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Original Article

Therapeutic drug monitoring of vancomycin by AUC_{τ}-MIC ratio in patients with chronic kidney disease

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Abstract

In this study which was conducted in Alzahra University Hospital (Isfahan, I.R. Iran), the therapeutic drug monitoring of vancomycin focused on determining area under the concentration-time curve at dosing interval (τ) at steady state/minimum inhibitory concentration (AUC_{τ}/MIC) was carried out in chronic kidney disease (CKD) patients. The study population was selected from patients with the history of CKD (stages 3 or 4) treated by intravenous vancomycin. To determine vancomycin AUC_{τ}, blood samples were taken at four different occasions (trough-1, peak, random, trough-2) between the fourth and fifth doses of vancomycin. Drug concentration was determined by fluorescence polarization technique, and the E-TEST technique was used to determine the MIC. Nineteen patients were included. For 8 (42%), 7 (37%), and 4 (21%) patients, trough concentration levels were found to be less than 10 mg/L, 10-20 mg/L, and more than 20 mg/L, respectively. The mean value of AUC_{τ} for studied patients was 470.7 ± 228.3 mg.h/L and the mean MIC values was 1.04 ± 0.43 mg/L. Ten patients (53%) and 9 patients (47%) had the AUC_{τ}/MIC ratios above 400 and below 400, respectively, with the average of 519.4 ± 391.3 h. Vancomycin dosing based on patient glomerular filtration rate (GFR), as a traditional method, is not accurate enough to gain the most desired vancomycin concentration in patients with decreased or changing kidney function. Measuring drug concentration and observing its therapeutic effects accordingly is inevitable in susceptible populations receiving vital drugs such as vancomycin.

Keywords: AUC_{τ}/MIC; Chronic kidney disease; Therapeutic drug monitoring; Vancomycin.

INTRODUCTION

Therapeutic drug monitoring (TDM) is used for dosage prescription of drugs with narrow therapeutic window for individualization purposes (1,2). The aim of TDM process is to reduce drug toxicity and achieve the most desired dosage of drug for any patient, through regular monitoring of the medication serum concentration. This process can significantly prevent unwanted drug complications (due to boosted dosage of drug), and additionally reduce the possibility of therapeutic failure (due to absence of desired drug concentration) (1).

The TDM process is practiced through determining drug concentration in serum with specific scheduling and then drawing the concentration-time curve of drug. It is logical to practice this process for drugs with direct relationship between blood/plasma concentration and drug effectiveness/toxicity, and drugs that possess a narrow therapeutic window (2).

Vancomycin is a glycopeptide antibiotic acting against ram-positive organisms, which is used as the first choice to treat methicillin-resistant *Staphylococcus aureus* (MRSA) infections (3). The most concerning complication of this antibiotic is kidney toxicity. Moreover, patients with chronic kidney disease (CKD) generally show higher sensitivity to this adverse effect, compared to patients with normal kidney function (4).

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Due to current increase in usage of vancomycin and the growth of resistant microorganism, guidelines recommend, considering higher trough concentrations for patients with MRSA infection (3). This concern explains the necessity of considering TDM for patients under vancomycin treatment, specifically patients with CKD.

In the study setting, vancomycin dosing for all patients as well as those with kidney diseases is traditionally done through calculating patient's creatinine clearance using serum creatinine levels and determining the drug dosage accordingly. Determining the vancomycin dosage based on glomerular filtration rate (GFR) for patients with kidney disease is discussed in a previous study and a nomogram of vancomycin dosage has been sketched, considering 15 mg/L concentration for vancomycin as the desired average trough level at steady state (5). However, probably due to reduced prevalence of vancomycin administration and consequently lower bacterial resistance to this drug during past years, vancomycin trough concentrations are purposed very low in this study and other similar studies (4). This dosing method has not been validated yet by randomized controlled clinical trials. It is not clear if current nomograms are suitable for special situations of renal function. Of note, the matter of increasing bacterial resistance holds the necessity to consider higher trough concentrations of vancomycin (4). These concerns emphasize more on conducting TDM process to reach the most desired therapeutic outcomes for patients with CKD.

However, considering a trough concentration and interpreting it as an independent value dissembles the true concentration-time profile which is the actual determinant of clinical events in a given patient. Several studies have revealed that the area under the serum concentration-time curve at dosing interval (τ) at steady state (AUC_τ)/minimum inhibitory concentration (MIC) is a more rational index for therapeutic monitoring based on limited data obtained from animal models, *in vitro* studies and some small human studies. These findings resulted in more recent recommendations on vancomycin therapeutic monitoring which introduce AUC_τ/MIC measurement as the preferred method of vancomycin TDM (6).

In this study for the first time, the TDM of vancomycin focused on determining steady state trough concentration and AUC_τ/MIC was carried out in the population of CKD patients.

MATERIALS AND METHODS

This experimental study was conducted in Alzahra hospital, a tertiary-care referral hospital, affiliated to Isfahan University of Medical Sciences (Isfahan, I.R. Iran) from October 2015 to March 2016. The study protocol was approved by the Ethics Committee of our university (Project No. 194171). The study population was selected from patients with the history of CKD (stages 3 or 4 as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guideline) (7), who admitted to different departments of Alzahra hospital and were treated by intravenous vancomycin. Conscious consent was obtained from eligible patients.

The complete medical histories, data of physical examination and patients' records were reviewed to select patients. Factors considered for distinguishing acute kidney injury (AKI) from CKD in patients with diminished kidney function, were as following: the cause of admission, whether previous serum creatinine levels were relatively stable or not, amount of fluid intake/output during the past days, present history of trauma, dehydration, acute infectious disease, severe bleeding, surgery in the last few days, and administration of simultaneous nephrotoxic drugs.

To determine the stage of renal function based on estimated GFR (eGFR), the chronic kidney disease epidemiology collaboration (CKD-EPI) equation was used (8). This equation estimates kidney function based on serum creatinine level, patient's age, race, and gender. In this study, patients with stable renal function who had an eGFR in the range of 15-60 mL/min/1.73 m^2 were included.

To determine vancomycin AUC_τ, blood samples were taken at four various times, based on valid recommendations for TDM of

vancomycin in patients with impaired renal function, as (a),vancomycin trough-1 concentration, within 30 min before the 4th or higher dose of vancomycin; (b), vancomycin peak concentration, 2 h after finishing the administration of vancomycin (considering 2 h as a standard period for vancomycin infusion); (c), vancomycin random concentration which was drawn between sampling time of peak concentration and the next dose of vancomycin; and (d) vancomycin trough-2 concentration, within 30 min before the 5th dose of vancomycin (9).

At each stage of blood sampling, 5 mL of whole blood was taken by experienced nurses and transferred to heparinized tube. Heparinized specimens were put into cold box and rapidly transferred to the laboratory where they were centrifuged at 5000 rpm for 5 min. The surface serum was then separated by sampler and stored within the sterile falcon tube in the freezer at -80 °C.

The drug concentration in specimens was determined by fluorescence polarization technique using the COBAS INTEGRA® 400 plus analyzer (Roche Diagnostics International Ltd, Basle, Switzerland) which can determine the vancomycin concentration in serum or heparinized plasma. This instrument is an analyzer with different measuring technologies which can be used for routine clinical chemistry tests, measuring specific proteins, screening drugs of abuse and therapeutic drug monitoring. One of the limitations of this method is that the minimum measurable concentration by this device with 95% confidence interval was 0.74 µg/mL (0.51 µmol/L) (10).

In this study, the E-TEST (bioMérieux, France) technique was used to determine the MIC in the derived specimen from each patient (11). To perform this procedure, the blood or urine specimens were first cultured and kept for 24 h; if the patient's kidney function remained stable during sampling period, an MIC determination was performed on the culture.

AUC_{τ} was calculated by measuring the area under the concentration-time curve which was drawn separately for each patient using four concentrations obtained at different sampling times. Vancomycin pharmacokinetic was assumed to follow a one-compartment model (12,13). The measured trough concentration of vancomycin and the calculated AUC_{τ}/MIC is presented separately for each patient. Also, the mean ± SD (standard deviation) values of these parameters are reported.

RESULTS

Our study included 22 patients suffering from chronic kidney disease (eGFR: 15-60 mL/min/1.73 m^2) who were under vancomycin treatment. Of the study population, 12 (54.4%) were male and 10 (45.5%) were female.

The average age of patients was 68 ± 18 years and the mean eGFR was 46 ± 13 mL/min/1.73 m^2. From all included patients, 7 (32%) were infected with MRSA, 7 (32%) were vancomycin-sensitive *Enterococcus* infected, 3 patients (14%) had methicillin-resistant *Staphylococcus epidermidis*-related infections, 2 (9%) were infected with vancomycin-resistant *Enterococcus*, 2 patients (9%) had vancomycin-sensitive *Staphylococcus aureus*-related infections, and 1 patient (4%) had methicillin-sensitive *Staphylococcus aureus*-related infection.

Of total 22 patients, one was excluded due to occurrence of AKI, while for two other patients the process of blood sampling could not be completed (data limited to trough-1 concentration). Accordingly, 19 patients completed the study. The results of measurement of serum vancomycin concentrations at different sampling times are presented in Table 1.

Serum vancomycin concentrations for each patient at different sampling times (trough-1, peak, random, trough-2) are shown in Figs. 1-3, as concentration-time curves. For each patient, the AUC_{τ} was calculated as the area under each one's curve. Figs 1-3 display the concentrations obtained from every 12 h, every 24 h, or every 48 h dosing of vancomycin, respectively, in the studied patients.

The case numbers of patients in these figures conform to the patients' codes demonstrated in Table 1.

Table 1. Patient demographics and serum vancomycin concentrations at different sampling times

Patient's code	Demographic data	Vancomycin concentration type	Sampling time (h)	Vancomycin concentration (mg/L)	Patient eGFR (mL/min/1.73 m^2)	Desired dose of vancomycin based on patient eGFR and body weight*	Administered dose of vancomycin	AUC_τ	MIC (mg/L)	AUC_τ/MIC
1	Male Age (y): 76 BW (kg): 65	Trough-1 Peak Random Trough-2	0 2.5 4.5 12	53 72.7 65 52	56	1000 mg (Q 12 h)	1000 mg (Q 12 h)	722.33	1	722.33
2	Female Age (y): 93 BW (kg): 57	Trough-1 Peak Random Trough-2	0 2.5 5 12	14 32.24 28 22.7	60	750 mg (Q 12 h)	1000 mg (Q 12 h)	310.6	1	310.6
3	Female Age (y): 67 BW (kg): 67	Trough-1 Peak Random Trough-2	0 2.5 5 12	21.1 53.68 38.5 19.1	50	1000 mg (Q 12-24 h)	1000 mg (Q 12 h)	385.14	1	385.14
4	Male Age (y): 79 BW (kg): 66	Trough-1 Peak Random Trough-2	0 3 8 12	28 44 33 30	58	1000 mg (Q12 h)	1000 mg (Q 12 h)	423.42	1	423.42
5	Female Age (y): 57 Wt (kg): 69	Trough-1 Peak Random Trough-2	0 3 5.5 12	18.7 38 33 20	49	1000 mg (Q 12-24 h)	1000 mg (Q 12 h)	371.12	0.75	494.82
6	Male Age (y): 93 BW (kg): 56	Trough-1 Peak Random Trough-2	0 3.25 9 12.25	36 47 37 34	55	750 mg (Q 12 h)	1000 mg (Q 12 h)	486.43	0.75	648.57
7	Female Age (y): 52 BW (kg): 68	Trough-1 Peak Random Trough-2	0 3 6.5 12	5.5 18.8 10.3 7	55	1000 mg (Q 12 h)	1000 mg (Q 12 h)	134.78	0.75	179.70
8	Female Age (y): 84 BW (kg): 52	Trough-1 Peak Random Trough-2	0 3 6.5 12	46 86 71 41.8	58	750 mg (Q 12 h)	1000 mg (Q 12 h)	758.1	2	379.05
9	Female Age (y): 94 BW (kg): 50	Trough-1 Peak Random Trough-2	0 2.5 8 12	21 28 21.9 19.77	56	750 mg (Q 12 h)	1000 mg (Q 12 h)	278.36	1	278.36
10	Male Age (y): 44 BW (kg): 72	Trough-1 Peak Random Trough-2	0 2.5 13.75 24	2.9 20.681 6.6 2	50	1000 mg (Q 12-24 h)	500 mg (Q 24 h)	203.28	1	203.28

Table 1. (Continued)

Patient's code	Demographic data	Vancomycin concentration type	Sampling time (h)	Vancomycin concentration (mg/L)	Patient eGFR (mL/min/1.73 m^2)	Desired dose of vancomycin based on patient eGFR and body weight*	Administered dose of vancomycin	AUC_τ	MIC (mg/L)	AUC_τ/MIC
11	Male Age (y): 73 BW (kg): 65	Trough-1 Peak Random Trough-2	0 2.5 8.5 24	14.1 28 22.5 11.1	23	1000 mg (Q 24 h)	500 mg (Q 24 h)	461.27	1	461.27
12	Male Age (y): 50 BW (kg): 68	Trough-1 Peak Random Trough-2	0 2.5 8.75 24	5.3 69.1 35.2 8.5	17	1000 mg (Q 24 h)	1000 mg (Q 24 h)	729.73	1.5	486.48
13	Male Age (y): 32 BW (kg): 84	Trough-1 Peak Random Trough-2	0 2.5 13.5 24	10.7 37.4 18.9 12.6	36	1250 mg (Q 24 h)	1000 mg (Q 24 h)	504.07	1	504.07
14	Male Age (y): 74 BW (kg): 62	Trough-1 Peak Random Trough-2	0 3 22.5 48	1.5 14.6 11.3 2	39	1000 mg (Q 24 h)	1000 mg (Q 48 h)	536.85	0.75	715.8
15	Female Age (y): 45 BW (kg): 58	Trough-1 Peak Random Trough-2	0 4.25 19.25 48	13 38 17.9 4.4	30	750 mg (Q 24 h)	1000 mg (Q 48 h)	778.08	2	389.04
16	Female Age (y): 60 BW (kg): 72	Trough-1 Peak Random Trough-2	0 2.5 17 45.5	6 25 14.3 6.7	38	1000 mg (Q 24 h)	1000 mg (Q 48 h)	592.02	0.5	1184.04
17	Male Age (y): 82 BW (kg): 59	Trough-1 Peak Random Trough-2	0 2.5 13.75 47	0.74 12.91 6.9 2	60	750 mg (Q 12 h)	1000 mg (Q 48 h)	269.83	1.5	179.88
18	Male Age (y): 73 BW (kg): 60	Trough-1 Peak Random Trough-2	0 3 16.5 47.5	20.2 21 20 16.3	36	750-1000 mg (Q 24 h)	1000 mg (Q 48 h)	887.66	0.5	1775.32
19	Female Age (y): 63 BW (kg): 57	Trough-1 Peak Random Trough-2	0 3 11.25 48	4 16 6.4 2	48	750 mg (Q 24 h)	1000 mg (Q 48 h)	110.23	0.75	146.97

*Based on recommended dosage in Golightly *et al.* (20). eGFR, estimated glomerular filtration rate (based on CKD-EPI equation); AUC, area under the (concentration-time) curve at dosing interval (τ) at steady state; MIC, minimum inhibitory concentration; CKD-EPI, chronic kidney disease epidemiology collaboration; h, hour; y, years; BW: body weight; kg: kilograms.

For 8 (42%), 7 (37%), and 4 (21%) patients, trough concentrations were found to be less than 10 mg/L, 10-20 mg/L, and more than 20 mg/L, respectively. The mean value of AUC_{τ} for the studied patients was 470.7 ± 228.3 mg.h/L.

The mean of MIC values for patients was calculated as 1.04 ± 0.43 mg/L. Regarding AUC_{τ}/MIC values, 10 patients (53%) and 9 patients (47%) had the AUC_{τ}/MIC ratio above 400 and below 400, respectively, with the average of 519.4 ± 391.3 h.

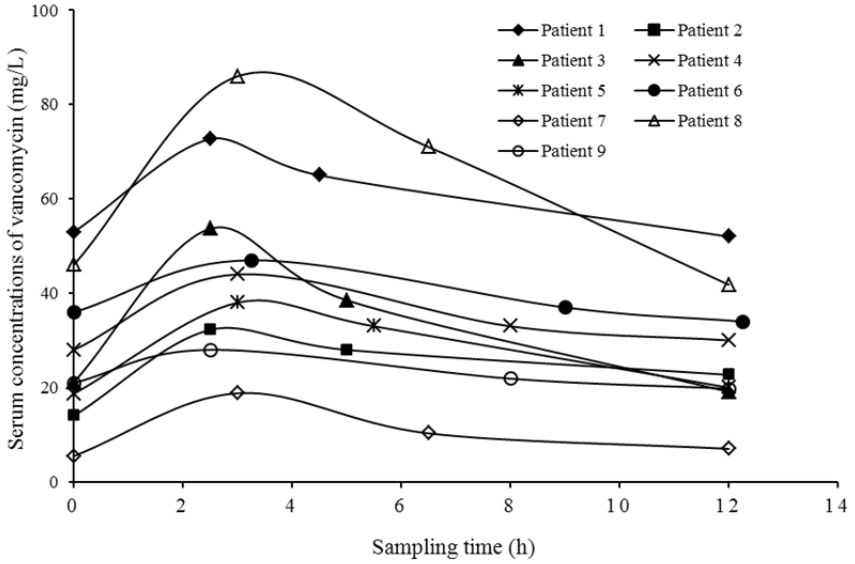

Fig. 1. Serum vancomycin concentrations at different sampling times (trough-1, peak, random, trough-2) obtained from every 12-h dosing of vancomycin in the studied patients. Drug concentration in serum specimens was determined by fluorescence polarization technique. The case numbers of patients in this figure conform to the patients' codes demonstrated in Table 1.

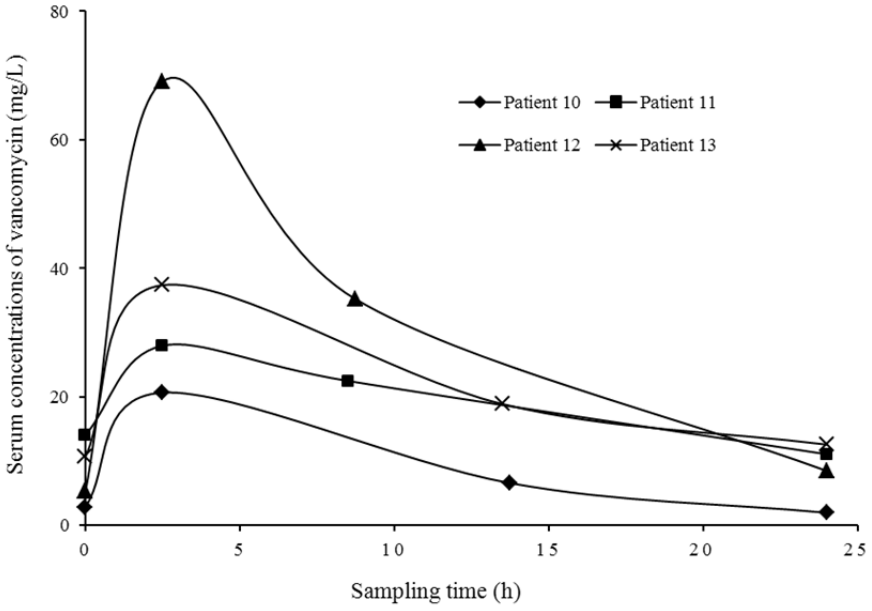

Fig. 2. Serum vancomycin concentrations at different sampling times (trough-1, peak, random, trough-2) obtained from every 24-h dosing of vancomycin in the studied patients. Drug concentration in serum specimens was determined by fluorescence polarization technique. The case numbers of patients in this figure conform to the patients' codes demonstrated in Table 1.

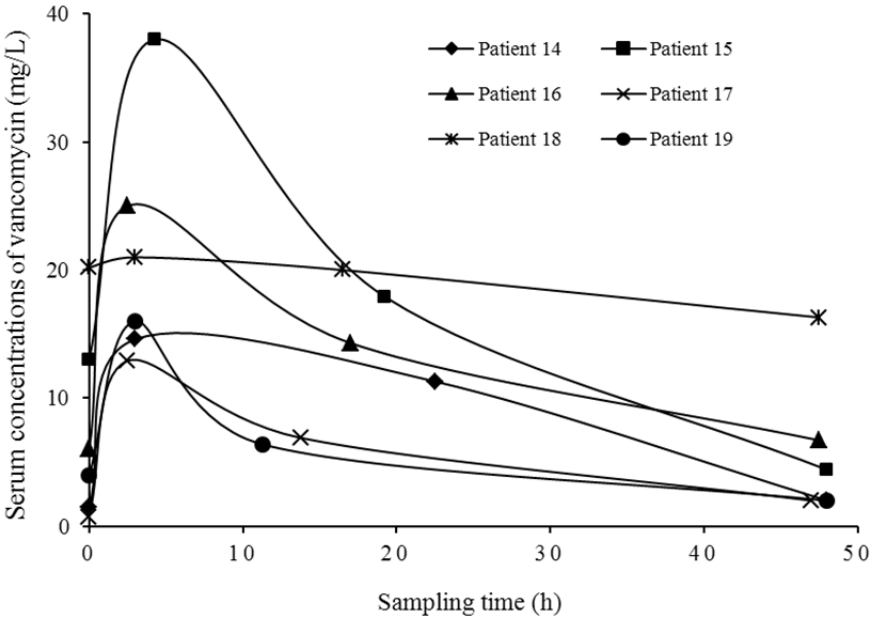

Fig. 3. Serum vancomycin concentrations at different sampling times (trough-1, peak, random, trough-2) obtained from every 48-h dosing of vancomycin in the studied patients. Drug concentration in serum specimens was determined by fluorescence polarization technique. The case numbers of patients in this figure conform to the patients' codes demonstrated in Table 1.

DISCUSSION

Increasing prevalence of MRSA-related infections leads to growing administration of vancomycin in many hospital settings. Recently, infections arising from vancomycin-resistant *Staphylococcal aureus* is becoming more prevalent in hospital settings (3-5). This finding necessitates for antibiotic dosing and administration according to latest guidelines, which unanimously recommend achieving higher trough concentrations, particularly for MRSA infections. Given that the patients suffering from CKD are at higher risk for developing vancomycin complications namely AKI, it seems necessary to advise for TDM at this susceptible population (14-16).

Several studies confirm that there is a significant rising trend in vancomycin-induced nephrotoxicity which leads to increased hospital mortality and morbidity, increased duration of hospitalization, and finally increasing remedial costs. CKD is considered as one of the major risk factors for AKI (4,15). Hsu *et al*. reported that in cases with eGFR less than 60 mL/min/1.73 m^2, there is an increasing rate of AKI incidence (15). According to their findings, patients with eGFR in the range of 49-59 have double rate of AKI risk in comparison with those having eGFR higher than 60 mL/min/1.73 m^2.

According to recommendations of updated and validated guidelines, trough concentration of vancomycin must be kept in the range of 10-15 mg/L for most usual infections, while this concentration must be in the range of 15-20 mg/L in more severe situations such as MRSA infection. Furthermore, the newer guidelines focus on AUC_{τ}/MIC as the preferred pharmacokinetic predictor of therapeutic effects of vancomycin. According to these instructions, the AUC_{τ}/MIC ratio in patients taking vancomycin must be more than 400 (3,6,14,16).

In the present study, about 42% and 37% of patients had trough concentrations below 10 mg/L and between 10-20 mg/L, respectively. The trough concentrations in about 21% of patients were higher than 20 mg/L. These findings reemphasize that even if the drug was dosed based on the recommended dosing protocol given in drug information databases, likewise the pharmacokinetic-based dosing of vancomycin via regular TDM would still be necessary in such population of patients. Otherwise,

vancomycin administration can be hazardous, both due to sub-therapeutic levels which may lead to bacterial resistance and treatment failure, and even due to the possibility of developing adverse reactions at high levels, mainly nephrotoxicity. Also regarding AUC_τ/MIC, in this study about 53% and % of patients had AUC_τ/MIC more than 400 h, and less than 400 h, respectively.

As shown in Table 1, very high AUC_τ/MIC ratios belongs to those patients with low MIC (0.5 mg/L). This greatens the fact that the role of two important components in this context, namely AUC as well as MIC, should be focused concomitantly together. Practitioners may meet patients with low MIC for vancomycin, which means needing to less doses; however, not considering the MIC component may lead to very high AUC_τ/MIC (such as cases number 16 and 18), which imposes the patients to adverse drug reactions.

Jin *et al*. evaluated 596 adult patients with normal kidney function who were under treatment with vancomycin (1 g twice daily). Average trough concentration and average AUC_τ were reported as 10 mg/L and 392 mg.h/L, respectively. Assuming that the MIC for the studied population was 1 mg/L, ratio of AUC_τ/MIC was higher than 400 h in 48% of the population (17). This finding is very similar to ours, regarding the proportion of patients with higher values of AUCτ/MIC.

Oh *et al*. evaluated 216 patients with normal kidney function. Patients were classified into two groups for monitoring of trough concentration. The first group had the goal trough concentration of 5-15 mg/L, and the second group had the goal trough concentration of 15-20 mg/L. AUC_τ/MIC of 400 h or more was reported in 73.1% of patients in the first group, and in 71.3% of the patients in the second group, with no significant difference (18). In this study population, the target level of AUC_τ/MIC > 400 h was achieved in more patients compared to our study, which may be discussed by differences in the included patients, mainly their kidney function.

Recently, one study evaluated the concentration of vancomycin in 96 patients with CKD of varying severity. The minimum and maximum concentrations of vancomycin at steady-state were measured and compared with recommended therapeutic ranges. Considering minimum concentration, only about 50% of the patients achieved the therapeutic range. The values of the peak concentrations of vancomycin also showed that only 46% was within the recommended range, while 50% were classified as sub-therapeutic. The study emphasized on the monitoring of drug concentrations to ensure the effectiveness and reduce the incidence of undesirable effects (19). This study was similar to ours regarding the studied population, however, it just evaluated trough and peak concentrations and lacks the measurement of AUC_τ or AUC_τ/MIC.

As presented in Table 1, there are some cases with the same demographic and clinical data, i.e. age, sex, creatinine clearance, and dosing pattern of vancomycin (cases number 1 vs. number 4, number 2 vs. number 8, number 5 vs. number 7, number 14 vs. number 18, and number 16 vs. number 19), however, there is substantial difference in their serum vancomycin level. This finding emphasizes more on the necessity of dosing individualization by applying TDM for each patient with susceptible conditions namely kidney disease.

CONCLUSION

Our study was the first report on vancomycin monitoring by AUC_τ/MIC in CKD patients. In the studied setting, dosage changing is only applied when significant changes happen at the patient's eGFR. Also, because of the possibility of AKI risk in this patient population, vancomycin initial dose is selected cautiously, and this may lead to low trough concentrations and AUC_τ, as seen in our findings. The major limitation of the present study was relatively small sample size which hindered the researchers to conclude any relationship between the selected maintenance dose for each patient and the measured AUC_τ. However, many individualized and intrapatient's variables may have roles in this context and make it difficult to find any precise relationship, nevertheless,

the necessity of measuring drug concentration and observing its therapeutic effects accordingly is inevitable in patients with decreased or changing kidney function receiving vital drugs such as vancomycin.

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