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Drug Utilization Evaluation of Vancomycin in a Referral Infectious Center in Mazandaran Province

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ABSTRACT

Background: DUE (Drug Utilization Evaluation) studies can help identify and correct problems associated with irrational use of drugs. Considering lack of data regarding how rational vancomycin is being used, we evaluated this DUE study in a referral infectious center to evaluate compliance with guidelines in terms of rational use of this valuable antibiotic.
Methods: This retrospective study was done for 6 months from March to September 2012 at Razi hospital, an educational hospital affiliated to Mazandaran University of Medical Sciences. Data including patients' demographics, vancomycin dose, kidney function assessment, dose adjustments, sampling and culture were collected. Based on the HICPAC (Hospital Infection Control Practices Advisory Committee) and Up-to-date 2012 advices, the concordance of practice with standard guidelines was assessed.
Results: One hundred and forty six medical records were reviewed in this study. Fever and shortness of breath were the most common symptoms at the time of initiation of vancomycin. Skin infections, lower respiratory tract infection and septicemia were the most common initial diagnosis of patients. Sampling was done in almost one-third of patients. Most of patient with a specific order were received vancomycin in half an hour. Considering the indication, Vancomycin was administered appropriately in 58 percent of patients.
Conclusion: Vancomycin was used irrationally in a great proportion of patients. The main observed drawbacks were empiric use of vancomycin without subsequent adjustment of antimicrobial agent according to culture and sensitivity data and lack of paying enough attention to calculation of creatinine clearance and dosage adjustment.

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Introduction

Resistance of microorganisms to the antibiotics is a serious concern in the treatment of infectious diseases worldwide. This led to the slogan of the 2012 "World Health Organization" as "resistance to antibiotics, a global threat". Over four decades, Methicillin-Resistant Staphylococcus Aureus (MRSA) and Methicillin-Resistant Staphylococcus Epidermidis (MRSE) emerged and now have an important role in hospital infections (1, 2). Also strains of Penicillin-Resistant Streptococcus Pneumoniae (PRSP) have emerged, few years ago (3). Vancomycin, an antibiotic of glycopeptide family, initially had limited use due to side effects but with the emergence of MRSA, its use has been increased again (4, 5).Currently, vancomycin is choice for most patients with known infections of MRSA or MRSE. Furthermore, the use of vancomycin for life-threatening infections caused by Pneumococcal organism is recommended until the culture results are available (6).

Vancomycin is a valuable drug in the treatment of infections caused by Enterococcus, although the incidence of Vancomycin-Resistant Enterococcus (VRE) over the past two decades increased and has questioned the efficacy of vancomycin. Enterococcus causes bacteremia, urinary tract infections, endocarditis, intra-abdominal and surgical site infections. Unfortunately, VRE spp. has been found throughout the world and is one of the main causes of nosocomial infections (7). Infections caused by VRE may increase morbidity, prolong hospital stay, increase costs and is associated with more deaths (8). In addition, Staphylococcus Aureus with intermediate susceptibility to Vancomycin (VISA) and Vancomycin Resistant StuphAureus (VRSA) have been reported (9). Given the prevalence of resistant gram-positive organisms to vancomycin, Hospital Infection Control Practices Advisory Committee (HICPAC), a subset of the Centers for Disease Control and Prevention (CDC), published appropriate and inappropriate usage of vancomycin in 1995(10) and advised physicians to observe these guidelines to reduce the incidence of vancomycin-resistant strains.

Drug Utilization Evaluation (DUE) studies are type of studies that have been recommended for drugs with narrow therapeutic index, high cost drugs and also for drugs which their inappropriate use can cause serious problems (11, 12). Since we did not have any data regarding how rational vancomycin is being used in our referral infectious disease, we conducted this DUE study to determine rate of rational use of vancomycin according to the standard guidelines.

Patients and Methods

This retrospective cross-sectional study was done in Razi hospital, a teaching hospital affiliated to Mazandaran University of Medical Sciences. Medical records of all patients hospitalized during March until September 2012 and received vancomycin were reviewed. According to HICPAC recommendations and UpToDate 2012, data relating to the administration of vancomycin were collected (10, 13). Demographic data, dose of vancomycin, duration of infusion, duration of treatment with vancomycin, serum creatinine monitoring, calculation of creatinine clearance based on Cockroft-Gault equation, time of sampling and implying of appropriateness or inappropriateness of vancomycin indication based on HICPAC recommendations were collected.

Data were entered in 16 SPSS software. Independent sample T-test and Chi square test were used to compare quantitative and qualitative variables, respectively. Data were expressed as mean ± SD or percentage. P-value less than 0.05 was considered as statistically significant difference.

Results

Demographic and clinical data of 146 patients were presented in Table 1. Fever and shortness of breath were the most common symptoms at the time of initiation of vancomycin. Skin infection, lower respiratory tract infection, and septicemia were the most common initial diagnosis.

The average age of patients and duration of hospitalization were 53.4 years and 14.5 days, respectively, with no significant differences between two sexes. Sampling was done in almost one-third of patients; where blood, sputum and urine were the most common samples taken for microbiological study (Table 1).

Vancomycin dose, duration of treatment, and dosage adjustment according to creatinine clearance have been presented in table 2. Only 5.5% of patients had documented creatinine clearance calculation (Table 2). The rate of vancomycin infusion was presented in Table 3. Almost in three quarters of the patients (73.6%) there was not any order regarding duration of infusion. Most of patient with a specific order were received vancomycin in half an hour (Table 3).

The adherence to HICPAC recommendations in our study was as following (Table 4). Appropriate indication and appropriate duration of treatment were observed in 58% and 55% of patients, respectively.

Discussion

In this DUE study, we found a high level of inappropriateness use of vancomycin in Razi infectious center. Indeed, more than forty percent of patients were received vancomycin without fulfilling the HICPAC criteria. In our study, the main non-compliance with standard recommendations was high level of empiric use without following culture/sensitivity and lack of creatinine clearance calculation in most of patients. The rate of adherence to HICPAC recommendations was lower

Table 1. Demographic and clinical characteristics of the patients (n=146).

Sex	
Male	86 (58.9%)
Female	60 (41.1%)
Age€; years	53.4±20.2
Duration of Hospitalization€ (days)	14.5±12.2
Initial Diagnosis	
Skin infection	28 (19.3%)
Lower respiratory tract infection	19 (13.1%)
Septicemia	15 (10.3%)
Catheter-related infection	7 (4.8%)
Urinary tract infection	3 (2.1%)
Peritonitis	2 (1.4%)
Endocarditis	1 (0.7%)
Others	70 (48.3%)
Symptoms	
Fever	70 (50.7%)
Shortness of breath	10 (7.2%)
Hypotension	8 (5.8%)
Sputum	8 (5.8%)
Tachycardia	6 (4.3%)
Leukocytosis	3 (2.2%)
Others	28 (24%)
Sampling	44 (30.1 % of all patients)
Type of Samples	
Blood	21 (47.7%)
Sputum	9 (20.5%)
Urine	8 (18.2)
Ulcer	4 (9.1)
IV or CV-line	2 (4.6%)

€: Mean ± standard deviation (no significant differences between two sexes by independent samples t-test; P=0.65 and P=0.39 for Age and Duration of Hospitalization, respectively)

in our study compared to other trials including Alfandari (14), Wright's (15) and Melo (16) studies, which the rate of appropriate use were 71%, 60% and 95% , respectively. In other hand, in another Iranian DUE study in a center in Shiraz, Askarian et al., (17) reported that only 6% of their patients received vancomycin appropriately.

Our study demonstrated that most patients received vancomycin as empiric therapy and the rate of culture and sensitivity was really low (30.1%), a finding that commonly observed in other studies (16-18). Most of vancomycin administration in our center was in skin infections. Since we did not have any data regarding the culture results, the clinical diagnosis was considered for demonstrating the type of infection. So, it is not clear that if the skin involvements were just colonization or true infection.

In some life-threatening infections, such as those caused by methicillin resistant Streptococcus pneumonia, MRSA and MRSE, vancomycin could be a life-saving antibiotic. Irrational use of vancomycin could lead to development of resistant microorganisms. In spite of emphasis on culture and antibiogram to document the status of resistance of microorganisms (19, 20), this practice is not commonly performed in our centers.

Several reasons have been proposed for common use of vancomycin in hospitals including lack of attention to its indications, lack of efficacy of old medicines and/or unreliability of the culture (18).

Given the importance of infusion rate and occurrence of "red man syndrome" by vancomycin, we found that in

Table 2. Data relating to the administration of vancomycin.

	All Patients (n=146)	Male (n=86)	Female (n=60)	P-value
Vancomycin Dose€ (mg)	1400±500	1400±500	1300±500	0.36
Duration of treatment with Vancomycin€	9.3± 8.1	10.7± 9.0	7.3 ± 6.1	0.01
Serum creatinine€	1.1 ± 0.8	1.2 ± 1.0	0.9± 0.6	0.05
Number of patients with documented calculated creatinine clearance	8 (5.5%)	2 (2.4%)	6 (10%)	NA

€: Mean ± standard deviation, NA: Not applicable

Table 3. The rate of vancomycin infusion.

Order regarding duration of vancomycin infusion	N (%)
Without any specific order	107 (73.3%)
Half an hour	33 (22.6%)
One hour	5 (3.4%)
Two hours	1 (0.7%)

Table 4. Adherence to HICPAC recommendations.

Appropriate indication	58%
Appropriate duration of treatment	55%
Appropriate dose (including dose in patients with renal insufficiency)	52-93%
Appropriate co-administration of other antibiotics	48%
Appropriate Sampling and antibiogram order during the first 24 h	68%

73.3% of case, there was not any specific order about the infusion rate. Up-to-date and other references recommends that the time of infusion should be $\geq$ 30 minutes per 500 mg dose of vancomycin (13, 21). Although there was not any documented "red man syndrome" in the medical records, this cannot exclude the occurrence of pruritus, erythema, angioedema and cardiovascular depression (22) associated with this syndrome.

Since 80 to 90% of vancomycin is excreted unchanged in the urine, dosage adjustment in patients with renal insufficiency/failure has a great significant importance (13).It has been suggested that creatinine clearance, but no creatinine, is relatively good estimates for renal dosage adjustment(23). In this study just for 5.5 % of patients creatinine clearance has been calculated. Vancomycin nephrotoxicity is one of the most common complications, so daily monitoring of serum creatinine and estimated creatinine clearance in addition to ensuring the proper dose of medication, can be effective in preventing renal toxicity(13, 24). The maximum duration of treatment with vancomycin was 48 days and minimum period 1 day (median=6). Most infections including Gram-positive bacteria resistant to beta-lactam, patient with a history of anaphylaxis reactions and or allergic urticaria to beta-lactams and MRSA could be treated for less than 15 days with vancomycin, but in febrile neutropenia, vancomycin should be continued until the rise of neutrophils and also duration of treatment with vancomycin for endocarditis and osteomyelitis is an 8-week period (25). Vancomycin was administrated less than 15 days for 81% of patiens.

In conclusion, according to the results of this DUE study, vancomycin is being used irrationally in a great proportion of patients. The main observed drawback was empiric use of vancomycin without subsequent adjustment of antimicrobial agent according to culture and sensitivity data. Lack of paying enough attention to dosage adjustment based on calculation of creatinine clearance was another defect found in this study.

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