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Population pharmacokinetics of gentamicin in premature newborns

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***Objectives*: To determine the pharmacokinetic parameters of gentamicin in a population of 200 premature newborns and to investigate the influence of several clinical and physiopathological covariates on the pharmacokinetics of the drug. To validate the pharmacokinetic analysis performed in another population of 50 premature newborns.**

***Methods*: A total of 200 premature newborns were evaluated at the neonatal intensive care unit of Severo Ochoa Hospital (Madrid, Spain). Four hundred and seventeen serum drug concentrations were included. Mean gestational age (GA) was 32.19 ± 2.97 weeks, mean postnatal age (PNA) was 5.49 ± 5.41 days and mean body weight (BW) was 1.68 ± 0.63 kg. Fifty additional newborns were studied for validation (mean GA 32.62 ± 3.07 weeks, mean PNA 5.17 ± 3.77 days and mean BW 1.80 ± 0.67 kg). Dosing, serum gentamicin concentrations and 15 covariates were collected. Data analysis was performed with NONMEM. One- and two-compartment open models were evaluated. Four parameters were analysed with the two-compartment open model: clearance (CL), central volume (Vc), peripheral volume (Vp) and intercompartmental clearance (Q).**

***Results and conclusions*: The two-compartment open model was found to significantly better describe gentamicin pharmacokinetics in the neonate. More than PNA or GA, creatinine clearance (CL_{CR}) plays an important role in the elimination of gentamicin in premature newborns. Creatinine clearance is also related to GA. The appropriate dosing regimens given in accordance with the characteristics of the patients are 5 mg/kg/48 h and 4 mg/kg/24 or 36 h for neonates <32 weeks and ≥32 weeks of GA, respectively.**

Keywords: NONMEM, aminoglycosides, neonates

Introduction

Gentamicin has traditionally been the aminoglycoside most commonly used in the prophylaxis and treatment of serious Gram-negative infections in the neonate including the frequently isolated coagulase-negative staphylococci. However, the clinical use of aminoglycosides is limited by their potential ototoxicity and nephrotoxicity.[1]

The risk of nephrotoxicity is related to the renal cortical aminoglycoside concentration. The saturable cortical uptake suggests that high but transient aminoglycoside concentrations may be less nephrotoxic than persistent low concentrations.[2] Although nephrotoxicity is generally reversible because the cells lining the renal proximal tubes can regenerate, it is prudent for trough concentrations to be <2 mg/L.[3] Ototoxicity is more likely to be associated with repeated exposure to aminoglycosides and prolonged courses than to transient elevated peak concentrations >12 mg/L.[2] Nevertheless, the incidence of ototoxicity and nephrotoxicity associated with aminoglycosides is controversial in newborns; however, it must still be considered a potential hazard related to drug accumulation.[4] Therefore, individualization of dosage regimens and monitoring of gentamicin concentrations are routinely performed in neonates to ensure that peak concentrations are high enough to elicit the therapeutic response while potential toxicity resulting from prolonged exposure to high trough concentrations is avoided.

A prerequisite for an optimal outcome with aminoglycoside therapy is the estimation of pharmacokinetic parameters in individual patients; however, these studies are frequently compromised in neonates by the limited number of serum concentrations

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(one or two levels) that can be reasonably obtained in clinical practice. For this reason, it is especially interesting to obtain pharmacokinetic information about the population. The non-linear mixed-effects model (NONMEM) has been widely used to estimate the population mean values of pharmacokinetic parameters and their inter- and intra-individual variabilities. With NONMEM it is also possible to study the influence of various clinical characteristics on drug disposition such as disease states, concurrent medications and physiological variables.

It has been well established that the pharmacokinetic properties of aminoglycosides from different patient populations and between healthy volunteers and patients are quite different.[5,6] Although several gentamicin population pharmacokinetic studies have been performed in the newborn,[7–10] few of them have been performed in premature patients. Some studies have been published using the non-parametric estimation of maximization method (NPEM program) in populations of 34[11] and 71[12] preterm infants and also utilizing the more recent modelling tool WinBUGS in populations of 53[13] and 55[14] neonates, respectively. However, these studies often include heterogeneous study groups of small numbers with differences in gestational ages (GAs), disease states and drug administrations. For instance, GA is strongly correlated with the development of glomerular filtration, especially taking into consideration that aminoglycosides are almost entirely eliminated in the kidney by glomerular filtration. Younger GA neonates show a decrease in gentamicin clearance as a consequence of their immature renal function.

The purposes of the present work were to determine the population pharmacokinetic parameters of gentamicin in a large group of premature neonates (n = 200) and to investigate the influence of several clinical and physiopathological covariates on the pharmacokinetic profile of the drug. Moreover, a predictive performance analysis was performed to determine the difference between predicted and observed serum gentamicin concentrations (SGC) in a separate group of neonates (n = 50) used as a validation population.

Materials and methods

Subjects and data collection

This was a retrospective study with prospective validation in which data were retrospectively obtained from medical records and routine gentamicin monitoring of hospitalized premature newborns at the Severo Ochoa Hospital of Leganés (Madrid, Spain). Data retrieval and handling were performed following ethical norms of the Severo Ochoa Hospital. Neonates were started on gentamicin according to the discretion of the attending neonatologist for suspected or culture-proven infection including bacterial sepsis, pneumonia or necrotizing enterocolitis.

Newborns were divided into two groups. The first group was called the 'population group' and consisted of 200 premature neonates admitted to the neonatology unit of the Severo Ochoa Hospital of Leganés who received gentamicin as part of their treatment for suspected infectious disease. At the time of serum concentration measurements all newborns were less than 37 weeks of GA and less than 30 days of postnatal age (PNA). This group was used to build the population model.

The second group was the 'validation group'. This validation group consisted of 50 new preterm newborns and was used to verify the predictive performance of the population group.

Comprehensive gentamicin dosing history, including date of infusion, doses and infusion time, was collected from the neonatology nurse card. Serum sampling date, time and assay concentration were also recorded. Individual information about neonates included anthropometric data [birth weight (BW), actual weight, height and cranial perimeter], neonatal age (postnatal and gestational) and gender. Laboratory data collected included serum creatinine and pH. The serum creatinine concentration (S_{CR}) was used to estimate the glomerular filtration rate (GFR) according to the formula given by Brion *et al.*:[15] GFR = $K \times \text{length}/S_{CR}$. K has a value of 0.45 for term infants whose weight is appropriate for GA and 0.33 for low-BW infants.

The following pertinent neonatal laboratory and clinical data were retrospectively recorded when available: 1 and 5 min Apgar scores, phototherapy, mechanical ventilation, concurrent treatment with sympathomimetic amines (dobutamine or dopamine), furosemide, indometacin, fentanyl, phenobarbital, pancuronium and total parenteral nutrition.

Gentamicin administration

Gentamicin was administered by means of IVAC® syringe pump (IVAC corp., USA). Doses were given as intravenous infusions over 20 min. All doses and times of administration were recorded. Gentamicin administered before 1996 was through conventional dosage of 2.5 mg/kg every 18, 24 or 36 h. After 1996 an extended interval regimen was performed (Table 1).

Serum concentrations

Serum sampling date, time and corresponding concentration were appropriately recorded. Peak SGC were collected at least 1 h after beginning the infusion. Trough SGC were obtained just before administering a new gentamicin dose. Blood samples were obtained 24 h or more after the first dose was given.

Blood for serum drug concentration measurements was drawn immediately prior (trough) to and ~30 min after (peak) the end of the gentamicin infusion.

The number of measurements of SGC per patient ranged from 1 to 4. In most patients two measurements (peak and trough) were performed as part of routine therapeutic drug monitoring during one hospitalization event. Because blood samples were obtained in the usual routine no informed consent was necessary in the study. All relevant demographic and medication details were also recorded.

A total of 417 gentamicin measurements were obtained for the population group of patients and 109 measurements were obtained for the validation group.

Analytical technique

All SGC were determined on a routine basis by fluorescence polarization immunoassay (Abbott TDX, Abbott Park, IL, USA). The concentration range was 0.5–10 mg/L with a coefficient of variation of 1.41% at a concentration of 4 mg/L. The intra- and inter-assay errors of the method were 4.3% and 5.3%, respectively.[16]

Table 1. Dosage regimens used in the neonatal population after 1996

Gestational age (weeks)	Dosage
<32	4 mg/kg/48 h
32–37	4 mg/kg/24 h or 36 h
>37	4 mg/kg/24 h

Data analysis

All concentration-time data were analysed simultaneously by non-linear regression analysis using the computer program NONMEM (version v), which has been developed by Beal and Sheiner,[17] with FO method.[18] A mixed-effects regression model was used to estimate the population mean and variance of the pharmacokinetic parameters. In addition, NONMEM is a useful instrument to search for factors that may influence the parameters. Effectively, the influence of covariates can be assessed by incorporating regression relations of the pharmacokinetic parameters on these covariates within the pharmacokinetic model.

To find the best model that fits our data we implemented a stepwise procedure previously used by Aarons *et al*.[19] for estimating the population pharmacokinetics of tobramycin.

Model building was performed in three steps using a simplification of the general procedure described by Mandema *et al*.:[20] (i) choice of the basic pharmacokinetic model; (ii) evaluation of the influence of covariates; and (iii) choice of the residual error model.

Choice of the basic pharmacokinetic model. This model is characterized by simple description of the pharmacokinetic parameters without establishing a relationship between them and clinical covariates. Because aminoglycosides show a biphasic elimination, one- and two-compartment open models with first-order elimination without including any covariates were compared applying ADVAN1 TRANS2 and ADVAN3 TRANS4 subroutines, respectively. In both analyses, an exponential error model for both intra- and inter-individual variabilities was assumed.

Proportional inter-individual variability models were applied for CL and Vc as follows:

$$\mathrm{CL} = \mathrm{TVCL}(1 + \eta_{\mathrm{CL}})$$
$$\mathrm{V_C} = \mathrm{TVVC}(1 + \eta_{\mathrm{Vc}})$$

where TVCL and TVVC are the typical values of CL and Vc predicted under the regression model, and η terms are random variables with mean zero and variances ω_1^2 and ω_2^2, respectively. When modelled in this way, ω represents the estimate of the coefficient of variation (CV) of the parameter in the population.

Residual intra-individual variability was modelled with a proportional error model as follows:

$$\mathrm{Cobs},\ ij = \mathrm{Cpred},\ ij(1 + \varepsilon ij)$$

where Cobs, *ij* and Cpred, *ij* represent the *i*th observed and predicted plasma gentamicin concentrations in the *j*th patient, respectively. εij corresponds to the deviation between observed and predicted concentrations being called random intra-individual variability, and it is distributed with mean zero and variance σ^2. Intra-individual variability accounts for all other sources of residual error, such as model misspecification, reported time of dosing, reported time of sampling and analytical errors.

In this phase of the process, mean values of the pharmacokinetic parameters and an estimate of the predictable variability in terms of inter-individual and residual errors were obtained.

Evaluation of the influence of covariates. After selecting the most adequate pharmacokinetic model, a model-building procedure was carried out, in which fixed effects likely to influence the pharmacokinetic parameters of gentamicin were gradually included in the model. Initially, birth and actual body weight, GA, PNA and $\mathrm{CL_{CR}}$ were included as main variables in the regression models after examining for trends the scatter plots of pharmacokinetic parameters against each covariate. Covariates selected were incorporated one by one in the population model in both linear and non-linear ways, including log-transformation.

The regression model was developed using the forward inclusion-backward elimination method. In order to choose among models, goodness of fit was evaluated according to the following criteria:

- Differences in the minimum value of the objective function (OBJ) produced after the addition of a new factor in the regression model. This function is minimized by the NONMEM program in order to estimate the model parameters. This difference corresponds to the log-likelihood ratio and it is asymptotically χ^2 distributed. The accepted level of significance was a difference of 7.9 associated with a P value of <0.005 (1 degree of freedom).
- Decreases in inter- or intra-individual variabilities.
- Visual examination of the scatter plots using weighted residual errors, which are calculated as the difference between model-predicted concentrations and measured values expressed as population standard deviation units.[21,22]
- A full model was determined when no additional improvement seemed possible. Only covariates showing a significant contribution were considered in the final model. At the end of the analysis, all patient characteristics with influence on the pharmacokinetic parameters were re-evaluated by comparing the full model (including all the factors) with a regression model from which one of the factors was deleted (backward elimination).

Choice of the residual error model. Once the final structural model was selected, the shape of the intra-individual error distribution was analysed by plotting the individual weighted residual errors versus the individual concentration predictions, both computed by means of the individual Bayes estimates of the population pharmacokinetic parameters. Additive and proportional error distributions were compared.

Validation

In a separate group of 50 patients, blood for serum drug concentration measurements was drawn immediately prior to (trough) and ~30 min after (peak) the end of the gentamicin infusion. Knowing the drug-dosing history, time of sampling and patient characteristics with proven influence on gentamicin pharmacokinetics, predictions of SGC and their standard deviation were made and compared with the measured SGC. With a *t*-test we evaluated whether the mean of the standardized predictions errors (SPE) (i.e. the difference between observed and predicted SGC divided by the standard deviation) was significantly different from zero. If the regression model is correct and the parameter estimates are unbiased, the mean value of SPE (MSPE) and its standard deviation ($\mathrm{SD_{SPE}}$) should be close to zero and unity, respectively.

Design of dosing regimen

Once the population pharmacokinetic study was performed, we could use the regression model and the estimates of the pharmacokinetic parameters to predict the average and the variability of SGC in patients under different dosing schemes. For this, we searched for a dosage regimen that guaranteed peak SGC ranging between 8 and 12 mg/L and trough SGC below 1 mg/L. Target peak levels were set around 10 times the MIC for the infecting microorganism because of the possibility of emergence of resistance. The MIC for the most important Gram-negative pathogen *Escherichia coli* is 1 mg/L, so target peak levels must lie around 8–12 mg/L.

Table 2. Mean demographic data for the 'population' and 'validation' groups

Variable	Population group (n = 200) mean ± SD	Validation group (n = 50) mean ± SD
GA (weeks)	32.19 ± 2.97	32.62 ± 3.07
PNA (days)	5.49 ± 5.41	5.17 ± 3.77
BW (kg)	1.68 ± 0.63	1.80 ± 0.67
M/F	130/70	34/16

GA, gestational age; BW, weight; PNA, postnatal age; M, male; F, female.

Table 3. Pharmacokinetic parameters for the 'population group' (n = 200)

Parameter	Mean estimate (SE)
Clearance (CL)	0.0674 L/h (0.003)
Central volume (Vc)	0.252 L (0.011)
Intercompartmental clearance (Q)	0.307 L/h (0.019)
Peripheral volume (Vp)	1.35 L (0.151)
Between-subject variability in CL (ω^2_{CL})	0.181 (0.097)
Between-subject variability in Vd (ω^2_{Vd})	130 (55)
Residual unexplained variability (σ^2)	0.133 (0.025)

SE, standard error.

Results

Demographics

Data from 235 neonates were entered into the study. Thirty-five patients were discarded because serum creatinine data (S_{CR}) were not available. From the group of 200 neonates, a total of 417 SGC were available. The population consisted of 130 males and 70 females. The patients had an average GA of 32.19 ± 2.97 weeks and BW of 1.68 ± 0.63 kg. Other demographics are described in Table 2.

Basic pharmacokinetic model

Our basic population model was a one-compartment open model with proportional inter-individual variability associated to CL and Vd (CL = θ_1; V = θ_2). Application of a two-compartment open model produced a decrease in the OBF of 318 points when compared with the one-compartment model. This difference in the OBF corresponds to a P value <0.0005 if χ^2 distribution is assumed. Accordingly, a two-compartment model was used for the rest of the analysis. Residual variability was initially modelled as proportional. The pharmacokinetic parameters estimated without including any covariates are summarized in Table 3.

Influence of covariates

The evolution of the models from the simplest one (basic) to the full model is shown in Table 4. In the case of the basic model, clearance (CL) as well as central and peripheral volumes of distribution (Vc and Vp) were initially assumed to be the same for all individuals (model 1). Representation of weighted residuals (WRES) from model 1 versus BW, PNA, GA and CL_{CR} showed a marked bias, indicating poor goodness of fit of this basic model. Bias was greater with BW than with the other predictors, indicating that this covariate should be introduced in the model. Bias between BW and WRES is illustrated in Figure 1(a). BW was introduced in CL, Vc and Vp as described in model 2 but a plot of WRES versus BW also showed a bias between both variables. For this reason, BW was added again in the clearance equation (model 3). Graphic analysis showed that no obvious pattern in the plot of WRES versus BW (Figure 1b) was obtained.

GA was introduced as a covariate in model 2 instead of BW but no improvement in OBJ or inter-individual variability was seen. For this reason, BW was the best single estimator of both gentamicin clearance and volume of distribution in our population. The scatter plot showed no bias between WRES and GA but a clear pattern with CL_{CR} and PNA resulted. The addition of estimated CL_{CR} (model 4) and PNA (model 5) significantly influenced gentamicin clearance.

No model improvements were obtained when the following categorical variables were incorporated to the clearance: sex, low BW (≤1.5 kg), Apgar score at 5 min <5 and treatment with sympathomimetic amines.

Table 4. Selection of the best pharmacostatistical models for population pharmacokinetics of gentamicin in premature newborns

Model	Description	OBJ	DOBJ	P value
1	CL = θ_1 Vc = θ_2 Q = θ_3 Vp = θ_4	940		
2	CL = θ_1 * BW Vc = θ_2 * BW Q = θ_3 Vp = θ_4 * BW	578	362	<0.005
3	CL = θ_1 * BW^2 Vc = θ_2 * BW Q = θ_3 Vp = θ_4 * BW	557	383	<0.005
4	CL = (θ_1 * BW + θ_4 * CL_{CR}) * BW Vc = θ_2 * BW Q = θ_3 Vp = θ_4 * BW	466	474	<0.005
5	CL = (θ_1* BW + θ_5 * CL_{CR}) * BW + θ_6*PNA Vc = θ_2 * BW Q = θ_3 Vp = θ_4 * BW	443	497	<0.005

BW, body weight; CL, gentamicin clearance; CL_{CR}, estimated creatinine clearance (mL/min/1.73 m^2); OBJ, minimum objective function; DOBJ, difference in OBJ; PNA, postnatal age (days); θ, regression parameters estimated by NONMEM; Vc, volume of the central compartment; Q, intercompartmental clearance; Vp, volume of the peripheral compartment.

Validation

From the information on dosing history and patient characteristics of a group of 50 new preterm neonates, predictions of the SGC

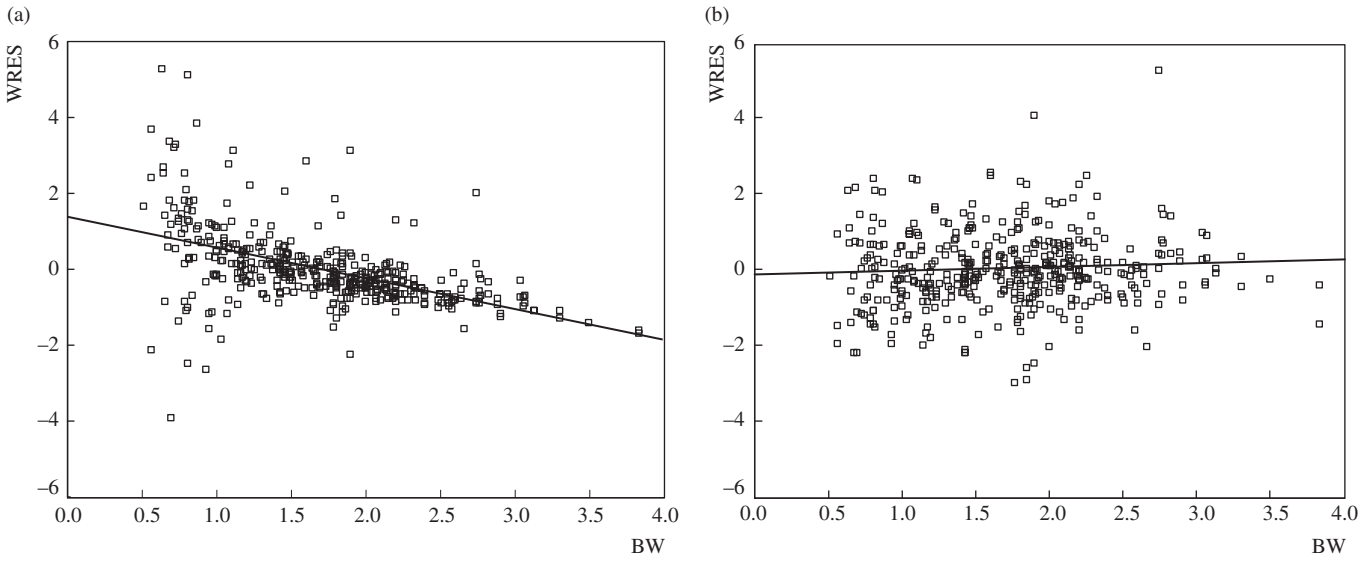

Figure 1. Scatter plot of weighted residuals (WRES) versus body weight (BW) for the basic model (a) and for the intermediate model where BW was introduced as covariate (b).

Table 5. Mean standardized prediction errors (MSPE), their standard deviations (SD_{SPE}) and confidence limits estimated for the validation population

Gentamicin concentration	MSPE	SD_{SPE}
Trough	0.026 ± 0.308	1.072 ± 0.650
	(–0.282:0.334)	(0.422:1.722)
Peak	0.063 ± 0.340	1.018 ± 0.233
	(–0.277:0.367)	(0.785:1.251)

for both peak and trough concentrations and their standard deviations were calculated with our population pharmacokinetic model with all covariates included and were compared with the real observations to determine the predictive performance of the model. To do so, for both peak and trough concentrations, we have used the SPE, defined as the difference between the observed (Cobs) and the predicted (Cpred) concentrations divided by the estimate of the standard deviation in the predicted values[23] (SDpred):

$$\mathrm{SPE} = (\mathrm{Cobs} - \mathrm{Cpred})/\mathrm{SDpred}$$

According to this equation, if the regression model is correct and the parameter estimates are unbiased, the mean value of SPE and its standard deviation should be close to 0 (*t*-test for statistical significance) and unity, respectively. According to our results (Table 5), SPE was found to have a mean value of 0.063 and 0.026 for peak and trough concentrations, respectively, and the SD_{SPE} values were 1.018 (peak concentration) and 1.072 (trough concentration), which are close to the expected value of 1. Confidence limits for mean SPE and their standard deviations were calculated by bootstrapping techniques,[24] using nboot = 100. Concentration was the unit bootstrapped.

Figure 2 shows the scatter plot of observed versus predicted gentamicin concentrations (trough and peak concentrations, including the identity line) after applying the final population model estimates to the validation population. As can be seen, an excellent correlation between observed and predicted concentrations was obtained.

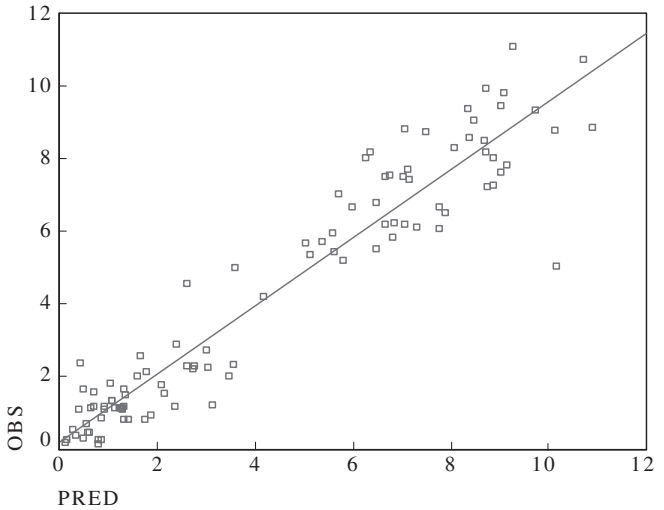

Figure 2. Scatter plot of observed versus predicted gentamicin concentrations (trough and peak concentrations, including the identity line) after applying the final population model estimates to the validation population.

In the validation population, mean GA was 32.62 ± 3.07 weeks, mean PNA was 5.17 ± 3.77 days and mean BW was 1.80 ± 0.67 kg (Table 2). Non-statistically significant differences were found between both the population group and the validation group for the mean and variance of GA, PNA and BW.

Final model

After completing the validation of our model, we pooled both datasets (the population and validation groups) and estimated the regression parameters based on the best model. The values

Table 6. Final parameter estimates for gentamicin in the neonatal population

Parameter	Meaning	Mean estimated value ± SE	Estimation variability (%)
θ_1	coefficient for BW in CL (kg)	0.00582 ± 0.00207	
θ_2	coefficient for BW in Vc (kg)	0.484 ± 0.00890	
θ_3	coefficient for Q (L/h)	0.0157 ± 0.00425	
θ_4	coefficient for Vp (L)	1.25 ± 0.360	
θ_5	coefficient for CL_{CR} in CL (mL/min/1.73 m^2)	0.00106 ± 0.000209	
θ_6	coefficient for PNA in CL (days)	0.00131 ± 0.000494	
ω_{CL}	between-subject variability in CL		24.39
ω_{Vd}	between-subject variability in Vd		18.79
σ	residual unexplained variability		17.05

θ, regression parameters estimated by NONMEM; BW, body weight; CL, gentamicin clearance; Vc, volume of the central compartment; Q, intercompartmental clearance; Vp, volume of the peripheral compartment; CL_{CR}, creatinine clearance; PNA, postnatal age.

Table 7. Mean demographic data for the 'population' and 'validation' groups

GA (weeks)	BW (kg)	Dosage
<32	0.75–1.5	5 mg/kg/48 h
32–34	1.25–2.0	4 mg/kg/36 h
>34	1.75–2.50	4 mg/kg/24 h

GA, gestational age; BW, weight.

estimated for the pharmacokinetic parameters of gentamicin in this group of premature neonates are summarized in Table 6.

Dosing recommendations

The estimation of the population pharmacokinetic parameters that describe the dose–plasma concentration relationship and its variability in patients is very useful for development of dosage recommendations. NONMEM was used to perform simulations in order to obtain peak plasma concentrations ranging from 8 to 12 mg/L and trough concentrations below 1 mg/L. Simulations have been performed using as CL_{CR} the mean values obtained from our population classified by GA (good correlation was obtained between both parameters). In Table 7 the recommended dosing regimens obtained for premature neonates with different GAs and body weight are given.

Discussion

In the present study we have obtained population pharmacokinetic parameters of gentamicin in a group of 200 premature neonates admitted to our neonatology unit. The estimation has been performed with a sparse number of samples per individual collected during routine clinical practice. The large size of the sample studied and the fact that young premature babies may belong to a separate population within a heterogeneous population due to renal immaturity give relevance to the study performed. For instance, other population studies made in premature neonates included populations of only 34 prematures,[11] 84 preterm infants,[25] 71,[12] or a more recent study performed in 177 subjects including preterm but also term neonates.[26]

In our population, one- or two-compartment open models can adequately describe the time course of SGC. Our protocol precluded sampling in the early distributional phase and most samples were drawn 30 min after the end of gentamicin infusion. For this reason, a one-compartment pharmacokinetic model could adequately describe the routine data in our population. Since the difference in the OBJ between both models was 448, the two-compartment model was found to significantly better describe our data than the one-compartment model. To date and due to its simplicity, most of the published population pharmacokinetic analyses of gentamicin in neonates have applied one-compartment open models,[7–10,27] despite the fact that gentamicin pharmacokinetics shows a bi-exponential decay.[28] For instance, in a population analysis performed with netilmicin, a gentamicin-related aminoglycoside, it was demonstrated that a two-compartment model performed better.[29]

Neonates have reduced clearance and increased volume of distribution of aminoglycosides compared with the adult population, with considerable inter-patient variability. Estimated absolute gentamicin clearance in our population group was 0.0674 L/h. Assuming a mean body weight of 1.69 kg, the mean of relative gentamicin clearance exhibited a value of 0.039 L/h/kg. This value is lower than 0.051 L/h/kg, which was cited by Vervelde *et al.*[11] in preterm neonates. This difference could be due to the fact that in his population neonates with GA of <38 weeks (n = 34) were included whereas our group of newborns had GA <37 weeks (n = 200).

Population pharmacokinetics is a very useful instrument to provide quantitative inspection of the influence of several pathophysiological and clinical covariates on the pharmacokinetic profile of drugs. In our study, the main physiological variables that may influence gentamicin disposition in premature neonates have been investigated: BW, PNA and CL_{CR}. Exploratory graphic analysis showed that BW was highly correlated with WRES. A similar pattern was observed for the other physiological variables although the correlation observed was lower. For this reason, BW was the first predictor included in the model. Total body clearance (CL) showed a strong association with BW. Two additional factors found to influence CL were PNA and CL_{CR}. Moreover, volumes of central (Vc) and peripheral (Vp) compartments were also related to BW.

Contrary to our study some authors have found no pattern in the plot of WRES versus PNA.[8,9] This fact can be explained by

the small range presented by this variable in these studies where most patients were within their first week of life. However, when the population presents a wider range of days of life, PNA can be introduced in the model, as demonstrated by Grasela *et al*.[25] In that study the population included patients with PNA ranging from 2 to 85 days.

Gentamicin is predominantly excreted by the kidneys through glomerular filtration, making CL_{CR} one of the important factors characterizing gentamicin kinetics. A significant correlation has been demonstrated between gentamicin CL and CL_{CR}.[8] For this reason, it is reasonable that CL_{CR} acts as an important covariate in the gentamicin CL equation. In our study, both S_{CR} and CL_{CR} have been used during the model-building process, finding that CL_{CR} is a better covariate.

The above models show that optimal characterization of gentamicin pharmacokinetics depends on actual BW, GA, PNA and CL_{CR}. However, of these four fixed-effects covariates, BW is by far the most important one being the single best estimator of gentamicin clearance. This is because none of these factors was superior to BW nor improved the fit based on BW alone.

For dosage recommendations, the predictive performance of the population pharmacokinetic model developed for gentamicin was tested using the SPE method, which takes into account variability and correlation of observations within an individual.[30] The validity of the parameter estimates and the regression model derived in the current study was confirmed in a separate group of 50 neonates. No significant bias was found for the prediction of the serum concentrations (peak and trough values) in our validation group as can be observed by the results obtained for SPE and SD_{SPE} (Table 5).

Simulations performed with NONMEM were used to determine dosage recommendations. Mean values of CL_{CR} obtained from our population (classified by GA) were utilized. For this reason CL_{CR} is included in Table 7, in which dosing recommendations are summarized. Dosing recommendations given will therefore be applicable for normal CL_{CR} values (15–30 mL/min). For lower CL_{CR} values, which imply severe renal impairment, we recommend monitoring SGC 24 h after administration (dosage chosen as indicated in the Table) and, if necessary, proceed to dosage readjustment.

With respect to PNA, a covariate that was included in our final model, when performing dosage simulations it was found that its influence was covered by the modifications of BW with respect to GA.

Conclusions

Gentamicin exhibits two-compartment kinetics in the neonate where BW, CL_{CR} and PNA can be included as covariates in order to determine individual pharmacokinetic parameters and thus making it possible to individualize dosage regimens. The appropriate dosing regimens given in accordance with the characteristics of the patients are 5 mg/kg/48 h and 4 mg/kg/24 or 36 h for neonates <32 weeks and ≥32 weeks of GA, respectively.

Transparency declarations

None to declare.

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