Population Pharmacokinetics of Gentamicin and Dosing Optimization for Infants

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The aim of this study was to characterize and validate the population pharmacokinetics of gentamicin in infants and to determine the influences of clinically relevant covariates to explain the inter- and intraindividual variabilities associated with this drug. Infants receiving intravenous gentamicin and with routine therapeutic drug monitoring were consecutively enrolled in the study. Plasma concentration and time data were retrospectively collected from 208 infants (1 to 24 months old) of the Hospital Universitario Severo Ochoa (Spain), of whom 44% were males (mean age [$\pm$ standard deviation], 5.8 ± 4.8 months; mean body weight, 6.4 ± 2.2 kg). Data analysis was performed with NONMEM 7.2. One- and two-compartment open models were analyzed to estimate the gentamicin population parameters and the influences of several covariates. External validation was carried out in another population of 55 infants. The behavior of gentamicin in infants exhibits two-compartment pharmacokinetics, with total body weight being the covariate that mainly influences central volume (V_c) and clearance (CL); this parameter was also related to creatinine clearance. Both parameters are age related and different from those reported for neonatal populations. On the basis of clinical presentation and diagnosis, a once-daily dosage regimen of 7 mg/kg of body weight every 24 h is proposed for intravenous gentamicin, followed by therapeutic drug monitoring in order to avoid toxicity and ensure efficacy with minimal blood sampling. Gentamicin pharmacokinetics and disposition were accurately characterized in this pediatric population (infants), with the parameters obtained being different from those reported for neonates and children. These differences should be considered in the dosing and therapeutic monitoring of this antibiotic.

Aminoglycosides are among the most commonly used broad-spectrum antibiotics used in anti-infective therapy (1, 2). Despite their potential for renal toxicity, ototoxicity, and bacterial resistance, several aminoglycosides continue to play an important role in the treatment of infections (3, 4). Of the aminoglycosides, gentamicin is one of the most commonly used due to its low cost and broad-spectrum efficacy (5, 6). Gentamicin is commonly used to treat infections caused by both Gram-negative and Gram-positive bacilli, such as *Escherichia coli*, *Proteus* spp., *Pseudomonas* spp., *Serratia* spp., and *Staphylococcus* spp. Other clinical applications of gentamicin include the treatment of infections of the central nervous system (CNS), respiratory, abdominal, and urinary systems, bones, skin and soft tissues and endocarditis and septicemia; it is also used in combination with ampicillin as empirical therapy for sepsis in newborns and infants (7).

Drug pharmacokinetics and disposition are different in pediatric patients compared to those in adults (8). In this context, the Food and Drug Administration (FDA), in considering the complex changes and the anatomic, biochemical, and physiological differences related to age, proposed to classify pediatric populations as neonate (birth to 1 month of life), infant (between 1 and 24 months), child, and adolescent (9). Growth, development, and maturation of enzymatic processes are features with marked physiological influence from birth to adulthood (10). For these reasons, the pharmacokinetic differences found between newborns and adults justify the need to perform pharmacokinetic studies, especially during the first months of life. For instance, in very premature neonates (gestational age, <32 weeks), the pharmacokinetic characteristics of antibiotics may vary from those in full-term neonates due to differences in drug absorption, distribution,

metabolism, and excretion, being that all of these processes rapidly develop during the first year of life (11, 12).

In adults, the dosage regimens for gentamicin have evolved from multiple daily dosing to extended-interval dosing. This change has also been applied to the establishment of gentamicin dosing in pediatrics (1, 5, 13, 14). However, its pharmacokinetics in infants exhibits large inter- and intraindividual variability, mainly due to the developmental changes occurring from the first month of life (15). In clinical practice, individualization of dosage regimens and monitoring of gentamicin concentrations are routinely performed in order to ensure that peak blood concentrations are sufficiently high to elicit a therapeutic response while avoiding high trough concentrations, which would be potentially toxic after prolonged drug exposure (11, 16, 17).

A nonlinear mixed-effects modeling methodology was introduced to population pharmacokinetic analysis several years ago and has become a standard procedure employed to analyze sparse data (18). This situation applies to data collected from infant pop-

Received 11 July 2014 Returned for modification 16 August 2014

Accepted 31 October 2014

Accepted manuscript posted online 10 November 2014

Citation Medellín-Garibay SE, Rueda-Naharro A, Peña-Cabía S, García B, Romano-Moreno S, Barcia E. 2015. Population pharmacokinetics of gentamicin and dosing optimization for infants. *Antimicrob Agents Chemother* 59:482–489. doi:10.1128/AAC.03464-14.

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doi:10.1128/AAC.03464-14

ulations, in which usually only one or two blood serum concentrations can be reasonably obtained in clinical practice. A recent review conducted on population pharmacokinetic analyses performed during the first 2 years of life showed antibiotics to be the drug class most cited (44%), with vancomycin and gentamicin representing the two agents studied the most. Age was one of most frequently evaluated covariates in pharmacokinetic analyses. The majority of the studies were conducted on populations of 25 to 100 neonates with a postnatal age (PNA) ranging from the first day of life to 1 month (19).

It was therefore the purpose of this study to calculate the population pharmacokinetic parameters of gentamicin in a large population of infants (age range, 1 to 24 months) and to validate the predictive performance of the population analysis in another population with the same characteristics in order to establish the most appropriate dosage regimens to maximize the safety and efficacy of gentamicin in infants.

MATERIALS AND METHODS

Infants from 1 to 24 months of age receiving gentamicin by intravenous infusion were included in the current study, with routine therapeutic drug monitoring (TDM) in the Hospital Universitario Severo Ochoa (Leganes, Spain) occurring between 1990 and 2011. The data collection and handling were performed according to the ethics procedures of the hospital.

The total population was divided into two groups: one composed of 208 infants, which was used to build the population pharmacokinetic model (population study group), and the other composed of 55 infants (validation study group) used for validating the predictive performance of the first population. The assignment of the infants to one of the two groups was carried out randomly.

The following data were collected from the medical record of each infant: age, sex, weight, height, serum creatinine (CR_S), creatinine clearance (CL_{CR}), and body mass index (BMI). CR_S was used to estimate the CL_{CR} of gentamicin using the Schwartz equation $CL_{CR} = K \times \text{length}/CR_S$, where K is set to 0.45 for term infants whose weight is appropriate for age, 0.33 for low-weight infants, and 0.55 for infants >1 year old (7, 20). This formula applies to alkaline picrate (Jaffe) methods, even those traceable to isotope dilution mass spectrometry (IDMS), as applied for the current work for CR_S measurement. The details of gentamicin administration were also retrieved from the records of each patient (doses, start of infusion, infusion rate, and dosing interval) as were data from TDM (serum sampling date and time, as well as assay concentration).

The administration of gentamicin was performed by means of an IVAC syringe pump (IVAC Corp., USA) as intravenous infusions given over a period of 20 min. The empirical dosing regimen for infants is 2.5 mg/kg of body weight/8 h or 4.5 to 7.5 mg/kg/24 h (7). Nevertheless, infants who received doses of ≥ 7 mg/kg and had a sample drawn 1 h after the start of the infusion were excluded (21).

Gentamicin analysis. Gentamicin serum concentrations were determined by a fluorescence polarization immunoassay (Abbott TDx, Abbott Park, IL, USA). The calibration curves for gentamicin in human serum ranged from 0.5 mg/liter to 10 mg/liter, with a coefficient of variation of 1.4% for the concentration of 4 mg/liter. The intra- and interday coefficients of variation of the method were 4.3% and 5.3%, respectively. All plasma concentrations below the limit of quantification were not considered for the population analysis.

Pharmacokinetic analysis. Pharmacokinetic modeling was performed using nonlinear mixed effects analysis with NONMEM 7.2 (Icon Development Solutions, Ellicott City, MD, USA). The subroutines ADVAN1 TRANS2 and ADVAN3 TRANS4 were used to evaluate the one- and two-compartment pharmacokinetic open models, respectively. First-order conditional estimation (FOCE) was employed to calculate the mean and variance of the population pharmacokinetic parameters. The fixed-effects parameters estimated directly from the one-compartment open

model were total clearance (CL) and volume of distribution (V). For the two-compartment open model, the estimated pharmacokinetic parameters were total clearance (CL), central volume of distribution (V_c), intercompartmental clearance (Q), and peripheral volume of distribution (V_p).

The statistical models used to account for interindividual variability in the pharmacokinetic parameters as well as for the residual error were modeled with homoscedastic (additive), heteroscedastic (proportional), and exponential error.

The Akaike information criterion (AIC) was calculated based on the objective function (OBJ) for comparing structural models; a drop of 2 was the threshold for considering one model over another ($AIC = OBJ \times n_p$, where n_p is the total number of parameters in the model). Graphical analysis and a generalized additive model (GAM) were employed to evaluate the influences of the covariates on the population pharmacokinetic parameters estimated from both base pharmacokinetic models. Covariates were introduced into the population model using linear, allometric, or exponential functions. Changes occurring in the OBJ and caused by the addition of covariates to the regression model are χ^2 asymptotically distributed, with degrees of freedom equal to the difference in the number of parameters between the models. A difference (ΔOBJ) of >3.8 ($P < 0.05$, $df = 1$) was considered significant for the addition of a covariate. An intermediate model was obtained by first adding the continuous covariates that showed an influence on the base model and keeping only those that significantly diminished the OBJ, as mentioned before. Each covariate was added individually, starting with the most important ones, with the rest of them being added or dropped according to the same criteria. The model was selected when no further improvement occurred. Finally, the discrete covariate with influence over the intermediate model was selected as mentioned before, followed by a graphical assessment. An evaluation of the final model was performed by means of backward elimination, in which each of the covariates was deleted in the same order as it was introduced into the model, and considering a ΔOBJ of >10.836 ($P < 0.001$, $df = 1$) to be significant. Therefore, clinically relevant covariates that explain interindividual variability showing a significant contribution to the estimation of the fixed parameters were kept (18, 22).

The precision of the parameter estimate was reported as the standard error (SE) reported in the covariance tables given by NONMEM. The confidence intervals were estimated as the parameter value ± 1.96 SE.

Bootstrap analysis was performed with 200 replicates to report the confidence intervals (CI) for each parameter; the 95% CI had to cover the true value of the parameter estimated to prove the stability of the final model (18).

Validation. External validation was carried out in a separate group of infants ($n = 55$) who had similar characteristics to those of the population study group. The predictive performance of the population pharmacokinetic model was evaluated using a previous method. The gentamicin serum concentrations of the validation group were compared to their predicted values in order to estimate the precision of the population model that was built. The bias fit was evaluated by means of the mean prediction error (MPE). Precision was estimated using the absolute prediction error (APE), the mean-squared prediction error (MSPE), and the root-mean-squared of the prediction error (RMSPE) (23, 24).

RESULTS

Demographics. The population study group was composed of 208 infants, and 55 infants were in the validation study group. Considering both populations, 56% were females and 44% males. The demographic characteristics of the groups assayed (population study group and validation study group) are summarized in Table 1.

Both populations were classified by weight according to age (months) and sex, according to the WHO child growth standards (25); 12.1% of the infants were 1 to 11 months old with low body

TABLE 1 General characteristics of the populations assayed^a

Characteristic	Population group (n = 208)	Validation group (n = 55)
Age (mo)	5.8 ± 4.8	5.5 ± 4.4
BW (kg)	6.4 ± 2.2	6.7 ± 2.3
Ht (cm)	62.6 ± 9.1	62.8 ± 8.8
BMI (kg/m ²)	15.8 ± 2.1	16.5 ± 2.7
CR _S (mg/dl)	0.42 ± 0.1	0.44 ± 0.2
CL _{CR} (ml/min/1.73 m ²)	76.7 ± 36.9	76.7 ± 44.3

^a Data are shown as the mean ± standard deviation. BW, body weight; Ht, height; BMI, body mass index; CR_S, serum creatinine; CL_{CR}, creatinine clearance.

weight (BW) (INF 0), 72.9% of the infants were 1 to 11 months old with normal BW (INF 1), and 15% were infants >1 year old with normal BW (INF 2).

In the Hospital Universitario Severo Ochoa, different dosage regimens were used during the period studied, with mean gentamicin doses (± standard deviations [SD]) of 6.0 ± 1.5 mg/kg/day and 5.5 ± 1.2 mg/kg/day for the population and validation study groups, respectively. In the population study group, 4 infants received a mean gentamicin dose of 2.3 mg/kg/6 h (total daily dose, 9.4 mg/kg), 98 received a mean dose of 2.3 mg/kg/8 h (total daily dose, 6.8 mg/kg), 3 received 3.05 mg/kg/12 h (total daily dose, 6.1 mg/kg), and the rest (103 infants) received a single daily dose of 4.8 mg/kg. Regarding the validation study group (n = 55), 26 infants received a mean dose of 2.1 mg/kg/8 h (total daily dose, 6.4 mg/kg/24 h), whereas 29 infants received a single daily dose of 4.6 mg/kg.

For both populations, a total of 421 serum gentamicin concentrations were available, ranging from 1 to 6 gentamicin serum concentrations per infant. Of these, 335 serum concentrations corresponded to the population study group and 86 to the validation study group. For most infants (96.2%), one or two gentamicin serum concentrations were obtained; of these, 45% had one and 51.2% had two.

Figure 1 shows gentamicin serum concentrations obtained related to blood sampling times. The gentamicin serum concentra-

TABLE 2 Pharmacokinetic parameters and interindividual variability values obtained for the base two-compartment open model without the inclusion of covariates^a

Pharmacokinetic model	Parameter	Mean ± SE
CL (liters/h)	θ ₁	0.83 ± 0.05
V _c (liters)	θ ₂	1.9 ± 0.06
Q (liters/h)	θ ₃	0.31 ± 0.06
V _p (liters)	θ ₄	4.9 ± 1.0
Interindividual variability associated with CL (%)	ω ² _{CL}	59.3 ± 22.4
Interindividual variability associated with V _c (%)	ω ² _{Vc}	43.8 ± 14.1
Residual variability (%)	σ	12.0 ± 4.0

^a OBJ = 520.85, AIC = 528.85.

tions ranged from 0.5 to 15.9 mg/liter, with a mean value of 4.8 mg/liter. The blood sampling times ranged from 1 to 321 h (mean, 56.3 h); 8.6% of the samples were collected within the first 24 h, 66.1% between 24 and 72 h, and 25.2% from 72 to 321 h.

Base pharmacokinetic models and covariate additions. The first pharmacokinetic model evaluated was the one-compartment open model with exponential interindividual variability associated with both CL (θ₁) and V (θ₂). Residual variability was modeled as homoscedastic (additive) error. For this model, the OBJ was 564.3.

When using a two-compartment open model, the OBJ decreased 43.5 units compared to that of the one-compartment open model. This difference in OBJ corresponds to a P value of <0.005 (χ² is assumed). Table 2 summarizes the pharmacokinetic parameters estimated using a two-compartment pharmacokinetic model.

Initially, the influence of covariates was evaluated with the one-compartment model in which CL and V were assumed to be the same for all individuals in the population study group; next, the two-compartment open model was evaluated, assuming the same CL, V_c, V_p, and Q. When applying the two-compartment open model, ΔOBJ was statistically significant, but the coefficients of

FIG 1 Gentamicin serum concentrations versus blood sampling times (n = 335) for the population study group.

TABLE 3 Pharmacokinetic parameters and interindividual variability values obtained for the final two-compartment open model and bootstrap results ($n = 200$)^a

Pharmacokinetic model	Parameter	Mean $\pm$ SE	Bootstrap values		
			Median	5th percentile	95th percentile
CL (liters/h $\cdot$ kg) ^b	θ_1	0.12 $\pm$ 0.01	0.12	0.09	0.13
	θ_5	0.06 $\pm$ 0.11	0.10	0.007	0.24
V_c (liters/kg)	θ_2	0.35 $\pm$ 0.02	0.34	0.27	0.37
Q (liters/h)	θ_3	0.23 $\pm$ 0.05	0.24	0.15	0.45
V_p (liters)	θ_4	2.3 $\pm$ 1.0	2.9	1.3	6.7
Interindividual variability associated with CL	ω^2_{CL}	26.4 $\pm$ 14.1	28.3	22.4	34.6
Interindividual variability associated with V_c	ω^2_{Vc}	26.5 $\pm$ 14.0	24.5	20.0	33.2
Residual variability	σ	11.2 $\pm$ 2.9	11.0	8.1	12.5

^a OBJ = 197.27.^b CL = $\theta_1 \times BW + \theta_5 \times (CL_{CR}/75)$. $V_c = \theta_2 \times BW$.

variation (%CVs) obtained for residual variability differed slightly (0.2%) from those of both pharmacokinetic models, with %CVs of interindividual variability associated with both CL and V being higher for the two-compartment open model. Table 3 summarizes the population parameters and interindividual variability values obtained for the final pharmacokinetic model.

For the one-compartment open model, the influence of BW on V was evaluated, taking into consideration the classification of the population study group according to differences in age and BW, as stated previously. For this analysis, interindividual variability associated with V was significantly reduced. When introducing CL_{CR} in the base one-compartment model, a significant reduction in the interindividual variability associated with CL was also observed. However, the covariate of sex did not have any influence on the performance of the model.

When applying the same choice of covariates to the two-compartment model, the influences of both BW and CL_{CR} on CL and V_c were demonstrated. In this case, the interindividual variabilities associated with CL and V_c were significantly reduced regardless of the characteristics (age and BW) of the infants (population study group).

Figure 2 shows the scatter plots of predicted versus observed gentamicin concentrations for the base and final two-compartment open models. As can be observed, the introduction of covariates in the model clearly reduced the dispersion of the points around the identity line. Moreover, the scatter plots of conditional weighted residuals (CWRES) versus BW (including the identity line) are also shown, demonstrating the influence that BW has on the pharmacokinetic model. The incorporation of BW with CL and V improves the goodness of fit for the group of infants with low BW, for whom initial overestimation occurred as for infants with normal BW, for whom underestimation was initially obtained. The shrinkages for interindividual and residual variability obtained for the final two-compartment model were 29 to 17% and 48%, respectively.

After the selection of the final model, a bootstrap analysis was performed with 200 replicates from the original data set to adequately reflect the parameter distributions. The results obtained are summarized in Table 3. In this table, the same number of fixed parameters (θ) corresponding to the final two-compartment open model with covariates are indicated as median and standard error. The percentiles, reported by bootstrapping, cover the mean values shown in Table 3 for each parameter, which reflects the symmetry

of the distribution and allows an assumption of stability in the final model.

Validation. A recent literature review found that validations of pharmacokinetic models are performed in only 17% of published pharmacokinetic-pharmacodynamic pediatric studies and in 28% of adult studies; however, adequate model validation is essential for model building (26). The characteristics of the validation group are summarized in Table 1. The validation study group was composed of 55 infants whose mean age ($\pm$ SD) was 5.5 $\pm$ 4.4 months, similar to that of the population study group. Their mean BW was 6.7 $\pm$ 2.3 kg.

Figure 3 shows the scatter plot of the predicted versus observed gentamicin concentrations corresponding to the validation group, as well as those obtained for the final two-compartment open model. Table 4 summarizes the mean prediction errors obtained from the validation of the final model compared to those corresponding to the base model.

The mean prediction errors (MPE) for the two-compartment model include zero in the 95% CI, thereby indicating that from a statistical point of view, the model is not conditioned to over- or underestimation.

A decrease in the difference obtained between the upper and lower limits of the 95% CI can be observed in a comparison of the final model to the base one, thereby indicating the higher precision of the model. This is also confirmed by the absolute precision error (APE) value obtained. Similarly, mean-squared prediction error (MSPE) and root-mean-squared prediction error (RMPSE) are clearly reduced, thereby confirming the improvement of the precision obtained in the prediction of the final pharmacokinetic model.

DISCUSSION

A population pharmacokinetic analysis of gentamicin in infants was performed in order to define the disposition of aminoglycosides in newer populations that have not been already recorded in the literature. This population of infants exhibits different characteristics than those of newborns or adults (13, 27, 28). In the current study, the population pharmacokinetic parameters of gentamicin were retrospectively estimated by NONMEM 7.2 in a total population of 263 infants who were admitted to the Hospital Universitario Severo Ochoa (Leganés, Spain) between the years 1990 and 2011 and who received gentamicin as part of their treatment.

FIG 2 (a and b) Scatter plots of predicted versus observed gentamicin concentrations (including the identity line) for the base (a) and final (b) two-compartment open model. (c and d) Scatter plots of conditional weighed residuals (CWRES) versus BW (including the identity line) for the base (c) and final (d) two-compartment open model, and corresponding to the population study group.

Both one- and two-compartment pharmacokinetic models can adequately describe the pharmacokinetics of gentamicin in infants. However, the two-compartment open model showed improved goodness of fit to represent the disposition of gentamicin in the population studied. Previous reports have also proposed the use of the two-compartment model to describe the pharmacokinetic behavior of gentamicin in different populations of infants (27, 28).

In order to explain the variability we found, physiological

variables (BW, height, age, sex, and CL_{CR}) were analyzed to evaluate their influence on the pharmacokinetic parameters of gentamicin. BW exhibited the highest correlation, which was followed by CL_{CR} . Gentamicin CL and V are different in infants compared to those in adults, showing wide interindividual variability.

This difference can be attributed to several factors that contribute to the modification of the distribution of gentamicin, such as protein binding, blood flow to tissues, membrane permeability,

FIG 3 Scatter plot of predicted (PRED) versus observed (DV) gentamicin concentrations corresponding to the validation group and obtained for the final two-compartment open model.

and drug affinity for different tissues (27–29). The fact that gentamicin is a polar compound with low plasma protein binding (<30%) makes its V directly related to extracellular body fluid (5). In this respect and during the first 2 years of life, the compartmentalization of body water changes continuously; total body water decreases, and adipose tissue increases (29), resulting in a higher volume of distribution in newborns and infants than that in older children. BW also increases significantly during the first year of life; therefore, the introduction of such a covariate in the population pharmacokinetic analysis allows for a comparison of V with that of other populations. The mean value obtained for this parameter is in accordance with that of other studies, being lower than that reported for adult populations (0.28 liters/kg) and higher than that given for newborns (0.48 liters/kg) (27, 28).

Touw, Westerman, and Sprij (11) demonstrated that the nor-

malization of gentamicin V by BW (V/kg) clearly decreases with age. After applying the two-compartment open model to our population, differences in V were not observed, probably due to the age range of the population assayed (1 to 24 months). Despite this fact, in the current study, V was determined for a population which has not been described in the literature, since most studies are carried out in populations ranging from 6 months to 4 years or up to 18 years of age (30, 31). Differences in gentamicin V by age were not found when applying the two-compartment pharmacokinetic model, which simplifies the population model by considering total BW only.

The categorical variable of sex did not exert any influence on the pharmacokinetic parameters of gentamicin, which is in accordance with other studies that have demonstrated that creatinine serum concentration and muscular body mass do not exhibit significant differences between males and females before adolescence (20). The variability found in V demonstrates the need to monitor plasma gentamicin concentrations in order to improve the efficacy of the drug and avoid the toxicity effects associated with aminoglycosides.

Gentamicin is excreted by the kidneys, mainly by glomerular filtration, with 50 to 93% of the drug recovered in urine 24 h after administration in individuals with renal impairment. Due to the immaturity of newborns, most of the processes involved in renal excretion of drugs require several weeks to >1 year to reach maturity, thereby influencing the disposition of polar drugs, such as gentamicin (10, 11, 19).

TABLE 4 Prediction errors estimated for the validation group with the base and final two-compartment open model

Prediction error type ^a	Base model	Final model
MPE	0.3 ± 2.5 (−0.3, 0.8)	-0.2 ± 1.5 (−0.6, 0.1)
APE	1.6 ± 1.9 (1.2, 2.0)	0.9 ± 1.2 (0.7, 1.2)
MSPE	6.1 ± 11.6 (3.6, 8.1)	2.3 ± 5.7 (1.0, 3.5)
RMSE	2.5 (1.9, 2.8)	1.5 (1.0, 1.9)

^a MPE, mean prediction error; APE, absolute prediction error; MSPE, mean-squared prediction error; RMSE, root-mean-squared prediction error.

FIG 4 Plasma concentrations shown as median and 5th to 95th percentiles for a 6-month-old infant receiving 7 mg/kg of intravenous gentamicin. The median values for a simulated 1-month-old infant with low BW and data from a simulated infant with low CR_s are also depicted ($n = 1,000$ infants simulated for each situation).

For the population in the current study, the mean gentamicin CL obtained was 0.12 ± 0.01 liters/h/kg, and this is comparable to that reported by Taketomo, Hodding, and Kraus (7), which was 0.1 liters/h/kg. Drug clearance depends mainly on the functional capacity of the kidneys and renal blood flow, which increases from 12 ml/min at birth up to 140 ml/min at around 1 year of age. In this population of infants, CL is influenced by both BW and CL_{CR} .

Dosing and TDM recommendations. Through the estimation of the pharmacokinetic parameters of gentamicin and their variabilities, it is feasible to propose a dosing scheme based on simulations using the model generated from this infant population. Once-daily dosing is preferred to avoid toxicity. In order to reach a peak value of >10 mg/liter, a dose of 7 mg/kg of gentamicin should be given, followed by serum concentration monitoring. According to the simulated population, 6 to 10 h after starting, the infusion gentamicin concentrations ranging from 0.8 to 2 mg/liter will be expected. This time range is optimal to ensure detectable serum concentrations of gentamicin; 70% of the simulated infants were over the limit of quantification (0.5 mg/liter) of the routinely used immunoassays. In fact, the maximum concentration of drug in serum (C_{max}) should not be measured until 2 h after a 30-min infusion to ensure postdistributional samples in 7 mg/kg once-daily dosing (21). Despite the postantibiotic effect, trough serum concentrations of <0.5 mg/liter should not last for >6 to 8 h in order to ensure the optimal efficacy of this antibiotic (13, 14, 16, 32).

Figure 4 shows the mean gentamicin plasma concentrations and 5th to 95th percentiles corresponding to 1,000 simulations obtained for the final two-compartment model, as generated by NONMEM and using data obtained from a standard 6-month-old infant weighing 8 kg, having a CR_s of 0.4 mg/dl, and receiving 7 mg/kg/24 h of intravenous gentamicin. The data from a simulated low-weight 1-month-old infant and low- CR_s 6-month-old infant are also shown in Fig. 4, where the median values for plasmatic

concentrations are not significantly different from those obtained by a standard infant receiving the same dose.

For infants, intravenous gentamicin is best represented by two-compartment pharmacokinetics in which total body weight and creatinine clearance exhibit an influence on the volume of distribution and clearance of the drug. It was feasible to distinguish the differences between neonates and infants, making it possible to individualize the dosing regimens for this population. The proposed scheme is a once-daily dosage of 7 mg/kg, followed by therapeutic drug monitoring to avoid toxicity and ensure efficacy with minimal blood sampling.

ACKNOWLEDGMENTS

We acknowledge the assistance of the pharmacists, analytical technicians, nurses, and medical staff of the Hospital Universitario Severo Ochoa (Leganes, Spain) for their contributions to the present study.

This study was conducted as part of routine work; no external funding was received. Financial support was given to S. E. Medellín-Garibay by the National Research Council of Science and Technology (CONACYT) from Mexico during her research stay performed in Spain (grant 309952).

We declare no conflicts of interest.

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