ORIGINAL ARTICLE

PHARMACOKINETIC CHARACTERISTICS OF VANCOMYCIN IN THE TREATMENT OF CRITICALLY ILL PATIENTS WITH PULMONARY INFECTIONS

QINGXIA ZHENG[1], LIPING LIU[1], XIAOWEI MA[1], RUI YANG[1]*

[1]*Critical Care Medicine, Hongqi Hospital of Mudanjiang Medical University, MuDanjiang City, 157011, China*

**corresponding author: dr_yangrui@yahoo.com*

Manuscript received: January 2017

Abstract

The aim of this study was to analyse the pharmacokinetics of vancomycin in the anti-infective treatment of critically ill patients from Intensive Care Unit (ICU) with pulmonary infections. The ICU patients were divided according to endogenous creatinine clearance rate (CL_{CR}) into two groups: the normal renal function group (CL_{CR} > 90 mL/min, n = 10) and the renal dysfunction group (CL_{CR} < 90mL/min, n = 10). The endogenous creatinine clearance rate (CL_{CR}) was calculated by determining the serum creatinine. The liver and kidney function, circulatory system function, infection index, age and body weights of patients were analysed. The pharmacokinetic parameters were calculated using DAS2.0 software. The pharmacokinetic parameters obtained were $t_{1/2\alpha}$ = 0.38 h, V_d = 0.41 L/kg, $t_{1/2\beta}$ = 9.81 h, CL = 0.059 L/min, the peak concentration of treatment was 42.69 mg/L, and the lowest concentration was 11.97 mg/L. The pharmacokinetic parameters of the normal renal function group were $t_{1/2\alpha}$ = 0.26 h, $t_{1/2\beta}$ = 7.68 h, V_d = 0.28 L/kg, CL = 0.065 L/min. The pharmacokinetic parameters of the renal dysfunction group were $t_{1/2\alpha}$ = 0.43 h, $t_{1/2\beta}$ = 11.41 h, V_d = 0.42 L/kg, CL = 0.058 L/min. Creatinine clearance showed that the initial dose of vancomycin administered to the patients could not reach the treatment goal, so a new dose is needed to be administered in order to improve the treatment compliance. ICU patients have high drug metabolism and high circulating dynamic state, the age and renal function being the main factors that influence the drug metabolism.

Rezumat

Scopul prezentului studiu a fost analiza farmacocineticii vancomicinei în tratamentul anti-infecţios al pacienţilor aflaţi în stare critică, în secţia de Terapie Intensivă, cu infecţii pulmonare. Pacienţii au fost împărţiţi în funcţie de *clearance*-ul creatininei endogene în 2 loturi: lotul cu funcţie renală normală (CL_{CR} > 90 mL/min, n = 10) şi lotul cu dinsfuncţie renală (CL_{CR} < 90 mL/min, n = 10). *Clearance*-ul creatininei a fost calculat cu ajutorul creatininei serice. Au fost analizate funcţiile hepatice, renale, funcţiile sistemului circulator, indexul infecţiei, vârsta şi greutatea pacienţilor. Parametrii farmacocinetici au fost calculaţi cu ajutorul software-ul DAS2.0. Parametrii farmacocinetici obţinuţi au fost $t_{1/2\alpha}$ = 0,38 h, V_d = 0,41 L/kg, $t_{1/2\beta}$ = 9,81 h, CL = 0,059 L/min, concentraţia plasmatică maximă a fost de 42,69 mg/L, iar concentraţia minimă a fost de 11,97 mg/L. Parametrii farmacocinetici la lotul cu funcţie renală normală au fost $t_{1/2\alpha}$ = 0,26 h, $t_{1/2\beta}$ = 7,68 h, V_d = 0,28 L/kg, CL = 0,065 L/min. Parametrii farmacocinetici la lotul cu disfuncţii renale au fost $t_{1/2\alpha}$ = 0,43 h, $t_{1/2\beta}$ = 11,41 h, V_d = 0,42 L/kg, CL= 0,058 L/min. *Clearance*-ul creatininei a arătat că doza iniţială de vancomicină administrată la pacienţi nu este suficientă, fiind necesară administrarea unei doze suplimentare. Pacienţii din terapie intensivă prezintă un metabolism crescut al medicamentelor şi o fază circulatorie dinamică crescută, iar vârsta şi funcţia renală sunt principalii factori ce influenţează acest proces.

Keywords: vancomycin, Intensive Care Unit (ICU), pharmacokinetics, pulmonary infections

Introduction

Severe infection is the most common disease in intensive care units (ICU), and the cost of anti-microbial drugs is the highest in the total cost of ICU drugs [31]. The cases of severe infections that require hospitalization in ICU are multiple, their complexity being proportional with the clinical status and comorbidities presented by these patients. The patients may have multiple causes of severe infections such as: complicated surgical site infections [4, 6, 8, 32], organ transplantation in which severe fungal infections especially *Aspergillus* and *Fusarium* [35] species overlap the bacterial infections, complicated pulmonary infections accompanied by pleurisy [5, 37], urinary infections in patients with comorbidities such as diabetes or stroke that were initially asymptomatic and develop unfavourable clinical evolution [12, 21]. The critically ill patients are more likely to develop multidrug resistant infections (MDR), such as hospital acquired pneumonia (HAP) and ventilation-associated pneumonia (VAP) due to poor health status, multiple diseases, impaired immune system and long-term antimicrobials treatment [11]. With the use of anti-biotics, bacterial resistance including Methicillin Resistant *Staphylococcus aureus* (MRSA) is increasing [15, 29]. With the extensive administration of anti-

biotics, the resistance of bacteria has been increasing every year. The emergence of new antibiotics in clinical practice has a certain lag [23], which has brought new challenges for the anti-infective treatment. Vancomycin is a middle molecular weight drug, and it is used especially in the treatment of infectious diseases caused by MRSA [30], being preferred to other anti-infective treatments.

In vitro vancomycin pharmacokinetic studies have shown that it has a great variability [13, 22, 26]. The pharmacokinetic studies on patients, especially on critically ill patients, have shown that the Therapeutic Drug Monitoring (TDM) is necessary during the treatment of vancomycin [1, 10, 27]. The main reason is that critically ill patients' status varied according to disease situation, organ function, positive pressure ventilation and blood purification. Also, it is not possible to give a uniform dosage adjustment strategy because of the different morbid state of the patients. In this study, we selected patients treated with vancomycin in the ICU wards from which we collected blood samples before and after drug administration. We monitored and analysed the pharmacokinetic characteristics in correlation with the clinical data of the patients.

Materials and Methods

General materials

Drugs: Vancomycin Hydrochloride used for Injection (Wancocin® CP, 0.5 g, Eli Lilly, Japan).

The main instruments: Abbott AxSYM System: MDF-382E (N) type ultra-low temperature refrigerator; Baiyang 52A medical low-speed centrifuge; GEM® premier 3000 blood gas/electrolyte analyser; Vortex-Genie 2 vortex mixer; Thermo Scientific Heraeus® Pico 17 type micro-desktop centrifuge; GEM premier 3000 blood gas/electrolyte analyser (provided by Leidu mite Medical Equipment Co., Ltd); DDG-3300K system (Shanghai Tongge Medical Devices Co., Ltd); Renal function test instrument - PA8800 type provided by Beijing Perlong New Technology Co., Ltd.); ZXG-E type automatic cardiovascular deep level analyzer (Anhui Longguang Medical Technology Co., Ltd.); Heart rate tester (Shenzhen Dick Medical Technology Co., Ltd.).

Patients

We enrolled were included patients diagnosed with pulmonary infection that needed anti-infective treatment with vancomycin hospitalised within ICU wards of Hongqi Hospital of Mudanjiang Medical University, China, between May 2014 and July 2016. The patients were divided according to the International Society of Nephrology on renal function evaluation criteria in 2 groups: normal renal function group (n = 10, $CL_{CR} \geq 90$ mL/min) and renal dysfunction group (n = 10, $CL_{CR} < 90$ mL/min) group. The study was approved by the Ethics Committee of Hongqi Hospital of Mudanjiang Medical University, China, and the informed consent was signed by the patients or legal guardians before enrolment.

Before and during the treatment with vancomycin, the patients had various basic checks such as blood routine (haemoglobin - Hb), liver function (albumin - Alb), renal function (blood urea nitrogen - BUN), heart rate (HR), mean arterial pressure (MAP) and other basic items checks. Each blood sampling time was: 1 h before administration, 0 h at the end of administration, 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h and 8 h after the administration. The time of the next administration is described in detail below. The routine blood test, liver and kidney function and the basic indexes were reviewed. The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) were used to evaluate patients with severe illness. Endogenous creatinine clearance rate (CL_{CR}) was calculated as follows: $CL_{CR} = [(140 - age) \times weight\ (kg)]/[0.818 \times S_{CR}\ (\mu mol/L)]$, where S_{CR} = serum creatinine. For females the results were multiplied by a factor of 0.85.

Research Methods

Basic examination: routine blood test: Hb test was performed using GEM premier 3000 blood gas/ electrolyte analyser (provided by Leidu mite Medical Equipment Co., Ltd). Liver function test: Liver function analyser (a DDG-3300K system that provided by Shanghai Tongge Medical Devices Co., Ltd) was used to detect Alb and other indexes. Renal function test: Renal function test instrument (PA8800 type provided by Beijing Perlong New Technology Co., Ltd.) was used to detect BUN, S_{CR} and other indicators. When the value of CL_{CR} drops to 0.5 - 0.6 mL/s/m^2 (52 - 63 mL/min/1.73 m^2), the glomerular filtration function gradually decrease. Heart rate test: Heart rate tester (Shenzhen Dick Medical Technology Co., Ltd.) was used to detect the heart rate. Cardio cerebrovascular test: ZXG-E type automatic cardiovascular deep level analyser (Anhui Longguang Medical Technology Co., Ltd.) was used to detect MAP value and other parameters.

Administration methods: The dose of vancomycin was 1 g every 12 h, the standard dose of vancomycin. The dose was reduced appropriately in the patients with severe renal impairment. The vancomycin was diluted to 5 mg/mL with 0.9% NaCl and administered by intravenous infusion.

Sample collection: the venous blood of the patients was collected at pre-dose (-1 h), end of administration (0 h), and 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h after administration. The supernatant (plasma) was placed in Eppendorf tubes at -80ºC for standby after 4000 rpm × 5 min centrifugation.

Sample treatment and determination: The collected plasma samples were thawed at room temperature. 300 µL samples were selected and placed in AxSYM

Sample Cups for sample determination. The serum concentration of vancomycin was measured by fluorescence polarization immunoassay (FPIA) method. *Establishment of FPIA detection method*: The Abbott AxSYM Plus automatic immunoassay analyser and the corresponding reagents of Abbott Company were used for testing. The relevant operations were carried out in strict accordance with the instrument standards, operating specifications and reagents instructions. Each batch of reagents was calibrated before use (Van II was selected to set the calibration status). The calibration reagents (6 different levels from A to F) were respectively absorbed and calibrated from low to high. When the instrument calibration was finished, the samples of low (L), medium (M) and high (H) quality control samples were measured. According to the quality control standard, the three horizontal quality control values are within the required range (shown in Table I). Each time the reagent box was replaced and the blood sample was measured at each start-up, the experiments were conducted in a low, medium, and high order cycle. When the measured values of low, medium and high-quality control were within the required range, they can be used for sample determination; otherwise, standard curves should be reconsidered. When developing the standard curves, low, medium and high-quality control samples should be measured at the same time. The FPIA method is validated by the National Committee for Clinical Laboratory Standards (NCCLS).

Table I

Results of 3 quality control samples (mg/L)

Level	Target	Range	Detection					Mean	SD
L	7.0	5.20 - 8.80	6.80	7.67	6.97	7.56	7.31	7.26	0.37
M	35.0	30.0 - 40.0	35.38	35.91	36.56	35.64	36.17	35.93	0.21
H	75.0	62.0 - 88.0	79.87	71.44	78.23	74.18	76.85	76.11	11.18

Statistical analysis: DAS2.0 pharmacokinetic analysis software package was used to calculate the pharmacokinetic parameters. Other clinical data was analysed by SPSS 19.0 statistical software package. The normal distribution or the approximate normal distribution was expressed as mean ± standard deviation ($\bar{x} \pm s$). For independent samples, Student's t test was used to compare the data of the two groups, and the one-way ANOVA was used to compare data of multiple samples. The Fisher's test or chi-square test was used to compare the sample rates. Spearman rank correlation analysis was also employed. $p < 0.05$ was considered as statistical significant.

Results and Discussion

Clinical data

The clinical evaluation of the patients in the 2 groups is presented in Table II. Analysing the clinical data of the patients from the 2 groups, the only parameters that were statistically different, were the kidney function indicators (S_{CR}, CL_{CR}) ($p < 0.05$).

Table II

General situation of patients in the studied groups

Types	The normal renal function n = 10		The renal dysfunction group n = 10		p value
	$\bar{x} \pm s$	Range	$\bar{x} \pm s$	Range	
Age	73.4 ± 7.2	63.3 - 76.5	76.2 ± 6.4	62.5 - 82.1	0.232
Weight (kg)	61.8 ± 11.7	43.9 - 75.8	75.2 ± 15.8	57 - 112	0.108
Urine volume(Ml/day)	2665 ± 1011	1460 - 4262	2451 ± 1438	50 - 4505	0.756
APARCH II Score	19.7 ± 6.3	12 - 31	19.6 ± 2.7	15 - 24	0.932
SOFA Score	8.7 ± 2.4	5 - 12	8.6 ± 3.3	5 - 14	0.916
SCr (μmol/L)	45 ± 14.2	24 - 66	106 ± 40.9	71 - 183	0.008
CL_{CR} (Ml/min)	107.3 ± 10.2	90.7 - 116.2	60.2 ± 17.3	22.9 - 76.3	< 0.001
MAP (mmHg)	87.9 ± 10.3	75.6 - 100.0	86.9 ± 16.5	66.7 - 110.3	0.936
BUN (mmol/L)	13.58 ± 6.05	8.27 - 22.65	11.26 ± 5.93	5.32 - 20.24	0.519
HR (bpm)	112 ± 10.22	98 - 123	95 ± 22.48	23 - 118	0.212
Hb (g/L)	109.2 ± 11.3	97.4 - 120.9	102.3 ± 13.5	84.2 - 114.2	0.382
Alb (g/L)	27.1 ± 2.28	25.3 - 29.9	26.8 ± 5.95	20.8 - 36.7	0.795
FiO_2 (%)	42.3 ± 16.2	30 - 70	46.9 ± 15.3	30 - 80	0.623
Arterial blood pH	7.45 ± 0.82	7.37 - 7.58	7.45 ± 0.69	7.31 - 7.55	0.334
Arterial blood PaO	72 ± 8.3	65 - 87	87 ± 36.8	40 - 159	0.402
The actual dosage (g/day)	2200 ± 430	2000 - 3000	1705 ± 482	1000 - 2000	0.112
The calculated dosage (g/day)	1668 ± 162	1395 - 1810	920 ± 277	360 - 1180	< 0.001

Notes: MAP = Mean Artery Pressure, HR = Heart Rate, BUN = Blood Urea Nitrogen, Hb = Haemoglobin, Alb = Plasma Albumin

Pharmacokinetic analysis

The pharmacokinetic process of vancomycin *in vivo* is a multi-compartment model, usually calculated as a two-compartment model. In this study, 200 blood samples were collected from 20 patients. The drug concentration was assayed by DAS 2.0 pharmacokinetic fitting, and the metabolic process presented a multi-compartment model. The relevant pharmacokinetic parameters were calculated by the two-compartment model fitting, as shown in Table III.

Table III

Pharmacokinetic analysis results

	All patients n = 20		The normal renal function n = 10		The renal dysfunction n = 10		p value
	$\bar{x} \pm s$	Range	$\bar{x} \pm s$	Range	$\bar{x} \pm s$	Range	
C_{max} (mg/L)	42.69 ± 17.58	18.90 - 79.37	39.90 ± 15.30	24.58 - 64.11	44.81 ± 19.87	18.90 - 79.51	0.657
C_{min} (mg/L)	11.97 ± 7.52	4.40 - 31.05	10.90 ± 4.83	4.83 - 18.13	12.86 ± 9.30	4.36 - 31.05	0.662
V_d (L/kg)	0.41 ± 0.32	0.03 - 1.21	0.28 ± 0.13	0.085 - 0.403	0.42 ± 0.38	0.03 - 1.21	0.239
CL (L/min)	0.059 ± 0.021	0.014 - 0.106	0.065 ± 0.023	0.034 - 0.095	0.058 ± 0.030	0.015 - 0.106	0.701
$t_{1/2\alpha}$ (h)	0.38 ± 0.016	0.11 - 0.66	0.26 ± 0.11	0.13 - 0.38	0.43 ± 0.16	0.17 - 0.65	0.039
$t_{1/2\beta}$ (h)	9.81 ± 3.32	5.04 - 15.78	7.68 ± 1.83	5.96 - 9.77	11.41 ± 3.55	5.03 - 15.80	0.071
AUC_{0-t} ((mg/L)*h)	210 ± 102	115 - 425	188 ± 86	115 - 335	220 ± 108	115 - 420	0.612
AUC ((mg/L)*h)	425 ± 190	230 - 845	390 ± 150	243 - 650	450 ± 220	230 - 845	0.628

Note: AUC (Area Under the Curve) is the area under the curve, which indicates the degree that the drug is absorbed and utilized in the human body, and the bioavailability is high if AUC is high, while on the contrary, it is low.

From the data in Table III, the overall pharmacokinetic parameters were as follows: distribution phase was $t_{1/2\alpha}$ = 0.38 h, the distribution volume (V_d) was 0.41 L/kg, the elimination phase was $t_{1/2\beta}$ = 9.81 h, the total elimination rate was CL = 0.059 L/min, AUC_{0-t} = 210 (mg/L)*h after the single dose, the treatment peak concentration was 42.69 mg/L, and the trough concentration was 11.97 mg/L. Compared with the results of previous population pharmacokinetic studies [25, 38], V_d was reduced, and this phenomenon was especially obvious in patients with normal renal function (0.13 - 0.38 h *vs.* 0.5 - 1.0 h). This proves that the patient's high metabolism and high circulating dynamic state can lead to the rapid increase of drug distribution in patients, which made the peak concentration rapidly to decline after administration, and this can avoid the increase of the adverse reactions caused by the excessive drug concentration. But it also suggests that when the dose was low, the drug concentration *in vivo* cannot reach the antibacterial concentration. This is more obvious after the first dose. The latest clinical administration recommendations [17, 28] suggest that the treatment of critically ill patients should be started with 25 - 30 mg/kg b.w. (body weight) vancomycin. In our case, after drugs' administration, it was rapidly distributed, and the high peak concentration provided a higher concentration of the drug in the elimination phase. In this way it can effectively ensure that an effective antimicrobial concentration may be reached the second dose that will improve the AUC value and ensure the efficacy.

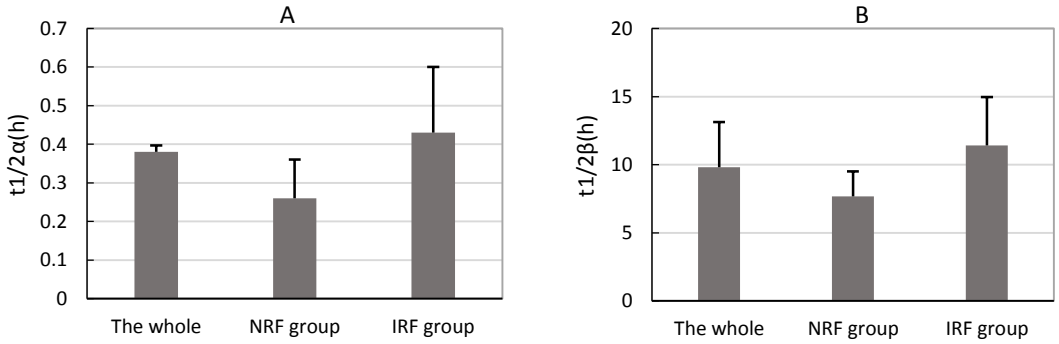

Figure 1.

The half-life of vancomycin in treated patients with severe disease pulmonary infections

(NRF group: the normal renal function, IRF group: the renal dysfunction; A: drug distribution half-life $t_{1/2\alpha}$, B: drug elimination half-life $t_{1/2\beta}$)

From Figure 1 we can see that the distribution of vancomycin in patients with renal dysfunction was slower than in patients with normal renal function, and the drug elimination slowed down, but the total clearance rate of drugs presented no significant differences.

Correlation analysis of vancomycin pharmacokinetic parameters and clinical indicators

When the patients undertake the continuous veno-venous hemofiltration (CVVH), the clearance rate of drugs is $CL = CL' + C_{LR} + CL_{NR}$ (CL' is the rate of clearance *in vitro*, CL_R is the ratio of renal

clearance, and the CL_{NR} is the clearance rate without kidney). The correlation analysis results of the pharmacokinetic parameters and physiological indicators are shown in Table IV.

Table IV

Correlation between the pharmacokinetic parameters and the clinical indicators

		$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	CL (L/min)	S_{CR} (μmol/L)	Alb (g/L)	V_d (L/kg)	CL_{CR} (mL/min)	Age (years)	AUC ((mg/L)*h)	SOFA Score
$t_{1/2\alpha}$	r	1	0.537	0.168	0.668	-0.701	0.702	-0.760	0.660	-0.193	-0.091
(h)	p		0.106	0.638	0.037	0.036	0.021	0.012	0.034	0.577	0.079
$t_{1/2\beta}$	r	0.537	1	-0.683	0.306	-0.632	-0.135	-0.537	0.452	0.611	-0.650
(h)	p	0.106		0.019	0.341	0.038	0.697	0.081	0.153	0.046	0.026
CL	r	0.168	-0.683	1	-0.007	0.047	0.682	0.025	0.190	-0.917	0.451
(L/min)	p	0.638	0.019		0.981	0.893	0.022	0.951	0.567	< 0.001	0.164
S_{CR}	r	0.668	0.306	-0.007	1	-0.424	0.256	-0.880	0.258	-0.019	0.163
(μmol/L)	p	0.037	0.341	0.981		0.201	0.438	< 0.001	0.450	0.963	0.636
Alb	r	-0.701	-0.632	0.047	-0.424	1	-0.354	0.552	-0.809	0.110	0.304
(g/L)	p	0.036	0.038	0.893	0.201		0.283	0.083	0.003	0.757	0.371
V_d	r	0.702	-0.135	0.682	0.256	-0.354	1	-0.274	0.592	-0.685	0.085
(L/kg)	p	0.021	0.697	0.022	0.438	0.283		0.421	0.056	0.022	0.802
CL_{CR}	r	-0.760	-0.537	0.025	-0.880	0.552	-0.274	1	-0.488	-0.031	0.191
(mL/min)	p	0.012	0.081	0.951	< 0.001	0.083	0.421		0.128	0.924	0.584
Age	r	0.660	0.452	0.190	0.258	-0.809	0.592	-0.488	1	-0.234	-0.417
(years)	p	0.034	0.153	0.567	0.450	0.003	0.056	0.128		0.487	0.205
AUC	r	-0.193	0.611	-0.917	-0.019	0.110	-0.685	-0.031	-0.234	1	-0.306
((mg/L)*h)	p	0.577	0.046	< 0.001	0.963	0.757	0.022	0.924	0.487		0.361
SOFA Score	r	-0.091	-0.650	0.451	0.163	0.304	0.085	0.191	-0.417	-0.306	1
	p	0.079	0.026	0.164	0.636	0.371	0.802	0.584	0.205	0.361	

The results presented in Table IV show that CL_{CR}, age, SOFA score, S_{CR}, and Alb are the main clinical parameters associated with the pharmacokinetic parameters. SOFA score is a comprehensive evaluation of the organ function in critically ill patients, in which the renal function score includes serum creatinine value and urine volume. The serum creatinine value is the clinical observation indicator calculated by creatinine clearance rate. It suggests that the renal function, age and Alb levels may be the main factors affecting vancomycin drug clearance.

Alb is the major protein that binds to drugs *in vivo* and plays an important role in the transport and storage of drugs. The functional status of the organism gradually decline with age, and this is more evident in the patients from ICU wards especially due to associated diseases. In these patients the absorption of the nutrients decrease, leading to malnutrition and low - blood protein levels (the correlation of age and Alb level is $R = 0.880$, $p < 0.001$). At the same time, glomerular filtration function decrease, being associated with the organ dysfunction, leading to the hypofunction of the renal system, decrease of the drug clearance and increase of the drug half-life (CL_{CR} - $t_{1/2\beta}$ shows a negative correlation $r = -0.537$, $p = 0.081$). These two factors explain how the age influences the drugs pharmacokinetics.

Vancomycin is a moderate plasma protein binding drug, and its pharmacokinetic studies show that the individual differences in vancomycin plasma protein binding rate are more obvious [14, 36]. In this study, the average level of Alb was 27.1 g/L, lower than the normal level, while the vancomycin kinetic analysis showed a decrease in V_d, indicating that the plasma protein binding had a certain effect on the *in vivo* distribution and clearance of vancomycin distribution, and it was necessary to consider to the patients the right initial dose and thus shorten the dosing intervals in order to improve the efficacy.

Alb is an important factor in the production of plasma colloid osmotic pressure [37]. The leakage of Alb during the inflammatory response increases the tissue oedema. The hypoproteinemia will lead to the increase of free drugs. Therefore, it can be concluded that inflammatory response and hypoproteinemia are the main factors that influence the *in vivo* distribution of the vancomycin [34]. When patients develop infections, the pathogen will release the endotoxin or the exotoxin, which will lead to systemic inflammatory response, imbalanced body's homeostasis, damaged vascular endothelium, increased capillary permeability that will determine an increase of the interstitial fluid volume [3]. All these are responsible for a significant increase of V_d [16, 25], drug dilution, and a downward trend of plasma and tissue drug concentration [18, 24]. The decrease in protein synthesis due to impaired liver function and nutrient uptake leads to hypoproteinemia, decreased plasma colloid osmotic pressure and increased sodium and water retention, all this contributing to further increase of V_d [2, 9, 19].

At the same time, due to coma, organ blood perfusion redistribution and other factors, the

severe patients' drug therapy is usually intravenous. This way of administration can speed up the metabolism of body fluids [20], so, the drug in body will be rapidly diluted, manifested as the acceleration of the drug distribution and the increase of the V_d. Due to the increase of the renal blood flow, the drug clearance rate is also improved. The infusion of colloid and dehydration diuretic therapy make the body fluids migrate from the organization to the blood vessels and lead to the reduction of the distribution of drugs, the increase of the plasma drug distribution, and the decrease of V_d. But the dilution produced by the blood return of liquid makes the plasma drug concentration decrease. Diuretic effect can make renal excretion increase, so the total drug clearance increases. In this study, the V_d of patients in the 2 groups decreased compared with the normal population, and it was related to the protein supplementation, colloid infusion and dehydration therapy.

Conclusions

In summary, compared with the normal population, the pharmacokinetic parameters of vancomycin used to treat critically ill patients was significant modified, its distribution *in vivo* being increased compared with the normal population. Patients have high metabolism and high blood pressure, and the age and renal function are the main factors that affect the drug metabolism. In addition, a loading dose should be given to critically ill patients at the beginning of the treatment in order to achieve a better compliance.

References

1. Anderson B.J., Allegaert K., Van den Anker J.N., Cossey V., Holford N.H., Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br. J. Clin. Pharmacol.*, 2007; 63(1): 75.
2. Balik M., Sedivy J., Waldauf P., Kolar M., Smejkalova V., Pachl J., Can bioimpedance determine the volume of distribution of antibiotics in sepsis?. *Anaesth. Intensive Care.*, 2005; 33(3): 345-350.
3. Bochud P.Y., Calandra T., Pathogenesis of sepsis: new concepts and implications for future treatment. *B.M.J.*, 2003; 326(326): 262-266.
4. Călina D., Docea A.O., Roşu L., Zlatian O., Roşu A.F., Anghelina F., Rogoveanu O., Arsene A., Nicolae A.C., Drăgoi C.M., Tsiaoussis J., Tsatsakis A.M., Spandidos D.A., Drakoulis N., Gofiţă E., Antimicrobial resistance development following surgical site infections. *Mol. Med. Rep.*, 2017; 15(2): 681-688.
5. Călina D., Roșu L., Roşu A.F., Ianoşi G., Ianoşi S., Zlatian O., Mitruț R., Docea A.O., Rogoveanu O., Mitruț P., Nicolae A.C., Drăgoi C.M., Gofiţă E., Etiological diagnosis and pharmacotherapeutic management of parapneumonic pleurisy. *Farmacia*, 2016; 64(6): 946-952.
6. Colcea C., Călina D., Zlatian O., Rosu L., Chiutu L., Docea A.O., Rosu A.F., Correlation between antimicrobial consumption in the intensive care unit and prevalence and resistance of *Staphylococcus aureus*. *Eur. J. Hosp. Pharm.*, 2014; 21: A15-A16.
7. Colcea C., Zlatian O.M., Rosu L., Călina D., Rosu A.F., Chiutu L., Docea A., Correlation between consumption of antimicrobials in the intensive care unit and resistance of *Pseudomonas* and *Klebsiella* in pulmonary infections. *Eur. J. Hosp. Pharm.*, 2014; 21(Suppl1): A16.
8. Cristea O.M., Zlatian O.M., Dinescu S.N., Bălăşoiu T., Avrămescu C., Bălăşoiu M., Niculescu M., Călina D., A comparative study on antibiotic resistance of *Klebsiella* strains from surgical and intensive care wards. *Curr. Health Sci. J.*, 2016; 42(2): 169-179.
9. del Mar Fernández de Gatta Garcia M., Revilla N., Calvo M.V., Domínguez-Gil A., Sánchez Navarro A., Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. *Intensive Care Med.*, 2007; 33(2): 279-285.
10. Del Dot M.E., Lipman J., Tett S.E., Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenoushaemodiafiltration. *Br. J. Clin. Pharmacol.*, 2004; 58(3): 259-268.
11. Draganescu M., Iancu A.V., Firescu D., Buzia O.D., Diaconu C., Rebegea L., Trends in antimicrobials consumption and antimicrobial resistance in an infectious diseases hospital from the south-eastern region of Romania. *Farmacia*, 2016; 64(5): 770-774.
12. Filip L., Călina D., Bocşaru C., Docea A., Mitrut P., Bubulica M.V., Balasoiu M., Zlatian O., Rosu L., The importance of assessing asymptomatic bacteriuria in hospitalised patients. *Eur. J. Hosp. Pharm.*, 2016; 23(Suppl1): A1-262.
13. Golestaneh L., Gofran A., Mokrzycki M.H., Chen J.L., Removal of vancomycin in sustained low-efficiency dialysis (SLED): a need for better surveillance and dosing. *Clin. Nephrol.*, 2009; 72(4): 286-291.
14. Honda H., Doern C.D., Michael-Dunne W., Warren D.K., The impact of vancomycin susceptibility on treatment outcomes among patients with methicillin resistant *Staphylococcus aureus* bacteremia. *B.M.C. Infect. Dis.*, 2011; 11(1): 335.
15. Humphreys H., Can we do better in controlling and preventing methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care unit (ICU)?. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2008; 27(6): 409-413.
16. Imaura M., Yokoyama H., Kohyama T., Nagafuchi H., Kohata Y., Takahashi H., Yamada Y., Prediction of distribution volume of vancomycin in critically ill patients using extravascular lung water and pulmonary vascular permeability indices. *Int. J. Clin. Pharmacol. Ther.*, 2012; 50(11): 814-820.
17. Jeurissen A., Sluyts I., Rutsaert R., A higher dose of vancomycin in continuous infusion is needed in critically ill patients. *Int. J. Antimicrob. Agents*, 2011; 37(1): 75-77.
18. Katip W., Jaruratanasirikul S., Pattharachayakul S., Wongpoowarak W., Jitsurong A., Lucksiri A., The

pharmacokinetics of vancomycin during the initial loading dose in patients with septic shock. *Infect. Drug. Resist.*, 2016; 9: 253-260.
19. Mahmoud M.A., Ebid A.H., Shouman S.A., Ebid E.N., Pharmacokinetics of Vancomycin in Oncology Egyptian Paediatrics: A Dosage Adjustment Trial. *Ind. J. Pharm. Sci.*, 2014; 76(1): 82-86.
20. Marqués-Miñana M.R., Saadeddin A., Peris J.E., Population pharmacokinetic analysis of vancomycin in neonates. A new proposal of initial dosage guideline. *Br. J. Clin. Pharmacol.*, 2010; 70(5): 713-720.
21. Micu C., Roşu A.F., Biță A., Călina D., Roşu L., Zlatian O., Brumar A., Antimicrobial resistance of urinary *Escherichia coli* isolates. *Eur. J. Hosp. Pharm.*, 2012; 19: 250-251.
22. Murray E.C., Marek A., Thomson P.C., Coia J.E., Gram-negative bacteraemia in haemodialysis. *Nephrol. Dial. Transplant*, 2015; 30(7): 1202-1208.
23. Nikhilesh A., Nagendra Nayak I.M., Advaitha M.V., Thaikattil N.J., Kantanavar K.A., Anand S., Antimicrobial agents' utilization and cost pattern in an Intensive Care Unit of a Teaching Hospital in South India. *Ind. J. Crit. Care Med.*, 2016; 20(5): 274-279.
24. Paciullo C.A., Harned K.C., Davis G.A., Connor M.J. Jr, Winstead P.S., Vancomycin clearance in high-volume venovenous hemofiltration. *Ann. Pharmacother.*, 2013; 47(3): e14.
25. Petejova N., Martinek A., Zahalkova J., Duricova J., Brozmannova H., Urbanek K., Grundmann M., Plasek J., Kacirova I., Vancomycin pharmacokinetics during high-volume continuous venovenous hemofiltration in critically ill septic patients. *Biomed. Pap. Med. Fac. Univ. Palacky. Olomouc. Czech Repub.*, 2014; 158(1): 65-72.
26. Revilla N., Martín-Suárez A., Pérez M.P., González F.M., del Mar Fernández de Gatta Garcia M., Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/ pharmacodynamics simulation. *Br. J. Clin. Pharmacol.*, 2010; 70(2): 201-212.
27. Rybak M.J., The Pharmacokinetic and Pharmacodynamic Properties of Vancomycin. *Clin. Infect. Dis.*, 2006; 42(Suppl 1): S35-39.
28. Rybak M., Lomaestro B., Rotschafer J.C., Moellering R. Jr, Craig W., Billeter M., Dalovisio J.R., Levine D.P., Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am. J. Healt. Syst. Pharm.*, 2009; 66(1): 82-98.
29. Salgado F.X.C., Sanchez T.E.G., Silva N.B.D., Oliveira H.B., Karnikowski M., Evaluation of rational use of antimicrobial agents in a Brazilian intensive care unit. *Health*, 2014; 6(2): 188-194.
30. Schairer J., Sankri-Tarbichi A.G., Fairfax M.R., Salimnia H., Guzman J.A., Methicillin-resistant *Staphylococcus aureus* infection with intermediate sensitivity to vancomycin: a case report and literature review. *J. Intensive. Care. Med.*, 2008ş 23(5): 338-341.
31. Shelat P.R., Gandhi A.M., Patel P.P., A Study of Utilization of Antimicrobial Agents in Patients on Ventilator in Intensive Care Unit (ICU) at Tertiary Care Teaching Hospital, India. *J. Clin. Diagn. Res.*, 2014; 8(11): 9-13.
32. Staicus C.I., Călina D., Rosu L., Rosu A.F., Zlatian O., Involvement of microbial flora in aetiology of surgical site infections. *Eur. J. Hosp. Pharm.*, 2015; 22: A57.
33. Staicus C.I., Călina D., Rosu L., Rosu A.F., Zlatian O., The pharmacotherapeutic management of parapneumonic pleurisy. *Eur. J. Hosp. Pharm.*, 2015; 22: A58-A59.
34. Stove V., Coene L., Carlier M., De Waele J.J., Fiers T., Verstraete A.G., Measuring unbound *versus* total vancomycin concentrations in serum and plasma: methodological issues and relevance. *Ther. Drug Monit.*, 2014; 37(2): 180-187.
35. Tănase A., Coliță A., Ianoşi G., Neagoe D., Brănişteanu D.E., Călina D., Docea A.O., Tsatsakis A., Ianoşi S.L., Rare case of disseminated fusariosis in a young patient with graft *vs.* host disease following an allogeneic transplant. *Exp. Ther. Med.*, 2016; 12: 2078-2082.
36. Tewari V.P., Errata: 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(9): 1465-1465.
37. Tsuji B.T., Leonard S.N., Rhomberg P.R., Jones R.N., Rybak M.J., Evaluation of daptomycin, telavancin, teicoplanin, and vancomycin activity in the presence of albumin or serum. *Diagn. Microbiol. Infect. Dis.*, 2008, 60(4): 441-444.
38. Zhang H., Wang Y., Gao P., Hu J., Chen Y., Zhang L., Shen X., Xu H., Xu Q., Pharmacokinetic characteristics and clinical outcomes of vancomycin in young children with various degrees of renal function. *J. Clin. Pharmacol.*, 2015; 56(6): 740-748.