Vancomycin pharmacokinetics during high-volume continuous venovenous hemofiltration in critically ill septic patients

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Aims. To assess the influence of continuous venovenous hemofiltration (CVVH) at a filtration rate of 45 mL/kg/h on vancomycin pharmacokinetics in critically ill septic patients with acute kidney injury (AKI).
Methods. Seventeen adult septic patients with acute kidney injury treated with CVVH and vancomycin were included. All patients received first dose of 1.0 g intravenously followed by 1.0 g/12 h if not adjusted. In sixteen patients vancomycin was introduced on the day of the start of CRRT therapy. Blood samples and ultrafiltrates were obtained before and 0.5, 1, 6 and 12 h after vancomycin administration.
Results. On the first day, the median total vancomycin clearance (Cl_{tot}) was 0.89 mL/min/kg (range 0.31 - 2.16). CRRT clearance accounted for around 50-60% of the total clearance of vancomycin found in a population with normal renal function (0.97 mL/min/kg). Vancomycin serum concentrations after the first dose were below the required target of 10 mg/L as early as 6 h in 10 patients, AUC_{0-24}/MIC ≥ 400 ratio was achieved in 10 patients on the first day.
Conclusions. CVVH at a filtration rate of 45 mL/kg/h leads to high and rapid extracorporeal removal of vancomycin in critically ill patients. Due to the rapid change in patient clinical status it was impossible to predict a fixed dosage regimen. We recommend blood sampling as early as 6 h after first vancomycin dose with maintenance dose based on vancomycin serum level monitoring.

Key words: acute kidney injury, critically ill patients, renal replacement therapy, sepsis, drug monitoring, vancomycin

Received: April 16, 2012; Accepted with revision: September 18, 2012; Available online: November 6, 2012
http://dx.doi.org/10.5507/bp.2012.092

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INTRODUCTION

Acute kidney injury (AKI) is a common complication of critical illness[1]. Between 45-70% of all AKI is associated with sepsis[2]. Patients with septic AKI have increased risk of death and longer hospitalization[3].

Critically ill patients in intensive care units are also at high risk of bacterial superinfection caused by nosocomial agents in particular. Both patient status and surroundings contribute to the occurrence of the infection[3].

Superinfection may be due to type of gram-positive strains of *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterococcus*[4]. Treatment with glycopeptid antibiotic agent vancomycin is often required according to the observed sensitivity of bacterial agents[5]. Septic patients with acute kidney injury who are hemodynamically unstable and require high vasopressor support, can be treated with continuous renal replacement therapy (CRRT). Drugs with a molecular weight less than 5000 Da, low plasma protein binding, small volume of distribution, and low endogenous clearance are effectively removed by continuous venovenous hemofiltration (CVVH) (ref.[6]). Many drugs used in critically ill patients meet these criteria, complicating dosing regimens in patients receiving CVVH (ref.[7]).

The pharmacokinetics of vancomycin can be affected by the filtration dose, physical properties of elimination therapy, type of membrane and also by the properties of the antibiotic agent itself[8]. Dosing and pharmacokinetic data in patients receiving intermittent hemodialysis are not applicable to those receiving CRRT because of substantial differences in procedure, filters and timing. The clearance of vancomycin changes and can be increased using high-flux membranes[9]. An AUC/MIC ratio of ≥ 400 has been advocated as a target to achieve clinical effectiveness with vancomycin. However, trough vancomycin serum concentration C_{min} > 10 mg/L is more practical method for monitoring vancomycin effectiveness[10].

The purpose of this study was to assess the influence of CVVH at a filtration rate of 45 mL/kg/h on vancomycin pharmacokinetics in critically ill septic patients with AKI. Using pharmacokinetic modelling, we sought an optimal dosing regimen for maximising target vancomycin exposure.

PATIENTS AND METHODS

This was an open, prospective, clinical study carried out at the University hospital Ostrava, Czech Republic. The study protocol was approved by the hospital Ethics Committee. Written informed consent was obtained from patients and two unrelated physicians. Therapeutic monitoring of vancomycin levels is a standard procedure during vancomycin therapy in our hospital.

Seventeen critically ill adult patients (six women) with severe sepsis requiring CRRT in CVVH mode on vancomycin therapy were included. Acute kidney injury was classified according to the RIFLE score: eleven patients belonged to RIFLE F; six patients were in RIFLE I. They were followed up for 2 days. All received vancomycin (Edicin, Sandoz, Lek Pharmaceuticals d.d, Lek, Ljubljana, Slovenia) first dose of 1.0 g intravenously followed by 1 g/12 h if not adjusted.

In sixteen patients, vancomycin was introduced on the day of the commencement of CRRT therapy. In one patient, CRRT was initiated in the course of vancomycin treatment. Antibiotic agent was reconstituted with 0.9% Sodium Chloride 100 mL solution and administered at an infusion rate of 100 mL per hour. Blood samples and ultrafiltrates were obtained before vancomycin administration and 0.5, 1, 6 and 12 h after vancomycin administration. Blood samples were collected into 4.9 mL neutral tubes (Sarstedt-Monovette) and centrifuged. Serum and ultrafiltrate vancomycin concentrations were determined using fluorescence polarisation immunoassay method (AbboTT AxSYM™; Abbott Laboratories, Diagnostic Division, Abbott Park, IL 60064 USA). Coefficient of variation of the analysis ranged depending on the concentration from 3.36% to 6.11% with an average value of 5.04%. Vancomycin dose was adjusted according to vancomycin level simulation using a pharmacokinetic programme MWPharm, version 3.30 (MEDIWARE, Groningen, the Netherlands). A vancomycin trough concentration of 10-15 mg/L was chosen as a target concentration for vancomycin dosage adjustment. Minimal inhibitory concentration of pathogen was determined by the microdilution broth method.

The following pharmacokinetic parameters were calculated for each patient: total drug clearance (Cl_{tot}), volume of distribution (Vd), elimination half-life ($t_{1/2}$) and area under the serum concentration time curve (AUC_{0-24}). Pharmacokinetic parameters were calculated using pharmacokinetic programme KINFIT (MWPharm,

Table 1. Demografic data of the study patients.

Patient	Age (years)	Sex	Weight (kg)	RIFLE stage	SOFA	APACHE II	IL 6 (ng/L)	Diagnosis	Pathogen/ MIC
1	68	†	113	F	16	34	251	Peritonitis	*Staph.species/0.5*
2	73	¤	73	F	21	31	> 1000	MODS	*Staph. species/1.0*
3	44	†	90	F	16	31	67	Polytrauma, Sepsis	*Ent. faecium/0.5*
4	57	†	110	F	17	35	> 1000	CA - bypass,sepsis	*Staph. species/1.0*
5	71	†	90	I	21	32	> 1000	Pyartros genus l.dx	*Str. pyogenes/0.125*
6	28	†	80	F	18	26	> 1000	Infectious endocarditis	*Staph. aureus/0.5*
7	68	¤	70	F	21	31	-	Pneumonia	*Staph. species/1.0*
8	79	†	80	F	14	34	-	Infectious endocarditis	*empirically*
9	59	†	100	F	14	28	14	Pneumonia	*Staph. species/0.5*
10	45	¤	58	I	15	33	> 1000	Peritonitis	*Staph. species/-*
11	54	†	100	I	17	33	-	Sepsis	*Ent. faecalis/1.0*
12	50	†	110	I	15	33	75	Mediastinitis	*Strep. anginosus/0.25*
13	70	†	75	F	19	35	62	Wound infection	*Staph. haemolyticus/0.5*
14	51	¤	65	I	14	28	160	Spondylodiscitis	*MRSA/0.25*
15	61	†	90	F	16	34	448	Pneumonia	*MRSA/0.25*
16	61	¤	120	F	21	32	59	Mediastinitis	*Ent. faecalis/1.0*
17	34	¤	102	I	18	22	134	Sepsis	*Ent. faecalis/2.0*
Median	58		90		17	32	71		
Range	28-79		58-120		14-21	22-35	14->1000		

SOFA – sequential organ failure assessment – score, APACHE - acute physiology and chronic health evaluation - score, IL – interleukin, MIC – minimal inhibitory concentration, RIFLE – AKI classification system, F-failure, I-injury, †-men, ¤-women, MODS – multiple organ dysfunction syndrome, MRSA – methicillin resistant *Staphylococcus aureus*, CA bypass - coronary artery bypass

MEDIWARE version 3.60, Groningen, the Netherlands). The selected model was based on a one-compartment model.

CVVH was performed in all patients using a high-flux polysulphone membrane: 1.4 m^2 AV 600 (5 patients with a body weight less than 80 kg) and 1.8 m^2 AV 1000 (Fresenius Medical Care, Germany), the blood flow rate (Q_b) was 200 ml/min, ultrafiltrate flow rate (Q_f) was 45 mL/kg/h in pre-postdilution mode (50/50). This procedure was performed using a Multifiltrate machine (Fresenius Medical Care, Germany). The hemofilter was changed every 24 hours. Bicarbonate replacement fluids (Multibic K0-4) were purchased from Fresenius Medical Care, Germany. Low molecular heparin (nadroparine) was used as an anticoagulation, antiXa levels were maintained at 0.3-0.5. CVVH was performed through a double-lumen 14-F catheter inserted into the jugular or femoral vein. CRRT clearance was calculated using the following formula:

$$Cl_{CRRT} = Cl_{CRRT}(post) + Cl_{CRRT}(pre)$$

$$Cl_{CRRT}(post) = Q_f \times Sc \qquad Cl_{CRRT}(pre) = Q_f \times Sc \times CF$$

$$CF = Q_b/(Q_b+Q_{rep}) \text{ (ref.}^{5}\text{)}$$

where Cl_{CRRT}(post) = CRRT is the clearance from CRRT using post-filter hemodilution; Q_f is the ultrafiltration rate; Cl_{CRRT}(pre) = CRRT is the clearance from CRRT using pre-filter hemodilution; Q_b is the blood flow rate; Q_{rep} is the pre-dilution replacement rate and CF the correction factor.

Sieving coefficient was calculated following the formula $C_f/C_{pl,}$ where C_f was vancomycin concentration in ultrafiltrate fluid and C_{pl} was vancomycin serum concentration. Data are expressed as median and range. The Spearman correlation was used for correlation coefficients. A p-value of < 0.05 was considered statistically significant. GraphPad Prism for Windows version 5.0 (GraphPad Prism Software, Inc.) was used to perform the statistical analysis.

RESULTS

The clinical characteristics of the patients studied are summarized in Table 1. All patients suffered from severe sepsis and were treated with mechanical ventilation. Infections were caused by Gram-positive agents: *Staphylococcus species coagulase negat,* Methicillin-resistant *Staphylococcus aureus (MRSA), Staphylococcus haemolyticus, Streptococcus anginosus, Streptococcus pyogenes, Enterococcus faecalis* and *Enterococcus faecium.* Median Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores at inclusion were 32 (22-35) and 17 (14-21). Diuresis was preserved in 11 patients on the first day of the study (range 30-315 mL/h) and in 5 patients on the second study day (range 37-267 mL/h). Diuresis was supported by the diuretic agent furosemide 1.0 g/24 h (Table 2). Median estimated glomerular filtration by MDRD was 0.4 (0.1-0.6) mL/s in both study days.

Table 2. Urine output and ultrafiltration rate in study patients.

Patient	Diuresis (mL/h)		Ultrafiltration rate (mL/24 h)	
	Day 1	Day 2	Day 1	Day 2
1	160	–	3400	–
2	anuria	anuria	1700	2300
3	30	37	2800	4500
4	210	133	0	0
5	anuria	anuria	5570	6850
6	204	–	0	–
7	anuria	anuria	6000	6000
8	66	anuria	0	1700
9	36	anuria	4670	4540
10	315	–	1900	–
11	100	267	1700	2000
12	80	75	1900	5100
13	anuria	anuria	1400	2300
14	139	113	1700	4200
15	anuria	anuria	3065	4740
16	anuria	anuria	750	3250
17	81	–	800	–

Vancomycin dosage regimen and vancomycin serum concentrations during both days of the study are depicted in Tables 3 and 4. In three patients, a lower vancomycin dose of 1 g/24 h was given on the first day, due to acute surgical intervention. Vancomycin serum concentrations after the first dose were below the required target of 10 mg/L as early as 6 h in 10 patients. CRRT therapy was discontinued in 5 patients during the second day and these patients were excluded from further analysis. In the remaining 12 patients, the dose was adjusted in 8 patients. $AUC_{0\text{-}24}/MIC \geq 400$ ratio was achieved in 10 patients on the first day and in 6 patients on the second day. In 2 patients this ratio could not be determined due to unknown MIC value of pathogen (Tables 5 and 6). The pharmacokinetic parameters are summarized in Tables 5 and 6. On the first day of treatment, the total clearance of vancomycin (median 0.89 mL/min/kg, range 0.31-2.16 mL/min/kg) approached the average value of total clearance in patients without renal failure (0.97 mL/min/kg) (ref.[10]) in 7 of our patients, in 4 patients the total clearance of vancomycin was even higher. On day two the total clearance of vancomycin was equal to the average value of total clearance in only 4 patients. We found a significant correlation between the total vancomycin clearance and the dose/weight (r_s=0.8289, P=0.0009) on the second day of the treatment (Fig. 1). No significant relationship between the total clearance of vancomycin and residual renal function was found (P>0.05).

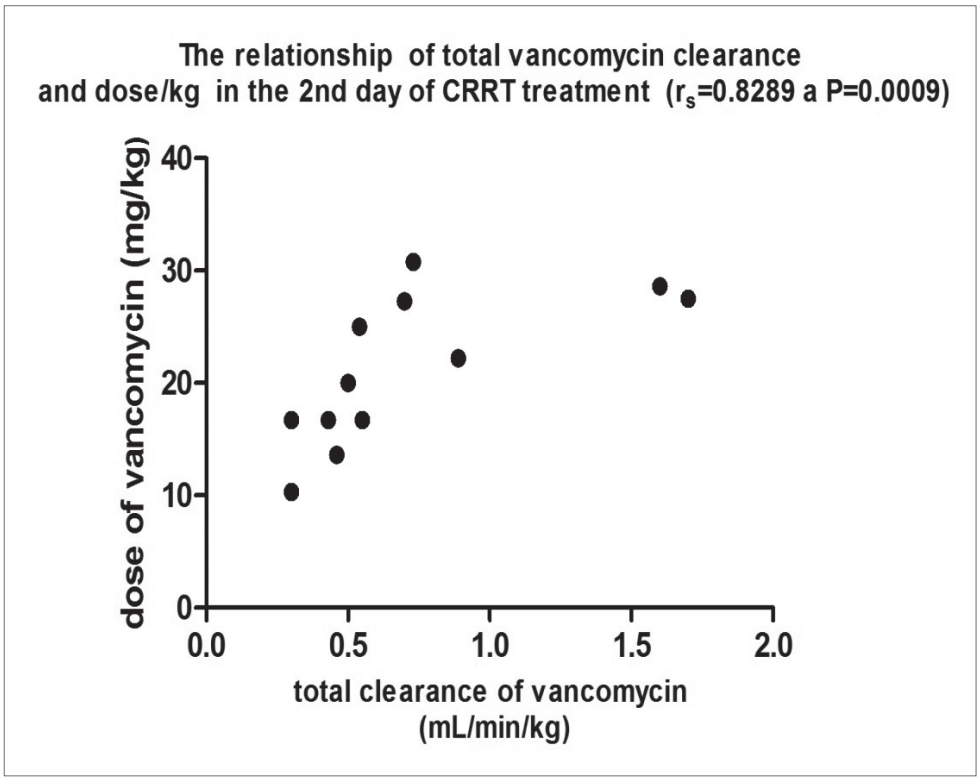

Fig. 1. The relationship between total vancomycin clearance and dose/kg on the second day of CRRT treatment (r_s=0.8289, *P*=0.0009).

Table 3. Vancomycin dose and individual serum concentrations on the first day of study.

			Day 1					
Patient	Vancomycin dose (g)	Dose/ weight (mg/kg)	1.C_{van} 1 h (mg/L)	1.C_{van} 6 h (mg/L)	1.C_{van} 12 h (mg/L)	2.C_{van} 1 h (mg/L)	2.C_{van} 6 h (mg/L)	2.C_{van} 12 h (mg/L)
1	1.0 /12 h	17.7	15.42	7.08	3.50	14.34	9.40	5.90
2	1.0 /12 h	27.4	32.50	21.10	18.38	27.28	19.49	15.66
3	1.0 /12 h	22.2	30.17	20.02	-	25.35	-	13.41
4	1.0 /12 h	18.2	16.58	5.37	4.00	13.70	6.83	-
5	1.0 /12 h	22.2	12.02	6.65	5.53	18.69	11.02	7.65
6	1-1.25-1.25	43.8	24.99	10.96	-	29.49	13.74	-
7	1.0/ 24 h	14.3	15.01	8.37	6.60	-	-	-
8	1.0 /12 h	25.0	14.63	6.53	3.53	27.20	9.81	7.00
9	1.0 /12 h	20.0	12.88	10.33	6.37	21.61	13.83	10.46
10	1.0 /12 h	34.0	22.81	4.02	3.18	20.60	8.43	5.00
11	1.0 /12 h	20.0	14.74	9.74	5.05	10.14	7.04	5.53
12	1.0 /24 h	9.1	26.55	18.10	11.25	-	-	-
13	0.75/12 h	20.0	24.18	-	12.78	19.34	-	12.22
14	1.0 /12 h	30.8	31.06	14.80	11.00	20.55	18.15	11.00
15	1.0 /12 h	22.2	10.84	7.33	5.33	16.86	11.83	9.83
16	1.0 /24 h	8.3	26.54	8.40	-	-	-	-
17	1.0 /12 h	19.6	15.21	5.42	3.19	17.37	6.39	3.99
Median		20.0	16.60	8.38	5.43	19.95	9.81	8.74
Range		8.3-43.8	10.84-32.50	4.02-21.10	3.18-18.38	10.14-29.49	6.39-19.49	3.99-15.66

1.C_{van} 1 h - vancomycin serum concentration 1 hour after 1st dose administration. 1.C_{van} 6 h –vancomycin serum concentration 6 h after 1st dose administration. 1.C_{van} 12 h - vancomycin serum concentration 12 h after 1st dose administration. 2.C_{van} 1 h - vancomycin serum concentration 1 h after 2nd dose administration. 2.C_{van} 6 h - vancomycin serum concentration 6 h after 2nd dose administration. 2.C_{van} 12 h - vancomycin serum concentration 12 h after 2nd dose administration.

Table 4. Vancomycin dose and individual serum concentrations on the second day of study.

	Day 2							
Patient	Vancomycin dose (g)	Dose/weight (mg/kg)	$1.C_{van}$ 1 h (mg/L)	$1.C_{van}$ 6 h (mg/L)	$1.C_{van}$ 12 h (mg/L)	$2.C_{van}$ 1 h (mg/L)	$2.C_{van}$ 6 h (mg/L)	$2.C_{van}$ 12 h (mg/L)
1	-	-	-	-	-	-	-	-
2	1.0 /24 h	10.3	25.68	18.82	16.63	-	-	-
3	1.0-0.5	16.7	21.22	22.57	15.51	18.58	18.29	12.55
4	1.0 /8 h	27.3	17.79	10.25	-	17.82	12.27	-
5	0.75/12 h	16.7	21.38	13.60	10.75	22.79	13.39	10.31
6	-	-	-	-	-	-	-	-
7	1.0/12 h	28.6	14.94	7.76	6.43	21.30	12.56	9.52
8	1.0/12 h	25.0	22.12	13.91	10.69	22.62	16.01	13.79
9	1.0/12 h	20.0	22.39	13.00	10.00	27.01	18.11	12.09
10	-	-	-	-	-	-	-	-
11	1.25-1.5	27.5	24.36	10.21	6.46	35.52	8.70	6.82
12	0.75/12 h	13.6	15.22	8.31	8.22	22.68	11.05	8.28
13	-	-	-	-	-	-	-	-
14	1.0/12 h	30.8	36.35	19.18	11.00	25.74	16.78	10.00
15	1.0/12 h	22.2	20.55	10.56	8.56	21.54	-	13.00
16	1.0/12 h	16.7	13.32	8.22	6.40	17.20	14.52	10.00
17	-	-	-	-	-	-	-	-
Median		21.1	21.30	11.78	10.00	22.62	13.96	10.16
Range		10.3-30.8	13.32-36.35	7.76-22.57	6.40-16.63	17.20-35.52	8.70-18.29	6.82-13.79

$1.C_{van}$ 1 h - vancomycin serum concentration 1 h after 1st dose administration. $1.C_{van}$ 6 h - vancomycin serum concentration 6 h after 1st dose administration. $1.C_{van}$ 12 h - vancomycin serum concentration 12 h after 1st dose administration. $2.C_{van}$ 1 h - vancomycin serum concentration 1 h after 2nd dose administration. $2.C_{van}$ 6 h - vancomycin serum concentration 6 h after 2nd dose administration. $2.C_{van}$ 12 h - vancomycin serum concentration 12 h after 2nd dose administration.

DISCUSSION

We studied the pharmacokinetics of vancomycin in critically ill septic patients with acute kidney injury treated with CRRT in order to establish practical recommendations for a vancomycin dosage regimen. CVVH at a filtration rate of 45 mL/kg/h led to high and rapid extracorporeal removal of vancomycin in critically ill patients. However, due to rapid change in patient clinical status it was impossible to predict a fixed dosage regimen.

Extracorporeal elimination is clinically significant if it achieves 25-30% of total drug clearance[5]. Deldot et al. studied vancomycin clearance in 10 critically ill patients treated with continuous venovenous hemodiafiltration at a dialysis dose of 1000 mL/h and a filtration dose of 2000 mL/h. The total vancomycin clearance was 2.5±0.7 L/h and CVVHDF clearance was 76±16.5% of a total drug clearance[11]. Uchino et al. observed vancomycin clearance in 7 septic patients with multiple organ failure and AKI treated with high-volume venovenous hemofiltration at a filtration rate of 6 L/h with varying pre and postdilution flow rate[12]. They found that total vancomycin clearance increased when predilution flow rate was reduced from 4 L to 2 L in the range of 53.9 to 67.2 mL/min. Shah et al. describes a 14-year-old critically ill patient with AKI treated with CVVH at a filtration rate of 1800 mL/h, CVVH clearance was 26±0.8 mL/min[13]. In our study CRRT clearance at a filtration rate of 45 mL/kg/h accounted for approximately 50-60% of the total clearance of vancomycin found in a population with normal renal function, therefore it contributes significantly to the elimination of vancomycin in septic patients with AKI. Interestingly in three anuric patients, the total clearance of vancomycin was higher than the CRRT clearance and approached the plasma clearance of vancomycin in populations without renal impairment (0.97 mL/min/kg) (ref.[10,14,15]). In four patients, the total clearance of vancomycin was even higher than in populations without renal disease (1.24 to 2.16 mL/min/kg).

The total drug clearance is the sum of non-CRRT and CRRT clearance, which means that different factors are involved in the excretion of antibiotics. One of the important factors is residual renal function. Patients with residual diuresis may require an increased dose of vancomycin to maintain desired serum levels. In our study, however, we found no significant correlation between the total clearance of vancomycin and residual diuresis. In patients with oligoanuric AKI a substantial non-renal

Table 5. Pharmacokinetic/pharmacodynamic parameters of vancomycin during CRRT (45 mL/kg/h) treatment on the first day of study.

Day 1							
Patient	Cl_{tot} (mL/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	AUC_{0-24}	AUC_{0-24}/MIC	Cl_{CRRT} (mL/min/kg)	Sc
1	0.89	0.43	5.80	245.9	**491.8**	0.5	0.64
2	0.45	0.38	9.88	559.7	**559.7**	0.5	0.72
3	0.38	0.34	11.06	515.0	**1030.0**	0.4	0.65
4	1.24	0.46	4.32	184.8	184.8	0.5	0.68
5	0.97	0.71	8.34	233.8	**1870.1**	0.6	0.78
6	1.04	0.49	5.49	396.1	**792.2**	0.6	0.73
7	1.07	1.06	11.48	170.4	170.4	0.6	0.73
8	1.32	0.57	4.99	256.8	-	0.6	0.80
9	0.68	0.56	9.83	280.2	**560.4**	0.6	0.73
10	2.16	0.77	4.14	246.8	-	0.8	0.77
11	0.96	0.74	8.95	205.7	205.7	0.6	0.73
12	0.31	0.35	13.22	329.9	**1319.6**	0.6	0.73
13	0.49	0.51	11.68	375.0	**750.0**	0.5	0.73
14	0.73	0.55	8.88	410.9	**1640.0**	0.6	0.73
15	0.86	0.69	9.31	142.0	**568.0**	0.6	0.78
16	0.59	0.32	6.33	192.4	192.4	0.6	0.77
17	1.38	0.61	5.25	181.9	90.9	0.6	0.73
Median	0.89	0.55	8.88			0.6	0.73
Range	0.31-2.16	0.32-1.06	4.14-13.22			0.4-0.8	0.64-0.80

Cl_{tot} – total drug clearance. Vd – volume of distribution. $t_{1/2}$ – elimination half-life. Cl_{CRRT} – CRRT clearance. Sc – sieving coefficient. AUC_{0-24}/MIC – area under the serum concentration time curve 0-24 h to minimal inhibitory concentration ratio

Table 6. Pharmacokinetic/pharmacodynamic parameters of vancomycin during CRRT (45 mL/kg/h) treatment on the second day of study.

Day 2							
Patient	Cl_{tot} (mL/min/kg)	Vd (L/kg)	$t_{1/2}$ (h)	AUC_{0-24}	AUC_{0-24}/MIC	Cl_{CRRT} (mL/min/kg)	Sc
1	-	-	-	-	-	-	-
2	0.30	0.34	12.85	351.2	351.2	0.6	0.75
3	0.30	0.37	14.15	342.7	**685.4**	0.5	0.69
4	0.70	0.34	5.61	366.2	366.2	0.5	0.63
5	0.43	0.35	9.41	360.0	**2880.0**	0.6	0.74
6	-	-	-	-	-	-	-
7	1.06	0.77	8.41	278.1	278.1	0.5	0.67
8	0.54	0.53	11.77	384.5	-	0.5	0.63
9	0.50	0.38	8.67	395.1	**790.2**	0.6	0.76
10	-	-	-	-	-	-	-
11	1.07	0.43	4.71	343.6	343.6	0.5	0.68
12	0.46	0.36	9.06	287.3	**1149.2**	0.5	0.65
13	-	-	-	-	-	-	-
14	0.73	0.43	6.81	485.5	**1942.0**	0.5	0.63
15	0.89	0.78	10.85	230.3	**921.2**	0.6	0.73
16	0.55	0.54	11.66	270.5	270.5	0.5	0.63
17	-	-	-	-	-	-	-
Median	0.55	0.41	9.24			0.5	0.68
Range	0.30-1.07	0.34-0.78	4.71-14.15			0.5-0.6	0.63-0.76

Cl_{tot} – total drug clearance. Vd – volume of distribution. $t_{1/2}$ – elimination half-life. Cl_{CRRT} – CRRT clearance. Sc – sieving coefficient. AUC_{0-24}/MIC – area under the serum concentration time curve 0-24 h to minimal inhibitory concentration ratio

clearance initially has been observed[16]. The proportion of non-renal clearance can vary between 3.8 to 23.3 mL/min in patients with AKI compared with only 4-6 mL/min in patients with chronic renal failure[17]. Further vancomycin adsorption to hemofilter has also been described[18]. These factors could explain the discrepancy observed between total vancomycin clearance and CRRT clearance in our anuric patients and lack of correlation between the total clearance and diuresis. In four cases, we found paradoxically lower total clearance of vancomycin than CRRT clearance. The only explanation for this discrepancy is that these patients were disconnected from continuous elimination for several hours due to urgent intervention or due to repeated precipitation which led to the reduction in the total vancomycin clearance.

Sepsis can lead to endothelial damage with increased capillary permeability and can change the volume of distribution. Changes in the volume of distribution are important especially for hydrophilic substances. Increased volume of distribution has been observed for example in septic patients treated with aminoglycosides requiring an increase of daily dose to achieve therapeutic concentrations[19]. However, it seems that changes in fluid balance have less impact on the volume of distribution with vancomycin than with aminoglycosides. In our patients, we observed approximately the same volume of distribution as described in healthy volunteers[17]. Choi et al. describes volume of distribution of 0.55 ± 0.12 L/kg in septic patients treated with CVVH which corresponds to our findings[20]. Elimination half-life of vancomycin was longer in our patients (ranging from 4.14 h to 14.15 h) than in non-septic patients without renal impairment (approximately 4-6 h) (ref.[10,14,15]).

Trotman et al. recommends in critically ill patients an initial dose of vancomycin 15-20 mg/kg and a maintenance dose of 500 mg to 1500 mg every 24 h to 48 h in CVVHD and a dose of 1000-1500 mg every 24 h in CVVHDF to achieve trough concentration in the range of 10-15 mg/L (ref.[19]). Veltri et al. recommended an initial dose of 10-15 mg/kg parenterally followed by vancomycin concentrations monitoring in septic patients treated with CRRT in all modes[21]. The initial median daily dose of vancomycin in our group of patients was 20.0 mg/kg (8.3 to 43.8) with a loading dose of 1.0 g, maintenance dose was based on vancomycin serum concentrations. Total clearance of patients varied in a wide range and thus reflected the need for different weight-based doses of vancomycin. However, giving a standard initial dose of 1 g intravenously has lead to a drop of trough levels below 10 mg/L as early as 6 h after first drug administration in 10 of our patients. A weight-based initial vancomycin dose rather than fixed dose is proposed to rapidly achieve optimal therapeutic vancomycin concentrations. A loading dose of 25-30 mg/kg has been recommended in an effort of minimizing subtherapeutic exposures within the first 24 h (ref.[10]). However caution should be taken when applying this recommendation to the population with renal impairment. Septic patients are usually in a severe catabolic status and often need a different dose of RRT. They might often require changes in ultrafiltration flow rates leading to different elimination of antibiotics and thus making drug dosage more difficult. Boumann et al. observed a significant discrepancy between predicted and observed vancomycin removal with the need for dose adjustments and more frequent monitoring of serum levels in 45 oligoanuric patients treated with CVVH (ref.[22]). Due to rapid changes in patient clinical status and CRRT conditions, it may be therefore impossible to derive a fixed dosage regimen in critically ill septic patients and maintenance doses should be based on vancomycin concentration monitoring.

An AUC/MIC ratio ≥ 400 has been advocated as a target to achieve clinical effectiveness with vancomycin therapy[10]. However, because it can be difficult in the clinical setting to obtain multiple serum vancomycin concentrations to determine AUC and then calculate AUC/MIC, trough serum concentration monitoring, which can be used as a surrogate marker for AUC, is recommended as the most accurate and most practical method for vancomycin monitoring. Trough vancomycin serum concentrations maintained above 10 mg/L are recommended[10]. The desired $AUC_{0\text{-}24}$/MIC ≥ 400 was achieved in 67% of patients on the first day and 55% on the second day of treatment. The desired AUC/MIC ratio was achieved almost only in patients with vancomycin MIC < 1.0 mg/L. Recent study recommends a higher trough vancomycin concentration of between 15-20 mg/L especially in the treatment of complicated infections (e.g. ventilatory associated pneumonia) and for a pathogen with an MIC of 1 mg/L in order to attain target vancomycin exposure[10,23]. Higher trough vancomycin concentrations may also increase the potential for nephrotoxicity but the extent of this risk is yet to be determined. Vancomycin-induced nephrotoxicity is related to drug plasma concentrations[24]. Nephrotoxicity is a concern for those hemodialysis patients who have some residual renal function and mainly for those patients with AKI. A target AUC/MIC ≥ 400 is not achievable with conventional dosing methods if the pathogen vancomycin MIC is ≥ 2 mg/L, achievement of this ratio would lead to undesirable vancomycin toxicity. To further improve treatment options, use of predictive pharmacokinetic simulation for predicting plasma levels of vancomycin is recommended[25].

CONCLUSION

Therapeutic monitoring of vancomycin levels in critically ill septic patients treated with renal replacement therapy is a valuable tool in drug dosage adjustment. Due to the unstable patient's clinical status and possible changing conditions of RRT daily monitoring of vancomycin serum levels is necessary at least for the first days after antibiotic introduction. Achievement of adequate vancomycin concentration on the first day of treatment of septic patients is of high clinical importance. We recommend performance of blood sample as early as 6 h after first vancomycin dose in case of a need of early dose adjustment.

ACKNOWLEDGEMENTS

The authors thank all of the doctors and nurses of all the intensive care units that contributed to this study. This project was supported by grant IGA MZCR NS 103 09-3/2009.

CONFLICT OF INTEREST STATEMENT

The authors stated that there are no conflicts of interest regarding the publication of this article.

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