

Research Article

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Therapeutic Drug Monitoring of Vancomycin: The Relationship Between Trough Plasma Concentration and Creatinine Clearance

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Abstract

Background: In this study which was conducted in Besat hospital (Hamadan, Iran), the therapeutic drug monitoring (TDM) of vancomycin (VAN) was carried out based on the quantification of VAN trough in intensive care unit (ICU) patients.

Methods: The study population was selected from ICU patients treated by intravenous VAN. To determine VAN trough, blood samples were taken from patients before the fourth dose. Then, trough concentrations were determined by newly developed high-performance liquid chromatography (HPLC) and compared with the conventional method of immunoassay. Twenty patients were included based on the aim of the study.

Results: The mean value of the trough for the studied patients was 26.31 ± 18.05 µg/mL. For 16 (80%) patients, trough levels were found to be less than 10 µg/mL. For 12 (60%) patients, creatinine clearance was less than 90 mL/min and more than 120 mL/min. The mean value of creatinine clearance for the studied patients was 95.49 ± 25.74 mL/min. Based on the results, there was a significant relationship between VAN trough concentration and creatinine clearance ($P=0.045$).

Conclusion: In general, the HPLC method is more sensitive than immunoassay for the determination of VAN in plasma samples. However, VAN dosing based on creatinine clearance is not enough for achieving the goal trough level but measuring the creatinine clearance and trough concentration are considered as vital aspects for the TDM of VAN.

Keywords: Vancomycin, Therapeutic drug monitoring, Trough concentration, Creatinine clearance, Intensive care unit

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Introduction

Therapeutic drug monitoring (TDM) is a clinical procedure that is used for the optimization of individualized dosage regimens. In fact, TDM is a type of plasma concentration management in the blood through which the plasma levels of the drug would not be more than the minimum toxic concentration and less than the minimum effective concentration. Several criteria are necessary for TDM, including fluctuations in the drug plasma concentration, drugs which have adverse effects, and a narrow therapeutic index, and these parameters are useful for maintaining drug concentrations within a target range (1,2). The importance of TDM in intensive care unit (ICU) is related to factors such as a wide variety of diseases, different patients with various pharmacokinetic and pharmacodynamics conditions, and drug interactions

thus the monitoring of treatment is necessary at ICU (3).

Vancomycin (VAN), as a tricyclic glycopeptide antibiotic is used against infections caused by Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* (MRSA) (4). Nephrotoxicity is one of the most important side effects of VAN and patients with abnormal renal functions show higher sensitivity to this unwanted effect compared to patients with normal renal functions (5). Due to the increased usage of antibiotics such as VAN and microbial resistance, VAN resistance enterococci and the centers for disease control and prevention have provided effective steps to implement new policies and decrease microbial resistance (6,7). In this study, VAN dosing for all patients was traditionally done through creatinine clearance using creatinine serum levels. Selecting VAN dosage based on creatinine clearance is not enough for

TDM and in ICU patients, and the importance of TDM in ICU is related to factors such as various diseases, different patients with a wide variety of pharmacokinetic and pharmacodynamics conditions, and drug interactions (3). The desired average serum trough in a steady-state concentration is 15 µg/mL (8).

Many methods have been developed and validated for the determination of VAN in plasma, biological fluids, and cerebrospinal fluid, including radioimmunoassay (RIA), fluorescence polarization immunoassay, LC mass, and high-performance liquid chromatography (HPLC) with UV detection, photon diode array detection, and fluorescence detection (9).

These methods were compared with each other from sensitivity, simplicity, precision, correlation coefficient, and fastness. Depending on the application, the method of choice would be different. A good correlation coefficient is usually observed between RIA and HPLC or FPIA and HPLC. The limit of detection (LOD) and limit of quantification (LOQ) are considered as the most important parameters (10). The lowest LOD is the most valid data which needs more sensitive methods. RIA has been selected for clinical practices because of its speed and simplicity whereas HPLC or *liquid chromatography-mass spectrometry/mass spectrometry* methods have been widely used in laboratory experiments. When low levels of VAN are expected, chromatography methods typically applicable (11,12).

In this study, a rapid, simple, and sensitive HPLC method was developed for determining VAN serum trough concentrations. Then, VAN dosing for all patients with kidney diseases was traditionally done through calculating the patient's creatinine clearance using serum creatinine levels and determining its relationship with the drug level.

Materials and Methods

This study was conducted in Besat hospital, which is an educational and medicinal center affiliated to Hamadan University of Medical Sciences (Hamadan, Iran), from February 2018 to September 2018. The study procedure was approved by the Ethics Committee of Hamadan University of Medical Sciences (IR.UMSHA.REC.1398.88). The study population was determined from among the patients by considering the inclusion and exclusion criteria, namely, the Kidney Disease: Improving Global Outcomes Guideline (13). The data related to physical examinations and patients records were documented based on the study purpose. The inclusion criteria were the age range of 18-60 years, positive culture of MRSA, empirical treatment, and passing at least 3 days of the initiation of VAN treatment. On the other hand, the exclusion criteria included hypersensitivity to VAN and the concurrent prescription of VAN with aminoglycosides. To determine VAN trough, blood samples were taken from patients 30 minutes before the fourth dose. For blood sampling, 5 mL of the blood was taken from each patient by expert nurses and transferred

to a heparinized tube. Then, heparinized tubes were rapidly transferred to the laboratory where blood samples were centrifuged at 3500 rpm for 5 minutes by technicians. The supernatant layer (serum) was then separated by the sampler and transferred to a polypropylene test tube and stored in the freezer at -70°C.

In this study, the Pearson correlation was used to evaluate the relationship between trough and creatinine clearance. Then, the Bland-Altman plot test was applied to evaluate the comparison between HPLC and immunoassay (ABBOTT) according to Usman and Hempel (14).

Materials

VAN, caffeine (Internal standard, Figure 1), ammonium di-hydrogen phosphate buffer, and perchloric acid 60% were prepared from Sigma Aldrich. In addition, ethyl acetate, methanol, and acetonitrile were purchased from Merck. Solvents were of HPLC grade and all reagents were of analytical grade. The fresh frozen plasma was prepared by the Blood Transfusion Department, Hamadan.

Methods

The stock solution (100 µg/mL) was prepared and spiked in plasma. Calibration standard curves were prepared with the serial dilutions of VAN spiked in plasma. The last calibration standard concentrations were 1, 20, 40, 60, 80, and 100 µg/mL. For drug analysis, to 200 mL of plasma samples, 40 µL of the internal standard (caffeine), and 15 µL of perchloric acid (60%) were added, respectively, and the resulting suspension was centrifuged at 12000 rpm for 10 minutes after vortex mixing for 1 minute. The supernatant was separated by aspiration into a clean 2-mL polypropylene test tube, and 1 mL of ethyl acetate was added as well. The resulting vortex was mixed for 1 minute and then centrifuged at 2000 rpm for 2 minutes. Finally, 25 µL of the aqueous layer was injected into the HPLC system.

Chromatography Conditions

The concentration of VAN was determined by HPLC (Schimadzu), a UV detector SPD-10A (Germany, Frankfurt), and a C18 column (Nucleodur®, 150 mm ×

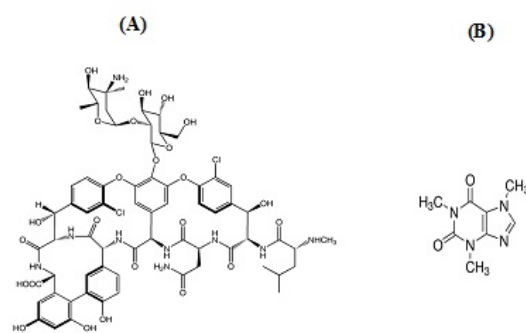


Figure 1. Chemical Structure of Vancomycin (A) and Caffeine (B).

4.6 mm, Germany). The column temperature was set at 25°C. A mixture of $\text{NH}_4\text{H}_2\text{PO}_4$ buffer (10 mM, pH=3) and acetonitrile (85:15, v/v) was used as the mobile phase with a 50 μL injection volume and a flow rate of 0.6 mL/min. The detection wavelengths were set at 280 nm (14).

Validation of Analytical Methods

Linearity, LOD, LOQ, accuracy, and precision (intraday and interday) were studied during method validation. Calibration curves, with triplicates at each concentration level (1-100 $\mu\text{g/mL}$) were performed at three consecutive days to determine intra and inter day precision and accuracy. Precision for all concentrations was accepted if the coefficient of variation (CV) fell within $\pm 15\%$. The accuracy was determined by comparing the calculated concentrations from standard curves to theoretical concentrations. Finally, the limits for accuracy values were set in the range of 85%-115% (15,16).

Statistical Methods

Pearson correlation was prepared for the evaluation of the relationship between trough and creatinine clearance in patients.

The Bland-Altman plot test was done to evaluate the difference between analysis methods (i.e., HPLC and immunoassay).

Kolmogorov-Smirnov and Shapiro-Wilk tests were conducted to check the normality of trough and creatinine clearance data.

Results

Our study involved 20 patients suffering from infectious diseases who were under VAN treatment, including 12 (60%) males and 8 (40%) females. The average age of patients was 53.5 ± 17 years. Table 1 presents the demographic information of patients and serum trough concentrations for each patient.

The calibration curves ($n=5$) were linear with $r \geq 0.99$ over the range of 1-100 $\mu\text{g/mL}$ and a lower LOD of 250 ng/mL (Figure 2). The coefficient of variation (CV %), accuracy values were within the acceptable limits (Table 2). The VAN retention time was about 4 minutes, and there was no interference with the peaks of plasma proteins. The internal standard (caffeine) retention time was about 10 minutes thus the resolution between VAN and internal standard peaks was acceptable and the method was selective for VAN identification (Figure 3).

Trough concentrations were found to be less than 10 $\mu\text{g/mL}$, 10-20 $\mu\text{g/mL}$, and more than 20 $\mu\text{g/mL}$ for 5 (25%), 4 (20%), and 11 (55%) patients. The mean value of trough was 26.31 ± 18.05 $\mu\text{g/mL}$.

The normal quantile-quantile plots for trough and creatinine clearance data showed the levels of normality distributions for the observed values from the expected values (Figures 4 and 5)

According to the results of the Kolmogorov-Smirnov

test, the statistic values of trough and GFR (glomerular filtration rate) were 0.126 and 0.87, respectively. The significance level for trough and GFR was 0.2 thus the normality deviation was not significant (> 0.05) for both parameters and they had a normal distribution (Table 3).

Based on Shapiro-Wilk test results, the statistic value of

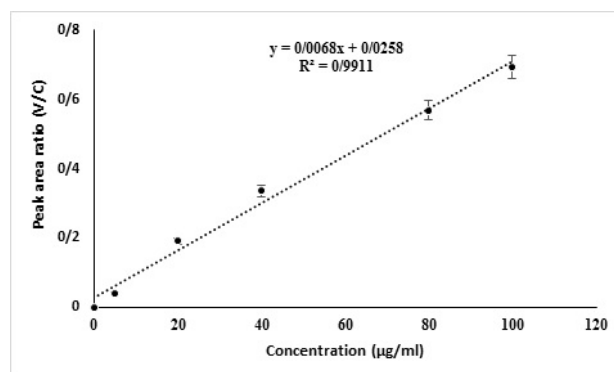


Figure 2. Calibration Curve of Vancomycin Analysis in Human Plasma.

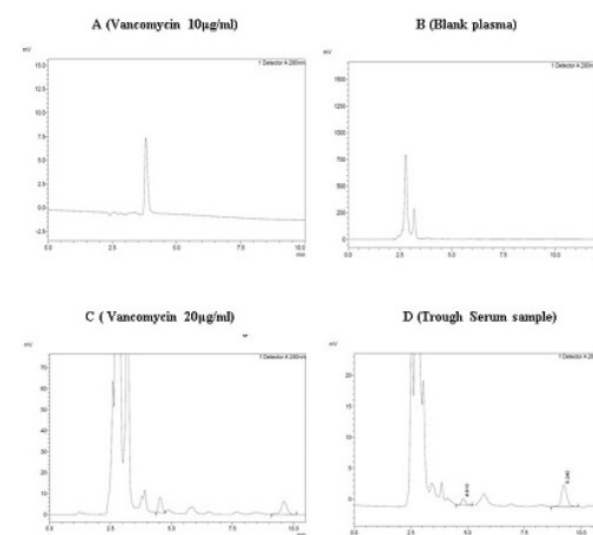


Figure 3 . (A) HPLC Chromatograms of Vancomycin 10 $\mu\text{g/mL}$, (B) Blank Plasma, (C) Vancomycin and Caffeine 20 $\mu\text{g/mL}$ Spiked in Plasma, and (D) Human Trough Sample (5.54 $\mu\text{g/mL}$). Note. HPLC: High-performance liquid chromatography.

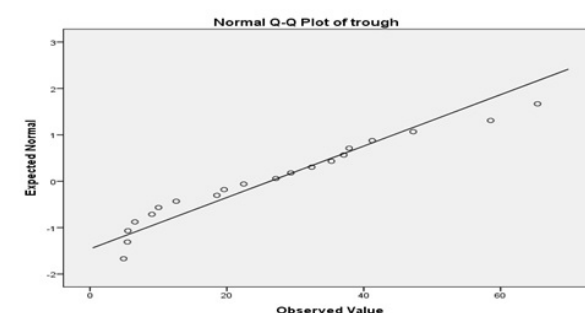


Figure 4. Normal Q-Q Plot of Trough Data. Note. Q-Q: Quantile-quantile.

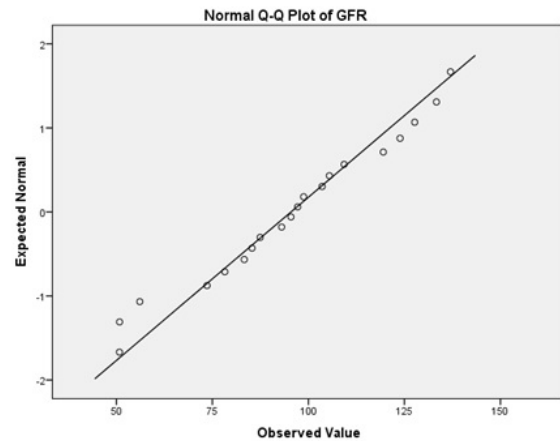


Figure 5. Normal Q-Q Plot of GFR Data. Note. Q-Q: Quantile-quantile; GFR: Glomerular filtration rate.

trough and GFR was 0.9, and the significance level for both parameters was 0.148 and 0.578, respectively. Therefore, the deviation from normality was not significant (>0.05) for both of them and they represented had a normal distribution (Table 4).

According to the Cockcroft-Gault equation, GFR data were calculated for men and women, equations (1) and (2), respectively. Based on the results, creatinine clearance was less than 90 mL/min, 90-120 mL/min, and more than 120 mL/min for 8 (40%), 8 (40%), and 4 (20) patients, respectively (Figure 5). The mean value of creatinine clearance was 95.49 ± 25.74 mL/min. According to the

Pearson correlation, there was a significant correlation between trough and creatinine clearance ($P=0.045$), the details of which are provided in Table 5. Equation (1) Cockcroft-Gault formula for men:

Cockcroft-Gault formulation: $GFR (CrCl) = (140 - \text{age} \times \text{weight}) / 72 \times \text{serum creatinine} (\times 0.85: \text{for female})$

In addition to the HPLC method, serum trough samples were determined with the immunoassay method (ABBOTT). Figure 6 shows the result of the Bland-Altman plot test for the comparison of this method with ABBOTT. Based on the Bland-Altman plot, there was a significant difference between HPLC and the immunoassay method ($P=0.019$). The mean of HPLC and immunoassay trough data was 9.34, and the lowest LOD and the lowest LOQ were 0.42 and 3 $\mu\text{g/mL}$, respectively.

The descriptive statistics of trough data approved that the lower and upper bounds were 83.4438 and 107.53 in a 95% confidence interval, respectively. The median and variance were 96.3350 and 662.38. Other descriptive data are shown in Table 6.

Based on the descriptive statistics of GFR data, the lower and upper bounds were 17.86 and 34.76 in a 95% confidence interval, respectively. Finally, the median and variance were 24.81 and 325.82. Table 7 summarizes other descriptive data.

Discussion

Due to increasing MRSA susceptible infections, the growing administration of VAN in many hospital

Table 1. Patient's Demographics and Serum Trough Concentrations of Patients

Patient Code	Sex	Age (y)	Weight (kg)	Trough ($\mu\text{g/mL}$)	Creatinine Clearance (mL/min)
1	Male	60	80	58.55	98.76
2	Female	61	75	12.60	87.43
3	Female	65	65	47.23	56.10
4	Female	43	65	19.60	93.04
5	Male	59	75	32.40	105.46
6	Male	41	66	5.54	127.67
7	Male	35	80	5.47	87.30
8	Male	56	80	6.56	133.33
9	Male	59	85	4.91	119.5
10	Female	27	65	9.05	123.87
11	Male	67	57	10.01	95.47
12	Female	60	52	22.46	97.20
13	Female	34	60	29.35	73.60
14	Female	46	56	18.54	103.57
15	Male	73	66	35.28	50.79
16	Male	80	61	27.17	50.83
17	Male	75	52	41.24	78.24
18	Male	66	75	37.08	109.30
19	Female	42	59	37.87	85.32
20	Male	21	60	65.40	137

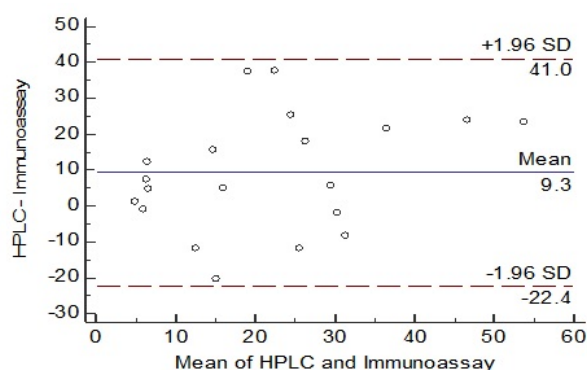


Figure 6. Bland-Altman Plot: A Comparison Between HPLC and Immunoassay (ABBOTT). Note. HPLC: High-performance liquid chromatography.

settings is probable (17). These findings show that VAN administration and its dosing according to the latest guidelines are highly recommended for achieving the target serum trough concentration. Previous studies showed that highly accurate dosing of VAN with TDM can reduce microbial resistance while improving the outcome (18,19). According to findings, several dependent parameters can affect the trough level and administration, including age, gender, weight, dose, and renal function. Loading dose can affect the administration as well (5).

In this study, most patients had abnormal trough levels and there was a relationship between trough and creatinine clearance. In other words, cases with low levels of creatinine clearance had higher trough levels. Nephrotoxicity is one of the reversible side effects of VAN predicted by VAN trough level. The results revealed that achieving target serum trough concentrations in chronic kidney disease or dialysis patients is more important and receiving higher doses of VAN for achieving this target range is a high risk for the incidence of nephrotoxicity. Critically ill patients, those receiving nephrotoxic agents, and patients with undesired renal functions are at a high risk of VAN-induced – nephrotoxicity (10).

According to the recommendations of updated guidelines, the trough range must be kept at 10 – 20 µg/mL for most usual infections while this concentration must be in the range of 15-20 µg/mL in severe infections, and the trough level of more than 15 µg/mL is in a high risk of nephrotoxicity. It should be noted that the trough level depends on concurrent administered drugs, different

diseases, and different physiological disorders (12,13,20).

Rybak et al (21) showed that the incidence of acute kidney injury with the concurrent administration of VAN and piperacillin-tazobactam is more prevalent (21%) compared to monotherapy with VAN (8.3%).

The initiation dose relies on weight, and dose adjustment should be checked at a body mass index of ≥ 30 . However, the routine dosage is the choice of treatment for those who are not obese (22). In the current study, the Bland-Altman plot was used for a comparison between HPLC and immunoassay. A mean difference of 9.3 demonstrated that there was a significant difference between both methods, and our HPLC method was more sensitive than ABBOTT (14).

Conclusion

High trough levels of VAN can lead to abnormality in creatinine clearance and the incidence of nephrotoxicity. Therefore, the concurrent evaluation of the trough level and creatinine clearance is necessary. The major limitation of our study was the small sample size which was highly

Table 2. Within- and Between-day Validation of Vancomycin in Human Plasma

Vancomycin Concentration (µg/mL)	Within Day		Between Day	
	CV (%)	Accuracy (%)	CV (%)	Accuracy (%)
1	8.24	98.74	7.68	97.25
40	0.26	104.03	0.52	105.11
100	1.52	99.30	1.07	98.54

Note. CV: Coefficient of variation.

Table 3. Kolmogorov-Smirnov Normality Test

Kolmogorov-Smirnov			
	Statistic	df	P value
Through	0.126	20	0.200
GFR	0.87	20	0.200

Note. GFR: Glomerular filtration rate.

Table 4. Shapiro-Wilk Normality Test

Shapiro-Wilk			
	Statistic	df	P value
Through	0.929	20	0.148
GFR	0.929	20	0.578

Note. GFR: Glomerular filtration rate.

Table 5. Evaluation of the Relationship Between Trough and GFR

Trough Level	Less than Normal (%)	Normal (%)	Higher than Normal (%)	Statistic	P value
GFR					
Less than normal	1 (12.5)	1 (12.5)	6 (75)	4.02	0.045
Normal	1 (12.5)	3 (75)	4 (50)	-	-
Higher than normal	3 (75)	0 (0)	1 (25)		-

Note. GFR: Glomerular filtration rate.

Table 6. Descriptive Statistics of Trough Data

Trough (µg/mL)	Statistic
Mean	26.3155
95% confidence interval	
Lower bound	17.8676
Upper bound	34.7634
5% Trimmed mean	25.3333
Median	24.8150
Variance	325.824
Standard deviation	18.0509
Minimum	4.91
Maximum	65.40
Interquartile range	28.38
Range	60.49
Skewness	0.607
Kurtosis	-0.388

Table 7. Descriptive Statistics of GFR Data

GFR (mL/min)	Statistic
Mean	95.4890
95% confidence interval	
Lower bound	83.4438
Upper bound	107.5342
5% trimmed mean	95.6661
Median	96.3350

Note. GFR: Glomerular filtration rate.

associated with the discontinued of VAN and creatinine clearance crisis in some patients. The current HPLC method for the determination of the serum trough level of VAN is sensitive, selective, and cost-effective. Eventually, the HPLC method is more selective and sensitive compared to immunoassay.

Conflict of Interests

The authors report no conflict of interests.

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