Correlation between 61 risk factors and vancomycin blood concentration reached based on real world data

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Research article

Keywords: Real-world research; Vancomycin; Blood concentration monitoring; Influencing factor; Logistic regression analysis

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Abstract

Background: Vancomycin (VAN), an antibiotic produced by microbial fermentation, is used to treat gram-positive infections. With extensive broad-spectrum antibiotics use, bacterial resistance to vancomycin continues to increase. In this study, we explored the factors affecting the blood concentration of vancomycin and established a prediction equation for VAN blood concentration, providing a reference for the individual application of vancomycin. Methods: We used a single-center, retrospective, case-control study design based on real-world data from the Hospital Information System of the First Affiliated Hospital of the Teaching Hospital of Bengbu Medical School from January 1, 2017, to December 31, 2018. Inpatients whose VAN blood concentration (enzyme amplification immunoassay) was monitored were selected. Single-factor and multivariate logistic regression analyses were performed using SPSS 21.0 software to screen factors affecting VAN blood concentration compliance rate. VAN blood concentration was then determined. A receiver operator characteristic (ROC) curve of influencing factors was then used to establish a prediction model. Results: In total, 168 patients (122 males and 46 females) were enrolled. Eighty-one had their VAN blood concentration monitored, and 87 had concentrations that did not reach the standard. Multivariate logistic model analyses showed that patient drug allergy history, alanine aminotransferase (ALT), aspartate aminotransferase (AST), patient infusion volume, and urine volume influenced VAN blood concentration compliance rate. According to logistic model analysis, a history of drug allergy (95% CI: 1.225-24.850, P<0.05), ALT (95% CI: 0.979-0.999, P<0.05), AST (95% CI: 1.003-1.027, P<0.05), patient infusion volume (95% CI: 0.996-0.998, P<0.05), patient urine volume (95% CI: 1.001-1.003, P<0.05), and combined predictors were used to construct ROC curves. For combined predictive factors, area under the ROC curve (0.829, 95% CI: 0.755-0.902, P<0.005) was greater than that of the five individual indicators and was predicted to be the preferred value. Conclusions: In clinical practice, the patient's daily average infusion and urine volumes can be substituted into the joint predictor calculation formula: P=1/[1+e-(0.940-0.004*Xinfusion+0.002*Xurine)]. By calculating the combined predictive factor to predict VAN blood concentration compliance rate, the dosing regimen can be adjusted. Keywords: Real-world research; Vancomycin; Blood concentration monitoring; Influencing factor; Logistic regression analysis

Background

Vancomycin (VAN), a natural antibiotic produced by microbial fermentation, is a tricyclic glycopeptide antibiotic and was the first glycopeptide antibiotic [1]. Clinically, it is used to treat gram-positive bacterial infections, such as those caused by hemolytic streptococcus, or pneumococcus, among others. VAN is one of the first-line drugs for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and related infections, as directed by many authoritative guides [2]. Differences in the blood concentration of VAN have been observed in different individuals. If its blood concentration is too low, the drug might not be effective or might not reach its effective trough concentration. However, a concentration that is too high can lead to adverse drug reactions, such as ototoxicity and nephrotoxicity [3, 4]. If administered according to the recommended dosage found in the instructions, a significant portion of the patient's blood concentration does not appear to be within the therapeutic window [5-7]. Thus, it is clinically necessary to monitor VAN blood concentration. Monitoring methods mainly include high-performance liquid chromatography, radioimmunoassay, and enzyme amplification immunoassay [8]. Since VAN is a time-dependent antibacterial drug, the key to ensuring its efficacy is extending the antibacterial drug infusion time such that the drug concentration is always higher than the target organism's minimum inhibitory concentration [9]. However, routine monitoring of peak concentration [10] does not correlate with monitoring efficacy. Furthermore, as the distribution of VAN into tissues is slow, its peak concentration is challenging to monitor [1]. Some studies [11] suggest that the peak concentration of VAN does not correlate well with its efficacy, and its concentration can be used as a surrogate for its area under the curve, which currently is widely accepted. According to the Guide to the Monitoring of Chinese Vancomycin Therapeutic Drugs [12], patients with normal renal function have a VAN half-life of 6-12 h, with stable blood concentration achieved after 4

to 5 half-lives. On the third day (48 h after the first dose), monitoring of patient VAN can be initiated. However, for patients with renal insufficiency, upon first administration, monitoring is initiated 72 h after drug administration. Accurate determination of VAN trough concentration not only avoids poor therapeutic or adverse effects caused by too low or too high a concentration of vancomycin, but also facilitates clinicians to develop individualized dosing regimens for patients. Chen et al. [13-19] showed that VAN blood concentration is related to age, dose, urine volume, creatinine clearance, blood urea nitrogen, plasma albumin in critically ill patients. The blood concentration of VAN in children studied by Xingru et al. [5, 20, 21] was shown to be related to serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine clearance, glutamyl transaminase, and gestational age. Qingrong S [22] showed that the blood concentration of VAN in patients (≧18 years old) is related to age, albumin, liver and kidney function, usage and dosage, etc. Although the effects of individual factors on the blood concentration of vancomycin have been discussed in previous studies, there are fewer factors involved. Besides, the research populations used for these analyses were relatively small (e.g., studies on children only), the entire population was not analyzed, and a prediction model has not been established. In the present work, a real-world single-center, retrospective, case-control study was conducted to investigate the effects of age, sex, liver and kidney function, and solvent on the blood concentration of VAN. The factors involved were found to be more extensive and more comprehensive. By combining single-factor analysis and multi-factor logistic analysis, a receiver operating characteristic (ROC) curve was generated, and the prediction equation for VAN blood concentration was fitted to provide a basis for clinical pharmacists to guide clinicians in the use of this drug.

Methods

Research design

We performed a single-center, retrospective, case-control research design study. The First Affiliated Hospital of Bengbu Medical College, the ethics committee of clinical medical research (scientific research project) approval number: 2018KY008, the approval date was August 28, 2018, and on June 23, 2019, the registration number of the China Clinical Trial Registration Center was ChiCTR1900024062. Based on real-world data present in the Hospital Information System (HIS). HIS is a database that stores the information recorded during an inpatient's stay at the hospital. It includes their basic information, daily medication during hospitalization, care, admission, and expenses incurred. According to the Guide to the Monitoring of Chinese Vancomycin Therapeutic Drugs [12], when patient blood concentration was monitored, VAN had to be within the effective concentration range (10-20 μg/mL). The population was divided into the standard group, including patients whose blood concentration, as measured after the intake of VAN, was within the range of 10-20 μg/mL, and the substandard group, including patients with VAN trough concentrations outside the range of 10-20 μg/mL.

Blood drug concentration monitoring method

The VAN blood concentration was monitored by enzyme amplification immunoassay, using enzyme reagent 1 (vancomycin labeled with bacterial glucose-6-phosphate dehydrogenase [0.21U/mL], hydroxyethy1 piperazine ethy1 sulfuric acid buffer liquid calf serum albumin, preservatives, and stabilizers) and reagents 2 (antibody/substrate: murine monoclonal vancomycin antibody [27μg/mL], calf serum albumin, glucose-6-phosphate [44mM], nicotinamide adenine dinucleotide [36mM], preservatives, and stabilizers) were monitored by a fully automated biochemical analyzer (Viva-E: YZB/HOL 1746-2010).

Research object

This study was performed at the First Affiliated Hospital of Bengbu Medical College from January 1, 2017, to December 31, 2018. Patients whose VAN blood concentration was being monitored were selected. The study protocol was reviewed and approved by the hospital ethics committee. Inclusion criteria were as follows: (1) patients treated with VAN for clinical infections who had their VAN blood concentration monitored; (2) trough concentration of VAN blood concentration and not peak concentration or concentration found immediately after administration; (3) influencing factors of the control group had to be consistent with the influencing factors in the observation group; (4) complete patient data;(5) patients are Asian races. Exclusion criteria were as follows: (1) vancomycin was not used as the clinical treatment for infection; however, cases treated with norvancomycin were included; (2) patients whose VAN blood concentration was monitored as peak concentration; (3) differing statistical factors between the observation group and control group; (4) invalid clinical data.

Data collection

According to the characteristics of VAN and the actual situation provided in the HIS, the electronic database was designed to collect the following data: (1) demography: age and sex; (2) past history of drug allergy, smoking, and alcohol abuse; (3) vital signs: body temperature (36.1-37 °C); (4) infection: pulmonary, intracranial, central nervous system, and bronchiectasis infection; (5) history of disease: history of chronic diseases such as diabetes and hypertension, and infectious diseases such as tuberculosis; (6) hospitalization: number of operations and operations performed before each blood concentration measurement, fluid infusion amount, urine amount, whether critical illness occurred during hospitalization, Glasgow coma score (GCS), including blink response, speech response, and limb movement, mild coma: 13-14 points, moderate coma: 9-12 points, severe coma: 3-8 points, normal: >14 points, length of hospital stay, admission department, western medicine fee, antibiotic cost, and antibiotic use during hospitalization, total cost of western medicine; (7) patient medication during hospitalization: vancomycin (dose, frequency of administration, vehicle, and days of drug use), antibiotics and other drugs used in combination with VAN, treatment options are correct, whether there are indications; (8) safety test indicators: ALT: 0-40 IU/L, AST: 0-45 IU/L, alkaline phosphatase (ALP): 40-160 IU/L, glutamyl transpeptidase (GGT): 0-50 IU/L, total protein (TP): 60-80 g/L, albumin (A): 35-55 g/L, G: 9-23 mg/ml, total bilirubin: 1.7-17.1 μmol/L, serum urea: 1.8-7.1 mmol/L, serum creatinine: 44-133 μmol/L, serum creatinine clearance rate: 80-120 ml/min, white blood cell count: 4-10×10^9/L, hemoglobin: (120-160 g/L), platelets: 100-300 × 10^9/L; and (9) observed outcome indicators: monitoring values of VAN blood concentration per patient per time.

Data processing and assignment

Univariate and multivariate logistic regression analyses were used to screen independent risk factors for the compliance of patients receiving VAN. According to the information retrieved for each patient, the assignment of various influencing factors is shown in Table 1.

Statistical analysis

Data were processed using SPSS 21.0 statistical software (IBM, Armonk, NY, USA). A Pearson's chi-square test was used to analyze classification data, whereas a t-test was used to analyze continuous data. Univariate risk factors affecting VAN blood concentration were determined by a single factor and multivariate regression analyses. According to the multivariate logistic model analysis results, joint predictors were set and included in the logistic model for analysis. The model equation and ROC curves were then derived. Curve, screen cut points, area under the curve, and the predictive efficacy of various indicators were then derived. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Unless otherwise stated, results are expressed as the mean ± standard deviation, and lost data were processed using the mean substitution method.

Table 1. Influence factor assignment table.

Factors	Assignment
Sex	Male=0, female=1
History of drug allergy	Yes=1, no=0
History of smoking	Yes=1, no=0
History of alcohol abuse	Yes=1, no=0
Indication	Yes=1, no=0
Treatment programs*	Reasonable=1, unreasonable=0
Critical	Yes=1, no=0
Admission department	ICU=0, Respiratory =1, Neurosurgery=2, Pediatrics=3, General Medicine=4, Orthopedics=5, Nephrology=6, Oncology=7, Infectious Diseases=8, Gastrointestinal Surgery=9, Cardiology=10, Hematology=11, Stomatology=12, Emergency =13, Gynecology=14
Frequency of administration	q12h=0, q8h=1, q6h=2, q24h=3
Solvent	0.9% sodium chloride injection=0, 5% glucose injection=1, 10% glucose injection=2
Infected site	
Lung	Yes=1, no=0
Intracranial	Yes=1, no=0
Central nervous system	Yes=1, no=0
Bronchiectasis	Yes=1, no=0
Combined chronic disease	
Diabetes	Yes=1, no=0
Hypertension	Yes=1, no=0
Coronary heart disease	Yes=1, no=0
Rheumatoid arthritis	Yes=1, no=0
Heart disease	Yes=1, no=0
Chronic bronchitis	Yes=1, no=0
Concomitant infectious disease	
Hepatitis B	Yes=1, no=0
Tuberculosis	Yes=1, no=0
Combined antibacterial drugs	
Carbapenem	Yes=1, no=0
Aminoglycosides	Yes=1, no=0
Macrolides	Yes=1, no=0
β-lactam	Yes=1, no=0
Fluoroquinolone	Yes=1, no=0
Glycopeptide	Yes=1, no=0
Antifungal	Yes=1, no=0
Other drugs used in combination	
Enteral nutrition suspension	Yes=1, no=0
Adenosylmethionine	Yes=1, no=0
Reduced glutathione	Yes=1, no=0
Pantoprazole sodium	Yes=1, no=0
Furosemide	Yes=1, no=0
Human	Yes=1, no=0

*Regarding whether the treatment plan was reasonable: "The vancomycin clinical application of Chinese experts consensus" 2011 version and vancomycin instructions were jointly used to judge whether the patient's treatment plan was reasonable.

Results

Patient demographic characteristics

A total of 168 patients (81 patients who met the standard and 87 patients who did not meet the standard) were enrolled. Hospital admissions included 38 (22.62%) in the respiratory department, 28 in pediatrics (16.67%), 24 in the ICU (14.29%), and 18 in the RICU (10.71%). There were 15 cases of neurosurgery (8.93%), 12 cases of infection (7.14%), 11 cases of PICU (6.55%), 4 cases of general medicine and nephrology (2.38%), 3 cardiovascular cases (1.79%), 2 cases from the gastrointestinal surgery, stomatology, emergency department (1.90%), and 1 case in orthopedics, intratumor, extratumor, hematology, and gynecology (0.60%); details are presented in Table 2.

Table 2. Patient demographic characteristics

Grouping	sex (male/female)	Age(years)	Number of days in the hospital	Medication days	Dose (g)	Total drug cost (yuan)	Antibacterial cost (yuan)
Compliance	55/26	46.30±27.72	25.94±12.19	12.62±6.52	0.70±0.38	26729.37±19885.35	13267.19±10608.97
Substandard	67/20	42.08±27.40	30.68±22.47	13.67±7.28	0.65±0.40	34011.88±37704.42	16016.87±15649.98

Univariate analysis of compliance and non-standardized data

VAN blood concentration was found to adhere to the standard. In addition, patients' drug allergy history, rheumatoid arthritis, combined use of human immunoglobulin, hospital days, AST, G, daily average infusion of patients, and urine volume showed statistical differences (to avoid missing essential factors in the single factor analysis process, The range of P values was set to< 0.1, to include more potential influencing factors, see Table 3).

Table 3. Single factor analysis of patient information and observation indicators

Influencing factor	Compliance group (n=81)	Substandard group (n=87)	*P*
Sex			0.186[a]
Male	55（32.74）	67（39.88）	
Female	26（15.48）	20（11.90）	
Age (year)	81(48.21)	87（51.79）	0.326[b]
Surgery and operation times	81(48.21)	87（51.79）	0.815[b]
History of drug allergy	6（3.57）	17（10.12）	0.022[a]
History of smoking	3（1.79）	1（0.60）	0.563[a]
History of alcohol abuse	3（1.79）	3（1.79）	1.000[a]
Treatment programs*	34（20.24）	29（17.26）	0.248[a]
Indication	73（43.45）	75（44.64）	0.433[a]
Critical	51（30.36）	60（35.71）	0.412[a]
GCS score	81(48.21)	87（51.79）	0.439[b]
Hospital stay (days)	81(48.21)	87（51.79）	0.090[b]
Admission department			0.201[a]
ICU	26（15.48）	27（16.07）	
Respiratory	18（10.71）	20（11.90）	
Neurosurgery	8（4.76）	7（4.17）	
Pediatrics	13（7.74）	15（8.93）	
General medicine	3（1.79）	1（0.60）	
Orthopedics	1（0.60）	0（0）	
Nephrology	1（0.60）	3（1.79）	
Oncology	2（1.19）	0（0）	
Infectious Diseases	5（2.98）	7（4.17）	
Gastrointestinal Surgery	2（1.19）	0（0）	
Cardiology	2（1.19）	1（0.60）	
Hematology	0（0）	1（0.60）	
Stomatology	0（0）	2（1.19）	
Emergency	0（0）	2（1.19）	
Gynecology	0（0）	1（0.60）	
Diabetes	11（6.55）	11（6.55）	0.857[a]
Hypertension	19（11.31）	19（11.31）	0.802[a]
Coronary heart disease	4（2.38）	1（0.60）	0.322[a]
Rheumatoid arthritis	6（3.57）	0（0）	0.030[a]
Heart disease	3（1.79）	6（3.57）	0.565[a]
Chronic bronchitis	4（2.38）	2（1.19）	0.613[a]
Hepatitis B	3（1.79）	3（1.79）	1.000[a]
Tuberculosis	5（2.98）	10（5.95）	0.227[a]
Bronchiectasis	4（2.38）	6（3.57）	0.834[a]
Single dose(g)	81(48.21)	87（51.79）	0.390[b]
Frequency of administration			0.383[a]
q12h	50（29.76）	54（32.14）	
q8h	18（10.71）	22（13.10）	
q6h	10（5.95）	5（2.98）	
q24h	3（1.79）	6（3.57）	
Medication days (days)	81(48.21)	87（51.79）	0.331[b]
Daily average infusion (ml)	81(48.21)	87 (51.79)	0.001[b]
Daily average urine volume (ml)	81(48.21)	87 (51.79)	0.076[b]
Solvent			0.516[a]
0.9% sodium chloride injection	54（32.14）	55（32.74）	
5% glucose injection	18（10.71）	17（10.12）	
10% glucose injection	9（5.36）	15（8.93）	
Serum creatinine clearance	81(48.21)	87（51.79）	0.889[b]
Body temperature	81(48.21)	87（51.79）	0.574[b]
ALT	81(48.21)	87（51.79）	0.374[b]
AST	81(48.21)	87（51.79）	0.057[b]
ALP	81(48.21)	87（51.79）	0.183[b]
GGT	81(48.21)	87（51.79）	0.438[b]
TP	81(48.21)	87（51.79）	0.199[b]
A	81(48.21)	87（51.79）	0.689[b]
G	81(48.21)	87（51.79）	0.068[b]
Total bilirubin	81(48.21)	87（51.79）	0.259[b]
Serum urea	81(48.21)	87（51.79）	0.746[b]
Serum creatinine	81(48.21)	87（51.79）	0.298[b]
White blood cell count	81(48.21)	87（51.79）	0.699[b]
Hemoglobin	81(48.21)	87（51.79）	0.492[b]
Platelet	81(48.21)	87（51.79）	0.484[b]
Carbapenem	17（10.12）	14（8.33）	0.414[a]
Aminoglycosides	3（1.79）	1（0.60）	0.563[a]
Macrolides	1（0.60）	1（0.60）	1.000[a]
β-lactam	4（2.38）	4（2.38）	1.000[a]
Fluoroquinolone	3（1.79）	5（2.98）	0.796[a]
Glycopeptide	0（0）	1（0.60）	1.000[a]
Antifungal	2（1.19）	1（0.60）	0.950[a]
Enteral nutrition	6（3.57）	7（4.17）	0.877[a]

				suspension			
Total drug cost (yuan)	81(48.21)	87（51.79）	0.118[b]	Adenosylmethionine	4（2.38）	4（2.38）	1.000[a]
Antibacterial cost (yuan)	81(48.21)	87（51.79）	0.185[b]	Reduced glutathione	2（1.19）	6（3.57）	0.325[a]
Antibacterial cost: total drug cost	81(48.21)	87（51.79）	0.669[b]	Pantoprazole sodium	4（2.38）	4（2.38）	1.000[a]
Lung	44（26.19）	47（27.98）	0.969[a]	Furosemide	7（4.17）	4（2.38）	0.290[a]
Intracranial	10（5.95）	9（5.36）	0.682[a]	Human immunoglobulin	8（4.76）	0（0）	0.008[a]
Central nervous system	5（2.98）	5（2.98）	0.641[a]				

*（[a]based on x^2 text, [b]based on t text. Data reported herein are for patients who indicated “Yes” and “reasonable” in the study.

Multi-factor analysis of compliance and non-standardized data

Multivariate logistic regression analysis showed that allergic history, ALT, AST, daily average infusion volume, and daily mean urine volume were significantly associated with patient VAN blood concentration (P < 0.05, Table 4). The general trend of VAN blood concentration as a function of ALT, AST, daily average infusion volume, and daily average urine volume is presented in Figures 1-3.

Table 4. Multivariate logistic regression analysis of factors influencing vancomycin blood serum concentration.

Indexes	Multi-factor analysis				
	B	SE	Wald X^2	*P*	95%CI
Allergies	1.708	0.768	4.948	0.026	1.225-24.850
Alanine aminotransferase	-0.011	0.005	4.342	0.037	0.979-0.999
Aspartate aminotransferase	0.014	0.006	5.820	0.016	1.003--1.027
Daily average infusion	-0.003	0.001	16.411	0.000	0.996-0.998
Daily average urine volume	0.002	0.001	12.834	0.000	1.001-1.003

Prediction and analysis of VAN blood concentration by logistic model and ROC curve

Stepwise logistic regression analysis showed that daily mean infusion volume and daily mean urine volume were statistically independent risk factors. Taking patient VAN blood concentration as the dependent variable, a logistic model equation was established with daily average infusion volume and daily average urine volume as independent variables. This equation was transformed to obtain the joint predictor (Y joint). The equations (Formula 1 and Formula 2) were then used to calculate the joint predictor, enabling the construction of a ROC curve of the joint predictor (Figure 4). The area under the curve was 0.829, (95% CI: 0.755-0.902, P < 0.005).

$$\text{Logit}(P) = 0.940-0.004*X_{infusion}+0.002*X_{urine} \quad \text{Formula 1}$$

$$P=1/[1+e^{-(0.940-0.004*X_{infusion}+0.002*X_{urine})}] \quad \text{Formula 2}$$

Discussion

VAN blood concentration standard prediction index

With the extensive use of broad-spectrum antibiotics, the severity of bacterial resistance to VAN continues to increase [23]. Because creatinine clearance was found to increase by 26.5 μmol/L or 50% within 14 days after VAN use, and/or because urine volume was < 0.5 ml/(kg·h) in more than 6 h [24], kidney damage was determined. Therefore, urine volume was identified as an important factor. In this study, daily average infusion volume of patients and daily average urine volume were independent factors, as reported by Jiyao [18]. Typically VAN is not considered to be metabolized in the body, and at 24 h, its level is maintained at 90% for elimination via the kidney by the prototype [25]. However, because of the different treatment options and doses required by different patients, a previous study could not report a stable clearance rate for clinical reference [26, 27]. Infusion volume and urine volume serve as factors that can affect the distribution volume and clearance rate of VAN in patients, thereby affecting its concentration. By fitting the prediction equation, patient's daily average infusion volume and daily average urine volume were substituted into the formula to predict their VAN blood concentration compliance rate and facilitate the timely adjustment of their medication regimen during treatment. When the ratio of the daily average infusion volume to the daily average urine volume was in the range of 0.35-1, a high VAN blood concentration was found; when the ratio was in the range of 0.48-1, VAN blood concentration was at its highest, and the rest of the concentrations were either higher or lower than the normal value; Further, when the ratio was greater than 1 (only three cases in this study), infusion volume was found to be greater than urine volume. Subsequently, a higher utilization rate of pigment led to a corresponding reduction in free VAN and an increase in the trough concentration. However, it cannot be excluded that urine volume still contained a large amount of free VAN when patient input (including the amount of daily intake such as infusion volume and drinking water) is greater than the infusion volume.

Correlation between the history of drug allergy and the compliance rate of VAN blood concentration

A patient's history of drug allergy in single factor (P=0.022) and multivariate (P=0.026) analysis was found to influence VAN blood concentration. However, there was no evidence that the blood concentration of VAN is related to a history of drug allergy. Herein, we excluded the possibility that VAN-treated patients could be sensitive to the drug, but we found that their VAN blood concentration was related to a history of allergies. This implies that patients might be sensitive to other drugs, thereby causing sensitivity to VAN via individual differences. This finding could be used to clinically adjust VAN concentrations; however, such an important consideration requires further large-scale prospective research for verification.

Analysis of single factor results and multivariate logistic regression analysis

Univariate analysis can influence multivariate analysis as the latter excludes the effects of each factor. Relevant factors (ALT) that were not obtained by univariate analysis, such as VAN blood concentration, could be obtained by multivariate analysis. However, in the present study, this was rare. As confounding factors might distort the correlation variable and independent variable, such correlation distortion can either be an enhancing or diminishing effect.

Research limitations

In this study, factors influencing the compliance rate of VAN blood concentration were described using logistic models and ROC curves. Furthermore, the rate of VAN blood concentration was predicted. To our knowledge, a study similar to that reported herein has not been previously published. Nonetheless, our study had some limitations as follows: (1) different batches of VAN or VAN from different regions could affect blood concentration; therefore, a comparative study is needed to confirm our results; and (2) as we could not analyze unknown confounding factors, the results presented are limited [38].

Conclusions

In summary, although the dosing regimen and monitoring procedures for VAN have been largely established via pharmacodynamic and pharmacokinetic studies, personalized drug regimens are still needed for specific patients. In the present study, the combined predictive factor formula for the patient's daily average infusion volume and urine volume could predict the compliance rate of VAN blood concentration. This will allow clinicians to identify problems and adjust the medication plan to promote the safe and effective use of VAN [39].

Abbreviations

Vancomycin, VAN;

Methicillin-resistant Staphylococcus aureus, MRSA;

Aspartate aminotransferase, AST;

Receiver operating characteristic, ROC;

Hospital Information Management System, HIS;

Glasgow coma score, GCS;

Alkaline phosphatase, ALP;

Glutamyl transpeptidase, GGT;

Total protein, TP

Declarations

Ethics approval and consent to participate

The study was approved by The First Affiliated Hospital of Bengbu Medical College, the ethics committee of clinical medical research (scientific research project) approval number: 2018KY008, the approval data: August 28, 2018; on June 23, 2019, the registration number of the China Clinical Trial Registration Center was assigned as ChiCTR1900024062. Informed consent was not needed because this study is a low-risk study and meets the IRB exemption informed consent requirements: Research using anonymous or no-risk tests, surveys, interviews, or observations.

Consent to publish

Not Applicable

Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Lingti K, Yulin Z, and Jinxiu Z gathered patients for enrolment in the study and monitored patient VAN blood concentration; Haiqin C collected the data and wrote the manuscript; Qingping S provided the research ideas and revised the manuscript. All authors read and approved the final manuscript.

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References

1. Zhichao H, Junyan W, Kaifeng Q. Clinical pharmacist guidelines for individualized administration of vancomycin. Pharmacy Today. 2015;25(02):78-82.
2. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011;52(3):285-292.
3. Jin H, Qiuyan W, Jingjing W, Ruming L, Shanshan L, Yiyi Q, et al. Analysis of vancomycin blood concentration and drug administration in elderly patients. Chin J Hosp Pharm. 2018;38(06):630-633.
4. Sinclair EA, Yenokyan G, McMunn A, Fadrowski JJ, Milstone AM, Lee CK. Factors associated with acute kidney injury in children receiving vancomycin. Ann Pharmacother. 2014;48(12):1555-1562.
5. Xingru T, Haiyan C. Analysis of factors affecting the blood concentration of vancomycin in newborns. Chin Pharm. 2016;27(29):4067-4069.
6. Dongjie G, Pengmei L, Wenwen D, Gang C, Wenqian C, Xianglin Z. Cross-sectional survey of vancomycin treatment drug monitoring in our hospital. Chin Pharm. 2016;27(24):3320-3323.
7. Hwang D, Chiu NC, Chang L, Peng CC, Huang DT, Huang FY, et al. Vancomycin dosing and target attainment in children. J Microbiol Immunol Infect. 2017;50(4):494-499.
8. Usman M, Hempel G. Development and validation of an HPLC method for the determination of vancomycin in human plasma and its comparison with an immunoassay (PETINIA). Springerplus. 2016.5:1-7.
9. Lodise TP, Lomaestro BM, Drusano GL; Society of Infectious Diseases Pharmacists. Application of antimicrobial pharmacodynamic concepts into clinical practice: focus on beta-lactam antibiotics: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2006;26(9):1320-1332.
10. Saunders NJ. Why monitor peak vancomycin concentrations? Lancet. 1994;344(8939-8940):1748-1750.
11. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006;42 Suppl 1:S35-39.
12. Ye ZK, Chen YL, Chen K, Zhang XL, Du GH, He B, et al. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. J Antimicrob Chemother. 2016;71(11):3020-3025.
13. Limin C, Tianfeng H, Min Y. Analysis of the related factors of vancomycin blood concentration in critically ill patients. Lingnan Journal of Emergency Medicine. 2018;23(05):419-421+427.
14. Yanyan Y, Jing Z, Li J. Analysis of related factors of vancomycin blood concentration in ICU patients. China Medical Herald, 2018;15(21):110-113.
15. Zhongbo Z, Guofu L. Analysis of related factors of vancomycin blood concentration in ICU patients. Chinese community Doctors. 2017;33(14):82-83.
16. Xiayin L, Xiuzhuang Z, Jiawei Z, Jie C, Xiao C. Analysis of influencing factors of vancomycin blood concentration in critically ill patients receiving venous-venous hemofiltration in a hospital. Journal of China Prescription Drug. 2016;14(10):2-4.
17. Wei D, Ruixiang C, Jin W, Meifang Y. Factors influencing blood concentration of vancomycin after application of vancomycin in patients with severe pneumonia. J Trop Med. 2018;18(06):795-798+834.
18. Jiyao C. Study on the influencing factors of vancomycin blood concentration in critically ill patients, 2017, Jilin University.
19. Hua K. Analysis of the factors affecting the serum concentration of vancomycin.Chinese Journal of Urban and Rural Enterprise. 2017;32(11):49-51.

20. Hanjing C, Weiyang D, Yanling H. Analysis of factors affecting the blood concentration of vancomycin in children. Pharmacy Today. 2019;29(04):251-254.
21. Yuanyuan L, Guangli Z, Xiaoyin T, Huan M, Lin T, Qiyu Z, et al. Analysis of factors affecting vancomycin blood concentration in children with Gram-positive cocci in severe pneumonia. J Clin Pediatr. 2017;35(06):421-424.
22. Qingrong S, Gang L, Qiuyu L, Luping L, Qingdong M. Analysis of the influencing factors of vancomycin blood concentration. Chinese Journal of Antibiotics. 2017;42(05):429-434.
23. Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA. 2007;298(15):1763-1771.
24. Gibson CM, Pride YB, Hochberg CP, Sloan S, Sabatine MS, Cannon CP, et al. Effect of intensive statin therapy on clinical outcomes among patients undergoing percutaneous coronary intervention for acute coronary syndrome. PCI-PROVE IT: A PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) Substudy. J Am Coll Cardiol. 2009;54(24):2290-2295.
25. Chinese expert consensus on clinical application of vancomycin (2011 edition). Chinese J New Drugs Clin Med. 2011;30(08):561-573.
26. Bouman CS, van Kan HJ, Koopmans RP, Korevaar JC, Schultz MJ, Vroom MB. Discrepancies between observed and predicted continuous venovenous hemofiltration removal of antimicrobial agents in critically ill patients and the effects on dosing. Intensive Care Med. 2006;32(12):2013-2019.
27. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis. 2005;41(8):1159-1166.
28. Jianying H, Yu C. Analysis of blood concentration of vancomycin in children and discussion on drug administration plan. Strait Pharmaceutical Journal 2015;27(10):264-266.
29. Fontana RJ, Watkins PB, Bonkocsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009;32(1):55-68.
30. Harada H, Miyagawa S, Kawasaki S, Hayashi K, Kitamura H, Katsuyama Y, et al. Study of the pharmacokinetics of vancomycin in patients with impaired liver function. J Infect Chemother. 1999;5(2):104-107.
31. Guiding Principles for Clinical Application of Antibacterials. Chinese Medicine Modern Distance Education of China, 2005;3(02):13-15.
32. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, et al. 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. Clin Biochem Rev. 2010;31(1):21-24.
33. Defeng L, Jingjing Q, Zhenhong Z. Analysis of the results of monitoring the blood concentration of vancomycin in severely infected neonates in our hospital. China pharmacy. 2015;26(15):2041-2043.
34. Jeon YL, Kim MH, Yang HS, Kang SY, Lee WI. Optimum initial loading dose of vancomycin for pneumonia caused by methicillin-resistant Staphylococcus aureus. J Infect. 2016;72(1):115-118.
35. Eliakim-Raz N, Yahav D, Bishara J. Trimethoprim/sulfamethoxazole versus vancomycin in the treatment of healthcare/ventilator-associated MRSA pneumonia: a case-control study. J Antimicrob Chemother. 2017;72(3):882-887.
36. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrob Agents Chemother. 2011;55(12):5475-5479.
37. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus

pneumonia. Clin Ther. 2007;29(6):1107-1115.

38. Pengfei L, Xianbin Z, Yanming X, Wei Y, Yuanyuan L, Wei Y, et al. Discussion on the effect of Dengzhan Xixin injection on the outcome of coronary heart disease based on propensity score. China Journal of Chinese Materia Medica 2013;38(18):3121-3128.
39. Feng D, Qingping S, Xiaodong J, Yan L, Ran S, Jinxiu Z, et al. Predictive analysis of adverse reactions induced by Shenmai injection by Logistic model and ROC curve. China Journal of Chinese Materia Medica. 2015;40(07):1404-1409.

Figures

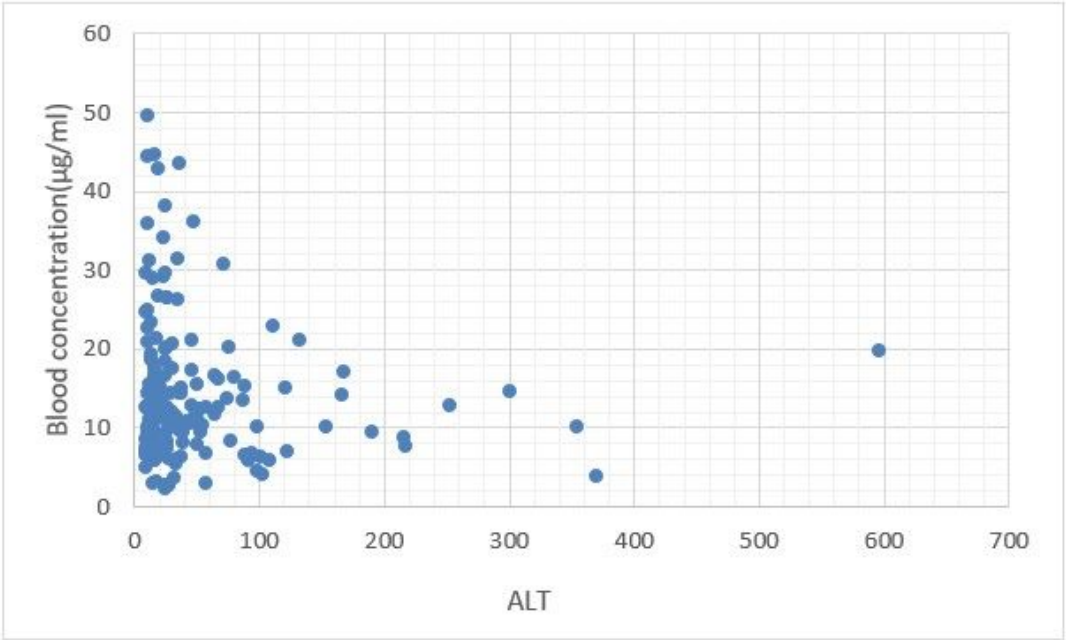

Figure 1

Relationship between Alanine aminotransferase (ALT) and blood serum.

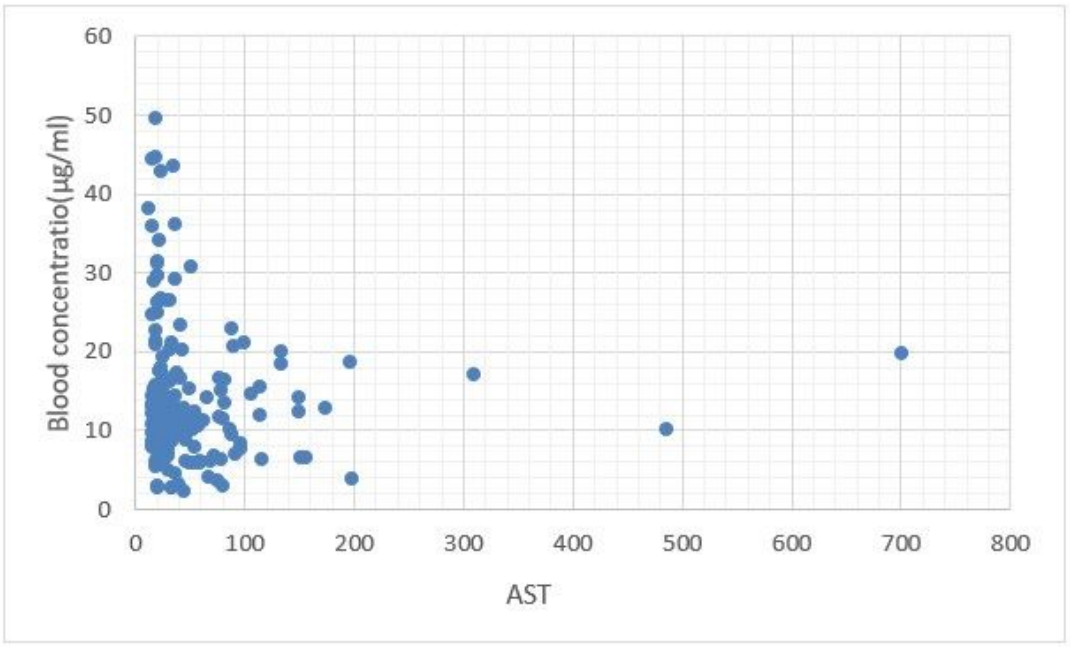

Figure 2

Relationship between Aspartate aminotransferase (AST) and blood serum.

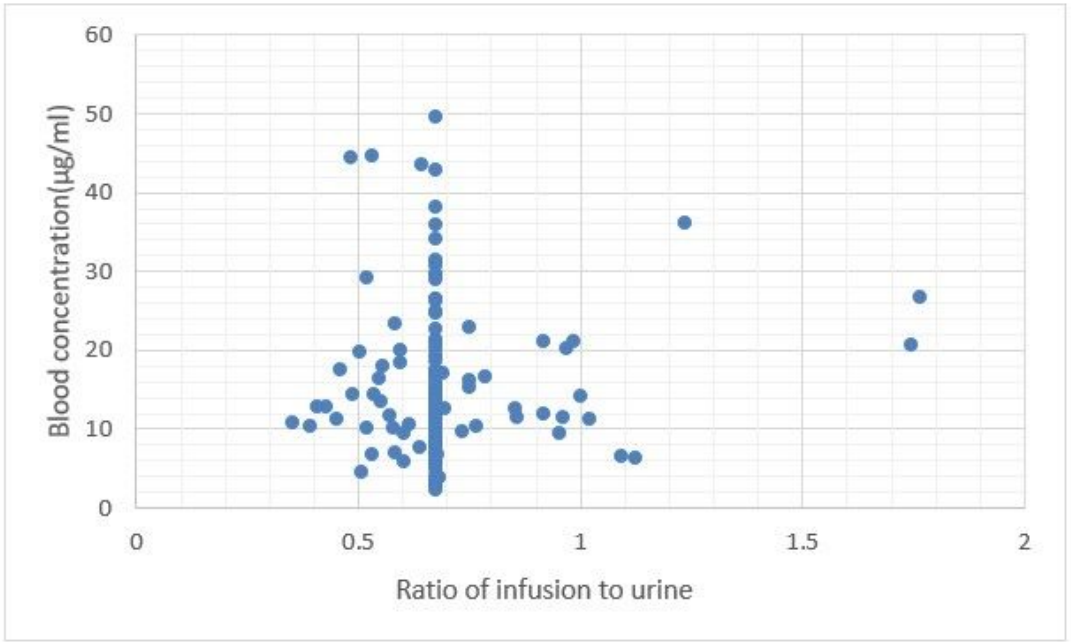

Figure 3

Relationship between ratio of infusion to urine and blood serum.

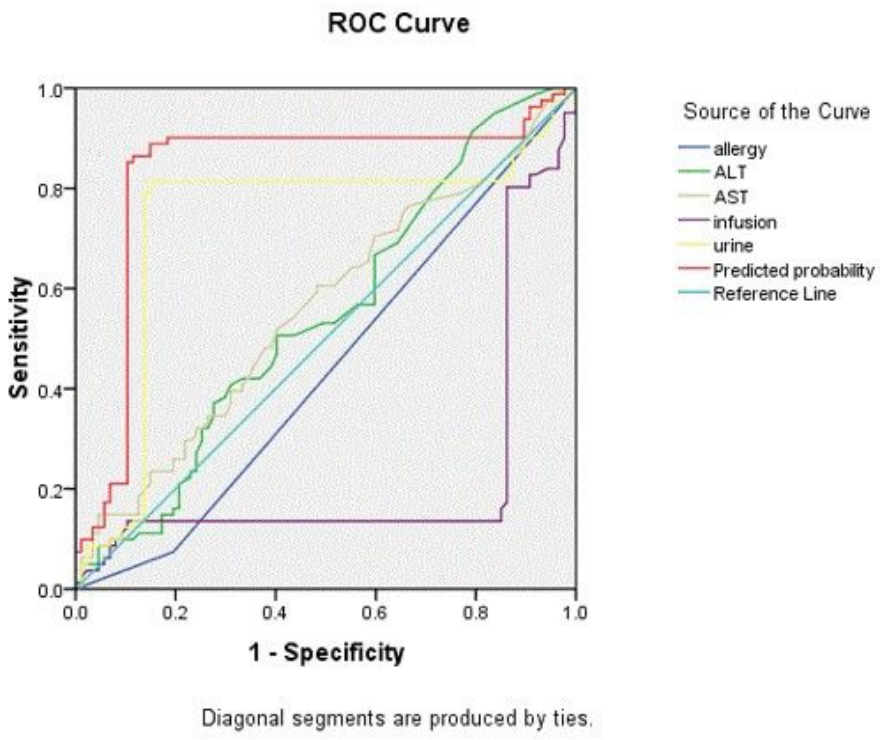

Figure 4

Receiver operator characteristic (ROC) curve of joint predictor.

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