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Original Article

Serum vancomycin levels in critically ill elderly patients undergoing continuous renal replacement therapy

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Abstract: Objective: To determine the pharmacokinetic parameters of vancomycin in critically ill elderly patients undergoing Continuous Renal Replacement Therapy (CRRT) and provide a baseline for dose adjustment. Methods: We carried out a prospective study that included 10 critically ill elderly patients aged ≥72 years. Vancomycin was given on the day when patients received CRRT. The CRRT parameters were as follows: a blood flow rate of 180 ml/min, a 3000 ml/h dialysate flow rate, and a 200 ml/h ultrafiltration clearance rate. Blood samples were collected at 0.25 h, 0.5 h, 0.75 h, 1 h, 2 h, 2.5 h, 3 h, 4 h, 8 h, 12 h and 24 h after vancomycin administration. Results: Vancomycin levels peaked at 1.5 h and remain plateaued at 8 h after dosing, insufficient or excessive drug concentrations were found in several time points. The estimated Vd, total clearance, AUC0-24 h and t1/2 were 28.38±7.00 L, 1.82±1.34 L/h, 282.51±77.87 mg L/h and 20.28±13.22 h. Vancomycin concentration ≥20 mg/L had a sensitivity of 25%, a specificity of 100%, a PPV of 100% and a NPV of 67% to predict AUC/MIC0-24 >400. The vancomycin concentration threshold associated with a PPV of 100% was 15 mg/L. Conclusion: This study revealed that vancomycin can be removed by CRRT. In critical ill elderly patients, a dose regimen of 1 g every 24 h was unable to provide a steady-state trough concentration of 15-20 mg/L. The fact that the pharmacokinetic parameters varied among these patients suggests the importance of monitoring vancomycin concentrations in critically ill elderly patients.

Keywords: Vancomycin, critically ill elderly patients, continuous renal replacement therapy, pharmacokinetic parameter

Introduction

Critically ill patients in intensive care units (ICU) are at high risk of bacterial infections, especially if those patients are elderly. The early and effective use of the appropriate antibiotics reduces mortality rates in these patients [1]. However, the effectiveness of antibiotics decreases in elderly patients with decreased physiological functions [2]. Critically ill elderly patients with or without decreased renal function who are hemodynamically unstable and require vasopressor support might receive continuous renal replacement therapy (CRRT) depending on the patient's clinical condition [3]. CRRT can effectively remove drugs from a patient's bloodstream, with drugs with a molecular weight less than 500 Da, a low protein-binding rate, small volume of distribution and low endogenous clearance exhibiting particularly easy removal [4, 5].

Because deficient immune responses are more likely to exist in elderly patients with increased age and severe underlying diseases, gram-positive infections are more frequent in the elderly patients [6]. Vancomycin is one of the most widely used antibiotics for serious gram-positive infections, including methicillin-resistant Staphylococcus aureus (MRSA) [7]. Some studies have confirmed that vancomycin can be removed during CRRT treatment, making pharmacokinetic models for this drug complex and scarce [8]. Recommendations have changed over time, we required higher vancomycin trough serum levels than before depending on the pathogen identified, especially in severe infections [9]. A trough level of between 15-20

mg/L was recommended in guidelines for achieving effective treatment and preventing resistance [10]. Nevertheless, patient's basic characteristics included location of infection, weight, glomerular filtration rate, co-medication and so on make it a great challenge to achieve appropriate trough serum levels. It is reported that hypoproteinemia can increase clearance rate in critically ill patients because of the increase of the unbound drug concentration [11, 12]. While vancomycin clearance in critically ill patients undergoing CRRT has already been explored, the pharmacokinetic parameters of vancomycin in critically ill elderly patients receiving CRRT remains unknown.

The purpose of this study was to explore the pharmacokinetic parameters of critically ill elderly patients receiving vancomycin during CRRT and provide evidence for dose adjustments.

Materials and methods

Study design

This prospective study was carried out in the Medical Intensive Care Unit (MICU) of the General Hospital of Guangzhou Military Command (Guangzhou, China) between January 2015 and June 2015. This study was conducted in accordance with the 1975 Helsinki Declaration and approved by the Ethics Committee of the General Hospital of Guangzhou Military Command, Guangzhou, China (Approval ID: 2014 [128]). We prospectively studied ten adult patients who were treated with vancomycin as monotherapy or combined with other antibiotics undergoing CRRT treatment. Inclusion criteria included that patients were aged ≥72 years, having an ICU stay for at least 48 h.

Dosing regimen

The dose regimen was selected based on the recommendation in patients with renal dysfunction. A 3000 ml/h dialysate flow rate was used in our study, thus we assumed that the creatinine clearance of these patients is 50 ml/min. Vancomycin serum concentration between 20-30 mg/L was defined as adequate concentration, and insufficient or excessive drug concentrations were defined as <20 mg/L or >30 mg/L. All of the patients received vancomycin (Edicin, Sandoz, Lek Pharmaceuticals d.d., Ljubljana, Slovenia) at a dose of 0.5 g every 12 hours. The vancomycin was dissolved and diluted in 100 ml of 0.9% sodium chloride solution and administered at an infusion rate of 50 ml per hour. In addition to vancomycin, the patients also received other prescribed drugs based on their conditions.

CRRT

Vancomycin was introduced on the day of CRRT treatment for all of the patients. The modality of CRRT was CVVHDF. The patients received 24 h CRRT with a 180 ml/min blood flow rate, 3000 ml/h dialysate flow rate, and a 200 ml/h ultrafiltration clearance rate. Blood samples were obtained 0.25 h, 0.5 h, 0.75 h, 1 h, 2 h, 2.5 h, 3 h, 4 h, 8 h, 12 h and 24 h after vancomycin administration. Blood samples were collected and centrifuged at 500 g for 5 min. Serum vancomycin concentrations were determined using the fluorescence polarization immunoassay method with the AxSYM Vancomycin II Reagent Pack (Abbott, Wiesbaden, Germany). The assay was performed according to the instructions provided in the manufacturer's manual.

Pharmacokinetic and statistical analysis

The following pharmacokinetic parameters were calculated using Kinetica v5.1 software (Thermo Fisher, USA): total clearance (CL_{tot}), volume of distribution (V_d), elimination half-life ($t_{1/2}$) and area under the serum concentration time curve (AUC_{0-24}). GraphPad Prism for Windows v5 (GraphPad Prism Software, Inc.) was used to graph the results.

Results

Patient characteristics

The patient characteristics are shown in **Table 1**. The study included 4 females and 5 male patients with ages ranging from 72-96 years. Three patients were diagnosed with bloodstream infection and the rest of them were diagnosed with pneumonia. All of the patients shown oliguria, in which three of them were defined with an AKIN degree of 3. The pathogens infecting the patients included *Staphylococcus haemolyticus, Enterococcus faecium, Staphylococcus epidermidis, Staphylococcus*

Table 1. Patient characteristics

Patient	Gender	Age	Pathogen infection	Infection site	APACHE II	SOFA	Albumin (g/L)	Creatinine (μmol/L)	Co-comorbidities	AKIN degree	Clinical status
1	Female	84	S. haemolyticus	Urinary	23	4	28.6	350	N	2	Severe sepsis
2	Male	96	E. faecium	Bloodstream	26	12	21.6	185	N	2	Severe sepsis
3	Male	72	S. epidermidis	Pulmonary	28	10	36.8	388	ARDS/AHF/AKI/AGI	2	Severe sepsis
4	Female	84	S. epidermidis	Bloodstream	23	4	29.7	99	N	2	Severe sepsis
5	Male	93	S. epidermidis	Pulmonary	33	8	29.1	64	AHF/AKI	3	Septic shock
6	Male	89	S. faecium	Pulmonary	24	7	31.5	121	N	2	Severe sepsis
7	Male	90	S. hominis	Pulmonary	37	11	32.8	213	ARDS	2	Severe sepsis
8	Male	90	S. epidermidis	Pulmonary	24	8	37.9	79	AHF/ALI/AGI	3	Septic shock
9	Male	83	E. faecium	Pulmonary	33	11	27.7	123	AHF	2	Severe sepsis
10	Male	84	S. haemolyticus	Pulmonary	24	9	32.1	836	ARDS/AHF/AKI/AGI	3	Severe sepsis
$\bar{X}$±SD	--	86.50±6.70	--		27.50±5.06	8.40±2.79	30.78±4.66	245.80±235.06			

Abbreviations: S. epidermidis, Staphylococcus epidermidis; E. coli, Escherichia coli; S. hominis, Staphylococcus hominis; E. faecium, Enterococcus faecium; S. aureus, Staphylococcus aureus; Y: Yes; N: No; ARDS: acute respiratory distress syndrome; AHF: acute heart failure; AKI: acute kidney injury; AGI: acute gastrointestinal injury; ALI: acute lung injury.

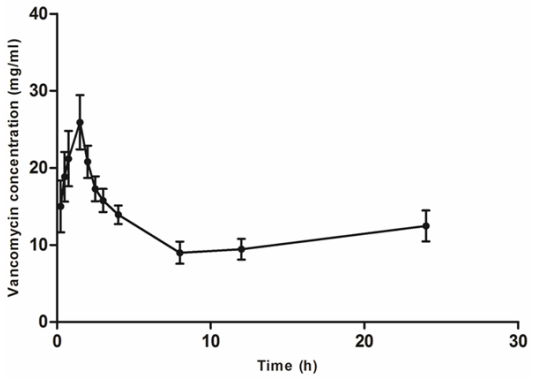

Figure 1. Vancomycin concentrations in patients undergoing CRRT. Each time point represents the average value from 9 patients. There are 11 time points in total, including 0.25 h, 0.5 h, 0.75 h, 1 h, 2 h, 2.5 h, 3 h, 4 h, 8 h, 12 h and 24 h after vancomycin administration.

hominis and *Staphylococcus aureus*. The mean APACHE II score for the patients was 27.50±5.06, varying from 23 to 37. The mean serum albumin level was 30.78±4.66 g/L, ranging from 21.6 to 37.9 g/L. The serum albumin levels for all of the patients were lower than the reference range. The mean creatinine level was 245.80±235.06 μmol/L, with a range of 64 to 836 μmol/L. The infection sites were mainly in bloodstream and pulmonary tissues.

Vancomycin serum levels and time course of vancomycin therapy targets

The time course of vancomycin levels is displayed in **Figure 1**. Altogether, according to the time course, the achieved median serum vancomycin concentration was 15.00, 18.84, 21.19, 25.92, 20.80, 17.27, 15.77, 13.91, 8.99, 9.45 and 12.46, respectively. Vancomycin levels peak at 1.5 h after dosing, dropped below 10 μg/mL 8h and remain subtherapeutic status at 24 h, median vancomycin concentrations were 25.92 mg/L, 8.99 mg/L and 12.46 mg/L at 1.5 h, 8 h and 24 h. The distribution of serum vancomycin concentrations in the insufficient concentration (<20 mg/L), adequate concentration (20-30 mg/L) and excessive concentration (>30 mg/L) were shown in **Figure 2**. Vancomycin concentration remain insufficient concentration in more than 50% of critically ill septic patients undergoing CRRT at 2.5 h after dosing or displayed excessive drug concentrations in 10%, 20%, 30%, 30% and 20% at 15 min, 30 min, 45 min and 1.5 h.

The individual and population pharmacokinetic parameters of vancomycin

The individual pharmacokinetic parameters of vancomycin are summarized in **Table 2**. Over the 24 h period, the estimated V_d was 28.38± 7.00 L, with a range from 22.10 to 44.81 L. The total clearance was 1.82±1.34 L/h, with a range of 0.30 to 4.69 L/h. The mean $AUC_{0\text{-}24\ h}$ was 282.51±77.87 mg h/L, ranging from 189.10 to 409.68 mg L/h. Lastly, $t_{1/2}$ was 20.28±13.22 h, with a range of 8.33 to 54.65 h. The mean and 95% CI of the variables about population pharmacokinetics are shown in **Table 3**.

When considering the AUC/MIC ratio for different MICs, we found that the present regimen provided AUC/MIC >400 in only one patient. Vancomycin concentration ≥ 20 mg/L had a sensitivity of 25%, a specificity of 100%, a PPV of 100% and a NPV of 67% to predict $AUC/MIC_{0\text{-}24}$ >400. The vancomycin concentration threshold associated with a PPV of 100% was 15 mg/L (**Figure 3**).

Discussion

In this study, we evaluated the effect of a dosing regimen in medical ICU elderly patients undergoing CRRT therapy. According to the results of our study, the dosing regimen we used was able to reach a sufficient vancomycin concentration during the very early phase of therapy. However, subtherapeutic drug concentration was observed at most of the time points. Finally, the recommended vancomycin concentrations (20-30 mg/L) that are associated with AUC/MIC >400 were not useful in our patients.

There is still insufficient evidence to guide a confirmed recommended vancomycin dose regimen for patients with reduced kidney function, moreover, the method of drug infusion and the CRRT parameters can affect vancomycin therapy [13, 14]. In order to reduce the different elimination rate caused by the therapy itself, we used the same infusion procedure and set CRRT parameters that were appropriate for all of the patients. In our study, we found a larger V_d and a longer $t_{1/2}$ a faster clearance of 28.38±7.00 L and 20.28±13.22 h, respectively, with the pharmacokinetic parameters varying among the 10 patients. Previous research indicates that the V_d of vancomycin in critically

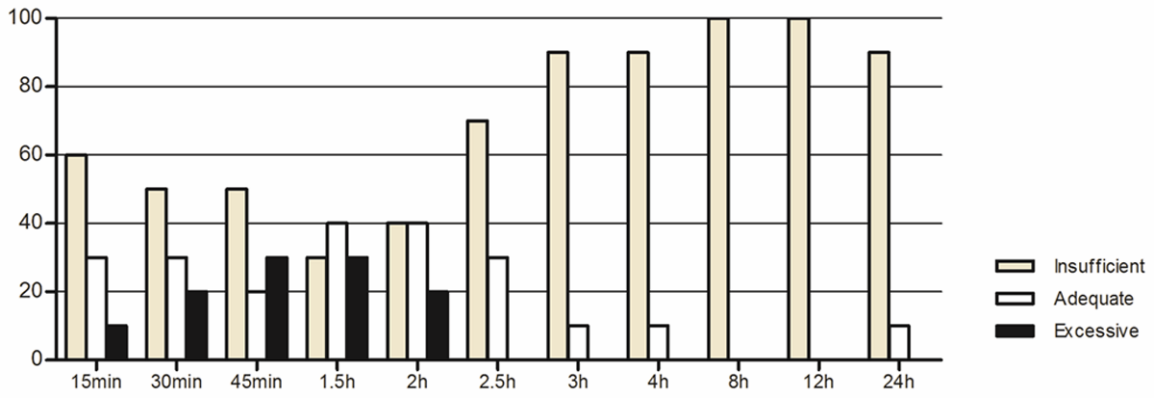

Figure 2. The proportion of patients with different vancomycin concentration levels. According to the time course of vancomycin treatment, the distribution (%) of patients with a concentration below 20 mg/L, within the range of 20-30 mg/L and above 30 mg/L.

Table 2. The pharmacokinetic parameters of vancomycin in 9 critically ill elderly patients

Patient	V_d (L)	AUC (mg L/h)	CL_{tot} (L/h)	κ_e (h^{-1})	$t_{1/2}$ (h)
1	23.83	409.68	0.30	0.013	54.65
2	24.54	311.74	0.84	0.034	20.32
3	22.87	212.21	1.95	0.042	16.27
4	44.81	198.82	4.69	0.052	13.12
5	27.52	207.98	1.80	0.066	10.58
6	28.25	281.59	0.99	0.035	19.69
7	26.72	189.10	2.22	0.083	8.33
8	26.97	318.11	0.70	0.026	26.71
9	36.18	375.23	3.32	0.059	19.68
10	22.10	320.66	1.35	0.051	13.49
$\bar{x}$±SD	28.38±7.00	282.51±77.87	1.82±1.34	0.05±0.02	20.28±13.22

Abbreviations: V_d: volume of distribution; AUC: Area under the concentration-time-curve; CL_{tot}, Total clearance; κ_e: elimination rate constant; $t_{1/2}$, Terminal half-life.

Table 3. Population pharmacokinetics parameters

	Mean	95% CI
Volume	24.66	19.91-29.41
Kel	0.031	0.018-0.045
Ycalc	19.28	17.69-20.86
Residual	-2.55	-5.31-0.20
Isd	7.70	7.07-8.34
Pred	18.24	16.71-19.77

Ycalc: Predicted concentration; Isd: Square root of the diagonal in the variance matrix; Pred: Predicted values of dependent variable completed with the population mean values of parameter.

ill patients is 24.69±11.00 L with a $t_{1/2}$ of 12.02±7.00 [15]. In patients with moderate to severe chronic kidney disease (CKD) and those who develop to acute kidney injury (AKI) may present an increased V_d [16, 17]. Llopis suggested that the accumulation of fluid in the third space due to tissue oedema induced by sepsis might be a possible reasonfor an elevated V_d [18]. In addition, hypoalbuminemia may affect vancomycin concentrations and present a high concentration based on active unbound drug concentration and cover the fact that the total drug concentration may be reduced [19, 20]. The albumin levels observed in our study was ranging from 21.6 to 32 g/L, which is lower than the reference range. Thus the reason of the longer $t_{1/2}$ of vancomycin may contribute to hypoalbuminemia. Our result was corresponded to the previous report.

Trough vancomycin concentrations have been regularly measured to prevent the toxicity and drug ineffectiveness caused by subtherapeutic and excessive concentrations [21]. Weerachai Chaijamorn revealed that vancomycin concentrations in critically ill patients started to decrease due to CRRT at 0.5 h after dosing during the infusion period and that the vancomycin concentration remained at 15-20 μg/mL 7.5 h after dosing [22]. In our study, the vancomycin concentration in critically ill elderly patients

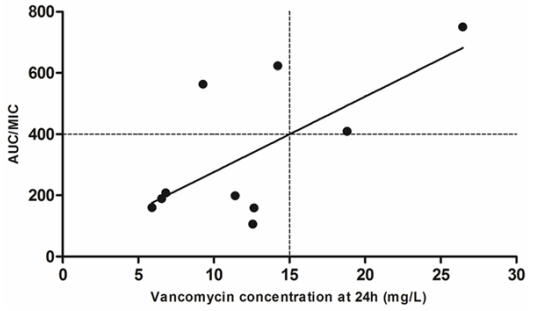

Figure 3. Relationship between drug concentration at 24 h of vancomycin therapy and AUC/MIC ratio. The vancomycin concentration threshold associated with a PPV of 100% was 15 mg/L.

dropped below 10 μg/mL 8 h and remain subtherapeutic status till 24 h. Vancomycin concentration remains insufficient concentration at most of the time point. Our result was corresponding to other report and indicated an effective clearance of CRRT therapy. In addition, the pharmacodynamics parameter that is thought to best predict vancomycin efficacy is the ratio of the 24-hour area under the concentration-time curve to MIC (AUC/MIC) [23, 24]. The guideline recommended a vancomycin target AUC/MIC of >400, it is considered to be more accurate than other related measures and evaluating clinical success [25]. However, the result of our study shown that the ratio of achievement of adequate vancomycin concentration and AUC/MIC >400 was rather low. These results suggest that it is important to track vancomycin concentration in elderly critically ill patients and appropriately adjust the dose to maintain an effective concentration.

A few limitations of our study need to be mentioned here. First, the number of patients enrolled in this study was relatively small. Thus, our results may have a limitation for expand to a large amount of critically ill elderly patients. A further study with a larger sample size was needed to be performed. Second, patients in this study mostly shown oliguria or anuria, theoretically speaking, the creatinine clearance from the patient can be omitted. In our study, a 3000 ml/h dialysate flow rate was used, thus we consider that the creatinine clearance of these patients is 50 ml/min. According to the manufacturer's description, the recommended dosage was 770 mg every 24 hours under 50 ml/min creatinine clearance. However, the regular therapeutic drug monitoring of vancomycin suggested that the patients can hardly reach the target trough concentration in this condition. Consider the efficacy and safety, we set a dose of 1 g every day for these oliguric or anuric patients undergoing a 3000 ml/h dialysate flow rate CRRT treatment, then perform the therapy drug monitoring (TDM). We find that even with a dose of 1 g every 24 hours, the patients still can't reach the target concentration of 15-20 mg/L. The possible reason may be: (1) Oliguric or anuric patients still retain renal excretion function in a certain extent; (2) The vancomycin removal was also depended on the dialyzer, dialysate flow rate and treatment time. Thus, we suggested that sieving coefficient (SC) of vancomycin should be measured to better predict the vancomycin removal and a body weight adapted loading dose was also suggested in the further experiment.

In conclusion, this study revealed that vancomycin can be removed by CRRT, which may reduce the effectiveness of this antibiotic. The pharmacokinetic parameters of vancomycin in elderly critically ill patients show an increase in V_d and $t_{1/2}$ compared to non-elderly critically ill patients. The pharmacokinetic parameters varied among these patients, suggesting the importance of monitoring vancomycin concentrations in critically ill elderly patients.

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Disclosure of conflict of interest

None.

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