Population Pharmacokinetics of Arbekacin, Vancomycin, and Panipenem in Neonates

Toshimi Kimura,1* Keisuke Sunakawa,2 Nobuo Matsuura,3 Hiroaki Kubo,4 Shigeihko Shimada,1 and Kazuo Yago1

Department of Pharmacy1 and Division of Neonatology,2 Kitasato University Hospital, and Division of Infectious Disease, Kitasato University School of Medicine,3 1-15-1 Kitasato, Sagamihara-shi, Kanagawa 228-8555, and Laboratory of Analytical Chemistry, School of Pharmaceutical Sciences, Kitasato University, 108-8641 Shirogane, Minatoku, Tokyo,4 Japan

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Immature renal function in neonates requires antibiotic dosage adjustment. Population pharmacokinetic studies were performed to determine the optimal dosage regimens for three types of antibiotics: an aminoglycoside, arbekacin; a glycopeptide, vancomycin; and a carbapenem, panipenem. Eighty-three neonates received arbekacin (n = 41), vancomycin (n = 19), or panipenem (n = 23). The postconceptional ages (PCAs) were 24.1 to 48.4 weeks, and the body weights (BWs) ranged from 458 to 5,200 g. A one-compartment open model with first-order elimination was applied and evaluated with a nonlinear mixed-effect model for population pharmacokinetic analysis. In the fitting process, the fixed effects significantly related to clearance (CL) were PCA, postnatal age, gestational age, BW, and serum creatinine level; and the fixed effect significantly related to the volume of distribution (V) was BW. The final formulas for the population pharmacokinetic parameters are as follows:

- For arbekacin, CLarbekacin = 0.0328 × BW/serum creatinine level for PCAs of <33 weeks and CLarbekacin > 0.0367 × BW/serum creatinine level for PCAs of ≥33 weeks, Varbekacin = 0.54 liters/kg, CLvancomycin = 0.0250 × BW/serum creatinine level for PCAs of <34 weeks and CLvancomycin > 0.0323 × BW/serum creatinine level for PCAs of ≥34 weeks, Vvancomycin = 0.66 liters/kg, CLpanipenem = 0.0832 for PCAs of <33 weeks and CLpanipenem = 0.179 × BW for PCAs of ≥33 weeks, and Vpanipenem = 0.53 liters/kg. When the CL of each drug was evaluated by the nonlinear mixed-effect model, we found that the mean CL for subjects with PCAs of <33 to 34 weeks was significantly smaller than those with PCAs of ≥33 to 34 weeks, and CL showed an exponential increase with PCA. Many antibiotics are excreted by glomerular filtration, and maturation of glomerular filtration is the most important factor for estimation of antibiotic clearance. Clinicians should consider PCA, serum creatinine level, BW, and chemical features when determining the initial antibiotic dosing regimen for neonates.

Nasocomial infections are an important cause of morbidity and mortality in neonates (16, 33). Antibiotics are widely used for the treatment of suspected or confirmed neonatal infections due to an immature immune system. As many antibiotics are principally eliminated by renal excretion, the initial doses are normally based on renal function. Although dosage adjustment is necessary for neonates because of their immature renal function, dosage regimens are not well defined for this population because of pharmacokinetic variability and difficulty with blood sampling. Dosage regimens need to be designed for neonates with various levels of maturation for safe dosing. The use of a population pharmacokinetic (PPK) approach with the nonlinear mixed-effect model (NONMEM) program for evaluation of the pharmacokinetics of panipenem according to various indices of maturation was reported previously (27). In the present study, three different types of antibiotics were selected: an aminoglycoside, arbekacin; a glycopeptide, vancomycin; and a carbapenem, panipenem. The PPKs of these antibiotics in neonates of various PCAs were analyzed and compared. Aminoglycosides are the basic compounds with which clearance (CL) is considered since excretion appears to correlate best with the glomerular filtration rate (GFR) (49). The level of excretion of vancomycin is similar to that of the aminoglycosides, but the CL-to-GFR ratio is smaller for vancomycin because of its higher level of protein binding in adults. Carbapenems (19) have a non-renal-related CL that is greater than the GFR (15, 39). Studies with neonates have previously identified correlations between pharmacokinetic parameters and body weight (BW), PCA, gestational age (GA), postnatal age (PNA), and serum creatinine concentration (Cr).

MATERIALS AND METHODS

Patients. Eighty-three neonates from the neonatal intensive care unit of Kitasato University Hospital, Kanagawa, Japan, who required intensive care and who antibiotic treatment were eligible for inclusion in the study. Informed consent to enter this study was given by the parents. Neonates were enrolled in three groups, which comprised those treated with arbekacin (n = 41), vancomycin (n = 19), and panipenem (n = 23). Table 1 shows the characteristics of the patients. Biochemical data and detailed dosing histories were obtained from computer records or patient case notes, with the following continuous clinical covariates noted: PNA, PCA, GA, and BW.

Dosing and sampling procedures. The following antibiotics were compared: arbekacin sulfate (Meiji Seika, Tokyo, Japan), vancomycin hydrochloride (Shionogi Pharmaceutical, Osaka, Japan), and panipenem (Sankyo, Tokyo, Japan). Arbekacin was administered at a dose of 2 to 3 mg/kg of body weight every 12 h over 30 min by intravenous infusion (actual dosages, between 2.2 and 4.1 mg/kg/dose; mean dosage, 3.0 mg/kg/dose). Vancomycin was administered at a dose of 15 mg/kg every 12 h (for those with a chronic age of 1 to 7 days) or 15 mg/kg every 8 h (for those >7 days old) over 60 min by intravenous infusion. Nine patients received two daily doses of vancomycin intravenously, and 10
Table 1. Patient demographic data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arbekacin</th>
<th>Vancomycin</th>
<th>Panipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects and sex</td>
<td>15 females, 26 males</td>
<td>10 females, 9 males</td>
<td>13 females, 10 males</td>
</tr>
<tr>
<td>PCA range (wk)</td>
<td>24.1–46.3</td>
<td>25.1–48.4</td>
<td>24.7–42.6</td>
</tr>
<tr>
<td>No. of patients of the following PCA (wk)&lt;sup&gt;3&lt;/sup&gt;:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;26</td>
<td>9</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>&lt;30</td>
<td>12</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>&lt;34</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&lt;38</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>&lt;42</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>42±</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GA range (wk)</td>
<td>24.1–43.4</td>
<td>24.1–41.3</td>
<td>24.7–41.4</td>
</tr>
<tr>
<td>PNA range (days)</td>
<td>0–57</td>
<td>3–71</td>
<td>0–42</td>
</tr>
<tr>
<td>BW range (g)</td>
<td>458–4,455</td>
<td>710–5,200</td>
<td>530–4,455</td>
</tr>
<tr>
<td>Cr range (mg/dL)</td>
<td>0.2–3.0</td>
<td>0.2–0.9</td>
<td>0.3–2.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> A total of 83 neonates in the neonatal intensive care unit at Kitasato University Hospital were studied.

<sup>b</sup> Number of subjects of each PCA on the first day of therapy.

Table 2. Hypothesis testing for influence of fixed effects on pharmacokinetic parameters for three types of antibiotics

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter and fixed effect&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Arbekacin</th>
<th>Vancomycin</th>
<th>Panipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>14.49 (0.001)</td>
<td>5.13 (0.001)</td>
<td>11.82 (0.001)</td>
</tr>
<tr>
<td>exp(PC A × 0)</td>
<td>52.14 (0.001)</td>
<td>21.60 (0.001)</td>
<td>42.03 (0.001)</td>
</tr>
<tr>
<td>GA</td>
<td>11.93 (0.001)</td>
<td>19.23 (0.001)</td>
<td>10.57 (0.001)</td>
</tr>
<tr>
<td>PNA</td>
<td>14.03 (0.01)</td>
<td>1.15 (NS&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>9.08 (0.01)</td>
</tr>
<tr>
<td>BW</td>
<td>54.32 (0.001)</td>
<td>22.50 (0.001)</td>
<td>37.49 (0.001)</td>
</tr>
<tr>
<td>APG&lt;sup&gt;c&lt;/sup&gt;-S&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.2 (NS)</td>
<td>1.80 (NS)</td>
<td>2.80 (NS)</td>
</tr>
<tr>
<td>1/Cr</td>
<td>63.78 (0.001)</td>
<td>40.19 (0.001)</td>
<td>13.98 (0.001)</td>
</tr>
<tr>
<td>BW/Cr</td>
<td>101.60 (0.001)</td>
<td>50.71 (0.001)</td>
<td>28.45 (0.001)</td>
</tr>
<tr>
<td>PCA&lt;sup&gt;d&lt;/sup&gt;</td>
<td>61.64 (0.001)</td>
<td>21.60 (0.001)</td>
<td>24.46 (0.001)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Three degree of freedom were used to model the effect on CL and V.<br><sup>b</sup> NS, not significant.<br><sup>c</sup> APG-S, Apgar score.<br><sup>d</sup> The values for PCA apply to PCAs of 33 weeks for arbekacin and panipenem and 34 weeks for vancomycin.

Pharmacokinetic analysis. The simultaneous analysis of all concentration-time and patient physiologic data was performed by using the NONMEM program with first-order methods (double precision, version 5, level 1.0), a computer program developed for PPK analysis on a PCAT computer running under a Windows system. The concentration-time courses of each antibiotic were described by use of a one-compartment model (in accordance with the available post-distribution phase data) with a short infusion and first-order elimination. Fixed- and random-effect parameters were estimated by use of the NONMEM program. The basic pharmacokinetic parameters of CL and the volume of distribution (V) corresponding to the proposed model were determined for each patient by using the PREDPP subroutines supplied with ADVAN/TRANSF from the NONMEM library. In the first phase of the analysis, a basic model with no covariates on CL or V was used. Additive, proportional, and log-linear error models were compared for determination of the interindividual variability in CL and V and for the residual variability in the drug concentration. Proportional interindividually variability models were invoked for each CL and V as follows:

\[ CL = \frac{CL_0}{1 + \eta CL} \]
\[ V = \frac{V_0}{1 + \eta V} \]

Table 3. Hypothesis testing according to intersubject variability by using reduced models of the full model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P value</th>
<th>Parameter</th>
<th>P value</th>
<th>Parameter</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbekacin (PCA, n = 33 wk)</td>
<td></td>
<td>Vancomycin (PCA, n = 34 wk)</td>
<td></td>
<td>Panipenem (PCA, n = 33 wk)</td>
<td></td>
</tr>
<tr>
<td>01</td>
<td>&lt;0.001</td>
<td>01</td>
<td>&lt;0.001</td>
<td>01</td>
<td>NS&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>02</td>
<td>&lt;0.001</td>
<td>02</td>
<td>&lt;0.001</td>
<td>02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>03</td>
<td>&lt;0.001</td>
<td>03</td>
<td>&lt;0.001</td>
<td>03</td>
<td>NS</td>
</tr>
<tr>
<td>04</td>
<td>NS</td>
<td>04</td>
<td>NS</td>
<td>04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>05</td>
<td>&lt;0.001</td>
<td>05</td>
<td>&lt;0.001</td>
<td>05</td>
<td>NS</td>
</tr>
<tr>
<td>06</td>
<td>&lt;0.001</td>
<td>06</td>
<td>&lt;0.001</td>
<td>06</td>
<td>NS</td>
</tr>
<tr>
<td>07</td>
<td>NS</td>
<td>07</td>
<td>NS</td>
<td>07</td>
<td>NS</td>
</tr>
<tr>
<td>08</td>
<td>&lt;0.001</td>
<td>08</td>
<td>&lt;0.001</td>
<td>08</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup> NS, not significant.
where $\text{CL}$ and $\bar{V}$ are the population parameters. $\eta_{\text{CL}}$ and $\eta_V$ are random variables with a mean of zero and a variance of $\omega^2$. CL and $V_i$ are the individualized estimated parameters.

The additive error model was used for residual variability:

$$C_i = C_i^* + \epsilon_i$$

where $C_i$ is the $i$th measured concentration in serum in individual $j$, $C_i^*$ is the estimated concentration in serum (as determined from the pharmacokinetic data), and $\epsilon_i$ is the independent identically distributed statistical error with a mean of zero and a variance of $\sigma^2$.

**Fixed-effects modeling.** In the fitting process, the following patient demographic and biochemical data were used as covariables in the population model: PCA, GA, PNA, Apgar score, BW, and Cr. Covariates were investigated on the basis of the CL and $V$ values for each antibiotic. The candidate covariate was screened in turn by adding it to the basic model: $\text{CL} = 01 \times \text{BW}/\text{Cr}$ (PCA, $\geq 33$ wk); $\text{CL} = 02 \times \text{BW}/\text{Cr}$ (PCA, $< 33$ wk); $V = 03 \times \text{BW}$.

### TABLE 4. Final estimates for the population pharmacokinetic parameters for antibiotics in neonates

<table>
<thead>
<tr>
<th>Data set and parameter</th>
<th>Arbekacin</th>
<th>Vancomycin</th>
<th>Panipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original data set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>$0.0367$</td>
<td>$0.0323$</td>
<td>$0.0832$</td>
</tr>
<tr>
<td>$\omega_{\text{CL}}$ (%)</td>
<td>$35.5$</td>
<td>$22.9$</td>
<td>$23.9$</td>
</tr>
<tr>
<td>$\omega_V$ (%)</td>
<td>$42.5$</td>
<td>$20.8$</td>
<td>$28.5$</td>
</tr>
<tr>
<td>$\epsilon$ (mg/liter)</td>
<td>$2.43$</td>
<td>$3.22$</td>
<td>$4.20$</td>
</tr>
<tr>
<td>Variability (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 500 bootstrap replication |           |            |           |
| Mean                   | $0.0378$  | $0.0344$   | $0.0846$  |
| $\omega_{\text{CL}}$ (%) | $36.2$    | $25.8$     | $24.5$    |
| $\omega_V$ (%)         | $43.4$    | $22.3$     | $30.1$    |
| $\epsilon$ (mg/liter)  | $3.41$    | $3.38$     | $4.40$    |

The horizontal lines show the average $C_{arbekacin}$ for neonates with PCAs of $<33$ and $\geq 33$ weeks. $C_{arbekacin}$ was normalized by weight but depends on PCA and Cr (Scr).

**FIG. 1.** Relationship between $C_{arbekacin}$ normalized by weight and PCA. $C_{arbekacin}$ was estimated by the Bayesian method. The horizontal lines show the average $C_{arbekacin}$ for neonates with PCAs of $<33$ and $\geq 33$ weeks. $C_{arbekacin}$ was normalized by weight but depends on PCA and Cr (Scr).
\[ V = 01 + 02 \times \text{covariate}, \text{ where } 01 \text{ and } 02 \text{ are the intercept and slope parameters, respectively. An objective function value (the negative value of twice the log-likelihood difference [–2 l.l.d.]) is produced by the NONMEM program for each model in this regression. Comparisons among the different models were based on the differences in the minimum value of the objective function. Changes in the objective function greater than 6.635 indicate a statistically significant (\( P < 0.01 \)) improvement in the fit of the data on the basis of a \( \chi^2 \) distribution with 1 degree of freedom. On the basis of these results, all significant factors were used to construct the full regression equation. A stepwise procedure was used to determine the final model. The final model was obtained by removing covariates from the full model. After deletion of each factor in the full model, the objective function value of this reduced model was compared with that of the full model. At that time, a more restrictive criterion was adopted, and a \( \chi^2 \) distribution with more than 7.8 was required to maintain covariates for the final model (\( P < 0.005 \)). The final estimates of the PPK parameters were defined. Individual estimates of the CL and \( V \) values for each antibiotic were generated by Bayesian feedback with the NONMEM program after the population analysis.

FIG. 2. Relationship between CL\(_{\text{vancomycin}}\) normalized by weight and PCA. CL\(_{\text{vancomycin}}\) was estimated by the Bayesian method. The horizontal lines shows the average CL\(_{\text{vancomycin}}\) for neonates with PCAs of <34 and \( \geq 34 \) weeks. CL\(_{\text{vancomycin}}\) normalized by weight still depends on PCA and Cr (Scr).

FIG. 3. Relationship between CL\(_{\text{panipenem}}\) and PCA. CL\(_{\text{panipenem}}\) for neonates with PCAs of <33 weeks was not dependent on maturation but was constant for extrarenal CL\(_e\); CL\(_{\text{panipenem}}\) for neonates with PCAs of \( \geq 34 \) weeks increased by PCA.
observed concentrations in serum. The distribution of their distribution against the linear regression of the predicted versus the pharmacokinetic parameters derived in this study were evaluated by determinations of their distribution against the linear regression of the predicted versus the observed concentrations in serum.

**RESULTS**

The study plan included the collection of nine samples from each subject over 6 days. The actual number of samples collected was as follows: 114 samples from the 41 neonates receiving arbekacin, 88 samples from the 19 neonates receiving vancomycin, and 108 samples from 23 neonates receiving panipenem. All subjects tolerated the antibiotics well, with no evidence of drug-associated toxicity. All data could be used for the pharmacokinetic evaluation.

The mean CL and V values were as follows: $CL_{arbekacin} = 0.107$ liters/h, $V_{arbekacin} = 0.91$ liters, $CL_{vancomycin} = 0.105$ liters/h, $V_{vancomycin} = 0.91$ liters, $CL_{panipenem} = 0.175$ liters/h, and $V_{panipenem} = 0.55$ liters. Table 2 summarizes the main covariate models that were tested by use of the NONMEM program. In the fitting process, the NONMEM analysis with single covariates identified PCA, GA, PNA (except with vancomycin), BW, inverted Cr, exponential PCA, the complex factor of BW, and inverted Cr (BW/Cr) as having an influence on CL. The Apgar score was not significantly correlated. The values of $-2\,\text{LL}$ for the effects of different PCAs on CL were minimal for PCAs of 33 to 34 weeks. When evaluating each CL, we found that the mean CL for the subjects with PCAs of <33 to 34 weeks was significantly smaller than the mean CL for those with PCAs of ≥33 to 34 weeks, and for all three antibiotics CL showed an exponential increase with PCA. The influence of PCAs of <33 to 34 weeks, 33 to 34 weeks, or ≥33 to 34 weeks on the CL was chosen for the next analysis step.

BW, inverted Cr, and PCA were selected for the full regression analysis. No significant correlation was found between CL and PCA when PCA and BW were analyzed at the same time. We found that PCA closely correlates with BW. Because CL is a function of PCA, BW, and Cr, the following fixed-effect model was assumed for the pharmacokinetic model: $CL = 0.01 + 0.02 \times BW \times (1 + 0.03/Cr) \times (PCAs, <33 or 34 weeks), CL = 0.04 + 0.05 \times BW \times (1 + 0.06/Cr) \times (PCAs, ≥33 or 34 weeks), and V = 0.07 + 0.08 \times BW$, where 0.03 to 0.08 are the intercept or slope parameters.

Each parameter was eliminated from the full model (Table 3). The final model with PCA, Cr, and BW was examined; and the final regression equations and parameter estimates are shown in Table 4. The final formulas for the PPK parameters were as follows: $CL_{arbekacin} = 0.0238 \times BW/Cr$ for PCAs of <33 weeks and $CL_{arbekacin} = 0.0367 \times BW/Cr$ for PCAs of ≥33 weeks, $V_{ arbekacin} = 0.54$ liters/kg, $CL_{vancomycin} = 0.0250 \times BW/Cr$ for PCAs of <33 weeks and $CL_{vancomycin} = 0.0323 \times BW/Cr$ for PCAs of ≥33 weeks, $V_{vancomycin} = 0.66$ liters/kg, $CL_{panipenem} = 0.0832$ for PCAs of <33 weeks and $CL_{panipenem} = 0.179 \times BW$ for PCAs of ≥33 weeks, and $V_{panipenem} = 0.53$ liters/kg.

The interindividual coefficients of variation for CL and V were as follows: $CL_{arbekacin} = 35.5\%$, $V_{arbekacin} = 42.5\%$, $CL_{vancomycin} = 22.9\%$, $V_{vancomycin} = 20.8\%$, $CL_{panipenem} = 23.9\%$, and $V_{panipenem} = 28.5\%$.

The standard deviations in intraindividual variability were determined to be 2.43, 3.22, and 4.2 mg/liter for arbekacin, vancomycin, and panipenem, respectively. The highly signi-

**FIG. 4.** Scatterplot of $V_{arbekacin}$, $V_{vancomycin}$, and $V_{panipenem}$ versus PCA. Each value of V was estimated by the Bayesian method. There was no significant relationship between V and time.
relationships between pharmacokinetic parameters and physiologic factors are presented in Fig. 1 to 4. These parameters were estimated by Bayesian feedback with the NONMEM program.

The results of the 500 bootstrap procedure are shown in Table 4. The mean values from the bootstrap procedure were similar to the parameter estimates from the original data set, indicating that the model that was developed is stable.

Figure 5 shows a scatterplot of the observed concentrations and the estimated concentrations. The mean values for the population analyzed showed a good predictive performance. The distribution of the plot against the line for the formula for CL displays a bilateral symmetry around the regression, so the observed population mean was assumed to be an unprejudiced parameter.

**DISCUSSION**

PPK analysis is very useful in situations in which the data are sparse and when ethical and logistical issues must be taken into account when neonates of various levels of maturation are studied (20, 48). The PPK study described here was conducted to determine adequate treatments with three typical antibiotics by characterization of the pharmacokinetics of the antibiotics in neonates. Although two-compartment models are used for many antibiotics with short infusions, a one-compartment model analysis was adopted in this study. The two-compartment model is not important for clinical dosage regimens, as shown by the method of Sawchuk-Zaske (41), for neonates, for whom minimization of blood loss is critical.

In the present study, PCA, GA, PNA, Cr, and BW were important factors that correlated with individual estimates of CL (Table 2); but the correlation for PNA was not clearly significant. Many investigators have reported a high correlation between GA and antibiotic CL (7, 8, 23, 45, 46). Clinically, renal function is the most important factor for elimination because many antibiotics are completely excreted in urine. Many studies have evaluated the changes in renal function during development in neonates according to their GAs. Although PNA must be considered along with GA to evaluate renal function correctly, it is difficult to identify the significant covariate in the process of determining population parameters (17). The use of a large number of patients of the same GA with various PNAs is necessary for analysis of a small population. For this reason, the use of PCA is an obvious choice for the evaluation of renal function in neonates. Our results showed that the mean CL of antibiotics in patients with PCAs of <33 to 34 weeks was significantly lower than that in patients with PCAs of ≥33 to 34 weeks, and CL showed a logarithmic rise with PCA. Many investigators (2, 3, 18, 29) have reported that changes in the development of the renal function in neonates are correlated with PCAs and that renal function increases after 34 to 35 weeks. These associations suggest that antibiotic CL steeply increases in neonates with PCAs of 33 to 36 weeks.

If patients with a wider range of renal function had been available, it is likely that creatinine CL would have been a significant predictor of CL for antibiotics excreted mainly by glomerular filtration. Schwartz et al. (42) estimate GFR (in millimeters per minute per 1.73 m²) as follows: GFR = k • HT/Cr, where HT is the height (in centimeters) and k is a constant proportional to HT/Cr. Although HT or body surface area might be more accurate for estimation of GFR, many dosages have previously been normalized per kilogram of BW. After the inclusion of Cr and BW in the regression model, BW/Cr was a powerful predictor of the CL of each antibiotic in the early stages of the model-building process, but for panipenem it was not significant in the final model.

In this study, significant covariates related to CLpanipenem were found, and it was confirmed that CLpanipenem does not depend on the maturation process. Panipenem and other carbapenems are metabolized by the enzyme dehydropeptidase-1 and are very unstable in solution (34). The renal function of...
low-birth-weight babies is extremely low; therefore, CL by extrarenal pathways is relatively greater than that by the renal pathway according to the level of maturation of the neonate. Our results indicate that CLpanipenem (0.179 liter/h) was almost identical to GFR in full-term babies (0.144 liter/h; GA, 38 to 41 weeks) (24), and similar CLs were observed for other carbapenems, such as meropenem (0.157 liter/h/kg) (46) and imipenem (0.150 liter/h/kg) (39).

The renal CL of antibiotics is affected by glomerular filtration, tubular secretion, and tubular reabsorption (35). Antibiotics with high degrees of binding to serum proteins show a markedly lower renal CL (6). We reviewed 14 reports in the literature about the relationship between plasma protein binding and renal CL for seven antibiotics in neonates, and the results are shown in Fig. 6. With some exceptions, protein binding ratios provide good theoretical values of renal CL (renal CL = fu × GFR) in neonates (fu is the unbound fraction of antibiotic). A similar result was shown in the present study.

FIG. 6. Correlation between total and renal CL of antibiotics with protein binding ratios reported in the literature. Fourteen antibiotics were reviewed in 16 studies. The values of antibiotic CL from the literature were divided into two groups: circles indicate PCA of ≥33 weeks or BW of ≥2,000 g for amikacin (36), amoxicillin (11, 23), aztreonam (13), cefoperazone (38), cefotaxime (21), ceftazidime (40, 44), ceftriaxone (32), meropenem (46), and piperacillin (25); squares indicate PCA of <33 weeks or BW of <2,000 g for cefoperazone (8), flucloxacillin (10), piperacillin (25), ticarcillin (11), and vancomycin (12). The figure shows that CL is associated with protein binding ratios and that the relationship between renal CL and protein binding is stronger than that between total CL and protein binding.

FIG. 7. Correlation between PCA and CL of arbekacin, vancomycin, and panipenem. Antibiotic CL was estimated by the Bayesian method.
vancomycin was lower than CL arbekacin. The levels of protein
between protein binding ratio and 
meropenem (46), piperacillin (25), and ticarcillin (10) are low (less than 0.4 liters/kg) in adults due to aqueous solubility. (B) Correlation
activity (11, 23), cefazolin (14), cefoperazone (8, 38), cefotaxime (21), ceftazidime (40, 44), ceftizoxime (26), ceftriaxone (30, 32), fluclaxillin
levels, CL vancomycin and
small CL, and low body protein levels, CL vancomycin and
Because of the high degree of interpatient variability, very
small CL, and low body protein levels, CL vancomycin and
CLarbekacin were similar in neonates with PCAs of less than 33
weeks. However, in the group with PCAs of >33 weeks, CLvancomycin was lower than CLarbekacin. The levels of protein
binding of vancomycin and arbekacin are less than 10 to 82%
(1) and less than 15% (31), respectively.

CL is the most important factor in determining the daily
dose of antibiotics, and the comparative CLs obtained by PPK
analysis (Fig. 7) define the correct dosage regimen for
neonates. The dosage regimen is based on consideration of (i)
PCAs of 33 to 36 weeks, (ii) BW and inverted Cr, (iii) chemical
stability (extrarenal CL), and (iv) protein binding.

In the present study, NONMEM analysis showed that V of
the antibiotics was best described by using BW, but the time-
dependent differences in water balance, such as those according
to PNA, were unexpected. It is known that in neonates V of
hydrophilic antibiotics is affected by total body water content
and extracellular fluid volume (35). The extracellular fluid
volume is large in neonates, especially those with low birth
weights, and it decreases postnaturally (43). Some of the limita-
tions of PPK studies with neonates are the sparse data on the
concentration in serum; the small sample size; and the consid-
erable variability among neonates in terms of fluid intake,
sodium concentrations, urine output, and the occurrence of diarrhea and fever.

In our study the mean Vvancomycin for the neonates was
smaller than that for adults, and conversely, the mean Varbekacin
and Vpanipenem for the neonates were larger than those for
adults. Those findings confirm the findings of other investiga-
tors with the same group of antibiotics (4, 17, 27, 49). We
suggest that the discrepancy may be due to estimation of the
distribution property in adults. Although some antibiotics are
extensively bound to tissue and plasma proteins and have very
large V in adults, many antibiotics show small apparent V (0.1
to 0.3 liters/kg) due to high levels of aqueous solubility. Antibi-
otic diffusion from blood to extracellular fluid depends on
many factors, such as tissue binding, free drug concentration
(plasma protein binding), pK, molecular weight, and lipid
solubility (37, 47). Plasma protein binding may interfere with
the extravascular distribution (9). The distribution profiles of
12 antibiotics with a wide range of protein binding values in
neonates and the relationship between V in neonates and V in
adults are reviewed and presented in Fig. 8. V in neonates is
difficult to estimate from values for adults (Fig. 8), but it
depends on the level of protein binding and the amount of
extracellular fluid. While protein binding is an important factor
for estimation of pharmacokinetics parameters, we need to
consider the significant differences between neonates and
adults. In our study Varbekacin and Vpanipenem were double those
for adults because of low plasma protein binding levels. Be-
cause Vvancomycin is large (more than 0.6 liters/kg) in adults, the
drug is likely extensively distributed in tissue, in addition to
extracellular fluid. The apparent Vvancomycin in neonates tends
to be small compared to that in adults, even though the anti-
biotic is hydrophilic; the reason may be that increased BW is
the result of increased extracellular fluid levels in neonates
and, thus, Vvancomycin is relatively small because vancomycin
does not distribute to extracellular fluid. These data on hydro-
philic antibiotics assume that the value of V in neonates, which
is less than 0.4 liters/kg in adults, depends on the protein
binding ratio. For antibiotics for which the values of V are >0.6
liters/kg in adults, the values of V are smaller in neonates.

In conclusion, the comparative PPK analysis described here

FIG. 8. (A) Correlation between apparent V for antibiotics in adults and neonates reported in the literature. Apparent V for amikacin (36),
amoxicillin (11, 23), cefazolin (14), cefoperazone (8, 38), cefotaxime (21), ceftazidime (40, 44), ceftizoxime (26), ceftriaxone (30, 32), fluclaxillin
(22), meropenem (46), piperacillin (25), and ticarcillin (10) are low (less than 0.4 liters/kg) in adults due to aqueous solubility. (B) Correlation
between protein binding ratio and V. The apparent V was strongly associated with the protein binding ratio. As the protein binding ratio increases
in serum (f decreases), the apparent V is decreased.
identified important covariates for determination of initial drug dosing in neonates: PCA, Cr, and BW. Chemical features such as chemical stability and protein binding should also be considered for determination of the correct dosage regimens for neonates.

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