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Vancomycin Utilization Evaluation: Are We Dosing Appropriately?

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ABSTRACT

Background: Inappropriate use of vancomycin not only increase health care costs but also contribute to the emergence of resistant organisms. Higher trough serum vancomycin concentrations (>10mg/L) has been recommended for avoidance of development of resistance. We aim to compare the administered dose with recommended doses based on guideline-recommended weight-based dosing.

Methods: In a cross sectional study, all patients who received vancomycin between July and October 2013, in infectious disease, internal medicine wards and emergency department of a teaching hospital in Tehran, Iran were entered to the study. Indication of vancomycin and necessary data for dose calculation including height and serum creatinine were recorded. Prescribed doses were compared with recommended doses in guidelines and calculated Glomerular filtration rate (GFR) for each patient.

Results: One hundred and four patients (45 females and 59 males) recruited in the study. Our results indicated that, from all administered doses of vancomycin, 64.4% and 88.8% differs significantly (more than 20%) based on American Pharmacist Association (AphA) vancomycin monograph and guideline-recommended, weight-based vancomycin dosing (for adults), respectively.

Conclusion: Underdosing of vancomycin is a major risk factor for developing resistance of gram positive organisms to this glycopeptide. Our results showed that more than half of patients receiving vancomycin are in the risk of low drug levels based on guidelines. So, having a comprehensive plan for the proper use of this drug especially designing effective internal guidelines can prevent emergence of resistance to vancomycin in future.

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Introduction

During the last decade, utilization of vancomycin has increased. Inappropriate use of vancomycin has not only increased health care costs but also contribute to the emergence of resistant organisms (1). The rapid emergence of multi drug resistant organisms such as Methicillin-Resistant Staphylococcus Aureus (MRSA) and Vancomycin-Resistant Enterococci (VRE) is considered a big issue in medical practice (2, 3). Adjustment and targeting of specific serum concentration of vancomycin above the Minimum Inhibitory Concentration (MIC) for the offended organisms is recommended for avoidance of bacterial resistance (4). To achieve this target higher

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Table1. American Pharmacists Association (APhA) vancomycin monograph recommended dosing based on Creatinine Clearance

Creatinine Clearance (ml/min)	Starting dose
>50	15-20 mg/kg/dose (usual: 750-1500 mg) every 8-12 hours
20-49	15-20 mg/kg/dose (usual: 750-1500 mg) every 8-12 hours
<20	Will need longer intervals; determine by serum concentration monitoring

Note: In the critically-ill patient with renal insufficiency, the initial loading dose (25-30 mg/kg) should not be reduced. However, subsequent dosage adjustments should be made based on renal function and trough serum concentrations.

vancomycin doses and high trough concentration are required. Weight-based dosing was recommended to achieve these new targets (4). We performed this study to review vancomycin usage in a teaching hospital with approximately 453 beds and to compare the administered dose with recommended doses based on American Pharmacist Association (AphA) (5) vancomycin monograph and guideline recommended weight-based dosing of vancomycin in adults (4).

Patients and Methods

In a cross sectional study, all patients (>18 years old) who received vancomycin between 23 July /2013, and 22 October/2013, in infectious disease, internal medicine wards and emergency department of a teaching hospital in Tehran, Iran were included in the study. Three pharmacists with supervision of a clinical pharmacist actively gathered necessary information including demographic data, vancomycin indication, dosing regimen, route of administration, duration of treatment microbiological culture/sensitivity testing and serum creatinine (up to 7 days after the first dose of vancomycin). Data were collected prospectively from the inpatient charts. Missed data were collected using hospital information system. The data were recorded in a predesigned data collection form.

Glomerular Filtration Rate (GFR) was calculated for all patients using Cockroft-Gualt formula as an estimation of creatinine clearance. Administered doses of vancomycin were compared to recommended doses based on calculated GFR in American Pharmacists Association (APhA) vancomycin monograph (Table1) (5) and weight-based dosing of vancomycin recommended for adults (Table 2) (6). Dose difference more than 20% was considered as incorrect dose.

All data were entered to Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA). We conducted descriptive analyses of key descriptive study variables.

Results

During 3-months of study period total number of 104 patients (59 males and 45 females), received vancomycin. Twenty patients were excluded: 12 of them, because lack of information, Five patients weighting less than 50 Kg which dosing data for them were not available (we analyze them just based on doses recommend in AphA vancomycin monograph). Another 3 patients had creatinine clearance less than 10 ml/min which based on guideline need Therapeutic Drug Monitoring (TDM). Unfortunately TDM was not done for these patients and they were analyzed just based on APhA recommendation.

The mean age and weight of patients were 57.34 years (range 13-91, SD= 20.79) and 67.05kg (range 30-150, SD=16.83) respectively. The main reasons of vancomycin administration were sepsis (31.5%) and pneumonia (17%). Internal medicine wards had highest rate of vancomycin administration using Defined Daily Dose (DDD) per 100 bed/day followed by infectious disease ward.

We compared prescribed doses with recommended doses based on two different standardized methods (APhA recommendation and guideline recommended weight-base dosing of vancomycin for adults) for vancomycin dose adjustment according to patient's GFR. Data are shown in table 3.

Our results showed that, from all doses of vancomycin administered, 64.4% were incorrect based on drug monograph and 88.8% were incorrect based on weight-based dosing of vancomycin for adults, respectively (Table 3).

Discussion

Our results suggest that vancomycin dosing is often empiric and without consideration of GFR or any other characterization of patients. In addition, physicians prescribe sub-therapeutic doses of vancomycin due to fear of its potential nephrotoxicity. Data derived from more recent studies and vancomycin guideline of Infectious Disease Society of America (IDSA) appear to suggest that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages (7-9). But resistant to vancomycin, this valuable drug can occur in sub-therapeutic doses.

The study designed in Shiraz Medical University by Vazin et al., suggested that 68.63% of vancomycin used for the patients with febrile neutropenia was compatible with IDSA vancomycin guideline. The initial dosage of vancomycin in 68.63%, rate of infusion in 100%, and dilution of vancomycin in100% of cases, were appropriate.

Table 2. Recommended Weight-based dosing of vancomycin for adults

Initial dose: 20 mg/Kg (rounded to nearest 250mg)						
Maintenance dose: based on estimated creatinine clearance, weight and target trough (see below)						
Creatinine clearance (ml/min)	Weight (actual)					
	50-59 Kg	60-69 Kg	70-79 Kg	80-89 Kg	90-99 Kg	100 Kg
Target trough 15-20 mcg/ml						
<10	Repeat dose when spot serum concentration ≤20 mcg/ml					
10-19	750 mg q 48 h	1000 mg q 48 h	100 mg q 48 h	1250 mg q 48 h	1250 mg q 48 h	1500 mg q 48 h
20-29	500 mg q 24 h	750 mg q 24 h	1000 mg q 36 h	1250 mg q 36 h	1250 mg q 36 h	1250 mg q 36 h
30-39	750 mg q 24 h	750 mg q 24 h	1000 mg q 24 h	1250 mg q 24 h	1250 mg q 24 h	1250 mg q 24 h
40-49	750 mg q 18 h	750 mg q 18 h	1000 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h
50-59	750 mg q 18 h	1000 mg q 18 h	1000 mg q 18 h	1250 mg q 18 h	1250 mg q 18 h	1500 mg q 18 h
60-69	750 mg q 12 h	750 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h
70-79	750 mg q 12 h	1000 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h
80-89	750 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h
90-99	1000 mg q 12 h	1000 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h
≥100	1000 mg q 12 h	1250 mg q 12 h	1250 mg q 12 h	1500 mg q 12 h	1500 mg q 12 h	1750 mg q 12 h

Inappropriate use was more evident in the continuation of vancomycin and reported in 50% of the patients. For 50% of the patients, dose adjustment based on serum creatinine was inappropriate (10). Similar study by Fahimi et al., at hematology-oncology ward and Intensive Care Unit (ICU) of a teaching hospital in Tehran (in 2013), showed that 97.7% of patients had inappropriate dosing regimens of vancomycin (11).

In Chicago, Roghmann et al., assessed the use of vancomycin in a hospital with endemic vancomycin-resistant enterococci and a vancomycin restriction program. Based on their results, only 68% of vancomycin was prescribed appropriately. Inappropriate use was due primarily to empirical therapy. In the patients with a microbiological diagnosis following empirical therapy, 83% (25/30) had infections due to bacteria sensitive to an appropriate antibiotic other than vancomycin. However, only 60% (15/25) of these patients had their vancomycin orders changed (12).

IDSA guideline for vancomycin administration (2009), recommended that dosages should be calculated initially based on Actual Body Weight and adjusted based on serum vancomycin concentrations to achieve therapeutic levels. Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness (8).

According to the American pharmaceutical Association recommendations, vancomycin initially should be started at 30-60 mg/kg/day and then it should be adjusted based on trough serum concentrations (as mentioned previously in this article, vancomycin serum concentration doesn't measure routinely in this hospital). On the other hand, dose requires adjustment in renal impairment (5, 8). But, our study indicated that 64.6% of dose adjustment according to APhA recommendation and 88.8% according to weight-based dosing of vancomycin (for adults) was incorrect. Therefore, it doesn't appear to reach therapeutic serum concentration. Other studies did not observe a significant relationship between weight-based guideline-recommended dosing and nephrotoxicity (13). Also this method of dosing did not reduce mortality of patients (14).

In conclusion, this study suggests that more than half of patients receiving vancomycin are not in therapeutic window based on international dosing guidelines. Determining dose of vancomycin based on serum creatinine and other patient's characteristics such as weight, especially in countries like Iran which vancomycin serum concentration level monitoring is not routine in practice, should be considered in clinical practice.

Recommendations

Informing physicians about hazards of vancomycin underdosing such as antimicrobial resistance and increased length of hospital stay and having a comprehensive plan for the proper use of this drug especially designing effective internal guidelines, can prevent emergence of resistant to vancomycin in future. Also, presence of a clinical pharmacist in therapeutic team could be helpful.

Table 3. Variation in vancomycin dose based on AphA and weight-based dosing of vancomycin.

Wards	Percent of error based on APhA	Percent of error based on weight-based dosing of vancomycin
Internal medicine	71.7 %	90.2 %
Infectious disease	58.1 %	86.4 %
Emergency department	62.0 %	92.6 %
Total	**64.4 %**	**88.8 %**

APhA: American Pharmacists Association

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