International Journal of Antimicrobial Agents 41 (2013) 261–266

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

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

Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy

Cecilia Covajes[a], Sabino Scolletta[a], Laura Penaccini[a], Eva Ocampos-Martinez[a], Ali Abdelhadii[a], Marjorie Beumier[a], Frédérique Jacobs[b], Daniel de Backer[a], Jean-Louis Vincent[a], Fabio Silvio Taccone[a,*]

[a] Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles (ULB), Route de Lennik 808, 1070 Brussels, Belgium
[b] Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles (ULB), Route de Lennik 808, 1070 Brussels, Belgium

ARTICLE INFO

Article history:
Received 29 August 2012
Accepted 29 October 2012

Keywords:
Vancomycin
Continuous infusion
Continuous renal replacement therapy
Renal failure
Pharmacokinetic
Sepsis

ABSTRACT

Vancomycin is frequently administered as a continuous infusion to treat severe infections caused by Gram-positive bacteria. Previous studies have suggested a loading dose of 15 mg/kg followed by continuous infusion of 30 mg/kg in patients with normal renal function; however, there are no dosing recommendations in patients with renal failure undergoing continuous renal replacement therapy (CRRT). Data from all adult septic patients admitted to a Department of Intensive Care over a 3-year period in whom vancomycin was given as a continuous infusion were reviewed. Patients were included if they received vancomycin for ≥48 h during CRRT. Vancomycin levels were obtained daily. During the study period, 85 patients (56 male; mean age 65 ± 15 years; weight 85 ± 24 kg) met the inclusion criteria. Median (interquartile range) APACHE II and SOFA scores were 24 (20–29) and 11 (7–14), respectively, and the overall mortality rate was 59%. Mean vancomycin doses were 16.4 ± 6.4 (loading dose), 23.5 ± 8.1 (Day 1), 23.2 ± 7.4 (Day 2) and 23.3 ± 11.0 (Day 3) mg/kg, resulting in blood concentrations of 24.7 ± 9.0 (Day 1), 26.0 ± 8.1 (Day 2) and 27.7 ± 9.3 (Day 3) μg/mL. On Day 1, 43 patients (51%) had adequate drug concentrations (20–30 μg/mL), 17 (20%) had levels >30 μg/mL and 25 (29%) had levels <20 μg/mL. Most patients with adequate drug concentrations received a daily dose of 16–35 mg/kg. The intensity of CRRT directly influenced vancomycin concentrations on Day 1 of therapy.

1. Introduction

Vancomycin remains one of the first options for treating nosocomial infections caused by meticillin-resistant *Staphylococcus aureus* (MRSA) or other resistant Gram-positive bacteria such as coagulase-negative staphylococci (CoNS) and ampicillin-resistant enterococci [1]. Nevertheless, several studies have shown that current dosing regimens are not adequate to produce clinical efficacy against more resistant strains of MRSA, especially those with a minimum inhibitory concentration for the drug of >1 μg/mL [2]. These regimens would also produce inadequate drug concentrations in pulmonary tissue when treating lung infections caused by less susceptible staphylococci [3].

Moreover, recommended drug dosages were derived from studies on healthy volunteers or patients with uncomplicated infections, so that it is difficult to extrapolate these data to the critically ill population [4]. In particular, sepsis can significantly alter the pharmacokinetics of vancomycin, inducing an increase in the volume of distribution and altered drug metabolism and clearance, which may result in subtherapeutic antibiotic concentrations [5].

The need for higher-dose vancomycin regimens has been shown in clinical trials on critically ill patients with head trauma and sepsis [6]. In this setting, continuous infusion of vancomycin may provide an alternative mode of drug administration to treat severe MRSA infections [5]. In a randomised clinical trial, patients receiving continuous infusions of vancomycin achieved optimal drug concentrations faster with a lower daily dose and lower treatment costs than those receiving standard intermittent infusions, although with similar efficacy and tolerance [7]. The authors of this study suggested a loading dose of 15 mg/kg followed by continuous infusion of 30 mg/kg in patients with normal renal function [7]. However, this strategy has not been validated in the setting of acute kidney injury (AKI), which is associated with reduced drug clearance and an increased risk of accumulation and toxicity [8].

Continuous renal replacement therapy (CRRT) is increasingly being used to manage patients with AKI [9]. However, CRRT can further complicate the pharmacokinetics of antimicrobials depending on the duration, membrane permeability and type of CRRT technique that is used [10]. Although high-dose vancomycin regimens may increase the risk of additional renal damage in patients with AKI, this treatment is frequently used in patients receiving CRRT;

* Corresponding author. Tel.: +32 2 555 5587; fax: +32 2 555 4698.
E-mail address: ftaccone@ulb.ac.be (F.S. Taccone).

0924-8579/$ – see front matter © 2012 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
http://dx.doi.org/10.1016/j.ijantimicag.2012.10.018

however, few studies have reported removal rates for vancomycin during CRRT [10–13]. Accordingly, the vancomycin dose interval should be prolonged compared with patients with normal renal function, and doses increased to 500–1000 mg twice a day [8]. No study has evaluated drug concentrations during continuous vancomycin infusion in critically ill patients undergoing CRRT. The aim of this study was therefore to evaluate continuous vancomycin infusion regimens in a large cohort of septic patients treated with CRRT.

2. Methods

The medical charts of all adult patients who were treated with a continuous infusion of vancomycin, either as monotherapy or combined with other antimicrobials, in the multidisciplinary 35-bed Department of Intensive Care of Erasme Hospital (Brussels, Belgium) over a 3-year period (January 2008 to December 2010) were reviewed. Patients were identified from the patient data monitoring system (PDMS) (Picis Critical Care Manager; Picis Inc., Wakefield, MA).

Patients were included in the study if they met the following criteria: (a) age >18 years; (b) had sepsis according to standard criteria [14]; (c) had received vancomycin for ≥48 h; (d) were concomitantly treated with CRRT; and (e) had daily measurement of vancomycin levels. Patients with previous administration of vancomycin by intermittent infusion (within 48 h of the start of the continuous infusion) were excluded, as were those with residual urine output >500 mL/day, pregnancy, burns or cystic fibrosis. No patient included in a previous publication [15] was included in the present cohort. The study was approved by the Ethics Committee of Erasme Hospital, which waived the need for informed consent.

The following data were collected for all patients: demographics; pre-existing chronic diseases; admission diagnosis; and microbiological findings. The severity of illness of each patient was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score [16] on admission and the Sequential Organ Failure Assessment (SOFA) score [17] at the onset of therapy. Use of vasopressor agents or mechanical ventilation was recorded, as was the length of Intensive Care Unit (ICU) stay and outcome.

Vancomycin (Vancocin®; Eli Lilly, Saint-Cloud, France) was reconstituted according to the manufacturer's guidelines. In patients undergoing CRRT, the loading dose of vancomycin was 15 mg/kg based on total body weight, and the daily dose was 20–30 mg/kg, adjusted to provide serum concentrations of 20–30 μg/mL (considered as 'adequate'). If the serum vancomycin concentration was <20 μg/mL ('insufficient'), an additional dose of 500–1000 mg was given followed by an increase in the daily dose by 500–1000 mg. If the concentration was >30 μg/mL ('excessive'), the continuous infusion was discontinued for 4–8 h and the daily dose was reduced by 500–1000 mg/day.

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

The decision to initiate CRRT was made according to standard practice, and CRRT was performed through a double-lumen catheter inserted into the subclavian, femoral or internal jugular vein. Continuous venovenous haemodiafiltration (CVVHDF) or continuous venovenous haemofiltration (CVVHF) was performed using a Prisma® or PrismaFlex® machine (Gambro Hospal, Bologna, Italy), with polyacrylonitrile (AN69; Hospal, Meyzieu, France) or polysulfone (Gambro Lundia AB, Lund, Sweden) haemofilters.

Table 1
Characteristics of the patients ($n = 85$).

Characteristic	Data [a]
Age (years)	65 ± 15
Male/female	56/29
Body weight (kg)	85 ± 24
Pre-existing chronic diseases	
COPD, asthma	19 (22)
Hypertension	20 (24)
Cardiopathy	42 (49)
Diabetes	23 (27)
Liver cirrhosis	12 (14)
Cancer	13 (15)
Immunosuppressive therapy	22 (26)
Thromboembolic disease	4 (5)
Medical admission	59 (69)
APACHE II score on ICU admission	24 [20–29]
SOFA score at the onset of therapy	11 [7–14]
Septic shock	70 (82)
Mechanical ventilation	71 (84)
ICU stay (days)	12 [6–20]
ICU mortality	50 (59)

COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment.

[a] Data are expressed as n (%), mean ± standard deviation, or median [interquartile range].

Anticoagulation was obtained using continuous infusion of either heparin or citrate. Characteristics of the CRRT, including blood flow, ultrafiltration and dialysate rates, were recorded for each patient. The intensity of CRRT was assessed using the formula: ultrafiltration rate (mL/kg/h) + dialysate rate (mL/kg/h). Patients were a priori divided into four groups according to the intensity of CRRT (<20, 20–30, 31–40 and >40 mL/kg/h).

Statistical analyses were performed using SPSS 18.0 for Windows (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. 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. One-way analysis of variance (ANOVA) with a Dunn's test was used to compare different groups of CRRT intensity. Multivariate logistic regression analysis with vancomycin concentrations on Day 1 as the dependent variable was conducted; drug levels on Day 1 of therapy were selected because they represent the combination of the effects of loading and daily doses as well as CRRT intensity, whereas drug concentrations thereafter would also be influenced by dosing adaption by the attending physician. Only variables showing a significant association ($P < 0.2$) with vancomycin concentrations in the univariate analysis were introduced in the multivariate model. Collinearity between variables was excluded prior to modelling. Variables considered in the analysis were demographics, co-morbidities, APACHE II and SOFA scores, presence of bacteraemia, type of admission (medical or surgical), loading and daily dose of vancomycin, mechanical ventilation, administration of vasopressor agents, and CRRT blood flow and intensity. Discrete variables are expressed as number (%) and continuous variables as mean ± standard deviation or median (interquartile range). A P-value of <0.05 was considered statistically significant.

3. Results

In total, 85 patients met the inclusion criteria during the study period and their characteristics are shown in Table 1. A Gram-positive pathogen was identified in 47 patients (55%), including meticillin-sensitive *S. aureus* in 7 patients, MRSA in 12 patients,

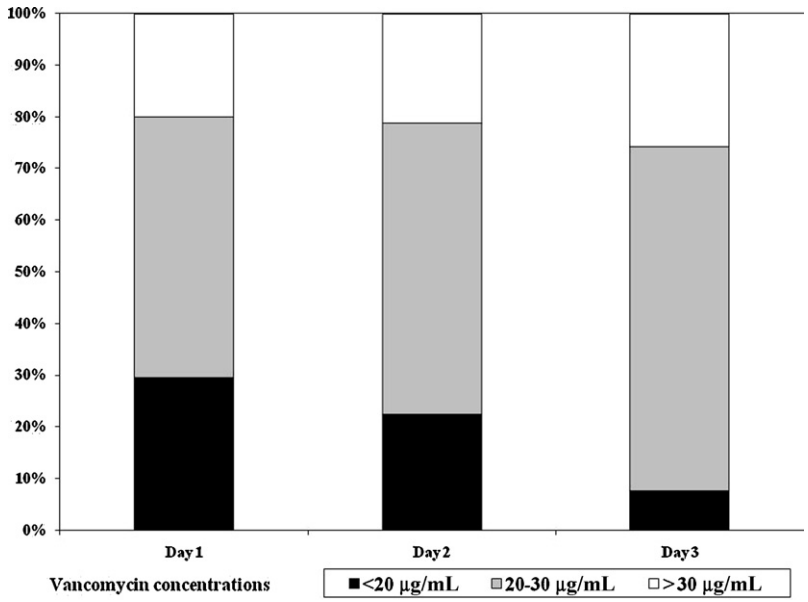

Fig. 1. Proportion of patients with inadequate (<20 μg/mL), adequate (20–30 μg/mL) and excessive (>30 μg/mL) vancomycin concentrations on the first 3 days of therapy.

CoNS in 18 patients and *Enterococcus* spp. in 10 patients. The most common sites of infection were the lung ($n = 39$) and abdomen ($n = 27$); 28 patients (33%) had concomitant bacteraemia. The characteristics of CRRT are shown in Table 2. The median intensity of CRRT was 28 (21–40), 29 (18–41) and 25 (18–39) mL/kg/h on Days 1, 2 and 3, respectively.

The mean loading and daily doses of vancomycin during the first 3 days of therapy are shown in Table 3. Mean drug concentrations were 24.7 ± 9.0, 26.0 ± 8.1 and 27.7 ± 9.3 μg/mL on Days 1, 2 and 3, respectively. Overall, vancomycin concentrations were adequate in 43/85 patients (51%) on Day 1, 48/85 (56%) on Day 2 and 44/66 (67%) on Day 3 (Fig. 1). In addition, 17/85 patients (20%) had vancomycin concentrations >30 μg/mL on Day 1 (range 31–49 μg/mL), 18/85 (21%) on Day 2 (31–51 μg/mL) and 17/66 (26%) on Day 3 (32–49 μg/mL). The proportion of patients with insufficient drug concentrations (<20 μg/mL) decreased significantly from 29% on Day 1 to 22% and 8% on Days 2 and 3, respectively ($P = 0.04$). The proportion of patients with adequate drug concentrations on Day 1 was 27% with a daily vancomycin dose ≤15 mg/kg, 60% with a dose of 16–20 mg/kg, 50% with a dose of 21–25 mg/kg, 55% with a dose of 26–35 mg/kg and 50% with a dose >35 mg/kg (Fig. 2). The proportion of patients with vancomycin concentrations >30 μg/mL increased significantly from 6% with a daily dose ≤15 mg/kg to 20% with a dose of 16–20 mg/kg, 23% with a dose of 21–25 mg/kg,

Table 2
Characteristics of continuous renal replacement therapy.

Characteristic	Median [IQR] [a]
CVVHF/CVVHDF on Day 1 (n)	43/42
Blood flow (mL/min)	
$n = 85$, Day 1	150 [130–150]
$n = 85$, Day 2	150 [130–150]
$n = 66$, Day 3	150 [130–150]
Ultrafiltrate (mL/kg/h)	
$n = 85$, Day 1	21 [17–25]
$n = 85$, Day 2	20 [15–25]
$n = 66$, Day 3	22 [18–29]
Dialysate rate (mL/kg/h)	
$n = 42$, Day 1	19 [15–23]
$n = 44$, Day 2	21 [18–24]
$n = 17$, Day 3	20 [19–23]
Fluid removal (mL/day)	
$n = 36$, Day 1	1100 [650–1800]
$n = 16$, Day 2	300 [200–462]
$n = 19$, Day 3	250 [200–400]

IQR, interquartile range; CVVHF, continuous venovenous haemofiltration; CVVHDF, continuous venovenous haemodiafiltration.
[a] Data are expressed as median (IQR) unless otherwise stated.

Table 3
Characteristics of vancomycin therapy ($n = 85$).

Characteristic	Data [a]
Duration of therapy (days)	4 [3–7]
Dose (mg/kg)	
Loading dose	16.4 ± 6.4
Day 1	23.5 ± 8.1
Day 2	23.2 ± 7.4
Day 3	23.3 ± 11.0
Vancomycin concentration (μg/mL)	
Day 1	24.7 ± 9.0
Day 2	26.0 ± 8.1
Day 3	27.7 ± 9.3
Delay to target concentrations (days)	1 [1–2]

[a] Data are expressed as median [interquartile range] or mean ± standard deviation.

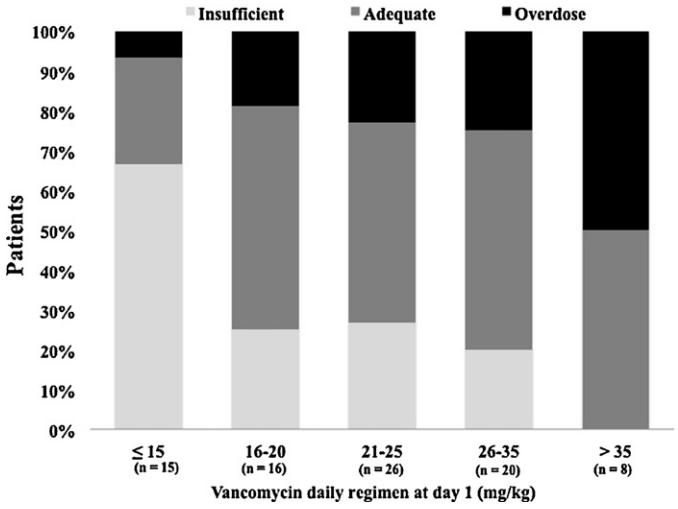

Fig. 2. Proportion of patients with inadequate (<20 μg/mL), adequate (20–30 μg/mL) and excessive (>30 μg/mL) vancomycin concentrations on the first day of therapy according to the daily vancomycin regimen (mg/kg).

Table 4
Evolution of vancomycin concentrations and daily doses over the first 3 days of continuous renal replacement therapy (CRRT), according to CRRT intensity.

CRRT intensity (mL/kg/h)	Vancomycin concentration (μg/mL)[a]			Vancomycin daily dose (mg/kg)[a]		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
<20	25 [19–27] (*n* = 21)	26 [23–30] (*n* = 25)	27 [24–33] (*n* = 23)	17 [12–24] (*n* = 21)	20 [13–24] (*n* = 25)	19 [17–24] (*n* = 23)
20–30	23 [18–32] (*n* = 26)	25 [21–30] (*n* = 19)	26 [21–31] (*n* = 16)	23 [18–30] (*n* = 26)	22 [18–29] (*n* = 19)	24 [21–25] (*n* = 16)
31–40	22 [20–27] (*n* = 20)	23 [18–28] (*n* = 19)	25 [25–31] (*n* = 15)	25 [20–30] (*n* = 20)	25 [20–27] (*n* = 19)	25 [20–32] (*n* = 15)
>40	22 [17–26] (*n* = 18)	24 [21–36] (*n* = 22)	25 [23–33] (*n* = 12)	28 [24–31] (*n* = 18)	25 [22–32] (*n* = 22)	25 [21–35] (*n* = 12)

[a] Data are expressed as median [interquartile range].

25% with a dose of 26–35 mg/kg and 50% with a dose >35 mg/kg ($P = 0.02$).

After similar loading doses, higher daily doses were needed in patients with the largest CRRT intensity (>40 mL/kg/h) than in other patients ($P < 0.05$) (Table 4; Fig. 3). In the multivariate analysis, age and daily vancomycin doses were significantly associated with higher drug concentrations on Day 1, whereas greater CRRT intensity was independently associated with lower vancomycin levels on Day 1 of therapy (Table 5).

4. Discussion

This study showed that continuous infusion of vancomycin given during CRRT achieved adequate drug concentrations in most critically ill septic patients. Greater CRRT intensity was associated with an increased need for higher-dose vancomycin regimens in order to achieve adequate drug concentrations. Daily vancomycin dose and the intensity of CRRT were the main determinants of drug concentrations in the early phase of therapy.

The pharmacokinetic characteristics of vancomycin have been extensively studied in recent human investigations; because the drug is primarily excreted unchanged in the urine, dosage must be adapted in patients with impaired renal function to avoid drug accumulation [1]. Although results from clinical trials have suggested use of continuous vancomycin infusion regimens for patients without AKI [7], there are no clear recommendations on continuous infusion dosing for vancomycin during CRRT and regimens are adapted from conventional haemodialysis (HD) data.

During HD, vancomycin clearance is only minimally influenced by body weight, duration of dialysis, blood flow and dialysate rate, whereas marked differences have been shown if low- or high-permeability membranes are used [18]. Hence, a supplemental dose of the drug could be administered when a high-flux membrane is used, whereas once-weekly dosing is frequently sufficient in the case of low-flux devices [19]. Nevertheless, vancomycin dosing in HD cannot be extrapolated to CRRT because of the differences in filters, the continuous distribution of drug removal during CRRT, and the different techniques for performing CRRT; haemodiafiltration provides the most effective removal of drugs with high molecular weights [10].

Previous studies have shown that there are significant changes in vancomycin pharmacokinetics during critical illness and these changes are further enhanced if the drug is administered during CRRT [4,5]. The volume of distribution increased almost two-fold in CRRT patients compared with healthy volunteers with normal renal function [20,21], especially in the case of concomitant vasopressor therapy [22]. Furthermore, several studies have reported varying vancomycin clearance rates during CRRT. Macias et al. showed that nearly 50% of drug removal was attributed to CRRT, with residual renal function or non-renal elimination responsible for the remaining drug clearance [23]. In another study, almost 20% of the drug dose was eliminated by CRRT and an ultrafiltration rate of 800–1200 mL/h resulted in a vancomycin clearance rate of 0.73 ± 0.21 L/h [13]; the optimal vancomycin dose to maintain drug concentrations between 15 μg/mL and 20 μg/mL was 500–750 mg every 12 h (q12 h). Joy et al. [11] showed that for a blood flow of 100 mL/min and ultrafiltration rate of 500–1000 mL/h, drug clearance ranged from 0.28 L/h to 0.36 L/h and was independent of the type of membrane used. In another study, an ultrafiltration rate of 1600 mL/h gave a drug clearance of 1.3–1.4 L/h and the

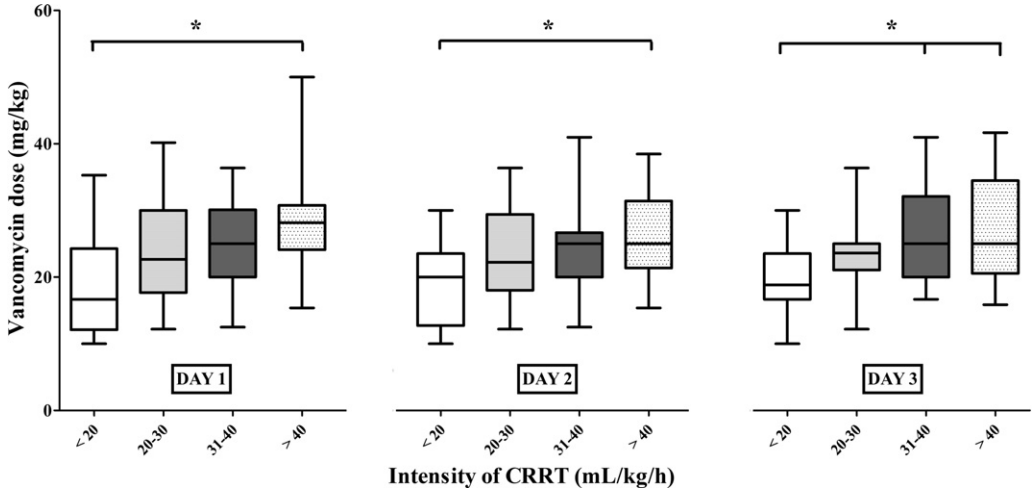

Fig. 3. Differences in required daily vancomycin dose according to different continuous renal replacement therapy (CRRT) intensities on the first 3 days of therapy.

Table 5
Determinants of vancomycin concentrations on Day 1 of therapy by univariate and multivariate backward logistic regression analysis.

Variable	Univariate analysis			Multivariate analysis		
	B factor	SE	*P*-value	*B* factor	SE	*P*-value
Age (years)	−0.135	0.063	0.03	−0.136	0.56	0.03
Male	−1.362	2.075	0.51			
Weight (kg)	0.024	0.041	0.55			
COPD/asthma	−0.792	2.366	0.74			
Hypertension	−3.328	2.297	0.15			
Cardiopathy	−1.696	1.964	0.39			
Diabetes	−3.866	2.180	0.08			
Cancer	4.354	2.699	0.11			
Liver cirrhosis	0.801	2.832	0.78			
Medical admission	2.280	2.242	0.31			
APACHE II score	0.008	0.134	0.95			
SOFA score	0.68	0.249	0.79			
Bacteraemia	−0.717	2.097	0.73			
Loading dose (mg/kg)	0.338	0.182	0.17			
Daily dose (mg/kg)	0.327	0.117	<0.01	0.491	0.113	0.006
Vasopressors	−1.732	2.581	0.50			
Mechanical ventilation	−0.917	2.658	0.73			
Blood flow (mL/min)	−0.51	0.48	0.29			
Intensity of CRRT (<20, 20–30, 31–40, >40 mL/kg/h)	−0.166	0.075	0.03	−0.274	0.071	0.007

SE, standard error; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy.

authors recommended that the first dose of vancomycin should be 15–20 mg/kg body weight followed by 250–500 mg q12 h starting 24 h after the first dose [24]. DelDot et al. [25] reported that for a vancomycin regimen of 750 mg q12 h and a CRRT intensity of 3000 mL/h, drug clearance was 1.8 L/h, which constituted 76% of the total drug clearance. The authors proposed a maintenance dose of 450 mg q12 h to achieve a target concentration of 15 μg/mL at steady state.

These studies show that although there is some non-renal clearance of vancomycin during CRRT, which may significantly affect drug elimination, characteristics of CRRT such as blood flow or dialysate rate may alter drug clearance thus increasing drug requirements. Most of these studies have limited statistical power because of small sample sizes or because they evaluated only specific CRRT conditions, e.g. pre-defined dialysate or ultrafiltrate rates, haemofilter type and only patients without residual renal function, limiting the generalisation of these results to general critically ill populations in whom CRRT is not standardised and may vary over time. Moreover, some of these studies used low-intensity CRRT techniques, which achieve lower drug clearance rates than currently used methods. The current study focused on a large cohort of patients with severe sepsis and septic shock with high mortality rates, a population in whom optimisation of antibiotic therapy is mandatory. In addition, a wide range of CRRT intensities and characteristics was analysed, and patients with minimal residual renal function were included. This study showed that a daily dose of 16–35 mg/kg was necessary to achieve adequate drug concentrations in >60% of patients. Nevertheless, in the early phase of treatment almost 20% of patients had insufficient vancomycin levels to treat less susceptible strains, such as MRSA, and 20% had concentrations above the drug threshold associated with the development of adverse events such as renal failure.

In this study, the intensity of CRRT influenced drug elimination. This observation may be explained by the hydrophilic composition of vancomycin, which influences the body's elimination of similar medications by purification devices [10]. Hence, CRRT characteristics should be taken into account when determining daily vancomycin dosages in order to avoid inadequate drug concentrations. This suggestion has already been made in another study, in which a change in CRRT intensity (i.e. from CVVHF to CVVHDF) increased drug clearance from 62% to 90%, whereas drug concentrations were only minimally affected by the type of membrane used during CRRT [11]. Similar findings have been shown for other hydrophilic β-lactams, with drug clearances significantly increased when higher dialysate rates were used [26]. Moreover, van de Vijsel et al. [20] recently showed that the ultrafiltrate rate was one of the most important determinants of vancomycin distribution volume in a cohort of 24 critically ill patients undergoing CRRT. Nevertheless, Roberts et al. recently reported that vancomycin concentrations were not affected by the intensity of CRRT [27]; however, these authors studied only 10 patients at different time points after the initiation of therapy, limiting the extrapolation of these data to larger ICU populations. Other factors, such as endogenous non-renal clearance and changes in volume of distribution over time, may also influence vancomycin concentrations during CRRT [27]. These observations support the importance of therapeutic drug monitoring in this population.

This study has some limitations. First, vancomycin data were analysed only during the first 3 days of therapy and this may not represent the steady state. However, it is of crucial importance that drug levels be optimised in the early phase of therapy [28]. Second, the target drug concentrations were between 20 μg/mL and 30 μg/mL to optimise the benefit/risk ratio, but others may use different targets [15]. Third, antibiotic removal through CRRT should be proportional to the concentration of unbound free drug. Berthoin et al. showed that total vancomycin concentration was not predictive of free drug concentration, suggesting that direct determination of the free component may be desirable [29]. Further studies are needed to explore this hypothesis, comparing both total and free vancomycin concentrations to drug removal during CRRT. Fourth, because of the retrospective nature of the study, it was not possible to correct drug prescription for delay and interruption of CRRT during therapy, which may have altered drug elimination. Fifth, no data on efficacy were collected, as this was not within the scope of this study. Finally, no optimal drug dosage can be proposed from this study; further studies are needed to provide some practical guidelines for drug dosage in this setting, taking into account the impact of CRRT intensity and pharmacokinetic alterations induced by sepsis.

5. Conclusions

Standard vancomycin doses of 16–35 mg/kg/day are adequate in most critically ill patients treated with a continuous infusion of

vancomycin during CRRT. However, drug prescription should take into account the intensity of CRRT.

Acknowledgments

The authors would like to thank the staff of the Department of Intensive Care (Erasme Hospital, Brussels, Belgium) for their support.

Funding: No funding sources.

Competing interests: None declared.

Ethical approval: The Ethics Committee of Erasme Hospital (Brussels, Belgium) approved the present protocol and waived the consent from patients because of its retrospective nature.

References

[1] Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 2009;49:325–7.

[2] van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis 2012;54:755–71.

[3] Cruciani M, Gatti G, Lazzarini L, Furlan G, Broccali G, Malena M, et al. Penetration of vancomycin into human lung tissue. J Antimicrob Chemother 1996;38:865–9.

[4] Aubron C, Corallo CE, Nunn MO, Dooley MJ, Cheng AC. Evaluation of the accuracy of a pharmacokinetic dosing program in predicting serum vancomycin concentrations in critically ill patients. Ann Pharmacother 2011;45:1193–8.

[5] Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840–51.

[6] Patanwala AE, Norris CJ, Nix DE, Kopp BJ, Erstad BL. Vancomycin dosing for pneumonia in critically ill trauma patients. J Trauma 2009;67:802–4.

[7] Wysocki M, Delatour F, Faurisson F, Rauss A, Pean Y, Misset B, et al. Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 2001;45:2460–7.

[8] Vandecasteele SJ, De Vriese AS. Recent changes in vancomycin use in renal failure. Kidney Int 2010;77:760–4.

[9] Hoste EA, Dhondt A. Clinical review: use of renal replacement therapies in special groups of ICU patients. Crit Care 2012;16:201.

[10] Wilson FP, Berns JS. Vancomycin levels are frequently subtherapeutic during continuous venovenous hemodialysis (CVVHD). Clin Nephrol 2012;77:329–31.

[11] Joy MS, Matzke GR, Frye RF, Palevsky PM. Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. Am J Kidney Dis 1998;31:1019–27.

[12] Santre C, Leroy O, Simon M, Georges H, Guery B, Beuscart C, et al. Pharmacokinetics of vancomycin during continuous hemodiafiltration. Intensive Care Med 1993;19:347–50.

[13] Chaijamorn W, Jitsurong A, Wiwattanawongsa K, Wanakamanee U, Dandecha P. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. Int J Antimicrob Agents 2011;38:152–6.

[14] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. SCCM/ESICM/ACCP/ATS/SI.S. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.

[15] Ocampos-Martinez E, Penaccini L, Scolletta S, Abdelhadii A, Devigili A, Cianferoni S, et al. Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients. Int J Antimicrob Agents 2012;39:332–7.

[16] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.

[17] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.

[18] Vandecasteele SJ, De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. Semin Dial 2011;24:50–5.

[19] Pollard TA, Lampasona V, Akkerman S, Tom K, Hooks MA, Mullins RE, et al. Vancomycin redistribution: dosing recommendations following high-flux hemodialysis. Kidney Int 1994;45:232–7.

[20] van de Vijsel LM, Walker SA, Walker SE, Yamashita S, Simor A, Hladunewich M. Initial vancomycin dosing recommendations for critically ill patients undergoing continuous venovenous hemodialysis. Can J Hosp Pharm 2010;63:196–206.

[21] del Mar Fernández de Gatta Garcia M, Revilla N, Calvo MV, Domínguez-Gil A, Sánchez Navarro A. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 2007;33:279–85.

[22] Pea F, Porreca L, Baraldo M, Furlanut M. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. J Antimicrob Chemother 2000;45:329–35.

[23] Macias WL, Mueller BA, Scarim SK. Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. Clin Pharmacol Ther 1991;50:688–94.

[24] Boereboom FT, Ververs FF, Blankestijn PJ, Savelkoul TJ, van Dijk A. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. Intensive Care Med 1999;25:1100–4.

[25] DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. Br J Clin Pharmacol 2004;58:259–68.

[26] Valtonen M, Tiula E, Takkunen O, Backman JT, Neuvonen PJ. Elimination of the piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. J Antimicrob Chemother 2001;48:881–5.

[27] Roberts DM, Roberts JA, Roberts MS, Liu X, Nair P, Cole L, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicenter pharmacokinetic study. Crit Care Med 2012;40:1523–8.

[28] Seyler L, Cotton F, Taccone FS, De Backer D, Macours P, Vincent JL, et al. Recommended β-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 2011;15:R137.

[29] Berthoin K, Ampe E, Tulkens PM, Carryn S. Correlation between free and total vancomycin serum concentrations in patients treated for Gram-positive infections. Int J Antimicrob Agents 2009;34:555–60.