International Journal of Antimicrobial Agents 41 (2013) 434–438

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Factors associated with inadequate early vancomycin levels in critically ill patients treated with continuous infusion

J.J. De Waele[a,*], I. Danneels[b], P. Depuydt[a], J. Decruyenaere[a], M. Bourgeois[c], E. Hoste[a]

[a] Department of Critical Care Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium
[b] Department of Anesthesia, AZ St Lucas, Bruges, Belgium
[c] Department of Anesthesia, AZ St Jan, Bruges, Belgium

ARTICLE INFO

Article history:
Received 17 September 2012
Accepted 21 December 2012

Keywords:
Vancomycin
Continuous infusion
Therapeutic drug monitoring

ABSTRACT

Vancomycin administration using a loading dose and continuous infusion (CI) results in more rapid attainment of adequate concentrations. The aim of this retrospective study of ICU patients receiving vancomycin was to determine the efficacy of a vancomycin dosing protocol using a weight-based loading dose and to identify factors associated with inadequate concentrations. Patients received a loading dose (<65 kg, 1000 mg; ≥65 kg, 1500 mg), and 2000 mg/24 h CI with subsequent dose adaptation. Adequate levels were defined as concentrations ≥15 mg/L. In total, 227 patients (154 males) were included in the study (mean age 56.5 ± 16.1 years; mean APACHE II score 19.30 ± 7.7). The mean loading dose was 1129 ± 369 mg (15.07 ± 4.99 mg/kg). The dosing protocol was applied in 126 patients (55.5%). Mean vancomycin levels were 19.32 mg/L and 21.08 mg/L on Days 2 and 3, respectively. Vancomycin levels on Day 2 were adequate in 70.5% of patients, increasing to 84.1% on Day 3. Patients who received an appropriate loading dose more often had adequate vancomycin levels on Day 2. Older age, female sex, higher creatinine concentration, lower body temperature and use of a loading dose according to the vancomycin dosing protocol were independently associated with adequate vancomycin levels. A weight-based loading dose plus CI of vancomycin resulted in adequate concentrations in most patients and was superior compared with a non-standardised loading dose. Some patients may require higher doses, and factors other than weight, such as kidney function, age and sex, play a role.

1. Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) has become a significant cause of nosocomial, and to a lesser extent community-acquired, infections [1]. Although several new antibiotics have been introduced that cover MRSA, vancomycin remains an important treatment option [2]. Intermittent infusion (II) has been the sole method of administration for many years, but initial bolus dosing followed by continuous infusion (CI) is increasingly being used [3]. As for other infections, early adequate antimicrobial therapy against MRSA infections is essential, and reaching an adequate serum concentration is important both for II and CI regimens.

When using CI, a loading dose is an essential component to achieve therapeutic concentrations rapidly, but in critically ill patients the pharmacokinetics of vancomycin is highly variable [4]. Several studies have found that vancomycin concentrations are often too low, and various nomograms and models have been proposed to overcome this issue [5]. Overall, a common recommendation is that critically ill patients without kidney dysfunction require higher daily doses to reach adequate concentrations [6,7].

Owing to an increased volume of distribution, higher loading doses are also probably required. Mohammedi et al. found that 500 mg is inadequate and recommended higher doses based on the weight of the patient [8]. Based on these findings, a vancomycin dosing protocol consisting of a standardised loading dose (1000 mg for patients with a total body weight <65 kg, and 1500 mg for patients with a total body weight ≥65 kg) followed by CI of vancomycin was introduced in the Department of Critical Care Medicine of Ghent University Hospital (Gent, Belgium). Recent data suggest that a more sophisticated approach using a loading dose of up to 35 mg/kg total body weight results in higher target attainment rates [7]. As there may be risks associated with the resulting higher vancomycin concentrations, such as nephrotoxicity [9,10], we wanted to evaluate the dosing protocol used in this unit before considering using these higher loading doses.

Therefore, the aim of this study was: (i) to study the efficacy of the vancomycin dosing protocol in obtaining early (<48 h) adequate

* Corresponding author. Tel.: +32 93 32 62 19; fax: +32 93 32 49 95.
E-mail address: Jan.DeWaele@UGent.be (J.J. De Waele).

0924-8579/$ – see front matter
http://dx.doi.org/10.1016/j.ijantimicag.2012.12.015

serum levels using a weight-based loading dose followed by CI; and (ii) to identify factors associated with early inadequate vancomycin levels in critically ill patients.

2. Methods

2.1. Study design

This retrospective study included all patients admitted to one of the intensive care units (ICUs) of the Department of Critical Care Medicine of Ghent University Hospital from September 2003 until December 2008 who were treated with CI of vancomycin. Paediatric patients, patients in whom the treatment was initiated elsewhere, and patients without sufficient data or who were treated for <48 h were excluded from the study.

Patient data were retrieved from the patient data management system (PDMS) and included age, sex, weight, height, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, admitting type of ICU (medical, surgical or cardiac surgery), morbidity at the start of vancomycin (need for mechanical ventilation, use of vasopressors, need for renal replacement therapy, serum creatinine concentration, maximum temperature and C-reactive protein level), fluid balance during the first day of vancomycin administration, and outcome. Details on vancomycin administration during the first 3 days as well as vancomycin serum levels were also retrieved from the electronic patient records. Data were anonymised and downloaded as an electronic file for further analysis.

A waiver of consent was granted by the ethics committee as this was a retrospective analysis of anonymous patient data.

2.2. Vancomycin administration and protocol

The vancomycin dosing protocol used throughout the study period consisted of a loading dose of 1000 mg for patients with a body weight <65 kg, and 1500 mg for patients with a body weight ≥65 kg. Following administration of the loading dose, CI of 2000 mg/24 h was started.

Target levels for vancomycin were 15–25 mg/L based on the assumption that a steady-state 24-h area under the concentration–time curve divided by the minimum inhibitory concentration ratio ($AUC_{24\,h}$/MIC) of ≥350 is associated with increased clinical success [11]. Vancomycin levels are routinely sampled at 06:00 h each day and the dose adapted in the next 6 h. If the drug concentration was too low, the maintenance dose was increased by 500 mg per day until target levels were reached.

Application of the vancomycin dosing protocol in the individual patient was decided by the attending physician.

2.3. Definitions and data analysis

Protocol adherence was defined as administration of the correct loading dose according to the above protocol and subsequent start of CI at the pre-defined dose.

Adequate vancomycin levels were defined as vancomycin levels of ≥15 mg/L. Patients with adequate vancomycin concentrations on Day 2 were compared with patients with inadequate targets.

2.4. Statistical analysis

Continuous variables are presented as mean (± standard deviation). For comparative tests on continuous variables, the Mann–Whitney *U*-test and *t*-test were used as appropriate, depending on variable distribution. For categorical variables, the Pearson χ^2 test or the Fisher's exact test were used as appropriate. Statistical analysis was done using IBM SPSS Statistics 19.0 (SPSS Inc., Chicago, IL). All tests were two-tailed and statistical significance was defined as $P < 0.05$.

Parameters found to be different in the two groups in the univariate analysis with a *P*-value of ≤0.10 were entered in a logistic regression model with early (<48 h) adequate vancomycin level as the dependent variable. The model was tested for correlations and interactions, and goodness of fit was evaluated by the Hosmer–Lemeshow test and receiver operator characteristic (ROC) curve analysis. A ROC curve was constructed to assess the discriminative power of this model in predicting early adequate vancomycin levels.

3. Results

3.1. Patient population

Data on 325 patients were extracted from the PDMS; 98 patients were excluded from the analysis, including 8 paediatric patients, 23 patients who were treated with II, 52 patients because the therapy was initiated on another ward and 15 because of insufficient data (5 with no data on vancomycin levels within first 72 h and 10 with no weight recorded). Thus, 227 patients who received a loading dose and CI of vancomycin with levels available within 72 h of the start of therapy were available for analysis.

The mean age of the patients was 56.5 ± 16.1 years and 154 (67.8%) were male. The mean APACHE II score on admission to the ICU was 19.30 ± 7.7; 172 patients (75.8%) were mechanically ventilated at the time of initiation of vancomycin, 111 (48.9%) received vasoactive drugs, and the mean serum creatinine was 0.86 ± 0.70 mg/dL.

3.2. Vancomycin dosing and protocol adherence

The vancomycin dosing protocol was correctly applied in 126 patients (55.5%); in 98 patients the loading dose was too low compared with the vancomycin dosing protocol and in 3 patients it was too high. Patients in whom the vancomycin dosing protocol was applied correctly received significantly higher loading doses of vancomycin (18.31 ± 2.73 mg/kg vs. 10.80 ± 4.00 mg/kg; $P < 0.001$). Patients who were administered a lower loading dose than advised in the protocol had a higher serum creatinine and more were treated with renal replacement therapy compared with patients who received the correct or higher loading dose. Otherwise, both groups were comparable (Table 1).

3.3. Vancomycin serum levels

Mean vancomycin levels obtained in the study group were 19.32 ± 6.12 mg/L on Day 2 and 21.08 ± 7.11 on Day 3.

Vancomycin levels on Day 2 were adequate in 70.5% of the patients, increasing to 84.1% on Day 3; levels of ≥20 mg/L were obtained in only 44.3% and 55.7% of patients on Days 2 and 3, respectively. On Days 2 and 3, 12.9% and 20.7% of the patients, respectively, had levels of ≥25 mg/L.

Although vancomycin serum levels obtained were not statistically different in patients receiving a loading dose lower than described in the vancomycin dosing protocol, the percentage of early (<48 h) target attainment (both using 15 mg/L and 20 mg/L as targets) was higher in patients who received a loading dose according to the protocol (Table 1).

Patients received a mean loading dose of 1129 ± 369 mg, corresponding to 15.07 ± 4.99 mg/kg. Patients who received an effective loading dose >15 mg/kg, irrespective of the application of the vancomycin dosing protocol, had higher target attainment rates on