Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens

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Received 8 December 2010/Returned for modification 21 January 2011/Accepted 3 March 2011

Despite the development of novel antibiotics active against Gram-positive bacteria, vancomycin generally remains the first treatment, although rapidly achieving concentrations associated with maximal efficacy provides an unresolved challenge. The objective of this study was to conduct a population pharmacokinetic analysis of vancomycin in a large population of critically ill patients. This was a retrospective data collection of 206 adult septic critically ill patients who were administered vancomycin as a loading dose followed by continuous infusion. The concentration-versus-time data for vancomycin in serum was analyzed by a nonlinear mixed-effects modeling approach using NONMEM. Monte Carlo simulations were performed using the final covariate model. We found that the best population pharmacokinetic model consisted of a one-compartment linear model with combined proportional and additive residual unknown variability. The volume of distribution of vancomycin (1.5 liters/kg) was described by total body weight and clearance (4.6 liters/h) by 24-hour urinary creatinine clearance (CrCl), normalized to body surface area. Simulation data showed that a 35-mg/kg loading dose was necessary to rapidly achieve vancomycin concentrations of 20 mg/liter. Daily vancomycin requirements were dependent on CrCl, such that a patient with a CrCl of 100 ml/min/1.73 m2 would require at least 35 mg/kg per day by continuous infusion to maintain target concentrations. In conclusion, we have found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations in these patients.

Infections in critically ill patients occur frequently and may lead to the development of sepsis or septic shock. The morbidity and mortality rates for sepsis and septic shock remain unacceptably high, with septic shock still associated with a 35 to 65% in-hospital mortality rate (5, 9). A significant body of work now describes the importance of early and appropriate antibiotic therapy as the intervention likely to minimize therapeutic failure (10, 17, 18).

Of significant concern for clinicians is the increasing prevalence of multidrug-resistant bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA), which has been found to be the causative pathogen in more than 10% of infections resulting in septic shock (9). Furthermore, data from the United States have reported that 25.8% of bacteraemias are due to MRSA (4), with mortality rates for MRSA bacteremia in critically ill patients being reported as between 45 and 55% (3, 13). Certainly, mortality rates for MRSA pneumonia in critically ill patients may be even higher (12). While newer agents are now available, vancomycin remains the standard of care for treatment of MRSA infections in the intensive care unit (ICU) (30).

Despite vancomycin being in ubiquitous use for over 50 years, dosing in specific populations, particularly the critically ill, remains confused. Conventional dosing regimens of 500 mg every 6 h or 1 g every 12 h have little evidence supporting their efficacy (7), while data from the work of Moise-Broder et al. (22) for MRSA pneumonia suggest that standard dosing approaches are unlikely to achieve the required pharmacodynamic index of vancomycin exposure needed for optimal activity. Pursuant to this, a consensus review in 2009 by the American Society of Health System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Disease Pharmacists (ASHP/IDSA/SDIP) recommended more-aggressive vancomycin dosing to achieve the pharmacodynamic index associated with efficacy (30).

Continuous infusion (CI) of vancomycin allows more rapid achievement of therapeutic drug concentrations than does intermittent infusion and may optimize its bactericidal activity. Recent publications recommend a loading dose of 15 mg/kg of body weight followed by a daily dose of 30 mg/kg (33); however, data on the efficacy of this strategy in a septic population are scarce.

In this respect, the aim of this study was to conduct a population pharmacokinetic (PK) analysis of vancomycin continuous administration in a large cohort of critically ill patients, in order to better inform dosing in this population and to reduce the risks for subtherapeutic drug exposure.

MATERIALS AND METHODS

Patients and data collection. We reviewed all the medical charts of patients with a diagnosis of sepsis (18) admitted to the Intensive Care Unit (ICU) at Erasme Hospital (Brussels, Belgium) between January 2008 and December 2009, to whom continuous infusion (CI) of vancomycin, either in monotherapy or
combined with other antimicrobials, was administered. Patients meeting any of the following criteria were excluded: (i) age less than 18 yrs; (ii) previous ad-
ministration of vancomycin by intermittent infusion (<45 h from the onset of CI); (iii) renal replacement therapy; (iv) duration of CI of vancomycin of <48 h; and (v) pregnancy, burns, or cystic fibrosis (because of altered pharmacokinetics, independent of sepsis). The study period was limited to the ICU stay. Ethical approval to conduct the study was granted by the local ethics committee.

For all study patients, data were collected in an institutional database. The severity of illness of each patient was characterized using the Acute Physiology and Chronic Health Evaluation (APACHE) II (16) and sepsis organ failure assessment (SOFA) (32) scores determined on the first day of antibiotic treat-
ment. Urinary creatinine clearance (CrCl) was collected as a routine procedure in all of the patients, calculated daily, and normalized to body surface area (BSA). Treatment of patients with catecholamines or mechanical ventilation was also recorded, as was length of ICU and hospital stay, overall mortality, and cause of death.

Vancomycin treatment. Administration of vancomycin (Vancocin; Eli Lilly, Indianapolis, IN) was by continuous infusion in accordance with local guidelines and often empirical in the setting of presumed or documented Gram-positive hospital- or ICU-acquired infections, especially when MRSA or other resistant Gram-positive bacteria (i.e., Staphylococcus epidermidis or ampicillin-resistant Enterococcus) were suspected. Continuous infusion is the preferred method of administration in the unit where the data collection occurred because we believe dose adjustment to achieve therapeutic concentrations to be easier with contin-
uous infusion than with intermittent infusion. Previous clinical outcome studies have shown equivalent outcomes for vancomycin administered by either ap-
proach (33). In this study, the choice of antibiotic regimen was at the discretion of the clinician; published recommendations (15-mg/kg loading dose followed by 30-mg/kg daily dose calculated on the total body weight [TBW]) (33), with doses rounded off to 125 mg, were used in some patients. In others, local simplified recommendations were used, consisting of a 750-mg (if TBW was <70 kg) or a 1,000-mg (if TBW was >70 kg) loading dose diluted in 100 ml of 5% dextrose in water and administered over 30 min, followed by a 2,000-mg (if TBW was <70 kg) or a 3,000-mg (if TBW was >70 kg) daily dose of vancomycin, diluted in 250 ml of 5% dextrose in water and infused over 24 h in the case of normal renal function. In the case of renal failure, the loading dose was unchanged but the daily dose was adapted to the renal clearance. The aim of this regimen was to provide serum drug concentrations between 20 and 30 mg/liter (28). Where concentrations were less than 20 mg/liter, a loading dose of 500 mg was used and an increase of 500 to 1,000 mg per day of total dose was made. In patients where concentrations were greater than 30 mg/liter, CI was discontinued for 4 h and the total dose was reduced by 500 to 1,000 mg per day.

Vancomycin assay. Concentrations of vancomycin in serum were determined by NMR spectroscopy. The assay was performed using a clinical analyzer (Roche, Indianapolis, IN). The assay limits and intraday and between-day coef-
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distribution. The final objective function for the base model was 2,817,420. The covariate that best described vancomycin volume of distribution was TBW. The addition of this covariate reduced the objective function by 6,129 (statistically significant change is 3.84 units). The covariate that best described vancomycin clearance was urinary CrCl normalized to 100 ml/min/1.73 m². The addition of this parameter improved the between-subject variability for clearance by 10% and improved the goodness-of-fit plots. The final population model for vancomycin was represented by equations 3 and 4:

\[ TVV = (\theta_1 \cdot TBW) \]
\[ TVCL = (\theta_2 \cdot CrCl/100) \]

where TVV is the typical value of volume of distribution, TBW is total body weight, and TVCL is the typical value of vancomycin clearance. None of the other covariates statistically significantly improved the model, and therefore, they could not be included.

The values of the parameters for the final model are given in Table 2 and include the 95% confidence intervals for the parameters computed from all bootstrap runs. The population value for clearance of vancomycin was 4.6 liters/h (95% confidence interval, 4.1 to 5.2), and that for volume of distribution was 1.5 liters/kg (95% confidence interval, 1.3 to 1.7) (Table 2).

Figure 1 displays the goodness-of-fit plots for the final model. Each of the patients contributed 2 to 3 samples, and of the 579 samples included in the analysis, 10 samples had a concentration greater than 2 standard deviations outside that predicted by the model, which we considered acceptable given the level of sickness severity and likely pharmacokinetic heterogeneity of the patient cohort. All subsequent dosing simulations were then based on this model. All other visual predictive checks were acceptable and confirmed the goodness of fit of the model. The plots in Fig. 1 show that the final pharmacokinetic model describes the measured vancomycin concentrations adequately.

**Dosing simulations.** A loading dose of at least 35 mg/kg TBW would have been necessary to rapidly achieve vancomycin concentrations of >20 mg/liter within a few hours from the onset of infusion (Fig. 2). A standard loading dose of 15 mg/kg would have resulted in inadequate drug concentrations for the first 24 h of therapy, despite an appropriate maintenance regimen. The respective values for area under the concentration-time curve from 0 to 24 h (AUC_{0-24}) for these simulations from 0 to 24 h were as follows: 5 mg/kg, 245 mg · h/liter; 15 mg/kg, 330 mg · h/liter; 20 mg/kg, 370 mg · h/liter; 25 mg/kg, 409 mg · h/liter; 30 mg/kg, 442 mg · h/liter; 35 mg/kg, 485 mg · h/liter; and 40 mg/kg, 532 mg · h/liter.

Figure 3 describes the impact of different values of creatinine clearance on vancomycin concentrations. In spite of an effective loading dose of 35 mg/kg, a daily dose of 35 mg/kg could not keep vancomycin concentrations within target levels if the CrCl was 100 ml/min/1.73 m². If patients had even higher CrCl values, a larger daily dose would have been necessary to maintain desired drug levels over the first 24 h of therapy. In the case of an altered CrCl (50 ml/min/1.73 m²), a 35-mg/kg daily dose could raise vancomycin levels to concentrations of >30 mg/liter within the first 24 to 48 h of infusion (Fig. 3). To demonstrate the importance of adequate maintenance doses for maintaining therapeutic exposures, the respective AUCs for these simulations of CrCl from 24 to 48 h were as follows: 50 ml/min, 811 mg · h/liter; 200 ml/min, 542 mg · h/liter; 150 ml/min, 387 mg · h/liter; 200 ml/min, 293 mg · h/liter; and 250 ml/min, 232 mg · h/liter. When lower CrCl values were simulated, the simulations suggested the following requirements: 7 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m², 10 mg/kg over 24 h when the CrCl was 30 ml/min/1.73 m², and 14 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m².

Figure 4 describes the vancomycin concentrations resulting from various weight-based dosing infusions after an adequate 35-mg/kg loading dose to rapidly achieve a target concentration of 20 mg/liter. The simulations show that a dose of at least 35 mg/kg is required to maintain a therapeutic concentration for a patient with a CrCl of 100 ml/min/1.73 m². The respective AUCs for these simulations of CrCl from 24 to 48 h were as follows: 20 mg/kg, 362 mg · h/liter; 25 mg/kg, 419 mg · h/liter; 30 mg/kg, 475 mg · h/liter; 35 mg/kg, 532 mg · h/liter; and 40 mg/kg, 589 mg · h/liter.

**DISCUSSION**

This paper has provided a rational approach for optimized vancomycin dosing by continuous infusion in critically ill pa-

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**TABLE 1. Demographic and clinical characteristics of patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58.1 ± 14.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.8 ± 15.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9 ± 5.4</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>61.6</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>90.7 ± 60.4</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21 (16–27)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>7.6 ± 4.2</td>
</tr>
</tbody>
</table>

* Data are described as mean ± standard deviation or median (interquartile range).

**TABLE 2. Bootstrap parameter final estimates of the final covariate model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>percentile</td>
</tr>
<tr>
<td>Fixed effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance (liters/h)</td>
<td>4.58</td>
<td>4.09</td>
</tr>
<tr>
<td>Volume of distribution (liters/kg)</td>
<td>1.53</td>
<td>1.31</td>
</tr>
<tr>
<td>Random effects: between-subject variability, h_{HUV} (% coefficient of variation)</td>
<td>38.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Clearance</td>
<td>37.4</td>
<td>28.3</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>16.6</td>
<td>55.6</td>
</tr>
<tr>
<td>Random error</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual unexplained variability (% coefficient of variation)</td>
<td>19.9</td>
<td>14.5</td>
</tr>
<tr>
<td>SD (mg/liter)</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

mg/kg, 330 mg · h/liter; 20 mg/kg, 370 mg · h/liter; 25 mg/kg, 409 mg · h/liter; 30 mg/kg, 442 mg · h/liter; 35 mg/kg, 485 mg · h/liter; and 40 mg/kg, 532 mg · h/liter.

Figure 3 describes the impact of different values of creatinine clearance on vancomycin concentrations. In spite of an effective loading dose of 35 mg/kg, a daily dose of 35 mg/kg could not keep vancomycin concentrations within target levels if the CrCl was 100 ml/min/1.73 m². If patients had even higher CrCl values, a larger daily dose would have been necessary to maintain desired drug levels over the first 24 h of therapy. In the case of an altered CrCl (50 ml/min/1.73 m²), a 35-mg/kg daily dose could raise vancomycin levels to concentrations of >30 mg/liter within the first 24 to 48 h of infusion (Fig. 3). To demonstrate the importance of adequate maintenance doses for maintaining therapeutic exposures, the respective AUCs for these simulations of CrCl from 24 to 48 h were as follows: 50 ml/min, 811 mg · h/liter; 200 ml/min, 542 mg · h/liter; 150 ml/min, 387 mg · h/liter; 200 ml/min, 293 mg · h/liter; and 250 ml/min, 232 mg · h/liter. When lower CrCl values were simulated, the simulations suggested the following requirements: 7 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m², 10 mg/kg over 24 h when the CrCl was 30 ml/min/1.73 m², and 14 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m².

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tients and is the largest pharmacokinetic study on vancomycin
in this setting. Our results show that a loading dose based on
TBW is mandatory to rapidly achieve therapeutic concentra-
tions and suggest that a minimum loading dose of 35 mg/kg is
necessary to achieve target steady-state concentrations of 20
mg/liter or greater. To maintain this concentration, the dose to
be administered by continuous infusion can be accurately cal-
culated using data from CrCl. A daily dose of at least 35 mg/kg
would be necessary to maintain steady-state drug levels in the
therapeutic range. Such an approach to dosing will increase the
likelihood of achieving vancomycin concentrations associated
with improved antimicrobial activity and, potentially, positive
clinical outcomes (15, 22).

Achieving pharmacokinetic/pharmacodynamic targets is
likely to be very important for optimizing the clinical efficacy of
vancomycin. Consensus supports the view that the pharmaco-
kinetic-pharmacodynamic parameter best correlated with the
efficacy of vancomycin is the AUC0–24/MIC (AUC0–24/
MIC) ratio (8, 11, 29). In a retrospective study, Moise-Broder
et al. (22) evaluated the relationship between AUC0–24/MIC
ratio and clinical outcomes in patients with MRSA pneumonia.
The authors found that an AUC0–24/MIC ratio of ≥350 was
associated with clinical success and suggested an AUC0–24/
MIC ratio of ≥400 as a target predictive of optimal outcomes.
On the basis of the results of this study and the frequency with
which lung infections occur in critically ill patients, it has been
advocated that achieving this pharmacokinetic-pharmacody-
namic target of AUC0–24/MIC ratio of ≥400 should optimize
clinical benefit (6). Although AUC0–24 is not routinely moni-
tored in clinical practice, Jeffres et al. (14) have shown that
trough concentrations from intermittent dosing are correlated
with AUC and thus are regarded as an appropriate surrogate
measure for the AUC0–24 and as the most practical method to
monitor vancomycin dosing (26, 28). Some studies have suc-
cessfully described use of a nomogram to guide continuous-
infusion dosing (24).

We have shown that dosing to meet these targets needs to be
individualized according to the patient’s TBW and renal func-
tion. Data supporting the strong relationship between vanco-
mycin volume of distribution and TBW have been described in
various vancomycin pharmacokinetic studies, particularly in
obese patients (1). Data supporting the importance of renal
function on vancomycin clearance are also prominent (25).
Augmented renal clearance is common in hyperdynamic crit-
ically ill patients and may increase the risk for subtherapeutic
vancomycin exposure (27, 31). This population analysis ex-
tends upon these previous data and demonstrates how both
TBW and CrCl explain a significant amount of the pharmaco-
kinetic variability in critically ill patients.

Curiously, we did not observe an effect of the level of sick-
ess severity on volume of distribution, as has previously been
described for aminoglycosides (20). We believe that this may
be due to the dominant contribution of TBW as well as the
inherently larger volume of distribution of vancomycin (0.8 to

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\text{FIG. 1. Diagnostic plots for the final population pharmacokinetic covariate model. (Left) Observed concentrations versus the population predicted concentrations \((r^2 = 0.07)\). (Right) Observed concentrations versus the individual predicted concentrations \((r^2 = 0.60)\). The nonlinear regression line of fit is shown by the solid black line, and the line of } x = y \text{ is the gray dotted line.}
\]

\[
\text{FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simu-
lated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m², followed by administration as a 35-mg/kg/day contin-
uous infusion.}
\]

\[
\text{FIG. 3. The effect of creatinine clearance on vancomycin concen-
trations administered by continuous infusion (35 mg/kg per day after
35-mg/kg loading dose).}
\]

\[
\]
centrations during the early phase of sepsis, and higher doses loading and daily doses would result in insufficient drug concentration and the possibility of subtherapeutic drug exposure. Recommended loading and daily doses would result in insufficient drug concentrations during the early phase of sepsis, and higher doses should be used in this setting. We would advocate that a clinical study be undertaken to validate the findings of these simulations.

There are some limitations of our study. First, this modeling approach utilized sparse samples, such that we were not able to describe a two-compartment model, which mechanistically would be more in keeping with the pharmacokinetics of vancomycin. However, use of the program NONMEM for this modeling analysis was widely recognized to be robust for such analyses and the predictive performance of the model was deemed sufficient. Second, this was an analysis of retrospective data, which may have resulted in unforeseen errors in data collection. We believe that this effect would be very minor because of the use of continuous infusion of vancomycin and sampling after a pharmacokinetic steady state had been reached, in addition to the accuracy of the data collected on CrCl. Third, the suggested approach to dosing should be used only in patients who match the demographic and clinical characteristics of the enrolled cohort. Therefore, it cannot be used for patients requiring different types of renal replacement therapies and should be used with caution in obese patients and those with low creatinine clearances. Finally, the simulations suggest more aggressive doses than those that are typically prescribed, and therefore, any prospective validation study would need to closely monitor for potential vancomycin toxicities to confirm that these are not increased in frequency by this approach to dosing.

In conclusion, dose optimization of vancomycin by CI can be best accomplished using a rational approach that considers individual patient and disease characteristics. Specifically, TBW should be considered for initial dosing, as it is an accurate descriptor of volume of distribution of vancomycin. Maintenance dosing can then be guided by CrCl. Such an approach would need to closely monitor for potential vancomycin toxicity.

Note: The diagram and figures are not transcribed in the text format.


