The Appropriateness of Initial Vancomycin Dosing

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Background. Vancomycin use has markedly increased over the past several years because of an increased incidence of resistant organisms, particularly methicillin-resistant *Staphylococcus aureus*. Despite the availability of dosing nomograms and the use of peak and trough levels, vancomycin dosing has remained problematic.

Methods. All intravenous vancomycin orders over a 3-month period in a community and teaching hospital were screened for appropriateness of initial dosing based on available dosing nomograms.

Results. Of the 48 patients who received intravenous vancomycin, only 19 (39.6%) were given initial doses that achieved the desired serum concentration. There were no significant differences in the appropriateness of initial dosing between family medicine residents, attending physicians, and private staff physicians. Older patients in our study were at higher risk for overdosing, whereas younger patients were more likely to be underdosed. In this study, nomogram use could have yielded correct initial dosages in 40 of the 48 patients (83.3%).

Conclusions. Our study indicates a high percentage of inappropriate initial vancomycin dosing in a community and teaching hospital. The investigators believe inappropriate initial vancomycin dosing is common and may result in unnecessary expense, increased risk of therapeutic failures, and greater potential for adverse drug reactions. Increased use of vancomycin dosing nomograms could improve the rate of correct initial dosages.

Key words. Vancomycin; methicillin resistance; *Staphylococcus aureus*. (*J Fam Pract 1994; 38:473-477*)

The increasing use of broad-spectrum antibiotics has led to an increase in the incidence of bacterial resistance to these agents. An example is the emerging resistance of methicillin-resistant *Staphylococcus aureus* and *S epidermidis* bacteria to penicillins and cephalosporins. Because treatment of these resistant organisms requires vancomycin, the use of this medication has greatly increased in the recent past.[1,2] Intravenous vancomycin has also been proven therapeutically beneficial for other gram-positive bacterial infections, such as shunt infections in dialysis patients, and for infections in patients allergic to penicillin.[3,4] Although many family physicians choose to manage these types of patients in conjunction with consultants, family physicians are, by virtue of their primary care role, increasingly responsible for the initial dosing of this medication.

Along with its obvious potential therapeutic benefits, vancomycin also has potential toxicities. Research has associated vancomycin with ototoxicity when serum levels are elevated. Nephrotoxicity is another problem associated with increased vancomycin serum levels, particularly when it is used in combination with another nephrotoxic drug, such as an aminoglycoside.[5,6] Consequently, it is important to adjust initial dosages for elderly patients, patients with low body weight, and patients with impaired renal function.[7,8]

Although vancomycin has been used for over three decades, dosing of this agent remains problematic. The drug has a multicompartment pharmacokinetic elimination profile with an initial distribution phase of 1 to 3 hours, followed by a beta-elimination phase.[9] Because of this complex pharmacokinetic profile, serum drug mon-

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itoring of vancomycin has engendered controversy regarding if and when to obtain peak serum samples and how to interpret the serum levels. There is also a debate about whether vancomycin serum drug monitoring is useful at all.[10] Most clinicians believe vancomycin serum monitoring is necessary for appropriate use.

A preliminary survey of the family medicine residents from our institution found that the majority used either clinical judgment or a standardized dosing guide to initiate vancomycin therapy. Because neither of these methods accurately assessed renal function in their patients, the residents did not adjust the dosage for patients with decreased renal function.

Numerous attempts have been made to develop dosing guidelines to aid clinicians in the initial dosing of vancomycin. The most popular guidelines include the Moellering[8] and Matzke[11] nomograms and the method of Lake and Peterson.[12] These guides adjust vancomycin dosages based on patient weight and renal function. Although they are helpful in many instances for initial vancomycin dosing, it is our experience that these guides are underused by physicians. The result is that initial vancomycin dosing is performed incorrectly, causing either subtherapeutic, ineffective serum drug levels or, more commonly, excessive and unnecessary doses producing potentially toxic serum levels.

With proper vancomycin serum monitoring, appropriate dosage adjustments can be made following the initial dosage regimen. However, by the time serum levels are monitored, many patients have already received needless doses of vancomycin that put them at risk of drug toxicity and accrue unnecessary costs for the drug and its administration. Correcting these initial dosing errors would not only improve the quality of patient care but also amount to financial savings for medical centers. The objective of this study was to formally evaluate the initial dosing of vancomycin in our institution.

Methods

All new adult intravenous vancomycin orders in our medical center were screened for 3 consecutive months. Using a standardized monitoring form, the following information was recorded: patient name, age, weight, height, sex, serum creatinine, blood urea nitrogen, estimated creatinine clearance, pathogens isolated (if any), indication for vancomycin, initial vancomycin dosage regimen, prescribing physician's name and status (ie, resident, attending, staff), and concurrent antibiotics. Only patients who had initial vancomycin doses followed by steady-state serum levels based on the initial dose were entered into the study.

Table 1. Vancomycin Initial Dosage Guide Based on Matzke Nomogram (Initial dose: 15 to 19 mg/kg of total body weight)

Estimated Creatinine Clearance (mL/min)	Dosing Interval (hours)
>94	12
75–94	18
55–74	24
35–54	36
25–34	48
<25	(see below)*

Table based on data from Matzke, et al.[11]
**For creatinine clearance <25 mL/min, give single dose of 15 to 19 mg/kg and adjust dosage based on serum concentrations.*

NOTE: Estimated creatinine clearance is derived from Cockcroft-Gault equation[15]:

$$\text{Cr clearance (mL/min)} = \frac{(140 - \text{age})(\text{ideal body weight}) \times 0.85 \text{ if female}}{(\text{serum creatinine})(72)}$$

The initial dosage given was compared with a dosing nomogram and was judged as inappropriate if it varied from the dosing guide recommendations by more than 20% or varied in dosing interval by more than 8 hours. The study dosing guide utilized was adapted from the Matzke nomogram[11] and adjusts doses with respect to patient weight and estimated creatinine clearance (Table 1). The total number and percentage of inappropriate initial vancomycin doses were recorded from all orders.

Additionally, a second method of evaluation was performed on the data. Peak serum levels in the range of 20 to 50 mg/L and trough serum levels in the range of 5 to 15 mg/L were considered therapeutic. By use of these serum levels, patient-specific pharmacokinetic measurements, such as elimination half-life and apparent volume of distribution, were calculated. With the use of these patient-specific pharmacokinetic values, vancomycin peak and trough levels were predicted for the same study subjects based on new, nomogram-derived doses. The patients with recorded therapeutic peak and trough levels from the original non-nomogram utilized doses were then compared with the patients with predicted therapeutic peak and trough levels from the nomogram-derived doses.

Differences in age, weight, and estimated creatinine clearance between groups were assessed by means of the Student's *t* test for independent samples. Chi-square distribution was used to statistically analyze dosing correctness of non-nomogram and nomogram-derived regi-

mens. An a priori P value of .05 was deemed statistically significant for both tests.

Results

Sixty-one patients who received intravenous vancomycin were evaluated during a 3-month study period. Valid vancomycin serum peak and trough levels were recorded for 48 patients: 29 men and 19 women. Mean age of the subjects was 59.4 ± 19.9 years. Mean weight was 71.7 ± 19.0 kg, and the estimated creatinine clearance for these patients was 84.0 ± 40.5 mL/min (1.40 ± 0.68 mL/s). Thirteen of the 61 patients were excluded from analysis: 10 because they received vancomycin therapy without subsequent serum level monitoring; two because of end-stage, dialysis-dependent renal disease that resulted in the recording of only random vancomycin serum levels; and one patient who had pre–steady-state vancomycin serum levels drawn, thus yielding invalid levels.

The majority of vancomycin perscriptions were ordered by staff physicians (64.6%). Eight orders were written by family medicine residents (16.7%) and nine by attending physicians (18.8%).

The first evaluation method used revealed that 30 of 48 orders differed from nomogram-recommended doses. Of these, 10 varied from the nomogram-derived dosing interval by more than 8 hours. Thirteen differed from the nomogram dose amount recommendations by more than 20%. The remaining seven orders differed from the nomogram-recommended dosage by both dosing interval and dose amount.

The second evaluation method revealed that concomitant therapeutic peak and trough vancomycin levels following initial dosing were obtained in 19 (39.6%) of the study patients. Sixteen patients (33.3%) were found to have serum vancomycin trough levels either above or below the target trough range of 5 to 15 mg/L. Eighteen patients (37.5%), including five who also had subtherapeutic trough levels, were found to have inadequate peak vancomycin levels of <20 mg/L (Table 2). Younger patients (mean age, 48.5 ± 17.9 years) were more likely to have inadequate trough levels, and older patients (mean age, 70.3 ± 16.8 years) were more likely to have potentially toxic trough concentrations (P = .029) (Table 3).

Renal function also correlated with serum vancomycin levels. Patients with higher estimated creatinine clearances (>90 mL/min [>1.50 mL/s]) showed a propensity for subtherapeutic trough levels when being dosed without the use of a dosing nomogram. Conversely, patients with lower estimated creatinine clearances (<45 mL/min [0.75 mL/s]) tended to have higher serum vancomycin trough levels (P = .001).

Table 2. Results of Evaluating Serum Vancomycin Levels in 48 Patients Following Initial Doses

Variable	Peak 20–50 mg/L Trough 5–15 mg/L	Peak <20 or >50 mg/L Trough 5–15 mg/L	Peak 20–50 mg/L Trough <5 or >15 mg/L	Peak <20 or >50 mg/L Trough <5 or >15 mg/L
No. of patients*	19	13	16	5
Percent of patients†	39.6	27.1	33.3	10.4

**Total exceeds 48 by including patients counted in column 2 or 3.*
†Total exceeds 100% because of including patients counted in column 2 or 3.

For the 29 patients who were found to have inappropriate serum peak or trough levels, our dosing nomogram was employed. By using patient-specific pharmacokinetic measurements to calculate elimination half-life and apparent distribution volumes, inappropriate dosing might have been avoided in 22 of the 29 patients with use of the nomogram. Twelve of the 22 discrepancies between actual and nomogram-derived dosages were attributed to failure to lengthen the dosing interval because of a patient's underlying renal insufficiency. Ten of the 22 disparities resulted from a difference in dose amount by greater than 20% in either direction. The nomogram would have recommended similar initial doses for the remaining seven patients whose initial doses yielded nontherapeutic serum levels and, thus, would not have given any better initial serum levels.

The 19 non–nomogram-derived doses that achieved therapeutic peak and trough vancomycin levels were also compared with our nomogram-derived doses. Eleven of these doses were similar to nomogram doses. Eight varied from nomogram-obtained doses either by dosing interval (four) or by being 20% lower in dosage amount (four). By use of pharmacokinetic principles, it appears

Table 3. Characteristics of Patients with Nontherapeutic Trough Levels

Characteristic	Trough <5 mg/L	Trough >15 mg/L	P Value
No. of patients	9	6	
Age (y ± SD)	48.5 ± 17.9	70.3 ± 16.8	.029
Estimated creatinine clearance (mL/min)	>90	<45	.001

NOTE: Estimated creatinine clearance is derived from Cockcroft-Gault equation[15]:

$$\text{Cr clearance (mL/min)} = \frac{(140 - \text{age})(\text{ideal body weight}) \times 0.85 \text{ if female}}{(\text{serum creatinine})(72)}$$

Table 4. Patients with Therapeutic Peak and Trough Levels Following Initial Vancomycin Dose

Dosing Method	No. Correct	% Correct	*P* Value
Non-nomogram	19	39.6	<.01
Nomogram	40	83.3	

that seven of these eight patients would have achieved therapeutic serum vancomycin levels with the nomogram-derived dose as well. The one patient who would not have received a correct dose through use of the nomogram appeared to have much better renal function than predicted. This produced a faster elimination rate for vancomycin, yielding lower serum trough levels.

When totaled, the nomogram would have initially dosed 40 of the 48 study subjects correctly (83.3%), a significant improvement over the 39.6% achieved by non-nomogram methods ($P < .01$) (Table 4).

Prescribing physician status had no correlation with initial dosage correctness. Attending physicians prescribed correct initial dosages in 4 of 12 (33%) patients, as compared with staff physicians, 11 of 28 (39%), and resident physicians, 3 of 8 (38%).

Discussion

Vancomycin has now become the cornerstone for treatment of methicillin-resistant staphylococcal infections. Unfortunately, it appears that proper dosing strategies for this drug are not widely used in our hospital. The underlying reason for inappropriate vancomycin dosing may be lack of familiarity with standard dosing nomograms.

Although no one method for predicting proper vancomycin dosing in patients has been 100% correct, the nomograms of Matzke[11] and Moellering[8] have proved to be the most precise, producing therapeutic vancomycin serum levels in 72% to 96% of patients.[13,14] There are, however, certain shortcomings to both nomograms. Both were derived from studies evaluating relatively small numbers of patients (Matzke, 56 patients; Moellering, 17 patients), and both assume a fixed volume of distribution for vancomycin at 0.9 L/kg. According to Matzke,[11] this value appears to be more accurate for patients over 65 years of age, but for patients less than 65 years old, a volume of distribution of 0.7 L/kg may be more accurate. The modified nomogram used in this study has been adjusted for the apparent difference in distribution volumes between age groups. Either of these nomograms can be considered accurate methods for the initial dosing of vancomycin.

By the criteria defined in this study, correct vancomycin dosing occurred in only 39.6% of the study patients, which is lower than the 72% to 96% accuracy reported with the use of vancomycin nomograms. Although it is probably unrealistic to expect 96% accuracy in an uncontrolled clinical setting, improvement from 39.6% of correct initial dosing to 83.3% seems feasible and could possibly improve the care given to these patients.

The results of this study suggest that older patients may be at higher risk for being overdosed with vancomycin. Longer dosing intervals for elderly patients may be needed to allow for the increased elimination half-life of vancomycin in this subgroup of patients. Although it was not the goal of this study to assess toxicity, elderly patients tend to be at higher risk for adverse drug effects than younger patients. Therefore, increased initial doses may place elderly patients at increased risk for adverse drug reactions. For elderly patients, dosage reduction, mainly by dosage interval lengthening, would not only lessen the chance of renal or otic toxicity but also would allow for decreased drug and drug administration costs.

In contrast, younger patients appear to be at risk for underdosing, which could lead to therapeutic failures in these patients. In this study, patients with higher calculated creatinine clearances were at risk of being underdosed, and patients with lower creatinine clearances had a tendency to be overdosed. Therefore, it is important to have an estimation of renal function before initiating intravenous vancomycin therapy.

The most accurate routine means of measuring creatinine clearance is with a 24-hour urine collection. Unfortunately, the clinician may not have the opportunity to do this before beginning treatment of a critically ill patient. A reasonable estimation of renal function may be obtained by using the Cockcroft-Gault formula.[15] The nomograms described above incorporate this formula into their dosing guidelines.

The investigators believe that underuse of vancomycin dosing nomograms may be common in other medical centers and that greater use of dosing nomograms by prescribing clinicians could improve initial vancomycin dosing. The authors believe that educational measures such as distribution of dosing nomograms and instruction on their use should be integrated into medical school and residency training programs and would have a positive impact on appropriate initial dosing of vancomycin.

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