Published in final edited form as:
Am J Med. 2008 June ; 121(6): 515–518. doi:10.1016/j.amjmed.2008.01.046.

Multicenter Evaluation of Vancomycin Dosing – Emphasis on Obesity

Ronald G. Hall II, PharmD[1,2,3], **Kenna D. Payne, PharmD**[1,2], **Amy M. Bain, PharmD**[1,2], **Anita P. Rahman, PharmD**[1,2], **Sean T. Nguyen, PharmD**[1,4], **Susan A. Eaton, PharmD**[1,4], **Anthony J. Busti, PharmD**[1,2], **Stephen L. Vu, MD**[5], and **Roger Bedimo, MD, MS**[6,7]

1*Department of Pharmacy Practice, Texas Tech University Health Sciences Center, School of Pharmacy*

2*Department of Pharmacy, North Texas Veterans Health Care System*

3*Department of Clinical Sciences, The University of Texas Southwestern Medical Center*

4*Department of Pharmacy, Presbyterian Hospital of Dallas*

5*Department of Internal Medicine, Presbyterian Hospital*

6*Department of Medicine, North Texas Veterans Health Care System*

7*Department of Medicine, The University of Texas Southwestern Medical Center*

Abstract

Background—There is a paucity of data available regarding the dosing of antimicrobials in obesity. However, data are available demonstrating that vancomycin should be dosed based on actual body weight.

Methods—This study was conducted at two tertiary care medical centers that did not have pharmacy-guided vancomycin dosing programs or other institutional vancomycin dosing policies or protocols. Patients who received vancomycin between 7/1/2003 and 6/30/2006 were stratified by body mass index and randomly selected from the computer-generated queries. Patients ≥ 18 years of age and a creatinine clearance ≥ 60 ml/min who received vancomycin for ≥ 36 hours were included.

Results—Data were collected on a random sampling of 421 patients, stratified by body mass index, who met the inclusion criteria. Most patients in each body mass index category received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). Adequate initial dosing (≥ 10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients ($p < 0.0001$). Ninety-seven percent of underweight, 46% of normal weight, 1% of overweight, and 0.6% of obese patients received ≥ 15 mg/kg/dose recommended by several Infectious Diseases Society of America guidelines. Pharmacists also failed to correct inadequate dosing as only 3.3% of patients receiving < 10 mg/kg/dose had their regimen changed in the first 24 hours of therapy.

Conclusion—In this multi-center pilot study, obese patients routinely received inadequate empiric vancomycin utilizing a lenient assessment of dosing. Greater efforts should be undertaken to ensure

Corresponding Author: Ronald G. Hall, PharmD, BCPS, 4500 S Lancaster, Bldg. 7, R# 119A, Dallas, Texas 75216, Telephone: 214-372-5300 ext. 234, Fax: 214-372-5020, E-mail: ronald.hall@ttuhsc.edu.

patients received weight-based dosing as inadequate dosing can lead to subtherapeutic concentrations and potentially worse clinical outcomes.

Keywords

Obesity; vancomycin; dosing

Introduction

Approximately one-third of Americans are obese, which is defined as a body mass index (BMI) of ≥ 30 kg/m^2, and 4.8% are extremely obese (BMI ≥ 40kg/m^2).[1] There is little information available regarding the pharmacokinetics, pharmacodynamics, and optimal dosing of most antimicrobials for obese patients.[2] However, multiple pharmacokinetic studies have demonstrated that actual body weight is the preferred method to dose vancomycin in obese patients.[3–5] As a result, several consensus guidelines written or endorsed by the Infectious Diseases Society of America recommend weight-based dosing for vancomycin.[6–9]

In spite of the aforementioned literature, many studies continue to utilize a flat vancomycin 1 gram every 12 hour dosing regimen to evaluate new agents for the treatment of gram-positive infections including methicillin-resistant *Staphylococcus aureus* (MRSA).[10–15] Use of flat dosing regimens in clinical trials may teach clinicians that weight-based dosing is not important. However, recent literature has created an increased awareness of *Staphylococcus aureus* isolates that are heterogeneously resistant to vancomycin otherwise known as hVISA.[16, 17] The development of hVISA is associated with low vancomycin concentrations making the appropriate empiric dosing of vancomycin critical if clinicians want to have vancomycin available as an option for the treatment of MRSA in the future.

Methods

Selection and description of participants

This study was conducted at two tertiary care medical centers that did not have pharmacy-guided vancomycin dosing programs or other institutional vancomycin dosing policies or protocols. After Institutional Review Board approval by both institutions and Texas Tech University Health Sciences Center, subjects were identified through a retrospective search of pharmacy prescription files to include all patients who received vancomycin between July 1, 2003 and June 30, 2006. BMI was calculated as weight (kg) divided by height squared (m^2).[18] Patients were divided into cohorts based upon their BMI: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30 kg/m^2). A sample of patients in each BMI cohort were randomly selected by a computer-based random number generator. The electronic medical record of selected patients was reviewed for demographic characteristics and information regarding the initial vancomycin regimen, serum creatinine, whether the dose was appropriately weight-based, and whether the dose was changed within 24 hours (if initially inappropriate). Site of infection and vancomycin drug concentrations were not evaluated, as the primary focus of this study was to characterize the adequacy of recommended empiric weight based vancomycin dosing practices. Patients ≥ 18 years of age were included if they received ≥ 1 dose of vancomycin during an inpatient stay at either medical center and vancomycin was continued for ≥ 36 hours. Patients were excluded if their creatinine clearance was < 60 ml/minute as assessed by Cockcoft and Gault equation. If a patient received more than one course of vancomycin therapy during the same hospitalization, only the first course was included in the analysis.

Study Endpoints

The primary endpoint was to determine the frequency of adequate empiric vancomycin dosing, defined for the purposes of this study as ≥ 10 mg/kg/dose, for each of the BMI cohorts. This dose is lower than the 15 mg/kg/dose recommended in several Infectious Diseases Society of America guidelines, but was chosen to allow for dose rounding to the nearest vial size. Secondary endpoints included the percentage of patients receiving initial empiric doses of ≥ 15 mg/kg/dose, ≥ 20 mg/kg/dose, and ≥ 20 mg/kg/day for each of the BMI cohorts. The frequency of adequate empiric dosing was also assessed for the three classes of obesity (Class I: 30.0–34.9 kg/m^2, Class II 35.0–39.9 kg/m^2, and Class III ≥ 40 kg/m^2). The percentage of inadequate doses (< 10 mg/kg/dose) changed within 24 hours of initiation was assessed to determine if pharmacists or physicians changed inadequate doses in a timely manner.

Statistical Analysis

The data were analyzed using SAS software version 9.13. A statistically significant difference between the appropriate weight-based dosing of vancomycin in underweight, normal weight, overweight, and obese patients was determined using the Cochran-armitage test. Continuous variables were assessed using ANOVA. Since this is a pilot study, a power analysis was not performed. A priori, it was decided to review the charts of ≥ 50 patients per hospital per cohort. A smaller sample size was accepted for the underweight population since this was not a primary focus.

Results

Data were collected on a random sampling of 421 patients, stratified by BMI, who met the inclusion criteria. Baseline characteristics were similar except for expected differences in weight and BMI. The average age was 56.6 ± 13.9 years, 78.4% were male, and the average creatinine clearance was 102 ± 35.8 ml/min. The mean initial dose (mg/dose) and total daily dose (mg/dose) were similar in all groups (Table 1). The vast majority of patients included in the study received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). A significant association ($p < 0.0001$) was observed between increasing BMI group and the average initial vancomycin dose (mg/kg/dose).

Adequate initial dosing (> 10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients ($p < 0.0001$). This trend was also observed when evaluating the frequency of adequate initial dosing in the previously defined obesity subgroups (Class I = 43.4%, Class II = 16.3%, Class III = 0%). Ninety-seven percent of underweight, 46% of normal weight, 1% of overweight, and 0.6% of obese patients received ≥ 15 mg/kg/dose recommended by several Infectious Diseases Society of America guidelines.

None of the normal weight and overweight patients with initial doses < 10 mg/kg/dose had their doses corrected within 24 hours. Only 3.5% of obese patients who received < 10 mg/kg/dose had their doses corrected.

Discussion

Our multi-center pilot study observed that obese patients are more likely to receive inadequate empiric dosing compared to other BMI groups. When evaluating patients by the 15 mg/kg/dose recommended by several Infectious Diseases Society of America guidelines, less than half of normal weight patients and only two patients in the overweight and obese groups received adequate doses.[6–9]

Previous pharmacokinetic studies have established total body weight as the preferred method to calculate vancomycin dosing. Blouin and colleagues evaluated vancomycin pharmacokinetics in 4 normal weight and 6 morbidly obese subjects.[4] They observed that similar milligram per kilogram doses of vancomycin based upon actual body weight were required to produce an average steady-state concentration of 15 μg/ml for normal weight (23.4 ± 1.5 mg/kg) and obese (24.0 ± 3.4 mg/kg) subjects. Vance-Bryan et al. evaluated 95 nonobese and 135 obese patients and found that actual body weight was a more accurate predictor of vancomycin pharmacokinetic parameters when compared with lean body weight.[3] Bauer and colleagues concluded that a 30 mg/kg/day dose based on total body weight is needed for obese patients.[5] These investigators also suggested that shorter dosing intervals may be needed to achieve goal vancomycin trough concentrations.

Vancomycin does not have a pharmacodynamic endpoint which has been validated in a prospective study. Two retrospective studies suggest an area under the curve to minimum inhibitory concentration ratio of ≥ 400 is associated with improved clinical outcomes.[19, 20] A recent study calculated area under the curve values of 318 ± 111 μg/h/ml for patients with receiving low dose vancomycin (mean trough concentration = 9.4) and 418 ± 152 for patients receiving high dose vancomycin (mean trough concentration 20.4 μg/ml).[21] A Monte Carlo simulation utilizing these pharmacokinetic data demonstrated that the high dose regimen had a 20% higher probability of achieving the pharmacodynamic target for MRSA isolates with a vancomycin MIC of 1 μg/ml, while pharmacodynamic target attainment rates for higher or lower MIC values were not significantly affected by dosing strategy.[22] Optimizing vancomycin dosing is important as 70% of MRSA isolates in a recent study had a vancomycin MIC of 1 μg/ml.[23] These data are not specific to obese patients, but the pharmacodynamic principles should transcend BMI classes.

Our findings should be considered a pilot study focused on characterizing the empiric dosing of vancomycin across BMI cohorts. It did not include data regarding infection type, serum vancomycin concentrations, minimum inhibitory concentrations, and clinical outcomes. However, clinicians do not have minimum inhibitory concentration or pharmacokinetic data and may not be certain of the infection source when initiating therapy. We acknowledge that 1 gram every 12 hours may be acceptable for some disease states such as cellulitis, but the association of low vancomycin concentrations and the development of hVISA is still worrisome in these populations.[16, 17] Therefore, these observations were not deemed necessary for this pilot study. In addition, clinical outcomes were not evaluated because some patients receiving empiric therapy may not ultimately have an infection with a gram-positive pathogen. Others may correctly state that the pharmacodynamic target for vancomycin has not been prospectively defined. While this is true, there is substantial data that vancomycin concentrations are affected by weight and vancomycin should be dosed based on actual body weight.[2–5] If 1 gram administered intravenously every 12 hours is satisfactory for the "average" patient, it should be understood that obese patients will require higher doses. Our results highlight the fact that obese patients may be routinely underdosed as a result of the widespread practice of prescribing fixed-dose vancomycin.

It is equally important to note that pharmacists routinely failed to correct inadequate dosing in a timely period in this study. This result highlights that weight-based dosing recommendations for vancomycin are not routinely implemented in clinical practice by multiple disciplines. Therefore, all healthcare professionals involved in the utilization of medications for obese patients should be vigilant in using a weight based approach to drug dosing when appropriate. Neither study institution has a pharmacist-guided vancomycin or aminoglycoside dosing program, which may decrease the frequency of inadequate initial dosing.

In this multi-center pilot study, obese patients were routinely underdosed utilizing a lenient assessment of dosing. More than half of normal weight and 99% of overweight patients did not receive the 15 mg/kg/dose recommended in several Infectious Diseases Society of America guidelines. Greater efforts should be undertaken to ensure patients receive weight-based dosing as inadequate dosing can lead to subtherapeutic concentrations and worse clinical outcomes.

Acknowledgements

We would like to thank Travis Cooper, PharmD, BCPS for his critical review of this manuscript. This project was supported by Grant Number KL2RR024983, titled, "North and Central Texas Clinical and Translational Science Initiative" (Milton Packer, M.D., PI) from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research, and its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

References

1. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295(13):1549–1555. [PubMed: 16595758]
2. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy 2007;27(8):1081–1091. [PubMed: 17655508]
3. 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(3):436–440. [PubMed: 8460912]
4. Blouin RA, Bauer LA, Miller DD, et al. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother 1982;21(4):575–580. [PubMed: 7081978]
5. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol 1998;54(8):621–625. [PubMed: 9860149]
6. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39(9):1267–1284. [PubMed: 15494903]
7. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis 2005;41(10):1373–1406. [PubMed: 16231249]
8. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171(4):388–416. [PubMed: 15699079]
9. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111(23):e394–e434. [PubMed: 15956145]
10. Seltzer E, Dorr MB, Goldstein BP, et al. Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. Clin Infect Dis 2003;37(10): 1298–1303. [PubMed: 14583862]
11. Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005;49(6):2260–2266. [PubMed: 15917519]
12. Wunderink RG, Cammarata SK, Oliphant TH, Kollef MH. Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. Clin Ther 2003;25(3):980–992. [PubMed: 12852712]
13. Rubinstein E, Cammarata S, Oliphant T, Wunderink R. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001;32(3):402–412. [PubMed: 11170948]

14. Ellis-Grosse EJ, Babinchak T, Dartois N, et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. Clin Infect Dis 2005;41:S341–S353. [PubMed: 16080072]

15. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006;355(7):653–665. [PubMed: 16914701]

16. Charles PG, Ward PB, Johnson PD, et al. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate Staphylococcus aureus. Clin Infect Dis 2004;38(3):448–451. [PubMed: 14727222]

17. Tsuji BT, Rybak MJ, Lau KL, Sakoulas G. Evaluation of accessory gene regulator (agr) group and function in the proclivity towards vancomycin intermediate resistance in Staphylococcus aureus. Antimicrob Agents Chemother 2007;51(3):1089–1091. [PubMed: 17158941]

18. Obesity: preventing and managing the global epidemic. Geneva: World Health Organization; 2000. (WHO Technical Report Series, No. 894)

19. Moise PA, Schentag JJ. Vancomycin treatment failures in Staphylococcus aureus lower respiratory tract infections. Int J Antimicrob Agents 2000;16:S31–S34. [PubMed: 11137406]

20. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 2004;43(13):925–942. [PubMed: 15509186]

21. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of Mortality for Methicillin-Resistant Staphylococcus aureus Health-Care-Associated Pneumonia: Specific Evaluation of Vancomycin Pharmacokinetic Indices. Chest 2006;130(4):947–955. [PubMed: 17035423]

22. Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2007;44(12):1536–1542. [PubMed: 17516395]

23. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate Staphylococcus aureus (VISA), vancomycin-susceptible clinical methicillin-resistant S. aureus (MRSA) blood isolates from 2001 05. J Antimicrob Chemother 2007;60(4):788–794. [PubMed: 17623693]

Results

Table 1

Dosing characteristic		BMI[a] < 18.5 kg/m^2 (n = 67)	BMI[a] 18.5–24.9 kg/m^2 (n = 100)	BMI[a] 25.0–29.9 kg/m^2 (n = 99)	BMI[a] ≥ 30.0 kg/m^2 (n = 155)
Initial dose (mg/dose), mean (SD[b])		1009.0 ± 132.3	1000.0 ± 35.5	1000.0 ± 123.7	1014.5 ± 128.2
Total daily dose (mg/day), mean (SD[b])		1853.7 ± 464.0	1900 ± 309.8	1929.3 ± 384.7	1983.9 ± 334.3
Initial dose (mg/kg/dose), mean (SD[b])		20.6 ± 4.7	14.9 ± 2.1	12.2 ± 2.0	9.2 ± 1.9
Weight-based dose (%)					
	≥ 10 mg/kg/dose	100	99	93.9	27.7
	≥ 15 mg/kg/dose	97	46	1	0.6
	≥ 20 mg/kg/dose	44.8	0	1	0
	≥ 20 mg/kg/day	91	92	84.8	27.1
Initial dose < 10 mg/kg/dose changed within 24 hours (%)		Not applicable	0 (0/1)	0 (0/6)	3.5 (4/113)

[a] BMI = body mass index

[b] SD = standard deviation