Identification of Risk Factors for Initial Elevated Vancomycin Trough Concentrations

Journal of Pharmacy Technology
2016, Vol. 32(1) 29–33
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DOI: 10.1177/8755122515599553
pharmatech.sagepub.com

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Abstract

Background: Recent literature suggests that elevated vancomycin trough concentrations (>20 $\mu\text{g/mL}$) may be associated with an increased risk of nephrotoxicity and lead to an increase in mortality and hospital length of stay. **Objective:** The purpose of this study was to identify variables that may be predictive of elevated initial vancomycin trough concentrations. **Methods:** Retrospective case–control study of all adult patients who had an initial vancomycin trough concentration measured between January 1, 2013, and December 31, 2014. Case patients had an initial trough concentration >20 $\mu\text{g/mL}$, while control patients had an initial trough concentration of ≤ 20 $\mu\text{g/mL}$. Patients were excluded from the study if they were in the intensive care unit, had unstable renal function, or if they had cystic fibrosis, solid organ transplant, or bone marrow transplant. **Results:** Of the 512 vancomycin trough concentrations reviewed, 54 patients met the case definition, while 140 patients were randomly selected as controls. In a multivariate model, baseline serum creatinine, body mass index, heart failure, and malignancy were all independently predictive of an initial vancomycin concentration >20 $\mu\text{g/mL}$. **Conclusions:** Reduced baseline renal function coupled with increasing body mass index is associated with an increased risk of an elevated initial vancomycin trough concentration. This risk is further enhanced by the presence of heart failure and/or malignancy. When these risk factors are present, it may be prudent to consider implementation of individualized dosing to achieve initial target concentrations.

Keywords

vancomycin, therapeutic drug monitoring, pharmacokinetics, obesity, clinical pharmacy, clinical practice

Introduction

Vancomycin is a glycopeptide antibiotic used for the treatment of infections due to suspected or documented gram-positive microorganisms including methicillin-resistant *Staphylococcus aureus*. In an effort to maximize treatment efficacy, an area under the curve/minimum inhibitory concentration ratio of ≥ 400 has been advocated as a target.¹ To achieve this area under the curve/minimum inhibitory concentration ratio, vancomycin trough concentrations should be maintained between 15 and 20 $\mu\text{g/mL}$.¹ This concentration range is recommended for the treatment of complicated infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by *Staphylococcus aureus*.¹ Recent literature suggests that trough concentrations that exceed 20 $\mu\text{g/mL}$ may be associated with an increased risk of nephrotoxicity and increased mortality and hospital length of stay.^{2–5} The University of Vermont Medical Center uses a vancomycin dosage nomogram that generally maintains vancomycin trough concentrations ≤ 20 $\mu\text{g/mL}$. However, there remain a proportion of

patients for whom initial trough concentrations exceed 20 $\mu\text{g/mL}$ for reasons that are not clear. The primary objective of this investigation was to identify adult demographic and clinical variables that may be predictive of elevated initial vancomycin trough concentrations in our adult population.

Patients and Methods

The University of Vermont Medical Center is a 562-bed tertiary care academic medical center that is located in Burlington, Vermont. A retrospective chart review was performed on all patients who had vancomycin trough concentrations measured between January 1, 2013, and December 31, 2014. Patients were identified through a query of the

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laboratory database. To be included in the investigation, patients had to meet the following criteria: (a) age ≥ 18 years; (b) trough concentration drawn by venipuncture; (c) trough concentration drawn within 1 hour of the expected next dose; (d) trough concentration drawn at steady state, which was defined as the trough measurement being obtained after 4 predicted half-lives; (e) received a prescribed vancomycin dosage that was within 10% of the dosage recommended by the institution's nomogram. Patients residing in the intensive care unit and patients with cystic fibrosis, solid organ transplant, or bone marrow transplant were excluded due to the potential for variable vancomycin pharmacokinetics. In addition, dialysis patients or patients with unstable renal function were also excluded from the investigation. Unstable renal function was defined as an increase or decrease in serum creatinine of >0.2 mg/dL from the start of vancomycin therapy until the measurement of the vancomycin trough concentration.⁶

The study protocol was approved by the University of Vermont Committees on Human Subjects.

Cases were defined as patients with an initial vancomycin trough concentration of >20 $\mu\text{g/mL}$. Controls were defined as patients with an initial trough concentration ≤ 20 $\mu\text{g/mL}$. Repeat trough concentrations were not evaluated. To identify potential risk factors, cases and controls underwent an electronic medical record review by one of the authors (JM) using a standardized data collection form. This included a review of demographic factors, medication data, and clinical variables. The data extracted from each record were validated by a second investigator (JA). All potential risk factors were identified *a priori*.

A vancomycin dosage nomogram was used to help guide intravenous vancomycin dosing. The nomogram recommends dosing vancomycin at 15 mg/kg at a frequency based on the patient's estimated normalized creatinine clearance (CrCl, mL/min/72 kg). Vancomycin dosing frequency was determined as follows: CrCl greater than or equal to 70 mL/min dosed every 12 hours, CrCl 30 to 69 mL/min dosed every 24 hours, CrCl 20 to 29 mL/min dosed every 48 hours, and less than 20 mL/min dosed every 3 to 7 days depending on serum drug concentrations. An initial single dose of 20 mg/kg could be administered to patients with severe illness. Doses were based on total body weight with no maximum upward limit on single or total daily doses.

Dichotomous variables were compared using the Fischer's exact test. Continuous variables were compared with the Wilcoxon rank sum test. Variables with a *P* value of less than .25 on univariate analysis were included in the logistic regression model. Statistical significance was set at a *P* value of less than .05 for all analyses except as otherwise described. To assess the ability of the model to distinguish between patients who did or did not have an initial vancomycin trough concentration >20 $\mu\text{g/mL}$, an area under the receiver operating characteristic curve was calculated.

Statistical analysis was performed using SAS (Version, 9.4, SAS Institute Inc, Cary, NC).

Results

During the study period, 512 vancomycin trough concentrations were reviewed after excluding for intensive care unit and dialysis patients. Of these trough concentrations, 316 were excluded most commonly for trough concentrations not being drawn by venipuncture ($n = 122$), incomplete documentation ($n = 56$), and troughs being drawn prior to steady state ($n = 40$). Other reasons for exclusion included a 0.2 mg/dL change in serum creatinine ($n = 38$), $>10\%$ dosage deviation from the vancomycin dosage nomogram ($n = 28$), having cystic fibrosis ($n = 22$), or being a bone marrow or solid organ transplant patient ($n = 10$).

One hundred and ninety-six patients were included in the study. Of these 196 patients, 54 patients were cases and 140 were controls. The primary indication for vancomycin therapy was for the treatment of skin and soft tissue infections (26.8% cases, 21.4% controls; $P = .454$). Blood stream infections accounted for 8.9% of the cases and 11.4% of the controls ($P = .799$). Demographic and clinical characteristics are presented in Table 1. Relative to the controls, the cases were heavier (body mass index [BMI] of 37 vs 28, $P < .001$), had a higher baseline serum creatinine (0.95 vs 0.75, $P < .001$), and had more total comorbidities (2 vs 1, $P < .001$). Of the comorbidities, diabetes (43% vs 24%, $P = .015$), heart failure (14% vs 1%, $P = .001$), hypertension (64% vs 46%, $P = .027$), and ischemic heart disease (39% vs 17%, $P = .001$) occurred more commonly in the cases versus the controls. No patients in either group had human immunodeficiency virus. The mean initial vancomycin concentration was higher in the cases than in the controls (24.3 vs 11.1 $\mu\text{g/mL}$, $P < .001$). Vancomycin concentrations ranged from 20.2 to 31.8 $\mu\text{g/mL}$ in the case group and from 2.9 to 20 $\mu\text{g/mL}$ in the control group. Patients in the case group were more likely to receive >4 g of vancomycin a day (12.5% vs 1.4%, $P < .001$). Six cases and 13 controls received a loading dose of 20 mg/kg; however, on univariate analysis this was not significant ($P = .791$). The length of stay was longer for the cases than the controls (13.9 vs 9.2 days) but this difference was not statistically significant. Mortality at discharge was not different between the cases and the controls.

Variables on the univariate analysis with a *P* value of $<.25$ (age, amputation, baseline serum creatinine, CrCl, BMI, diabetes, heart failure, hypertension, ischemic heart disease, malignancy, total comorbidities, and total daily dose >4 g) were initially included in the logistic regression model. The final regression model revealed baseline serum creatinine, BMI, heart failure, and malignancy were independently predictive of an elevated initial vancomycin trough concentration (Table 2). Ischemic heart disease and CrCl were not included in the final model because of

Table 1. Univariate Analysis of Baseline Demographics and Clinical Characteristics^a.

Demographic Data	Case (n = 54)	Control (n = 140)	P Value
Age, years	57 ± 13	54 ± 18	.217
Sex, male	38 (67.9)	90 (64.3)	.74
Height, in.	65.7 ± 6	67.1 ± 4	.318
Weight, kg	102.5 ± 32	82.8 ± 24	<.001
Body mass index (BMI), kg/m ²	37 ± 12	28 ± 7	<.001
BMI category			
<18.5	0 (0)	7 (5)	
18.5-24.9	8 (14.3)	41 (29.3)	
25-29.9	7 (12.5)	46 (32.9)	
30-34.9	15 (26.8)	24 (17.1)	
≥35	26 (46.4)	22 (15.7)	
Comorbidities			
Amputation ^b	5 (8.9)	4 (2.9)	.122
Diabetes	24 (42.9)	34 (24.3)	.015
Cirrhosis	4 (7.1)	9 (6.4)	1
Chronic obstructive pulmonary disease	7 (12.5)	13 (9.3)	.602
Heart failure	8 (14.3)	2 (1.4)	.001
Hypertension	36 (64.3)	65 (46.4)	.027
Ischemic heart disease	22 (39.3)	24 (17.1)	.002
Malignancy	21 (37.5)	36 (25.7)	.118
Spinal cord injury	1 (1.8)	3 (2.1)	1
Total comorbidities	2 ± 1	1 ± 1	<.001
Baseline serum creatinine, mg/dL	0.95 ± 0.4	0.75 ± 0.3	<.001
Initial vancomycin concentration, µg/mL	24.3 ± 3.2	11.1 ± 4.1	<.001
Total daily dose >4 g	7 (12.5)	2 (1.4)	<.001
Creatinine clearance (mL/min/72 kg) ^c	89.6 ± 4.9	108.7 ± 4.3	.017
Length of stay, days	13.9 ± 18.7	9.2 ± 9.9	.236
Vancomycin trough level	24.3 ± 3.2	11.1 ± 4.1	<.001
Survival to discharge	53 (94.6)	138 (98.6)	.142

^aData are n (%) of patients or mean ± standard deviation unless otherwise indicated.

^bAmputations above the knee, below the knee, or both.

^cPatients who are >60 years old who have a reported serum creatinine <1 mg/dL; serum creatinine is rounded to 1.0 mg/dL.

Table 2. Multivariate Regression Analysis.

	Coefficient	OR	95% CI	P
Baseline Scr	2.022	1.224	1.079, 1.388	.002
BMI	0.125	1.867	1.469, 2.372	<.001
Heart failure	2.451	11.596	1.825, 73.667	.009
Malignancy	0.986	2.681	1.182, 6.078	.018
	AUC	95% CI		
Area under ROC curve	0.813	0.745, 0.881		

Abbreviations: OR, odds ratio; CI, confidence interval; Scr, serum creatinine; BMI, body mass index; AUC, area under the curve; ROC, receiver operating characteristic curve.

concerns of collinearity with heart failure and baseline serum creatinine, respectively. Of the 10 heart failure patients, 8 were cases and 2 were controls of which 6 (75%) and 0 (0%) had systolic heart failure, respectively. Of the 57 malignancy patients, 20 were cases and 37 were controls of

which 5 (28%) and 12 (33%) had a hematologic malignancy, respectively. The area under the receiver operating characteristic curve indicates the model discriminates well between those with and without elevated initial vancomycin trough concentrations (Table 2).

Discussion

There have been an increasing number of literature reports that suggest vancomycin trough concentrations of $>20 \mu\text{g/mL}$ are associated with an increased risk of nephrotoxicity.²⁻⁵ This is concerning as nephrotoxicity has been associated with an increase in overall mortality and prolonged hospital length of stay.²⁻⁵ Several publications have examined the role of risk factors for vancomycin toxicity.²⁻⁵ However, to our knowledge, this is the first investigation to specifically look at demographic and clinical variables that may predispose patients to a higher probability of an initial vancomycin concentration that exceeds $20 \mu\text{g/mL}$.

Defining clinical profiles of patients that may be at increased risk for experiencing initial elevated vancomycin concentrations would help clinicians identify patients that may not be suitable candidates for standard dosage guidelines as these recommendations may not take into account these risk factors. On multivariate analysis, baseline serum creatinine, BMI, heart failure, and malignancy were independently predictive of an initial vancomycin concentration $>20 \mu\text{g/mL}$. In terms of the continuous variables, each 0.1 mg/dL increase in serum creatinine and each 5 kg/m^2 increase in BMI increased the likelihood of an initial elevated vancomycin trough concentration by 1.2-fold and 1.8-fold, respectively. With the use of our nomogram, in the absence of heart failure and malignancy, a patient with a BMI of 20 kg/m^2 would have a greater than 50% probability of experiencing an elevated initial vancomycin concentration at a serum creatinine of 2.3 mg/dL . However, if this BMI doubles to 40 kg/m^2 , this probability ($>50\%$) is observed at a serum creatinine value of 1.3 mg/dL . These trends suggest that increasing body mass increases the likelihood of higher vancomycin concentrations along the continuum of baseline renal function as reflected by serum creatinine. This observation is consistent with published data that suggests obesity increases the likelihood of elevated vancomycin trough concentrations with standard dosage regimens.⁷⁻¹¹ In morbidly and extremely obese patients ($\geq 35 \text{ kg/m}^2$ and $\geq 40 \text{ kg/m}^2$, respectively), a large vancomycin volume of distribution relative to vancomycin clearance will decrease overall vancomycin elimination and lead to a prolongation of the half-life.^{8,9}

In terms of the dichotomous variables, the presence of heart failure increased the likelihood of an elevated initial vancomycin concentration by 11.59-fold. Data from Tominari et al demonstrated decreasing vancomycin clearance with decreasing left ventricular ejection fraction.¹² The precise mechanism for decreased vancomycin clearance in heart failure is not clear but it may be related to a decrease in renal perfusion.¹² In addition, the presence of malignancy increased the likelihood of an elevated initial vancomycin trough concentration by 2.68-fold. Conflicting literature reports make it difficult to assess the overall impact of malignancy on vancomycin pharmacokinetics. For example, Jarkowski et al studied acute myeloid leukemia patients

and concluded that total clearance was reduced but volume of distribution was unchanged.¹³ Second, Al-Kofide et al studied a group of cancer patients with leukemia, lymphoma, breast cancer, and colon cancer and concluded that clearance and volume of distribution are increased in cancer patients.¹⁴ Last, Omote et al studied a diverse group of cancer patients and concluded that vancomycin clearance is not significantly different in cancer patients versus non-cancer patients.¹⁵ It is possible that differing types of malignancies may affect vancomycin disposition in different ways.

There are limitations to this investigation. First, the study was a retrospective design. This can lead to data in records that may have been incomplete and/or unavailable. Second, this was a single-center study that used an empiric vancomycin dosage nomogram derived from a specific patient population. As a result, its findings may not be generalizable to other populations with differing patient demographics. Third, the small number of heart failure patients that were analyzed in this investigation precluded a precise measurement of risk as evidenced by the wide confidence interval. Fourth, the heterogeneity in the malignancy group may make its predictive value low. Fifth, the study did not follow-up on patients after their initial trough concentration was drawn, so no conclusions can be drawn about whether elevated initial trough concentrations increase probability of subsequent rise in creatinine. Last, another potential limitation is that we do not place an upward limit on single or total daily doses, which is in contrast to the current guidelines; however, these higher daily doses were not found to be independently predictive of elevated initial vancomycin trough concentrations on multivariate analysis.¹ This suggests that not capping doses was not the reason why we saw elevated initial vancomycin trough concentrations in morbidly and extremely obese patients.

Conclusion

In conclusion, reduced baseline renal function coupled with increasing BMI is associated with an increased risk of an elevated initial vancomycin trough concentration. This risk is further enhanced by the presence of malignancy and/or heart failure. When these risk factors are present, it may be prudent to consider implementation of individualized dosing to achieve initial target trough concentrations as opposed to using a standard dosing nomogram.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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