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The effect of sepsis upon gentamicin pharmacokinetics in neonates

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Aim
To investigate the effect of sepsis upon the volume of distribution (Vd) of gentamicin in neonates.

Methods
A retrospective chart review was conducted of neonates admitted to Dunedin Hospital who had gentamicin concentrations performed between 1st January 2000 and 30th October 2003. Data from 277 neonates, including a total of 576 gentamicin concentrations, were included in the pharmacokinetic analysis. Fifteen (5.4%) of the neonates had confirmed sepsis. Pharmacokinetic analyses were performed with NONMEM using a one compartment first order elimination model. Duration of infusion (D) was included as a parameter in the model. Covariates included sepsis (SEP), chronological age, gestational age (GA), birth weight, current weight, gender, Apgar score at 1 (AP1) and 5 (AP2) minutes, plasma C-reactive protein and serum creatinine.

Results
The initial model provided a mean estimates of clearance (CL) of 0.0460 l kg^{-1} h^{-1}, volume of distribution (Vd) of 0.483 l kg^{-1} and D of 0.748 h. The magnitudes of interpatient variability, expressed as CV%, were 29.2% for CL, 20.8% for Vd and 71.5% for D. The magnitude of residual variability in gentamicin concentrations was 88.0%. The final pharmacokinetic model was: CL = (0.0177 + 0.00147 • (GA-20) +0.000635 • AP2) l kg^{-1} h^{-1}, Vd = (0.483 +0.0656 • sepsis) l kg^{-1}, D = 0.672 h. The interpatient variability (CV%) was 22.8% for CL, 22.8% for Vd and 97.7% for D. The magnitude of residual variability in gentamicin concentrations was 83.3%.

Conclusions
The 14% increase in Vd in septic neonates implies that larger doses may be required to achieve peak therapeutic concentrations in the presence of sepsis. D is an important parameter in neonatal pharmacokinetic models.

Introduction

Little is known about how the gentamicin volume of distribution in neonates changes with sepsis, although there appears to be an increase in the volume of distribution in septic infants [1]. Previous studies in critically ill adults indicate that the gentamicin volume of distribution (Vd) is increased during sepsis [2–8]. Among patients with sepsis, large interindividual differences in pharmacokinetics have been reported [4]. Septic shock is a dynamic disease process that usually becomes rapidly worse and may end in death [9]. During the acute phase of sepsis, the patient may be given vigorous volume expansion to counteract shock. Endothelial damage may occur resulting in capillary leak and interstitial

oedema with prolonged water accumulation. Fluid retention may also occur in response to a failing heart and/or renal failure, with consequent changes in total body water and the apparent Vd of the drug [3]. This would result in a lower gentamicin concentration due to the increase in Vd [3, 6, 7]. Half of the deaths secondary to Gram-negative bacteraemia occur in the initial 24–48 h [10]. Hence a delay in achieving adequate peak gentamicin concentration within the first 24 h of infection could result in markedly higher mortality rates in patients with sepsis [11].

An increased Vd for aminoglycosides is seen in neonates compared with children and adults because of increased extracellular fluid volume in neonates [12–14]. There is a gradual decrease from infancy to adulthood in the Vd relative to bodyweight. Therefore neonates require larger doses on a mg/kg basis to obtain optimal peak concentrations [12, 13, 15]. Further, the reduced CL and higher Vd seen in neonates results in a longer elimination half-life ($t_{1/2}$) for aminoglycosides resulting in a greater risk of drug accumulation [14].

Aim

The aim of the present study was to investigate the effect of sepsis upon the Vd of gentamicin in neonates.

Methods

Patients

A retrospective chart review was conducted of neonates admitted to Dunedin Hospital who had gentamicin concentrations performed between 1st January 2000 and 30th October 2003. Neonates were included if their gestational age at birth plus postnatal age was less than 48 weeks, they had possible sepsis, received gentamicin as a part of their antibiotic treatment and had at least one gentamicin concentration taken. All patients were treated with at least 48 h of antibiotics. Gestational age at birth (GA) ranged from 22 to 42 weeks (Table 1). Birth weights ranged from 0.47 to 5.08 kg (mean 2.47 kg).

Gentamicin dosing and concentrations

Gentamicin dose, time of dose, gentamicin concentration and time of concentration were recorded. All patients received a gentamicin loading dose of 4 mg kg^{-1} intravenously over 30 min as a continuous infusion. The intravenous line was flushed with 0.3 ml 0.9% NaCl solution upon completion of the gentamicin infusion. The maintenance dose (2.5 mg kg^{-1}) was administered by intravenous bolus over 3–5 min. The gentamicin dosing regimen for infants weighing <1000 g and/or GA < 29 weeks was 24-hourly; for neonates weighing 1000–1500 g and/or GA 30–36 weeks, dosing was 18-hourly; for neonates with GA of 30–36 weeks and/or >7 (postnatal) days age, 12 hourly and for neonates with a corrected age of >37 weeks, dosing was every 8 h. The target peak concentration was 5–10 mg l^{-1} and the target trough concentration was 1–2 mg l^{-1}. Trough and peak concentrations were drawn pre dose and 1 h post dose, respectively. The concentra-

Table 1
General characteristics of the study population

	Proven sepsis *n* = 15	Not septic *n* = 262	All *n* = 277
Birth weight (kg)*	3 (1.0–4.2)	2.46 (0.47–5.08)	2.47 (0.47–5.08)
Current weight (kg)*	3 (1–4.45)	2.47 (0.47–5.08)	2.52 (0.47–5.08)
Maximum CRP (mg l^{-1})*	10 (1–222)	4 (1–116)	5 (1–222)
Postnatal age (days)*	1 (0–21)	0 (0–27)	0 (0–27)
Male gender†	7 (47%)	157 (60%)	164 (59%)
Apgar at 1 min*	9 (1–9)	8 (1–10)	8 (0–10)
Apgar at 5 min*	10 (8–10)	10 (0–10)	10 (0–10)
Gestational age (weeks)*	36 (28–41)	35 (22–42)	36 (22–42)
Creatinine (μmol l^{-1})*	69 (26–90)	72 (34–245)	70 (26–245)
Peak concentration,*	6.1 (1.6)	6.6 (1.5)	6.5 (1.4)
Trough concentration*	1.7 (0.6)	1.8 (0.8)	1.8 (0.7)
Samples per patient*	2 (1–4)	2 (1–7)	2 (1–7)

*Mean ± SD, *median (range), †n (%).*

tions were assayed by fluorescence polarization immunoassay (FPIA Abbot- AxSYM system), performed by the Dunedin Hospital clinical laboratories. The limit of detection of the assay was 0.3 mg l^{-1} with a SD of 0.29 mg l^{-1} to 5.0 mg l^{-1} and 5.5% above 5.0 mg l^{-1}.

Modelling

Pharmacokinetic analyses were performed using NONMEM version 5 (Globo Max, 7250 Parkway Drive, Hanover, MD, USA). A single-compartment model with first-order elimination was employed using the subroutines ADVAN1 and TRANS2. First order conditional estimation (FOCE) without interaction was used. D was added to the structural model as a parameter because it resulted in considerable improvement in the minimum objective function (MOF). The interindividual error was modelled used an exponential error model. The residual error was modelled using an additive model. The covariate data were: sepsis (defined as a positive bacterial culture from a normally sterile body fluid), chronological age, gestational age, day of treatment, birth weight, current weight, gender, Apgar score at 1 and 5 min, plasma C-reactive protein (CRP) concentration and serum creatinine. Gestational age was also expressed both as weeks of GA after 20 weeks gestation (GA-20) and as weeks of birth prior to 42 weeks gestation (42-GA). The outcome variables (dependent variables) were the pharmacokinetic parameters: volume of distribution (Vd), clearance (CL) and duration of infusion (D).

Statistical analysis

The covariate model was built by stepwise multiple regression by including those covariates with a statistical significance $P < 0.01$ on univariate analysis. Forward stepwise regression was performed by including covariates in the model in the order of decreasing change in objective function on univariate analysis. If the covariate had a statistically significant contribution to the model by further minimizing the MOF by more than 3.84, corresponding to a P-value of <0.05, it was retained in the model [16]. Subsequently a backward stepwise regression was performed. The protocol was approved by the Otago Ethics Committee.

Results

A total of 324 neonates had gentamicin concentrations recorded during the time period of the study and data from 277 were included in the pharmacokinetic analysis. Data from 47 patients were excluded due to incomplete clinical data. There were a total of 576 gentamicin concentrations, ranging from 0.3 to 12.5 mg l^{-1}. Of the gentamicin concentrations, 43 (7.5%) were collected on day 1 of treatment; 230 (39.9%) on day 2; 222 (38.5%) on day 3; and 81 (14.1%) on day 4 or later. The general characteristics of the study population are presented in Table 1. The patients with confirmed sepsis had a higher mean CRP than the group without confirmed sepsis. Other than this the two populations were similar. For the 15 patients with confirmed sepsis, the causative organisms were: E Coli [4], group B beta-haemolytic streptococci [4], coagulase negative staphylococci [3], *Staphylococcus aureus* [2], *Enterococcus faecalis* [1], and *Klebsiella oxytoca* [1]. Ten patients were diagnosed with septicaemia, two with meningitis, two with urinary tract infections and one with omphalitis.

The initial (structural) model was a one-compartment, first order elimination model with D included as a parameter. Normalizing dose by current body weight greatly improved the fit of the model. The initial model estimated mean (95% CI for the estimate) CL, Vd and D as: 0.0460 (0.0455–0.0465) 1 kg^{-1} h^{-1}, 0.483 (0.454–0.512) 1 kg^{-1} and 0.748 (0.747–0.749) hours, respectively. The magnitudes of interpatient variability (CV%) were 0.0851 (29.2%) for CL, 0.0431 (20.8%) for Vd and 0.512 (71.5%) for D. The magnitude of residual variability (CV%) in gentamicin concentrations was 0.774 (88.0%). The correlation coefficient between CL and Vd was –0.519, D and Vd was 0.729 and CL and D was –0.313. On univariate analysis, the only covariate with a significant effect upon Vd was sepsis (Table 2). There were no interactions between sepsis and the day of treatment, or the maximum CRP. Clearance was influenced by gestational age, Apgars at one and five minutes and creatinine (Table 3). D was not influenced by any of the covariates.

The final model included GA and AP2 in relation to CL, and sepsis in relation to Vd, and resulted in improved fit of the model (Figure 1). Inclusion of AP1 and creatinine did not result in a statistically significant improvement in the model (Table 4). Sepsis contributed to a 14% increase in Vd. The final covariate model was: CL = (0.0177 + 0.00147 • (GA-20) + 0.000635 • AP2) 1 kg^{-1} h^{-1}, Vd = (0.483 + 0.0656 • sepsis) 1 kg^{-1}, D = 0.672 h. The interpatient variability (CV%) for CL was 0.0522 (22.8%), for Vd was 0.052 (22.8%) and for D was 0.954 (97.7%), where GA is expressed in weeks, sepsis is coded as 1 if present and 0 if absent, and apgar score is expressed as the raw score. The residual variability was 0.694 (83.3%).

Discussion

Due to the morbidity and death associated with sepsis, early attainment and maintenance of therapeutic concentrations of gentamicin is essential [17, 18]. The problem of increased Vd due to sepsis can be addressed by

Table 2
Univariate analyse of effect upon Vd (dose normalized to weight)

Variable Volume of distribution	Formula	MOF	Change in MOF	*P*-value
Base model	$Vd = \theta_2$	889		
Gestational age	$Vd = \theta_2 + \theta_4 \bullet (42 - GA)$	898	+9	>0.05
Proven sepsis	$Vd = \theta_2 + \theta_4 \bullet SEP$	881	–8	<0.01
CRP	$Vd = \theta_2 + \theta_4 \bullet CRP$	893	+4	>0.05
CRPM	$Vd = \theta_2 + \theta_4 \bullet CRPM$	912	+13	>0.05
Day of treatment	$Vd = \theta_2 + \theta_4 \bullet DAY$	892	+3	>0.05
Day of treatment × sepsis	$Vd = \theta_2 + \theta_4 \bullet DAY \bullet SEP$	887	–2	>0.05
CRPM × sepsis	$Vd = \theta_2 + \theta_4 \bullet CRPM \bullet SEP$	899	+10	>0.05
Male gender	$Vd = \theta_2 + \theta_4 \bullet SEX$	894	+5	>0.05
Female gender	$Vd = \theta_2 + \theta_4 \bullet (1\text{-}SEX)$	893	+4	>0.05
Apgar at 1 min	$Vd = \theta_2 + \theta_4 \bullet (10\text{-}AP1)$	892	+3	>0.05
Apgar at 5 min	$Vd = \theta_2 + \theta_4 \bullet (10\text{-}AP2)$	936	+37	>0.05
Age in days	$Vd = \theta_2 + \theta_4/(1 + AGE)$	891	+2	>0.05

Table 3
Univariate analyse of effect upon CL (dose normalized to weight)

Variable Clearance	Formula	MOF	Change in MOF	*P*-value
Base model	$CL = \theta_1$	889		
Gestational age, weeks	$CL = \theta_1 + \theta_4 \bullet (42\text{-}GA)$ #	890	+1	>0.05
Gestational age, weeks	$CL = \theta_1 + \theta_4 \bullet (GA\text{-}20)$	817	–72	<0.001
Current weight, kg	$CL = \theta_1 + \theta_4 \bullet CWT$	843	–46	<0.001
Current weight$^{2/3}$, kg$^{2/3}$	$CL = \theta_1 + \theta_4 \bullet CWT^{2/3}$	848	–41	<0.001
Current weight$^{3/4}$, kg$^{3/4}$	$CL = \theta_1 + \theta_4 \bullet CWT^{3/4}$	830	–59	<0.001
Proven sepsis	$CL = \theta_1 + \theta_4 \bullet SEP$	888	–1	>0.05
Absence of proven sepsis	$CL = \theta_1 + \theta_4 \bullet (1\text{-}SEP)$	889	0	>0.05
CRP	$CL = \theta_1 + \theta_4 \bullet (CRP)$	884	–5	<0.05
Male gender	$CL = \theta_1 + \theta_4 \bullet SEX$	894	+6	>0.05
Female gender	$CL = \theta_1 + \theta_4 \bullet (1\text{-}SEX)$	891	+2	>0.05
Day of treatment	$CL = \theta_2 + \theta_4 \bullet DAY$	894	+5	>0.05
Apgar at 1 min	$CL = \theta_1 + \theta_4 \bullet AP1$	880	–9	<0.01
Apgar at 5 min	$CL = \theta_1 + \theta_4 \bullet AP2$	875	–14	<0.001
Age, days	$CL = \theta_1 + \theta_4 \bullet AGE$	911	+22	>0.05
Creatinine	$CL = \theta_1 + \theta_4/CR$	882	–7	<0.01

using an extended dose-interval approach [19, 20]. A number of studies have reported improved therapeutic blood monitoring results with extended dosing interval regimens compared with the more traditional multiple daily dosing regimens [15, 20–24]. The benefits from the extended dosing interval regimens are: ease of administration, less chance of error, reduction in consumables such as syringes, and a more consistent approach to monitoring blood concentration [14, 19, 22]. The traditional dosing regimen often results in unacceptable high trough concentration and sub therapeutic peak concentration [21–23].

Previously, an initial loading dose has been advised for neonates to ensure achievement of early therapeutic peak serum gentamicin concentrations [13, 21, 25–27]. Several investigators recommend a loading dose of between 3.5 and 5 mg kg^{-1} [13, 14, 21, 25, 27]. *Watterberg et al.* [13] evaluated the need for a loading

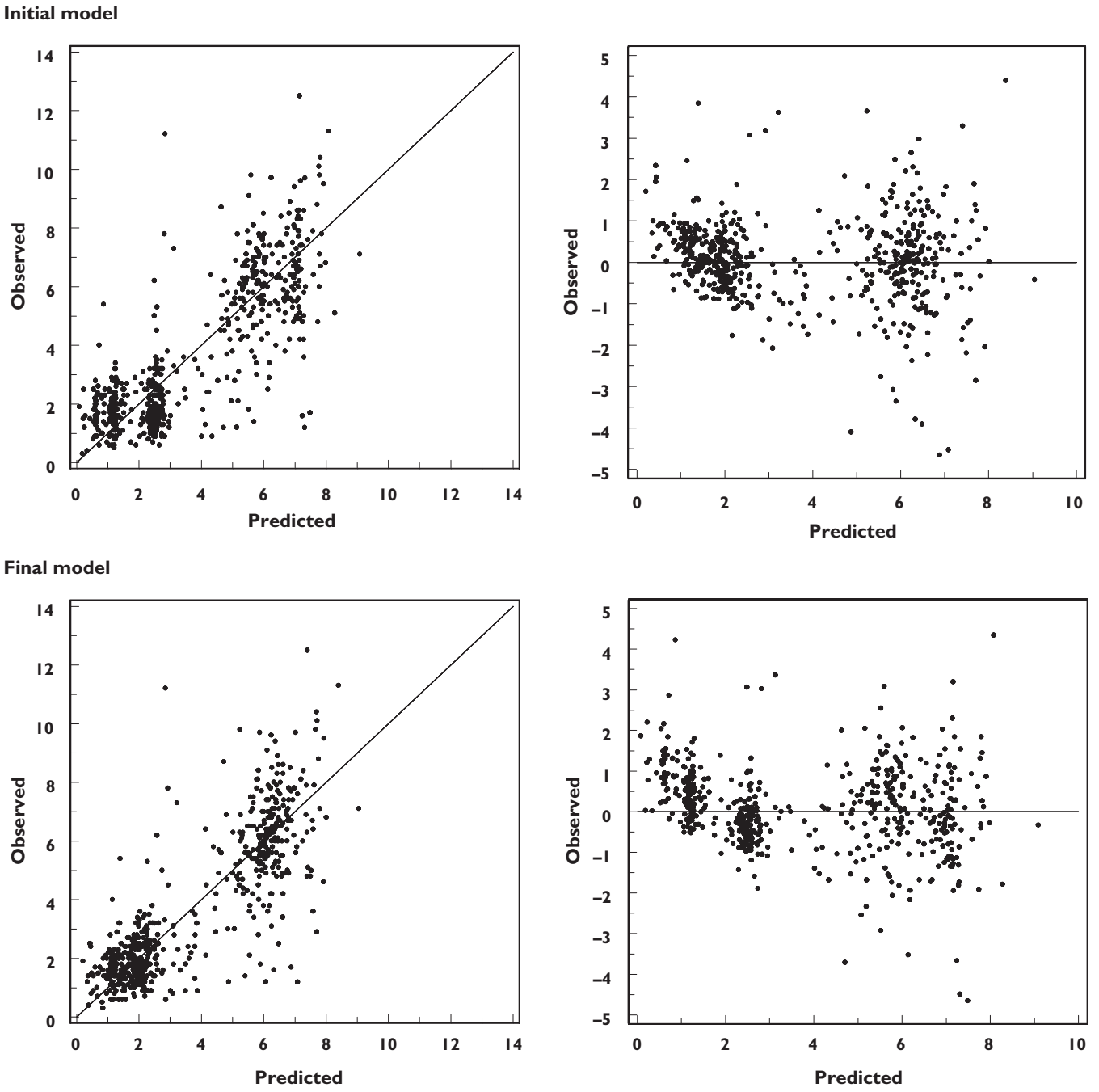

Figure 1
Comparison of initial and final models

dose to attain early optimal serum gentamicin concentration in neonates. Their results showed that a significant number of neonates would not achieve optimal peak gentamicin serum concentration during the initial phase of therapy without a loading dose of 4 mg kg^{-1}.

In adult studies it has been shown that septic patients have higher aminoglycoside Vd (30–70%) than that of nonseptic patients [2, 5–8]. *Triginer et al.* [7] observed a significant decrease in mean Vd from 0.43 l kg^{-1} at day two after admission, to 0.29 l kg^{-1} on the seventh day of treatment in critically ill adult patients. The smaller increase in Vd (14%) that we observed in neonates compared with adults (30–70%) during the septic phase may be because neonates start at a higher base Vd since they possess a larger extracellular fluid volume [28]. If we had designed our study differently and only included the

Table 4
Steps in the forward and backward stepwise multiple regression

Model	MOF	Change in MOF	*P*-value
Forward stepwise			
$CL = \theta_1$ $Vd = \theta_2$ $D = \theta_3$	889		
$CL = \theta_1 + \theta_4 \bullet (GA-20)$ $Vd = \theta_2$ $D = \theta_3$	817	−64	<0.001
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet CWT^{3/4}$ $Vd = \theta_2$ $D = \theta_3$	819	+2	>0.05
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet CWT$ $Vd = \theta_2$ $D = \theta_3$	823	+6	>0.05
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet CWT^{2/3}$ $Vd = \theta_2$ $D = \theta_3$	823	+6	>0.05
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2$ $Vd = \theta_2$ $D = \theta_3$	805	−14	<0.001
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2 + \theta_6 \bullet AP1$ $Vd = \theta_2$ $D = \theta_3$	814	+9	>0.05
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2$ $Vd = \theta_2 + \theta_6 \bullet SEP$ $D = \theta_3$	799	−6	<0.05
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2 + \theta_7/CR$ $Vd = \theta_2 + \theta_6 \bullet SEP$ $D = \theta_3$	799	0	
Backward stepwise			
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2$ $Vd = \theta_2 + \theta_6 \bullet SEP$ $D = \theta_3$	799		
$CL = \theta_1 + \theta_4 \bullet (GA-20)$ $Vd = \theta_2 + \theta_5 \bullet SEP$ $D = \theta_3$	816	+17	<0.001
$CL = \theta_1 + \theta_4 \bullet AP2$ $Vd = \theta_2 + \theta_5 \bullet SEP$ $D = \theta_3$	877	+78	<0.001
$CL = \theta_1 + \theta_4 \bullet (GA-20) + \theta_5 \bullet AP2$ $Vd = \theta_2$ $D = \theta_3$	805	+6	<0.05

first days instead of including the whole period of treatment, it is likely that a larger difference in Vd than 14% between septic and nonseptic neonates would have been found.

Recent research suggests that higher doses administered less frequently may improve efficacy and reduce toxicity associated with gentamicin therapy [20, 22]. Since gentamicin is excreted almost exclusively by renal filtration, its pharmacokinetics are closely linked to the glomerular filtration rate (GFR) at all ages [29]. The lower GFR seen in neonates results in slower CL of aminoglycosides [14]. A low Apgar score at 5 min age is an indicator of birth asphyxia, which in turn may decrease GFR secondary to renal hypoxic injury. The postnatal increase of GFR in the first week of life is known to be slow in infants with gestational age (GA) of 25–34 weeks when compared with full term infants [26]. In some full term infants the GFR doubles within the first few days of life [30].

In the present study the duration of the infusion was found to be an important pharmacokinetic parameter in neonates, in terms of explaining variability. In our final

model, the duration of the infusion was found to be 0.672 h, which is greater than the expected duration. The increased duration may be due to the dead space in the administration tubing. This dead space, in combination with low infusion rates means it takes considerably longer than anticipated to give the entire dose. The smaller infants have lower background infusion rates so it takes longer to flush the gentamicin from the tubing into the patient. An effect of the longer duration is that the neonate may not achieve an adequate peak concentration. Also, the timing of the collection of the peak concentration should take the duration of infusion into account.

Some limitations should be considered when interpreting the results of the present study. The number of patients with proven sepsis was low due to a low prevalence of proven sepsis among neonates with suspected sepsis. Another limitation of our analysis was that day-1 gentamicin serum concentrations were not available for many of the neonates studied. If day-1 concentrations had been available we might have been able to show a larger increase than 14% in gentamicin Vd during the septic period in the neonates. There are also limitations with using patient therapeutic drug monitoring data, such as the error due to inaccurate dosing times and error in the laboratory assay, which contribute to the residual error. Finally, we had to exclude 47 sets of patient data due to incomplete clinical data. The missing data represent a potential source of bias.

In conclusion, the 14% increase in Vd in septic neonates implies that larger doses may be required to achieve peak therapeutic concentrations in the presence of sepsis. Duration of infusion is an important parameter in neonatal pharmacokinetic models. Further research is required into causes of variability in the duration of infusion in neonates.

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