Improvement of Predictivity of Teicoplanin Serum Trough Concentrations at Steady State Calculated by Vancomycin Pharmacokinetic Parameter

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According to a recent study and meta-analysis, trough levels of $\geq 10 \mu g/mL$ teicoplanin (TEIC) may be acceptable for the treatment of uncomplicated infection, but no method of TEIC personalized medicine has been established. Vancomycin (VCM) and TEIC are glycopeptide antibiotic agents effective against methicillin-resistant *Staphylococcus aureus*. This study aimed to establish TEIC personalized medicine at a steady state calculated by VCM pharmacokinetic parameters. Bayesian forecasting and population mean methods were employed to estimate individual total VCM clearance (CL) using existing population pharmacokinetics (PPK) parameter, and the differences between the CL calculated by these two methods were defined as $\Delta$CL. Serum drug concentration data for patients treated with TEIC were collected at a steady state concentration ($>96$ h post infusion). There was a significant relationship between the prediction error of TEIC trough level and $\Delta$CL. The relation between $\Delta$CL and TEIC trough concentration at steady state was used to develop the following equation to determine the maintenance dose: $\text{TEIC (}\mu g/mL) = 1.1119X - 6.124\text{CL} + 3.9164$ ($X$ is defined as TEIC trough concentration calculated from the PPK parameter). The results of this study indicated that it is possible to improve the prediction error of TEIC trough concentration at a steady state for patients who have received VCM therapy.

Key words—vancomycin; teicoplanin; therapeutic drug monitoring; Bayesian method; population pharmacokinetics

INTRODUCTION

Teicoplanin (TEIC) is a glycopeptide antimicrobial drug used mainly for the treatment of systemic infections by methicillin-resistant *Staphylococcus aureus* (MRSA).\(^1\) It is generally considered that the trough concentration of TEIC should be $>10 \mu g/mL$ for MRSA infections and $>20 \mu g/mL$ for deep-seated infections, such as endocarditis, bone and joint infection, and osteomyelitis.\(^2-4\)

Although an intravenous loading regimen for TEIC consisting of 400 mg every 12 h for the first three doses has been recommended in many countries, some studies have reported to remain $<10-15 \mu g/mL$.\(^5\) There are some reports that a high-loading dose regimen (6 mg/kg twice daily) resulted in a mean trough concentration of 19.1 $\mu g/mL$ 72 h after administration. However, high-loading dose regimens in patients with impaired renal function have not been established. In fact, the mean trough concentration exceeded 30 $\mu g/mL$ under the high-dosing regimen of 6 mg/kg twice daily for 3 d.\(^6,7\)

Therapeutic drug monitoring (TDM) is recommended to ensure an adequate trough concentration at steady state according to renal function. Recent reports have indicated that dose adjustment based on individual renal function and weight using TDM software for TEIC, based on population pharmacokinetics (PPK), is useful for determining the dose of TEIC. However, the prediction error of drug concentration based on the population mean method could have been observed.\(^8\)

Similar to TEIC, vancomycin (VCM) is a renally eliminated drug, which is an important pharmacokinetic parameter that must be considered in calculating the dose of VCM or TEIC to achieve therapeutic concentration range.

VCM is a first-line treatment for MRSA infection, but meta-analysis suggested apparently lower rates of adverse events with TEIC than VCM, particularly nephrotoxicity.\(^9\) Therefore, the use of teicoplanin for treatment of MRSA could be considered for patients who have risk factors which could accelerate the occurrence of vancomycin nephrotoxicity (treatment with concomitant nephrotoxic agents, prolonged therapy and admittance to an ICU).\(^10\)

The aim of the present study was to analyze the similarity of drug elimination between VCM and
TEIC to minimize prediction error and to establish TEIC personalized medicine at steady state to avoid the risks of over- and underdosing.

**PATIENTS AND METHODS**

The authors conducted a retrospective review of medical records to obtain clinical data of adult patients (≥18 years) from April 2012 to March 2013, and the study was approved by the institutional review board of Jichi Medical University. Patients who were younger than 18 years of age or undergoing hemodialysis were excluded. The following clinical data were recorded on the first day of VCM administration. The retrieved demographic and laboratory data included patients’ age, sex, body weight (kg), serum creatinine concentration (mg/dL), serum concentration (μg/mL) of TEIC, and VCM at steady state. Creatinine clearance (CLcr) was calculated by the formula of Cockcroft and Gault.\(^{11}\) VCM serum samples were obtained for 20 patients who received multiple intravenous TEIC administrations after VCM therapy and received TDM for treatment of MRSA infection. Serum blood samples of VCM were obtained within 1 h of the subsequent administration at steady state, which occurred after at least the fourth dose of VCM administration. Using anthropometric data and VCM trough measurements, VCM clearance (CL) was calculated by Bayesian or population mean methods. The serum concentrations of vancomycin were determined by utilizing a chemiluminescent immunoassay.

A two-compartment population model in adult Japanese patients was used.\(^{12,13}\) A proportional error model was used to describe inter-individual variability and residual variability (Table 1). The Bayesian method was applied using the nonlinear multiple regression computer program MULT2.\(^{14}\)

TEIC was administered by an initial loading dose of 400 mg every 12 h for three doses (regardless of renal function), followed by a maintenance dose of 400 mg every 24 h. TEIC trough samples were obtained within 1 h of the subsequent administration at steady state concentration (≥4 d after first TEIC infusion). The serum concentrations of TEIC were determined by utilizing a latex agglutination turbidimetry.

Univariate analysis was performed to identify significant covariates [VCM PK parameter (ΔCL) or PEVCM] associated with TEIC trough concentration at steady state. Covariates determined to be significant in univariate analysis were then included in multiple regression analysis to estimate a regression equation.

\[
PEVCM (\mu g/mL) = \text{observed VCM trough} - \text{predicted VCM trough based on population mean method}
\]

\[
PETEIC (\mu g/mL) = \text{observed TEIC trough} - \text{predicted TEIC trough based on population mean method}
\]

\[
\Delta CL (L/h) = \text{calculated CL of VCM based on Bayesian forecasting method} - \text{predicted CL of VCM based on population mean method}
\]

In evaluation of the prediction accuracy of TEIC trough concentration at steady state by the regression equation, the bias of prediction [mean prediction error (ME)], accuracy of prediction [mean absolute prediction error (MAE)], and 95% confidence interval (95% CI) were calculated based on the approach of Sheiner and Beal.\(^{15}\)

ME (μg/mL) = \frac{1}{n} \Sigma (\text{predicted concentration} - \text{observed concentration})

MAE (μg/mL) = \frac{1}{n} \Sigma |\text{predicted concentration} - \text{observed concentration}|

Statistical analysis in this study was descriptive, with continuous variables summarized as mean±S.D. A p value <0.05 was considered to be statistical-

**Table 1. Population Pharmacokinetic Parameter in Japanese Adult Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population mean</th>
<th>Interindividual variability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>0.0322×CLcr + 0.32</td>
<td>37.5</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>0.478×BW</td>
<td>18.2</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>60.6</td>
<td>72.8</td>
</tr>
<tr>
<td>Q (L/h)</td>
<td>8.81</td>
<td>19.2</td>
</tr>
</tbody>
</table>

Intraindividual residual variability: σ=14.3%.

TEIC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population mean</th>
<th>Interindividual variability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>0.00498×CLcr + 0.00426×BW</td>
<td>22.1</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>10.4</td>
<td>26.7</td>
</tr>
<tr>
<td>K12 (/h)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>K21 (/h)</td>
<td>0.0485</td>
<td>24.5</td>
</tr>
</tbody>
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Intraindividual residual variability: σ=15.6%.

Population pharmacokinetics model. Wherein CL is clearance, Vc is the volume of the central compartment, Vp is the volume of the peripheral compartment, Q is the inter-compartment clearance, K12 and K21 are intra-compartmental rate constants.
RESULTS

The authors included 20 patients (14 males and 6 females) between April 2012 and March 2013. The demographic and clinical characteristics of the subjects at the point estimate of each drug pharmacokinetics parameters are summarized in Table 2. The time of first infusion of TEIC from VCM parameters calculated was 8.6±11.3 d.

The results for the relationship between PETEIC and PEVCM or ΔCL are shown in Fig. 1. Univariate regression analysis of ΔCL and PETEIC showed a negative correlation ($R^2=0.383$, $p=0.0029$), but the relationship between PEVCM and PETEIC showed a low positive correlation ($R^2=0.271$, $p=0.0173$). The regression equation for the predicted TEIC concentrations using ΔCL is given as follows: TEIC (µg/mL) = 1.1119X−6.124ΔCL+3.9164 (Equation 1). $X$ represents TEIC trough concentrations calculated from the PPK parameter. The prediction accuracies for concentrations obtained using population mean method and equation 1 are shown in Fig. 2. There was good agreement between the measured serum TEIC trough concentration and that predicted by equation 1. In the estimate calculated by equation 1, ME and MAE were 0.0 and 4.29 µg/mL respectively, whereas in the estimate by the population mean method, ME and MAE were −2.88 and 5.47 µg/mL respectively.

Fig. 1. Relation between PEVCM and PE TEIC or ΔCL Calculated by VCM Parameter

PEVCM (µg/mL) = Observed VCM trough−Predicted VCM trough based on population mean method

PE TEIC (µg/mL) = Observed TEIC trough−Predicted TEIC trough based on population mean method

ΔCL (L/h) = Calculated CL of VCM based on the Bayesian forecasting method−Predicted CL of VCM based on population mean method

DISCUSSION

TEIC has a long serum half life and accordingly takes time to reach a optimal trough concentration at steady state. TEIC needs a loading dose to enable a prompt increase in serum concentration. Several studies have shown a relationship between TEIC serum concentration and clinical efficiency.1,6,16 A logistic regression analysis showed that the probability of successful treatment with TEIC declined with age and increased with mean concentration at non-steady state.5 A appropriate loading dose regimen must be considered mandatory for all patients, regardless of their renal function, to reach the range of appropriate concentrations early in the treatment period.17 However, for adequate trough level at steady state, each patient’s individual renal function must be considered. A multivariate analysis indicated that TEIC trough concentrations during the first few days of therapy were directly influenced only by dose/kg, but
from day 4 trough level was also influenced by renal function.\textsuperscript{7)}

TEIC clearance decreased with renal failure, a response attributed to the reduction of urinary excretion of TEIC in patients with chronic renal impairment.\textsuperscript{18)}

PEVCM and PETEIC showed a low positive correlation ($R^2=0.271, p=0.0173$). The Cockcroft and Gault equation is the most commonly used in clinical practice to estimate drug clearance. As shown in Table 1, creatinine clearance is a covariate of interpatient variability for VCM and TEIC. Each drug is widely used for the treatment of infections caused by MRSA, in which pharmacokinetic parameters (volume of distribution and drug clearance) are affected by the patient’s condition. These drugs display altered pharmacokinetics for critical characteristics, such as illness severity, suggesting that the pathophysiological factors enhance drug clearance. Furthermore, increased drug clearance and thus, an increased dose were required to reach an exposure in patients with hematological malignancies similar to that in the general population.\textsuperscript{19–22)} It has been shown that similar to VCM, TEIC is eliminated with higher clearance than that expected from already available data for the general population. Thus, VCM and TEIC are apparently influenced by the same factors changing drug disposition.

In this study, there was a significant relationship between $\Delta$CL and PETEIC, which showed a negative correlation ($R^2=0.383, p=0.0029$). The Bayesian method for estimating accurate pharmacokinetic parameters was superior to the population mean method. Furthermore, the predicted trough concentration error at steady state was influenced mostly by the difference in clearance between population and actual values, considering that the trough level at steady state is affected by drug clearance even more than the volume of distribution. Thus, the Bayesian method can more accurately estimate VCM clearance and account for actual VCM clearance in individual patients, providing additional data for improving the prediction of TEIC concentration at steady state and thereby requiring dosage adaptation to avoid the risk of over- and underdosing. We expect that such a mechanism will affect the elimination of all renally eliminated drugs.

TEIC binds strongly to serum proteins and patients with hypoalbuminemia were indicated to have lower serum trough concentrations than healthy volunteers.\textsuperscript{23)} Demographic data had indicated that all patients had decreased albumin concentrations ($2.8 \pm 0.49$ g/dL) at the point estimate VCM parameters. We calculated VCM clearance used by Bayesian method based on VCM PPK parameters.
which is estimated from patients with lower albumin concentrations (the mean value was 2.56 g/dL). Albumin concentrations were introduced in clearance model equation as a possible factor. However, TEIC concentrations with hypoalbuminemia patients is the almost same as compared with the clearance calculated by equation without albumin concentration. Therefore, hypoalbuminemia may contribute to TEIC trough concentrations, but the role of hypoalbuminemia is limited in case of simulation based on TEIC PPK parameters.

The results of this study indicated that predicted VCM concentrations are higher than observed concentrations. In contrast, predicted TEIC concentrations are slightly lower than observed concentrations. Imai et al. have reported that VCM predicted concentrations calculated by VCM PPK parameters is higher than observed concentrations, which means that clearance predicted using PPK could be underestimated. In contrast, Niwa et al. have reported the predicted TEIC concentrations in patients were similar to the observed concentrations. Our results are consistent with their studies. The x-intercept in Fig.1 is different from zero for the relationship between ΔCL and PETEIC, suggesting that ΔCL comprise underestimation of VCM clearance in addition to the common variation pharmacokinetics factors between VCM and TEIC.

We acknowledge that the main limitation of this study is the small sample size for analysis. However, equation 1, which includes VCM pharmacokinetic parameters, could improve the predictivity of trough concentration of TEIC at steady state, considering that ΔCL includes various factors that affect TEIC clearance. These findings suggest that the individual adjustment of maintenance doses based on equation 1 is useful for reaching an adequate therapeutic TEIC concentration range.

Conflicts of Interest The authors declare non conflict of interest.

REFERENCES


