Pharmacokinetic basis for the use of extended interval dosage regimens of gentamicin in neonates

José M. Lanao1*, Mª Victoria Calvo2, José Antonio Mesa2, Ana Martín-Suárez1, Mª Teresa Carbajosa3, Francisco Miguelez1 and Alfonso Domínguez-Gil1,2

Departments of 1Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, and 2Pharmacy Service; 3Neonatology Unit, Pediatrics Service, University Hospital, University of Salamanca, Salamanca, Spain

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Objectives: To analyse the pharmacokinetic basis for the use of extended-interval dosage regimens of gentamicin in neonates using population pharmacokinetics.

Patients and methods: The population pharmacokinetics of gentamicin was studied retrospectively in a population of 113 neonates divided into two groups: one for computing the population model (n = 97) and another for validation (n = 36). A one-compartment pharmacokinetic model and non-linear mixed-effects modelling were used to assess the population pharmacokinetic model.

Results: Weight (W) and postnatal age (PA) were the covariates that influenced the pharmacokinetic parameters of gentamicin. The final population model obtained was: distribution volume, V (L) = 0.636 × W (kg)0.852; clearance, Cl (L/h) = 0.032 × W (kg)1.482 + 0.0024 × PA (days). The predictive performance of the model in the population validation was adequate for clinical purposes. The optimized population model allowed us to simulate gentamicin serum levels and their variability, in this kind of patient, when extended-interval dosage administration regimens were implemented.

Conclusions: According to our pharmacokinetic population model, initial doses of gentamicin of 10 mg/kg, and dosage intervals between 36–48 h, appear to be appropriate to achieve target peak and trough serum levels of 15–20 and <0.5 mg/L, respectively, when extended-interval dosage regimens are implemented in newborns. The half-life of gentamicin in premature babies of very low weight and gestational age <31 weeks is long. Thus, to achieve serum concentrations in the 1–10 mg/L range, the use of dosage regimens of 5 mg/kg at 36–48 h dosage intervals seems suitable.

Keywords: population pharmacokinetics, extended-interval dosage regimens, aminoglycosides

Introduction

Gentamicin, in association with other antibiotics, is often used in premature babies and newborn patients for the treatment of presumed neonatal sepsis.1,2 In neonates, as in other patients, it is crucial promptly to set up a suitable dosage regimen that will afford optimum serum concentrations from the start of treatment.3 However, dosing with this antibiotic is hampered by the inter- and intra-individual variability in the kinetic behaviour of gentamicin in this type of patient. Different factors and developmental variables may alter the dosage requirements of gentamicin, such as birthweight, gestational age (GA), post-natal age (PA) and renal function, among others.4,5 In view of the changes that occur in the pharmacokinetics of aminoglycoside antibiotics, some authors use subpopulations based either on GA or the birthweight of the patient when a maximum a posteriori (MAP) Bayesian approach is used for pharmacokinetic and dosage individualization.6

Currently, the dosage regimens of aminoglycosides in this kind of patient are based either on conventional administration (8–12 h dosage interval) or on extended-interval dosage administration (once daily). Nevertheless, there is no consensus concerning current criteria for gentamicin dosing regimens in neonates.6 In patients with high distribution volumes and prolonged gentamicin serum half-lives, as in the case of neonates, the standard guidelines for extended-interval dosage administration as applied to adults are not applicable, and specific pharmacokinetic considerations are required for such situations.

*Corresponding author. Tel: +34-923-294536; Fax: +34-923-294515; E-mail: jmlanao@usal.es
The aim of the present work was to characterize the population pharmacokinetics of gentamicin in neonates, in order to determine the kinetic profile of this drug when extended-interval dosage regimens are used and to facilitate a MAP Bayesian approach in clinical practice.

Patients and methods

Patients
A retrospective review of pharmacokinetic data of gentamicin was conducted in 133 newborn patients admitted during 1999–2003 in the Neonatology Unit of the University Hospital in Salamanca (Spain). These data were obtained as part of our routine therapeutic drug monitoring (TDM) of aminoglycoside therapy in paediatric patients. They were suffering from severe infective processes, proven (11%) or suspected, and were being treated with gentamicin either alone or in combination with other antibiotics. Patients were included if their postnatal age was ≤30 days, and if data were available for the following: at least two serum gentamicin concentrations (2 and 24 h), sampling times, GA, PA, weight and dosing schedule. The patients were divided into two groups: one for building the population model (n = 97) and the other for validation (n = 36). Table 1 summarizes the patients’ characteristics. Plasma creatinine levels were not included because in the first 2 weeks of life this parameter does not reflect a patient’s renal function.5

Gentamicin dosing and sampling procedure

Gentamicin was administered to patients suspected of suffering from infection due to Gram-negative microorganisms, regardless of whether this had been confirmed in the antibiogram.

Gentamicin was dispensed in the form of an intravenous (iv) infusion of a 1 mg/mL solution over 30–60 min at GA-dependent doses and intervals. In patients with GA <31 weeks, initial doses of 5 mg/kg at dosage intervals of 36 h (GA 26–30 weeks) or 48 h (GA <26 weeks) were used to target peak and trough levels of 7–10 and 1–2 mg/L, respectively. In patients with GA >31 weeks, initial doses of 10 mg/kg at 36 h dosage intervals (term newborns) or 12 mg/kg at 48 h dosage intervals (GA 31–38 weeks) were used to produce the desired peak and trough levels of 15–20 mg/L and <0.5 mg/L, respectively. These dosage recommendations were designed on the basis of the pharmacokinetic parameters of gentamicin published previously.7

Two blood samples (2 and 24 h after the end of the infusion) for drug levels were collected routinely by venipuncture after the administration of the second dose of the treatment. We monitored intermediate levels, bearing in mind that trough levels could be below the sensitivity level of the analytical technique. Serum gentamicin levels were measured by fluorescence polarization immunoassay AXYM (Abbott Laboratories, Chicago, IL, USA). The sensitivity limit of this method is 0.3 mg/L, the variation coefficient <5% and the calibration range 0.3–10 mg/L. On the basis of these levels, individual adjustments of the dose or dosage interval to achieve target levels were performed by a computer-assisted MAP Bayesian approach (Abbottbase pharmacokinetic systems; Program PKS; Abbott Laboratories, Chicago, IL, USA).

Population pharmacokinetic analysis

For the population pharmacokinetic analysis, the serum levels data were fitted to a one-compartment kinetic model with first-order elimination. The pharmacokinetic parameters of the model were clearance (Cl) and the apparent distribution volume (V).

The basic structural model for the pharmacokinetic parameter (P) initially considered was $P = \theta$, where $\theta$ represents the fixed-effect parameter of the structural model to be estimated. Selection of a final population model was accomplished by evaluating the incorporation of continuous covariates in different linear and non-linear ways, according to the following general equation:

$$P = \sum_{i=1}^{N} \theta_{2i-1}.\text{Cov}_{i}^{b}$$

where $P$ represents the pharmacokinetic parameter, and $\text{Cov}_{i}$ the $i^{th}$ covariate included. The covariates analysed were weight, GA, post-conceptional age and PA.

The statistical model used to describe intersubject variability in the clearance and apparent distribution volume of gentamicin was proportional:

$$P_{j} = P.(1 + \eta_{p})$$

Table 1. Demographic and clinical data of the patients included in the population-based study

<table>
<thead>
<tr>
<th></th>
<th>Model building</th>
<th>Model validation</th>
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<tbody>
<tr>
<td>$n$</td>
<td>97</td>
<td>36</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>33.24 ± 4.15 (24–39)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31.80 ± 4.82 (25–40)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GA &lt; 31 weeks (n%)</td>
<td>25/26</td>
<td>17/47</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>1.93 ± 0.84 (0.6–4.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.75 ± 0.91 (0.6–3.8)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PA (days)</td>
<td>4.61 ± 4.74 (1–26)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.60 ± 1.61 (1–10)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>APGAR&lt;sup&gt;5&lt;/sup&gt;</td>
<td>9 (3–10)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>8 (5–10)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gentamicin dose (mg/kg/day)</td>
<td>5.11 ± 1.53 (1.64–7.89)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.59 ± 1.54 (3.17–8.44)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Gestational age.
<sup>b</sup>mean ± s.d. (range).
<sup>c</sup>post-natal age.
<sup>d</sup>APGAR score 5 min after birth.
<sup>f</sup>median (range).
where $P_j$ is the individual pharmacokinetic parameter; $P$ represents the population parameter to be estimated, and $\eta_j$ the individual variations from the population value.

To describe the residual error in the concentration, an additive model was chosen:

$$C_j = C + \varepsilon$$

where $C_j$ is the observed gentamicin concentration and $C$ is the corresponding concentration predicted by the pharmacokinetic model; $\varepsilon$ represents the residual errors that describe the differences between the measured and predicted concentrations.

The fixed and random parameters of gentamicin were estimated using non-linear mixed-effects modelling, as implemented in the WINNONLIN software package (Pharsight Corp., Mountain View, CA, USA) bundled with the Compaq Visual Fortran compiler (Compaq Computer Corp., Houston, TX, USA). The mixed-effects modelling estimation was accomplished using a first-order estimation method.

Statistical comparison of different population models was based on a $\chi^2$ test of the difference in the objective function. The final regression model was developed using the forward inclusion and backward elimination technique. Each covariate was incorporated stepwise, either linearly or non-linearly, into the basic population model (forward inclusion). Changes in the objective function upon addition of a covariate approximated the $\chi^2$ distribution with 1 degree of freedom. A decrease in the objective function ($P < 0.05$) was considered significant during the forward inclusion analysis. The full model was created by incorporating all covariates, which led to a significant decrease in the objective function. The objective function of the full model was used to test the effect of removing each covariate (backward elimination). Only covariates showing an increase in the objective function ($P < 0.01$) upon removal from the full model were retained. The goodness of fit of each analysis run was also assessed by the examination of scatterplots of predicted versus measured gentamicin concentrations, weighted residuals versus dependent and independent variables, the variation coefficient of the mean parameter, changes in the estimates of interindividual and residual variability resulting from the addition or deletion of a covariate and Akaike’s Information Criterion.8,9

Using the final population model, individual estimates of the pharmacokinetic parameters were obtained based on fixed-effects population parameters and subject-specific random effects.

The final population model obtained was used to predict a priori serum gentamicin concentrations in the validation population. Predicted peak and intermediate serum gentamicin concentrations were compared with measured concentrations to determine the predictive performance of the final model. Correlation analysis, standardized mean prediction error and standard deviation of standardized mean prediction error were used. The predictive performance of our population model (model 1) was compared with two other previously published population pharmacokinetic models of gentamicin in neonates using mixed-effects modelling (model 211 and model 315).

The other models tested were the following: Model 211: $Cl (L/h) = 0.120 \times [weight (kg)]^{0.31} \times [GA (weeks)] \times P$ (where $P = 1.2$ for girls and 1.0 for boys); $V (L) = 0.472 \times [birth\ weight (kg)]$.

Model 315: $Cl (L/h) = 0.001 \times [birth\ weight (kg)] \times [GA (weeks)] \times [weight (kg)]^{0.65} \times [post\ natal\ age (days)] \times 0.852 + 0.032$. $V (L) = 0.429 \times [weight (kg)]^{0.482} + 365.12$.

### Results

Initial evaluation of the basic pharmacokinetic model ($Cl = \theta_1$, $V = \theta_2$) combining the different error models pointed to the superiority of the proportional error model for estimating interindividual variability and of the additive error model for estimating residual variability. Accordingly, both variability error models were used in all subsequent analyses. Patient covariates were tested individually for $Cl$ and $V$ in order to select a final population model. Table 2 shows the fixed- and random-effects parameters and the objective function value obtained with the basic and final population models, respectively. Table 3 shows the population parameter estimates and associated percentage relative standard errors of the final model. According to the final population model obtained, weight influenced, in a non-linear way, the apparent distribution volume. It also influenced, in a non-linear way, together with PA the gentamicin serum clearance. Thus weight and PA are the covariates with a statistically significant effect on the population pharmacokinetics of gentamicin in neonates.

Figure 1 shows the plot of the observed versus predicted gentamicin serum concentrations from the basic to the final model tested.

GA and weight influenced the pharmacokinetic parameters of gentamicin in neonates: both clearance and apparent distribution volume. Figure 2 shows the potential correlation obtained between weight and the GA of the patients included in the study, showing the strong covariance between both covariates. Moreover, in the population model building process, a better goodness of fit was obtained using weight instead of GA.

### Table 2. Basic and final population pharmacokinetic models of gentamicin tested in the overall population of neonates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basic model</th>
<th>Final model</th>
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<tbody>
<tr>
<td>$V (L)$</td>
<td>0.959</td>
<td>0.636 x W (kg)$^{0.852}$ + 0.0024 x PA (days)</td>
</tr>
<tr>
<td>$Cl (L/h)$</td>
<td>0.127</td>
<td>0.032 x W (kg)$^{1.482}$</td>
</tr>
<tr>
<td>OF</td>
<td>618.22</td>
<td>365.12</td>
</tr>
<tr>
<td>Interindividual variability $\omega_1$: 33.1% (CV); $\omega_2$: 60.8% (CV)</td>
<td>$\omega_1$: 23.4% (CV); $\omega_2$: 23.7% (CV)</td>
<td></td>
</tr>
<tr>
<td>Residual variability $\sigma^2$: ± 3.941</td>
<td>$\sigma^2$: ± 0.342</td>
<td></td>
</tr>
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</table>

W, body weight; PA, post-natal age; OF, objective function.

### Table 3. Parameter estimates for the final population model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$</td>
<td>0.636</td>
<td>4.51</td>
<td>0.579–0.693</td>
</tr>
<tr>
<td>$\theta_2$</td>
<td>0.852</td>
<td>7.55</td>
<td>0.724–0.980</td>
</tr>
<tr>
<td>$\theta_3$</td>
<td>0.032</td>
<td>8.63</td>
<td>0.027–0.038</td>
</tr>
<tr>
<td>$\theta_4$</td>
<td>1.482</td>
<td>6.05</td>
<td>1.304–1.660</td>
</tr>
<tr>
<td>$\theta_5$</td>
<td>0.002</td>
<td>28.11</td>
<td>0.001–0.004</td>
</tr>
</tbody>
</table>

Interindividual variability: $\omega_1$: 23.4% (CV); $\omega_2$: 23.7% (CV); residual variability: $\sigma^2$: ± 0.342 mg/L.

CI, confidence intervals; $\theta$, population-specific pharmacokinetic parameter.

*Standard error of the estimate expressed as coefficient of variation (%).
Accordingly, GA was discarded in the final population model as a predictor variable.

The estimated population model allows prediction of gentamicin pharmacokinetics in the overall population of neonates. Figure 3 shows the surface plot using individual values established between the gentamicin clearance of the neonate with the weight and PA of the patient. As can be seen, a progressive increase in the neonate gentamicin clearance occurs, depending simultaneously on both covariates.

Table 4 shows the correlation analysis and the standardized mean prediction errors of the measured and predicted gentamicin serum concentrations obtained for the \textit{a priori} method in the validation patients for the three population pharmacokinetic models compared. The three models analysed had an acceptable performance as regards the prediction of gentamicin serum levels in neonates. However, a better predictive performance was obtained with our model; this could be attributed to an underprediction of the gentamicin distribution volume by the two models analysed in comparison with our own.

Figure 4 shows the linear relationship obtained between the individual estimates of the serum half-life of gentamicin and the GA of the patients.

Figure 5 shows the simulated gentamicin serum levels and 68% confidence intervals in two hypothetical newborns with weights of 1 and 3.5 kg and a PA of 3 days after administration of a dose of 10 mg/kg of gentamicin in a 0.5 h iv infusion.

**Discussion**

The results of the present study have allowed us to develop a simplified population pharmacokinetic model able to predict changes in the pharmacokinetics of gentamicin in the overall population of neonates. This population is characterized by high distribution volumes and long half-lives, with a strong dependence on patient weight. Other studies have reported similar results in neonates. In our study, the optimized population model allowed us to establish a potential relationship between both clearance and the apparent distribution volume of gentamicin and the weight of the patient, with a better prediction capacity of gentamicin pharmacokinetics in the overall neonate population. In such patients, other authors have also recommended the use of weight instead of GA as a predictive variable of clearance and the apparent distribution volume of gentamicin. The validation process carried out reveals the good predictive performance of our population model in the overall population of neonates.

The behaviour of gentamicin in this population allows one to evaluate the use of extended-interval dosage regimens in neonates from the pharmacokinetic perspective. In two recent reviews, in which once-daily dosing in infants was analysed, it
is reported that most authors use varying dosing intervals in the range of 24–48 h in newborns and premature infants, although extended-interval dosage regimens in neonates usually dose gentamicin every 24 h.\textsuperscript{18,19} Regarding the doses employed, most authors working with newborn infants with GA >29 weeks use doses between 2.5–5 mg/kg, with mean peak levels of 5.4–11.2 mg/L and mean trough levels between 0.8–1.7 mg/L being achieved.\textsuperscript{1–3,20–22} These dosage regimens achieve serum levels that resemble those obtained with the conventional dosage regimens in adults.

The pharmacological basis of extended-interval dosage regimens is to achieve levels that are \(\frac{C}{\text{MIC}}\) 8–10 times the MIC, so target peak levels must occur around 15–20 mg/L, increasing the post-antibiotic effect. Trough levels of <0.5 mg/L are desirable to guarantee the efficacy and safety of treatment.\textsuperscript{23} There are other published studies of extended interval-dosage regimens in paediatrics in which the peak and trough serum levels were >15 and <0.5 mg/L, respectively, these serum drug levels being similar to those obtained in adults with this kind of regimen, and the treatments were safe and effective.\textsuperscript{23,24}

In view of the pharmacokinetic behaviour of gentamicin in neonates—supported by our population model and characterized by high distribution volumes and long half-lives—for peak serum levels between 15–20 mg/L and trough levels <0.5 mg/L to be attained it is necessary to employ doses ≥10 mg/kg and dosage intervals >24 h. Figure 4 shows the correlation between the individual value of the half-life of gentamicin and the GA of the patients in our population. It may also be seen that the half-life of gentamicin reaches values >10 h in neonates with a very low weight and with a GA of <31 weeks, and thereafter decreases steadily until values of 5–6 h are attained in term newborns. The progressive evolution of the half-life of gentamicin with the GA or with the weight of the patient makes it necessary progressively to increase the gentamicin dosing interval up to 36–48 h in order to attain similar peak and trough serum levels. In adult patients, extended-interval dosage regimens of aminoglycosides with high peaks and intervals up to 48 h are used in patients with moderate renal impairment (\(\text{Cl}_{\text{CR}}\) 20–39 mL/min).\textsuperscript{25} The neonate population shows gentamicin serum half-lives that are very similar to those of adult patients with a moderate degree of renal impairment. As a result, as may be seen in Figure 5, for target peak serum levels between 15–20 mg/L and trough serum levels <0.5 mg/L of gentamicin to be reached in neonates—similar to those seen in adults with

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Correlation analysis} & \textbf{Peak (2 h)} & \textbf{intermediate (24 h)} \\
\hline
\textbf{Theoretical value} & intercept & slope & \(r^2\) & SMPE\textsuperscript{c} & SD\text{SMPE}\textsuperscript{c} & SMPE\textsuperscript{c} & SD\text{SMPE}\textsuperscript{c} \\
\hline
Model 1 & 0.353 & 0.945 & 0.968 & 0.09 & 1.13 & 0.12 & 0.74 \\
Model 2\textsuperscript{11} & -0.473 & 1.242 & 0.963 & -1.23 & 0.92 & 0.65 & 0.80 \\
Model 3\textsuperscript{12} & 0.903 & 1.140 & 0.957 & -0.24 & 0.67 & -0.85 & 0.69 \\
\hline
\end{tabular}
\caption{Predictive performance of the three gentamicin models tested in neonates}
\end{table}

\textsuperscript{a}Correlation coefficient.
\textsuperscript{b}Standardised mean prediction error.
\textsuperscript{c}Standard deviation of SMPE.

Figure 4. Correlation between serum half-life of gentamicin and GA of the patients \((\text{half-life (h)} = 21.832–0.397 \text{ GA (weeks)}, \ r = 0.793)\).

Figure 5. Simulated serum gentamicin concentrations and 68% confidence intervals using the final population model in a term newborn and in a premature infant following the administration of an iv dose of gentamicin of 10 mg/kg (0.5 h iv) to achieve target peak and trough serum levels of 15–20 mg/L and <0.5 mg/L, respectively.
extended-interval dosage regimens—the dosing intervals should initially range between 36–48 h. Nevertheless, the final adjustment of the interval may depend on the results of the monitoring of serum gentamicin levels.

From the pharmacokinetic point of view, most dosage recommendations in neonates based on the use of extended intervals and doses in the 3–5 mg/kg range provide peak and trough serum gentamicin levels similar to those obtained with conventional regimens used in adults and based on two to three daily administrations. The common practice of using fixed intervals of 24 h, especially in very low-weight and low GA neonates, may produce potentially toxic trough levels >2 mg/L.

In conclusion, the pharmacokinetic behaviour of gentamicin in neonates is characterized by high distribution volumes and long half-lives. In order to achieve peak serum levels—based on the concepts that support the benefit of extended-interval dosage regimens aimed at achieving higher peak/MIC ratios—initial doses of 10 mg/kg or higher, and dosage intervals >24 h, would be necessary in neonates with a GA of ≥31 weeks. However, in neonates with a GA of <31 weeks, characterized by half-lives of >10 h, dosage regimens of 5 mg/kg at 36–48 h dosage intervals would be appropriate. This would aim to reach trough and peak gentamicin serum concentrations in the range of 0.5–2 mg/L and 7–10 mg/L, respectively. Later monitoring (TDM) of serum gentamicin levels would use MAP Bayesian strategies on the basis of the population pharmacokinetic parameters. After adaptation of the model to typical TDM computer programs, such as PKS among others, this would permit adjustment of the dose and dosing interval to achieve the peak and trough serum levels of gentamicin associated with extended-interval dosage regimens.

References
