The effect of the body mass index and creatinine clearance on serum trough concentration of vancomycin in adult patients

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Abstract

Background: The aim of this study was to evaluate the influence of patient body mass index (BMI) and estimated creatinine clearance (CrCl) on serum vancomycin concentrations in order to define a possible optimal dosage regimen in overweight patients from data obtained during therapeutic drug monitoring.

Methods: This retrospective study used data collected from January 2017 to January 2019. Adult patients (n=204) receiving vancomycin treatment at a dose of 1000 mg in every 12 h and undergoing serum monitoring. Data collected included patient gender, age, height and weight, vancomycin regimens and concentrations, and serum creatinine. In this study, statistical comparisons were made on the results from patients according to serum vancomycin concentration.

Results: Serum vancomycin concentration was significantly related to BMI ($P < 0.001$) and CrCl ($P < 0.05$) in adult patients. Further, the trough serum vancomycin concentration showed a logarithmic correlation with BMI ($R = -0.5108$, 95 % CI: -0.6082 to -0.3982 , $P < 0.001$) and CrCl ($R = -0.5739$, 95 % CI: -0.6616 to -0.4707 , $P < 0.001$). In addition, the CrCl was significantly related to BMI ($P < 0.01$). Besides, some of the patients with higher BMI (≥ 24 kg/m²) met the goal trough concentration after an adjustment from 1000 mg every 12 h to 1000 mg every 8 h.

Conclusions: Serum vancomycin concentration decreases progressively with increasing BMI due to the augment in CrCl in adult patients. Therefore, dose adjustment should be based on BMI and CrCl for safe and effective use of vancomycin in adult patients (BMI ≥ 24 kg/m²).

Background

Vancomycin is a glycopeptide antibiotic produced by Streptococcus orientalis that has been used over half a century. Although many antibiotics have been developed and used, vancomycin remains the first-line therapy for the invasive multi-resistant gram-positive bacterial infections, particularly those involving methicillin-resistant Staphylococcus aureus (MRSA) [1]. As the therapeutic range is narrow in vancomycin, therapeutic drug monitoring (TDM) is necessary to maximize clinical efficacy while minimize the risk of toxicities [2]. We generally plan vancomycin administration using the trough concentration as one measure.

The clinical guidelines recommend always keeping trough vancomycin concentrations above 10 µg/mL, and a trough vancomycin concentration of 15–20 µg/mL is recommended in more serious infections [3]. As the elimination of vancomycin relies almost exclusively on glomerular filtration, renal function is one of the most important factors influencing patient exposure to vancomycin [4]. Creatinine clearance (CrCl) is the volume of blood plasma cleared of creatinine per unit time. It is a rapid and effective method for the measurement of renal function. In fact, it is more accurate and provides a better estimation of vancomycin pharmacokinetics to utilize patients' non-capped CrCl when determining a vancomycin dosing regimen [5].

A large number of studies have shown that CrCl is affected by factors such as age, muscle mass, diet, and proximal tubule secretion of creatinine [6–8]. Recently, one study indicated that increased total body weight impacted the CrCl and increased the rate of acute kidney injury among patients concurrently treated with piperacillin-tazobactam and vancomycin [9]. Pokorná and colleagues found that vancomycin pharmacokinetics was mainly influenced by actual body weight in neonates [10]. Another research reported that overweight patients have an increased glomerular filtration rate (GFR) and increased renal plasma flow [11]. Thus, the results of these studies indicate that body weight independently affects the filtering capacity of the kidneys and the pharmacokinetic properties of vancomycin. Clinical practice guideline by the Infectious Disease Society of America (IDSA) recommended a vancomycin dose of 15–20 mg/kg (as actual body weight) given every 8–12 h for adult patients with normal renal function, and 15 mg/kg every 6 h in children [12]. However, such recommendations may be inadequate in overweight patients due to increases in vancomycin clearance and volume of distribution [13]. As a result, a better assessment of renal function and dosage adjustment of vancomycin eliminated by the kidneys is needed in overweight patients [14]. We have treated many patients with relatively higher body mass index (BMI) in whom the serum vancomycin concentrations were found to be moderately lower based on TDM data obtained in our hospital. It is unclear whether the presence of higher BMI increases CrCl, resulting in larger vancomycin dosage requirements. In addition, to date there have been no reports focusing on the effect of both BMI and CrCl on serum vancomycin concentrations. Therefore, the purpose of our study was to determine whether both the BMI and CrCl influence trough concentrations of vancomycin in adult patients.

Methods

Patients

A single-center retrospective cohort study was conducted at the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, China. Adult patients ≥ 18 years of age admitted between January 2017 to January 2019 with suspected or documented Gram-positive infections and receiving empirical vancomycin therapy. This study was approved by decisions of the Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. Patient data were anonymized prior to analysis. Another pharmacist, who was not participating in the study, was responsible for anonymizing these data. The following information including patient demographics such as gender, age, height and weight; renal function test results such as serum creatinine concentration (Scr) were collected from the patient medical records. Other data collected included vancomycin indication, vancomycin dosing regimens, and vancomycin serum trough concentrations, dates, and collection times. Patients who were pregnant, received vancomycin as perioperative antibiotic prophylaxis or any modality of dialysis were excluded.

Groups

In this study, patients were divided into two groups to rule out the effect of age on results: Group A with age < 60 years (N = 88 patients), Group B with age ≥ 60 years (N = 116 patients). Underweight was defined as a BMI < 18 kg/m², normal weight as a BMI of 18~23.9 kg/m², overweight as a BMI of 24~27.9 kg/m², and obesity as a BMI ≥ 28 kg/m². Then, patients were cohorted by BMI (< 24 kg/m² and ≥ 24 kg/m²) [15] and CrCl (< 90 mL/min and ≥ 90 mL/min) [16].

Cockcroft-Gault formula: Estimated CrCl

CrCl can be estimated using Scr (μmol/L) levels. The Cockcroft–Gault formula is the most widely used clinical method for estimating CrCl (mL/min) to adjust drug dosages [17]. The resulting CrCl is multiplied by 0.85 if the patient is female to correct for the lower CrCl in females. Below is the formula:

$$\text{CrCl (Male)} = (140 - \text{age}) \times \text{weight (kg)} / [0.818 \times \text{Scr (}\mu\text{mol/L)}]$$

$$\text{CrCl (Female)} = 0.85 \times (140 - \text{age}) \times \text{weight (kg)} / [0.818 \times \text{Scr (}\mu\text{mol/L)}]$$

Administration and measurement of vancomycin

Patients were treated with vancomycin at dosages of 1000 mg every 12 h. Serum vancomycin concentration was considered to have achieved steady state if ≥ 3 half-lives have elapsed prior to first blood sampling. Dosage adjustment was performed on the subsequent days if necessary. Vancomycin serum levels were measured using enzyme multiplied immunoassay technique (EMIT) on the Siemens Viva-E analyzer (ELITechGroup B. V., Van Rensselaerweg 4 6956 AV, the Netherlands). The linear range for the assay was 2–50 μg/mL, and the limit of quantitation was 2 μg/mL.

Statistical analysis

Prim 6.0 was used for statistical analyses. Descriptive statistics were processed for all study variable and continuous variables were expressed as mean (standard deviation) or median (interquartile range) where applicable. Categorical variables were expressed as numbers (percentages) and analysed using the chi-squared test or Fisher's exact test. The linear regression analyses were performed to examine the interaction between steady-state trough concentration and CrCl, trough concentration and BMI. A *P*-value of < 0.05 was considered statistically significant.

Results

The main demographics and clinical variables of the patients listed in Table 1 were evaluated for their influence on the trough vancomycin concentration. The mean patient age was 60.7 years, and 65.2% were male patients. The median BMI was 23.8 kg/m², while median CrCl was 107.5 mL/min According to

the clinical guidelines of trough vancomycin concentration, a trough vancomycin concentration of $< 10 \mu\text{g/mL}$ was assigned to low concentration and a trough vancomycin concentration of $> 20 \mu\text{g/mL}$ was assigned to high concentration. As show in Table 1, the vancomycin concentration in Group A was significantly related to BMI ($P < 0.001$) and CrCl ($P = 0.0162$) respectively. However, there was no significant association of vancomycin concentration with gender. These parameters mentioned above showed the same tendencies in the elder population of Group B.

A total of 204 vancomycin observations from adult patients that received vancomycin at dosages of 1000 mg every 12 h were included in the Figure 1: as BMI and CrCl increased, the percentage of patients with adequate serum concentrations decreased. Most notably, trough serum vancomycin concentration showed a logarithmic correlation with BMI ($R = -0.5108$, 95 % confidence interval (CI): -0.6082 to -0.3982 , $P < 0.001$, Figure 1A) and CrCl ($R = -0.5739$, 95 % CI: -0.6616 to -0.4707 , $P < 0.001$, Figure 1B) in all adult patients included in this study.

To further investigate the relationship between CrCl and BMI, the statistic analysis of demographics and characteristics of the patients was showed the CrCl was significantly related to BMI (Table 2, Group A, $P = 0.0011$, Group B, $P = 0.0011$).

In addition, the dosage schedule of patients ($N = 24$) with higher BMI ($\geq 24 \text{ kg/m}^2$, $26.88 \pm 1.71 \text{ kg/m}^2$) in this study had been adjusted and the time to new steady-state was calculated. After an adjustment from 1000 mg every 12 h to 1000 mg every 8 h, the trough concentration in three patients increased from 4.00 to 20.30 $\mu\text{g/mL}$, 7.32 to 21.34 $\mu\text{g/mL}$ and 5.08 to 24.31 $\mu\text{g/mL}$, meanwhile the serum concentrations achieved the goal trough concentration in 87.5 % ($N = 21$) of these patients.

Discussion

Vancomycin pharmacokinetics is highly variable even among patients with similar characteristics. In recent years, how to improve the clinical efficacy of vancomycin and reduce its side effects has become the focus of clinical research. However, serum vancomycin concentrations often do not reach the target treatment level in overweight patients [18]. The world health organization (WHO) has published a standard for evaluating overweight and obesity in adults based on BMI [19], and there are also standard BMI values in China [15].

At present, the Chinese standard BMI cut-off points are $\geq 24 \text{ kg/m}^2$ for overweight and $\geq 28 \text{ kg/m}^2$ for obesity. It has been reported that the thresholds of BMI may be different by age group [20]. In this study, patients were divided into two groups to rule out the effect of age. Our study found that the steady-state trough vancomycin concentration was negatively correlated with BMI and CrCl. Meanwhile, the elder patients also showed significantly tendency in the same dosing regimen. In addition, we observed a significant logarithmic correlation between the steady-state trough concentration and BMI, the steady-state trough concentration and CrCl, respectively. It obviously showed that serum vancomycin concentration is strongly associated with BMI and CrCl in all adult patients. Notably, we found the CrCl

was positively related to BMI which indicated that CrCl is affected by BMI. Thus, increased initial loading dose or increased dosing frequency is necessary for patients with higher BMI. Indeed, we further adjusted the vancomycin dosage schedule (1000 mg every 8 h) in twenty-four patients with BMI ≥ 24 kg/m², most of them achieved successfully the goal trough concentration.

However, this study has several limitations to consider. The main limitation of the study was not a strictly controlled clinical trial but a retrospective investigation with data produced in clinical settings. Other limitations must also be considered, including the majority of the studies are of small size. We also didn't take into account the physical condition of the patients, such as a serious illness throughout their entire hospitalization. Lastly, we did not evaluate the clinical outcomes or adverse drug reactions of the patients.

In this study, we have tried to adjust the dosage regimen for patients with BMI ≥ 24 kg/m², and the effects were mostly ideal. Therefore, the combination of BMI, CrCl and serum vancomycin concentration monitoring should play an important role for dosage adjustment in individual patients.

Conclusion

Our results suggest that serum vancomycin concentration decreases progressively with increasing BMI due to the augment in CrCl in adult patients. Therefore, dose adjustment should be based on BMI and CrCl for safe and effective use of vancomycin in adult patients (BMI ≥ 24 kg/m²). Further research to confirm this negative association is needed.

Declarations

Supplementary information

Additional file 1. Dataset of cases. Data of cases used and analyzed during the current study.

Abbreviations

MRSA: methicillin-resistant *Staphylococcus aureus*, TDM: therapeutic drug monitoring, CrCl: Creatinine clearance, GFR: glomerular filtration rate, IDSA: Infectious Disease Society of America, BMI: body mass index, Scr: serum creatinine concentration, EMIT: enzyme multiplied immunoassay technique, CI: confidence interval, WHO: world health organization.

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Consent to publication

All authors approved of the manuscript and consented to its publication.

Authors' contributions

Yuyan Pan conceived and designed the study protocol, Yuyan Pan, Xiaomei He and Xinyu Yao performed experiments, Fengjiao Wang analyzed data, Yuyan Pan and Xinyuan Ding wrote the manuscript, Wenjuan Wang revised manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used and/or analyzed during the current study is available as Additional file 1.

Ethics approval and consent to participate

This study was approved by decisions of the Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University.

Competing interests

The authors declare they have no competing interests.

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Tables

Table 1: The correlation between serum vancomycin concentrations and characteristics of patients included in different groups.

Groups	demographics and characteristics	Case no.	Vancomycin concentration (μg/mL)			Chi-square	P-value
			< 10	10~20	> 20		
Group A	Gender					1.443	0.4861
		61	40	18	3		
	Male						
		27	15	9	3		
	Female						
	BMI (kg/m ²)					22.450	< 0.001***
		36	12	19	5		
	< 24						
		52	43	8	1		
Group B							
	≥ 24						
	CrCl (mL/min)					8.247	0.0162*
		21	9	8	4		
	< 90						
		67	46	19	2		
	≥ 90						
Group B	Gender					3.206	0.02013
		72	23	35	14		
	Male						
		44	8	23	13		
	Female						
	BMI (kg/m ²)					25.360	< 0.001***
		82	11	48	23		
	< 24						
		34	20	10	4		
Group B							
	≥ 24						

CrCl (mL/min)					18.320	0.0001***
	74	10	43	21		
< 90						
	42	21	15	6		
≥ 90						

P by Chi-square test, * *P* < 0.05, *** *P* < 0.001 were considered significant.

Table 2: The correlation between CrCl and BMI of patients included in different groups.

Groups	BMI (kg/m ²)	Case no.	CrCl (mL/min)		χ^2	<i>P</i> -value
			< 90	≥ 90		
Group A	< 24	36	15	21	10.628	0.0011**
		52	6	46		
	≥ 24					
Group B	< 24	82	60	22	10.652	0.0011**
		34	14	20		
	≥ 24					

P by Fisher's exact test, ** *P* < 0.01 was considered significant.

Figures

Figure 1

The relationships between steady-state trough vancomycin concentration and BMI, CrCl were linear. Trough serum vancomycin concentration showed a logarithmic correlation with BMI ($R = -0.5108$, 95 % CI: -0.6082 to -0.3982 , $P < 0.001$, Figure 1A) and CrCl ($R = -0.5739$, 95 % CI: -0.6616 to -0.4707 , $P < 0.001$, Figure 1B) in all adult patients included in our study.

Supplementary Files

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- [Dataset.xlsx](#)