Comparing two predictive methods for determining serum vancomycin concentrations at a Veterans Affairs medical center

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A recent study found that clinical and economic outcomes are improved for patients whose vancomycin therapy is managed by pharmacists. Pharmacokinetics is useful in predicting serum vancomycin concentrations (SVCs) and allows for the individualization of dosage regimens. Various vancomycin dosing methods have been described and are based on patient-specific factors such as weight, creatinine clearance (CL\textsubscript{cr}), and age.\textsuperscript{2-7} In a study of veterans, Leonard and Boro\textsuperscript{2} found that the equations $CL = 0.9 \times CL_{cr}$ (mL/min/kg) $\times$ ABW and $V = 0.7$ L/kg $\times$ ABW better predicted SVCs than the conventional method ($CL = 0.65 \times CL_{cr}$ [mL/min/kg] $\times$ ABW and $V = 0.7$ L/kg $\times$ ABW), where $V$, volume of distribution, ABW = actual body weight in kilograms, $CL = $ vancomycin clearance in milliliters per minute, and $CL_{cr}$ is based on a derivation of the Cockcroft and Gault equation,\textsuperscript{8} where no weight is entered to generate a $CL_{cr}$ in milliliters per minute per kilogram. The $0.9 \times CL_{cr}$ factor was derived retrospectively from regression analysis. Given the limitations in their plasma sampling strategy, which predominantly measured trough vancomycin concentrations, and sample size, Leonard and Boro\textsuperscript{4}

Purpose. Two predictive methods for determining serum vancomycin concentrations (SVCs) at a Veterans Affairs medical center were compared.

Methods. The data for inpatients at the San Francisco Veterans Affairs Medical Center who received i.v. vancomycin and had vancomycin concentrations recorded in 2003 were included in this retrospective study. Creatinine clearance was estimated by the Cockcroft and Gault equation. Volume of distribution and creatinine clearance were calculated for each patient, using the Leonard and Boro method and the Rushing and Ambrose method. The Sheiner and Beal method for determining precision and bias was used to evaluate whether the two methods significantly differed in their ability to predict SVCs.

Results. Of the 223 patients identified, 122 patients were included, and 212 SVCs were analyzed. The population was mostly male and had a mean age of 64.1 years. There were no significant differences in 95% confidence intervals for relative precision and relative bias between the two methods. In patients whose weight was within 120% of their ideal body weight (IBW), the Leonard and Boro method was significantly more precise and less biased in predicting SVCs. In patients whose weight exceeded 120% of their IBW, the Rushing and Ambrose method was less biased and tended to be more precise, although the difference in precision was not significant.

Conclusion. Both methods yielded similar predictability for SVCs in a veterans population. The Leonard and Boro method better predicted SVCs in patients weighing within 120% of their IBW, while the Rushing and Ambrose method appeared to be more appropriate for calculating vancomycin dosages in patients whose weight exceeded 120% of their IBW.

Index terms: Antibiotics; Blood levels; Dosage; Drugs, body distribution; Equations; Methodology; Vancomycin; Weight

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could not improve their estimate of V. In a comparative study, Rushing and Ambrose found that their study method better predicted SVCs than did the methods of Matzke, and the conven-
tional pharmacokinetic method. The Rushing and Ambrose method, derived retrospectively from multiple regression analysis, defines V as (0.17 × age) + (0.22 × ABW) + 15 and describes CL as CLcr (mL/min/kg) × (lesser of ABW or ideal body weight (IBW)).

Methods

This study was reviewed and approved by the institutional review board and committee on human research. The data for inpatients age 18 years or older at the San Francisco Veterans Affairs Medical Center who received i.v. vancomycin and had vancomycin concentrations recorded in 2003 were included in this retrospective study. Only the first course of therapy was analyzed in patients who received multiple vancomycin courses. In patients with stable renal function, all SVCs collected during the course of therapy were included; however, only one V and CL would be calculated per patient using each method. Patients with unstable renal function, defined as a change in serum creatinine concentration (SCr) of (1) >0.5 mg/dL in patients with an SCr of <2 mg/dL or (2) >20% in patients with an SCr of ≥2 mg/dL if the change occurred within four days, were excluded from the study.

Patients were also excluded if they received hemodialysis, there was uncertain documentation of vancomycin sampling time or dose administration, vancomycin sampling occurred during the distribution phase (within one hour from the end of the one-hour infusion), or there were undetectable SVCs (lower limit of detection was 5 mg/dL). Patients with inconsistent body weights (change of >10% with no indication of third spacing of fluid) during the course of vancomycin therapy or whose data were incomplete (missing information on height, weight, or SCr) were also excluded.

Patients' medical records were reviewed to collect information on age, sex, weight, height, SCr, SVCs, and vancomycin administration history. SCr values of <1 mg/dL were normalized to 1 mg/dL to estimate CLcr. When a patient had multiple SVCs recorded, an average SCr was used to calculate a single CLcr. CLcr was estimated by the Cockcroft and Gault equation. V and CL were calculated for each patient, using the Leonard and Boro method and the Rushing and Ambrose method. Each patient's data set of doses and SVCs, along with his or her individually calculated V and CL (using the Leonard and Boro method), was entered into the Therapeutic Drug Monitoring System, version 5.10 (Healthware Inc., San Diego, CA), to calculate the expected SVCs at the times when they were obtained. This process was then repeated with the V and CL calculated using the Rushing and Ambrose method. The SVCs were calculated using a non-steady-state, short-infusion model.

The Sheiner and Beal method for determining precision and bias was used to evaluate whether the Leonard and Boro and Rushing and Ambrose methods significantly differed in their ability to predict SVCs. Precision, determined by the root mean-squared prediction error (RMSE), was used to indicate how closely a prediction matched the measured concentration. The smaller the RMSE, the more precise the prediction. The relative difference of precision between two data sets is determined by the change in the mean-squared prediction error (MSE). Bias was determined using the mean prediction error (ME). Bias characterizes the tendency to overestimate or underestimate the measured concentrations. A smaller absolute ME indicates less bias. The change in ME describes the relative difference in bias between two data sets. The 95% confidence interval (CI) for the change in MSE and the change in ME, which considers sample size, was used to determine statistical significance. If the 95% CI for the change in MSE did not include zero, the method with the smaller RMSE was significantly more precise. If the 95% CI for the change in ME did not include zero, the method with the smaller absolute ME was significantly less biased.

Because the Rushing and Ambrose method incorporated the lesser of ABW or IBW in calculating CL, a subgroup analysis based on weight (≤120% or >120% of IBW) was conducted to assess the relative predictive performance of the two methods in obese and nonobese patient populations.

Results

Of the 223 patients identified, 122 patients were included, and 212 SVCs were analyzed. Of the 101 patients who were excluded, 33 had received hemodialysis, 28 had unstable renal function, 14 had incomplete patient data, and 13 had undetectable SVCs. Uncertain vancomycin administration history and uncertain SVC sampling history were the reasons for exclusion of 11 and 2 patients, respectively. Patient demographics are presented in Table 1. The study population was almost exclusively

Vancomycin concentrations

Am J Health-Syst Pharm—Vol 63 Oct 1, 2006 1873
male (97.5%) and of moderately advanced age (mean ± S.D. age, 64.1 ± 12.5 years). On average, the patients weighed 86.6 kg and had an IBW of 72 kg. A majority of the patients had one recorded SVC (65%), 25% had two or three recorded SVCs, and the remaining 10% had between four and nine recorded SVCs. The 212 SVCs were categorized as 7 peak (obtained two to three hours after the start of the one-hour infusion), 73 trough (within one hour of the next scheduled dose), and 132 random concentrations. Of the 132 random samples, the vast majority were obtained in the last quarter of the dosing interval. Precision and bias results for SVC predictability are presented in Table 2. When analyzing all SVCs, there were no significant differences in 95% CIs for relative precision and relative bias between the two methods.

A total of 141 SVCs were recorded for patients within 120% of their IBW (n = 73); 71 were recorded for patients weighing over 120% of their IBW (n = 49). The range of weight expressed as a percentage of IBW was narrower for patients within 120% of their IBW (76–120%; mean, 101%) and wider for patients over 120% of their IBW (121–304%; mean, 149%). Precision and bias results for the subgroups are presented in Table 3. In patients whose weight was within 120% of their IBW, the Leonard and Boro method was significantly more precise and less biased in predicting SVCs. In patients whose weight exceeded 120% of their IBW, the Rushing and Ambrose method was less biased and suggestive of greater precision, although the difference in precision was not significant.

Discussion

Several similarities and differences exist among the previous studies by Rushing and Ambrose and Leonard and Boro and the current study. The current study population resembled that of Leonard and Boro in that both were conducted in a veterans population, with nearly all male patients (97.5% and 100%, respectively) of moderately advanced age (mean ± S.D. age, 64.1 ± 12.5 years). On average, the patients weighed 86.6 kg and had an IBW of 72 kg. A majority of the patients had one recorded SVC (65%), 25% had two or three recorded SVCs, and the remaining 10% had between four and nine recorded SVCs. The 212 SVCs were categorized as 7 peak (obtained two to three hours after the start of the one-hour infusion), 73 trough (within one hour of the next scheduled dose), and 132 random concentrations. Of the 132 random samples, the vast majority were obtained in the last quarter of the dosing interval. Precision and bias results for SVC predictability are presented in Table 2. When analyzing all SVCs, there were no significant differences in 95% CIs for relative precision and relative bias between the two methods.

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Table 1. Patient Demographics and Characteristics (n = 122)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± S.D. (Range)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>64.1 ± 12.5 (35–88)</td>
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<tr>
<td>% Male</td>
<td>97.5</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>1.2 ± 0.7 (0.4–4.9)</td>
</tr>
<tr>
<td>Height (in.)</td>
<td>69.6 ± 2.7 (64–76)</td>
</tr>
<tr>
<td>ABW (kg)</td>
<td>86.6 ± 24.9 (54–207.7)</td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>72.0 ± 6.4 (54.2–86.8)</td>
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</table>

*SCr = serum creatinine concentration, ABW = actual body weight, IBW = ideal body weight.

Table 2. Performance of Two Methods of Predicting Serum Vancomycin Concentration

<table>
<thead>
<tr>
<th>Performance Variable</th>
<th>Value of Variable (mg/L) (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Leonard and Boro² Method</td>
</tr>
<tr>
<td>RMSEb</td>
<td>7.83 (6.58, 8.90)</td>
</tr>
<tr>
<td>MEc</td>
<td>−3.36 (−4.31, −2.41)</td>
</tr>
</tbody>
</table>

* CI = confidence interval, RMSE = root mean-squared prediction error, ME = mean prediction error.

Table 3. Performance of Two Methods of Predicting Serum Vancomycin Concentrations Stratified by Patient Weight

<table>
<thead>
<tr>
<th>Performance Variable</th>
<th>Value of Variable (mg/L) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤120% of IBW</td>
</tr>
<tr>
<td></td>
<td>Leonard and Boro² Method</td>
</tr>
<tr>
<td>RMSEb</td>
<td>8.33 (6.69, 9.70)</td>
</tr>
<tr>
<td>MEc</td>
<td>−3.31 (−4.57, −2.04)</td>
</tr>
</tbody>
</table>

* CI = confidence interval, IBW = ideal body weight, RMSE = root mean-squared prediction error, ME = mean prediction error.

The difference in mean-squared prediction errors was −3.84 mg/L (95% CI, −11.11, 3.43). Zero is included in the 95% CI, indicating no significant difference in precision between methods.

The difference in MEs was −0.23 mg/L (95% CI, −0.69, 0.24). Zero is included in the 95% CI, indicating no significant difference in bias between methods.

The difference in mean-squared prediction errors was −11.48 mg/L (95% CI, −15.99, −6.97) for the ≤120% of IBW group and 11.32 mg/L (95% CI, −8.40, 31.05) for the >120% of IBW group. Zero is not included in the 95% CI of the first group, indicating a significant difference in precision between methods.

The difference in mean prediction errors was 1.37 mg/L (95% CI, 1.12, 1.61) for the ≤120% of IBW group and −3.39 mg/L (95% CI, −4.33, −2.45) for the >120% of IBW group. Zero is not included in the 95% CI of either group, indicating a significant difference in bias between methods for both groups.
(mean age, 64 years for both studies). In contrast, only 56% of the patients studied by Rushing and Ambrose were male, and the mean age was 53 years. The average ABW was lowest in Leonard and Boro’s study (71 kg, 97% of IBW), higher in Rushing and Ambrose’s study (77 kg, 119% of IBW), and highest in this study (87 kg, 120% of IBW). This trend of increasing average percentage of IBW may be a random occurrence but is consistent with recent findings that obesity is a major medical issue for our society and the veterans population. The fact that the Leonard and Boro method was derived from patients with leaner weights may be one reason why that method gave more favorable predictions for patients within 120% of their IBW. In all three studies, SCR values of less than 1 mg/dL were normalized to 1 mg/dL when estimating CLcr. The sample size of this study (122 patients with 212 SVCs) is comparable to that of Leonard and Boro (113 patients with 266 SVCs) and Rushing and Ambrose (107 patients with 216 SVCs). The categories of SVCs in the three studies varied greatly. Rushing and Ambrose had 50% peak concentrations; Leonard and Boro had 31% peak concentrations. In this study, only 3% of the SVCs were peak concentrations, which is consistent with most current sampling strategies for vancomycin.

One limitation to this study is that it was conducted using a population of veterans, and these data may not be able to be generalized to other populations. One clear difference is the lack of women. Because vancomycin is eliminated almost exclusively by the renal route, it may be that as long as renal function can be accurately estimated, the findings of this study would apply to the female population as well.

The method of Rushing and Ambrose was less biased for the subset of obese patients. However, because of the limited number of obese patients, we were not able to determine which method was more precise. As obesity continues to grow as a health care concern, we need to determine how pharmacokinetics can be best applied to this patient population to ensure optimal drug therapy.

These data indicate that, for nonobese veterans, the Leonard and Boro method for calculating vancomycin V and CL when applied to a pharmacokinetic model should result in SVCs that are closer to the targeted or desired concentrations. There is an assumption that when applied to a reasonable practice model, achieving the target concentration will improve patient outcome.

Conclusion

Both methods yielded similar predictability for SVCs in a veterans method better predicted SVCs in patients weighing within 120% of their IBW, while the Rushing and Ambrose method appeared to be more appropriate for calculating vancomycin dosages in patients whose weight exceeded 120% of their IBW.

References