Initial Vancomycin Dosing Protocol to Achieve Therapeutic Serum Concentrations in Patients Undergoing Hemodialysis

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Background. Although recent consensus guidelines proposed more aggressive vancomycin troughs of >10 or 15–20 mg/L for complicated Staphylococcus aureus infections, dosing information to achieve these targets in patients undergoing hemodialysis (HD) is scarce.

Methods. We used Monte Carlo simulation (MCS) methods with a previously published population-pharmacokinetic model and relevant patient demographics to evaluate and revise our existing vancomycin dosing protocol (1000-mg load followed by 500-mg maintenance dose, with doses infused during the last hour of dialysis). A new protocol (1000-mg load followed by 500-mg maintenance dose for patients <70 kg, 1250-mg followed by 750-mg for those 70–100 kg, and 1500-mg followed by 1000-mg for those >100 kg) was developed and prospectively validated to achieve therapeutic serum troughs in patients undergoing high-flux HD.

Results. MCSs predicted that our existing protocol would be suboptimal in more than one-third of patients. Simulations predicted that the new vancomycin dosing protocol would achieve maintenance (pre-HD) troughs of 10–20 mg/L in 86.0% of cases including 15–20 mg/L in 35.2%. In prospective validation, the observed postload trough (pre-HD session 2) was 13.5 ± 3.4 mg/L with 76.9% of levels (20 of 26) between 10 and 20 mg/L. The observed maintenance trough was 17.3 ± 4.0 mg/L with 65.5% (19 of 29) between 10 and 20 mg/L and 89.7% (26 of 29) within 10% of the upper limit (ie, 10–22 mg/L).

Conclusions. In this study, a practical vancomycin dosing protocol for patients undergoing HD was developed and prospectively validated to achieve therapeutic serum concentrations in the clinical setting.

Consensus guidelines for vancomycin therapeutic drug monitoring were published in 2009 by the American Society of Hospital Pharmacists, Infectious Diseases Society of America, and Society of Infectious Disease Pharmacists [1]. The recommendations included more aggressive vancomycin dosing to achieve serum troughs >10 or 15–20 mg/L for complicated infections caused by Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA). The targets were supported by pharmacodynamic research, with increasing evidence that conventional vancomycin dosing with lower trough concentrations is suboptimal [1].

Higher failure rates, including relapse and mortality, have been reported in patients with S. aureus infections and vancomycin minimum inhibitory concentrations (MICs) >1 mg/L but within the susceptible range of ≤2 mg/L, according to the Clinical Laboratory Standards Institute [2–7]. In addition, reduced vancomycin susceptibility characterized by increasing MIC and tolerance has been described in patients with MRSA bacteremia and recent exposure to vancomycin [8, 9]. In an in vitro pharmacodynamic model, the emergence of reduced vancomycin susceptibility, including vancomycin-intermediate S. aureus (VISA), was observed during continuous infusions of vancomycin at...
concentrations $\leq 5$ mg/L, equivalent to total serum concentrations $\leq 10$ mg/L, based on an estimated 50% protein binding [10]. This is consistent with other in vitro investigations [11, 12] and a recent study of patients with MRSA bacteremia, in whom poor clinical outcomes were 16 times more likely in those with vancomycin troughs <10 mg/L [13].

Although the consensus guidelines for vancomycin are being adopted in the clinical management of patients undergoing hemodialysis (HD) [14, 15], dosing information to achieve therapeutic serum concentrations in this population is scarce [16]. Our goal was to develop a practical vancomycin dosing protocol to improve trough target attainment in patients undergoing high-flux HD. We used Monte Carlo simulations (MCSs) with a previously published vancomycin population–pharmacokinetic (PK) model and relevant patient demographics (1) to evaluate our existing vancomycin protocol (ie, 1000-mg load followed by 500-mg maintenance dose, with doses infused during the last hour of dialysis), originally developed to achieve pre-HD troughs of 5–15 mg/L, and (2) (if required) to develop and validate a new vancomycin protocol to attain pre-HD troughs of 10–20 mg/L, with an optimal target of 15–20 mg/L. Given the convenience and practical advantages to patients and HD units, we investigated vancomycin protocols with intradialytic administration (eg, infused during the last hour of dialysis).

To our knowledge, this is the first vancomycin dosing protocol with load and maintenance doses for patients undergoing HD validated in accordance with the consensus guidelines. Furthermore, this study demonstrates the value of MCS methods in translating antimicrobial research to the clinical setting.

MATERIALS AND METHODS

MCSs of Vancomycin Dosing in Patients Undergoing Hemodialysis

Study populations of 500, 1000, and 5000 cases were generated using MCSs (SYSTAT 12; Systat Software, Inc.). Simulations were conducted with PK input variables of 0.94 L/kg (±10%) for volume of distribution, 0.11 h$^{-1}$ (±20%) for intradialytic elimination rate constant (ke), 0.0035 h$^{-1}$ (±35%) for interdialytic ke and 79% (±16%) for bioavailability. The variability allowances were modeled as proportional errors randomly selected from Gaussian distributions. The PK data were based on our previously published population-PK model constructed using 49 samples from 22 patients undergoing high-flux HD and receiving vancomycin (1000-mg load and then 500-mg maintenance dose, with doses infused during the last hour of dialysis) [17]. Nonparametric expectation maximization population-modeling and Bayesian fitting were used to characterize the PKs using a one-compartment model with zero-order input and first-order elimination. The average pre-HD trough was $11.0 \pm 3.0$ mg/L. Because the population-PK model had not been previously validated, a retrospective validation of predicted vs observed vancomycin levels in 15 patients undergoing HD was conducted in advance. Using the methods described by Sheiner and Beal [18], the precision and bias of the model was 2.7 and $-1.7$ mg/L, respectively ($r^2 = 0.57$).

Because body weight was a significant covariate in the population-PK model, a relevant distribution of values was characterized in a random sample of 122 patients undergoing HD from five units in the Manitoba Renal Program. Body weight ranged from 43.2 to 113.0 kg, with a mean of 74.4 ± 18.3 kg and median of 71.4 kg (interquartile range, 59.9–88.9 kg). The parameter was simulated as a log normal (right-skewed) distribution with values truncated below 40 kg and above 115 kg.

MCSs were used to evaluate vancomycin dosing protocols based on their predicted target attainment or proportion of maintenance troughs between 10 and 20 mg/L with an optimal target of 15–20 mg/L. Steady-state serum concentrations before the fifth dose (ie, pre-HD maintenance trough) were simulated. Target attainment was predicted for our existing vancomycin protocol (ie, 1000-mg load followed by 500-mg maintenance dose, with doses infused during the last hour of dialysis) and for higher doses including 1250-mg or 1500-mg loads followed by 750-mg or 1000-mg maintenance doses, respectively. Weight-based dosing protocols, including algorithms using thresholds in 5-kg increments from 45 to 110 kg, were tested, successively collapsed, and retested.

Prospective Validation of a New Vancomycin Dosing Protocol for Patients Undergoing Hemodialysis

Approval was obtained from the University of Manitoba Health Research Ethics Board (study H2010:112). The prospective validation was conducted at the Health Sciences Centre and St Boniface General Hospital (Manitoba Renal Program) in patients undergoing HD requiring vancomycin therapy for suspected or documented infection. The standard dialyzer used during the time was the polysulfone Optiflux F160NR (Fresenius Medical Care Canada). Before the validation study, the Program adopted standard practices whereby 500-mg doses would be infused during the last 30 minutes, 750–1000-mg doses during the last 60 minutes, and 1250–1500-mg doses during the last 90 minutes of dialysis, compared with our simulations which used 60 minutes. Patient age, body weight, dialysis sessions, and vancomycin dosing were documented. HD sessions were numbered starting with the loading dose (session 1). Two pre-HD blood samples were requested, including one before HD session 2 (ie, postload trough) and another ideally after two maintenance doses or before HD session 4 (ie, maintenance trough). Target attainment was the percentage of patients with measured postload
RESULTS

MCSs of Vancomycin Dosing in Patients Undergoing Hemodialysis

There were no differences in vancomycin maintenance trough estimates or predicted target attainment in simulations generated with 500, 1000, or 5000 cases (data for the first are presented). As shown in Figure 1A, MCSs of our existing vancomycin protocol (1000-mg load followed by 500-mg maintenance doses, with doses infused during the last hour of dialysis) predicted a mean maintenance trough of 11.9 ± 3.9 mg/L, with 61.2% of levels between 10 and 20 mg/L but only 15.6% between 15 and 20 mg/L. Furthermore, 34.8% of expected levels were <10 mg/L. Figure 1B depicts MCS results for an empirical 50% dose increase to the existing vancomycin protocol (1500-mg load followed by 750-mg maintenance doses, with doses infused during the last hour of dialysis) with a mean maintenance trough of 17.8 ± 5.8 mg/L and 65.4% of levels between 10 and 20 mg/L and 34.2% between 15 and 20 mg/L. In this case, 30.8% of expected levels exceeded 20 mg/L.

Table 1 summarizes the predicted target attainment for vancomycin dosing wherein patients below the body weight threshold would receive our existing protocol and those above the threshold would receive a 50% dose increase (1000-mg load followed by 500-mg maintenance doses), with doses infused during the last hour of dialysis. As

and maintenance troughs of 10–20 mg/L, with an optimal target of 15–20 mg/L.

Table 1. Cumulative Target Attainment Based on Monte Carlo Simulations of Vancomycin Dosing

<table>
<thead>
<tr>
<th>Maintenance Prehemodialysis</th>
<th>CTA by Body Weight Threshold, %</th>
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<tbody>
<tr>
<td>Trough, mg/L</td>
<td>60 kg</td>
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<tr>
<td></td>
<td>≤10</td>
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<tr>
<td>≤10</td>
<td>5.0</td>
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<tr>
<td>10–14.9</td>
<td>38.6</td>
</tr>
<tr>
<td>15–20</td>
<td>39.6</td>
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<tr>
<td>&gt;20</td>
<td>16.8</td>
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Patients below the body weight threshold would receive our existing protocol (1000-mg load followed by 500-mg maintenance doses), and those above the threshold would receive a 50% dose increase (1500-mg load followed by 750-mg maintenance doses), with doses infused during the last hour of dialysis. Abbreviation: CTA, cumulative target attainment.

Figure 1. Predicted pre-hemodialysis maintenance troughs based on Monte Carlo simulations for our existing vancomycin protocol (1000-mg load followed by 500-mg maintenance doses) (A), an empirical 50% dose increase (1500-mg load followed by 750-mg maintenance doses) (B), or the new vancomycin dosing protocol (1000-mg load followed by 500-mg maintenance doses for patients <70 kg, 1250-mg load followed by 750-mg for patients 70–100 kg, and 1500-mg load followed by 1000-mg for patients >100 kg) (C), with doses infused during the last hour of dialysis.
shown in Figure 1C, MCSs of the new protocol predicted a mean maintenance trough of 14.6 ± 3.5 mg/L, with most levels (ie, 86.0%) between 10 and 20 mg/L and 35.2% between 15 and 20 mg/L. Furthermore, 7.6% and 6.4% of predicted levels were <10 or >20 mg/L, respectively.

**Prospective Validation of a New Vancomycin Dosing Protocol for Patients Undergoing HD**

Twenty-nine patients undergoing HD were enrolled into the validation study. Another four patients, whose vancomycin therapy was discontinued before complete sampling, were excluded. Twenty-six postload troughs (ie, pre-HD session 2) and 29 maintenance troughs (ie, pre-HD session 4, 5, or 6) were available for analysis. The validation group (n = 29) was 59.9 ± 12.9 years old and 75.7 ± 18.8 kg, consistent with the weight of 74.4 ± 18.3 kg used in our simulations. Eleven patients (37.9%) <70 kg received the 1000-mg load followed by 500-mg maintenance doses, 15 patients (51.7%) between 70 and 100 kg received the 1250-mg load followed by 750-mg maintenance doses, and 3 patients (10.3%) >100 kg received the 1500-mg load followed by 1000-mg maintenance doses. When normalized for body weight, the new vancomycin protocol delivered mean load and maintenance doses of 16.0 ± 1.9 and 9.1 ± 1.1 mg/kg, respectively.

Twenty of the postload troughs were collected after 48-hour and 6 after 72-hour interdialytic periods. With the new vancomycin protocol, the mean observed postload trough was 13.5 ± 3.4 mg/L with 76.9% of measured levels (20 of 26) between 10 and 20 mg/L, including 34.6% (9 of 26) between 15 and 20 mg/L. (Figure 2A)

Of the 29 maintenance troughs, 17 were collected after 48-hour and 12 after 72-hour interdialytic periods. Pre-HD blood samples were collected before session 3 in two cases, session 4 in 22 cases, session 5 in one case and session 6 or 7 in two cases each. As shown in Figure 2B, the new vancomycin protocol produced a maintenance trough of 17.3 ± 4.0 mg/L with 65.5% of levels (19 of 29) between 10 and 20 mg/L, including 37.9% (11 of 29) between 15 and 20 mg/L. With several levels slightly above 20 mg/L, 89.7% of observed maintenance troughs (26 of 29) were between 10 and 22 mg/L, with 62.1% (18 of 29) between 15 and 22 mg/L.

**DISCUSSION**

The consensus guidelines for vancomycin therapeutic drug monitoring were based on mounting evidence that conventional dosing is suboptimal [1]. High rates of treatment failure and the emergence of reduced vancomycin susceptibility during therapy are of increasing concern. In patients undergoing HD, the presence of indwelling catheters, immune deficiencies, and high rates of MRSA colonization significantly increase the risk of acquiring serious MRSA infections requiring vancomycin therapy.

Our MCSs predicted maintenance troughs <10 mg/L in 34.8% and between 15 and 20 mg/L in only 15.6% with our existing vancomycin protocol. As expected, an empirical 50% dose increase would result in a proportional change in mean trough from 11.9 ± 3.9 to 17.8 ± 5.8 mg/L. Although the percentage of predicted troughs between 10 and 20 mg/L were similar for our existing protocol (ie, 61.2%) and an empirical 50% dose increase (ie, 65.4%), the latter resulted in significantly more levels >20 mg/L. (Figure 1) The predicted target attainment with the new vancomycin dosing protocol was consistent with that observed in the validation study. The maintenance trough of 14.6 ± 3.5 mg/L was similar to the observed postload trough of 13.5 ± 3.4 mg/L but lower than the observed maintenance trough of 17.3 ± 4.0 mg/L. Two factors may have contributed to the higher-than-predicted maintenance
troughs in the validation study. First, our original population-PK model had a $\sim 1.7$ mg/L bias indicating the potential to underpredict vancomycin concentrations. Next, the 500-mg doses administered during the prospective validation were exposed to less drug removal by being infused during the last 30 minutes of dialysis compared with our simulations which used 60 minutes. Furthermore, 89.7% of observed maintenance troughs (26 of 29) were within 10% of the upper limit, between 10 and 22 mg/L, with 62.1% (18 of 29) between 15 and 22 mg/L in the prospective validation.

Few other studies have investigated new vancomycin dosing protocols to achieve therapeutic concentrations in patients undergoing HD. Taylor et al administered loads of 20 mg/kg, followed by 1000-mg maintenance doses during the last hour of dialysis to 32 patients ranging from 40 to 118 kg. The mean trough was $19 \pm 6.6$ mg/L, with 56% of levels between 10 and 20 mg/L, 23% between 20 and 25 mg/L and 15% >25 mg/L [19]. These findings, specifically the percentage of high concentrations, were consistent with our simulations and led to our selection of maintenance doses of 750-mg for patients between 70 and 100 kg and 500-mg for those <70 kg. Brown and colleagues conducted a retrospective evaluation of weight-based vancomycin loads infused after dialysis in 43 patients undergoing HD [20]. Their median dose of 14.1 mg/kg and pre-HD concentration of 14.9 mg/L were comparable to the median load of 15.8 mg/kg and postload trough of 14.0 mg/L observed in our prospective validation. Finally, Vandecasteele et al identified three significant factors for achieving vancomycin troughs of 15–20 mg/L, including prior trough level, body weight, and time to next dialysis session [21]. In contrast, our study addresses the common clinical scenario where initial vancomycin load and maintenance doses are ordered without access to patient-specific concentration data. As shown by Vandecasteele and colleagues, however, vancomycin therapeutic drug monitoring is valuable in guiding subsequent dose modifications to achieve targets.

Although one might assume that weight-based dosing (milligrams per kilogram) is optimal, our simulations showed no improvement in target attainment compared with a dosing algorithm using body weight thresholds. This may be due to significant variability in vancomycin PKs in patients undergoing HD, only partially explained by body weight. The potential benefits of weight-based dosing could be further diluted in the clinical setting by the common practice of selecting doses in 250-mg increments. Our new vancomycin dosing protocol proved to be an effective and more convenient initial approach to achieving therapeutic serum concentrations in patients undergoing HD.

MCS uses computational algorithms well suited to antimicrobial research, which involves numerous confounding variables related to patient demographics, pathogen profiles, and antimicrobial PKs and pharmacodynamics. The robust nature of MCS has proved valuable in determining optimal antimicrobial dosing and/or susceptibility break points [22]. Simulations can predict the probability of attaining pharmacodynamic targets for an MIC or MIC distribution of interest. The latter may include target attainment against specific pathogens (eg, MRSA) or distribution of pathogens associated with a particular infection (eg, bactemia). With more comprehensive clinical pharmacodynamic data, MCSs can be used to project the likelihood of achieving cure or experiencing toxic effects [23, 24]. Simulations are particularly useful in studying populations with unique PK or infection characteristics, such as critically ill patients, those with cystic fibrosis, and those undergoing HD [25–28].

Our study was limited by the use of pre-HD trough concentrations as the main pharmacodynamic index for vancomycin. Studies in patients with S. aureus pneumonia [29] and bacteemia [30] found better microbiological and clinical outcomes in those with vancomycin AUC24/MICs (area under the total serum concentration-time curve over 24 hours divided by the MIC) exceeding 400. Although AUC24/MIC is recognized as an important pharmacodynamic index for vancomycin, the characterization and relevance of this parameter in patients undergoing HD have not been investigated. Of note, the new therapeutic targets for vancomycin (ie, trough and AUC/MIC) rely on data related to S. aureus and their application to other common pathogens in patients undergoing HD, such as methicillin-resistant Staphylococcus epidermidis, is uncertain.

Our predicted target attainment results were specific for the simulated study population as described by the population-PK model and body weight distribution. Caution should be exercised in extrapolating our results to other populations, such as the morbidly obese. Furthermore, the new protocol was developed and validated in patients undergoing HD receiving vancomycin therapy for suspected or documented infection and may not represent those with more serious illness. The effectiveness of the new protocol may also be affected by significant variability among patients undergoing HD due to factors such as residual renal function, fluid status, HD sessions (dialyzer type, dialysis flow rate, duration) and the intradialytic administration of vancomycin. The potential for drug accumulation especially during prolonged therapy is an important caution with the new dosing protocol. Although vancomycin accumulation was not observed in our original population-PK study, the maintenance troughs were higher on average than the postload troughs in the prospective validation. This observation may be explained by the new vancomycin protocol, which does not have proportional increases in the load and maintenance doses across categories (eg, the 1000-mg load increases to 1250-mg, whereas the 500-mg maintenance dose increases to 750-mg). For these reasons, vancomycin therapy

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in patients undergoing HD should be accompanied by appropriate therapeutic drug monitoring.

Importantly, our study demonstrates the value of MCS methods in translating antimicrobial research to the clinical setting. When based on relevant and reliable input data, MCSs can provide an evidence-based decision tool for situations unlikely to be studied otherwise. In conclusion, conventional vancomycin therapy is no longer sufficient for treating serious S. aureus infections. In this study, an initial vancomycin dosing protocol for patients undergoing HD was developed and prospectively validated to achieve therapeutic serum concentrations in the clinical setting.

Notes

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