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Vancomycin dosing in low-flux hemodialysis; is adjustment of drug dosage necessary?

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ABSTRACT

Introduction: Vancomycin is a wide useable antibiotic against gram-positive bacteria species in different clinical setting particularly in hemodialysis patients.
Objectives: The present study aimed to assess the serum level of vancomycin before and after hemodialysis.
Patients and Methods: This cross-sectional study was performed on 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%. The mean reduction in the serum level of vancomycin was significantly higher in the patients aged higher than 60 years, as compared to other ones. But the level of drug was independent to gender or body mass index.
Conclusion: 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% that age was directly associated with the average reduction of the level of vancomycin. Therefore, adjusting and monitoring the serum level of drug in old ages even in the cases of using low-flux dialyzer membranes is recommended.

Implication for health policy/practice/research/medical education:
Given results of our study on assessing the serum level of vancomycin (the loading dose of 1000 mg followed by the maintenance dose of 500 mg) before and after hemodialysis, it is recommended to adjust and monitor the serum level of drug in old ages even in the cases of using low-flux dialyzer membranes.
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Original

Introduction

Vancomycin is a wide usable antibiotic against gram-positive bacteria species in different clinical setting particularly in hemodialysis patients (1). In fact, because of high incidence of stenting-related bacterial infections, following vascular accessing, vancomycin is widely administered 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. Therefore, plasma level of this drug should be monitored in patients who candidate for hemodialysis especially in those who receive high-flux hemodialysis (2-7). According to the common clinical approaches, this drug should be administered with a loading dose of 1 g 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 (5,7). To 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% may leading antibiotic treatment failure (8,9). It can causally occur on highly permeable dialysis membranes that results in the high clearance value in these patients. In such situations, therapeutic and non-toxic vancomycin

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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 the drug in those patients with renal insufficiency due to the failure of renal clearing process in nephrotoxicity may be predictable, leading high drug toxicity rate (11).

Objectives

The present study aimed to assess the serum level of vancomycin before and after hemodialysis. In other words, we aimed to determine the therapeutic dose of the drug and its main determinants in patients undergoing hemodialysis.

Patients and Methods

Study patient

This cross-sectional study was conducted at dialysis ward in Rasoul Akram hospital, between April and December 2015, on 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 in our study aged higher than 18 years who suffered end-stage renal disease requiring hemodialysis three times a week (every session for 3.5 to 4.0 hours). The subjects received vancomycin therapy due to prophylaxis protocol or to definitive diagnosis of bacterial infection. Dialysis was performed for them with a filter of a 1.3 m^2 surface area by low-flux dialyzer membrane (PS13 LF, Meditechsys Co, Tehran, Iran). The baseline characteristics including demographics, body mass index (BMI), underlying disorders led to end-stage renal disease (diabetes mellitus, hypertension, or other diseases), drug history, 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.

Ethical issues

This study was approved by the ethics committee of Iran University of Medical Sciences. Informed consent was obtained from all patients or their families. Human rights were respected in accordance with the Helsinki Declaration.

Statistical analysis

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-Smirnoff 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 and *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% aged higher than 60 years and 7.2% were obese (BMI > 30 kg/m^2). Regarding underlying disorders leading end-stage renal disease, 20% suffered diabetes mellitus type II, 38.0% were hypertensive, and 42.0% suffered other diseases. Overall, 78.2% suffered from chronic kidney disease undergoing chronic hemodialysis. Regarding 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 totally 17.65 ± 1.69% (ranged 12.43% to 21.56%) µg/mL (Table 2). There was no difference in the average reduction in the level of vancomycin between men and women (17.86% versus 17.33%, $P = 0.256$). However it was significantly higher in patients older than 60 years compared to younger ones (17.95% versus 16.90%, *P*

Table 1. Baseline characteristics of study population

Variable	No. (%)
Gender	
Male	33 (60.0)
Female	22 (40.0)
Age (y)	
>60	39 (70.9)
<60	16 (29.1)
BMI ($g/m^{2)}$	
>30	4 (7.27)
<30	51 (92.72)
Underlying disease	
Diabetes mellitus	11 (20.0)
Hypertension	20 (38.0)
Others	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)
Forth	7 (12.72)
Vascular access	
Fistula	9 (16.36)
Catheter	46 (83.64)

Abbreviation: BMI, Body mass index.

= 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 µg/mL) in 53 patients (96.4%); thus, adjusting the dose of the drug was required for only in 3.6%.

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 that 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 – which is used low flux – the average reduction in the serum level of vancomycin was revealed to be 17.6% that was comparable with the previous reports, indicating no need to adjust the dose of vancomycin during dialysis with low-flux membrane. More important, of baseline variables, only age was directly associated with average reduction of the level of vancomycin as reducing in the level of the drug in the serum increases in the patients older than 60 years compared to the younger ones; consequently, there is a need for controlling titration of the drug dosages, even after using low-flux dialysis membranes in these patients. On the other hand, the reduction of the level of the drug was completely independent to gender or BMI.

Table 2. The mean percent reduction in serum level of vancomycin before and after dialysis in the 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. The average reduction in the serum level of vancomycin (µg/mL)

	Average Reduction	*P* value
Gender		
Male	17.86	0.256
Female	17.33	
Age (y)		
>60	17.95	0.035
<60	16.90	
BMI ($g/m^{2)}$		
>30	17.76	0.891
<30	17.64	

Abbreviation: BMI, Body mass index.

In total, it seems that using a vancomycin dosing nomogram in conditions which high-flux membranes are used or in old patients who were planned to use low-flux membranes, can significantly improve and accelerate the achievement of the 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 membrane (15). However, except for the potential effects of type of the membrane, other probable confounding factors should be considered. Based on the results of our study, older age was the main factor that affects the clearance of vancomycin. As indicated in previous studies, preexisting renal impairment and concomitant therapy with other nephrotoxic should be also considered as potential confounders that may affect the efficacy of drug in dialysis patients. For instance, as shown in the literature, the accepted incidence of nephrotoxicity secondary to vancomycin monotherapy is <5% but increases to 43% in patients receiving concomitant nephrotoxic medications (16). In other words, considering concurrently administration of nephrotoxic agents is vital because it may lead to increase the toxicity of vancomycin synergistically, thus, adjusting the dose of vancomycin in these conditions is potentially required.

Conclusion

As a total rule, for optimal level of vancomycin during therapy, adequate through level of this drug should be maintained and below this level and also unexpected elevated peak level especially in old age and also in condition with concomitant other nephrotoxic drugs should be avoided. Therefore, routine monitoring of vancomycin in all conditions that high-flux membranes are applied, or other nephrotoxic agents are used should be planned. As an important point, in those conditions that low-flux membranes are used, monitoring the serum level of this drug should be also considered in older adults.

Limitations of the study

This study was conducted on a small proportion of dialysis individuals. We suggest a larger investigation on this aspect of renal failure patients.

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Authors' contribution

Conception and design of the study, or acquisition of data, or analysis and interpretation of data; NK. Drafting the article or revising it critically for important intellectual content; AF. Final approval of the version to be submitted; AJ and NK.

Conflicts of interest

There were no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The registration number of the thesis is 2052.

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