
Regular Article

Evaluation of Bayesian Predictability of Vancomycin Concentration Using Population Pharmacokinetic Parameters in Pediatric Patients

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Summary: The objective of this study was to evaluate the Bayesian predictability of vancomycin (VCM) pharmacokinetics in Japanese pediatric patients using one-compartment population pharmacokinetic (PPK) parameters, which we reported previously. The validity of the PPK model was evaluated by bootstrap method and cross validation method, and the Bayesian predictive performance was examined. The predictive performance of the PPK model for premature patients was also examined.

The cross validation method showed the predictability to be acceptable for practical use, especially for predicting trough concentration using other trough data. However, for the external premature patient data, this PPK model did not seem to be adequate.

A theoretical approach using a simulation technique was also examined to evaluate the predictive performance. The results suggested that the predictability at the peak was not necessarily good at all sampling times and the predictability at the trough was better when a later time point was used. The optimal sampling time for prediction of VCM concentration in pediatric patients is discussed.

Key words: Vancomycin; Bayesian predictability; Population pharmacokinetic parameter; Cross validation; Japanese pediatric patients; Therapeutic drug monitoring

Introduction

Vancomycin (VCM) is an effective glycopeptide antibiotic against gram-positive infections and has been widely used especially to treat patients with methicillin-resistant Staphylococcus aureus (MRSA). The clinical pharmacokinetics of VCM has been reviewed for adult and pediatric patients, and dosage regimens have been discussed for the optimization of VCM therapy. The pharmacokinetic profile of VCM is known to differ between pediatric and adult patients because of differences in body size and functions of the eliminating organ(s). To understand the pharmacokinetic properties of VCM in pediatric patients, we previously developed a population pharmacokinetic (PPK) model for Japanese pediatric patients.

The major side effect of VCM in adult patients is nephrotoxicity, and its occurrence is related to the high trough concentration of VCM. Although nephrotoxicity related to drug concentration in pediatric patients has not been clarified, guidelines for the recommended therapeutic window for adult patients are usually applied for pediatric patients to propose regimens. What is needed is a better understanding of the pharmacokinetic profiles of pediatric patients, as well as adult patients, for adequate clinical usage of VCM.

VCM is mainly eliminated via the kidney by glomerular filtration, and insufficient renal function in a patient can lead to a long elimination half-life and a high serum level of VCM, consequently increasing the risk of nephrotoxicity. In order to reduce the possibility of side effects and also to maintain an effective drug concentration, recommended therapeutic windows have been reported: a peak (1 to 2 hours after the end of infusion) concentration of below 25–40 μg/mL and a trough concentration of below 10 μg/mL. To control VCM concentration in these windows, therapeutic drug monitoring (TDM) is useful and allows the planning of individual optimal VCM dosage regimen. In TDM, because little drug concentration data are usually available, the Bayesian method is applied in combination with measured concentration data and PPK parameters to predict the drug concentration profile for each individual, using a sophisticated computer program.

We have already reported the PPK parameters of VCM for Japanese adult and pediatric patients, and
Table 1. Final population pharmacokinetic parameters and background of the pediatric patients

<table>
<thead>
<tr>
<th>Population mean</th>
<th>Inter-individual variability (CV (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL:</td>
<td></td>
</tr>
<tr>
<td>Age≤1, CL (L/hr) = (0.119 + 0.0619 × (Age−1)) × BWT</td>
<td>39.6%</td>
</tr>
<tr>
<td>Age&gt;1, CL (L/hr) = (0.119 + 0.00508 × (1−Age)) × BWT</td>
<td>18.8%</td>
</tr>
<tr>
<td>Vd:</td>
<td></td>
</tr>
<tr>
<td>Vd (Liter) = 0.522 × BWT</td>
<td>34.6%</td>
</tr>
<tr>
<td>Intra-individual variability (CV (%))</td>
<td></td>
</tr>
</tbody>
</table>

Background

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>49 (including 8 premature patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
</tr>
<tr>
<td>Number of observed serum concentration</td>
<td>181</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years old)</th>
<th>Mean ± S.D.</th>
<th>Range (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>9.49±10.8</td>
<td>[0.50–48.0]</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.39±0.34</td>
<td>[0.10–2.00]</td>
</tr>
</tbody>
</table>

1) [Minimum–Maximum], Refer to Ref. 8 for details., BWT: Body weight.

also developed a computer program to perform the Bayesian prediction.20 When a prediction method such as the Bayesian method is applied, it is important to know the predictability of the drug concentration and individual pharmacokinetic parameters because the predictability depends on the PPK parameters and also on the sampling time.21–23) We have already evaluated the predictive performance of PPK parameters of VCM based on a two-compartment model in Japanese adult patients.24) The pharmacokinetic variability of VCM in pediatric patients, especially neonates and premature neonates, is generally large because of the changes in body water volume and differences in the extent of renal function maturation.6,7) Thus, it is recommended that the VCM dosage in pediatric patients be individually adjusted using TDM. For this purpose, it is important to know the validity and the Bayesian predictive performance of the PPK parameters obtained for Japanese pediatric patients.

As internal data, we used the same data as those used for the PPK model development because no external data for pediatric patients were available. We applied two validation methods to evaluate the parameter stability and the robustness of the model. One was a bootstrap method25) to evaluate the stability of the PPK parameters, and the other was a cross validation method26) to confirm the robustness of the model. We also examined the Bayesian predictive performance of the PPK parameters. The Bayesian method was incorporated into the cross validation method as Ishibashi et al. had done previously.27) In addition, serum concentration data reported for premature patients28) were used as external data to evaluate the applicability of our PPK parameters for premature patients. Also, a theoretical approach using a simulation technique was performed to evaluate the influence of sampling time on the predictive performance.

Methods

Population pharmacokinetic parameters: PPK parameters reported for Japanese pediatric patients based on a one-compartment model8) were evaluated in this study. The final PPK model is referred to as the ‘reported’ PPK model in this paper. The reported PPK parameters and the background of the population are summarized in Table 1.

Validation of the reported PPK model and Bayesian predictability: Validation of the reported PPK model was performed by the bootstrap method and the cross validation method using internal data. The predictive performance of the Bayesian method was also evaluated as a part of the cross validation approach. The bootstrap method25) was used to evaluate the stability and confirm the robustness of the reported PPK model. One thousand bootstrap data sets were generated based on the reported PPK parameters, and the same model was fitted to each of the 1000 data sets. The average (mean), standard error (S.E.) and 95% confidence interval (95% C.I.) for estimates of the population mean and variance parameters were calculated and compared with the reported parameter estimates.

The cross validation method26) was also applied to evaluate the robustness of the reported PPK model. The data for all 49 patients were randomly divided into 10 data sets, which consisted of data for about 10% of the patients in each set.
patients of all patients without overlap. 10 subsets which consisted of one data set (10% patients) and the remaining nine data sets (90% patients) were generated using these 10 data sets. For each 10 subsets, the same model was fitted to the data for 90% patients, and the parameter estimates for 10 subsets were obtained. Next, Jackknife estimates for the mean, S.E. and 95% C.I. for each parameter were calculated and compared with those for the reported PPK parameters to confirm the robustness of the final model. ⁴⁻²⁷)

The predictive performance in the Bayesian method was examined by assuming a one-point Bayesian prediction, which predicts serum concentrations at designated times using one point of serum concentration data for a patient. The Bayesian prediction was performed using each PPK parameter set obtained from each 10 subsets for the rest of the data in each of the 10 subsets (i.e. each 10% of all patients’ data). The observed data from 0 to 3 hours after the end of intravenous infusion were chosen as ‘peak’ concentrations and those from 1 to 0 hour prior to the start of the next infusion were selected as ‘trough’ concentrations. For these data, the Bayesian predicted values were compared with the observed data. For all 49 patients, 27 patients with both ‘peak’ and ‘trough’ data during multiple dosing were used for this evaluation. For the Bayesian prediction, the peak or the trough concentration data on a day were used to predict the other peak and trough concentrations on subsequent days, and the predicted and observed concentrations at a corresponding time were compared for the predictive performance.

In order to examine the applicability of the reported PPK parameters to premature patients, we evaluated the Bayesian predictive performance using the serum concentration data reported for 10 Japanese premature patients. ²⁸) The patient characteristics are summarized as follows (mean ± S.D. [minimum–maximum]): gestational age 31.4 ± 5.5 [25–43] (weeks), postnatal age at the start of VCM dose 19.6 ± 9.5 [10–40] (days), and body weight 1081.5 ± 563.8 [442–2060] (g). VCM concentrations were measured at the start of infusion (used as ‘trough’ data) and 2 hours after the end of infusion (used as ‘peak’ data) on the 2nd and 5th dosing. Dose and dosing interval varied among the patients. ²⁸) For the Bayesian prediction, the observed peak or trough data on the 2nd dosing were used to predict the peak and trough concentrations on the 5th dosing.

The predictive performance was evaluated by comparing the observed and Bayesian predicted concentrations, using ‘mean prediction error (ME)’ as a measure of bias and ‘root mean squared error (RMSE)’ as a measure of precision ²⁹) given by Eqs. (1) and (2), respectively.

\[
ME = \frac{1}{N} \sum_{j=1}^{N} (C_{\text{obs},j} - C_{\text{pred},j})
\]

\[
RMSE = \sqrt{\frac{1}{N} \sum_{j=1}^{N} (C_{\text{obs},j} - C_{\text{pred},j})^2}
\]

N is the number of data points, \(C_{\text{obs},j}\) and \(C_{\text{pred},j}\) are the j-th observed and predicted concentrations, respectively. Although the indices, ME and RMSE, should be calculated using log-transformed concentrations as the reported PPK model assumes a log-normal distribution for intra-individual variability, in this paper, we define them by Eqs. (1) and (2), because we thought that evaluation of absolute prediction error is more practical and useful when considering a variable degree of concentrations for clinical use.

**Theoretical evaluation of predictive performance:** In order to theoretically assess the predictive performance and determine the optimal sampling time for the Bayesian prediction using the reported PPK parameters, we evaluated the prediction error of pharmacokinetic parameters and ME and RMSE of VCM concentrations using a simulated data set. Hypothetical serum VCM concentration profiles for 500 subjects were simulated based on the PPK parameters, by assuming a single infusion of 15 mg/kg for 1 hour. The age of each subject was randomly generated from a uniform distribution \(U [0.5, 15]\). The body weight of each subject was not generated, because the amount of the dose and both PPK parameters of CL and Vd are all given with respect to body weight. Individual CL and Vd were generated from a log-normal distribution with the PPK mean value as the mean and inter-individual variability as the variance. The sampling time points were 1, 2, 3, 4, 6, 8 and 12 hours after the start of infusion.

Using the simulated concentration data at any one of the sampling points for each subject, serum concentrations at the peak and the trough were predicted by the Bayesian method to evaluate the effect of sampling time on the predictive performance using ME and RMSE. In the simulation study, the peak and the trough were defined as the point at 2 and 8 hours after the start of infusion (i.e. at 1 and 7 hours after the end of infusion), respectively.

In the simulation study, the predictive performance of the pharmacokinetic parameters such as CL and Vd by the Bayesian method was evaluated based on the prediction error (PE) calculated by Eq. (3),

\[
PE_{jk}(\%) = \frac{P_{\text{pop},jk} - P_{\text{pred},jk}}{P_{\text{pop},jk}} \times 100
\]

where \(P_{\text{pop},jk}\) is an individual pharmacokinetic parameter predicted by population mean parameters and individual covariates, and \(P_{\text{pred},jk}\) is an individually predicted pharmacokinetic parameter by the Bayesian method,
### Table 2. Population pharmacokinetic parameters estimated by the bootstrap method and the cross validation method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PPK Mean</th>
<th>Bootstrap</th>
<th>95% C.I.</th>
<th>Cross validation</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept of CL</td>
<td>0.119</td>
<td>0.116</td>
<td>0.096-0.137</td>
<td>0.096-0.138</td>
<td></td>
</tr>
<tr>
<td>Slope of CL (Age ≤ 1)</td>
<td>0.0619</td>
<td>0.0587</td>
<td>0.0267-0.0907</td>
<td>0.0134</td>
<td></td>
</tr>
<tr>
<td>(Age &gt; 1)</td>
<td>0.00508</td>
<td>0.00481</td>
<td>0.00203-0.00760</td>
<td>0.00193-0.00712</td>
<td></td>
</tr>
<tr>
<td>Slope of Vd</td>
<td>0.522</td>
<td>0.499</td>
<td>0.424-0.574</td>
<td>0.424-0.589</td>
<td></td>
</tr>
<tr>
<td>$\omega^2$ of CL</td>
<td>39.6</td>
<td>38.3</td>
<td>28.2-48.5</td>
<td>30.2-52.8</td>
<td></td>
</tr>
<tr>
<td>$\omega^2$ of Vd</td>
<td>18.8</td>
<td>20.7</td>
<td>NA-42.2</td>
<td>NA-52.0</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>34.6</td>
<td>32.5</td>
<td>28.2-36.9</td>
<td>21.7-29.6</td>
<td></td>
</tr>
</tbody>
</table>

1) PPK: population pharmacokinetic parameters in the reported PPK model for Japanese pediatric patients.
2) Mean, S.E. and 95% C.I. are given as Jackknife estimates.
3) 95% C.I. is calculated from Mean ± 1.96 × S.E.
4) $\omega^2$ and $\sigma^2$ are inter- and intra-individual variability variance, shown as C.V. (%).
5) NA: Not applicable because of a negative value.

**Fig. 1.** Parameter estimates in the reported PPK model (closed circles) and for the 10 subsets for cross validation (open circles). Solid lines indicate the value of the reported PPK parameter estimates and dashed lines indicate ± 1 S.E. range.

1) Slope of CL (Age ≤ 1), 2) Slope of CL (Age > 1).

Results and Discussion

The results of the validation by the bootstrap method and the cross validation method are summarized in **Table 2**. The mean values of the bootstrap estimates for each PPK parameter were comparable with the reported PPK parameter estimates. The mean, S.E. and 95% C.I. for the Jackknife estimates of each parameter by the cross validation method are similar to those obtained by the bootstrap method and the Jackknife mean values are almost comparable with those from the

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**Software:** A computer program for nonlinear mixed effect modeling, NONMEM Version V, was used for the Bayesian prediction with a posthoc option, with a FORTRAN 77 compiler (Sun-Pro) on a Soralis 7 UNIX operation system (Sun Microsystems, U.S.A.). Generation of the simulation data sets was also performed by NONMEM.
reported PPK model. Figure 1 shows the plots of the mean parameter estimates for 10 subsets in the cross validation. The values for each subset are within the range of ±1 S.E. of the reported PPK parameters, thus confirming the robustness and stability of the reported PPK model.

The Bayesian predictability was also examined using the cross validation data sets. Table 3 shows the ME and RMSE values for possible peak/trough combinations from the Bayesian prediction. The values of ME were 1.84 and −0.68 μg/mL when the peak data for peak prediction and the trough data for trough prediction were used, respectively. When the trough concentration was predicted using other trough data, the ME seems to be enough small for practical use. When peak data were used for trough prediction or trough data for peak prediction, the ME values were −1.00 and 2.05 μg/mL, respectively. The RMSE are around 10 μg/mL for peak prediction and are smaller for trough prediction. Figure 2 shows the correlation between the observed and the predicted concentrations for each patient for all combinations in Table 3. When the observed values were greater than 40 μg/mL, the reported PPK parameter estimates tended to underestimate VCM concentrations. A possible explanation for this is the limitation of using a one-compartment model, i.e. the model can not accurately predict higher concentration data around the peak, which may actually be in the distribution phase. Thus, the predictive performance for the trough concentration was generally better than for the peak concentration (Table 3). We therefore conclude that it is better to use trough data for predicting the trough concentration. Considering this and the general understanding that nephrotoxicity is related to the trough concentration,9–11) we suggest that sampling at the trough is preferable for TDM for pediatric patients.

Table 4 shows the predictive performance for the premature patients. Figure 3 shows the correlation between the observed and the predicted concentrations for each combination of each patient. In some patients, there was a considerably large deviation, suggesting that the reported PPK model does not seem to have good applicability for premature patients. One possible reason for less predictability of the reported PPK model

### Table 3. ME and RMSE by cross validation

<table>
<thead>
<tr>
<th>Predicted data point for Bayesian method</th>
<th>Data point for Bayesian method</th>
<th>ME (μg/mL)</th>
<th>RMSE (μg/mL)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>Peak</td>
<td>1.84</td>
<td>10.17</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Trough</td>
<td>2.05</td>
<td>9.41</td>
<td>57</td>
</tr>
<tr>
<td>Trough</td>
<td>Peak</td>
<td>−1.00</td>
<td>5.61</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Trough</td>
<td>−0.68</td>
<td>2.85</td>
<td>48</td>
</tr>
</tbody>
</table>

### Table 4. ME and RMSE for the external premature data set

<table>
<thead>
<tr>
<th>Predicted data point (5th dosing)</th>
<th>Data point for Bayesian method (2nd dosing)</th>
<th>ME (μg/mL)</th>
<th>RMSE (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>Peak</td>
<td>1.92</td>
<td>11.25</td>
</tr>
<tr>
<td>Trough</td>
<td>Trough</td>
<td>−7.77</td>
<td>15.56</td>
</tr>
<tr>
<td>Trough</td>
<td>Peak</td>
<td>6.01</td>
<td>8.36</td>
</tr>
<tr>
<td>Trough</td>
<td>Trough</td>
<td>−1.55</td>
<td>8.52</td>
</tr>
</tbody>
</table>
for premature patients is a difference in the pharmacokinetic properties of VCM between pediatric and premature patients. Therefore, the reported PPK model could not adequately explain the subsequent pharmacokinetic profiles in the premature patients, although some were included in the population data. It is generally said that premature patients have a larger Vd and lower CL because of a larger amount of body water and incomplete maturation of the renal function compared with infants, children and adults.7) Another reason may be the existence of an unincorporated covariate for the inter-individual pharmacokinetic variability. The CL of VCM in premature patients has been reported to depend on their postconceptional age,32) but only the postnatal age is incorporated for the reported PPK parameters. Still another reason may be that the background of the premature population used in this study28) was to some extent different from that of the population used for the development of the reported PPK model.8)

We also examined the predictive performance of the two-point Bayesian method using both peak and trough concentrations in the internal data. ME and RMSE for the peak prediction were 2.43 μg/mL and 11.24 μg/mL and those for the trough prediction were 0.28 μg/mL and 2.96 μg/mL, respectively. These values were similar to those for the one-point Bayesian method (Table 3) and no clear improvement of the predictive performance was found. Therefore, it is considered that one sampling point at the trough is sufficient for prediction.

In the theoretical approach using simulated data, we focused on two predicted time points, peak and trough. Figure 4 shows the ME (Fig. 4(a)) and RMSE (Fig. 4(b)) for predicting peak and trough concentrations when data at several different sampling points were used for the Bayesian method. Regarding ME, peak concentrations tended to be slightly overestimated (less than 0) at all sampling points. However, the ME values are in general small enough for practical use at all sampling points for predicting both peak and trough levels. As shown in Fig. 4(b), the RMSE values for peak prediction are almost independent of the sampling times for the Bayesian estimation, and the predictive performance does not seem to be good even when any sampling points were used for the peak prediction. On the other hand, for the trough prediction, RMSE depended on the sampling times and a later sampling time tended to give smaller RMSE.

Figure 5 shows PE values for the Bayesian estimates of CL and Vd obtained from the simulated data. The plots illustrated that the PE of Vd is almost independent of the sampling time, but in the case of CL, PE is smaller at a later sampling time. Similar findings have been presented in a previous paper,29) and our results coincided well with them. The time dependence in RMSE observed for the trough prediction (Fig. 4(b)) may be related to the time dependence of the predictability for CL shown in Fig. 5(a), as the trough concentration is more informative for CL than other sampling points. Therefore, the trough concentration is considered to be appropriate for predicting trough concentration.

Some reports have appeared on the predictive performance of the Bayesian method for pediatric patients. Rodvold et al. showed that predictive performance is not necessarily acceptable when there is a long period between the times of the observed and predicted concentrations.33) This suggests that the most up-to-date data should be used for the Bayesian prediction, especially for pediatric patients who usually display large intra-individual pharmacokinetic variability. Wrishko et al. also evaluated the predictive performance of VCM concentration in pediatric patients and showed that trough sampling alone could provide clinically acceptable predictions of VCM concentrations at other sam-
Fig. 5. Prediction errors for Bayesian estimates of CL (a) and Vd (b) obtained from the simulated data set. X-axis represents the sampling time point used for the Bayesian method.

They also showed that a later sampling point improved the relative accuracy and precision of trough prediction. These findings coincide with our present results, although the compartment model used in each study is different.

In conclusion, the reported PPK model for pediatric patients was validated and it was confirmed that the Bayesian predictability, especially for the trough concentration, is acceptable, with support from the simulation study. However, the reported PPK model does not seem to have good applicability for premature patients. For pediatric patients, we recommend measuring the trough concentration as the first choice for an optimal sampling point for the Bayesian prediction.

References