

Single-center prospective study of obese patients comparing two vancomycin loading dose regimens

Abstract

Obesity alters the movement through the body of several antibiotics, including vancomycin. Based on literature to date, total body weight should be used to determine dosages and shorter dosing intervals may be needed. However, hospitals have different approaches to managing vancomycin in this patient population. The most common example is not exceeding a dose of 2,000mg of vancomycin at one time in these patients. However, some institutions including the Charleston Area Medical Center do not have a set maximum one time dose. To date, a study has not been done comparing two different dosing regimens in obese patients to determine if having a maximum dose cap is beneficial.

We are attempting to add to the limited existing body of literature in this field with our study. We hypothesize that optimizing the initial or loading vancomycin dose that obese patients receive will decrease the time to target concentrations. For this study we will randomize adult patients weighing > 100 kg to receive either 1)a loading dose of 20 mg/kg with a maximum dose up to 2,000mg OR 2)a loading dose of 20 mg/kg with a maximum dose of up to 4,000mg. Our primary aim is to determine differences in the vancomycin blood concentrations and the occurrence of adverse events.

Abstract word count: 208

Specific Aims and Hypothesis

1. To compare initial vancomycin trough levels (i.e. at 7.5-hours and the trough level before second vancomycin dose) between patients receiving a 20 mg/kg loading dose of vancomycin (capped at 4,000mg) and patients receiving 20 mg/kg loading dose capped at 2,000mg.
2. To determine if a 20 mg/kg loading dose of vancomycin not capped at 2,000mg will result in more reported adverse events in comparison to patients receiving a 20 mg/kg loading dose capped at 2,000mg.
3. To examine and compare the pharmacokinetic parameters of elimination rate constant (k_e) and volume of distribution (V_d) following the loading vancomycin dose in patients prior to the second dose of vancomycin.
4. Compare intensive care unit length of stay, hospital length of stay and in hospital mortality between the two vancomycin loading dose regimens.
5. To evaluate if obese patients receiving a 20 mg/kg loading dose of vancomycin not capped at 2,000mg will attain therapeutic vancomycin concentrations more quickly than patients receiving a 20 mg/kg loading dose capped at 2,000mg.

The null hypothesis is a 20 mg/kg loading dose of vancomycin not capped at 2,000mg will not result in patients having higher early vancomycin concentrations compared to patients who received a maximum of vancomycin 2,000mg.

The alternative hypothesis is that patients who receive a 20 mg/kg loading dose of vancomycin not capped at 2,000mg will have higher early concentrations compared to patients who only received vancomycin 2,000mg.

Background

Vancomycin is a glycopeptide antibiotic that is commonly used in the Emergency Department (ED) to target resistant gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). Infections that may involve these bacteria include skin and soft tissue infections (e.g. cellulitis, osteomyelitis, etc.), hospital acquired pneumonia, and sepsis. Even though other antibiotics have been developed to treat these infections, vancomycin remains the most frequently used in the acute care setting.² Vancomycin exhibits time-dependent bacterial killing, so maintaining adequate trough concentrations are important for this antibiotic.³ Furthermore, vancomycin is often involved in medication errors and is often monitored by hospital pharmacists.^{4,5}

The Food and Drug Administration does not consider obese individuals to be a special population, so pharmaceutical companies are not required to perform studies in this specific group of patients.⁶ Given that obesity continues to be a public health concern in the United States; studies evaluating the use of vancomycin in this population are needed. Vance-Bryan et al. found that total body weight was a significant predictor of vancomycin clearance and that vancomycin clearance decreased as total body weight increased.⁷ Two additional studies reviewing vancomycin pharmacokinetics in morbidly obese patients revealed that vancomycin clearance was greater in morbidly obese patients than in nonobese patients. A strong correlation between total body weight and vancomycin clearance was also evident.^{3,8} Despite these results, Leong et al. showed that adjusted body weight was superior to total body weight when estimating vancomycin clearance in overweight and obese patients.²

Vancomycin target troughs are important as they help providers ensure that the patient is getting enough of the antibiotic to target and treat their specific infection. Since the penetration of vancomycin varies depending on the site of the infection, different infections have different target troughs. However, the two most common target trough ranges are 10-15 mcg/mL for less serious infections like skin soft tissue infections and 15-20 mcg/mL for more serious infections like meningitis, osteomyelitis, and pneumonia.¹ If target trough values are not obtained, the patient's infection could worsen and he/she could even develop sepsis secondary to the worsening infection. Additionally, the 2009 consensus guidelines for vancomycin monitoring from Infectious Disease Society of America (IDSA) recommend that trough concentrations should be maintained above 10 mcg/mL to avoid the development of microbial resistance.¹ Of note, even though we are collecting in hospital mortality as a data point, there is no information available in the literature to suggest that different dosing regimens of vancomycin have been linked to increased mortality rates.

Even though there is data assessing the pharmacokinetics of vancomycin in obese patients, more studies are still needed to examine the use and dosing of vancomycin in this patient population.

Since West Virginia has one of the highest rates of obesity and vancomycin is frequently used, a study to evaluate the efficacy and safety of loading doses given to these patients in the ED is warranted.

The objectives of this prospective study are to evaluate in patients who weigh > 100kg whether (1) a loading dose of 20 mg/kg with a maximum dose up to 2,000mg or a loading dose of 20 mg/kg with a maximum dose of up to 4,000mg would result in the patients reaching higher vancomycin levels before their second vancomycin dose and (2) whether there is an impact on the number of adverse events reported including red man syndrome and nephrotoxicity. Red man syndrome is an infusion-related reaction associated with vancomycin. The reaction typically consists of pruritus and an erythematous rash that involves the face, neck, and upper torso. If this occurs, patients can still receive vancomycin, but the infusion needs to be slowed down. Diphenhydramine may also be given at the provider's discretion. Vancomycin doses in the second arm will be capped at 4,000mg as there is primary literature to support that larger doses (at least 4,000mg per day) are associated with an increased incidence of nephrotoxicity.¹⁰ Even though there is limited data regarding toxicities with higher doses, the study investigators wanted to err on the side of caution in regards to the dosing in this arm of the study. Other than the two adverse events commonly associated with vancomycin (i.e. red man syndrome and nephrotoxicity), there are no other risks to patients receiving more than 2,000mg as single dose in this study.

Significance

Obesity continues to be a primary concern for public health in the United States as the prevalence remains high with one-third of adults being obese. In conjunction with obesity, comes the challenge of dosing various medications in this patient population. Vancomycin is commonly used in the hospital setting for the empiric treatment of infections caused by gram-positive bacteria. There are a few studies in the primary literature that have reviewed the pharmacokinetics of vancomycin in obese patients but there has not been a prospective study to date comparing two different loading dose regimens of vancomycin in the Emergency Department. We hope to gain a better understanding of the dosing and pharmacokinetics of vancomycin in patients who weigh >100kg which may help us to better care for future patients.

Methodology

Design:

This is a single-center prospective study enrolling patients ≥18 years of age who present to the Charleston Area Medical Center Memorial Hospital Emergency Department and weigh >100 kg. The patients will be included in the study if they have an infection requiring both empiric intravenous vancomycin and admission to the hospital. Following informed consent, the patients will be randomized to receive either (1) 20 mg/kg of vancomycin up to a maximum dose of 2,000mg or (2) 20 mg/kg up to a maximum of 4,000mg.

Following administration of the initial loading dose, three additional, non-standard of care vancomycin levels will be ordered. The three additional levels include: (1) a post-load peak vancomycin

level to be drawn 1-2 hours after the initial loading dose, (2) vancomycin level to be drawn 7.5 hours after the initial loading dose, (3) a trough level 30 minutes before the patient's second scheduled dose of vancomycin. These additional levels will help determine differences between the two treatment vancomycin regimens for early serum levels and pharmacokinetics, the time needed to achieve target vancomycin concentrations, and the occurrence of adverse events. The addition of a 7.5-hour level will provide a consistent timed vancomycin level across all patients regardless of the timing of the second dose of vancomycin. If the patient is scheduled to receive vancomycin q8h, then he/she will only receive two vancomycin levels (instead of three) as part of the study protocol as the 7.5-hour level will also be the initial trough level.

Sample:

The sample will include patients ≥ 18 years of age who present to the Charleston Area Medical Center Memorial Hospital Emergency Department weighing $>100\text{kg}$ and who have an infection requiring initial treatment with intravenous vancomycin and admission to Memorial Hospital.

Following enrollment of the initial 7 patients, it was found that not all enrolled patients received vancomycin long enough to reach goal therapeutic trough levels, resulting in missing values for the outcome of time to therapeutic trough levels. Thus, the initial trough level (i.e. trough level between the first and second dose of vancomycin) appears to be a more appropriate primary outcome. With the change in primary outcome, we redid the sample size/power calculation. However, by keeping the effect size the same as the original power analysis (i.e. an effect size of 0.5), the same sample size of 128 patients (64 patients per group) is required in order to have a 16% change in the primary outcome measure (initial trough level: $15.0 \pm 5.0 \text{ mcg/mL}$) be statistically significant when using two-tail t-test analysis (power = 0.80, $p = 0.05$). This power analysis was performed using G*Power (Version 3.1.6).

Inclusion Criteria:

- Patients ≥ 18 years of age who present to the Charleston Area Medical Center-Memorial Hospital Emergency Department
- Weight $>100\text{kg}$
- Infection requiring intravenous vancomycin (i.e. patients received at least 1 administration of IV vancomycin) and admission to Memorial Hospital

Exclusion Criteria

- Any patient <18 years of age
- Patients on dialysis
- Patients with unstable renal function (a change of $>0.5 \text{ mg/dL}$ in SCr concentration in patients with a SCr of $<2 \text{ mg/dL}$ or a 20% change in SCr in patients with a SCr of $\geq 2 \text{ mg/dL}$)
- Patients with initial SCr of $>2.5 \text{ mg/dL}$

Procedures/Protocol:

Patients ≥ 18 years of age and an initial weight of >100 kg who present to the Charleston Area Medical Center Memorial Hospital Emergency Department (ED) with an infection requiring treatment with intravenous vancomycin will be invited to participate in this single-center prospective study. For patients to be included, they will also need to be admitted to the hospital. Study investigators and coordinators will identify and enroll patients in the ED. In addition to the following description of the study, please refer to Figure 1 for a procedural flowchart. Dr. Payne, and trained, IRB approved, investigators and coordinators will screen patients and obtain informed consent. In addition, Dr. Payne, Dr. Crawford, and/or other study investigators will educate all of the emergency medicine residents about the study, so that the study investigators can optimize patient enrollment.

Potential study patients will be screened by the study coordinators electronically using the triage list. Once a potential study patient is identified, the in-house study investigator (if exists) will be notified to consider patient eligibility. Estimated number of screened patients by the study coordinators is 5000 patients. All eligible patients will be informed about the study and asked to provide informed consent for the study by one of the study investigators or coordinators. If the patient agrees to participate, they will be consented with the consent form as written.

Consent will be obtained at any time after the patient is identified as being a potential candidate (i.e. meeting inclusion criteria) and prior to their loading dose of vancomycin. After informed consent is obtained, the patient will be randomized to one of two loading dose regimens for the initial dose of vancomycin. Sealed envelopes containing the randomized treatment protocol, determined by the statistician, will be maintained on the ED premises to be pulled consecutively after a patient has been consented to be in the study. Information in the envelope will provide investigators with the loading dose regimen that the patient will receive.

Patients will either be randomized to receive 20 mg/kg with a maximum dose of 2,000mg of vancomycin or with 20 mg/kg with a maximum dose of 4,000mg. Using the study-specific pharmacy order form, an investigator will order the initial vancomycin dose. The order will be faxed to Memorial Pharmacy.

The pharmacy department will complete the vancomycin order via their standard procedures. Investigators will then assist the patient's nurse with obtaining the medication from the pharmacy department to prevent any potential delay in the patient receiving the antibiotic. Various factors exist that could delay the medication from being delivered in a timely manner (e.g. interruptions in technology, etc.), so the investigators will work to prevent this from happening as the blood levels must be timed based on the administration of the medication.

Investigator/study coordinator will confirm vancomycin start and stop time with the ED nurse. The investigator will place an order for the 1st Vancomycin level (peak level) to be drawn 1 hour (time window allowance for draw: 60-120 minutes) after the first vancomycin infusion is done.

Written as part of the initial vancomycin order, a pharmacist will call and discuss with the investigator the study patient and his/her vancomycin dosing regimen. While on the phone the pharmacist will inform the investigator the study patient's 2nd vancomycin dose and time of the administration. The investigator will place the following orders for the study patient 1.) the second dose of vancomycin according to pharmacist's directions 2.) vancomycin level ordered to be drawn 7.5 hours (+/- 60 minutes) after the initial loading dose 3.) third vancomycin blood draw (i.e. the initial trough level), ordered to be obtained 30 minutes prior to the time 2nd vancomycin dose is scheduled to be administered (time window allowance for draw: 60 minutes on either side of the scheduled time of vancomycin dose as long as prior to 2nd vancomycin infusion). If the patient is scheduled to receive vancomycin q8h, then he/she will only receive two vancomycin levels as part of the study protocol, as the 7.5-hour level will also be the initial trough level. Levels falling outside the described time windows due to patient care activities (surgeries, procedures, imaging) occurring at the time of scheduled labs will not be used for data analysis.

Funds from the CAMC Foundation or other sources have been obtained to cover the three vancomycin levels as they are not standard of care. These additional levels will allow for two patient specific pharmacokinetic parameters to be determined (i.e. elimination rate constant (ke) and volume of distribution (Vd)). Dr. Payne, Dr Crawford, and/or other study investigators/personnel will educate the ED nursing staff and/or Memorial Pharmacy on the study as needed.

Following the vancomycin loading dose, vancomycin dosing will be at the discretion of the pharmacist and attending physician and will follow standard of care. At CAMC, pharmacy manages vancomycin dosing and monitoring for the majority of patients receiving this antibiotic via a standard protocol. The protocol is included in the submission as a separate attachment, but it is for a reference only and not for use in regards to the primary purpose of this study. Once a patient is discharged from the hospital, they would have completed the study for that particular hospital visit.

When 50% of patients (64 patients) have been enrolled in the study, an interim analysis will be performed independently from physicians and clinicians involved in the study. Occurrence of the side effects of red man's syndrome and nephrotoxicity will be specifically examined. Data analysis will be performed by CHOSR staff.

Data Collection/Instrumentation:

Data will be collected only for enrolled patients who meet the inclusion criteria and have signed an informed consent. Patient data will be collected by medical chart review using the Soarian/Cerner electronic medical record system:

Patient Information:

- Account number and medical record number
- Demographic data (age, gender, height, race, weight, body mass index)
- Date and time of ED presentation
- Admitting diagnosis
- Infection to be treated with vancomycin (pneumonia, sepsis, skin soft tissue, etc.)

- Pertinent past medical history: diabetes, heart failure, sepsis
- History of multi drug resistant organisms (yes/no)
- Lab values from Day 0 through Day 2 of the patient's admission: BUN; serum creatinine (SCr); white blood count (WBC); lactate; procalcitonin
- Sequential Organ Failure Assessment (SOFA) score
 - a. PaO₂/FiO₂
 - b. Platelets
 - c. Bilirubin
 - d. Mean arterial pressure (MAP)
 - e. Glasgow Coma Scale (GCS) Upon Presentation
 - f. SCr
 - g. Urine output

Other medications:

- Other antibiotics ordered for patient: name, date/time ordered, and date/time administered
- Other concomitant nephrotoxic medications or medications that may alter renal hemodynamics: acyclovir, aminoglycosides, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, cephalosporins, contrast dye, cyclosporine, diuretics, nonsteroidal anti-inflammatory drugs, tacrolimus, and vasopressors

Vancomycin levels and dosing:

- Goal vancomycin trough for infection
- Initial/load of vancomycin
 - Date and time of administration
 - Dose (mg/kg) and total dose (mg)
- Date/time/result of post-load (initial) vancomycin level (peak level)
- Date/time/result of 7.5-hour vancomycin level
- Date/time/result of vancomycin level 30 minutes prior to second dose (initial trough level)
- Was second dose of vancomycin regimen administered appropriately based on the time of administration of the loading dose (yes/no)

- ke and Vd for vancomycin initial dose *to be calculated*
 - $ke = [\ln(Cpk/Ctr)]/T$
 - $Vd = [k * (1 - e^{(-kt)})] / [k * (Cpk - (Ctr * e^{(-kt')})]$

- Adverse effects post initial vancomycin dose
 - Did the patient develop Red Man's syndrome during the initial infusion of vancomycin? (yes/no)
 - If yes, what was the vancomycin initial infusion rate? And was infusion rate decreased?

 - Did patient develop nephrotoxicity within 24 hours after the last vancomycin dose or by hospital discharge (whichever comes first) ? (yes/no)
 - If yes, when did patient first meet criteria for nephrotoxicity?
 - Did patient develop nephrotoxicity within 48 hours after the vancomycin loading dose? (yes/no)
 - Nephrotoxicity will be defined as an increase in SCr by 0.5 mg/dL or 50% from baseline on two consecutive measurements.*

- Maintenance dose initially ordered
 - mg/kg, total dose
 - Frequency of dosing
 - Time/date of when 2nd dose of vancomycin was ordered to be administered and when (date/time) it was actually administered
 - Was the initial trough level obtained appropriately based on the time that the second dose of vancomycin was scheduled to be administered? (yes/no)
- Who managed vancomycin maintenance regimen? (Pharmacy/Infectious disease/other)
- Date/time/result of vancomycin trough levels
 - Date, time, level and Time to first therapeutic vancomycin trough (hours)
 - Were the troughs drawn appropriately? (yes/no)
 - Date, time, and level of initial steady-state Trough level
 - l.e. after the 3rd maintenance vancomycin dose, prior to the 4th maintenance dose*
- Duration of vancomycin therapy, days and number of doses

Culture results:

- Culture site, time drawn, final results

Hospital Stay:

- Intensive care unit length of stay (hours)
- Hospital length of stay (days)
- In hospital mortality (yes/no)

Statistical analysis:

Basic descriptive statistics including means and standard deviations for continuous variables and proportions and frequencies for categorical variables will be used to describe the patient sample and infection characteristics.

We will evaluate if a vancomycin loading dose not capped at 2,000mg associates with higher initial vancomycin blood levels in comparison to a loading dose capped at 2000 mg (**Specific Aim 1**), by using t-tests, or Mann-Whitney U analysis. To determine if an uncapped vancomycin loading dose has a higher incidence of adverse events (**Specific Aim 2**) or in-hospital mortality (**Specific Aim 4**), we will use Chi-square analysis with continuity correction, or Fisher's exact test, when appropriate. To compare pharmacokinetic parameters (**Specific Aim 3**) and length of stays (**Specific Aim 4**), t-tests, or if the data is not normally distributed, Mann-Whitney U analyses will be performed. We will evaluate if a vancomycin loading dose not capped at 2,000mg associates with a shorten time to achieve goal trough levels in comparison to a loading dose capped at 2000 mg (**Specific Aim 5**), by using t-tests, or Mann-Whitney U analysis. To address **Specific Aim 5**, we will also stratify levels on if they are subtherapeutic, therapeutic or supratherapeutic, based on patients' goal vancomycin trough values.

For all comparisons, a p level of < 0.05 will be used to determine statistical significance. The statistical package SPSS (Version 19) will be used to analyze data.

Human Subjects

Recruitment methods:

Recruitment for this project will be performed by the study investigators and coordinators in the Charleston Area Medical Center Memorial Emergency Department. Potential study patients will be screened by the study coordinators electronically using the triage list. Once a potential study patient is identified, the in-house study investigator (if exists) will be notified to consider patient eligibility. Estimated number of screened patients by the study coordinators is 5000 patients. In addition, Dr. Payne, Crawford or another study investigator will educate all of the emergency medicine medical residents about the study, so that the study investigators can optimize patient enrollment. Informed consent will be obtained any time prior to the patient's initial dose of vancomycin as that dose will be determined based on the randomization process described above. One of the study investigators or coordinators will describe the study to the patient, answer all questions, and obtain the necessary informed consent, if the patient wishes to participate in the research.

Benefits:

If the patient agrees to take part in this study, we cannot guarantee any direct benefit to the patient. We hope to gain a better understanding of the dosing and pharmacokinetics of vancomycin in patients who weigh $>100\text{kg}$ which may help us to better care for future patients.

Risks and Discomforts:

The risks of the study include those associated with having blood drawn (such as pain, blood loss, infection) and potential nephrotoxicity. The amount of blood drawn for the three additional vancomycin levels that are not otherwise done will be minimal ($< 5\text{ mL}$) and will be obtained by a trained professional in a sterile fashion as to minimize any additional pain, bleeding, bruising, or infection. For the purposes of this study, nephrotoxicity will be defined as an increase in SCr by 0.5 mg/dL or 50% from baseline on two consecutive measurements. For this reason, we will be following SCr levels for 24 hours after the last dose of vancomycin or until discharge (whichever comes first). The risk will be minimal as the patients who receive vancomycin are followed closely by clinical pharmacy services, the infectious disease service if consulted, and other providers. Also, patients with unstable renal function or $\text{SCr} > 2.5\text{ mg/dL}$ or on dialysis are going to be excluded as mentioned previously.

Costs to subjects:

The patient/patient's guardian will be responsible for all co-pays and deductibles associated with routine care billable to the insurer. The vancomycin level obtained at 1-2 hours after the loading dose, at 7.5-hours post loading dose, and the level prior to the second dose will not be billed to the patient or his/her insurance provider as the researchers will be utilizing money from a private donor sepsis research fund.

Payments to subjects: None

Intervention:

If patients develop red man syndrome, the vancomycin infusion will be slowed down and the patient may receive diphenhydramine intravenously at the discretion of the attending physician. For those patients that develop nephrotoxicity, their SCr values will be monitored closely and their vancomycin maintenance regimens adjusted accordingly. The vancomycin may also be discontinued and changed to another antibiotic at the discretion of the attending physician. These are the same interventions that would occur if the patients were to experience these adverse events while receiving vancomycin and not be enrolled in this study.

Confidentiality:

Confidentiality of the participants in the study will be protected at all times. All identifying patient information will remain in the PI's locked office and if electronic, on a password protected computer in a password protected file. Paper forms will be shredded and electronic files will be deleted at the time of publication. All results will be reported with no identifiers.

Principle Investigator:

William Payne, MD – emergency medicine physician

Co-Investigators:

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