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

Yosuke Suzuki^a Kanako Kawasaki^a Yuhki Sato^a Issei Tokimatsu^b Hiroki Itoh^a
Kazufumi Hiramatsu^b Masaharu Takeyama^a Jun-ichi Kadota^b

^aDepartment of Clinical Pharmacy, Oita University Hospital, and ^bInternal Medicine II, Oita University Faculty of Medicine, Oita, Japan

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 ($C_{\min}$)/minimum inhibitory concentration (MIC) and area under the serum concentration-time curve (AUC_{0-24})/MIC were observed between the response and non-response groups. Significant differences in $C_{\min}$ and AUC_{0-24} were observed between the nephrotoxicity and non-nephrotoxicity groups. Receiver operating characteristic curves revealed high predictive values of $C_{\min}$ /MIC and AUC_{0-24} /MIC for efficacy and of $C_{\min}$ and AUC_{0-24} for safety of vancomycin. **Conclusions:** These results

suggest little need to use peak concentration in vancomycin TDM because $C_{\min}$ /MIC and $C_{\min}$ are sufficient to predict the efficacy and safety of vancomycin.

Copyright © 2012 S. Karger AG, Basel

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 ($C_{\min}$) between 15 and 20 $\mu\text{g/ml}$, 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 $C_{\min} > 15 \mu\text{g/ml}$ at steady state is a risk factor for nephrotoxicity [9]. Thus, $C_{\min}$ 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 ($C_{\max}$) and $C_{\min}$ of vancomycin are measured routinely for vancomycin TDM [10]. $C_{\max}$ is useful to predict the AUC, but it may be unnecessary if $C_{\min}$ and AUC are equally useful for predicting vancomycin efficacy. In this study, we analyzed the pharmacokinetic-pharmacodynamic relationship of vancomycin to determine the drug exposure parameters that correlate with the efficacy and safety of vancomycin and to evaluate whether $C_{\max}$ is needed for TDM in patients with MRSA pneumonia.

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., Ill., USA). With this method, the limit of detection was $0.8 \mu\text{g/ml}$ and the coefficient of variation was $< 5\%$ for routine clinical TDM. Furthermore, the measurement error was $< 10\%$ in se-

rum 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 (AUC_{0-24}), $C_{\max}$ and $C_{\min}$. The $C_{\max}$ and $C_{\min}$ values were estimated for individual patients at the end of infusion and immediately before starting the next infusion, respectively. The highest $C_{\max}$, $C_{\min}$ and AUC_{0-24} 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 $> 1 \log_{10}$ colony-forming units, and (3) poor response was defined as $< 1 \log_{10}$ 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 $C_{\max}/\text{MIC}$, $C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$ 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 $C_{\max}$, $C_{\min}$ and AUC_{0-24} 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-

Table 1. Patient characteristics at the first day of vancomycin administration and their drug exposure parameters

Characteristic	Value
Subjects	31
Males/females	28/3
Age, years	73.0 ± 9.2 (54–87)
Body weight, kg	52.8 ± 11.4 (35.7–77.0)
Blood urea nitrogen, mg/dl	23.4 ± 6.5 (13.4–34.9)
Serum creatinine, mg/dl	1.2 ± 0.4 (0.67–2.06)
Creatinine clearance, ml/min	61.8 ± 31.4 (24.0–153.5)
Serum vancomycin level data per patient, n	2.8 ± 1.1 (2–6)
MIC, µg/ml	0.92 ± 0.19 (0.5–1)
C _{max} , µg/ml	42.5 ± 9.9 (19.3–62.2)
C _{min} , µg/ml	16.3 ± 6.8 (3.2–29.8)
AUC _{0–24} , µg·h/ml	540.6 ± 165.0 (214.6–890.3)
C _{max} /MIC	49.1 ± 18.0 (19.3–98.3)
C _{min} /MIC	19.0 ± 10.0 (3.2–45.8)
AUC _{0–24} /MIC	629.1 ± 272.8 (214.6–1,320.6)

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

relation coefficient. To evaluate the diagnostic accuracy of the pharmacokinetic-pharmacodynamic parameters, receiver operating characteristic (ROC) curve and area under the ROC curve (AUC_{ROC}) were analyzed. All values are expressed as the mean ± SD. A *p* value <0.05 was considered statistically significant. Statistical analyses were performed using the R software version 2.14.2 (<http://www.r-project.org>) and Predictive Analysis Software Statistics version 18 (SPSS Inc., Chicago Ill., USA).

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 nephro-

toxicity 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 (*y* = 0.96*x* + 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 C_{min}/MIC and AUC_{0–24}/MIC (*p* = 0.049 and 0.044, respectively) were observed between the response and non-response group, while no significant difference in C_{max}/MIC (*p* = 0.222) was detected between the two groups. Significant differences in C_{min} and AUC_{0–24} (*p* = 0.011 and 0.014, respectively) were observed between the nephrotoxicity and non-nephrotoxicity group, while no significant difference in C_{max} (*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 AUC_{ROC} was 0.67, 0.77 and 0.76 for C_{max}/MIC, C_{min}/MIC and AUC_{0–24}/MIC, respectively. Similarly, figure 2b shows the ROC curves for nephrotoxicity associated with vancomycin comparing the pharmacokinetic parameters. The AUC_{ROC} was 0.63, 0.84 and 0.83 for C_{max}, C_{min} and AUC_{0–24}, respectively.

Discussion

Conventionally, C_{max} together with C_{min} are considered to be necessary in vancomycin TDM [5]. Geraci [14] recommended a C_{max} 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 C_{min} and to maintain C_{min} between 15 and 20 µg/ml. From the pharmacokinetic-pharmacodynamic viewpoint, several studies have proposed AUC/MIC as the preferred parameter [6–8]. An AUC_{0–24}/MIC ≥400 was recommended to optimize the pharmacokinetic-pharmacodynamic properties of vancomycin [15, 16]. Estimation of AUC is incomplete without the C_{max}; 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 C_{max} in vancomycin TDM by analyzing the pharmacokinetic-pharmacodynamic relationship with efficacy and safety.

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. $\circ$ = 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**).

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

in $C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$ were observed between the response and non-response group, while no significant difference in $C_{\max}/\text{MIC}$ was found between the two groups. In addition, ROC curves revealed equally high predictive powers for both $C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$, which were superior to that of $C_{\max}/\text{MIC}$. These results indicate that $C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$ are equally useful in predicting the efficacy of vancomycin in patients with MRSA pneumonia. Incidentally, no significant differences in both $C_{\min}$ 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 ($C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$) 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 differ-

ences in $C_{\min}$ and AUC_{0-24} were observed between the nephrotoxicity and non-nephrotoxicity group. In addition, ROC curves revealed equally high predictive powers for both $C_{\min}$ and AUC_{0-24} , which were superior to that of $C_{\max}$. These results indicate that $C_{\min}$ 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 $C_{\max}$ for vancomycin TDM because $C_{\min}/\text{MIC}$ and $C_{\min}$ are sufficient to predict the efficacy and safety of vancomycin. This is the first report indicating that $C_{\max}$ 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 $C_{\max}$ for TDM of vancomycin by analyzing the pharmacokinetic-pharmacodynamic relationship with efficacy and safety. In this study, $C_{\min}/\text{MIC}$ and $\text{AUC}_{0-24}/\text{MIC}$ were equally powerful to predict efficacy while $C_{\min}$ 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 $C_{\max}$ in vancomycin TDM.

References

- Rivera AM, Boucher HW: Current concepts in antimicrobial therapy against select Gram-positive organisms: methicillin-resistant *Staphylococcus aureus*, penicillin-resistant pneumococci, and vancomycin-resistant enterococci. *Mayo Clin Proc* 2011;86:1230–1243.
- Sanfilippo CM, Hesje CK, Haas W, et al: Topoisomerase mutations that are associated with high-level resistance to earlier fluoroquinolones in *Staphylococcus aureus* have less effect on the antibacterial activity of besifloxacin. *Chemotherapy* 2011;57:363–371.
- Yoon EJ, Lee CY, Shim MJ, et al: Extended spectrum of quinolone resistance, even to a potential latter third-generation agent, as a result of a minimum of two GrlA and two GyrA alterations in quinolone-resistant *Staphylococcus aureus*. *Chemotherapy* 2010;56:153–157.
- Moellering RC Jr: Vancomycin: a 50-year reassessment. *Clin Infect Dis* 2006;42(suppl 1):S3–S4.
- Rybak M, Lomaestro B, Rotschafer JC, et al: Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009;66:82–98.
- Rybak MJ: The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis* 2006;42(suppl 1):S35–S39.
- Craig WA: Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am* 2003;17:479–501.
- Craig WA: Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998;26:1–10.
- Bosso JA, Nappi J, Rudisill C, et al: Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. *Antimicrob Agents Chemother* 2011;55:5475–5479.
- Yasuhara M, Iga T, Zenda H, et al: Population pharmacokinetics of vancomycin in Japanese adult patients. *Ther Drug Monit* 1998;20:139–148.
- Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
- Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically. Approved Standard M7-A5, ed 5. Wayne, National Committee for Clinical Laboratory Standards, 2000.
- Lodise TP, Lomaestro B, Graves J, et al: Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother* 2008;52:1330–1336.
- Geraci JE: Vancomycin. *Mayo Clin Proc* 1977;52:631–634.
- Moise-Broder PA, Forrest A, Birmingham MC, et al: Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet* 2004;43:925–942.
- Kullar R, Davis SL, Levine DP, et al: Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis* 2011;52:975–981.
- Wong-Beringer A, Joo J, Tse E, et al: Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *Int J Antimicrob Agents* 2011;37:95–101.