

An Evaluation of Systemic Vancomycin Dosing in Obese Patients

David W. Kubiak, Mohammed Alquwaizani, David Sansonetti, Megan E. Barra, and Michael S. Calderwood

Brigham and Women's Hospital, Boston, Massachusetts

We retrospectively identified 67 patients with severe or morbid obesity (body mass index ≥ 35 kg/m²) who had received intravenous vancomycin at our institution. We observed that an initial dose of 45 to 65 mg/kg vancomycin per day based upon ideal body weight rather than actual body weight was more predictive of initial trough concentrations between 15 and 20 mcg/mL.

Keywords. obese; pharmacokinetics; vancomycin.

Close to one third of adults in the United States are obese (body mass index [BMI] ≥ 30 kg/m²) [1], and more than 600 million adults are obese worldwide [2]. Despite this, studies evaluating the pharmacokinetics of antimicrobial agents in obese patients are rare, because this is not required by the US Food and Drug Administration for drug approval. Further studies are needed to guide optimal dosing of antimicrobial agents in this patient population.

Current guidelines for systemic vancomycin dosing and monitoring recommend calculating initial doses (15–20 mg/kg every 8–12 hours) using actual body weight (ABW), regardless of BMI, followed by therapeutic drug monitoring for dose adjustments [3]. However, pharmacokinetic studies have differed in their support of this strategy in obese patients [4–10]. This has led to variability in practice. In fact, one study found that only one quarter of obese patients received doses of

vancomycin ≥ 10 mg/kg per dose (ABW), and <1% of these patients received doses ≥ 15 mg/kg per dose (ABW) [3, 7].

Vancomycin serum concentrations are impacted by increased clearance, increased volume of distribution, and a shorter terminal half-life of this drug in obese patients. In fact, some advocate for more frequent dosing of vancomycin in obese patients to mitigate toxicity and improve efficacy [11]. A better understanding of the optimal dosing strategy in obese patients is needed to help standardize practice.

In our institution, we have observed variability in the achievement of initial vancomycin serum trough concentrations between 15 and 20 mg/L in obese patients dosed using ABW. A trough concentration between 15 and 20 mg/L has been established as the best surrogate for the vancomycin pharmacodynamic target of an area under the concentration-time curve/minimum inhibitory concentration (MIC) >400 when the MIC is ≤ 1 mcg/mL for *Staphylococcus aureus* [3]. The aim of this study was to examine whether the initial trough concentration is better predicted by vancomycin dosing based on ABW, ideal body weight (IBW), or dosing body weight (DBW) in patients with severe or morbid obesity (BMI ≥ 35 kg/m²).

METHODS

We reviewed medical records for all adult patients (≥ 18 years old) with severe or morbid obesity (BMI ≥ 35 kg/m²) who were hospitalized at a single tertiary academic medical center between January 2011 and December 2013 and who had received at least 3 consecutive doses of systemic vancomycin. We identified these patients using a clinical data registry maintained by our hospital. Once identified, we performed clinical chart review and excluded any patients who had received a loading dose of vancomycin or who had a dosing change before their first measured trough concentration, those with a baseline creatinine clearance (CrCl) <45 mL/min (as calculated by the Cockcroft-Gault equation using IBW) [12], and those without at least 1 steady-state trough concentration measured ≤ 60 minutes before administration of the fourth (or later) dose of vancomycin.

Abstracted data included age, gender, weight (ABW, IBW, and DBW), baseline serum creatinine (Scr), calculated CrCl, vancomycin dose including frequency and total daily dose, and initial steady-state vancomycin serum trough concentration. Baseline CrCl was calculated using both the IBW and the DBW, because the DBW has been suggested to be a less biased estimate of CrCl in obese patients [13]. Ideal body weight was calculated using the following: IBW (male) = 50 kg + 2.3 (height [inches] – 60") kg, IBW (female) = 45.5 kg + 2.3 (height

Received 21 August 2015; accepted 10 November 2015.

Presented in part: IDWeek 2014, Philadelphia, PA.

Correspondence: David W. Kubiak, PharmD, BCPS-ID, Division of Infectious Diseases, Brigham and Women's Hospital, 181 Longwood Avenue, 5th floor, Boston, MA 02115 (dwkubiak@partners.org).

Open Forum Infectious Diseases

© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com.

DOI: 10.1093/ofid/ofv176

[inches] – 60”) kg. Dosing body weight was calculated as follows: DBW = 0.4 (ABW-IBW) + IBW. To account for fluctuations in CrCl before initiation of systemic vancomycin, we chose the lowest Scr \leq 72 hours before first dose of vancomycin for our minimum baseline value. The Partners Healthcare human research committee approved this study.

We used linear regression to predict the initial vancomycin trough concentration using total daily dose (mg/kg per day) based on ABW versus IBW versus DBW. We also analyzed the impact of age, gender, and SCr on the initial vancomycin trough concentration. The decision to include 1 or more of these covariates as secondary predictors in the final multivariable model was determined by a univariable P value $<.2$ for each included covariate. This was an a priori decision. We did not test CrCl or total daily dose in our final model, because both of these were felt to be collinear with the primary predictor (weight). However, we did test the interaction between dose and frequency. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

During the study period, we screened 251 eligible patients who were ≥ 18 years of age, had a BMI ≥ 35 kg/m², and had received at least 3 consecutive doses of systemic vancomycin. Fifty-seven patients were excluded because they received a loading dose or had a dosing change before the first steady-state serum vancomycin trough, 12 patients were excluded because of a baseline CrCl <45 mL/min, and 115 patients were excluded because they either had no serum vancomycin trough obtained or a trough drawn at an inappropriate time. This left a study population of 67 patients assessed in our analysis.

Table 1 shows the patient characteristics in our study population. When initial doses were calculated using ABW, 62 patients (93%) had received doses under the minimum guideline-recommended dose of 30 mg/kg per day (mean of 21.2 mg/kg per day). Among these patients, 17 (27%) had an initial serum vancomycin trough <10 mg/L and 35 (56%) had an initial trough <15 mg/L. In our overall cohort of 67 patients, 31 (46%) had an initial serum vancomycin trough ≥ 15 mg/L, and 22 (33%) were dosed more frequently than every 12 hours.

On univariable testing, vancomycin total daily dose (mg/kg per day) based on both IBW and DBW were noted to be significant predictors of initial vancomycin trough concentration, with P values of .001 and .012, respectively. However, vancomycin total daily dose (mg/kg per day) based on ABW failed to meet significance as a predictor of initial vancomycin trough concentration (P value .072). The 3 other covariates (age, gender, and Scr) all had P values $<.2$, thus meeting our a priori criteria for inclusion in the final multivariable model.

Table 1 also shows the R^2 for the 3 multivariable models (including age, gender, and Scr) and the vancomycin total daily

Table 1. Predicting the Initial Vancomycin Trough Concentration in Obese Patients

Study Population (n = 67)		
Age (yrs), mean (range)	53 (20–82)	
Female, N (%)	44 (66)	
BMI (kg/m ²), mean (range)	48 (35–79)	
ABW (kg), mean (range)	137 (91–256)	
IBW (kg), mean (range)	62 (43–92)	
DBW (kg), mean (range)	92 (65–145)	
Baseline creatinine (mg/dL), mean (range)	0.79 (0.23–1.37)	
Creatinine clearance based on IBW (mL/min), mean (range)	91.2 (48.4–216.5)	
Creatinine clearance based on DBW (mL/min), mean (range)	134.7 (67.9–300.8)	
Multivariable linear regression model predicting the initial vancomycin trough concentration		
	R^{2a}	P^b Value
Age, gender, and lowest serum creatinine ≤ 72 h before first dose of vancomycin plus vancomycin total daily dose (mg/kg per day) based on the following:		
ABW	0.30	.041
IBW	0.41	<.001
DBW	0.37	.004

Abbreviations: ABW, actual body weight; BMI, body mass index; DBW, dosing body weight; IBW, ideal body weight.

^a R^2 is a measure of goodness of fit for the overall multivariable model.

^b P indicates the significance of the covariate for vancomycin total daily dose (mg/kg per day) for each of the 3 dosing weights.

dose (mg/kg per day) based on ABW versus IBW versus DBW (scatter plots included in the [Supplementary Appendix](#)). R^2 is a measure of the goodness of fit (scatter around the regression line). In Table 1, we also show the P value indicating the significance of each of the 3 dosing strategies as a predictor of initial vancomycin steady-state trough concentration. After accounting for age, gender, and Scr, a dosing strategy using IBW produced the best prediction. However, even the best strategy only had a moderate correlation between predicted and actual vancomycin troughs ($R^2 = 0.41$). Inclusion of an interaction term to model the relationship between dose and frequency did not improve the prediction of vancomycin trough level.

For the average patient in our study population, a 30 mg/kg total daily dose of vancomycin based on IBW predicts a vancomycin serum trough concentration of 11–12 mg/L, with male patients and younger patients less likely to reach concentrations ≥ 10 mg/L. To achieve doses ≥ 15 mg/L as recommended for complicated infections caused by methicillin-resistant *Staphylococcus aureus* [14], our model suggests the need to use a minimum of 45 mg/kg per day of vancomycin if calculating the initial dose based on IBW. The median dose in our study population when using IBW was 45 mg/kg per day (interquartile range, 35–55). This means that half of the patients received

<45 mg/kg per day based on IBW. Of those patients receiving <45 mg/kg per day of vancomycin based on IBW, 73% had an initial vancomycin trough concentration <15 mg/L, compared with only 37% of those patients receiving ≥45 mg/kg per day of vancomycin based on IBW. On the other end, 67% of patients had an initial vancomycin trough concentration >20 mg/L once the total daily dose was higher than 65 mg/kg per day based on IBW.

DISCUSSION

Our findings suggest that initial vancomycin dosing based on IBW rather than ABW is a better predictor of steady-state vancomycin trough concentration in adult patients with severe or morbid obesity (BMI ≥35 kg/m²), after accounting for age, gender, and baseline Scr. These findings challenge the current recommendation of calculating initial vancomycin dosing based on ABW in this patient population. Instead, our results support a practice of starting 45–65 mg/kg per day of vancomycin based on IBW rather than 30 mg/kg per day of vancomycin based on ABW, especially when targeting steady-state trough concentrations of 15–20 mg/L. In addition, it may be preferred to select a dosing interval of 8 hours rather than 12 hours, based on prior published literature [11].

CONCLUSIONS

Because we found only moderate correlation in our final model between total daily dose of vancomycin based on IBW and the initial vancomycin serum trough concentration, it remains prudent to closely follow vancomycin serum trough concentrations and renal function with appropriate dose adjustment. The findings presented in this study are most relevant to selecting the initial vancomycin dose for treatment of a suspected or confirmed infectious process. In terms of limitations, this was an uncontrolled, retrospective, single-center study with a relatively small sample size. We did not include patients with impaired renal function, so the findings cannot be extrapolated to this population. In addition, although we included intensive care unit patients in our analysis, the altered volume of distribution in this patient population was not specifically studied. Finally, additional well designed pharmacokinetic studies in obese patients are greatly needed.

Supplementary Material

Supplementary material is available online at Open Forum Infectious Diseases (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

Acknowledgments

Disclaimer. The work was carried out as part of our routine clinical work.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009–2010. NCHS Data Brief **2012**; 1–8.
2. World Health Organization. Obesity and overweight. Fact sheet 311. Available at: <http://www.who.int/mediacentre/factsheets/fs311/en/>. Accessed 4 May 2015.
3. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm **2009**; 66:82–98.
4. Adane ED, Herald M, Koura F. Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed *Staphylococcus aureus* infections. Pharmacotherapy **2015**; 35:127–39.
5. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol **1998**; 54:621–5.
6. Blouin RA, Bauer LA, Miller DD, et al. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother **1982**; 21:575–80.
7. Hall RG II, Payne KD, Bain AM, et al. Multicenter evaluation of vancomycin dosing: emphasis on obesity. Am J Med **2008**; 121:515–8.
8. Penzak SR, Gubbins PO, Rodvold KA, Hickerson SL. Therapeutic drug monitoring of vancomycin in a morbidly obese patient. Ther Drug Monit **1998**; 20:261–5.
9. Richardson J, Scheetz M, O'Donnell EP. The association of elevated trough serum vancomycin concentrations with obesity. J Infect Chemother **2015**; 21:507–11.
10. Vance-Bryan K, Guay DR, Gilliland SS, et al. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother **1993**; 37:436–40.
11. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy **2007**; 27:1081–91.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron **1976**; 16:31–41.
13. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. Pharmacotherapy **2012**; 32:604–12.
14. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis **2011**; 52:e18–55.