Is Peak Concentration Needed in Therapeutic Drug Monitoring of Vancomycin? A Pharmacokinetic-Pharmacodynamic Analysis in Patients with Methicillin-Resistant Staphylococcus aureus Pneumonia

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Key Words
Vancomycin · Therapeutic drug monitoring · Peak concentration · Pharmacokinetic-pharmacodynamic relationship

Abstract
Background: We analyzed the pharmacokinetic-pharmacodynamic relationship of vancomycin to determine the drug exposure parameters that correlate with the efficacy and nephrotoxicity of vancomycin in patients with methicillin-resistant Staphylococcus aureus pneumonia and evaluated the need to use peak concentration in therapeutic drug monitoring (TDM). Methods: Serum drug concentrations of 31 hospitalized patients treated with vancomycin for methicillin-resistant S. aureus pneumonia were collected. Results: Significant differences in trough concentration (Cmin)/minimum inhibitory concentration (MIC) and area under the serum concentration-time curve (AUC0–24)/MIC were observed between the response and non-response groups. Significant differences in Cmin and AUC0–24 were observed between the nephrotoxicity and non-nephrotoxicity groups. Receiver operating characteristic curves revealed high predictive values of Cmin/MIC and AUC0–24/MIC for efficacy and of Cmin and AUC0–24 for safety of vancomycin. Conclusions: These results suggest little need to use peak concentration in vancomycin TDM because Cmin/MIC and Cmin are sufficient to predict the efficacy and safety of vancomycin.

Introduction
Throughout the world, the treatment of infectious diseases caused by Gram-positive bacteria has been complicated by the emergence of bacteria resistant to β-lactam, macrolide and fluoroquinolone antibacterial drugs [1–3]. Vancomycin is a glycopeptide antibiotic and one of the most widely used antibiotics for the treatment of serious infections by methicillin-resistant Staphylococcus aureus (MRSA) [4]. Recent vancomycin therapeutic monitoring guidelines recommend more aggressive vancomycin dosing regimens and maintaining vancomycin trough concentrations (Cmin) between 15 and 20 μg/ml, aiming to achieve optimal target serum vancomycin concentrations and improve clinical outcomes [5]. Given the link with pharmacodynamics, several studies have revealed that the area under the serum concentration-time curve (AUC)/minimum inhibitory concentration (MIC) is the preferred parameter for therapeutic monitoring based in
part on data obtained from animal models, in vitro studies and limited human studies [6–8]. On the other hand, a recent prospective multicenter trial has suggested that vancomycin Cmin >15 μg/ml at steady state is a risk factor for nephrotoxicity [9]. Thus, Cmin or AUC may be useful for therapeutic drug monitoring (TDM) of vancomycin.

Blood samplings at several time points are necessary for the accurate prediction of AUC. However, serial serum vancomycin concentrations are difficult to obtain in the clinical setting. In Japan, peak concentration (Cmax) and Cmin of vancomycin are measured routinely for vancomycin TDM. Furthermore, the measurement error was 5% for routine clini-

Patients and Methods

Patients
Medical records were reviewed to identify hospitalized patients treated with vancomycin for MRSA pneumonia at Oita University Hospital between June 2005 and December 2011. Patients who were younger than 18 years of age, hemodialyzed or received other anti-MRSA agents were excluded. MRSA pneumonia was diagnosed based on the following criteria: radiographically documented hospital-acquired pneumonia, sputum specimen positive for MRSA, fever and elevated white blood cell count or C-reactive protein. Serum drug concentrations (trough and peak) were obtained from routine TDM data. An average of 2.8 (range 2–6) serum vancomycin level data were available from each patient. The following clinical data recorded on the first day of vancomycin administration and on the same day as TDM were also collected: gender, age, body weight and serum creatinine. Creatinine clearance was calculated according to the Cockcroft-Gault equation [11]. This study was approved by the ethics committee of Oita University Hospital. Since blood samples were collected as part of the routine patient care for TDM and laboratory testing, written informed consent was not necessary.

Drug Concentration Monitoring

Vancomycin was infused intravenously over 1–2 h. Venous blood samples were collected within an hour before the next administration and from 1 to 2 h after vancomycin infusion. The exact times of dosing and blood sampling were always recorded. Vancomycin assay was performed as part of the routine laboratory test at Oita University Hospital. Serum vancomycin concentrations were determined by a particle-enhanced turbidimetric inhibition immunoassay based on Dimension® Xpand (Siemens Inc., III., USA). With this method, the limit of detection was 0.8 μg/ml and the coefficient of variation was <5% for routine clinical TDM. Furthermore, the measurement error was <10% in serum samples containing 30 mg/dl creatinine and 500 mg/dl urea, indicating that the measurements were not affected by the renal function of the patients.

Estimation of Pharmacokinetic Parameters
Pharmacokinetics of vancomycin were analyzed using a two-compartment model, with elimination of the central compartment. The Bayesian forecasting method was employed to estimate individual pharmacokinetic parameters including total body clearance, volume of distribution at steady state, transfer rate constant from central to peripheral, and transfer rate constant from peripheral to central, using individual serum drug concentrations and the population parameters [10]. The estimated parameters allowed prediction of an individual serum concentration-time curve and estimation of AUC from time 0 to 24 h (AUC0–24), Cmax and Cmin. The Cmax and Cmin values were estimated for individual patients at the end of infusion and immediately before starting the next infusion, respectively. The highest Cmax, Cmin and AUC0–24 values during the treatment period were used to analyze the potential association with efficacy and nephrotoxicity of vancomycin, because these individual values varied during treatment due to changes in dose and dosing interval according to TDM.

Determination of Bacteriological Efficacy and MIC
MRSA strains were identified by the Clinical Microbiology Laboratory in Oita University Hospital. The viable counts (colony-forming units) of MRSA in patient’s sputum samples were quantitatively determined before and >4 days after the first vancomycin infusion. Bacteriological efficacy was classified as follows: (1) excellent response was defined as eradication of MRSA; (2) good response was defined as a reduction in viable count of >1 log10 colony-forming units, and (3) poor response was defined as <1 log10 reduction, no change or increase in viable count. Patients with excellent and good responses were classified as the response group, and those with poor response as the non-response group. The MIC of vancomycin was determined by the broth microdilution method according to the guidelines of the National Committee for Clinical Laboratory Standards [12].

Evaluation of Nephrotoxicity
Occurrence of nephrotoxicity was defined as an increase in serum creatinine level of 0.5 mg/dl or a 50% increase, whichever was greater, on at least 2 consecutive days during the period from initiation of vancomycin therapy to 72 h after the completion of therapy [13].

Pharmacokinetic-Pharmacodynamic Analysis and Statistics
For the analysis of bacteriological efficacy, pharmacokinetic-pharmacodynamic parameters including Cmax/MIC, Cmin/MIC and AUC0–24/MIC were compared between response and non-response groups. Both MIC and pharmacokinetic-pharmacodynamic indices were assumed to show a log normal distribution. Therefore, the values for these variables were transformed to natural logarithm. For the analysis of nephrotoxicity, pharmacokinetic parameters including Cmax, Cmin and AUC0–24 were compared between the presence (nephrotoxicity group) and absence of nephrotoxicity (non-nephrotoxicity group). Differences between the two groups were analyzed by two-sided Student’s t test. The relationship between observed and predicted concentrations in individuals was analyzed by Pearson’s product-moment cor-

Is Peak Concentration Needed in TDM of Vancomycin?
Table 1. Patient characteristics at the first day of vancomycin administration and their drug exposure parameters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>31</td>
</tr>
<tr>
<td>Males/females</td>
<td>28/3</td>
</tr>
<tr>
<td>Age, years (y)</td>
<td>73.0 ± 9.2 (54–87)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>52.8 ± 11.4 (35.7–77.0)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>23.4 ± 6.5 (13.4–34.9)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>1.2 ± 0.4 (0.67–2.06)</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min</td>
<td>61.8 ± 31.4 (24.0–153.5)</td>
</tr>
<tr>
<td>Serum vancomycin Cmax, g/ml</td>
<td>2.8 ± 1.1 (2–6)</td>
</tr>
<tr>
<td>Cmin, g/ml</td>
<td>42.5 ± 9.9 (19.3–62.2)</td>
</tr>
<tr>
<td>AUC0–24, µg·h/ml</td>
<td>540.6 ± 165.0 (214.6–890.3)</td>
</tr>
<tr>
<td>Cmax/MIC</td>
<td>49.1 ± 18.0 (19.3–98.3)</td>
</tr>
<tr>
<td>Cmin/MIC</td>
<td>19.0 ± 10.0 (3.2–45.8)</td>
</tr>
<tr>
<td>AUC0–24/MIC</td>
<td>629.1 ± 272.8 (214.6–1320.6)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD, with ranges in parentheses. Creatinine clearance was calculated according to the Cockcroft-Gault equation.

Results

A review of patient records identified 31 patients who satisfied the inclusion criteria. Table 1 describes the characteristics of these patients on the first day of vancomycin administration. Of the 31 patients, 23 were assessed as showing response (response group) and 8 as showing no response (non-response group). The MIC of vancomycin was 0.5 µg/ml in 5 patients and 1 µg/ml in 18 patients in the response group, while the MIC was 1 µg/ml in all patients in the non-response group. The duration of vancomycin treatment was 12.3 ± 4.4 and 11.4 ± 4.2 days in the response and non-response group, respectively, with no significant difference between the two groups (p = 0.40). On the other hand, nephrotoxicity was observed in 7 patients. The duration of vancomycin treatment was 12.9 ± 5.2 and 11.9 ± 4.1 days in patients with nephrotoxicity and without nephrotoxicity, respectively, and did not differ significantly between the two groups (p = 0.60). Nephrotoxicity occurred 9.7 ± 4.8 days after initiation of vancomycin, after the period of blood sampling for TDM (5.0 ± 2.9 days). Scatter plots showed a good correlation between the observed and predicted concentrations of individuals (γ = 0.96x + 0.48; r = 0.95).

Figure 1 shows the box and whisker plots of the pharmacokinetic-pharmacodynamic parameters in the response and non-response groups (fig. 1a–c) and the pharmacokinetic parameters in the nephrotoxicity and non-nephrotoxicity groups (fig. 1d–f). Significant differences in Cmin/MIC and AUC0–24/MIC (p = 0.049 and 0.044, respectively) were observed between the response and non-response group, while no significant difference in Cmax/MIC (p = 0.222) was detected between the two groups. Significant differences in Cmin and AUC0–24 (p = 0.011 and 0.014, respectively) were observed between the nephrotoxicity and non-nephrotoxicity group, while no significant difference in Cmax (p = 0.498) was detected between the two groups. Figure 2a shows the ROC curves for the efficacy of vancomycin comparing the pharmacokinetic-pharmacodynamic parameters. The AUCROC was 0.67, 0.77 and 0.76 for Cmax/MIC, Cmin/MIC and AUC0–24/MIC, respectively. Similarly, figure 2b shows the ROC curves for nephrotoxicity associated with vancomycin comparing the pharmacokinetic parameters. The AUCROC was 0.63, 0.84 and 0.83 for Cmax, Cmin and AUC0–24, respectively.

Discussion

Conventionally, Cmax together with Cmin are considered to be necessary in vancomycin TDM [5]. Geraci [14] recommended a Cmax range of 30–40 µg/ml, but did not provide the basis of how it was derived. Recent vancomycin therapeutic monitoring guidelines recommend to measure Cmin and to maintain Cmin between 15 and 20 µg/ml. From the pharmacokinetic-pharmacodynamic viewpoint, several studies have proposed AUC/MIC as the preferred parameter [6–8]. An AUC0–24/MIC ≥400 was recommended to optimize the pharmacokinetic-pharmacodynamic properties of vancomycin [15, 16]. Estimation of AUC is incomplete without the Cmax; thus, blood samplings at 2 or more time points (including trough and peak) are necessary to evaluate AUC/MIC as an index for vancomycin efficacy. In this study, we attempted to evaluate the need to use Cmax in vancomycin TDM by analyzing the pharmacokinetic-pharmacodynamic relationship with efficacy and safety.
This study enrolled only patients with MRSA pneumonia not receiving any other anti-MRSA agents. This selection criterion precludes the bias due to differences in pathological conditions and other coadministered anti-MRSA agents. We selected bacteriological response as the criterion for efficacy of vancomycin, which allows more precise evaluation of the efficacy of vancomycin against MRSA pneumonia. To evaluate the adverse effect of vancomycin, we selected nephrotoxicity in view of the high incidence and clinical importance.

Vancomycin therapy was effective in approximately 74.2% of the patients in this study. Significant differences

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**Fig. 1.** Box and whisker plots of the pharmacokinetic-pharmacodynamic parameters in response and non-response groups (a–c) and pharmacokinetic parameters in nephrotoxicity and non-nephrotoxicity groups (d–f). Boxes indicate 25th, 50th and 75th percentiles, and whiskers show ±1.5 times the interquartile range. ○ = Outlier.

**Fig. 2.** ROC curves for the efficacy of vancomycin comparing various pharmacokinetic-pharmacodynamic parameters (a) and for nephrotoxicity associated with vancomycin comparing different pharmacokinetic parameters (b).
in C$_{\text{min}}$/MIC and AUC$_{0–24}$/MIC were observed between the response and non-response group, while no significant difference in C$_{\text{max}}$/MIC was found between the two groups. In addition, ROC curves revealed equally high predictive powers for both C$_{\text{min}}$/MIC and AUC$_{0–24}$/MIC, which were superior to that of C$_{\text{max}}$/MIC. These results indicate that C$_{\text{min}}$/MIC and AUC$_{0–24}$/MIC are equally useful in predicting the efficacy of vancomycin in patients with MRSA pneumonia. Incidentally, no significant differences in both C$_{\text{min}}$ and AUC$_{0–24}$ were observed between the response and non-response group (p = 0.186 and 0.212, respectively). This finding suggests that pharmacokinetic parameters alone are not useful to predict response, but pharmacokinetic-pharmacodynamic parameters (C$_{\text{min}}$/MIC and AUC$_{0–24}$/MIC) that take into account both pharmacokinetics of vancomycin and sensitivity of the MRSA strain infecting the patient are necessary to predict the efficacy of vancomycin treatment for MRSA infection in each individual. On the other hand, nephrotoxicity was observed in approximately 22.6% of the patients in this study. A review demonstrated that nephrotoxicity associated with vancomycin therapy was observed in 2–28% of patients [17]. The dose of vancomycin was relatively high in this study because all patients had MRSA pneumonia, which may account for the relatively high incidence of nephrotoxicity. Significant differences in C$_{\text{min}}$ and AUC$_{0–24}$ were observed between the nephrotoxicity and non-nephrotoxicity group. In addition, ROC curves revealed equally high predictive powers for both C$_{\text{min}}$ and AUC$_{0–24}$, which were superior to that of C$_{\text{max}}$. These results indicate that C$_{\text{min}}$ and AUC$_{0–24}$ are equally useful in predicting the safety of vancomycin in patients with MRSA pneumonia. Therefore, our results do not support the necessity to use C$_{\text{max}}$ for vancomycin TDM because C$_{\text{min}}$/MIC and C$_{\text{min}}$ are sufficient to predict the efficacy and safety of vancomycin. This is the first report indicating that C$_{\text{min}}$ has little use in vancomycin TDM, and our finding may contribute to reduce the labor and cost in vancomycin TDM. However, the present study has some limitations: the study was retrospective and analyzed a small number of patients. Further, a large-scale prospective study is required to verify whether a change in practice to measure trough level and MIC is appropriate in vancomycin TDM.

In conclusion, we evaluated the need to use C$_{\text{max}}$ for TDM of vancomycin by analyzing the pharmacokinetic-pharmacodynamic relationship with efficacy and safety. In this study, C$_{\text{min}}$/MIC and AUC$_{0–24}$/MIC were equally powerful to predict efficacy while C$_{\text{min}}$ and AUC$_{0–24}$ were equally powerful to predict safety of vancomycin in patients with MRSA pneumonia. These results suggest that there is little need to use C$_{\text{max}}$ in vancomycin TDM.

References