Open Forum Infectious Diseases

MAJOR ARTICLE

Evaluation of Vancomycin Accumulation in Patients With Obesity

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Background. Current vancomycin guidelines recommend early and frequent area-under-the-curve monitoring in patients with obesity. Vancomycin's volume of distribution is likely altered in patients with obesity, which may result in lower serum concentrations initially but lead to accumulation with continued use. The objective of this study was to evaluate the incidence of vancomycin accumulation in patients with obesity and identify potential factors associated with accumulation.

Methods. This was a single-center, retrospective, observational study at a tertiary academic medical center. Adult patients with a body mass index (BMI) $\geq$ 30 kg/m^2 and $\geq$ 2 vancomycin serum trough concentrations drawn in 2019 were screened for inclusion. The major endpoint was the incidence of vancomycin accumulation defined as $\geq$ 20% increase in trough concentration within the first 10 days of therapy. Key minor endpoints included incidence of acute kidney injury (AKI) and factors associated with accumulation.

Results. Of the 443 patients screened, 162 were included. The median age was 56.5 years (interquartile range [IQR], 43–65.3), and 62.3% were male. The median weight was 112.7 kg (IQR, 99.8–122.6) and the median BMI was 36.8 kg/m^2 (IQR, 33.1–41). The total daily dose median at initiation was 28.7 mg/kg per day (IQR, 25.4–31.2). Accumulation occurred in 99 of 162 patients (61.1%) and AKI occurred in 20 of 140 patients (14.3%). No specific factors were found to be associated with accumulation.

Conclusions. Patients with obesity are likely to experience vancomycin accumulation within the first 10 days of therapy. Clinicians should use frequent monitoring of vancomycin and use caution when interpreting early concentrations in patients with obesity.

Keywords. obesity; pharmacokinetics; vancomycin.

The prevalence of obesity in the United States has been steadily increasing over the past 20 years and now represents over 40% of the population [1]. The altered physiology of patients with obesity makes dosing medications at times difficult and unpredictable. Patients with obesity have increased adipose and muscle tissue, renal blood flow, and circulating plasma proteins, which can lead to an increased volume of distribution, increased excretion, and reduced free drug concentrations, respectively [2].

Current vancomycin guidelines recommend "early and frequent" monitoring in patients with obesity to guide dosing [3]. Vancomycin's volume of distribution (Vd) is likely to be altered in patients with obesity compared to those without [4]. Although their absolute Vd may be higher than the nonobese population, their weight-based Vd (in liters per kilogram) is often lower. The average vancomycin steady-state fat-to-serum ratio was 0.216 in 28 patients undergoing arterial reconstruction [5]. In addition, the median $AUC_{adipose\ tissue}/AUC_{plasma}$ was 0.31 (95%confidence interval, 0.16–0.46) after a single vancomycin dose in patients undergoing primary total knee replacement who had an average body mass index (BMI) of 30 kg/m^2 [6].

Although vancomycin initially distributes into adipose tissue in patients with obesity, it reaches a saturation point in which vancomycin serum concentrations can eventually accumulate with continued dosing once the capacity of the adipose tissue is exceeded. Vancomycin accumulation may place obese patients at increased risk for nephrotoxicity, which has been demonstrated in previous studies [7–9]. In a single-center, retrospective cohort study, 5 of 11 (45.5%) patients with obesity had supratherapeutic trough concentrations on subsequent draws despite initially being therapeutic on stable vancomycin dosage regimens [10]. However, 3 of 5 had a new onset acute kidney injury (AKI), and data were limited to 11 patients.

To the best of our knowledge, this is the first study to evaluate the incidence of vancomycin accumulation in patients with obesity within the first 10 days of therapy and identify potential factors associated with accumulation.

Received 25 July 2022; editorial decision 13 September 2022; accepted 20 September 2022; published online 21 September 2022

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Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac491

METHODS

We conducted a single-center, retrospective, observational analysis at Brigham and Women's Hospital, a tertiary academic medical center. Patients were included if they were ≥18 years old, had a BMI ≥30 kg/m^2, and had ≥2 vancomycin concentrations drawn within the same inpatient encounter between January 1, 2019 and December 31, 2019. Vancomycin trough-guided therapeutic monitoring was utilized during this time at our institution. Patients were excluded if they were pregnant, received fewer than 3 doses of intravenous vancomycin before the first vancomycin concentration was drawn, had inconsistent vancomycin dosing before the concentration was drawn, the concentration was drawn less than 3 hours after vancomycin administration, or if vancomycin was initiated at an outside institution. Patients were also excluded if they had baseline severe renal impairment defined as creatinine clearance <30 mL/minute, were receiving renal replacement therapy, or had AKI, defined as a serum creatinine (SCr) increase of ≥0.3 mg/dL or 50% increase from time of vancomycin initiation to first vancomycin concentration [11].

The major endpoint was the incidence of vancomycin accumulation, defined as a ≥20% increase from the first trough concentration (after at least 3 doses) to subsequent trough concentrations within the first 10 days of therapy. The minor endpoints included incidence of AKI between first trough concentration to 72 hours after stopping vancomycin, supratherapeutic concentrations (ie, >20 mcg/mL) at second concentration, and time to accumulation. In addition, age, male gender, BMI obesity class [12], initial dose in mg/kg per day, SCr, and number of doses per day were assessed for association with vancomycin accumulation.

Linear pharmacokinetics were used to extrapolate true trough concentrations if concentrations were drawn before the true trough [13]. To account for dose changes, we assumed equal ratios between vancomycin total daily dose and trough concentration (eg, if total daily dose was increased by 25%, we expected a 25% increase in trough concentration). Descriptive statistics were used to evaluate endpoints, and a multivariable logistic regression model was used to analyze potential factors associated with accumulation.

Patient Consent Statement

This study was approved by the institutional review board (IRB) at Mass General Brigham and conforms to standards currently applied in the country of origin. Patient's informed consent was waived by the IRB because of the retrospective nature of the study and due to the study not including factors necessitating patient consent.

RESULTS

Enrollment and Baseline Characteristics

A total of 443 patients with obesity and 2 or more vancomycin serum trough concentrations were identified, 162 of which were included in our analysis (Figure 1). Baseline characteristics are shown in Table 1. Body mass index obesity class distribution was 37%, 35%, and 28% for obesity classes I, II, and III, respectively [12]. The median time to vancomycin true trough concentrations was 0.88 hours (interquartile range [IQR], 0.21–1.68).

Major and Minor Endpoints

Vancomycin accumulation occurred in 99 of 162 patients (61.1%) within the first 10 days of vancomycin therapy. Accumulation occurred in 20 of 28 (71.4%) and 79 of 134 (59%) patients located in an intensive care unit (ICU) versus non-ICU, respectively. Accumulation was observed at similar rates regardless of vancomycin indication or designated trough

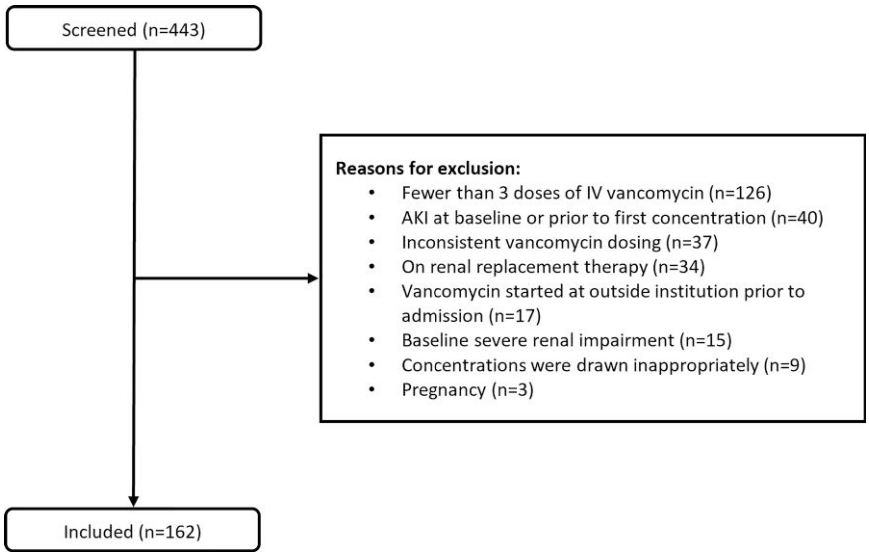

Figure 1. Enrollment.
AKI, acute kidney injury; IV, intravenous.

Table 1. Baseline Characteristics

Baseline characteristic	Value (N= 162)
Age (years)	56.5 (43–65.3)
Weight (kg)	112.7 (99.8–122.6)
Male[a]	101 (62%)
BMI (kg/m^2)	36.8 (33.1–41)
CrCl (mL/minute)	110.8 (79.8–139.3)
Initial dose (mg/kg per day)[b]	28.7 (25.4–31.2)
Initial dose <30 mg/kg per day[a,b]	103 (63.6%)
Initial dose 30–40 mg/kg per day[a,b]	43 (26.5%)
Initial dose >40 mg/kg per day[a,b]	16 (9.9%)
Duration of therapy (days)	7 (5–9)
Vancomycin Indications[a]	
Skin and soft tissue infections	35 (21.6%)
Bone or join infections	27 (16.0%)
Bacteremia	23 (14.2%)
Pneumonia	18 (11.1%)
Intra-abdominal infections	14 (8.6%)
Endocarditis	8 (4.9%)
Surgical prophylaxis	8 (4.9%)
Sepsis	7 (4.3%)
Febrile neutropenia	6 (3.7%)
Genitourinary infections	6 (3.7%)
Central nervous system infection	5 (3.1%)
Diabetic foot infection	3 (1.9%)
Vascular infections	2 (1.2%)
Location[a]	
ICU	28 (17.3%)
Non-ICU	133 (82.1%)
ED	1 (0.6%)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; ED, emergency department; ICU, intensive care unit.

NOTE: All variables reported as median (interquartile range), unless otherwise indicated.

[a]Number (%).

[b]Based on actual body weight.

goal (15–20 mcg/mL or 10–20 mcg/mL). Acute kidney injury occurred in 20 of 140 patients (14.3%) during vancomycin therapy. Acute kidney injury was not assessed in 22 patients due to missing baseline SCr. The vancomycin dose was changed between the first and subsequent concentrations in 100 patients (61.7%). Supratherapeutic vancomycin concentrations at the time of the second concentrations were observed in 46 patients (28.4%), 21 (45.7%) of whom had no dose changes (Figure 2). Accumulation occurred in 32 of 62 patients (51.6%) who did not have any vancomycin dose changes and 71 of 120 patients (69.2%) without AKI. Multivariable logistic regression analysis did not identify specific factors associated with accumulation, and vancomycin initial dose was not found to be a leading factor for accumulation (Table 2). The median time to vancomycin accumulation was 5 days (IQR, 4–6).

DISCUSSION

There have been several analyses published evaluating the effect of obesity on supratherapeutic vancomycin trough concentrations. Obesity, vancomycin dose, and age have been found to be statistically significant risk factors for vancomycin trough concentration >20 mg/L [14]. A Monte Carlo analysis found doses >4500 mg/day were not required to achieve an area under the curve (AUC)/minimum inhibitory concentration of ≥ 400, even in patients with extreme obesity [15]. In one retrospective study, a mean dose of 13.7 ± 2.7 mg/kg total body weight (TBW) was associated with vancomycin trough concentration of 15–20 mg/L in patients with BMI ≥ 25 kg/m^2 and suggested using the lower limit of recommended vancomycin dosing (15 mg/kg per dose) [16]. Likewise, a separate study found a dose of 30 mg/kg per day to be appropriate for optimal target trough concentration attainment in patients with obesity, whereas doses of 20–25 mg/kg per day were found to be appropriate for optimal trough concentration attainment in patients with extreme obesity [17]. Moreover, a previous retrospective study that was conducted here at Brigham and Women's Hospital found an initial dose of 45–65 mg/kg per day using ideal body weight was more predictive of initial trough concentrations of 15–20 mg/L compared to TBW [18].

In our cohort, the median initial vancomycin dose was 28.7 (25.4–31.2) mg/kg per day (TBW), which aligned with prior recommendations of using lower daily vancomycin dosing in patients with obesity. However, unlike previous studies, our study analyzed multiple vancomycin trough concentrations after first initial steady-state concentrations within the first 10 days of therapy. Vancomycin trough concentrations accumulated over time, and supratherapeutic trough concentrations were often observed on second draws.

Our findings suggest a potential for vancomycin accumulation in patients with obesity during the first 10 days of therapy, which has not been previously well described. Due to lack of definition for vancomycin accumulation, we utilized 20% increase between the first trough concentration and subsequent trough concentrations. This threshold was chosen as the small increase in vancomycin concentrations that may occur between the fourth dose and true steady state would not be expected to exceed this. We considered it to be a clinically significant increase because a trough concentration of at least 16.7 mcg/mL or an AUC of at least 500 mg $\times$ hour/L would become supratherapeutic with a 20% increase. It is interesting to note that accumulation was observed in 20 (71.4%) critically ill patients, and alteration in pharmacokinetics due to critical illness may have contributed to accumulation in this population. Our study did not assess the impact of a vancomycin loading dose, but it would be expected to reduce the difference between early and steady-state trough concentrations. Although risk factors for accumulation did not yield a statistically significant association with accumulation in our study, we did not have a comparative nonobese group to determine whether accumulation was due solely to obesity. We utilized Centers for Disease Control and Prevention and World Health Organization BMI

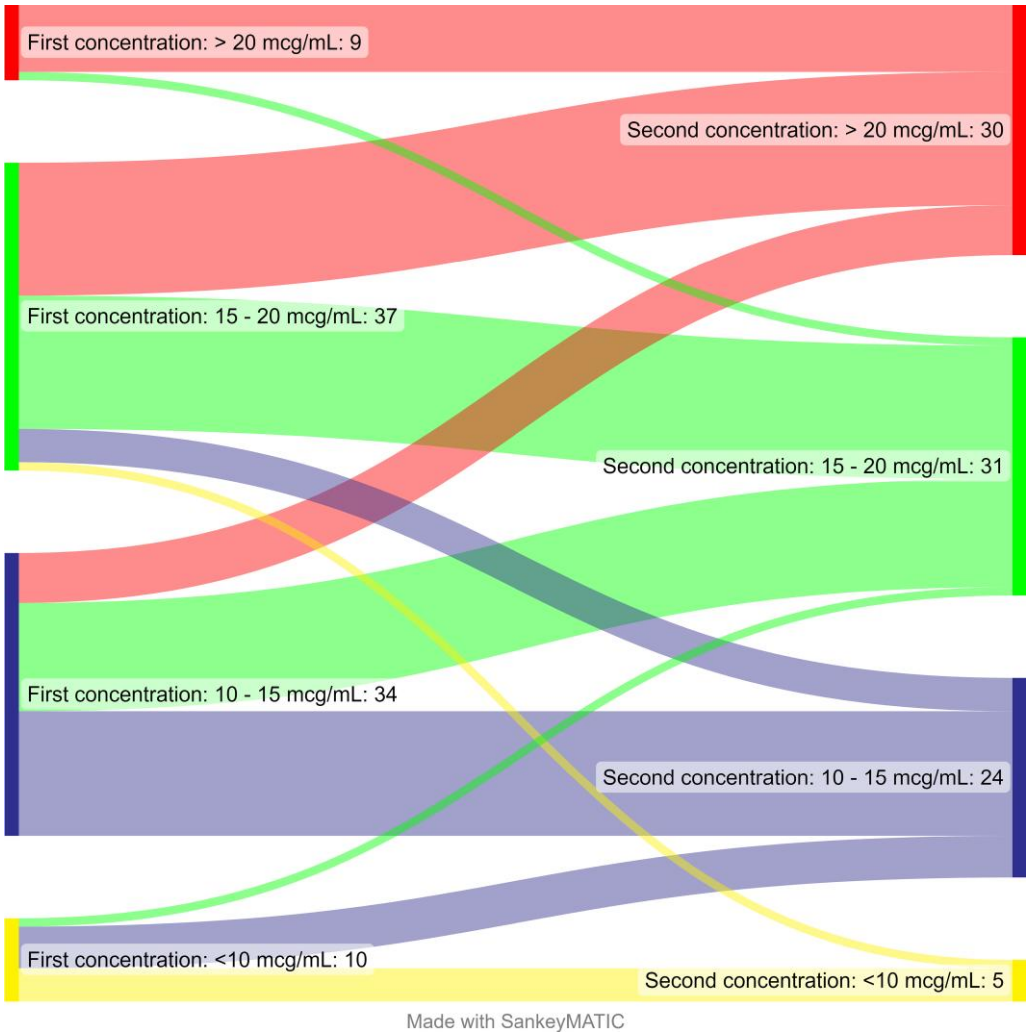

Figure 2. Vancomycin trough concentrations changes.
Schematic of progression from first to second vancomycin concentration in patients without dosage regimen changes.

Table 2. Multivariable Analysis of Vancomycin Accumulation

Variable	Odds Ratio	*P* Value	95% Confidence Interval
Age	1.009	0.452	0.986–1.033
Male gender	1.268	0.530	0.604–2.662
BMI obesity class[a]	0.885	0.603	0.558–1.403
Initial dose (mg/kg per day)[b]	0.940	0.085	0.876–1.009
SCr	0.522	0.247	0.174–1.569
Number of doses per day[c]	1.434	0.517	0.482–4.269

Abbreviations: BMI, body mass index; SCr, serum creatinine.

[a]Obesity class 1, 30 to <35 kg/m^2; obesity class 2, 35 to <40 kg/m^2; and obesity class 3, ≥40 kg/m^2.

[b]Based on actual body weight.

[c]1, 2, or 3 doses per day at initiation.

classifications to identify patients with obesity. It is important to highlight BMI has limitations because it does not differentiate between lean body mass and fat mass [19]. However, observation and epidemiological studies have shown BMI to provide acceptable estimation of total body fat [12]. In one study, a BMI cutoff of ≥30 kg/m^2 had sensitivity of 43% and specificity of 96% to detect the percentage of body fat [20].

Our study has several limitations: it was a single-center, retrospective, and noncomparative observational study. Trough concentrations were extrapolated using linear pharmacokinetic equations to allow comparisons regardless of timing of concentrations; however, the median time to trough concentrations was generally less than 1 hour, which makes linear extrapolation less likely to introduce extrapolation errors while helping to ensure fair comparison between concentrations. We also assumed equal ratios between vancomycin total daily dose and trough concentration to account for dose changes. Although trough concentrations do not always correspond linearly with dose, similar rates of accumulation were seen in patients with and without dose changes. Finally, although vancomycin area

under the concentration-time curve was not assessed in this analysis, vancomycin accumulation seen in this analysis is also expected to increase the vancomycin AUC. The AUC-guided therapy utilizing 2 postdistribution concentrations in patients with obesity would provide patient-specific pharmacokinetics, and future studies are warranted to further investigate this.

CONCLUSIONS

Patients with obesity are likely to experience vancomycin accumulation within the first 10 days of therapy. Clinicians should use frequent monitoring of vancomycin and use caution when interpreting early concentrations in patients with obesity. Future studies with a nonobese comparative group are warranted.

Acknowledgments

We acknowledge Kyle Molina and Taylor Morrisette for their insight on https://sankeymatic.com.

Author contributions. All authors contributed equally to this manuscript.

Financial support. none.

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

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

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