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Short communication

Vancomycin Dosing in Low Flux Hemodialysis: Is Adjustment of Drug Dosage Necessary?

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Abstract

Introduction. Vancomycin is a widely useable antibiotic against Gram-positive bacterial species in different clinical settings, particularly in hemodialysis patients; however, maintaining its optimal therapeutic serum level is necessary in such patients with the purpose of maximizing its efficacy and minimizing its toxicity. The present study aimed to assess the serum level of vancomycin before and after hemodialysis.

Methods. This cross-sectional study was performed in patients who were hospitalized and medicated by vancomycin with the loading dose of 1000 mg followed by the maintenance dose of 500 mg after each dialysis session every other day. All patients were dialyzed with a low-flux dialyzer membrane. Half an hour before and immediately after dialysis, 2 ml blood sample was taken and stored at -20°C until assaying the level of vancomycin.

Results. The average reduction in the serum level of vancomycin was totally 17.65±1.69% (ranged from 12.43% to 21.56%). The mean reduction in the serum level of vancomycin was significantly higher in patients aged higher than 60 years as compared to older ones (17.95% versus 16.90%, p=0.035). But, the level of drug was independent to gender or body mass index.

Conclusion. By using low-flux dialyzer membranes, the average reduction in the serum level of vancomycin is expected to be in the range of 12.43% to 21.56%. This reduction may significantly change by increasing age and thus adjusting and monitoring the serum level of drug in old ages even in the cases of using low-flux dialyzer membranes is recommended.

Keywords: vancomycin, hemodialysis. renal failure, drug toxicity

Introduction

Vancomycin is a wide useable antibiotic against Gram-positive bacterial species in different clinical settings, particularly in hemodialysis patients [1]. In fact, because of high incidence of stenting-related bacterial infections, following vascular accessing, vancomycin is widely used in hemodialysis patients. This antibiotic is excreted by kidneys and thus its renal clearance as well as its therapeutic plasma level should be monitored accurately, in patients who are candidates for hemodialysis, especially in those who receive high-flux hemodialysis [2-6]. According to the common clinical approaches, this drug should be administered with a loading dose of one gram following dialysis or within the last hour of each session of dialysis followed by administrating maintenance dose of the drug in the range of 0.5 g to 1.0 g after dialysis [5]. By this approach, the level of vancomycin is maintained between 5 -20 µg/ml in most of the patients; however, it may be leveled lower than 10 µg/ml in about 30 to 40% leading to antibiotic treatment failure [8,9]. It can especially occur on highly permeable dialysis membranes that results in high clearance value of this drug by the kidneys in these patients. In such situations, therapeutic and non-toxic vancomycin levels were recommended to be obtained by giving 1000 mg of vancomycin, intravenously, as a loading dosage and 500 mg during every subsequent dialysis to achieve optimal drug efficacy as well as appropriate drug clearance [10]. Moreover, increasing cumulative dosages of drug in those patients with renal failure due to the failure of renal clearing process in nephrotoxicity may be predictable, leading to high drug toxicity rate [11]. The present study aimed to assess the serum level of vancomycin before and after hemodialysis. In other words, we determined the therapeutic dose of drug and its main determinants in patients undergoing hemodialysis.

Materials and methods

This cross-sectional study was conducted at Dialysis wards in Rasoul-e-Akram Hospital, between April and December 2015, in patients who were hospitalized and medicated by vancomycin with the loading dose of 1000 mg followed by the maintenance dose of 500 mg after each dialysis session every other day. This study was approved by the Ethics Committee of the Iran University of Medical Sciences. Informed consent was obtained

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from all patients or their families. Human rights were respected in accordance with the Helsinki Declaration.
All patients in our study aged over 18 years who suffered from end-stage renal disease required hemodialysis three times a week (every session from 3.5 to 4.0 hours). The subjects received vancomycin therapy due to prophylaxis protocol or to definitive diagnosis of bacterial infection; dialysis were performed with a filter of a 1.3 m2 surface area by low-flux dialyzer membrane (PS13 LF, editechsys Co, Tehran, Iran). The baseline characteristics including demographics, body mass index (BMI), underlying disorders that led to end-stage renal disease (diabetes mellitus, hypertension, or other diseases), the type of renal disease requiring dialysis (acute or chronic kidney injury), drug history (categorized as nephrotoxic or non-nephrotoxic medications), the time of receiving vancomycin, and blood access of dialysis (catheter or fistula) were extracted from hospital files and entered into the study checklists. Half an hour before and immediately after dialysis, 2 ml blood sample was taken and stored at -20°C until assaying the level of vancomycin. According to the protocols, the therapeutic range of vancomycin was considered to be 10-20 mg/L.
Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t-test or Mann-Whitney U test. For the statistical analysis, the statistical software SPSS, version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In total, 55 patients (33 men and 22 women) were assessed. Of those, 70.9% were older than 60 years and 7.2% were obese (BMI>30 kg/m^2). Regarding underlying disorders leading to end-stage renal disease, 20% suffered from diabetes mellitus type II, 38.0% were hypertensive, and 42.0% suffered from other diseases. Overall, 78.2% suffered from chronic kidney disease undergoing chronic hemodialysis, while 21.8% were affected by acute kidney disease and 10.9% had received nephrotoxic drugs simultaneously with vancomycin. Regarding the dose of vancomycin, 9.1% received the first dose, 12.7% received the second dose, 65.4% received the third dose, and 12.7% received the fourth dose of vancomycin. Of 55 patients assessed in the present survey, 16.4% had fistula and 83.6% had catheter as vascular access (Table 1).
The average reduction in the serum level of vancomycin was 17.65±1.69% (ranged from 12.43% to 21.56%) (Table 2). There was no difference in the average reduction in the level of vancomycin between men and women (17.86% versus 17.33%, p=0.256), but it was significantly higher in patients aged over 60 years as compared to older ones (17.95% versus 16.90%, p=0.035). Also, no difference was revealed in the mean reduction of the level of drug between obese and non-obese patients (17.76% versus 17.64%, p=0.891) (Table 3). Of 55 patients assessed in the study, the post-dialysis serum level of vancomycin maintained at the therapeutic range (10-20 mg/L) in 53 patients (96.4%) and thus

Table 1. Baseline characteristics of study population

Gender	
Male	33 (60.0)
Female	22 (40.0)
Age	
More than 60 years	39 (70.9)
Less than 60 years	16 (29.1)
Body mass index	
Higher than 30 kg/m^2	4 (7.27)
Lower than 30 kg/m^2	51 (92.72)
Underlying disease	
Diabetes mellitus	11 (20.0)
Hypertension	20 (38.0)
Other	24 (42.0)
Type of kidney injury	
Chronic	43 (78.2)
Acute	12 (21.8)
Receiving nephrotoxic drugs	6 (10.9)
Dose of vancomycin	
First	5 (9.10)
Second	7 (12.72)
Third	36 (65.45)
Fourth	7 (12.72)
Vascular access	
Fistula	9 (16.36)
Catheter	46 (83.64)

Table 2. Average percent reduction in serum level of vancomycin before and after dialysis in patients, using low-flux polysulfone membranes 13

Average	17.6515
Mean	17.79
Standard deviation	1.69
Minimum	12.43
Maximum	21.56

Table 3. Average reduction in the serum level of vancomycin

	Average reduction	**P-value**
Gender		
Male	17.86	0.256
Female	17.33	
Age		
More than 60 years	17.95	0.035
Less than 60 years	16.90	
Body mass index		
Higher than 30 kg/m^2	17.76	0.891
Lower than 30 kg/m^2	17.64	

adjusting the dose of drug was required for only 3.6% of patients.

Discussion

According to the literature, the most important factor affecting the reduction of the level of vancomycin in hemodialysis patients was the type of dialysis membrane. The use of high-flux membranes might lead to an average reduction of 35% to 50% in the level of vancomycin [12]; thus, adjustment of drug dosage is essential to avoid antimicrobial treatment failure. In contrast, the average reduction of the level of vancomycin in low-flux membranes was shown to be about 17% without need to following an especial protocol for adjusting drug dosage [13]. According to our survey in which we used low flux, the average reduction in the serum level of vancomycin was revealed to be 17.6%. It was comparable with previous reports, indicating no need to adjust the dose of vancomycin during dialysis with low-flux membrane. Of baseline variables, only age was directly associated with average reduction of vancomycin level. Hence, lowering level of drug could be predictable in older patients, while the reduction of the level of drug was completely independent to gender or BMI. In other words, the likelihood for reducing drug level in the serum can increase in older ages and consequently need for controlling titration of drug dosages may be required in old ages, even after using low-flux dialysis membranes. Overall, it seems that using a vancomycin dosing nomogram in conditions when high-flux membranes are used or in older adults that are planned for low-flux membranes can significantly improve and accelerate the achievement of target trough concentrations [14]. As a rule, vancomycin is not significantly dialyzable when hemodialysis is performed using a low flux membrane, while vancomycin is dialyzable when hemodialysis is performed using a high flux membranes [15]. However, except for the potential effects of the type of the membrane, other probable confounding factors should be considered. Based on the results obtained in our study, older age is a main factor that affects the clearance of vancomycin. As indicated in previous studies, preexisting renal impairment and concomitant therapy with other nephrotoxic agents should also be considered as potential confounders that may affect the efficacy of the drug in dialysis patients. For instance, as presented in the literature, the accepted incidence of nephrotoxicity secondary to vancomycin monotherapy is <5%, but it increases to 43% in patients receiving concomitant nephrotoxic medications [16]. In other words, considering concurrent use of nephrotoxic agents is vital because it may lead to increased vancomycin toxicity synergistically; thus, adjusting the dose of vancomycin in these conditions is potentially required. As a total rule, for vancomycin therapy to be optimal, adequate trough concentrations of vancomycin should be maintained and elevated peak concentrations especially in older ages, as well as concomitant use of nephrotoxic drugs should be avoided. Therefore, routine monitoring of vancomycin in all conditions, in which high-flux membranes are applied or other nephrotoxic agents are used, should be planned. As an important point, in cases when low-flux membranes are used, drug dosage monitoring should also be considered in older adults.

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Conflict of interest statement. None declared.

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