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Effect of Obesity on Vancomycin Pharmacokinetic Parameters as Determined by Using a Bayesian Forecasting Technique

KYLE VANCE-BRYAN,[1,2] DAVID R. P. GUAY,[1,2] SUSAN S. GILLILAND,[2] KEITH A. RODVOLD,[3] AND JOHN C. ROTSCHAFER[1,2]*

College of Pharmacy, The University of Minnesota, Minneapolis, Minnesota 55455[1]; Section of Clinical Pharmacy, St. Paul-Ramsey Medical Center, St. Paul, Minnesota 55101[2]; and College of Pharmacy, The University of Illinois at Chicago, Chicago, Illinois 60680[3]

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Few data exist concerning the effect of obesity on the pharmacokinetic parameters of vancomycin. The purpose of this investigation was to assess the effect of obesity on vancomycin pharmacokinetic parameters in 95 nonobese and 135 obese adult patients (age range, 18 to 92 years) receiving vancomycin. All subjects had normal renal function as defined by a creatinine concentration in serum of ≤1.5 mg/dl (mean estimated creatinine clearance ± 1 standard deviation, 76 ± 34; range, 23 to 215 ml/min). Vancomycin concentrations in serum were determined by the fluorescence polarization immunoassay. All data for vancomycin concentration in serum versus time for each course of therapy were fitted by using a two-compartment Bayesian forecasting program. Subjects were stratified into nine groups on the basis of the percent difference between actual body weight (ABW) and lean body weight (LBW) (>−10%, −10 to 0%, >0 to 10%, >10 to 20%, >20 to 30%, >30 to 40%, >40 to 50%, >50 to 60%, >60%). Analysis of variance with post hoc Scheffe's testing revealed that statistically significant differences occurred in terminal disposition half-life ($t_{1/2\beta}$) between the extremes of modestly obese (group 4) and morbidly obese (group 9, $P < 0.05$) patients. Similar analysis with distribution volume (V) identified significant differences in patients at or near their LBW (groups 2 to 4) and patients who were morbidly obese (groups 8 and 9, $P < 0.05$). Multiple regression models for the pharmacokinetic parameters V, $t_{1/2\beta}$, and vancomycin total body clearance were developed to assess the joint predictive power of LBW, ABW, and percent over LBW, controlling for the effects of age, initial creatinine concentration in serum, initial creatinine clearance, and gender. In the final model for V, both ABW and percent over LBW were independent and significant predictors. For total body clearance, only ABW was significant and predictive. Percent over LBW was a significant and independent predictor of $t_{1/2\beta}$. LBW is not predictive of these pharmacokinetic parameters and should not be used for initial dosing. On the basis of these data, ABW appears to be superior to LBW for calculating initial dose requirements for vancomycin.

Vancomycin is presently considered to be the drug of choice for methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis* infections (7, 8, 12). Several investigators have suggested that peak and trough concentrations in serum be monitored and appropriately adjusted during therapy (12, 27, 28, 30). The value of such monitoring has been extensively debated in the literature and is beyond the scope of this report (11, 27).

A variety of pharmacokinetic models and dosing methods have been proposed for prospective dosage adjustment of vancomycin (24, 34). Virtually all of these methods are configured to adjust for age- or disease-related changes in renal function. None of the current vancomycin dosing methods adjusts dosage on the basis of the extent of obesity.

Blouin et al. studied six morbidly obese patients and four patients of normal body weight and concluded that total body weight should be used in the determination of vancomycin dosing (3). Conclusions drawn from this small study sample must be considered preliminary. A study of a larger number of patients is needed to determine whether lean (LBW) or actual (ABW) body weight or some hybrid (lean plus a percent of adipose) body weight parameter should be used to calculate vancomycin dosing requirements prior to the availability of actual data for vancomycin concentration in serum versus time.

The purposes of this investigation were (i) to determine whether obesity has a significant influence on the pharmacokinetic parameters of vancomycin in a large patient sample and (ii) to determine whether additional adjustments in vancomycin dosage calculations are required as a result of obesity.

MATERIALS AND METHODS

Two hundred thirty adult patients (age range, 18 to 92 years; mean ± 1 standard deviation, 54.1 ± 20.9 years) with normal renal function (creatinine concentration in serum, ≤1.5 mg/dl) who were consistently monitored by the antibiotic pharmacokinetic dosing service at the St. Paul-Ramsey Medical Center were studied. Patients were considered to have normal liver function; however, complete data on liver function were unavailable for all patients. Creatinine clearance was estimated for all patients by the method of Cockcroft and Gault (6). Patients received 10 to 15 mg of vancomycin per kg of body weight intravenously over 60 min. Vancomycin concentrations in serum post- and preinfusion were determined from samples obtained within 15 to

* Corresponding author.

30 min after infusion and 15 to 30 min before infusion, respectively. Initial vancomycin dosage intervals were determined by using the method described by Rodvold et al. (25). Trough and peak vancomycin concentrations in serum were determined at steady state (> five estimated terminal disposition half-lives [$t_{1/2\beta}$]). The dose and dosage interval were then adjusted to obtain peak and trough vancomycin concentrations in serum of 30 to 40 and 5 to 10 mg/liter, respectively. Peak vancomycin concentrations in serum were defined as the concentration at the end of intravenous infusion (time zero). The pharmacokinetic parameters evaluated were vancomycin clearance (CL), distribution volume (V), and $t_{1/2\beta}$.

Vancomycin concentrations in serum (range, 0.6 to 100 mg/liter) were measured in our laboratory by using a fluorescence polarization immunoassay (TDx; Abbott Laboratories, Irving, Tex.). Interassay and intraassay coefficients of variation were 6.1 and <4.7%, respectively. All data for vancomycin concentration in serum versus time for each patient, either three postinfusion levels after the initial dose plus a follow-up trough/peak determination or two trough/peak determinations (i.e., four samples), along with patient-specific vancomycin dosing history were entered into a commercially available pharmacokinetic software package, Abbottbase Pharmacokinetic Systems (Abbott Laboratories). These data were fitted to a two-compartment pharmacokinetic model previously described by Rodvold and colleagues which incorporates a Bayesian feedback loop (26). The central compartment volume (V_1) was assumed to be 0.21 liters/kg of ABW. Two-compartment pharmacokinetic microconstants K_{12} and K_{21} were assumed to be 1.12 Hr-1 and 0.48 Hr-1, respectively. Vancomycin clearance was calculated by using the following previously described regression equation (26): vancomycin clearance = 0.75 × creatinine clearance + 0.05. The creatinine clearance used in this equation was calculated by the method of Cockcroft and Gault (6). Bayesian feedback was used to refine pharmacokinetic parameter estimates with patient-specific data for vancomycin concentration in serum versus time as previously described. Fractional standard deviation was set at 20% for V_1, K_{12}, K_{21}, and nonrenal vancomycin clearance. Fractional standard deviation was set at 33% for the slope of the regression equation.

Patients were retrospectively stratified on the basis of the percent difference between their ABW and LBW. Nine patient groups were delineated, with differences between ABW and LBW of >−10%, −10 to 0%, >0 to 10%, >10 to 20%, >20 to 30%, >30 to 40%, >40 to 50%, >50 to 60%, and >60% (groups 1 through 9, respectively). LBW was calculated by the method of Devine, as follows: male LBW (kg) = 50 + 2.3 (number of inches >5 feet [1 in. = 2.54 cm; 1 ft = 30.48 cm]); female LBW (kg) = 45 + 2.3 (number of inches >5 feet) (10). Excess or adipose body weight (EBW) was defined as the difference between ABW and LBW. Obese patients were arbitrarily defined as those individuals >20% over LBW.

Standard regression analyses linking V, $t_{1/2\beta}$, and CL with extent of obesity were performed. Analysis of variance and post hoc Scheffe's testing were used to determine statistical differences ($P < 0.05$) in $t_{1/2\beta}$, CL, and V among the nine patient groups.

The effect of obesity on V was further examined by regressing V in liters against the following hybrid parameters: percent <LBW, LBW, LBW + 10% EBW, LBW + 20% EBW, LBW + 30% EBW, LBW + 40% EBW, LBW + 50% EBW, LBW + 60% EBW, LBW + 70% EBW, LBW + 80% EBW, and ABW. These analyses were performed first with all 230 patients and then only with the 135 obese patients.

Pharmacokinetic parameters were fitted to multiple linear regression models to control for the effect of demographic covariants available at the time of dosing. These demographic covariants included age, gender, initial creatinine concentration in serum, and initial creatinine clearance. Variables were entered by using stepwise forward entry algorithms. The order of variable entry into the final models was evaluated for each of the three models. Final models were selected by using the highest R^2 to account for the majority of the variance in the dependent variables by all factors and covariants.

RESULTS

Of the 230 patients, 9 (4%) were more than 10% below their LBW, 47 (20%) were 10% or less below their LBW, 39 (17%) were at or <10% above their LBW, and 28 (12%) were at or <20% above their LBW. The remaining 107 (47%) patients met the study definition of obesity. All statistical analyses were performed with commercial software (Statview; Brainpower, Inc., Calabasas, Calif.). There were no statistical differences in the mean patient age and creatinine clearance among the nine groups. There was a statistically significant difference in gender distribution between groups 7 and 9. Group 7 contained 8 males and 14 females, and group 9 contained 4 males and 10 females.

Mean (± standard deviation) vancomycin pharmacokinetic parameters were determined for each of the nine groups and are reported in Table 1. There were significant differences within the groups of obese patients. These differences were mainly between patient groups that were of low to near normal body weight versus those who were morbidly obese. Analysis of patients for which the ABW exceeded the LBW by 30% or more (groups 6 to 9) revealed a weaker correlation between V and percent over LBW (r = 0.65) compared with all weight groups. This difference was not statistically significant.

In order to determine whether obesity has a significant influence on the vancomycin pharmacokinetic parameters $t_{1/2\beta}$, CL, and V, weight was examined as a continuous variable. Patient demographic variables were entered into multiple regression models. The final regression model for V is presented in Table 2. Both ABW and percent over LBW were significant and independent predictors of V. In addition to the body mass parameter, age was also found to be an independent predictor of V. Initial creatinine concentration in serum, initial creatinine clearance, LBW, and gender were not significant predictors and were not included in the final V model.

Table 3 presents the final regression model for CL. After adjusting for the effects of age, gender, initial creatinine concentration in serum, and initial creatinine clearance, ABW was the only body mass parameter that was a significant predictor of CL. Additionally, significant predictors of CL were age and initial creatinine concentration in serum.

The final regression model for $t_{1/2\beta}$ is presented in Table 4. After adjusting for the effects of age, gender, initial creatinine concentration in serum, and initial creatinine clearance, percent over LBW was a significant predictor of $t_{1/2\beta}$. ABW and LBW were not significant predictors and were not included in the final $t_{1/2\beta}$ model. Additionally, age, gender, initial creatinine concentration in serum, and initial creatinine clearance were independent and significant predictors

TABLE 1. Mean demographic and pharmacokinetic parameters for study patients

Group[a]	Mean (± 1 SD)					
	Age, yr	$t_{1/2\beta}$[b], h	V[c], liters	CL[d], ml/min/kg	C_{max}[e], mg/liter	C_{min}[f], mg/liter
1	36.4 (15.9)	6.9 (4.1)	53.1 (16.8)	1.56 (0.47)	33.1 (15.9)	10.9 (11.8)
2	58.1 (23)	11.9 (0.94)	46.8 (12.5)	1.12 (0.63)	30.9 (14.6)	9.2 (5.5)
3	50.7 (21.5)	10.8 (8.4)	56.0 (15.4)	1.04 (0.54)	30.7 (13.2)	8.7 (6.3)
4	48.6 (18.7)	8.2 (4.8)	59.5 (15.7)	1.10 (0.43)	29.9 (13.4)	7.1 (4.8)
5	54.3 (22.8)	14.5 (13.1)	79.4 (34.6)	0.85 (0.39)	31.4 (10.5)	8.7 (5.7)
6	58.3 (18.8)	14.7 (12.9)	81.4 (24.3)	0.76 (0.46)	28.9 (10.9)	7.5 (4.6)
7	56.3 (21.3)	12.8 (9.6)	85.0 (22.6)	0.83 (0.50)	34 (18.1)	10.2 (4.6)
8	55.2 (18.9)	12.6 (6.1)	117.2 (30.9)	0.76 (0.23)	22.1 (4.9)	6.4 (3.2)
9	60.0 (13.1)	22.8 (21.5)	127.9 (57.8)	0.61 (0.38)	38.0 (12.6)	12.7 (8.5)

[a] Patients with differences between their ABW and LBW of >−10%, −10 to 0%, >0 to 10%, >10 to 20%, >20 to 30%, >30 to 40%, >40 to 50%, >50 to 60%, and >60% were divided into groups 1 to 9, respectively. For groups 1 to 9, n = 9, 47, 39, 28, 32, 28, 22, 11, and 14, respectively.
[b] Significant difference for group 4 versus 9 (Scheffe's test).
[c] Significant differences for groups 1 versus 8, 1 versus 9, 2 versus 5, 2 versus 6, 2 versus 7, 2 versus 8, 2 versus 9, 3 versus 6, 3 versus 7, 3 versus 8, 3 versus 9, 4 versus 8, 4 versus 9, 5 versus 8, 5 versus 9, 6 versus 9, and 7 versus 9 (Scheffe's test).
[d] Significant differences for groups 1 versus 6 and 1 versus 9 (Scheffe's test).
[e] C_{max}, peak vancomycin concentration in serum.
[f] C_{min}, trough vancomycin concentration in serum.

of $t_{1/2\beta}$. Piecewise exclusion of covariants was done with the same resulting model. Although initial creatinine concentration in serum and initial creatinine clearance are correlated, they apparently each contain independent information that accounts for a significant amount of the variability in $t_{1/2\beta}$. The strongest predictor of $t_{1/2\beta}$ appears to be initial creatinine concentration in serum.

DISCUSSION

Vancomycin pharmacokinetics have been evaluated by using monoexponential (18), biexponential (28), and triexponential (20) mathematical models. Several investigators have proposed Bayesian modeling techniques as an alternative to traditional pharmacokinetic monitoring (5, 15, 26). The validity of the method used in this study has been determined by our own intensive internal examination and independently confirmed by other investigators (15, 26).

The pharmacokinetics of vancomycin have also been studied in a variety of populations. Both normal volunteers and patient populations have been studied (13, 20, 28). Patients have been evaluated on the basis of normal or abnormal renal function (13, 20, 23, 28). Numerous studies characterizing vancomycin disposition in both hemodialysis and peritoneal dialysis patients have been published (2, 17, 19, 21, 33). Patients have also been characterized on the basis of normal or abnormal hepatic function (4). The effect of age on the pharmacokinetics of vancomycin has also been extensively studied (1, 9, 14, 16, 22, 31, 32). Vancomycin pharmacokinetics in unique patient populations such as burn patients and intravenous drug abusers have also been characterized (29). At the present time, there is an extremely limited amount of data characterizing the pharmacokinetics of vancomycin in obese patients (3). Blouin's study represents an uncontrolled trial comparing the pharmacokinetic parameters in six obese patients with those in four patients of normal body weight.

This study shows results for 230 adult patients spanning the entire spectrum of body mass composition. Fifty-six (25%) of our patients were at or below their LBW. Approximately 17% of our patient study population were at or within 10% of their LBW. Forty-seven percent of our patients met the study definition of obesity. In some cases, EBW may be the result of overhydration or other factors and not the result of adipose tissue. However, this phenomenon would likely be evenly distributed throughout our patient population. There are obviously more rigorous definitions of obesity such as body mass index and others that could have been but were not incorporated into this trial.

The vancomycin pharmacokinetic variable most influenced by body weight was V. Clearly, multiple regression analysis revealed that both ABW and percent over LBW are independent and significant predictors of V. A change of 10 kg in ABW is estimated to result in an 8.1-liter increase in V. An increase of 10% above LBW is estimated to produce a 5.4-liter increase in V compared with a 10-year increase in age, which is estimated to result in a 2.2-liter increase in V. The final model that included age, ABW, and percent over LBW accounted for the majority of the variability in the data (R^2 = 0.58). These demographic variables significantly influence vancomycin V. Undoubtedly, there are other factors not available in the current set of data that may explain the remaining 42% of the variability in V.

CL is predicted to decrease as ABW increases. A 10-kg increase would result in a drop of 0.09 ml/min/kg in CL. Age and initial creatinine concentration in serum are additional significant predictors. An increase of 10 years in age is

TABLE 2. Final stepwise regression model for V

Parameter	Value	SE	P
Intercept	−15.287		
Age (yr)	0.219	0.075	0.04
ABW (kg)	0.814	0.13	0.0001
% over LBW	0.536	0.094	0.0001

TABLE 3. Final stepwise regression model for CL

Parameter	Value	SE	P
Intercept	2.939		
Age (yr)	−0.012	0.001	0.0001
ABW (kg)	−0.009	0.002	0.0001
Initial SrCr[a] (mg/dl)	−0.68	0.11	0.0001

[a] SrCr, creatinine concentration in serum.

TABLE 4. Final stepwise regression model for $t_{1/2\beta}$

Parameter	Value	SE	P
Intercept	−32.733		
Age (yr)	0.293	0.055	0.0001
Initial SrCr[a] (mg/dl)	23.159	4.41	0.0001
Initial CL_{CR}[b] (ml/min)	0.124	0.048	0.011
% over LBW	0.085	0.028	0.0026
Gender	−5.909	1.5	0.0001

[a] SrCr, creatinine concentration in serum.
[b] CL_{CR}, creatinine clearance.

estimated to produce a decrease of 0.12 ml/min/kg in CL. An increase in creatinine concentration in serum of 0.5 mg/dl is estimated to decrease CL by 0.34 ml/min/kg. Thus, in this model of patients with a creatinine concentration in serum ≤1.5 mg/dl, initial creatinine concentration in serum is the better predictor of CL and ABW is the weakest predictor.

The final model for $t_{1/2\beta}$ predicts that an increase of 10% above LBW would be estimated to produce an increase in $t_{1/2\beta}$ of 0.85 h. However, an increase in initial creatinine concentration in serum would be estimated to result in a much greater change in $t_{1/2\beta}$ compared with the change produced by percent over LBW. A 0.5-mg/dl increase in initial creatinine concentration in serum would be estimated to produce an 11.6-h increase in $t_{1/2\beta}$. Therefore, percent over LBW is a poor predictor of $t_{1/2\beta}$.

All three vancomycin pharmacokinetic parameters were influenced by body weight. The vancomycin pharmacokinetic variable most influenced by body weight was V. Multiple regression analysis revealed that both ABW and percent over LBW were independent and significant predictors of V. The final regression model with age, ABW, and percent over LBW explained 58% of the variability of the V set of data.

By extrapolating these data to the patient care environment, clinicians attempting to generate initial dosing recommendations for vancomycin in patients with normal renal function may be assisted by these models. Models for all three pharmacokinetic parameters included body weight as a significant predictor. For obese patients, clinicians may well have to factor the patients' ABW, degree of obesity, and age into their determination of initial loading and maintenance doses. Further adjustments in vancomycin therapy should then be guided by accepted therapeutic drug monitoring practices. Unfortunately, this study does not provide insight as to how obese patients with additional complications such as renal and/or hepatic impairment, burns, endocarditis, and other pathophysiology should be managed. Empiric initial dosage regimens such as 500 mg every 6 h or 1 g every 12 h are likely to produce suboptimal peak and trough vancomycin concentrations in serum in obese patients compared with patients whose weights more closely approximate LBW. On the basis of these data, ABW appears to be superior to LBW for calculating initial dose requirements for vancomycin.

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