Journal of Critical Care 29 (2014) 351–355

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Evaluation of a dosing regimen for continuous vancomycin infusion in critically ill patients: An observational study in intensive care unit patients ☆

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ARTICLE INFO

Keywords:
Vancomycin
Continuous infusion
Therapeutic drug monitoring
Critical care
Intensive care unit

ABSTRACT

Purpose: We aimed to evaluate a dosing algorithm for continuous vancomycin administration in intensive care unit patients.
Materials and Methods: This observational study was conducted in a medical intensive care unit (German university hospital; June 2012-February 2013). Following a loading dose of 20 mg per kg actual body weight, vancomycin was administered continuously (20 or 30 mg of vancomycin per kg actual body weight over 24 hours depending on renal function). The vancomycin infusion rate was adjusted to achieve a target serum vancomycin concentration of 20-30 mg/L.
Results: Vancomycin was administered for a median (interquartile range) of 7 (5-9) days. The median vancomycin dose given as an initial bolus was 1750 (1400-2000) mg. The median daily vancomycin dose ranged from 480 (180–960) mg (day 6) to 3.120 (2596-3980) mg (day 1). Altogether, the achieved median serum vancomycin concentration was 29.0 (25.2-33.2) mg/L. On treatment days 1 to 7, we observed target serum vancomycin levels (20-30 mg/L) in 48%, 39%, 33%, 26%, 43%, 57%, and 69% of patients. Supra-therapeutic serum vancomycin concentrations (>30 mg/L) were observed in 36%, 52%, 61%, 63%, 39%, 19%, and 15% of patients on treatment days 1 to 7.
Conclusions: The evaluated vancomycin dosing regimen for continuous infusion allowed rapid achievement of sufficient vancomycin serum levels. However, we frequently observed supra-therapeutic serum vancomycin concentrations in the first days of vancomycin treatment.

1. Introduction

Vancomycin is a glycopeptide antibiotic that is very widely used for the treatment of infections caused by gram-positive bacteria [1-3].

Regarding vancomycin treatment in critically ill patients, there is still a controversy about the best administration route of vancomycin (ie, intermittent vs continuous dosing of the antibiotic): On the one hand, in a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists it is stated that a beneficial impact of continuous vancomycin treatment on outcome when compared with intermittent infusion is unlikely [1]. Data showing that continuous vancomycin infusion improves patient outcome compared with intermittent infusion are only available for intensive care unit (ICU) patients with ventilator-associated pneumonia caused by methicillin-resistant *Staphylococcus aureus* [4]. On the other hand, continuous administration of vancomycin instead of intermittent infusion of the drug has repeatedly been suggested, especially in ICU patients [5-13]. The physiologic rationale for continuous vancomycin infusion instead of intermittent administration is that the bactericidal activity of vancomycin is time-dependent [1,11]. The pharmacokinetic variable best reflecting vancomycin efficacy is the ratio between the area under the drug concentration time curve and the minimum inhibitory concentration of the bacterial pathogen [1,10,11].

Regarding continuous vancomycin administration in critically ill patients, different dosing regimens have been proposed in previous studies [6,7,10,11,14]. Some of these studies demonstrated that high doses of vancomycin are needed in this group of patients to achieve therapeutic serum concentrations [7,10,11,14]. This might be due to an increased volume of distribution associated with vascular permeability (eg, in patients with sepsis) [15,16]. Based on the results of previous studies proposing different dosing regimens [10,11,14], we developed a modified dosing scheme for continuous vancomycin infusion in medical ICU patients. The aim of this observational study

☆ Conflict of interest: All authors have no conflict of interest to declare.

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http://dx.doi.org/10.1016/j.jcrc.2013.12.007

performed under clinical routine conditions was to evaluate the clinical applicability and efficacy regarding achievement of target vancomycin serum levels of this new dosing algorithm for continuous vancomycin administration in unselected medical ICU patients.

2. Materials and methods

2.1. Study design, setting, and study protocol

After institutional review board approval, this observational study was conducted in a medical ICU of a German university hospital between June 2012 and February 2013. The need for informed consent was waived by the institutional review board.

The standard route for the administration of vancomycin in our ICU is a continuous infusion of the antibiotic with a daily adjustment of the administered dose according to the serum vancomycin concentration. According to the study protocol, all patients receiving a vancomycin bolus followed by continuous infusion of vancomycin in accordance with the dosing regimen described in detail below were eligible for study enrollment. The decision to use vancomycin for the treatment of suspected or proven infection with gram-positive bacteria was at the discretion of the treating ICU physicians. In the patients enrolled in the study, infused vancomycin doses and serum vancomycin concentrations were recorded daily from the medical ICU records and the electronic patient database. In addition, clinical characteristics were documented.

2.2. Patients

During the study period, 34 patients were treated with continuous vancomycin infusion according to the dosing algorithm we aimed to evaluate. The characteristics of these patients are presented in Table 1.

2.3. Dosing regimen for continuous vancomycin administration

In this study, we used a modified vancomycin dosing regimen similar to the one previously described by Ocampos-Martinez et al [10].

Table 1
Patients' characteristics

	Patients (n = 34)
Demographic data	
Sex (male), n (%)	21 (62)
Age, years	62 (49-71)
Height, cm	173 (165-181)
Actual body weight, kg	88 (79-100)
Body mass index, kg/m^2	28 (25-38)
Body surface area, m^2	2.02 (1.85-2.15)
Reason for intensive care unit admission	
Sepsis, n (%)	15 (44)
Cirrhosis of the liver and associated complications, n (%)	4 (12)
Acute respiratory insufficiency, n (%)	4 (12)
Gastrointestinal bleeding, n (%)	3 (9)
Acute pancreatitis, n (%)	2 (6)
Acute liver failure, n (%)	2 (6)
other, n (%)	4 (12)
Clinical characteristics (when vancomycin was started)	
Mechanical ventilation, n (%)	26 (76)
Norepinephrine/epinephrine therapy, n (%)	28 (82)
Acute Physiology and Chronic Health Evaluation II score, points	30 (21–36)
Simplified Acute Physiology Score II, points	52 (40–68)
Sequential Organ Failure Assessment score, points	13 (10–16)
Multiple organ dysfunction score, points	11 (7–12)
Therapeutic Intervention Scoring System, points	18 (18–23)
Outcome	
Intensive care unit mortality, n (%)	15 (44)
Hospital mortality, n (%)	20 (59)

Data are presented as absolute frequencies and percentages for qualitative parameters or as median and interquartile range for continuous parameters. Percentages may not sum up to 100% because of rounding.

A loading dose of 20 mg of vancomycin per kg actual body weight (maximum dose of 2000 mg of vancomycin) was initially given over 180 minutes independent from renal function (Fig. 1). Following this loading dose, we continuously infused 30 mg of vancomycin per kg actual body weight over 24 hours (maximum dose 3000 mg of vancomycin over 24 hours) in patients without renal insufficiency. In patients with renal impairment, this dose was reduced to 20 mg of vancomycin per kg actual body weight over 24 hours with a maximum dose of 2000 mg of vancomycin over 24 hours. It was at the discretion of the ICU physician starting vancomycin therapy to assume the presence of renal impairment based on a individual patient's creatinine level, urine production, and the need for renal replacement therapy. During vancomycin treatment, vancomycin infusion rates were adjusted by the treating ICU physicians in order to achieve a target serum vancomycin concentration of 20 to 30 mg/L as follows: When the serum vancomycin concentration was in a subtherapeutic range (<20 mg/L), we administered a vancomycin bolus of 500 mg and additionally increased the vancomycin dose given over 24 hours by 500 mg. In patients with a serum vancomycin concentration of >30 mg/L, we discontinued the vancomycin infusion for 4 hours and additionally reduced the vancomycin dose given over 24 hours by 500 mg. If we observed a serum vancomycin concentration of >40 mg/L we discontinued the vancomycin infusion for 12 hours and additionally reduced the vancomycin dose given over 24 hours by 1000 mg.

According to our ICU standard, serum vancomycin concentrations should be determined every day during vancomycin treatment. In some patients, serum vancomycin concentration values were missing on single days as indicated in the results section.

2.4. Statistical analysis

We used IBM SPSS Statistics version 21 (SPSS Inc, Chicago, IL) for the statistical analyses in this study. For continuous parameters, we calculated the median and interquartile ranges (ie, 25%-75% percentile range). To describe qualitative parameters we present absolute frequencies and percentages. All statistical tests were conducted two-sided and $P < .05$ was used to define statistical significance.

3. Results

3.1. Adherence to study protocol

This observational study was performed under routine clinical conditions in a medical ICU. Determinations of vancomycin serum concentrations were performed in 74% of patients on vancomycin treatment day 1 (day 2: 91%, day 3: 97%, day 4: 87%, day 5: 85%, day 6: 91%, day 7: 72%) (Table 2). Regarding the adequate adaption of the vancomycin dose according to the study protocol considering the serum vancomycin concentration, overall adherence to the study protocol was 82% (ie, in 18% of all single decisions regarding daily adjustment of the vancomycin dose the ICU physician in charge did not adhere to the dose adaption algorithm).

3.2. Vancomycin therapy

Vancomycin was administered for a median of 7 (5-9) days in the patients reported in this study. The median vancomycin dose given as an initial bolus when vancomycin therapy was started was 1750 (1400-2000) mg. For vancomycin treatment days 1 to 7, the median total vancomycin doses that were administered over 24 hours are shown separately for each day in Table 2.

3.3. Serum vancomycin concentrations

In this study a median of 0.9 (0.8-1.0) serum vancomycin concentrations were performed per vancomycin treatment day.