Monitoring of Blood Concentration and Clinical Efficacy of Vancomycin in the Treatment of Patients with Critically Ill Infections

Z. ZENG, Y. LIN AND KECHUAN PAN*

Department of Infectious Diseases, The First People's Hospital of Wenling, Wenling, Zhejiang Province 317500, China

We attempt to discuss the clinical efficacy and safety of vancomycin in different blood concentrations in patients with critically ill infections. We collected 50 patients who received vancomycin treatment from infectious diseases department in our hospital from June 2017 to June 2021. Monitored the trough concentration of vancomycin and selected the trough concentration after reaching the steady state. We divided patients into three groups according to the minimum blood concentration value i.e. minimum blood concentration <10 mg/l (n=16), minimum blood concentration 10 mg/l~15 mg/l (n=18) and minimum blood concentration >15 mg/l (n=16), compare the clinical effective rate and adverse reactions rate among the three groups of patients. 16 cases, 18 cases and 16 cases were enrolled into the three groups of minimum blood concentration <10, 10-15, >15 mg/l and the clinical cure rates were 68.8 %, 66.7 % and 66.7 % respectively. The differences in effective rates among the groups had no statistical significance (p=0.983); the overall adverse reactions rate in 50 patients was 18 % (9/50) and adverse reactions rate in minimum blood concentration >15 mg/l group was (43.8 %, 7/16), especially it is acute renal dysfunction, which is statistically different from the other two groups (p=0.025). The high blood concentration of vancomycin in patients with critically ill infection does not increase its clinical efficacy, but will increase adverse reactions rate in patients and provide a basis for providing the best vancomycin dose in clinical practice.

Key words: Vancomycin, blood concentration, critically ill infection, clinical efficacy, adverse reactions

Staphylococcus aureus (*S. aureus*) is the commonest gram-positive cocci and one type of common pathogen[1], which often appears in cardiovascular system, respiratory system and digestive system. Among them, Methicillin-Resistant *S. aureus* (MRSA) has become the leading cause of global health care and community-associated infections. MRSA accounted for 25.8 % of *S. aureus* infections in the United States[2], but among patients with *S. aureus* infection in Egypt, MRSA strains accounted for more than 70 % of hospital-related *S. aureus* isolates and more than 11.5 % of community-acquired *S. aureus* infection[3]; in Chinese patients with *S. aureus* infection, the prevalence of MRSA is very high (40 %~80 %)[4]; in Chinese Taiwan patients with *S. aureus* infection and the prevalence of MRSA in Intensive Care Unit (ICU) is above 80 %. It can be seen that MRSA is the most common in patients with *S. aureus* infection in ICU ward. Vancomycin has been widely used as a key antibiotic in the treatment of infections caused by various Gram-Positive Bacteria (GPB), which significantly reduces the severity of *S. aureus* infection, especially for MRSA and significantly improves the clinical efficacy and survival rate of severe patients[5,6]. However, there are many adverse drug reactions in the clinical use of vancomycin and its serious adverse reaction is nephrotoxicity[7]. Optimizing vancomycin treatment through Therapeutic Drug Monitoring (TDM) can effectively avoid nephrotoxicity and drug resistance, and improve the clinical treatment effect[8]. We often adopt Area Under Curve (AUC) to monitor the clinical efficacy of TDM, but it requires multiple blood samples from each patient, which is difficult to obtain[9,10]. Therefore, many studies have used vancomycin Valley concentration for TDM detection of vancomycin instead of AUC[11]. A recent 12 mo survey of 49 hospitals in the United States showed that 17 % of 419 cases of enterococcal bacteremia were caused by vancomycin resistant strains and these infections led to increased mortality and medical costs. Therefore, on the basis of ensuring the minimum nephrotoxicity of vancomycin, how to avoid vancomycin resistance and ensure its effectiveness is particularly important[12].

***Address for correspondence**
E-mail: pankechuan@163.com

Therefore, this study was retrospectively analyzed to explore the optimal valley concentration of vancomycin and the related clinical therapeutic effects. Let us check the following reports. We collected 50 patients who received vancomycin treatment from infectious diseases department in our hospital from June 2017 to June 2021 and divided them into three groups according to the minimum blood Concentration (C_{min}) value: C_{min} <10 mg/l (n=16), C_{min} 10 mg/l~15 mg/l (n=18) and C_{min} >15 mg/l (n=16), comparison of general information of three groups was listed in Table 1, all patients were monitored for C_{min} at least once during hospitalization. Inclusion criteria; all patients met the diagnosis of severe infection. Exclusion criteria; patients aged <18 y old; patients with a history of vancomycin allergy or intolerance to vancomycin; incomplete clinical data or discontinuation of treatment; patients with liver and kidney damage or hearing impairment; patients with unstable vital signs and patients with other drugs that interfere with vancomycin concentration monitoring in patient samples. After the patient's vancomycin concentration has stabilized, obtain the trough concentration of vancomycin before the next dose. Monitored peak drug concentration after 0.5 h-1 h at the end of the 5th dose, then observed the clinical efficacy and related biochemical functions. Acute Kidney Injury (AKI) is defined as one of the following criteria, serum creatinine increased more than 1.5 times the baseline value after using vancomycin and it is clear or inferred that the above situation occurred within 7 d and the decrease of urine volume was <0.5 ml/(kg/h) and lasted for more than 6 h[13]. Evaluated the clinical efficacy according to the recovery of clinical symptoms, signs, imaging and laboratory tests (including bacteriology) and the reference standards were as follows, recovery indicates a return to normal range of clinical symptoms, signs, imaging and laboratory tests (including bacteriology); significantly effective indicates a remarkable improvement of clinical symptoms, signs, imaging and laboratory tests (including bacteriology); invalid indicates no improvement of clinical symptoms, signs, imaging and laboratory tests (including bacteriology), even worse.

(Recovery+Significantly effective)/Total cases=Total clinical effective rate

Use Statistical Package for Social Sciences (SPSS) 20.0 software to analyze all data. Express the count data as n %, tested by Chi-square (χ^2). Measurement data conforms to normal distribution and homogeneity of variance as ($\bar{x}\pm s$). Use t-test for comparison between groups. $p<0.05$ indicated the differences possessed statistical significance. The basic information of patients in different C_{min} groups is as follows, ages of C_{min} <10 mg/l group were 59.69±11.32 y old, ages of C_{min} 10 mg/l-15 mg/l group were 60.17±11.38 y old, ages of C_{min} >15 mg/l group were 57.19±10.12 y old. The infection site is mainly distributed in the brain and the cardiovascular system and respiratory system are more common, the baseline data differences of groups had no statistical significance ($p>0.05$) as shown in Table 1. Cure rate of C_{min} <10 mg/l group, C_{min} 10 mg/l-15 mg/l group and C_{min} >15 mg/l group was 68.8 %, 66.7 % and 66.7 % respectively, effective rate was 25.0 %, 27.8 % and 18.8 % respectively, ineffective rate was all 6.25 %, clinical efficacy of three groups were similar, so it possessed statistical significance as shown in Table 2. C_{min} <10 mg/l group and C_{min} 10 mg/l-15 mg/l group had no adverse reactions of hearing loss and liver function damage and 1 case of each had renal function damage, but C_{min} >15 mg/l group had adverse reactions rate as high as 43.5 %, renal function impairment was the most common, accounting for 18.8 %, the differences among three groups possessed statistical significance, but C_{min} >15 mg/l group had the highest adverse reactions rate as shown in Table 3. This study found that there is no correlation between the clinical efficacy of vancomycin and vancomycin C_{min}, but C_{min} >15 mg/l group will significantly increase adverse reactions rates such as hearing impairment and liver and kidney function damage. AKI rate of C_{min} >15 mg/l group is about 18.8 % (3/16), which is more than three times of C_{min} <10 mg/l group (6.25 %). Optimal treatment strategies for severe MRSA infections remain of great interest, especially by ICU physicians. Vancomycin was developed and approved in the 1950s to treat gram-positive infections. For ease of administration and to simplify vancomycin dose adjustment and monitoring, in 2009 multiple organizations recommended trough monitoring and maintaining trough concentrations between 15 and 20 μg/ml[14], since the publication of these guidelines, multiple studies have evaluated the efficacy and safety of the recommended vancomycin trough concentrations (C_{min}) with conflicting results. Recent studies have shown that high Ventral-Temporal Cortex (VTC) is not associated with any significant improvement in treatment outcomes, whether in adults or children[15]. One study monitored the blood concentration of vancomycin in 86 critically ill patients and found that the average trough concentration was (12.29±9.33) mg/l^{-1} and the effective rate of treatment was as high as 75.58 %, and it was related to gender[16]. Other studies have shown that for patients with intracranial infection,

drug monitoring of vancomycin in cerebrospinal fluid should be performed together with treatment, which provides more reference for the medication of patients with central nervous system infection in neurosurgery[17]. Renal impairment is still considered to be the most serious adverse effect of vancomycin and is associated with increased mortality, length of hospital stay and medical costs, which may be related to the pharmacokinetics of vancomycin, because more than 90 % of the drug is excreted by the kidneys. The renal clearance of vancomycin mainly occurs through glomerular filtration and to some extent, through active renal tubular secretion, but its direct mechanism is still controversial. Studies have shown that vancomycin accumulates in proximal tubular cells, leading to cell necrosis or changes in mitochondrial function, resulting in decreased reabsorption of proximal tubular cells, leading to nephrotoxicity[18]. Besides tubulointerstitial nephritis, severe nephrotoxicity caused by vancomycin can also manifest as histological granuloma formation[19]. The incidence of nephrotoxicity varied widely among studies and a meta-analysis showed that the incidence of vancomycin related nephrotoxicity ranged from 5 % to 43 %. Other studies also showed that vancomycin C_{min} ≥15 mg/l and treatment time more than 14 d were independent risk factors for acute renal injury. This is similar to our study; C_{min} ≥15 mg/l increases the risk of nephrotoxicity. In addition, some studies have shown that the Body Mass Index (BMI) of patients has relationship with the curative effect. Patients with malnutrition may have serious infection, so the normal dose of vancomycin may not be effective[20]. This study has some limitations. Since our study population is mainly aimed at Chinese people, we need to be cautious about the interpretation of this result when it is extended to other populations; secondly, the sample size of our study is relatively small, which may bring some errors to the study results. High blood concentration of vancomycin in patients with severe infection does not increase its clinical efficacy, but increases adverse reactions rate in patients.

TABLE 1: COMPARISON OF BASELINE DATA AMONG DIFFERENT C_{min} GROUPS ($\bar{x}$±s)

	<10 mg/l (n=16)	10-15 mg/l (n=18)	>15 mg/l (n=16)	p
Age	59.69±11.32	60.17±11.38	57.19±10.12	0.716
BMI	22.25±3.78	24.00±3.46	23.06±2.87	0.303
Infection site				0.979
Intracranial infection	6 (37.5 %)	7 (38.9 %)	6 (37.5 %)	
Cardiovascular infection	5 (31.3 %)	5 (27.8 %)	4 (25.0 %)	
Respiratory infection	3 (18.8 %)	4 (22.2 %)	4 (25.0 %)	
Other site infection	2 (12.5 %)	2 (11.1 %)	2 (12.5 %)	

TABLE 2: COMPARISON OF CLINICAL EFFICACY AMONG DIFFERENT C_{min} GROUPS ($\bar{x}$±s)

	<10 mg/l (n=16)	10-15 mg/l (n=18)	>15 mg/l (n=16)	p
Clinical efficacy				0.983
Cure rate	11 (68.8 %)	12 (66.7 %)	12 (66.7 %)	
Effective rate	4 (25.0 %)	5 (27.8 %)	3 (18.8 %)	
Ineffective rate	1 (6.25 %)	1 (6.25 %)	1 (6.25 %)	

TABLE 3: COMPARISON OF ADVERSE REACTIONS RATE AMONG DIFFERENT C_{min} GROUPS ($\bar{x}$±s)

	<10 mg/l (n=16)	10-15 mg/l (n=18)	>15 mg/l (n=16)	p
Adverse reactions				0.025
Hearing loss	0 (0 %)	0 (0 %)	2 (12.5 %)*	
Liver function damage	0 (0 %)	0 (0 %)	2 (12.5 %)*	
Renal function damage	1 (6.25 %)	1 (6.25 %)	3 (18.8 %)*	
Total adverse reactions rate	1 (6.25 %)	1 (6.25 %)	7 (43.5 %)*	

Note: *p<0.05 *vs.* C_{min}<10 mg/l group

Conflict of interests:

The authors declared no conflict of interest.

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