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Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients

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ABSTRACT

Vancomycin is frequently administered to critically ill patients by continuous infusion in order to optimise drug efficacy; however, there are few data available on the efficacy of this strategy in septic patients. In this retrospective analysis, 261 patients treated with continuous infusion of vancomycin in the Department of Intensive Care at Hôpital Erasme (Brussels, Belgium) were evaluated. Creatinine clearance (CL_{Cr}) was calculated from 24-h urine collection and normalised to body surface area. During the study period, 139 patients (53%) had insufficient vancomycin concentrations (<20 μg/mL) on Day 1 and 87 patients (33%) on Day 2. Patients who had insufficient drug concentrations on Day 1 of therapy were more likely to be men, to have a higher CL_{Cr} and to have received lower loading and daily vancomycin doses than other patients, who received greater vasopressor support and had higher Sepsis-related Organ Failure Assessment scores. In multivariate regression analysis, high CL_{Cr} and male sex independently predicted the presence of insufficient vancomycin concentrations on Days 1 and 2 of therapy. Receiver operating characteristic curve analysis for CL_{Cr} showed an area under the concentration–time curve of 0.75 (95% confidence interval 0.69–0.81) to predict insufficient drug concentrations on Day 1 of therapy. A CL_{Cr} > 120 mL/min/1.73 m^2 had a sensitivity of 26%, a specificity of 94% and an 84% positive predictive value of 84% for vancomycin concentrations <20 μg/mL. In conclusion, approximately one-half of the septic Intensive Care Unit patients treated with continuous infusion of vancomycin at currently recommended doses had insufficient drug concentrations in the early phase of therapy. A high CL_{Cr} was the variable most strongly associated with insufficient drug concentrations.

1. Introduction

Sepsis is very common in patients admitted to the Intensive Care Unit (ICU) and remains a therapeutic challenge [1]. In addition to the in vitro susceptibility of the isolated strains and timely antibiotic administration [2], antimicrobial efficacy is dependent on the serum and tissue concentrations of the agent used [3]. Optimising antibiotic dosage regimens to achieve adequate antimicrobial concentrations may therefore reduce therapeutic failure [4].

Vancomycin is a glycopeptide drug active against a wide spectrum of Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci (CoNS) and *Enterococcus faecium*. Although some staphylococci and enterococci may be resistant to this drug, and alternative agents are available [5], vancomycin remains one of the first therapeutic options when these pathogens are suspected [6]. The most appropriate means of administering vancomycin, its optimal dose and the serum target concentration of the drug are still controversial [3]. Vancomycin can be administered as a 15 mg/kg intermittent infusion, twice daily, based on the patient's total body weight (TBW). Report of a higher proportion of failed vancomycin therapy in patients with MRSA infections with minimal inhibitory concentrations (MICs) > 1.5 μg/mL suggested the need for higher drug doses for these less susceptible pathogens [7]. Nevertheless, the efficacy of vancomycin is limited by poor penetration into solid organs, and simply increasing standard vancomycin doses may be associated with increased nephrotoxicity [8].

The ratio between the area under the concentration–time curve (AUC) and the MIC of the isolated strain is one of the most valuable pharmacokinetic parameters for predicting the outcome of staphylococcal infections treated with vancomycin [9]. One effective approach for maximising the antimicrobial activity of

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vancomycin is to use continuous infusions [10,11]. Although continuous infusion has not been shown to improve the clinical efficacy of vancomycin in MRSA infections compared with standard regimens, therapeutic ranges of drug concentrations can be achieved more rapidly with this strategy; use of continuous infusion may also facilitate dose adjustment and reduce variability in drug concentrations [12].

Sepsis can significantly alter the pharmacokinetics of antimicrobials, including increasing the volume of distribution (V_d), protein binding and drug clearance, thus resulting in insufficient drug concentrations when standard doses of antibiotics are administered [13]. Most data on continuous infusions of vancomycin have been published from studies in patients with severe MRSA infections, and the best regimen in critically ill septic patients still needs to be defined. The aims of this study were to evaluate: (i) vancomycin concentrations within the first 24–48 h of therapy in patients receiving continuous infusion; and (ii) the determinants of early insufficient vancomycin concentrations in this population.

2. Patients and methods

2.1. Patients and data collection

All adult patients treated with continuous infusion of vancomycin, either as monotherapy or combined with other antimicrobials, in the multidisciplinary Department of Intensive Care at Hôpital Erasme (Brussels, Belgium) over a 2-year period (2008–2009) were reviewed. The study was approved by the institutional Ethics Committee, which waived the need for informed consent. Patients were included in the analysis if they had: (i) a diagnosis of sepsis according to standard criteria [14]; (ii) daily drug monitoring; and (iii) TBW available in the medical file. Patients meeting the following criteria were excluded: (i) age <18 years; (ii) previous administration of vancomycin by intermittent infusion (within 48 h of the start of continuous infusion); (iii) chronic renal failure requiring dialysis; (iv) continuous renal replacement therapy; (v) duration of continuous infusion <48 h; and (vi) pregnancy, burns or cystic fibrosis (because of altered pharmacokinetics independent of the presence of sepsis). The study period was limited to the ICU stay. This cohort of patients has already been used in a previous publication for simulation of optimal vancomycin regimens in sepsis [15].

Patients who had received continuous infusion of vancomycin were identified from the patient data monitoring system (PDMS) (Picis Critical Care Manager; Picis Inc., Wakefield, MA). In all study patients, demographics, pre-existing chronic diseases, admission diagnosis, and biological and microbiological data were collected. The severity of illness of each patient was characterised using the Acute Physiology and Chronic Health Evaluation (APACHE) II score at inclusion [16] and the Sepsis-related Organ Failure Assessment (SOFA) score [17] determined on the first and second days of antibiotic treatment. Chronic renal insufficiency was defined as values of serum creatinine (S_{Cr}) > 2.0 mg/dL measured within 6 months from ICU admission. Creatinine clearance (CL_{Cr}) was obtained daily from 24-h urine collection as a routine procedure in the ICU and normalised to body surface area. Treatment of patients with catecholamines or mechanical ventilation was recorded as well as length of ICU stay and overall mortality.

2.2. Vancomycin treatment

Vancomycin (Vancocin®; Eli Lilly, Saint-Cloud, France) was reconstituted according to the manufacturer's guidelines. In Hôpital Erasme, continuous infusion is the standard mode of administration for vancomycin to ICU patients. The drug was prescribed to treat suspected or documented infections due to MRSA or other resistant Gram-positive cocci. The choice of antibiotic regimen was at the discretion of the clinician.

Serum concentrations of vancomycin were determined by particle-enhanced turbidimetric inhibition immunoassay (Dimension Xpand; Siemens Healthcare Diagnostics, Newark, DE). The limit of quantification and total imprecision of the assay were 0.8 μg/mL and <5%, respectively. Blood samples (3 mL) were taken every day at 08:00 am and were sent immediately to the central laboratory. A period of ≥16 h was allowed from the onset of continuous infusion before sampling. The exact sampling time was recorded by the nursing staff in the PDMS system.

Clinical trials in patients with severe MRSA infections have proposed a 15 mg/kg loading dose administered over 60–90 min (maximum rate, 1 g/h), followed by a 30 mg/kg daily dose calculated using TBW [11]. The aim of this regimen is to provide serum concentrations between 20 μg/mL and 30 μg/mL. If the serum vancomycin concentration was <20 μg/mL, an additional dose of 500 mg was given followed by an increase in the daily dose by 500–1000 mg. If the concentration was >30 μg/mL, continuous infusion was discontinued for ≥4 h and the daily dose was reduced by 500–1000 mg per day.

In the absence of a 24-h urine collection at the onset of therapy, the Cockroft–Gault formula was used to estimate CL_{Cr} (CG-CL_{Cr}) [18]; however, in patients with <0.5 mL/kg/h of urine output at the time of drug initiation, CL_{Cr} was considered to be <50 mL/min. For the first 24 h of treatment, in patients with CG-CL_{Cr} > 80 mL/min, the aforementioned dose, rounded off to multiples of 125 mg, was administered. In patients with CG-CL_{Cr} of 50–80 mL/min or <50 mL/min, the loading dose was unchanged but the daily dose was reduced to 20–30 mg/kg and 10–20 mg/kg, respectively. From the second day of treatment, daily doses were adapted according to serum concentrations as discussed earlier. The duration of vancomycin therapy was also recorded.

2.3. Definitions

Vancomycin concentrations were considered as 'adequate' at 20–30 μg/mL, 'insufficient' at <20 μg/mL and 'excessive' at >30 μg/mL. The early phase of treatment was considered as the first 2 days (<48 h) of drug administration. Augmented renal clearance (ARC) was defined as CL_{Cr} > 120 mL/min/1.73 m^2 [19].

2.4. Statistical analysis

Statistical analyses were performed using the SPSS 13.0 for Windows NT software package (SPSS Inc., Chicago, IL). Descriptive statistics were computed for all study variables. A Kolmogorov–Smirnov test was used, and histograms and normal quantile plots were examined to verify the normality of distribution of continuous variables. Discrete variables were expressed as counts (percentage), and continuous variables as mean ± standard deviation or median [interquartile range (IQR)]. Demographics and clinical differences between study groups were assessed using a χ^2 test, Fisher's exact test, Student's *t*-test or Mann–Whitney *U*-test, as appropriate. Multivariate logistic regression analyses with insufficient vancomycin concentrations on Days 1 and 2 of therapy as the dependent variables were conducted in all patients; only variables associated with a higher risk of inadequate concentrations ($P < 0.2$) on a univariate basis were introduced in the multivariate model. Collinearity between variables was excluded prior to modelling. Odds ratios with 95% confidence intervals (CIs) were computed. Variables considered in the analysis were demographic variables, co-morbidities, APACHE II score on admission, SOFA scores on Days 1 and 2, type of admission (medical or surgical), source of infection, mechanical ventilation, administration