European Review for Medical and Pharmacological Sciences 2022; 26: 4840-4845

Factors influencing the vancomycin trough level in patients admitted at King Fahad Specialist Hospital, Qassim, KSA

W.M. ALTOWAYAN[1], M.A. MOBARK[1,2], A.S. ALHARBI[3], A.A. ALDUHAMI[4], S.I. RABBANI[5]

[1]Department of Pharmacy Practice, College of Pharmacy, Qassim University, Buraidah, Qassim, Saudi Arabia
[2]Department of Pathology, Faculty of Medicine, University of Kordofan, El-Obeid, Sudan
[3]Clinical Pharmacy, King Fahad Specialist Hospital, Buraydah, Qassim, Saudi Arabia
[4]Department of Pharmacy Practice, [5]Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Qassim, Saudi Arabia

Abstract. – OBJECTIVE: Although vancomycin is an effective antibiotic against methicillin-resistant *Staphylococcus aureus*, its usage is often associated with nephrotoxicity which necessitates optimization of the vancomycin dose to be both precise and appropriate. To achieve this, the importance of therapeutic drug monitoring arises, and serum trough vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness and even risk of nephrotoxicity. This study evaluated the influences on the trough levels of vancomycin given to admitted patients at King Fahad Specialist Hospital (KFSH).

PATIENTS AND METHODS: This cross-sectional hospital-based study has been conducted at KFSH among 197 patients, of which 53.3% were male and 46.7% were female. They received intravenous vancomycin at intermittent dose of 30 mg/kg/day with no clinical or laboratory renal impairment. The serum was drawn trough concentrations within 15 to 45 minutes before the fourth vancomycin dose.

RESULTS: One-way ANOVA test showed a significantly higher trough level of vancomycin among females, patients older than 50 years, and CCU and CSICU admitted patients (p-value < 0.05). Spearman correlation test also showed significant correlation with the serum vancomycin trough levels, site of infection (Rho=0.406, p=0.009), age (Rho=0.341, p=0.044) and patients' admission (Rho=0.321, p=0.041).

CONCLUSIONS: Even at body adjusted dosing, vancomycin serum trough levels varied among patients with significant variations of age, gender, site of infection and type of admission, especially CCU and CSICU, which raises the concept of dose individualization, age and gender considerations especially among critically ill patients.

Key Words:
Vancomycin, Factors, Serum levels.

Introduction

Vancomycin is an effective antibiotic that is commonly used in treating serious bacterial infections caused by methicillin-resistant staphylococcus aureus. Although the mechanism is not well understood, vancomycin usage is often associated with nephrotoxicity[1]. The reported pathological changes associated with vancomycin include acute tubular necrosis and acute interstitial nephritis with the suggestion of an underlying allergic mechanism in some patients with vancomycin nephrotoxicity[2]. The optimization of vancomycin dosing is rather important when considering the emergence of vancomycin resistant strains, especially vancomycin-resistant enterococci, and more recently vancomycin-resistant *Staphylococcus aureus*. Vancomycin overdosing significantly raise the possibility of toxicity, while sub-dosing participates in vancomycin resistance and ineffective treatment[3]. These points raise the importance of therapeutic drug monitoring (TDM) in individualizing the dosage to achieve maximum efficacy of a drug and at the same time minimizing adverse drug reactions[4]. Hopefully, TDM is not needed for the majority of drugs and only needed for those with narrow therapeutic ranges, drugs with marked pharmacokinetic variability, medications for which target concentrations are difficult to monitor, and for drugs known to cause therapeutic and adverse effects[5]. The selection of the initial therapeutic goal is a very important clinical decision, since the goal choice (too high or too low serum concentration) can make the difference between effective therapy and toxic overdosage. Because of this, when planning the initial regimen for a new patient, it is necessary to consider how much each individual patient needs the drug in question[6].

Corresponding Author: Mohammed Waleed, MD; e-mail: w.altowayan@qu.edu.sa

The most accurate and effective method in monitoring and adjusting vancomycin dose is serum trough levels. Trough samples should be obtained just before the 4th dose in patients with normal renal functions to ensure that target concentrations are attained[7].

When interpreting the plasma drug concentration of a patient, it is necessary to modify the treatment based on patient physiological needs. So, beside drug concentration, clinicians need to consider patients' specific clinical features that may affect the association between concentration of a drug and its clinical effects[8].

The daily dose, the dose interval and the urine output are known factors that affect the trough levels of vancomycin[9]. However, other factors, including patient demographics, medical conditions, type and site of infections and the severity of the disease might affect vancomycin trough levels. Therefore, this study evaluated the possible influences on the trough levels of vancomycin given to admitted patients at KFSH in Qassim province in 2021. Its aim was to participate effectively in targeting individual optimization of therapeutic dosing and minimizing drug toxicity.

Patients and Methods

Study Design and Participants

A cross-sectional, hospital-based study was conducted at KFSH in Qassim province from 2 January to 30 March 2021. A total of 197 patients were included, based on the following criterium: "patient should be diagnosed with infection, given intravenous vancomycin at intermittent doses of 30 mg/kg/day and have serum creatinine within the range of 65 to 110 micromoles/liter." Patients with clinical or laboratory evidence of renal impairment and patients under 10 years old were excluded from the study. All serum vancomycin trough level assays were run at the hospital central laboratory and the samples were drawn within 15 to 45 minutes before the administration of the 4th vancomycin dose.

Data Collection

The patients' data were obtained from the laboratory and inpatients' records. A data collection sheet was designed into 3 parts: the first part included patients' demographics – age, gender, weight, height and body mass index. The second part concerned the medical condition – diagnosis, site of infection, type of organism, ICU *vs.* non-ICU admission. The third part targeted vancomycin related data – dose, frequency and the trough level.

Statistical Analysis

Statistical analysis of the results was done using the SPSS IBM software v. 25.0 (IBM Corp., Armonk, NY, USA). One-way ANOVA was used to determine the significant variation between treatment and baseline groups. Spearman correlation test was used to determine the association between the variables and serum trough level of vancomycin. The confidence interval of 95% (upper and lower) was computed for all the variables tested in the study. p-value <0.05 was considered to indicate the significance of the results.

Results

The Demographic Characteristics and Serum Vancomycin Trough Levels of Participants

Among the total of 197 patients, the gender distribution was found to be 53.3% male and 46.7% female. The female patients showed a significantly (p-value <0.05) higher trough level of vancomycin compared to baseline value. In the age groups, patients in the age group of 61-70 years were found to be the larger recipients of vancomycin (18%), followed by 51-60 years (15.5%) and 41-50 years (15%). Patients within the age group of 51-90 years had significantly (p-value <0.05) higher trough serum levels of vancomycin compared to baseline value. In addition, patients above 91 years indicated a further increase (p-value<0.01) in the trough level when compared with baseline data (Table I).

Effect of Body Weight and Body Mass Index on the Serum Trough Levels of Vancomycin

Table II suggests the influence of body weight and body mass index on the serum trough levels of vancomycin. The analysis suggested that the body weight of the patients did not significantly alter the trough levels of vancomycin. However, patients with 29.1-34.9 BMI and those less than 18 BMI showed significantly higher (p-value<0.05) trough levels of vancomycin compared to baseline value. The majority of patients receiving the vancomycin treatment had body weight between 50 and 100 kg (84%) and BMI was 18-25 (49.5%).

Table I. Serum trough levels of vancomycin according to demographic characters.

Demographic characters	Frequency (N and %)	Trough level
Baseline value	—	12.5 ± 0.83
Gender		
Male	105 (53.3)	16.29 ± 1.09
Female	92 (46.7)	17.91 ± 0.92*
Age		
10 - 20 years	9 (4.5)	14.42 ± 3.87
21 - 30 years	25 (12.5)	16.35 ± 2.22
31 - 40 years	19 (10)	16.64 ± 2.83
41 - 50 years	28 (15)	14.89 ± 1.74
51 - 60 years	31 (15.5)	17.46 ± 2.21*
61 - 70 years	36 (18)	17.07 ± 1.40*
71 - 80 years	24 (12)	17.65 ± 1.36*
81 - 90 years	20 (10)	17.85 ± 1.90*
91 years and above	5 (2.5)	22.13 ± 2.97**

Values are expressed as Mean ± S.E. Statistics: One-way ANOVA. *p < 0.05, **p < 0.01 compared with baseline value.

Effect of Type of Patients' Admission and Site of Infection on the Serum Trough Levels of Vancomycin

The results of serum vancomycin trough levels depending on the type of patients' admission and site of infection is represented in Table III. The analysis of the results indicated that CCU and CSICU admission patients had significantly higher trough levels of vancomycin (p-value<0.05) compared to baseline value. Similarly, the patients diagnosed with infections in the abdomen, heart, urinary tract and wounds had significantly higher trough levels of vancomycin (p-value<0.05) compared to baseline data. ICU patients (52%) treated for lung (42.3%) and blood (40.7%) infections were found to be the maximum receivers of vancomycin.

Table II. Effect of body weight and body mass index on the serum trough levels of vancomycin.

Variables	Frequency (N and %)	Trough level
Baseline value	—	12.5 ± 0.83
Body weight		
Less than 50 kgs	20 (11)	16.92 ± 3.47
50 - 70 kgs	84 (42)	12.21 ± 2.03
71 - 100 kgs	84 (42)	16.34 ± 1.21
Above 101 kgs	9 (5)	15.08 ± 2.16
Body mass index		
Less than 18	5 (2.5)	20.30 ± 6.06*
18 - 25	99 (49.5)	12.39 ± 1.96
25 - 29	48 (24)	15.15 ± 1.15
29.1 - 34.9	31 (15.5)	21.15 ± 2.23*
35 - 39.9	10 (6.5)	11.77 ± 2.20
Above 40	4 (2)	12.95 ± 0.92

Values are expressed as Mean ± S.E. Statistics: One-way ANOVA. *p < 0.05, **p < 0.01 compared with baseline value.

Table III. Effect of type of patients' admission and site of infection on the serum trough levels of vancomycin.

Type of patients' admission	Frequency (N and %)	Trough level
Baseline value	—	12.5 ± 0.83
Patients' admission		
CCU	14 (7)	23.57 ± 4.32*
ICU	105 (52)	16.71 ± 1.08
CSICU	2 (1)	27.60 ± 5.90*
Site of infection		
Blood	77 (40.7)	16.97 ± 3.99
Abdomen	3 (1.5)	21.50 ± 4.50*
Brain	4 (2.1)	11.52 ± 1.04
Heart	7 (3.7)	32.63 ± 4.50**
Sepsis risk	8 (4.2)	14.47 ± 3.63
Urinary tract	6 (3.2)	19.74 ± 5.50*
Wounds	4 (2.1)	17.14 ± 2.93*
Lungs	80 (42.3)	15.57 ± 1.13

Values are expressed as Mean ± S.E. Statistics: One-way ANOVA. *p < 0.05, **p < 0.01 compared with baseline value.

Correlation Summary of Various Variables on the Serum Trough Levels of Vancomycin

The summary of the correlation between the variables and the serum trough levels of vancomycin is shown in Table IV. The following variables showed a significant correlation with the serum vancomycin trough levels: site of infection (Rho=0.406, p=0.009), age (Rho=0.341, p=0.044) and patients' admission (Rho=0.321, p=0.041).

Discussion

This cross-sectional, hospital-based study evaluated the influence of vancomycin prescribed to patients admitted at KFSH on trough levels. Among 197 patients, there were more males than females; however, female patients showed significantly higher trough levels of vancomycin (p-value<0.05), a finding that reflects

Table IV. Correlation summary of various variables on the serum trough levels of vancomycin

Variables	Trough level			
	Spearman correlation (Rho)	Lower 95% CI	Upper 95% CI	*p*-value
Gender	0.012	- 0.132	0.232	0.345
Age	0.342	0.413	0.993	0.044
Body weight	0.009	- 0.380	0.106	0.103
BMI	0.135	0.560	0.820	0.203
Patient's admission	0.321	0.414	0.729	0.041
Site of infection	0.406	0.216	0.557	0.009

Statistics: Spearman correlation test. *p*-value indicated comparison between groups.

gender variation of vancomycin trough level. This finding is in line with a study[10] developed in 2017, as authors revealed supratherapeutic concentrations of vancomycin for females compared to males. In another study[11] in ICU patients the female gender also showed significantly higher vancomycin trough levels. Interestingly, in a systematic review[12] of preclinical studies in animals it was found that vancomycin dose-response curves were shifted left for females compared to males. Our results also found that patients aged 61-70 years were the larger recipients of vancomycin. Elderly patients need to be closely monitored and the dose perfectly adjusted as vancomycin-associated nephrotoxicity was reported to be higher among patients over 60 years[13,14]. Moreover, the patients in this study aged 51-90 years had significantly higher trough serum levels of vancomycin (p-value<0.05) compared to baseline value and patients over 91 years indicated an even greater increase (p-value<0.01). As previously reported[3,15,16], vancomycin associated nephrotoxicity linearly coexists with increased trough levels of vancomycin.

This study found that body weight of the patients did not significantly alter the trough levels of vancomycin. However, the significantly higher trough levels were seen in patients with 29.1-34.9 BMI and those with less than 18 BMI, while Zonozi et al[17] reported that "patients with higher body mass index had more elevated trough levels of vancomycin". Another study[18] also revealed that obese patients had significantly higher mean trough levels of vancomycin compared to non-obese patients.

Regarding the type of patients' admission and site of infection, the analysis of this study indicated that CCU and CSICU admitted patients had significantly higher trough levels of vancomycin (p-value<0.05) compared to baseline value. This could be explained by the state of hemodynamic changes among critically ill patients and in CSI-CU, the surgical situation further complicates this condition. Consistent with this, Qian et al[10] reported a significant variation in the concentration of vancomycin trough among ICU patients with a quarter of patients demonstrating supratherapeutic concentrations of vancomycin. Mann et al[19] highlighted the importance of individualized dosing for vancomycin, as dosing in critically ill patients using a common nomogram for varying renal function showed serum concentrations higher than expected. Besides this, we observed that ICU patients treated for lung and blood infections were found to be the maximum receivers of vancomycin. As mentioned earlier, the major concern behind supratherapeutic concentrations of vancomycin is the associated nephrotoxicity. Many studies[16,20,21] proposed that the higher doses of vancomycin (4 g/d), high serum trough concentrations and an increased duration of therapy in critically ill patients were associated with a significant nephrotoxicity.

This study also indicated that sites of infection influenced the serum concentration of vancomycin and that infections of the abdomen, heart, urinary tract and wounds had significantly higher trough levels of vancomycin (p-value<0.05) compared to baseline data. Inversely, Elyasi et al[22] reported no correlation between the patients' serum vancomycin trough levels and the type of infection. However, the high trough levels in this study could be explained by the state of critical illness rather than the site of infection. Hence, the effect of patient pathophysiological status on drug disposition and the marked heterogeneity of critically ill patients needs to be considered in vancomycin dosing, which further improves both precision and appropriateness of dosage selection in the target patients.

Limitations of the Study

The primary limitation of this study was the retrospective design with a limited number of patients. The inherent individual variation in reacting to pharmacodynamics and kinetics of medications has represented an additional limitation. Moreover, the COVID-19 pandemic and related protective measures constituted an obstacle to complete the research within the planned period of time.

Conclusions

Finally, we concluded that even at body adjusted dosing, vancomycin serum trough levels varied among patients with significant variation of age, gender, site of infection and type of admission, especially CCU and CSICU. These findings significantly increase the concept of dose individualization with consideration of gender, site and types of infection, especially among critically ill patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgments

The researchers would like to thank the Deanship of Scientific Research, Qassim University for funding the publication of this project.

Ethical Approval

This study was approved by the Qassim Region Research Ethics Committee, registered at National Committee of Bio and Med. Ethics (NCBE), numbered 1441-1064521, dated 21 January 2020.

Informed Consent

Confidentiality of patients' data was totally insured, and informed consent was provided to each participant.

Authors' Contributions

Waleed M. Altowayan: conceptualization, supervision and original draft preparation.
Mugahid A. Mobark: methodology, review and editing.
Abdulmajed ALharbi: data collection, data curation and validation.
Abdullah Ali Alduhami: data collection, data curation and visualization.
Syed Imam Rabbani: data analysis, review and editing.

ORCID ID

Waleed M. Altowayan: 0000-0002-7719-9308
Mugahid A. Mobark: 0000-0001-7087-2822
Syed Imam Rabbani: 0000-0001-6344-1071

References

1) Filippone EJ, Kraft WK, Farber JL. The Nephrotoxicity of Vancomycin. Clin Pharmacol Ther 2017; 102: 459-469.
2) Stokes MB. Vancomycin in the kidney—a novel cast nephropathy. JASN 2017; 28: 1669-1670.
3) Ingram PR, Lye DC, Tambyah PA, Goh WP, Tam VH, Fisher DA. Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy. J Antimicrob Chemother 2008; 62: 168-171.
4) Sheila Prus MLT. Handbook Of Drug Monitoring Methods: Therapeutics and Drugs of Abuse. Can J Med Lab Sci 2008; 70: 44.
5) Kang JS, Lee MH. Overview of Therapeutic Drug Monitoring. Korean J Intern Med 2009; 24: 1.
6) Jelliffe RW, Schumitzky A, Guilder M. Nonpharmacokinetic Clinical Factors Affecting Aminoglycoside Therapeutic Precision. Drug Invest 1992; 4: 20-29.
7) Rybak M, Lomaestro B, Rotschafer JC, Moellering JR, Craig W, Billeter M, Dalovisio JR, Levine DP. 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. AJHP 2009; 66: 82-98.
8) Reynolds DJ, Aronson JK. ABC of monitoring drug therapy. Making the most of plasma drug concentration measurements. BMJ 1993; 306: 48-51.
9) Lee B, Kim SJ, Park JD, Park J, Jung AH, Jung SH, Choi YH, Kang HG, Ha IS, Cheong HI. Factors affecting serum concentration of vancomycin in critically ill oliguric pediatric patients receiving continuous venovenous hemodiafiltration. PLoS One 2018; 13: e0199158.
10) Qian X, Du G, Weng C, Zhou H, Zhou X. Evaluation of the variability and safety of serum trough concentrations of vancomycin in patients admitted to the intensive care unit. Int J Infect Dis 2017; 60: 17-22.
11) Alshehri N, Ahmed AE, Yenugadhati N, Javad S, Al Sulaiman K, Al-Dorzi H M, Aljerasiy M, Badri M. Vancomycin in ICU patients with gram-positive infections: Initial trough levels and mortality. Ther Clin Risk Manag 2020; 16: 979-987.
12) O'Donnell JN, Rhodes NJ, Miglis CM, Catovic L, Liu J, Cluff C, Pais G, Avedissian S, Joshi MD, Griffin B, Prozialeck W. Dose, duration, and animal sex predict vancomycin-associated acute kidney injury in preclinical studies. Int J Antimicrob Agents 2018; 51: 239-243.

13) Vance-Bryan K, Rotschafer JC, Gilliland SS, Rodvold KA, Fitzgerald CM, Guay DR. A comparative assessment of vancomycin-associated nephrotoxicity in the young versus the elderly hospitalized patient. J Antimicrob Chemother 1994; 33: 811-821.

14) Liu Y, Yin Y, Liu XZ, Yao HJ, Li LX, Chen JH, Chen T, Lu XT, Bu SH, Zhang J. Retrospective analysis of vancomycin nephrotoxicity in elderly Chinese patients. Pharmacology 2015; 95: 279-284.

15) Hanrahan TP, Kotapati C, Roberts MJ, Rowland J, Lipman J, Roberts JA, Udy A. Factors associated with vancomycin nephrotoxicity in the critically ill. Anaesth Intensive Care 2015; 43: 594-599.

16) Pritchard L, Baker C, Leggett J, Sehdev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. Am J Med 2010; 123: 1143-1149.

17) Zonozi R, Wu A, Shin JI, Secora A, Coresh J, Inker LA, Chang AR, Grams ME. Elevated vancomycin trough levels in a tertiary health system: frequency, risk factors, and prognosis. Mayo Clin Proc 2019; 94: 17-26.

18) Richardson J, Scheetz M, O'Donnell EP. The association of elevated trough serum vancomycin concentrations with obesity. J Infect Chemother 2015; 21: 507–511.

19) Mann HJ, Fuhs DW, Cerra FB. Pharmacokinetics and pharmacodynamics in critically ill patients. World J Sur 1987; 11: 210-217.

20) Vincent JL. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. JAMA 2009; 302: 2323-2329.

21) Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity. Antimicrob Agents Chemother 2008; 52: 1330-1336.

22) Elyasi S, Khalili H, Dashti-Khavidaki S, Emadi-Koochak H, Mohammadpour A, Abdollahi A. Elevated vancomycin trough concentration: increased efficacy and/or toxicity?. IJPR 2014; 13: 1241.