first examined graphically and then generalized additive modelling (GAM) was undertaken using the Xpose package.[12] These screening approaches identified factors that should be explored further using NONMEM® and were repeated as the covariate model was developed. Potential covariates were added to and subtracted from the model in a stepwise fashion and the impact of order of addition was also investigated. A value for length was missing from one patient; therefore, the extrapolated value from a linear regression of length versus age (correlation coefficient 0.85) was used to estimate the missing length. This value was imputed into the data set and used in the covariate analysis. Statistical comparison of models was based on a χ^2 test with $P < 0.05$ significant [fall of 3.84 in the objective function value (OFV)].

Results

Participants and admission clinical characteristics

The study period was January–March 2005. Thirty-four children with severe malnutrition, as defined by the WHO, were entered into the study. A further 12 patients satisfied the anthropomorphic entrance criteria but either refused or died before consent or had a serum creatinine >160 μmol/L. A summary of the clinical characteristics of all the patients who were screened is presented in Table 1 and the characteristics of the patients included in the study are detailed in Table 2. The mean (SD) age of the study patients was 3.1 years (±2.2 years) and 62% were male. Marasmic malnutrition (with no oedema) was more common, 62% (21/34); 94% (17/18) of marasmic children had a weight for height Z score (WHZ) more than 3 SD below the mean. Thirty-eight percent (13/34) had oedematous malnutrition (kwashiorkor). Overall, the mean WHZ (±SD) was −3.3 ± 1.3, but was significantly lower in those presenting with marasmus (mean WHZ −3.67 ± 1.1) than in those with oedematous malnutrition (mean WHZ −2.42 ± 1.8); $P = 0.03$. In the group with kwashiorkor, a significantly greater proportion had MUAC scores <11 cm (8/13; 62%), dermatosis and hair changes associated with malnutrition (11/13; 85%) than the marasmic group.

Table 1. Characteristics of children screened for eligibility

Variable	Study patients ($n = 34$)	Exclusions ($n = 12$)
Age (years)	3.1 ± 2.2	1.7 ± 0.9
Male (%)	62	75
WHZ	−3.3 ± 1.3	−3.1 ± 1.2
MUAC <11 cm (%)	56	41
Oedema (%)	38	17
Admission temperature (°C)	37.6 ± 1.2	38.2 ± 1.0
Admission creatinine (μmol/L)	43 ± 22.7	68 ± 39.7
P. falciparum positive (%)	26	58
Urine culture positive	1/27	0/5
Culture-proven bacteraemia (%)	0	33[a]
HIV positive	8/25 (32%)	none tested
Mortality (%)	12	25

Values are means ± SD or percentages.
[a]*S. pneumoniae*, β-haemolytic streptococci, *Shigella* sp.

None of the study participants had a positive blood culture; however, one patient had a urinary tract infection (*E. coli*). In the group of patients who refused consent or were ineligible, a higher proportion were noted to have bacteraemia (4/12; 33%) and *Plasmodium falciparum* malaria (7/12; 58%). HIV testing, after informed consent, was offered to all patients in the study group; eight (24%) parents refused consent. Of those that were tested, 32% were found to be HIV antibody positive (8/25), including 2 infants <18 months (classified by WHO as HIV exposed). This compares with 8% in unselected children tested at Kilifi[13] and recent estimates, in all cases with severe malnutrition, of 27% (K. Maitland, unpublished results). Nine patients (26%) had detectable levels of malaria parasites on admission.

Table 2. Clinical characteristics of the patient group at the start of gentamicin therapy

Variable	Number	Median	Minimum	Maximum
Age (years)	34	2.4	0.5	9.9
Weight (kg)	34	7.85	4.60	13.70
Length (cm)	33	75.5	61.7	126.0
WHZ score	28	−3.2	−6.5	−1.0
Temperature (°C)	34	37.3	35.2	39.8
Sodium (mmol/L)	34	136	124	144
Potassium (mmol/L)	34	3.6	2.3	4.8
Creatinine (μmol/L)	34	40	17	117
Glucose (mmol/L)	34	4.2	0.7	11.1
Haemoglobin (g/dL)	34	8.4	3.7	11.0
White cell count ($\times 10^9$/L)	34	11.5	1.6	55.7
Platelet count ($\times 10^9$/L)	34	320	17	836
pH	32	7.358	7.094	7.455
$PaCO_2$ (kPa)	32	4.62	2.86	17.20
Bicarbonate (mmol/L)	32	19.5	7.4	26.6
Base deficit (mmol/L)	32	5.2	−4.9	22.6

Two patients were transfused on admission for severe anaemia (haemoglobin <4 g/dL); one child's condition was complicated by malaria and the other child presented with features of sickle cell disease. Five patients had a capillary refill time (CRT; a bedside test that is used to examine perfusion) of >3 s, but only one patient was treated for shock with iv fluids in accordance with the WHO recommendations—Patient 34 who later died. Four patients received iv fluids during the study period for other clinical indications (hypoglycaemia, hypokalaemia and a sickle cell crisis). Overall, four (12%) children died before discharge. One died 28 h after admission before HIV screening and the other three within 1–3 weeks of admission. Of these late deaths, two were HIV positive and one had severe cerebral palsy. The excluded patients had a higher mortality rate (3/12; 25%), and all three patients died within 36 h of admission.

Gentamicin assay data

Gentamicin concentration data were available from 34 infants and children; 4 from each subgroup, except A3 and B1 which each contained 3 infants. A total of 132 gentamicin concentration measurements, ranging from below the limit of quantification to 42.5 mg/L, were available for analysis. Sample times ranged from 0.4 to 24.6 h after the dose (median 12 h) and there were three to four (median of four) samples per patient. Eleven samples were taken within the first hour after administration (an estimate of the peak concentration) and 35 were taken more than 16 h after the dose (to assess the trough levels). Thirty-two measurements were below the limit of quantification; 12 of these samples represented baseline measurements before the first dose of gentamicin was administered and the remaining 20 samples were all taken more than 15 h after the previous dose.

As illustrated in Figure 1, gentamicin was absorbed rapidly with peak concentrations being observed at the post-first dose sampling time in each patient. All nine concentrations measured within the first 40 min were >15 mg/L and of the 17 samples taken within the first 2 h after the dose, all were >8 mg/L and 13 (76%) were >12 mg/L. Forty-seven samples were taken more than 20 h after the dose, of which 38 (80%) were <0.5 mg/L (including 17 below the limit of quantification) and 46 (98%) were <1 mg/L. One patient (Patient 34, Figure 1) had consistently high concentration measurements throughout the dosage interval and a trough of 5.5 mg/L.

Pharmacokinetic analysis

Concentration measurements below the limit of quantification were excluded from the population pharmacokinetic analysis but

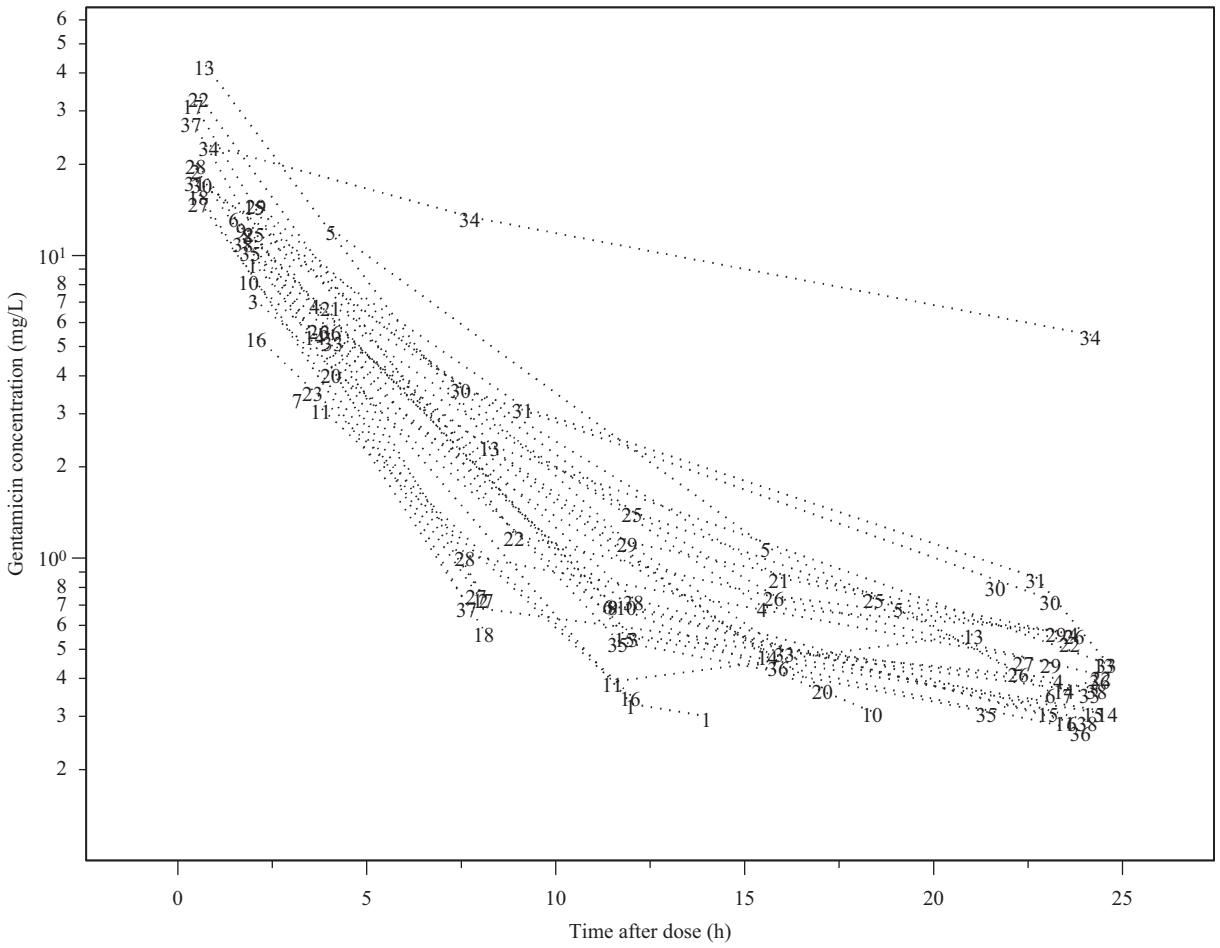

Figure 1. Plot of gentamicin concentrations versus time after dose in 34 infants and children with malnutrition who received 7.5 mg/kg daily by intramuscular injection. The numbers on the plot correspond to individual patients and the dotted lines indicate the profiles in each patient.

included in the data file as 'other' events, which allowed clinical data measured at these times to be included in the file.

A two-compartment model best described the concentration data, as illustrated by the biexponential decline shown in Figure 1. Since the maximum concentration was observed at the first sampling point in all cases, it was not possible to estimate the absorption rate constant. Fixing the absorption rate constant to a range of values offered no advantage in fitting the data, but increased model instability.

Interindividual variabilities in intercompartmental clearance (Q/F) and volume of the peripheral compartment (V2/F) were highly correlated and a single parameter proved sufficient to describe both. Covariance was allowed between interindividual variabilities in CL/F, volume of the central compartment (V1/F) and the combined Q/V2 variability. Residual error was adequately described by a proportional error model.

Graphical analysis identified possible relationships between clearance and weight, length, age, temperature, base deficit, bicarbonate concentration and serum creatinine concentration, as illustrated in Figure 2. Both V1/F and V2/F appeared to be related to weight, age and length. These size factors were highly correlated with each other, with correlation coefficients ranging from 0.81 to 0.85. Since base deficit and bicarbonate concentration were also highly correlated (correlation coefficient, 0.89), only the results obtained using base deficit are presented.

Patient 34 had a particularly low CL/F (0.02 L/h/kg, compared with the group median of 0.1 L/h/kg), which resulted in very high concentrations and was associated with derangement of several clinical factors (Figure 2). This patient had hypovolaemic shock, renal impairment and probable sepsis characterized by hypothermia, hyponatraemia, an elevated serum creatinine concentration (109 μmol/L) and a metabolic acidosis. He received iv fluid resuscitation but deteriorated and died within 36 h of admission. His creatinine measurement before death had risen to 177 μmol/L.

GAM identified age, weight and base deficit as the best predictors of gentamicin clearance. No trends were identified with the following biochemical and haematological measurements: serum potassium; serum glucose; haemoglobin concentration, white cell count; and platelet concentration. Other factors that were retained for further consideration were presence of oedema; CRT; serum sodium concentration; and use of iv fluids.

CL/F was related to weight using both a linear model and a standardized allometric approach.[14] However, scatterplots

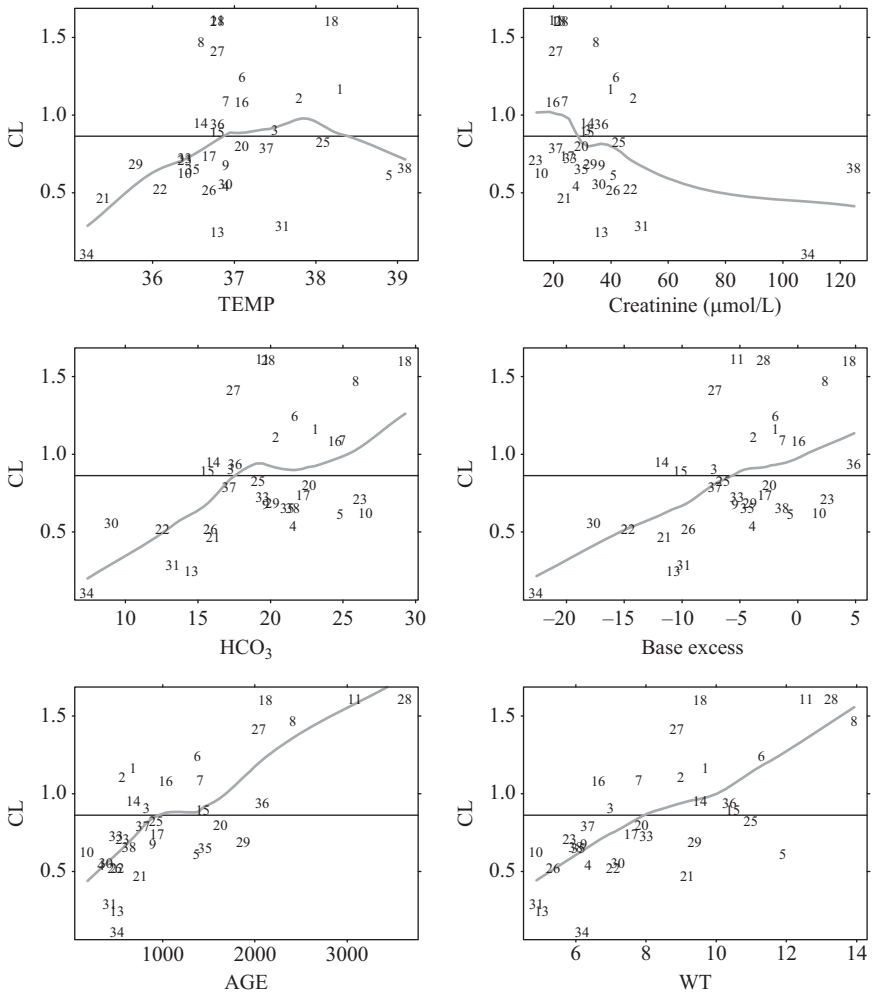

Figure 2. Scatterplots showing potential relationships between individual estimates of gentamicin clearance and a range of clinical factors. The numbers represent individual patients and the solid lines indicate a smooth through the data. CL, clearance/F; TEMP, temperature (°C); HCO_3, bicarbonate concentration (mmol/L); AGE, age (days); WT, body weight (kg). Note: base excess is the negative value of base deficit.

Table 3. Summary of the principal models tested during development of the covariate model

No.	Clearance/*F* model	V2/*F* model	*Q*/*F* model	cvCL	cvV1	cvV2,*Q*	OFV	ΔOFV	c.f. model
1				43	32	64	−17.9		
2	creatinine			37	33	60	−27.1	9.2	1
3	creatinine, BD			31	31	57	−39.4	12.3	2
4	creatinine, BD, temp			29	32	57	−46.1	6.7	3
5	creatinine, BD, temp	BD		26	32	51	−50.5	4.4	4
6	creatinine, BD, temp		BD	26	33	51	−53.9	7.8	4
7	**creatinine, BD, temp**	**BD**	**BD**	**26**	**33**	**52**	**− 57.9**	**4.0**	**6**
8	BD, temp	BD	BD	29	32	52	−52.7	−5.2	7
9	creatinine, BD	BD	BD	28	33	53	−51.7	−6.2	7
10	creatinine, temp	BD	BD	35	32	65	−35.3	−22.6	7

V2/*F*, volume of the peripheral compartment; *Q*/*F*, intercompartmental clearance; cvCL, interindividual variability in clearance/*F*; cvV1, interindividual variability in volume of the central compartment/*F*; cvV2,*Q*, interindividual variability in V2/*F* and *Q*/*F*; OFV, objective function value; ΔOFV, change in OFV, >3.84 is significant at $P < 0.05$ and >6.64 is significant at $P < 0.01$; c.f. model, compared with model number; BD, base deficit; temp, temperature (°C). Bold font indicates final model (no. 7).

suggested that the linear model was adequate and since the allometric approach also gave a slightly higher OFV, it was not considered further. The addition of creatinine to the weight corrected CL/*F* model provided an improvement in fit but length did not. A small influence of age was initially identified, but was no longer significant at later stages of the analysis.

The initial clearance model included weight, serum creatinine concentration, base deficit and temperature <36°C. Examination of scatterplots and a further GAM analysis at this stage identified CRT as a potential additional covariate on all parameters and base deficit and oedema on V2/*F* and *Q*/*F*. Although the addition of these clinical factors improved the OFV values, statistical significance varied according to the order of inclusion, there was often little or no reduction in the interindividual variability and some parameter estimates were poorly defined (relative standard errors >40%).

Table 3 summarizes the principal models that were tested. The final model contained weight, temperature, serum creatinine concentration and base deficit as factors influencing clearance. Base deficit also influenced V2/*F* and *Q*/*F*. However, the effects of

Table 4. Population and individual gentamicin pharmacokinetic parameter estimates from Model 7

Parameter and model	Parameter estimate	%RSE
$CL/F = CL_B \times [1 - \theta_{BD}\,(BD - 5.2)] \times (1 - \theta_{TP}) \times (Cr/33)\theta_{CR}$		
CL_B (L/h/kg)	0.103	5.4
θ_{BD}	0.0382	16
θ_{TP}	0.200	24
θ_{CR}	−0.161	53
IIV_{CL} (%)	26	34
V1/*F* (L/kg)	0.254	8.8
IIV_{V1} (%)	33	33
$V2/F = V2_B \times [1 - \theta_{BD}(BD - 5.2)]$		
$V2_B$ (L/kg)	0.406	14
θ_{BD}	0.0450	24
IIV_{V2} (%)	52	40
$Q/F = Q_B \times [1 - \theta_{BD}(BD - 5.2)]$		
Q_B (L/kg)	0.0239	12
θ_{BD}	0.0512	14
IIV_Q (%)	52	40
Residual error (%)	13.8	9.1

CL/*F*, clearance/bioavailability; CL_B, baseline clearance for a patient with a base deficit (BD) of 5.2, serum creatinine concentration (Cr) 33 μmol/L and temperature (TP) ≥36°C; θ, parameter estimate; V1/*F*, volume of the central compartment/bioavailability; V2/*F*, volume of the peripheral compartment/bioavailability; *Q*/*F*, intercompartmental clearance/bioavailability; %RSE, percentage relative standard error; IIV, interindividual variability expressed as % coefficient of variation.

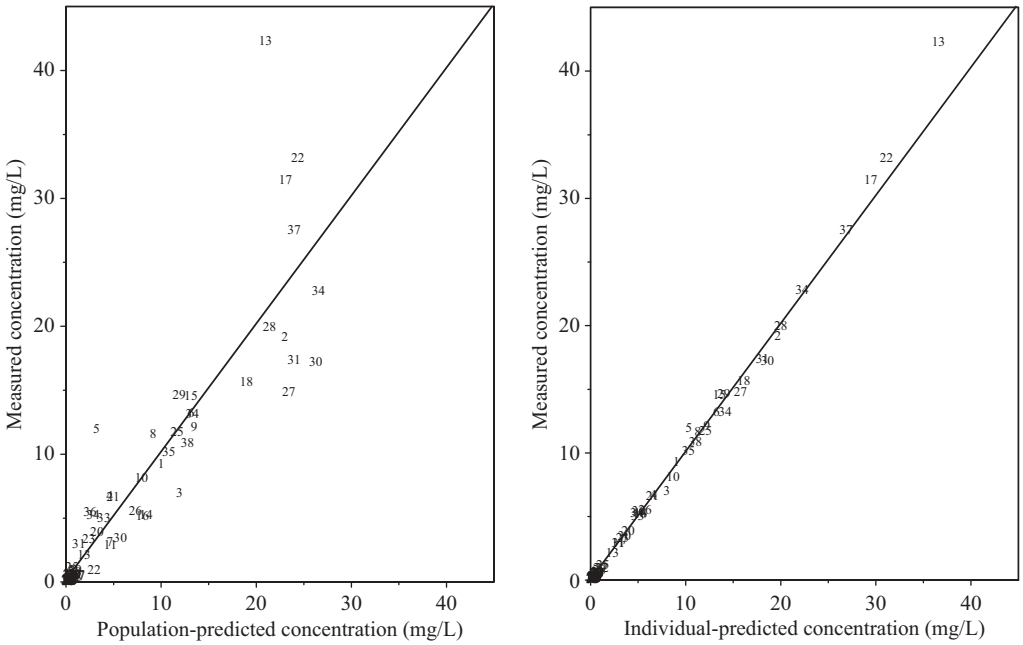

Figure 3. Measured gentamicin concentrations plotted against predicted concentrations obtained from the population pharmacokinetic model parameter estimates (left-hand panel) and predicted concentrations obtained from the individual pharmacokinetic parameter estimates (right-hand panel). The numbers represent individual patients and the solid lines are the lines of identity.

creatinine concentration and temperature on clearance and base deficit on Q/F failed to achieve statistical significance at $P < 0.01$. Population parameter estimates obtained with the final model are presented in Table 4 and measured versus population- and individual-predicted concentration measurements are presented in Figure 3. Individual CL/F estimates ranged from 0.02 to 0.16 L/h/kg (median 0.10 L/h/kg) and individual estimates of Vss/F (V1/F + V2/F) ranged from 0.26 to 1.31 L/kg (median 0.67 L/kg). These values translated to initial half-lives with a median (range) of 1.4 (0.8–5.0) h and terminal half-lives of 14.9 (13.3–16.4) h.

Discussion

This study has demonstrated that a single daily intramuscular dose of 7.5 mg/kg gentamicin is rapidly absorbed and consistently achieves peak concentrations >8 mg/L in infants and children with malnutrition. Trough concentrations were typically <0.5 mg/L, indicating a low potential for toxicity, although excessive accumulation was observed in one critically ill patient whose renal function deteriorated rapidly before death. A population pharmacokinetic analysis confirmed the influence of weight and renal function on gentamicin handling and additionally identified that indicators of sepsis and shock, such as low temperature and high base deficit, were associated with a reduced clearance.

This study is the first to attempt to provide the data that confirm the safety and likely efficacy (extrapolated from the pharmacokinetic data) of the current WHO antimicrobial guidelines in severely malnourished children. As the routine monitoring of gentamicin levels is not possible at most hospitals in Africa, these data are reassuring, particularly for children with uncomplicated presentations. A much larger study, conducted in over 300 Bangladeshi children hospitalized with malnutrition, pneumonia and diarrhoea, was recently published by Khan *et al.*[15] They found no significant differences in efficacy or toxicity when 5 mg/kg gentamicin was given as a single daily intramuscular dose or spilt into three, although there was a trend towards better efficacy and lower toxicity with the single daily dose. However, they used a gentamicin dose that is lower than is currently recommended. Furthermore, ceftriaxone, which is not currently recommended in the WHO guidelines, was used in combination with gentamicin. This antibiotic is not widely available in resource-poor countries and, in the absence of data to support its utility, is precluded from general recommendations on the basis of cost.

The overall mortality in our study was 12%, but 25% in excluded patients. One of the limitations of this study was that it did not include the most critically ill children as they were too unstable at admission to request consent, died before sample collection was possible or were excluded by the study protocol. This group also had higher admission temperatures, septicaemia rates and mortality and is thus likely to receive the most benefit from antimicrobial treatment. Paradoxically, this group is also at greatest risk of renal compromise and potential gentamicin toxicity. Information on the pharmacokinetics of gentamicin in this group is now needed.

Current evidence favours the use of extended interval gentamicin dosing in children.[16] However, in contrast to the adult population, where dosage adjustment guidelines and nomograms are available,[17,18] there is limited information on the influence of clinical factors on drug dosing requirements in this patient population. Additionally, the impact of intramuscular administration (the only feasible option in this clinical setting described in the present study) on absorption and peak concentrations is unclear.

A previous study[19] identified a wide variability in gentamicin concentrations observed 1 h after an intramuscular injection of

8 mg/kg to 107 infants aged 0–99 days. Although fewer patients contributed to the present study, rapid absorption from the intramuscular site was observed (Figure 1). Tighter control of drug administration and sampling may have contributed to this observation. Rapid absorption was also identified in another paediatric study ($n = 10$) in which concentrations averaging 7.2 mg/L were observed at 15 min and 8.9 mg/L at 30 min after a lower intramuscular dose of 4 mg/kg.[20] It was not possible to determine bioavailability in the present study since all doses were given intramuscularly, but the measured concentrations were high enough to suggest that absorption was not compromised by the intramuscular route.

Previous studies in infants and children given iv gentamicin have found estimates of volume of distribution to be ~0.3–0.5 L/kg.[21–24] Higher estimates were obtained in the current study with a mean (SD) Vss/*F* of 0.67 (0.22) L/kg and ranged 0.26–1.31 L/kg. Although the use of a two-compartment model and differences in the route of administration may have influenced these results, it is likely that malnutrition and sepsis also contributed. A 14% increase in the volume of distribution in septic neonates was reported by Lingvall *et al.*,[25] and in the present study, elevations of bicarbonate concentration and the derived factor, base deficit, were associated with an increased volume of distribution. Both the use of parenteral nutrition and clinical indicators of malnutrition have been associated with an increased gentamicin volume of distribution in adults,[26,27] but Samotra *et al.*[20] found no significant differences in gentamicin pharmacokinetics between malnourished and normal children given 4 mg/kg intramuscularly. However, their study only comprised 10 patients and both the age range (4–14 years) and the interpatient variability were wide. In contrast, Bravo *et al.*[28] administered a single iv dose of 3.5 mg/kg and identified lower gentamicin peaks and a higher volume of distribution (0.46 L/kg compared with 0.39 L/kg) in 11 malnourished infants with marasmus when compared with 7 eutrophic infants. The present study identified not only a higher value for apparent volume of distribution in severely malnourished children but also a wide range between patients. Higher values of base deficit were associated with larger values of volume of distribution and although a trend was also found with the presence of oedema, there were insufficient data to characterize the effect. A larger patient group would be required to investigate this further. Nevertheless, the recommended dose of 7.5 mg/kg achieved peak concentrations in the range associated with efficacy in the majority of patients.

The second factor to be considered is whether the dosage interval of 24 h is appropriate for all patients. Only 1 of 34 patients from subgroups tested on day 1, day 3 or day 5 (Groups A, B and C) had a trough concentration above 1 mg/L. This patient (number 34) developed renal failure and subsequently died. As expected, weight and serum creatinine concentration were the most important predictors of gentamicin clearance, but other factors such as low temperature, base deficit, prolonged CRT (markers of hypovolaemic shock) and oedema were also associated with low clearance values. Only temperature and base deficit achieved statistical significance, possibly due to the low patient numbers that were included and Patient 34, who was particularly unwell, was particularly influential in the model development. Buchanan *et al.*[29] noted a prolonged elimination of gentamicin in the acute phase of kwashiorkor, which they attributed to a reduction in glomerular filtration rate and which resolved following treatment. This suggests that the day of sampling and other therapy may also have influenced the results.

Due to the sampling times used in this study and the profile obtained, the initial half-lives of ~1.5 h probably represent a mixture of distribution and elimination, whereas the apparent elimination half-lives of ~15 h partially reflect the very slow terminal elimination phase. Similar results have been observed previously in gentamicin population studies in adults.[30,31] The slow terminal elimination of gentamicin normally only contributes a small proportion of the overall exposure and is often ignored for clinical purposes. However, a particularly slow elimination was observed in Patient 34, and, if therapy had continued, a dosage interval of 60–72 h would have been more appropriate for this individual. The current WHO guidelines recommend that the second dose of gentamicin should be withheld until the child is passing urine.[11] Current data support this conclusion, but further exploration of this group is warranted given the concern of the potential toxicity of the 24 h interval dosing in this group.

Conclusions

In an environment where routine analysis of gentamicin concentrations is not feasible, a population pharmacokinetic analysis can provide useful information on the clinical characteristics that might lead to underdosing or overdosing. Although further work is required to identify appropriate dosage regimens for patients with severe renal impairment or shock, this study has demonstrated that satisfactory gentamicin peak and trough concentrations are achieved in the majority of malnourished children who are given a single daily intramuscular dose of 7.5 mg/kg.

Acknowledgements

This paper is published with the permission of the Director of the Kenya Medical Research Institute (KEMRI). We would like to thank the hospital superintendent, clinicians, nursing staff and field workers of Kilifi District Hospital. The study was supported by the KEMRI and The Wellcome Trust. The funding sources had no role in study design, analysis or in the writing of the report.

Transparency declarations

None to declare.

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