Evaluation of efficacy and nephrotoxicity during vancomycin therapy: A retrospective study in China

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Received May 23, 2018; Accepted November 23, 2018

DOI: 10.3892/etm.2019.7188

Abstract. The aim of the present study was to investigate the predictive value of vancomycin serum concentrations regarding its efficacy and nephrotoxicity in a Chinese population and to determine a relatively safe optimal target concentration during vancomycin therapy. A total of 65 patients that received vancomycin between March 2013 and March 2018 at Shanghai 10th People's Hospital (Shanghai, China) were enrolled and their vancomycin trough and peak concentrations were monitored. Factor analysis was performed in order to exclude interaction between variables. Univariate and multivariate analyses were used to identify predictors of drug efficacy and nephrotoxicity. Receiver operating characteristic curve analysis was performed to determine the thresholds of the vancomycin trough and peak concentrations for optimal efficacy and acceptable nephrotoxicity, respectively. Among the 65 cases, treatment was deemed to be effective for 43 patients and ineffective for 22 patients. Furthermore, 20 patients fulfilled the criteria for nephrotoxicity. A total of 15 continuous variables loaded the first five factors by factor analysis (which converts large numbers of highly inter-correlated variables into a small number of comprehensive indicators that reflect a dimensionality reduction) and the factors were as follows: Inflammation, renal function, liver function, vancomycin trough and peak concentrations, and nutritional status. Univariate and multivariate analyses identified the trough concentration and peak concentration as independent variables associated with efficacy and nephrotoxicity of vancomycin, and the nutritional status was a risk factor associated with efficacy. Regarding efficacy, the critical values for the trough concentration and peak concentration were determined to be 9.02 mg/l (95.3% sensitivity and 68.2% specificity) and 23.62 mg/l (83.7% sensitivity and 59.1% specificity), respectively. The thresholds of vancomycin trough and peak concentrations for the development of nephrotoxicity were 16.08 mg/l (80.0% sensitivity and 84.4% specificity) and 30.42 mg/l (75.0% sensitivity and 73.3% specificity), respectively. In conclusion, during vancomycin therapy, the trough and peak concentrations are associated with efficacy and nephrotoxicity. Furthermore, a trough concentration between 9.02 and 16.08 mg/l and a peak concentration of 23.62-30.42 mg/l were determined to be relatively safe (the clinical trial registry no. ChiCTR-OPC-16007920).

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Key words: vancomycin, therapeutic drug monitoring, efficacy, nephrotoxicity

Introduction

Staphylococcus aureus, the most common type of Gram-positive coccus, is an important pathogenic bacterium. It is widely distributed in the environment and has strong pathogenicity; it is able to cause a number of common or complex infectious diseases, including pneumonia, arthritis, urinary tract infections, osteomyelitis and meningitis. Methicillin-resistant *S. aureus* (MRSA) accounts for >55% of all *S. aureus* infections in communal and health care-associated settings (1). With the prevalence of MRSA infections increasing, its morbidity, mortality and cost of medical care are increased (2).

Vancomycin, a glycopeptide antibiotic, is the first-line agent in the treatment of *S. aureus* strains that produce penicillinase, particularly for patients infected with MRSA (3-5). However, vancomycin is almost exclusively eliminated by the kidneys; therefore, a potentially serious adverse effect of vancomycin is nephrotoxicity (6,7). Optimization of vancomycin therapy with therapeutic drug monitoring (TDM) may improve the treatment efficacy, and avoid nephrotoxicity and drug resistance (8,9). It has been determined that the superior effect of vancomycin is highly correlated with the area under the concentration-time curve (AUC) and the minimum inhibitory concentration (MIC). However, it is difficult to obtain the AUC in the clinical setting. Thus, vancomycin serum trough concentrations may be used as a substitute for AUCs (10). A consensus review published by the Infectious Diseases Society of America (IDSA) provides recommendations that serum vancomycin trough concentrations should always be

maintained at >10 mg/l in order to avoid the development of vancomycin resistance in adult patients, and a vancomycin serum trough concentration of 15-20 mg/l is recommended for complicated infections (3). However, certain studies have indicated that higher vancomycin trough concentrations (≥15 mg/l) are associated with higher rates of nephrotoxicity. Furthermore, the results of studies on vancomycin TDM in China indicate that the dosage of vancomycin is generally low (11,12). Therefore, there is controversy regarding the optimal target concentration of vancomycin.

The present study performed a retrospective analysis in order to investigate the predictive value of vancomycin serum concentrations regarding the efficacy and nephrotoxicity in patients in China and to determine a relatively safe optimal target concentration during vancomycin therapy.

Patients and methods

Study design and patients. Hospitalized patients who received a course of vancomycin therapy between March 2013 and March 2018 at the Department of Respiratory Medicine of Shanghai 10th People's Hospital Affiliated to the Tongji University (Shanghai, China) were retrospectively reviewed. The inclusion criteria were as follows: i) Vancomycin therapy for at least 3 days; ii) requirement of TDM of vancomycin to assess efficacy and toxicity and iii) written informed consent. The exclusion criteria were as follows: i) Treatment with vancomycin within 72 h prior to the monitoring phase; ii) pregnant or breastfeeding women; iii) no availability of the laboratory data; iv) patients with diseases affecting the metabolism of vancomycin.

Data collection. The investigators observed the patients daily during vancomycin therapy until it was discontinued or the patient was discharged from the hospital, depending on which happened first. During the observation period, the following demographic information was collected: Gender, age, weight, height, diagnosis, the site of the Gram-positive cocci culture, length of hospitalization and whether the patient had undergone surgery, been implanted with medical devices or admitted to an intensive care unit (ICU). The vancomycin trough and peak concentrations were recorded. Trough concentrations were obtained just prior to the subsequent dose under steady-state conditions (approximately after the fourth dose). Peak concentration monitoring was performed 0.5-1 h after the end of the fifth dose. Laboratory values, medical history and comorbidities, concomitant medications (carbapenems, cephalosporins, aminoglycosides and quinolones), microbiologic data and details regarding vancomycin treatment (date, time, dosing regimen, initial dosing frequency and duration) were noted on a daily basis.

Definitions. The definition of comprehensive efficacy included the results of clinical efficacy evaluation and bacteriological efficacy evaluation as follows: The clinical symptoms and signs, as well as the radiologic and laboratory tests (including bacteriology) returned to normal or pre-infection status; and vancomycin was not required within 7 days after discontinuation of the drug. In the primary analysis, three definitions of nephrotoxicity were used: i) An increase in serum creatinine (SCr) to ≥0.5 mg/dl (44.2 mmol/l); and ii) a 50% increase in SCr; or iii) a 25% reduction in estimated creatinine clearance (CrCl) from the baseline level for ≥2 days. Collection of SCr values commenced prior to the start of vancomycin treatment and continued until 72 h after the treatment was completed. The CrCl value was estimated using the Cockcroft-Gault formula (13).

Statistical analysis. Data analysis was performed using SPSS Statistics software, version 20.0 (IBM Corp., Armonk, NY, USA). For the univariate analysis, Pearson's Chi-square test or Fisher's exact test were used to compare categorical variables, and Student's t-test or the Mann-Whitney U-test were used to compare continuous variables. Logistic regression analyses were used to identify predictors of efficacy and nephrotoxicity. Receiver operating characteristic (ROC) curve analysis was used to determine the thresholds of the vancomycin trough and peak concentrations for efficacy and nephrotoxicity, respectively. Values are expressed as the mean ± standard deviation. For all analyses, $P \leq 0.05$ was considered to indicate a statistically significant difference and all tests were two-tailed.

Selection of variables for analysis. In order to select variables for the regression model with the intent of minimizing multicollinearity, factor analysis was further performed on all continuous variables to reduce interaction between variables with orthogonal varimax rotation (14). Scree plots were used to describe the importance of the factors, and the number of components retained in the rotated structure was based on Jolliffe's criterion that eigenvalues should be >0.70 (15). The results are presented as rotated factor loadings, and the variables were sorted by factor according to the highest loading.

Results

Patient characteristics. The patients treated at Shanghai 10th People's Hospital (Shanghai, China) between March 2013 and March 2018 who met the inclusion criteria but not the exclusion criteria (n=65) were retrospectively enrolled in the present study. Among them, 38 were male and 27 were female, and the mean age was 61.9±20.1 years. Of these patients, 40 were admitted to the ICU. The primary site of infection was the lungs (80.0%) and the bloodstream (15.0%), while others accounted for 7.1%. Cardiovascular diseases (53.8%) and diabetes (24.6%) accounted for a large proportion of the underlying diseases. The mean vancomycin serum trough concentration and peak concentration were 13.7±9.1 and 28.2±8.7 mg/l, respectively. The mean total dosage of vancomycin was 19.5±12.2 g. The demographics and clinicopathological characteristics of the patients are presented in Table I.

Factor analysis. The first five comprehensive indicators representing 15 continuous variables were loaded by factor analysis with orthogonal varimax rotation, accounting for 75.7% of the total information (Table II). The importance of the factors was determined using scree plots and sorting of variables according to the largest absolute loading (Fig. 1). The rotated component matrix is presented in Table III and the results were as follows: Factor 1 was associated with inflammation (the percentage of neutrophils and lymphocytes); factor 2 was highly associated with the renal function [baseline blood urea neutrogen (BUN),

Table I. Demographics and clinicopathological characteristics of patients in the effective and ineffective treatment groups.

Characteristic/parameter	Total (n=65)	Effective group (n=43)	Ineffective group (n=22)	P-value
Males	38 (58.5)	26 (60.5)	12 (54.5)	0.647
Age (years)	61.9±20.1	60.7±20.1	64.2±20.2	0.509
BMI (kg/m^2)	22.5±4.0	23.4±3.6	20.7±4.2	0.010
Baseline laboratory parameters				
BUN (mmol/l)	8.0±5.1	6.8±3.5	10.3±6.8	0.009
Scr (μmol/l)	75.2±41.6	76.0±40.2	74.0±45.2	0.854
CrCl (ml/min)	96.2±50.8	95.6±41.9	97.4±66.1	0.892
ALT (U/l)	34.0±38.4	27.8±15.0	46.2±61.7	0.066
AST (U/l)	40.3±35.5	33.6±26.0	53.7±47.0	0.030
WBC (10^9/l)	10.8±5.6	10.7±5.7	11.0±5.7	0.808
Neutrophils (% in WBCs)	80.0±11.1	79.7±12.1	80.7±9.0	0.854
Lymphocytes (% in WBCs)	15.8±9.4	16.0±10.0	15.5±8.2	0.733
Albumin (g/l)	30.2±6.3	31.7±6.0	27.4±6.2	0.009
Baseline body temperature (˚C)	38.0±1.0	38.0±1.0	38.0±0.9	0.856
ICU patients	40 (61.5)	23 (53.5)	17 (77.3)	0.062
Primary site of infection				0.732
Respiratory tract	16 (80.0)	34 (75.6)		
Bloodstream	3 (15.0)	6 (13.3)		
Others	1 (5)	5 (11.1)		
Underlying disease				
Cardiovascular	35 (53.8)	26 (60.5)	9 (40.9)	0.109
Diabetes	16 (24.6)	13 (30.2)	3 (13.6)	0.224
Vancomycin concentration (mg/l)				
Trough	13.9±7.1	16.3±6.3	9.0±6.2	<0.001
Trough ≤15	32 (49.2)	14 (32.6)	18 (81.8)	<0.001
Trough >15	33 (50.8)	29 (67.4)	4 (18.2)	
Peak	28.2±8.7	30.4±7.8	23.8±8.8	0.003
Total vancomycin dose (g)	19.7±12.1	20.8±12.8	17.6±10.3	0.313

Values are expressed as n (%) or the mean ± standard deviation. BMI, body mass index (normal range, 18.5-24.9 kg/m^2); BUN, blood urea nitrogen (normal range, 3.2-7.1 mmol/l); Scr, serum creatinine (normal range, 44-133 μmol/l); CrCl, creatinine clearance (normal range, 80-120 ml/min); ALT, alanine aminotransferase (normal range, 5-40 U/l); AST, aspartate transaminase (normal range, 8-40 U/l); WBC, white blood cell (normal range, 4-10x10^9/l); ICU, intensive care unit. Neutrophil normal range, 50-70%, lymphocytes normal range, 20-40% and albumin normal range, 35-50 g/l.

Table II. Demographics and characteristics loaded over five factors explaining 75.7% of the information.

Factor	Variance explained (%)[a]	Factors
1	24.9	Baseline neutrophils, lymphocytes
2	16.8	Baseline BUN, Scr, CrCl
3	14.4	Baseline ALT, AST
4	10.4	Vancomycin trough concentration, peak concentration
5	9.2	BMI, baseline albumin

[a]Five factors were retained which comprised 24.9, 16.8, 14.4, 10.4 and 9.2% of the total variance, respectively. BMI, body mass index; BUN, blood urea nitrogen; Scr, serum creatinine; CrCl, creatinine clearance; ALT, alanine aminotransferase; AST, aspartate transaminase.

SCr and CrCl]; factor 3 was mainly associated with the liver function [baseline alanine aminotransferase and aspartate transaminase (AST)]; factor 4 was mainly determined by the vancomycin trough and peak concentrations; and factor 5 was mostly associated with the nutritional status [body mass index (BMI) and baseline albumin].

Parameters influencing the efficacy of vancomycin. Of the 65 eligible patients, vancomycin treatment was rated to be effective in 43 patients and ineffective in 22 patients. Overall, the effective group and the ineffective group were similar regarding the majority or clinicopathological and demographic parameters, but the BMI (P=0.010), baseline BUN (P=0.009), baseline AST (P=0.030), baseline albumin (P=0.009), vancomycin trough concentration (P<0.001) and vancomycin peak concentration (P=0.003) were significantly different between the effective group and the ineffective group. Stratification of the patients

Table III. Factor loadings in the total patients.

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Age	-0.546	0.058	-0.512	0.262	-0.289
Vancomycin trough concentration	-0.041	0.093	-0.051	0.893	0.121
Vancomycin peak concentration	0.065	-0.005	-0.200	0.869	-0.013
Baseline BUN	-0.054	0.806	-0.136	-0.15	-0.079
Baseline Scr	0.237	0.895	-0.023	0.156	0.183
Baseline CrCl	0.319	-0.758	0.269	-0.261	0.141
BMI	0.245	-0.214	0.068	0.193	0.832
Total vancomycin dose	0.273	-0.559	-0.365	0.115	0.466
Baseline WBC	-0.162	0.285	-0.142	-0.337	0.557
Baseline neutrophils	-0.976	0.036	-0.042	-0.071	-0.048
Baseline lymphocytes	0.956	-0.047	0.015	0.028	0.085
Baseline ALT	0.214	-0.025	0.830	-0.052	-0.017
Baseline AST	0.045	-0.058	0.667	-0.100	0.172
Baseline albumin	0.109	-0.001	0.519	0.120	0.700
Baseline body temperature	-0.263	-0.220	0.593	-0.094	-0.159

BMI, body mass index; BUN, blood urea nitrogen; Scr, serum creatinine; CrCl, creatinine clearance; ALT, alanine aminotransferase; AST, aspartate transaminase; WBC, white blood cell.

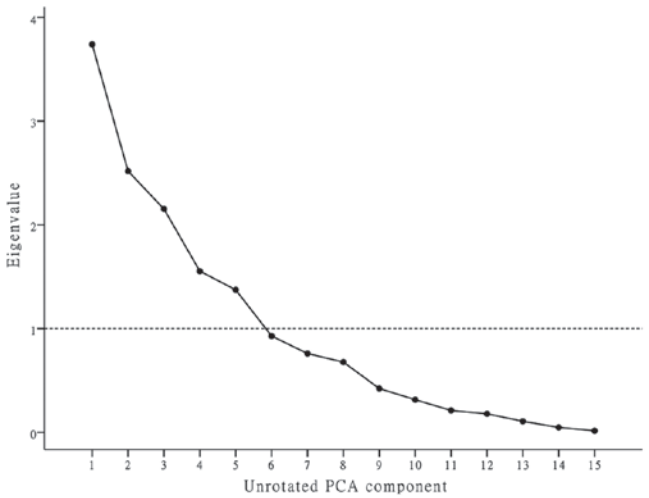

Figure 1. Scree plot of the full data set. Factors with eigenvalues >1 in the scree plot were retained. PCA, principal component analysis.

according to high and low trough concentration indicated that the frequency of ineffective treatment in the low (trough concentration, ≤15 mg/l) group (81.8%) was markedly higher than that in the high (trough concentration, >15 mg/l) group (18.2%). Analysis with the Chi-squared test indicated a high association between efficacy and a trough concentration of >15 mg/l (P<0.001; Table I).

Logistic regression analysis for efficacy. Logistic regression analysis was performed using the dimensional data reduced by factor analysis. The results confirmed that factor 4 [odds ratio (OR)=5.480; 95% confidence interval (CI): 1.734-17.325; P=0.004] and factor 5 (OR=3.164; 95% CI: 1.002-9.987; P=0.037) were independent influencing factors regarding efficacy. The other factors were not significantly associated with the efficacy and were therefore not included in the final model. Hence, the BMI, baseline albumin, and vancomycin trough and peak concentrations of the patients were associated with the efficacy of vancomycin (Table IV).

Table IV. Logistic regression analyses of independent influencing factors for efficacy in all subjects (n=65).

Factor	OR for efficacy	95% CI	P-value
1	1.703	0.566-5.127	0.344
2	0.566	0.253-1.266	0.166
3	0.953	0.509-1.783	0.879
4	5.480	1.734-17.325	0.004
5	3.164	1.002-9.987	0.037

OR, odds ratio; CI, confidence interval.

Parameters influencing the nephrotoxicity of vancomycin. Among the 65 patients, 20 met the criteria for nephrotoxicity. The baseline body temperature (P=0.014), total vancomycin dose (P=0.041), trough concentration (P<0.001) and peak concentration (P=0.020) exhibited significant differences between the groups of patients with and without nephrotoxicity. A significant difference in nephrotoxicity was also noted between the low and high trough concentration groups (P<0.001). The incidence of nephrotoxicity was only 15.0% in the low trough concentration group but 85.0% in the high trough concentration group (Table V).

Logistic regression analysis for nephrotoxicity. Logistic regression analysis for nephrotoxicity identified a significant

Table V. Comparison of characteristics between patients with and without nephrotoxicity (total n=65).

Characteristic	Nephrotoxicity group (n=20)	Non-nephrotoxicity group (n=45)	P-value
Males	14 (70.0)	24 (53.3)	0.208
Age (years)	66.7±18.1	59.8±20.7	0.207
BMI (kg/m^2)	23.0±3.96	22.3±4.0	0.497
Baseline laboratory parameters			
BUN (mmol/l)	7.5±3.5	8.2±5.7	0.607
Scr (μmol/l)	80.6±44.8	72.9±40.4	0.492
CrCl (ml/min)	87.5±43.1	100.0±53.9	0.368
ALT (U/l)	36.5±26.7	32.9±42.8	0.732
AST (U/l)	45.4±42.8	38.1±32.0	0.451
WBC (10^9/l)	12.3±5.0	10.1±5.7	0.141
Neutrophils (% in WBCs)	80.9±11.6	79.6±11.0	0.661
Lymphocytes (% in WBCs)	15.5±9.6	16.0±9.4	0.822
Albumin (g/l)	29.8±6.6	30.4±6.3	0.687
Baseline body temperature (˚C)	37.6±0.6	38.2±1.0	0.014
ICU patients	12 (60.0)	28 (62.2)	0.865
Primary site of infection			0.732
Respiratory tract	16 (80.0)	34 (75.6)	
Bloodstream	3 (15.0)	6 (13.3)	
Others	1 (5.0)	5 (11.1)	
Initial anti-infective treatment			
Carbapenems	8 (40.0)	10 (22.2)	0.139
Cephalosporins	3 (15.0)	11 (24.4)	0.393
Underlying disease			
Cardiovascular	14 (70.0)	21 (46.7)	0.082
Diabetes	9 (45.0)	7 (15.6)	0.011
Vancomycin concentration (mg/l)			
Trough	18.2±7.0	12.0±6.3	0.001
Trough ≤15	3 (15.0)	29 (64.4)	<0.001
Trough >15	17 (85.0)	16 (35.6)	
Peak	32.0±8.8	26.6±8.3	0.020
Total vancomycin dose (g)	24.3±14.1	17.7±10.6	0.041

Values are expressed as n (%) or the mean ± standard deviation. BMI, body mass index (normal range, 18.5-24.9 kg/m^2); BUN, blood urea nitrogen (normal range, 3.2-7.1 mmol/l); Scr, serum creatinine (normal range, 44-133 μmol/l); CrCl, creatinine clearance (normal range, 80-120 ml/min); ALT, alanine aminotransferase (normal range, 5-40 U/l); AST, aspartate transaminase (normal range, 8-40 U/l); WBC, white blood cell (normal range, 4-10x10^9/l; ICU, intensive care unit. Neutrophils normal range, 50-70%, lymphocytes normal range, 20-40% and albumin normal range 35-50 g/l.

association between nephrotoxicity and factor 4 (OR=2.388; 95% CI: 1.164-4.899; Table VI). Hence, higher initial trough and peak concentrations during vancomycin therapy bear a higher risk regarding the incidence of nephrotoxicity.

Prediction of the thresholds of vancomycin concentrations for efficacy. Fig. 2A presents ROC curves in which the vancomycin trough and peak concentrations were used as variables to predict the efficacy. The AUCs of the trough concentration and the peak concentration were 0.83 and 0.72, respectively. The critical values of the trough concentration and peak concentration were 9.02 mg/l (95.3% sensitivity and 68.2% specificity) and 23.62 mg/l (83.7% sensitivity and 59.1% specificity), respectively.

Table VI. Logistic regression analyses of independent risk factors for nephrotoxicity in the cohort (n=65).

Factor	OR for nephrotoxicity	95% CI	P-value
1	0.836	0.446-1.567	0.577
2	0.902	0.428-1.902	0.787
3	0.290	0.088-0.102	0.051
4	2.388	1.164-4.899	0.018
5	1.759	0.863-3.582	0.120

OR, odds ratio; CI, confidence interval.

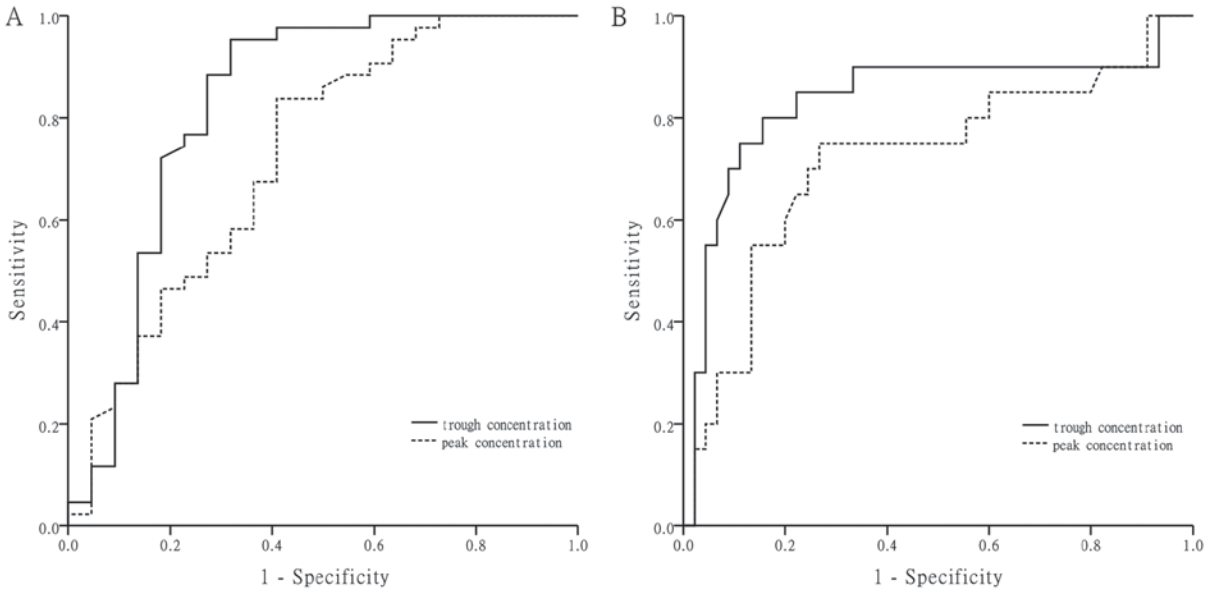

Figure 2. Receiver operating characteristic curves of vancomycin trough concentration and peak concentration. (A) Prediction of the critical value of vancomycin trough concentration and peak concentration for efficacy (cut-off value, 9.02 and 23.62 mg/l, respectively); (B) prediction of the threshold of vancomycin trough concentration and peak concentration for nephrotoxicity (cut-off value, 16.08 and 30.42 mg/l, respectively).

Prediction of the thresholds of vancomycin concentrations for nephrotoxicity. Fig. 2B presents the ROC curves for nephrotoxicity associated with the vancomycin trough and peak concentrations. The AUCs were 0.83 and 0.71 for the trough and peak concentration, respectively. The threshold vancomycin trough and peak concentrations for the development of nephrotoxicity were 16.08 mg/l (77.8% sensitivity and 84.2% specificity) and 30.42 mg/l (72.2% sensitivity and 76.3% specificity), respectively.

Based on the above results, a trough concentration between 9.02 and 16.08 mg/l and a peak concentration between 23.62 and 30.42 mg/l may be considered relatively safe, as these concentrations are not only effective but are also unlikely to induce nephrotoxicity.

Discussion

The present study investigated the predictive value of vancomycin serum concentrations regarding the drug's efficacy and nephrotoxicity. The results demonstrated that the differences in the trough concentration and peak concentration were statistically significant between the effective and ineffective groups, as well as between the nephrotoxicity and the non-nephrotoxicity groups. Furthermore, the critical values for the vancomycin serum concentration to achieve acceptable rates of efficacy and nephrotoxicity were identified.

Vancomycin was developed and approved in the 1950s for the treatment of infections with Gram-positive bacteria (16). Regarding the pharmacokinetics, >90% of vancomycin is eliminated by the kidneys, and only 5-8.5% of vancomycin may be metabolized through hepatic conjugation (17). Renal elimination of vancomycin mostly occurs through glomerular filtration and to a certain extent through active tubular secretion (18). Dieterich *et al* (19) reported that vancomycin accumulates in proximal tubular cells, leading to cell necrosis as a mechanism of nephrotoxicity. Nishino *et al* (20) and Oktem *et al* (21) suggested that oxidative stress and mitochondrial damage may contribute to vancomycin-associated renal injury. In addition to tubulointerstitial nephritis, severe vancomycin-induced nephrotoxicity may histologically manifest as granulomas in certain cases (22). The incidence of nephrotoxicity exhibits a wide variation and ranges from 5 to >35% among various studies (23,24). Therefore, the IDSA recommends that TDM is necessary to increase the rate of clinical efficacy and reduce the rate of nephrotoxicity during vancomycin therapy (3).

The bactericidal activity of vancomycin is thought to be time-dependent; therefore, it does not appear necessary to monitor peak concentrations. Suzuki *et al* (25) reported that it is not necessary to use peak concentrations of vancomycin in TDM, as the trough concentration/MIC and trough concentration ratio is sufficient to predict the efficacy and safety of vancomycin. However, there is support for a degree of concentration-dependent mortality associated with vancomycin (2). Iwamoto *et al* (26) indicated that monitoring of the peak concentration is essential for achieving an optimum clinical efficacy during vancomycin therapy, and a peak concentration of >25 mg/ml may be more effective than peak concentrations ≤25 mg/ml. In order to further elucidate the matter, the present study combined peak and trough concentrations during TDM to evaluate the efficacy and nephrotoxicity of vancomycin.

At present, the target vancomycin trough concentration for the optimum efficacy remains controversial. Chen *et al* (12) identified that the cut-off values of the first trough concentration were 7.9 mg/l for clinical efficacy and 21.1 mg/l for nephrotoxicity in Chinese patients. However, the IDSA provides recommendations that vancomycin trough concentrations should be maintained between 10 and 20 mg/l in order to avoid resistance and nephrotoxicity (3). In the present study, 80 samples from 65 patients were analyzed and only 58.0% were within the aforementioned range. The critical values for the trough concentration and peak concentration regarding

efficacy were 9.02 and 23.62 mg/l, respectively. The results demonstrate that the trough concentration together with the peak concentration provides a better assessment of the clinical efficacy of vancomycin than a trough concentration alone. In addition, it was identified that the BMI and albumin levels of the patients were associated with efficacy. Patients with poor nutrition may have serious infections, and normal doses of vancomycin may therefore not be effective.

It is well known that vancomycin has a significant nephrotoxicity; however, it remains elusive to what extent the vancomycin serum concentration is associated with nephrotoxicity. It has been demonstrated that an initial trough concentration of vancomycin of ≥15 mg/l and a duration of therapy of ≥14 days are independent risk factors associated with higher rates of nephrotoxicity (27-29). A retrospective study including 1,269 cases reported that trough concentrations of >12.1 mg/l were a major risk factor for vancomycin-induced nephrotoxicity (30). In the present study, the threshold vancomycin trough and peak concentrations for nephrotoxicity were determined to be 16.08 and 30.42 mg/l, respectively. This result is slightly higher, but similar with that of previous studies, in terms of vancomycin trough concentrations increasing the efficacy and increasing the risk of nephrotoxicity.

Of note, the present study has a number of limitations. First, it was a single-center retrospective study with a small sample size. Furthermore, the patients treated with vancomycin generally had a variety of underlying conditions, but there was no homogeneity. In addition, the possibility of data observation bias cannot be excluded. In the future, studies using a larger sample and with more detailed stratification are required in order to identify the associations between serum vancomycin concentrations, efficacy and nephrotoxicity.

In conclusion, the present study provides evidence that vancomycin trough and peak concentrations are associated with the efficacy and incidence of nephrotoxicity of patients receiving vancomycin therapy. A trough concentration between 9.02 and 16.08 mg/l is relatively safe, and the relatively safe range for the peak concentration was from 23.62-30.42 mg/l. These results may provide useful information to guide the development of individualized vancomycin therapy.

Acknowledgements

The authors would like to thank Mr Zhang and Mr Tan at the Department of Respiratory Medicine of Shanghai 10th People's Hospital (Shanghai, China). The authors would also like to recognize and Mr Yuan at the Department of Laboratory Medicine of Shanghai 10th People's Hospital (Shanghai, China) who participated in the data collection for their cooperation and support. The authors are also grateful to Mr Liang at the Institute of Antibiotics of Huashan Hospital, Fudan University (Shanghai, China) for providing technical support.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81472180). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

CHW and XLS conceived and designed the study, and critically revised the manuscript. LPW analyzed the data, interpreted the results and wrote the first draft of the manuscript. QY collected the clinical and laboratory data. MT and SSX were responsible for analysis of data and interpretation of results, as well as critical revision of the manuscript for important intellectual content. MT and SSX also approved the publication of the final manuscript. JFW was involved in detecting the vancomycin trough and peak concentrations. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of the Shanghai Tenth People's Hospital of Tongji University.

Patient consent for publication

All the enrolled subjects gave informed consent for the present study.

Competing interests

The authors have declare that they have no competing interests.

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