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Characterization of variables for potential impact on vancomycin pharmacokinetics in thermal or inhalation injury

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ABSTRACT

Objective: To characterize the pharmacokinetics of vancomycin dosing in thermal or inhalation injury as they relate to percent total body surface area burn (TBSA) and days since injury (DSI).
Methods: This retrospective 3-year study included patients with thermal or inhalation injury receiving vancomycin. Patient demographics and course data were collected using the institution's electronic medical record.
Results: Six hundred and fifty-four patients were included in the study; 124 remained after exclusion. Clearance (CL) was augmented in patients closer to their date of injury. CL and total daily dose requirements significantly increased with larger percent TBSA injured that was independent of volume of distribution (Vd). Larger percent TBSA also predicted increased occurrence of renal injury prior to vancomycin initiation. A modified sample set was also analyzed to control for renal dysfunction. Creatinine clearance (CrCl) estimated via the Cockcroft-Gault equation significantly impacted CL and total daily dose. To obtain a goal trough of 15–20 mg/L, the average patient in the modified sample with ≥10% TBSA required 64.7 mg/kg/day (or 16.2 mg/kg every 6 hours).
Conclusions: DSI, percent TBSA, and CrCl can be used to predict faster vancomycin CL and need for higher total daily doses. Augmented pharmacokinetics can occur as early as two days after injury and decrease with time. Acceptable target trough attainment is still lacking and this data should assist in performance improvements for initial vancomycin dosing.

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1. Introduction

Infection is the leading cause of morbidity and mortality following thermal injury [1]. While Gram-negative organisms predominate as the causative pathogen for most burn wound infections, Gram-positive pathogens can also present as common causes of infection, especially pneumonia and bacteremia [1,2]. Vancomycin is frequently chosen for empiric coverage or treatment of Gram-positive infections. It has been shown that patients who experience a thermal injury have altered processes that impact the absorption, metabolism, distribution, and elimination of drugs [3,4].

Several pharmacokinetic studies have been conducted in the burn population. Previous trials have compared non-burn patients to burn patients and found renal function to be a major factor responsible for vancomycin clearance (CL) in the burn population [5–7]. Burn patients were found to have faster renal CL of vancomycin and higher dosage requirements. The authors concluded that burn patients require dosage individualization and close monitoring.

Percent total body surface area (TBSA) and days since injury (DSI) have been shown as clinically important factors impacting the burn patient's metabolism, such as energy expenditure and utilization [8,9]. Vancomycin pharmacokinetics in patients with at least 10 percent TBSA burned have been studied in comparison to people without burn injuries [10]. CL was significantly faster than those without burn injuries resulting in the burn patients having lower trough concentrations, but it is unknown if percent TBSA impacted the results [10]. Additionally, vancomycin pharmacokinetics have been shown to vary with DSI. Forty-nine burn patients were evaluated for differences in pharmacokinetics with 14 days as the selected threshold. The authors found patients to have a greater CL within 14 days of injury, but it is unknown if an impact can be seen earlier [11].

Burn patients benefit from higher and more frequent doses [5–7,10,11]. The evident hyper-dynamics adds difficulty to achieving therapeutic vancomycin troughs. There is not a universally accepted vancomycin dosing strategy in burn patients secondary to remarkable intra- and inter-patient variability [4]. Several patient and injury factors have been proposed to explain the variability, but proof is lacking and more variables needed [12]. Currently, the only consensus among studies is to monitor closely and individualize dosing based on individual pharmacokinetics [4,12]. The purpose of this study is to more deeply characterize vancomycin pharmacokinetics in patients with thermal or inhalation injury by DSI and percent TBSA burn.

2. Methods

2.1. Patient population

This study was a retrospective, observational study conducted at a single burn center. Patients admitted October 20, 2012 to November 30, 2015 and received intravenous vancomycin for any indications were included for initial screening. Patients were excluded if they were under the age of eighteen; admitted for a reason other than thermal or inhalation injury; vancomycin was initiated less than forty-eight hours after injury; lacked 2 paired post-distribution concentrations (C_1 and C_2); had vancomycin concentrations that were not recorded, could not be accurately evaluated, or the concentrations were drawn prior to assumed steady-state. A 1 h distribution phase was assumed when evaluating vancomycin concentrations for inclusion [13].

2.2. Data collection

All retrospective data were collected using the institution's electronic medical record. Data collected included patient demographics and laboratory values pertinent to vancomycin therapy. Characteristics of patients' injuries were also collected. Data related to the vancomycin course were also collected including indications, doses, interval, and duration. Using the data collected, true peak (C_{max}), true trough (C_{min}), half-life, volume of distribution (Vd), 24-h area under the curve (AUC_{24}), clearance (CL), and predicted dose required to obtain target trough concentrations were calculated and described below. Additionally, patients were evaluated for acute kidney injury prior to vancomycin initiation and during therapy using the Acute Kidney Injury Network (AKIN) classification [14].

2.3. Pharmacokinetic analysis

Although vancomycin typically follows a two or three-compartment model, a one-compartment model was selected based on practicality of calculations and accuracy when concentrations are taken post-distribution [14]. Half-life was calculated as $[0.693/k_e]$. The elimination rate constant (k_e) was calculated as $[\ln (C_1/C_2)/(t_2-t_1)]$, where (t_2-t_1) represents the time between the two concentrations. C_{max} was $[C_1/e^{-ke^*t}]$, where t represents the amount of time after the end of infusion the concentration was drawn. C_{min} was $[C_2{}^*e^{-ke^*t}]$, where t represents the amount of time remaining in the interval from when the concentration was drawn. Vd was calculated as $[D/(k_e{}^*T)]^*[(1-e^{-ke^*T})/(C_{max}-(C_{min}{}^*e^{-ke^*T})]$, where D is the dose and T is the infusion time. AUC_{24} was calculated as $[D_{24}/(k_e{}^*Vd)]$, where D_{24} is the total dose in mg given during a 24-h period. CL was calculated as $[K_e{}^*Vd]$. Predicted interval (τ) was calculated as $[\ln (40/17.5)/k_e+T]$ and rounded to the nearest clinically feasible interval. Predicted dose was calculated as $[40^*k_e{}^*Vd^*T^*(1-e^{-ke^*\tau})/(1-e^{-ke^*T})]$ and rounded to the nearest 250 mg. The calculations performed in this study are identical to actual bedside practice at the authors' institution. Utilizing 40 and 17.5 mg/L for the target concentrations in the predicted equations allowed flexibility during rounding of each interval and dose for the trough to stay within the desired therapeutic range of 15–20 mg/L. Because of the up or down rounding, the final regimen for each patient would not actual target 17.5 mg/L, but fall between 15–20 mg/L. The new rounded predicted dose and interval were then mathematically validated, based on a predicted Cmin goal of 15–20 mg/L. Predicted C_{min} was calculated as $[\text{predicted } C_{max}{}^*e^{-ke^*(\tau-T)}]$, where predicted C_{max} was calculated as $[D/(k_e{}^*Vd^*T)]^*[(1-e^{-ke^*T})/(1-e^{-ke^*\tau})]$. Creatinine clearance was calculated according to the Cockcroft-Gault equation (CG) [15]. For authenticity,

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