Evaluation of Vancomycin Therapeutic Drug Monitoring in Intensive Care Units of a University Hospital

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Abstract

Aim: Therapeutic drug monitoring (TDM) of vancomycin aims to achieve an optimal response and minimize the risk of toxicity by keeping plasma levels within the therapeutic range. In this study, we aimed to evaluate the treatment and appropriateness of TDM in patients receiving vancomycin.

Methods: For this purpose, patients who received vancomycin in the ICUs of a university hospital during 8-month period between January and August 2022 were retrospectively evaluated. Demographic data, presence of renal dysfunction, length of stay, duration of treatment, dose, concomitant medications, presence of extracorporeal method, TDM, sampling time (trough and peak level) were collected.

Results: Within the scope of the study, 213 prescriptions of 202 patients were evaluated and it was revealed that TDM was performed in 18 (8%). A total of 26 trough (n=12) and peak (n=14) level were obtained. Three (25%) of the trough and eight (57%) of the peak samples were taken at the wrong time. 50% of the trough and 64% of the peak level results were outside the reference range. TDM was not performed in 174 patients taking nephrotoxic drugs concomitantly with vancomycin. There were 84 patients who developed acute kidney injury during treatment. TDM was performed in 10 (15%) of 65 patients with pretreatment renal dysfunction.

Conclusions: In order to minimize the risk of nephrotoxicity and to get the appropriate response, it is recommended that physicians should have a conscious approach, clinical pharmacists should take an active role and hospital pharmacists should make arrangements in the orders of patients who do not have TDM.

Keywords: *Vancomycin, TDM, intensive care unit, plasma level.*

1. Introduction

Critically ill patients in intensive care units (ICUs) receive polypharmacy for treatment and prophylaxis. Due to factors such as the variable condition of critically ill patients and polypharmacy, treatment is frequently reviewed and modified[1,2]. Therapeutic drug monitoring (TDM) enables narrow therapeutic range drugs to reach optimum therapeutic concentrations and individualization of doses to prevent/reduce potential toxicity. The availability of TDM in many hospitals plays an important role in personalized pharmacotherapy[3]. The aims of TDM are to inCrease drug efficacy and safety, minimize side effects and reduce drug costs. Vancomycin is a widely used antibiotic for the treatment of gram-positive bacterial infections, including *Methicillin-resistant Staphylococcus aureus* (MRSA)[4]. It is excreted from the kidneys largely unchanged. Vancomycin clearance is decreased in patients with reduced renal function. Therefore, doses should be reduced or dose intervals should be increased[5]. In addition, the dose should be adjusted due to the altered pharmacokinetics of the drug with the presence of obesity in patients.

The pharmacokinetic profile of vancomycin is characterized by pharmacokinetic/pharmacodynamic (PK/PD) properties that conform to a multicompartmental model (variable tissue penetration) showing that its efficacy and safety are multifactorial. The best PK/PD index to predict vancomycin activity is the ratio between area under the 24-hour concentration-time curve (AUC_{0-24}) and MIC (AUC/MIC), and a value above 400 is considered to indicate clinical and microbiological efficacy against serious infections. Therapeutic drug monitoring is recommended as a more practical alternative for monitoring the treatment, as calculating the AUC for monitoring the efficacy of vancomycin therapy requires the collection of multiple vancomycin serum concentrations and pharmacokinetic software that is not accessible in every institution. In order to reach the targeted AUC/MIC (>400) ratio, it is stated that the vancomycin trough level should be 15-20 µg/ml[6].

Optimal response is obtained when the plasma concentration of

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vancomycin is kept above the minimum inhibitory concentration values [5]. TDM of vancomycin is recommended both to ensure treatment efficacy and to prevent the development of acute kidney injury (AKI) [4]. This study aimed to evaluate the appropriateness of the TDM process and length of stay of patients receiving vancomycin treatment in adult ICUs of a university hospital.

2. Materials and methods

This retrospective and observational study was conducted at a university hospital. In this context, the files of patients who received vancomycin treatment in the hospital during the 8-month period between January 1, 2022 and August 31, 2022 were retrospectively analyzed. The study included;

- Patients treated in the adult intensive care units of x University Faculty of Medicine Hospital,
- On day one of vancomycin treatment between the specified dates,
- Received vancomycin treatment for at least 30 hours (time required to reach steady state),
- Patients aged 18 years and older were included.

Demographic characteristics of the included patients; gender, age, height/weight, body mass index, body surface area, APACHE II (Acute Physiology and Chronic Health Evaluation) and clinical data;

Pre-treatment renal dysfunction (GFR<50mL/min), duration of hospitalization, duration of vancomycin treatment, vancomycin dose information, concomitant medications, presence of extracorporeal method, plasma level monitoring process information [sampling time (trough and peak level), plasma level result] were scanned from the hospital information management system (Enlil HIS) and recorded in the data collection form used in the study.

Based on the information obtained, the appropriateness of the vancomycin dose was evaluated according to the patient's demographic characteristics and comorbidities (e.g. obesity and/or renal dysfunction and/or presence of extracorporeal method). For vancomycin plasma level monitoring, the accuracy of the sampling time and, if sampled, whether the trough or peak levels were within the reference range were examined by clinical pharmacist.

3. Results

Within the scope of the study, the vancomycin treatment process in 213 different hospitalizations of 202 patients who received vancomycin treatment and met the inclusion criteria was evaluated. Eleven of these patients were hospitalized in the specified ICUs in 2 different periods.

Renal dysfunction (GFR≤ 50 mL/min) was detected in 63 (31%) of 202 different patients who received vancomycin treatment in adult ICUs before vancomycin treatment. The median duration of hospitalization in the ICU was 18 days (2-92). The median duration of vancomycin treatment was 7 days (2-52). Descriptive statistical data of the patients are presented in Table 1.

In line with the findings obtained, it was determined that 43 of 174 patients whose body mass index was calculated were obese (Body mass index ≥ 30 kg/m^2) and the height and weight of 28 patients were not recorded. Vancomycin levels were measured in 6 of 43 obese patients. In 5 obese patients, it was determined that the vancomycin dose was not appropriate (low or high) during treatment. Of the 65 patients with renal dysfunction prior to vancomycin treatment, 29 patients had extracorporeal life support. There were 84 patients (39%) who developed AKI during vancomycin treatment. The mean number of drugs used in addition to vancomycin during hospitalization was 8.86 ± 2.68 and the mean number of nephrotoxic drugs was 1.44 ± 0.8 (0-4). TDM was not performed in 174 patients who used at least 1 nephrotoxic drug concomitantly with vancomycin. The number of patients using nephrotoxic drugs concomitantly with vancomycin is shown in Table 1. The sampling time of 6 of 15 samples taken from 11 patients who developed AKI and underwent TDM was incorrect. 4 vancomycin levels are within the reference range, 4 are in the supratherapeutic range and 1 are in the subtherapeutic range.

Vancomycin TDM was performed in 18 different patients from 213 vancomycin treatment courses evaluated within the scope of the study. A total of 12 trough levels and 14 peak levels were analyzed in these patients. Whether the trough and peak results were within the reference range was evaluated and given in Table 2. It was determined that dose adjustment was performed only in 4 out of these 18 patients after theevaluation of vancomycin plasma levels. The median duration of ICU stay of the 18 patients with vancomycin plasma levels was calculated as 13 days (3-44).

Timing of vancomycin samples taken, 3 out of 12 samples analyzed for trough level and 8 out of 14 samples analyzed for peak level were inappropriate. The distribution of trough and peak samples according to the time of collection is given in Table 3.

Plasma levels were monitored in 10 of 65 patients with renal dysfunction before vancomycin treatment. Also, plasma levels were monitored in 11 of 84 patients who developed AKI during vancomycin treatment. It was determined that no vancomycin TDM was performed in any patient included in the study in the neurosurgery ICU, neurology ICU, COVID-19 ICU. It was performed mainly in the medical ICU (7 of 85 patients), anesthesiology and reanimation ICU (7 of 39 patients), surgical ICU (3 of 22 patients), and coronary ICU (3 of 14 patients) (Table 4).

Table 1

Demographical Features of The Patients (n=202)

Demographics	
Female, n (%)	81 (40)
Age, years	58,90 ± 17,68
Patients with renal function pre-treatment, n (%)	65 (%31)
Length of stay (day), median (minimum-maximum)	18 (2-92)
Duration of vancomycin treatment (day), median (minimum-maximum)	7 (2-52)
Concomitant of Nephrotoxic Drugs, n (%)	
• 0	22 (%10)
• 1	94 (%44)
• 2	80 (%38)
• 3	16 (%7.5)
• 4	1 (%0.5)

Table 2

Distribution of Vancomycin Trough and Peak Levels

	Subtherapeutic Level (n)	Level Within Reference (n)	Supratherapeutic Level (n)	Total
Trough	2	6	4	12
Peak	5	5	4	14
Total	7	11	8	26

Table 3

Distribution of Vancomycin Sample Times

	Sampling Time	n
	Appropriate	
	After reaching steady state level	4
Trough Level	1-2 hours before the next dose	5
	Inappropriate	
	Without reaching a steady state level	1
	5-6 hours before the next dose	2
	Appropriate	
	1-2 hours after end of infusion	4
Peak Level	Inappropriate	
	Before distribution completed	8
	>2 hours after end of infusion	2

Table 4

Distribution of vancomycin plasma level monitoring according to intensive care

Intensive Care Unit	Number of Patients Receiving Vancomycin, n (%)	Number of Patients with Vancomycin Plasma Levels
Internal Medicine ICU	85 (%40)	7
Anesthesiology and Reanimation Unit	39 (%18)	7
Brain Surgery ICU	28 (%13)	0
General Surgery ICU	22 (%10)	3
Coronary ICU	14 (%7)	3
COVID-19 ICU	13 (%6)	0
Neurology ICU	12 (%6)	0

ICU: Intensive Care Unit

4. Discussion

In this study, we evaluated the appropriateness and outcomes of TDM of vancomycin in adult ICUs of a university hospital. For this purpose, the trough concentration of patients receiving vancomycin treatment should be monitored after the vancomycin serum level reaches steady state, i.e., 30-60 minutes before the 4th dose after at least three doses of vancomycin treatment every 12 hours by intravenous infusion. Vancomycin requires 5 half-lives to reach steady state. Elimination half-life is 6-12 hours in adults [7]. In this case, samples should be taken within 30-60 hours after vancomycin dosing to check the trough level. Therefore, patients who received vancomycin treatment for at least 30 hours were included in the study.

It has been reported that there is a continuous increase in the use of vancomycin, which is one of the most commonly prescribed antibiotics in hospitalized patients, in treatment and that this is mostly seen in ICUs [8,9]. Physiologic changes occurring during critical illness alter the pharmacokinetics of vancomycin and thus its plasma level. Therefore, TDM of vancomycin, which has a narrow therapeutic interval and is a hydrophilic drug, should be performed in appropriate indications in critically ill patients [10]. In the ICUs included in this study, 26 vancomycin concentrations were evaluated in only 18 (8%) different patients out of 213 vancomycin treatments and plasma levels were not monitored in 195 patients (92%).

Ye et al demonstrated that the clinical efficacy rate was higher and the risk of side effects was reduced in the group in which TDM of vancomycin was performed compared to the group in which it was not performed [11]. The retrospective evaluation of the data in our study and the low number of patients who underwent TDM (8%) limited the study and clinical efficacy, and safety comparisons could not be made between the two groups.

TDM should not be considered only as determining the drug level in the sample. When monitoring is performed, factors such as the purpose for which monitoring will be performed, when the sample is taken, and the method and time of administration of the drug should be taken into consideration [12]. Errors made in the timing of sampling are among the most important factors affecting the evaluation of the results [13]. Inaccurate evaluation of the results leads to inadequate response to treatment or toxicity [1]. In our study, in addition to the fact that the rate of vancomycin TDM was very low, it was found that 25% of the samples with trough levels and 57% of the samples with peak levels were taken at the wrong time.

Incorrect evaluation of plasma levels by physicians brings along problems such as increased treatment costs [1]. Darko and Gatta emphasized in their study that preventing the risk of vancomycin-related nephrotoxicity with TDM provides significant cost savings [14,15]. In the study by Ye et al., the duration of hospitalization in the TDM group was not found to be significantly shorter compared with the non-monitored group [11]. In our study, the median length of hospitalization of patients without plasma level monitoring during vancomycin treatment was 18 (2-92) days, while the median length of hospitalization of patients with plasma level monitoring decreased to 13 (3-44) days.

When determining the dose of vancomycin, the actual weight of the patient should be taken into account [16]. However, 43 of our patients were obese and it was observed that they did not receive appropriate doses when their doses were calculated based on their actual weight. In addition, it was determined that 37 of these patients did not receive TDM. In patients with impaired renal function and/or receiving extracorporeal therapy, dose assessment should be made according to the GFR value or the extracorporeal method used and the appropriateness of the dose should be evaluated with TDM at appropriate times [16]. Within the scope of the study, the dose of vancomycin treatment was evaluated by considering the mentioned factors and taking the guidelines as reference, and it was determined that the dose of 152 (71%), 25 (12%), and 7 (3%) patients were appropriate, high, and low, respectively, out of 213 patients. There were 29 (14%) patients whose vancomycin treatment dose was determined without evaluating the presence of obesity (without measuring height and weight). In a study by Carland et al., 42% of the vancomycin maintenance dose was found to be compatible with the guidelines, 34% was found to be low, and 24% was found to be high, and it was shown that 60% of subtherapeutics and 43% of supratherapeutics were not dose adjusted [4]. In our study, out of 26 plasma level results of 18 different patients, 15 plasma level results of 11 different patients were not in the therapeutic range. In 7 (64%) of these patients, no change was made in treatment. In 4 patients, the next dose was reduced and treatment was continued.

Vancomycin-induced AKI is defined as an increase of ≥ 0.5 mg/dL in serum creatinine level, a 50% increase compared to baseline or a 50% decrease in calculated creatinine clearance on two consecutive days compared to baseline. It has also been suggested that the risk of AKI increases when the trough concentration is above 15-20 mg/L [16]. In patients with renal dysfunction, vancomycin serum concentrations should be monitored and the dose should be repeated

after the plasma level reaches the target range [1]. In our study, vancomycin plasma concentrations were not monitored in 73 of 84 patients (87%) who developed vancomycin-induced AKI. In addition, trough level monitoring is recommended for all patients using nephrotoxic drugs concomitantly with vancomycin [17]. In this study, vancomycin plasma concentrations were not monitored in 174 (90%) of 191 patients who were found to use concomitant nephrotoxic drugs.

Although the retrospective nature of the study was a limiting factor, it led to objective results in line with the aim of the study, since the decisions of physicians in the treatment and therapeutic drug monitoring processes were not intervened. However, it also limited access to clinical efficacy and safety data. The fact that the study was conducted in the ICUs of a single university hospital and reflected a short period of 8 months brings along the necessity of conducting a larger study in our country.

5. Conclusions

In line with the findings, it has been determined that there is not enough TDM to ensure the efficacy and safety of vancomycin, one of the most commonly used antibiotics, in critically ill patients. Especially in critically ill patients, the pharmacokinetics and thus the effect of vancomycin changes with variable physiology and polypharmacy. In this study, it was revealed that the rate of TDM was very low in critically ill patients receiving vancomycin treatment despite the presence of risk factors such as concurrent nephrotoxic drug use, renal dysfunction and obesity. In addition, it was determined that in patients with TDM, samples were mostly taken at the wrong time. This situation caused physicians to misinterpret the results.

Previous studies and this study suggest that TDM, if performed at the right time and evaluated correctly, will both shorten the hospitalization period of the patient and would be also beneficial in minimization of treatment cost. Increased awareness of physicians and routine patient monitoring by clinical pharmacists will ensure the efficacy and safety of vancomycin treatment. In addition, it is recommended that hospital pharmacists should also monitor the vancomycin treatment process and new regulations should be introduced for the treatment approvals of critically ill patients whose vancomycin plasma levels are not monitored.

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Statement of ethics

This study was approved by Cukurova University Faculty of Medicine Ethics Committee for Animal Experimentation with the protocol number (134/62).

Conflict of interest statement

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