Weight-Based Loading of Vancomycin in Patients on Hemodialysis

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We evaluated weight-based loading doses of vancomycin and resulting initial prehemodialysis concentrations. Modeling demonstrated modest correlation between dose administered, age, and initial concentration achieved. Actual body weight–based loading of vancomycin predictably achieves therapeutic initial concentrations in patients who receive hemodialysis.

Vancomycin remains a critical antibiotic for the treatment of infections caused by Gram-positive organisms such as methicillin-resistant Staphylococcus aureus (MRSA). Recommended dosing of vancomycin has recently evolved to include emphasis on dosing based on actual weight, maintenance of trough levels of >10 mg/L to avoid the emergence of resistance in S. aureus, and goal trough levels of >15 mg/L in serious infections caused by S. aureus [1].

Vancomycin dosing in patients with end-stage renal disease (ESRD) who receive hemodialysis (HD) is poorly defined [2]. Using newer recommended target levels, a recent model of vancomycin dosing in HD patients estimated that one-third of trough levels obtained immediately before HD would be subtherapeutic [3]. Loading doses of 15–20 mg/kg are recommended for most patients with normal renal function and doses of 25–30 mg/kg are recommended for critically ill patients [4]. Recent guidelines do not address the HD population, and it is unclear what loading doses are best suited in ESRD [1]. This study sought to assess factors associated with therapeutic pre-HD serum vancomycin concentration.

METHODS

We conducted a retrospective medical record review of consecutive subjects admitted to Hahnemann University Hospital (Philadelphia, PA) between January 2008 and 2009 who received HD and a diagnosis of stage 5 chronic kidney disease. Subjects were included in the analysis if they received a single dose of vancomycin and had a serum vancomycin concentration obtained >4 hours after infusion and prior to their next HD session. Exclusion criteria included administration of the initial dose during HD and/or presence of nonoliguria (production of >400 mL of urine per day). Medical records were reviewed to identify subject demographics (age, race, height, body weight, and sex), medical history (length of time on HD, history of renal transplantation, and presence of anuria), and details of vancomycin therapy. Vancomycin dose, time of administration, serum vancomycin concentration, time and date of dialysis session, and the indication for vancomycin were collected for each subject as well. This study was approved by the institutional review board of Drexel University College of Medicine.

All serum vancomycin levels were analyzed by a particle-enhanced turbidimetric inhibition immunoassay (Synchron LX Systems; Beckman Coulter).

The primary objective of this study was to assess the loading dose (in units of milligrams per kilogram of body weight) associated with therapeutic serum pre-HD vancomycin level in the target range of 10–20 mg/L. The association between subject variables and the resulting pre-HD level was modeled using linear regression for continuous variables and the Student t test for dichotomous variables. Variables found to have a P value of <.1 in univariate analysis were incorporated into multivariate stepwise linear regression to identify variables predictive of the initial vancomycin concentration. This P value threshold of <.1 was chosen to avoid excluding potential predictors prematurely. Descriptive statistics were used for other characteristics of the sample. SPSS Statistics software (version 18; IBM) was used for all statistical analyses. A P value of <.05 was considered to be statistically significant.

RESULTS

A total of 301 subjects were screened for inclusion in this study. Forty-three subjects met the inclusion criteria. Most patients were excluded because they either did not have a vancomycin
concentration drawn prior to HD or they received multiple doses before a level was obtained. The mean age was 58 years (range, 25–86 years), 26 (60%) of the subjects were male, and 35 (81%) were African American. The mean actual body weight of subjects was 79.4 kg (range, 44.0–161.2 kg) and the mean dose of vancomycin was 1,003.5 mg, resulting in a mean vancomycin dose of 13.6 mg/kg (range, 5.2–22.7 mg/kg; median, 14.1 mg/kg). Average times from dose to trough level and from trough level to HD were 22.9 hours (range, 5.4–61.5 hours) and 10.7 hours (range, 0–48.5 hours), respectively. The resulting mean pre-HD concentration was 17.8 mg/L (range, 6.3–39.2 mg/L; median, 14.9 mg/L).

Univariate analysis revealed modest but significant correlations between the dose in milligrams per kilogram based on actual body weight and the resulting pre-HD trough level (P = .006; r = 0.411) (Figure 1; available online) as well as between age and resulting pre-HD trough level (P = .003; r = −0.449) (Figure 2; available online). We also calculated milligram-per-kilogram dose on the basis of both ideal and adjusted body weights and performed linear regression in the same manner as for the primary analysis. The results of these analyses demonstrated that actual body weight had a stronger correlation with the trough level than did ideal or adjusted body weight (data not shown). Other variables that exhibited significant associations with the resulting trough level included time from dose to trough level (P = .09; r = −0.262), anuria (mean ± SD for anuria and oliguria, 19.1 ± 8.2 mg/L and 14.1 ± 4.9 mg/L, respectively; P = .022), and history of renal transplantation (mean ± SD for prior transplantation and no prior transplantation; 22.8 ± 10.7 mg/L and 17.0 ± 7.0 mg/L, respectively; P = .09). The multivariate stepwise linear regression that included these variables demonstrated modest correlations of milligram-per-kilogram dose (P = .009) and age (P = .004) with pre-HD trough level. Table 1 summarizes the analysis demonstrating the expected trough levels of certain weight-based loading doses with and without consideration of age.

**DISCUSSION**

The best approach to quickly achieve therapeutic vancomycin levels in HD patients has not been elucidated thus far in the literature. Current guidelines recommend the use of weight-based loading doses adapted to various clinical situations (eg, seriously ill patients); however, the HD population is not addressed. This study investigated the relationship between initial trough values and the salient characteristics of HD patients in order to provide data to clinicians on how to reach therapeutic trough concentrations rapidly in HD patients.

These data suggest that a guideline-recommended 15-mg/kg loading dose would reach a mean initial pre-HD concentration of 19.0 mg/L ± 7.1 mg/L (standard error of the estimate [SEE]). Although many HD patients would be expected to have trough levels of >20 mg/L following a dose of 15 mg/kg, the implications are unclear, because concern for nephrotoxicity is irrelevant. On the basis of our multivariate stepwise linear regression, we found age to be a significant negative predictor of vancomycin level in HD patients, which warrants consideration when choosing a loading dose.

Our results are in line with the limited analogous data in the literature. One arm of a prospective crossover trial involving 9 otherwise healthy volunteers on long-term HD found a pre-HD vancomycin level of 23.8 ± 4.8 mg/L after 2 days following a 15-mg/kg dose [5]. A larger study in HD patients demonstrated that a 15-mg/kg dose would be expected to give an initial level of 12.6 mg/L and a 20-mg/kg dose a level of 16.3 mg/L after 48 hours [6]. In 8 subjects with a mean age of 50 years, a 20-mg/kg dose produced a mean level of 20.2 ± 3.6 mg/L [7].

The aforementioned studies of vancomycin dosing in HD patients did not specifically assess the impact of age on vancomycin dosing. Other studies are difficult to compare to our results because of differences in patient populations, timing of vancomycin dosing. Other studies are difficult to compare to our results because of differences in patient populations, timing of vancomycin level measurement (loading vs steady-state concentration), and vancomycin assay used. When the pharmacokinetics of a single 6-mg/kg dose of vancomycin were compared between 6 healthy young men and 6 healthy men aged >60 years, the latter group demonstrated a 20% reduction in maximum concentration, a 23% reduction in systemic clearance, and a 45% higher volume of distribution (Vd) [8]. This significant elevation in Vd in the older population could not be attributed to altered protein binding because the unbound fraction of serum vancomycin did not differ between young and elderly subjects. Instead, the authors

**Table 1. Expected Vancomycin Level With and Without Consideration of Age**

<table>
<thead>
<tr>
<th>Vancomycin dose, mg/kg</th>
<th>Expected vancomycin level (SEE), mg/L</th>
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<tbody>
<tr>
<td></td>
<td>All ages*</td>
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<tr>
<td>10</td>
<td>14.8 ± 7.1</td>
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<td>15</td>
<td>19.0 ± 7.1</td>
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<td>20</td>
<td>23.2 ± 7.1</td>
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<td>25</td>
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**NOTE.** SEE, standard error of the estimate.

* Univariate linear regression equation used to predict vancomycin level from milligram-per-kilogram dose with SEE, Y = 0.836x + 6.449.

b Multivariate stepwise linear regression equation used to predict vancomycin level from milligram-per-kilogram dose with SEE, Y = 0.731x − 0.198A + 19.417, where A is age in years.
concluded that the elevation in Vd was due to higher tissue affinity in the aged [8]. A similar elevation in Vd among subjects >60 years of age was observed in a large study of 1085 sets of steady-state vancomycin peak and trough levels [9].

The present study has several limitations. Our sample size was fairly small and all estimates are subject to considerable error. A notable difference between prior studies of weight-based loading dose of vancomycin and the present study is that our mean time from dose to trough level was 22.9 hours (range, 5.4–61.5 h)—significantly shorter than 48 hours, thus preempting further clearance by residual renal function and/or nonrenal clearance [10]. Although this introduces significant heterogeneity into the data, it potentially aids in the generalizability of the study conclusions. Additionally, not all of the trough values were measured in serum drawn immediately prior to HD. Approximately one-half of the trough values were measured in serum drawn >6 hours prior to HD. For patients with ESRD, the interdialysis clearance of vancomycin is low (6–10 mL/min), but whether this influenced the results is unclear [2]. In addition, the present study excluded subjects who received their loading dose of vancomycin during an HD session, which is a common technique in clinical practice. This practice would be expected to lower the level of vancomycin because a significant portion would be removed during the remaining HD session [11]. We cannot exclude the possibility that subjects received a dose of vancomycin prior to presentation to our institution. Many were sent directly from their outpatient dialysis unit, and vancomycin administered at their outpatient center may not have been included in the documentation.

A noteworthy issue with the study of vancomycin in the population of patients with ESRD is the validity of using the same goal levels of 10–20 and 15–20 mg/L in severe MRSA infections as in the population with normal renal function [1]. A ratio of the vancomycin level area under the curve to the minimum inhibitory concentration of the S. aureus isolate (AUC/MIC) of >400 may be a more important predictor of efficacy [12]. Because the value of AUC is significantly increased in ESRD, aggressively targeting a pre-HD level of 20 mg/L may not be needed to achieve an AUC/MIC ratio of >400 even in isolates with MICs approaching 2 mg/L. Prospective studies assessing the therapeutic efficacy of pre-HD levels and also AUC/MIC ratios will be able to determine the best therapeutic measure in the ESRD population.

In summary, we found that the weight-based loading dose of vancomycin for patients with ESRD who receive HD is very effective in the population with normal renal function [1]. A ratio of the concentration of the drug to the trough level was 22.9 hours (range, 5.4–61.5 h)—significantly shorter than 48 hours, thus preempting further clearance by residual renal function and/or nonrenal clearance [10]. Although this introduces significant heterogeneity into the data, it potentially aids in the generalizability of the study conclusions. Additionally, not all of the trough values were measured in serum drawn immediately prior to HD. Approximately one-half of the trough values were measured in serum drawn >6 hours prior to HD. For patients with ESRD, the interdialysis clearance of vancomycin is low (6–10 mL/min), but whether this influenced the results is unclear [2]. In addition, the present study excluded subjects who received their loading dose of vancomycin during an HD session, which is a common technique in clinical practice. This practice would be expected to lower the level of vancomycin because a significant portion would be removed during the remaining HD session [11]. We cannot exclude the possibility that subjects received a dose of vancomycin prior to presentation to our institution. Many were sent directly from their outpatient dialysis unit, and vancomycin administered at their outpatient center may not have been included in the documentation.

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In summary, we found that the weight-based loading dose of vancomycin for patients with ESRD who receive HD is very similar to that in current guideline recommendations for those patients with normal renal function. A 15-mg/kg loading dose should be expected to achieve a mean initial pre-HD concentration of 19.0 ± 7.1 mg/L (SEE). However, a higher loading dose of 15–20 mg/kg may be required in adults >65 years old with severe infections caused by S. aureus in order to achieve a comparable initial pre-HD level. Additional prospective studies should be performed that can help identify the best approach to prompt achievement of therapeutic vancomycin levels in HD patients.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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