Pharmacokinetics of Penicillin G in Infants with a Gestational Age of Less than 32 Weeks[▽]

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The pharmacokinetics of penicillin G were studied in 20 preterm neonates with a gestational age of less than 32 weeks on day 3 of life by using a population approach performed with the nonlinear mixed effects modeling program NONMEM. The derived population estimates and the correlation matrix of these estimates were used to perform Monte Carlo simulations and obtain the probability of target attainment (PTA). The pharmacokinetics of penicillin G were best described by a two-compartment pharmacokinetic model. The population estimates of the central volume of distribution, the peripheral volume of distribution, the intercompartmental clearance, and the total body clearance were 0.359 ± 0.06 liter, 0.152 ± 0.03 liter, 0.774 ± 0.28 liter/h, and 0.103 ± 0.01 liter/h (mean $\pm$ standard error), respectively. The terminal half-life was 3.9 h. Clearance increased significantly with increasing birth weight. Assuming the percentage of time that the concentration of unbound drug remained above the MIC of 50% for preterm neonates, the susceptibility breakpoint based on a 100% PTA was ≤ 4 mg/liter, simulating the current dosing regimen of 50,000 U/kg every 12 h. This regimen is therefore adequate for the treatment of common infections in neonates on the third day of life.

Penicillins are important antimicrobial agents for the treatment of bacterial infections in newborn infants, with a high degree of clinical efficacy in eradicating common pathogens in combination with a high degree of safety. Because of a lack of evidence from randomized clinical trials in favor of any particular antibiotic or antibiotic regimen (24), penicillin G remains important among the antibiotics most commonly given to neonates for the treatment of presumed early neonatal sepsis.

Infectious complications during the immediate postnatal period are not uncommon and require prompt antibiotic treatment (1, 5, 26, 28). Differences in body composition and organ function can significantly affect the pharmacokinetics of drugs in neonates. In very premature neonates (i.e., neonates with gestational ages of less than 32 weeks), the disposition of antibiotics may differ from that in full-term neonates as a result of differences in absorption, distribution, biotransformation, and excretion (6, 17, 27). As a result, dose estimation on the basis of body size or allometric scaling may be inadequate. Specifically, in very premature neonates the processes of mat-

uration of the organs may influence the relevant pharmacokinetic parameters.

The efficacies of the penicillins are primarily correlated to the percentage of time that the concentrations of unbound drug remained above the MIC ($fT > MIC$) (9, 18, 30). In general, the therapeutic goal for the cure of infections caused by gram-positive organisms is an $fT > MIC$ of the antimicrobial of at least 40%, which corresponds to an in vivo static effect in animal studies (8). Studies showing a clear relationship between exposure and efficacy in premature neonates are not available. Because premature neonates must be regarded as immunocompromised, in our opinion it is reasonable that in this patient group the exposure should correspond to exposures that correlate to a 1- to 2-log drop in the numbers of CFU in various models and thus be bactericidal rather than bacteriostatic. Thus, for penicillins, this percentage should be at least 50% (11). Since the goal of treatment is to attain this target for every individual in the population, the dosing regimen in this age group should be defined by taking the interindividual variability in pharmacokinetics into account. Monte Carlo simulation (MCS) is a technique that is commonly used to determine the probability of achieving therapeutic concentrations on the basis of population pharmacokinetic parameter estimates and their measures of dispersion (3, 12, 13, 21–23). We investigated the pharmacokinetics of penicillin G and the adequacy of the dosing regimen in very premature neonates on the third day of life to allow us to construct a population pharmacokinetic model and to use the parameter estimates to

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perform MCSs with this specific age group. We then used that information to define the optimal dosing regimens.

MATERIALS AND METHODS

Patients and treatment. Preterm neonates with suspected or documented septicemia or invasive infections were eligible for this study. The neonates were hemodynamically stable (diuresis, >1 ml/kg of body weight/h; systolic and diastolic blood pressure above the third percentile, adjusted for gestational age), had a normal liver function, had not received inotropic or nephrotoxic drugs, did not have an intracranial hemorrhage beyond grade II, and had an indwelling arterial catheter for clinical purposes. The partial pressure of oxygen in arterial blood was kept at greater than 50 mm Hg or oxygen saturation was kept between 87 and 92%, and hematocrit values were maintained above 0.32 by packed erythrocyte transfusions. Neonates were excluded from the study if they had life-threatening illnesses or became hemodynamically unstable (systolic and diastolic blood pressure below the third percentile, adjusted for gestational age; diuresis, <1 ml/kg/h). Also excluded were infants with severe asphyxia, who were defined as having profound umbilical artery acidemia (pH <7.00), the persistence of an Apgar score of 0 to 3 for longer than 5 min, neonatal neurological sequelae (e.g., seizures, coma, or hypotonia), and multiorgan system dysfunction (e.g., cardiovascular, gastrointestinal, hematologic, pulmonary, or renal dysfunction). The subjects were enrolled after informed consent was received from the parents. During that period, empirical treatment consisted of penicillin G or amoxicillin in combination with tobramycin or cefotaxime. Patients treated with penicillin G were eligible for this study.

Penicillin G was administered as an intravenous bolus injection of 50,000 U/kg every 12 h. For each subject, the leukocyte count, platelet count, and blood and superficial specimen cultures were performed as part of the routine workup.

Pharmacokinetics study. The pharmacokinetics of penicillin G were studied on day 3 of life. Blood samples (200 μ l) were taken from an indwelling arterial line just before the administration of an intravenous bolus dose and at 0.03, 0.5, 1, 2.5, 4, 8, and 12 h after administration. A sample was taken at 24 h from those patients who did not receive a subsequent dose. Samples were immediately centrifuged at $3,000 \times g$ in a microcentrifuge (Merck-type Eppendorf 5414) for 1 min, and the serum was stored at -70°C .

Penicillin G high-pressure liquid chromatography assay. Chromatographic analysis was performed with a glass-prepacked column (100 by 3 mm) containing ODS-2 Chromospher Spherisorb beads (5- μ m-diameter particle size; Chrompack, Middelburg, The Netherlands) combined with a guard column. A Bio LC pump (model 410; Perkin-Elmer, Norwalk, Conn.) was used to deliver the eluent, which consisted of 16% (vol/vol) acetonitrile and 50 mM sodium phosphate buffer (pH 6.9), at a flow rate of 0.8 ml/min. The separations were carried out at room temperature. The eluate was monitored with a Perkin-Elmer LC-95 UV/visible spectrophotometer detector at a wavelength of 215 nm. As an internal standard 25 μ g/ml methicillin in 100% (vol/vol) methanol was used. Briefly, 100 μ l of the internal standard was added to a 100- μ l aliquot of the serum sample. This mixture was immediately vortexed for 30 s. Subsequently, the sample was kept at -20°C for 10 min, again vortexed for 30 s, and finally, centrifuged at $1,500 \times g$ for 10 min at room temperature. The supernatant was filtered (Millipore), and 10 μ l was injected onto the column.

High-pressure liquid chromatography-grade acetonitrile was purchased from Rathburn (Walkerburn, Scotland). The other chemicals were purchased from Aldrich-Chemie (Steinheim, Germany). All chemicals applied were of the highest grade commercially available.

The lower limit of detection of penicillin was 0.5 μ g/ml. The coefficients of interassay variation determined at concentrations of 100 and 20 μ g/ml were 2.6% and 2.3%, respectively. The intra-assay values were 0.75% and 1.05%, respectively.

Pharmacokinetic analysis. Pharmacokinetic parameters were estimated by means of nonlinear mixed effect (population) modeling (NONMEM). This approach estimates the structural pharmacokinetic parameters by considering both the interindividual variability within the population and the intraindividual (i.e., residual) variability. The model was implemented in the NONMEM ADVANS subroutine, and the analysis was performed by using the first-order conditional estimation method with the interaction option. All fitting procedures were performed with the use of the Compaq Visual FORTRAN, standard edition 6.6 (Compaq Computer Cooperation, Euston, TX), and NONMEM, version V (NONMEM project group; University of California, San Francisco).

To determine the basic structural pharmacokinetic parameters, several models were evaluated. One-, two-, and three-compartment models were tested and evaluated for their goodness of fit. Model selection and the identification of variability were based on the likelihood ratio test, pharmacokinetic parameter

point estimates, and their respective confidence intervals and goodness-of-fit plots. For the likelihood ratio test for differences between two models, the objective function value with a prespecified level of significance of a P value of <0.001 was used. NONMEM minimizes an objective function in performing nonlinear regression analysis. To detect systematic deviations in the model fits, the goodness-of-fit plots were visually inspected. The data of individual observations versus individual or population predictions should be randomly distributed around the line of identity. The weighted residuals versus time or population predictions should be randomly distributed around zero.

The stochastic part of the model was selected to describe the interindividual variability in the pharmacokinetic parameters, and a lognormal distribution of all model parameters over the population was assumed. Therefore, an exponential distribution model was used to account for interindividual variability, as follows: $P_i = \theta \cdot \exp(\eta_i)$, where P_i is the value of the model parameter P for individual i , θ is the population estimate for parameter P , and η_i is the normally distributed interindividual random variable with mean zero and variance ω^2 . Selection of an appropriate residual error model was based on the likelihood ratio test and inspection of the goodness-of-fit plots. The model was modified to objectively account for unexplained inconsistencies in the data. To reduce the influence of neonates with large unexplained inconsistencies in the concentration-time profile on the population estimates, these neonates were objectively determined by means of the residual error and were weighted less in the estimates for the population.

To refine the stochastic model, covariate analysis was also performed. The estimated pharmacokinetic parameters were plotted independently against the covariates gestational age, birth weight, gender, and the presence of a dosing history to determine whether these influenced the pharmacokinetics. The effects of the covariates were tested for statistical significance by the likelihood ratio test, and the residual intra- and interindividual variabilities were visually evaluated. A covariate was retained in the model if it produced a decrease in objective function of >10.8 ($P < 0.001$). In addition, we investigated whether there were significant differences in the pharmacokinetics between neonates with birth weights of less than 1,000 g and neonates with birth weights of more than 1,000 g. The volume of distribution at steady state (V_{ss}) and the half-life ($t_{1/2}$) were calculated by standard procedures (15).

Estimation of $fT > \text{MIC}$ and MCSs. The estimates of the pharmacokinetic parameters and measures of dispersion were used to simulate various dosing regimens and obtain the percent $fT > \text{MIC}$ as a function of the MIC (23). Protein binding was estimated to be $40\% \pm 2.5\%$ (14). The protein binding of penicillin G in premature neonates is unknown. However, protein binding in neonates is generally less than that in adults. It is therefore likely that the estimated protein binding of 40% overestimates the nonactive protein-bound fraction of penicillin G in these neonates. The use of 40% is therefore a conservative estimate. MCS was performed by using the MICLAB (version 2.36) program (Medimatics, Maastricht, The Netherlands) by simulating 10,000 subjects for each regimen. The program allows inclusion of the covariance matrix (or correlation matrix) of the parameter estimates used in the simulations. The output consisted of a probability distribution, a cumulative probability distribution, and specific confidence intervals over user-defined MIC and percent $fT > \text{MIC}$ ranges.

RESULTS

Demographic data. Twenty neonates with gestational ages under 32 weeks were included in the study. The demographic, laboratory, and clinical parameters for the neonates are shown in Table 1. The average weight was 1,195 g (weight range, 650 to 2,030 g). Half of the subjects were born to mothers with preeclampsia or HELLP (hemolysis, elevated liver enzyme, and low platelet count) syndrome. Other reasons for premature birth were suspected intra-amniotic infection, preterm contractions with meconium-stained amniotic fluid, and preterm premature rupture of membranes.

Population pharmacokinetics. A total of 167 samples were included in the pharmacokinetic analysis. For 11 neonates, samples were obtained only in the first 12 h after the intravenous bolus, and for 9 neonates a sample could be obtained after 24 h. A biphasic rate of decline in the penicillin G concentration versus time (i.e., a two-compartment model) best described the data by use of a combined-error model with

TABLE 1. Demographic, laboratory, and clinical parameters for 20 patients studied on day 3 after birth

Parameter	Mean	SD	Range
Gestational age (wk)	29 5/7	1 5/7	26 3/7–32 0/7
Gender (no. of males/no. of females)	12/8		
Wt (g)	1,195	387	650–2,030
Hematocrit (%)	46	7	33–63
Leukocytes ($10^3/\text{mm}^3$)	15	13	5–54
Platelets ($10^3/\text{mm}^3$)	203	103	74–497
Creatinine	46	17	10–82
Apgar score at 1 min	6	3	1–10
Apgar score at 5 min	8	1	6–10
Artificial ventilation (no. yes/no. no)	9/11		
No. of positive blood cultures	0		
No. of positive superficial cultures ^a	1		

^a The culture was positive for *Streptococcus agalactiae*.

additive and proportional errors. Figure 1 shows the observed concentrations in the individual patients as well as the predicted concentration-time curves, as obtained from the final model, while Fig. 2 shows the observed concentrations versus the individual predicted concentrations for the whole population. The distribution around the reference line of perfect prediction was symmetric, with a correlation coefficient of 0.80, but it deviated significantly from 1. The pharmacokinetic parameter estimates are shown in Table 2. The percent coefficient of variation reflects both the interindividual and the intraindividual variabilities of the pharmacokinetic parameters.

FIG. 2. Plot of individual predicted versus observed concentrations of penicillin G for 20 patients. The correlation coefficient was 0.801. The individual datum points for the entire population and the x - y line are also shown.

Estimation of the interindividual variability was possible for the parameters clearance (CL) corrected for body weight, volume of distribution of the peripheral compartment (V_2), and the infusion rate (34.5% for CL corrected for body weight, 17.1% for V_2 , and 89.9% for the infusion rate). The residuals were generally small; but the additive errors for neonates 1, 3, and 6 differed 2.5 to 3.5 times from the median for these neonates.

We examined the relationship between CL and gestational age, gender, body weight, and the presence of a dosing history

FIG. 1. Individual plots for the 20 very preterm neonates. The black dots correspond to the individual datum points. The line represents the individual estimate, and the dotted line represents the population estimate. Neonates 1, 3, and 6 were weighted less in the population estimation. ID, neonate number.

TABLE 2. Pharmacokinetic parameters for penicillin G in 20 preterm neonates

Parameter ^a	Mean value	Standard error
Structural model parameters		
CL (liter/h)	0.103	0.0104
V_1 (liter)	0.359	0.0558
V_2 (liter)	0.152	0.0312
Q (liter/h)	0.774	0.277
Variance model parameters		
Interindividual variability in CL	0.164	0.0865
Interindividual variability in V_1	0.39	0.126
Residual variability (proportional component)	0.104	0.0316
Residual variability (additive component)	1.12	0.891
Derived pharmacokinetics parameters		
V_{ss} (liter)	0.540	
$t_{1/2\beta}$ (h)	3.9	

^a V_1 , volume of distribution in the central compartment; Q , intercompartmental clearance; the other abbreviations are defined in the text.

(i.e., whether the neonate had received a previous dose of penicillin or not). There were no significant correlations between CL and gender or the presence of a dosing history. CL increased significantly with increasing body weight ($P < 0.01$) (Fig. 3). The incorporation of body weight on CL into the model improved the model fit significantly. There was a significant correlation between gestational age and body weight ($P < 0.01$). The incorporation of gestational age did not further improve the model fit. No significant differences in pharmacokinetic parameter estimates could be demonstrated between neonates with birth weights of more than 1,000 g and those with birth weights of less than 1,000 g.

MCS was performed to determine the probability of target attainment (PTA) for the dosing regimen used. Assuming an $fT > MIC$ of 50% for preterm neonates, a PTA of 100% was reached with the currently recommended dosing regimen of 50,000 U/kg every 12 h for pathogens with MICs of ≤ 4 mg/liter. Figure 4 shows the percent $fT > MIC$ s for the dose of 50,000 U/kg and three different dosing intervals on the basis of

FIG. 3. Observed relation between body weight and clearance.

FIG. 4. $fT > MIC$ for penicillin G, based on the pharmacokinetic estimates and the correlation matrix of the parameter estimates, as a function of the MICs for three regimens.

the mean population parameter estimates and the correlation matrix of these estimates.

DISCUSSION

The pharmacokinetics of penicillin G in neonates with gestational ages of less than 32 weeks were best described by a two-compartment model, yielding estimates of the terminal $t_{1/2}$ ($t_{1/2\beta}$) of 3.9 h, V_{ss} of 0.54 liter, and CL of 0.103 liter/h. The dosing regimen of 50,000 U/kg every 12 h is adequate for the treatment of neonatal infections caused by common microorganisms on day 3 of life.

Most studies on the pharmacokinetics of penicillin G in neonates have been performed after intramuscular administration (19, 20, 25). However, the intramuscular route should be avoided, because this may result in erratic absorption in a sick, infected newborn with a restricted blood supply to the extremities (31). Mulhall (25) performed a study on the pharmacokinetics of penicillin G after intravenous administration in four neonates with gestational ages ranging from 27 to 40 weeks and found a CL of 0.12 ± 0.07 liter/h/kg (mean $\pm$ standard deviation), a V of 0.61 ± 0.28 liter/kg (mean $\pm$ standard deviation), and a $t_{1/2}$ of 3.8 h. These results are similar to our data.

Other penicillins have larger V and longer $t_{1/2\beta}$ values in premature neonates, especially compared with those in adults (11). V varied from 0.3 liter/kg for ampicillin to 0.41 to 0.68 liter/kg for amoxicillin in neonates (2, 16, 32), whereas V was 0.45 liter/kg for penicillin G in our study. The $t_{1/2\beta}$ of penicillin G in neonates with gestational ages of less than 32 weeks was longer than the value of 0.5 h reported for healthy adults (14), but it is in the same range as the values of between 2 and 9.5 h that have been reported for other penicillins in neonates (2, 7, 10, 11, 16, 32).

Among the limited number of samples available from patients in this age group, there was some unexplained inconsistency in the data. This might have been caused by the subcutaneous administration of penicillin G, erratic sampling times, or the accidental exchange of samples. Large unexplained inconsistencies in the data were found for three neonates, based objectively on their residual errors, and therefore, the data were weighted less in the population estimates. By using this

method, none of the neonates were excluded from the study and all data were used in the analysis. Consequently, there is a deviation between the line of identity and the regression line of the observed versus the predicted concentrations, indicating that the description of the pharmacokinetics in this age group can be improved. To this end, more data are needed.

The presence of a third elimination phase ($t_{1/2\gamma}$) for penicillin G has been described previously both in animal models and in adult humans (14, 29). Our data could not be described by a three-compartment model. The $t_{1/2\beta}$ found in our study, however, was comparable to the $t_{1/2\gamma}$ of 3.1 h in human adults (14). Both the limited number of samples taken in the initial distribution phase and the unique body composition of the neonate, which comprises approximately 75% water, complicate the distinction between the initial distribution and the second elimination phase. It is possible that the initial phase in our study represents both the initial and second phases found in the study of Ebert et al. (14). Thus, the slow elimination that we found may represent the third elimination phase for penicillin G determined in that study.

Interindividual variability was partly explained by variations in CL, V_2 , and the infusion rate. The variability in the infusion rate represents not only the variation in the rate of manual administration of the intravenous bolus injection but also the variation in the sampling times between the first samples. Especially for the first samples, the exact sampling times are crucial.

Growth and development are major aspects in infants; therefore, both size and gestational age may have an impact on the prediction of CL (4). The maturation of CL begins before birth, suggesting that gestational age would be a physiologically appropriate covariate to explain the time course of changes in CL (4). In our data, changes in CL were best explained by differences in body weight, probably because both gestational age and other factors influencing the development of renal function are represented by an adequate increase in body weight in time. Furthermore, the range of gestational ages of the neonates included in our study was relatively small. While CL slightly increased as a function of birth weight for the entire group, differences between the subgroup with birth weights of more than 1,000 g and the subgroup with birth weights of less than 1,000 g could not be demonstrated. The analysis of correlations between covariates and pharmacokinetic parameter estimates is more sensitive when the data for all neonates are included in the study.

The enhanced interindividual pharmacokinetic variability in premature neonates complicates the calculation of the therapeutic dosing regimen. The dosing regimen should be adequate for the entire population. We concluded that the 100% PTA obtained with simulation of the recommended regimen was adequate for the treatment of infections in neonates on the third day of life. In case of meningeal involvement, effective concentrations in the cerebrospinal fluid (CSF) are required. Little is known about the pharmacokinetics of penicillin G in the CSF of premature neonates. We do not know what percentage of penicillin G penetrates the CSF in premature neonates with meningitis. Given the low penicillin MIC for group B streptococci (up to 0.12 mg/liter), with the use of the currently recommended dosing regimen, it is sufficient when the level of penetration of penicillin into the CSF is at least 3%.

Shortening of the dosing interval to 8 h will not have additional value for the treatment of infections in neonates with gestational ages of less than 32 weeks. When these infections are caused by microorganisms with low MICs, like *Streptococcus agalactiae*, a regimen with a prolonged dosing interval of 24 h is also likely to have clinical success. For empirical therapy, however, this regimen is suboptimal.

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