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Original article

# The association of elevated trough serum vancomycin concentrations with obesity

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ABSTRACT

*Background:* Obese patients display differences in vancomycin drug disposition, which may complicate attainment of appropriate serum vancomycin concentrations (SVCs). This study was conducted to determine if obesity leads to trough SVCs above the therapeutic range.
*Methods:* This retrospective cohort study sought to determine the rate and predictors of high (i.e. >20 mg/L) serum trough levels according to level of obesity.
*Results:* Increasing BMI predicted SVCs > 20 mg/L after controlling for dose, age, and serum creatinine. Obese patients had significantly higher mean trough SVCs compared to non-obese patients (16.5 mg/L vs 12.1 mg/L, $p = 0.004$) and a significantly higher proportion of obese patients had trough SVCs > 20 mg/L (18.9% vs 4.2%, $p = 0.03$).
*Conclusion:* Increasing obesity predicted higher probabilities of SVCs > 20 mg/L. Development of alternative dosing and management strategies for vancomycin may be necessary to account for pharmacokinetic changes associated with obesity.


## 1. Introduction

Obesity has more than doubled worldwide since 1980 and it is estimated that 60% of the world's population will be classified as overweight or obese by the year 2030 [1]. Given this trend, it is becoming increasingly important to characterize the effect of obesity on drug disposition. A growing body of research has indicated that obese individuals have altered pharmacokinetic parameters, as compared to normal-weight individuals [2–8]. Studies of vancomycin have indicated that obese patients have a larger volume of distribution (VD), increased clearance and altered protein binding, which results in a reduced free fraction of vancomycin in the serum [8]. These pharmacokinetic alterations have implications on dosing and attainment of therapeutic serum vancomycin concentrations (SVCs).

Consensus guidelines recommend using total body weight (TBW) to dose vancomycin, because data has indicated TBW predicts vancomycin clearance in obese individuals [9]. However, in simple one-compartment models, drug disposition (i.e. volume of distribution) can be mistaken as clearance [10]. The proper dosing algorithm for obese patients remains a controversial topic, despite the consensus among researchers that obesity can alter drug disposition and complicate the achievement of desired vancomycin concentrations. One study demonstrated that an adjusted body weight (ABW) was more accurate at predicting vancomycin clearance in obese individuals and should therefore be used when dosing [5]. Another study reported utilizing TBW and vancomycin doses of 15–20 mg/kg every 8–12 h. Here vancomycin trough SVCs exceeded 20 mg/L in approximately 50% of their obese patient population [11]. As a result of this observation, the authors created a revised protocol for obese patients utilizing lower maintenance doses of 10 mg/kg every 12 h or 15 mg/kg every 24 h. When compared with the original dosing protocol, the revised protocol

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resulted in a significantly higher proportion of patients attaining trough SVCs in the target range of 10–20 mg/L and above-target SVCs were significantly less frequent with the revised protocol. However, utilizing the revised protocol's lower dosing also resulted in a significantly higher rate of below-target SVCs when compared with the original protocol (23% vs 9%, P = 0.033). This observation is clinically concerning given that other recent studies have indicated that targeting higher trough SVCs of 15–20 mg/L in patients with complicated, serious infections is associated with significantly higher success rates compared to less aggressive traditional dosing [12].

Considering the controversy surrounding dosing strategies necessary to obtain optimal SVCs in obese patients, we conducted a study investigating the effect of obesity and level of obesity on trough SVCs. The purpose of this study was to determine if body mass index (BMI) category or obesity classification was associated with vancomycin SVCs above the therapeutic range. Secondary objectives included characterizing clinical and safety outcomes associated with targeting trough SVCs > 15 mg/L.

## 2. Patients and methods

This retrospective study was conducted on a cohort of patients treated with intravenous (IV) vancomycin during routine practice at an institution that utilizes a pharmacist-managed dosing protocol. This study sought to classify the existence of trough SVCs above the desired therapeutic range (i.e. > 20 mg/L) according to BMI classification and obesity status. All patients were initiated with a vancomycin dose of 15 mg/kg TBW with a maximum initial dose of 2000 mg and subsequent dosing interval based on calculated creatinine clearance ($CL_{Cr}$) [13]. Full details of the dosing protocol can be found in Table 1.The dosing scheme utilized was in accordance with hospital guidelines. At the study institution, loading doses were not routinely administered. Patients were abstracted from pharmacy reports of all inpatient orders for vancomycin during the period of July through November 2011. This study was approved by the appropriate Institutional Review Boards.

Patients were included if they were 18 years of age or older with a BMI of at least 18 kg/m$^2$. In addition, patients were required to have a documented or clinically suspected infection with a corresponding goal trough SVC of 15–20 mg/L such as pneumonia, meningitis, endocarditis, osteomyelitis or bacteremia, consistent with American Society of Health-System Pharmacists (ASHP) and Infectious Diseases Society of America (IDSA) recommendations [9,14]. Patients with sepsis of unknown etiology were also included if at least two of the systemic inflammatory response criteria were met: body temperature < 36 °C or > 38 °C, heart rate > 90 beats per minute, respiration rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg, or white blood cell count > 12,000 cells/mL$^3$ of blood, < 4000 cells/mL$^3$ of blood or > 10% bands, or as suspected by the ordering physician [15]. To ensure that patients were approaching “steady-state” concentrations, a minimum of four IV vancomycin doses were required for patient inclusion. Trough SVC measurement no more than 2 h prior to the fourth or subsequent dose was done as recommended by current guidelines for therapeutic drug monitoring of vancomycin.[9]. Patients were excluded if they were younger than 18 years of age, had a $CL_{cr}$ less than 40 mL/min, received vancomycin within the 48 h prior to their hospital admission, were administered less than four doses of vancomycin, or received vancomycin for treatment of an infection with a goal trough SVC < 15 mg/L.

**Table 1**
Vancomycin dosing protocol (Adapted from Ref. [26]).

| Initial dose of 15 mg/kg using actual body weight administered at intervals based on estimated creatinine clearance ($CL_{cr}$) | |
|---|---|
| $CL_{cr}$ (ml/min)[1] | Dosing interval |
| 101–120+ | Every 8 h |
| 70–100 | Every 12 h |
| 40–69 | Every 24 h |
| 30–39 | Every 36 h |
| 20–29 | Every 48 h |
| <10 | Random[a] |

[a] Random doses of vancomycin administered based on random serum vancomycin concentrations with doses given when serum concentrations were <20 mg/L.

Body mass index was calculated and patients were classified as obese (BMI ≥ 30 kg/m$^2$) or non-obese (BMI < 30 kg/m$^2$) [1]. Patients were further characterized into World Health Organization obesity classes [16]. Comparisons planned a-priori included non-overweight individuals compared to each categorical group of overweight individuals (i.e. BMI < 24.99 kg/m$^2$ vs. BMI 25–29.99, 30–34.99, 35 to 39.99, and ≥40 kg/m$^2$). Physician report of comorbid diabetes, hypertension, congestive heart failure, sepsis or ascites was documented. Albumin was documented if available; hypoalbuminemia was defined as serum albumin < 3 g/dL. The type of documented or suspected infection was also characterized. Each vancomycin dose and time of administration were recorded, and renal function at each dose was calculated with the modified Cockcroft–Gault method[1] using an adjusted body weight in patients >20% over their ideal body weight [13,17].

Serum creatinine values < 0.8 mg/dL were rounded to 0.8 mg/dL [18] and acute kidney injury was defined as a 1.5-fold increase in serum creatinine from baseline (measured on the first day of vancomycin therapy) [19] Concurrent use of other nephrotoxic medications was documented if administered any time after the first vancomycin dose was given. Clinical response was defined as a normal or down-trending white blood cell count (4000–10,000 cells/mL$^3$) and absence of fever (temperature < 38 °C) for at least 24 h after the initiation of vancomycin. Severity of illness was characterized with Acute Physiology And Chronic Health Evaluation II (APACHE II) [20] and Sequential Organ Failure Assessment (SOFA) [21] scores. Hospital length-of-stay and in-hospital mortality were also recorded.

Secondarily, we sought to classify the likely percent of steady-state achieved in order to ensure that trough concentrations were comparable. Since obtaining greater than one serum concentration after a vancomycin dose is not standard of care at the study institution, volume of distribution and vancomycin clearance were estimated based on a modification [5] of the method described by Leonard and Boro [22] using an ABW to estimate vancomycin clearance and half-life. Approximation of the percent of steady-state[2] achieved was calculated.

Bi-variate statistical analyses were conducted using SPSS version 19.0 (SPSS, Inc., 2010, Chicago, IL). Continuous variables were evaluated using descriptive statistics and analyzed with the independent-sample Student's t-test or Mann–Whitney *U* test when appropriate. Categorical variables were analyzed with the Pearson chi-square test or Fisher's exact test when appropriate. Multivariate statistics were performed using STATA v.13 (Statacorp, College Station, TX). The multivariate model attempted to predict

[1] Modifed Cockcroft–Gault equation:
$CL_{cr} = \frac{(140-age)\times(Ideal\ or\ adjusted\ body\ weight\ in\ kg)}{72\times Serum\ creatinine} \times 0.85$ *if female*. Adjusted body weight = Ideal body weight + 0.4 × (Total body weight − ideal body weight).

[2] Percent of Steady State Achieved:
$1 - e^{((-0.693)*(\text{elapsed time from first dose until measured trough})\div(\text{estimated half-life}))}$