Prospective Drug Use Evaluation of Meropenem in a Teaching Referral Hospital, Mashhad, Iran

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ARTICLE INFO	ABSTRACT
Article type: Original article *Keywords:* Drug Utilization Review Meropenem Infection Medication Errors	***Background:*** Inappropriate use of antibiotic, leads to microbial resistance, nosocomial infections and increased hospital costs. Therefore, it is necessary to control and evaluate the use of these medications, especially broad-spectrum antibiotics. This study evaluated the pattern of meropenem utilization in Imam Reza hospital, Mashhad, Iran. ***Methods***: First, a guideline for proper indications of meropenem designed and finalized based on the clinical pharmacists and infectious disease specialist's comments. One hundred patients chose randomly from different wards of the hospital and their data were recorded in predesigned questionnaires. Then, the pattern of meropenem consumption analyzed according to the guideline. ***Results:*** This study performed in 100 patients, including 48 women and 52 men. In 13 cases (13%), patients had no approved indication for meropenem. The initial regimens were changed in 6 cases (6%) based on culture results and in 73 cases (73%) relied on clinical response. In 64 cases (64%), administrated doses were compatible with prepared guideline. Renal dose adjustment was acceptable based on guideline only in 30% of patients with renal impairment. Hypersensitivity reaction, one of the adverse reactions of meropenem, was seen in 1 patient (1%). ***Conclusion:*** considerable errors had occurred in meropenem administration and dosing. Therefore, it is necessary to design and implement a localized guideline for meropenem consumption in Imam Reza hospital of Mashhad, Iran.	

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Introduction

Drug use evaluation (DUE) is an important process that is performed by pharmacists to ensure appropriate

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administration and rational use of drugs. Due to the large number of medicines available at a hospital or clinic and complicated procedure of DUE, the drug and therapeutic committee must concentrate on those medicines with the highest potential for errors like those with higher cost, narrow therapeutic index or broad spectrum antibiotics (1, 2).

Antibiotics are the most frequently prescribed drugs in

Table 1. Demographic and clinical characteristics of the patients (N= 100).

Sex* (M\F)	52/48	
Age* (year)	41.58 ± 22.93	
Duration of hospitalization (day)	12.16 ± 4.62	
Diagnosis	Sepsis	30 (30%)
	Osteomyelitis	1 (1%)
	Cholangitis	1 (1%)
	Pneumonia	23 (23%)
	UTI	6 (6%)
	Fever and neutropenia	17 (17%)
	Abscess	1 (1%)
	Complicated skin infection	4 (4%)
	Empyema	3 (3%)
	Meningitis	1 (1%)
Wards	Hematology-oncology	33 (33%)
	Infectious	8 (8%)
	Pulmonary-endocrine	11 (11%)
	ICU	36 (36%)
	Burn	4 (4%)
	Rheumatology	7 (7%)
	Gastrointestinal	1 (1%)

*Values are presented as mean ± SD.

UTI: urinary tract infection, ICU: intensive care unit.

hospitals. About one-third of hospitalized patients receive antimicrobial therapy (3). Antimicrobial resistance is a great threat to human health worldwide which may be resulted by their widespread. Continuous antimicrobial inappropriate use, especially broad-spectrum antibiotics such as carbapenems, leads not only to poor patient outcome, adverse reactions and wasted resources, but also to emerging resistance of bacteria to antimicrobials. Thus, it is of high importance for the drug and therapeutic committee of the hospitals to pay particular attention to the issue of antimicrobial use (4, 5).

Meropenem is a broad-spectrum beta-lactam antibiotic from carbapenem class.[6]It has activity against gram-positive, gram-negative aerobic and anaerobic bacteria, which should be kept as an alternative therapy for critical infections not susceptible to the other antibiotics (7, 8). This study evaluated the pattern of meropenem utilization in Imam Reza hospital, Mashhad, Iran for the first time.

Methods

This prospective study was done in a 918-bed teaching hospital, affiliated to Mashhad University of Medical Sciences. The hospital includes all major departments and services, including twenty-five medical and surgical wards. This study was performed in selected wards including hematology-oncology, infectious, pulmonary, endocrine, intensive care unit (ICU), burn, rheumatology and gastrointestinal in which meropenem is mostly used in this center, based on health information system (HIS) information. DUE program was carried from March 2016 to October 2016 in three steps on one hundred patients who received meropenem. A standard protocol on meropenem indications, dosing and monitoring was designed by clinical pharmacists based on updated international consensus guidelines in literature that best matched local condition like American Hospital Formulary Service (AHFS) drug information, drug facts and comparisons, Applied clinical pharmacokinetics, Sanford guide for antimicrobial therapy and Up to date version 21.6 (6,9-12). A form for collection of meropenem consumption data was also developed by clinical pharmacists.

Table 2. Inappropriate indication and dose of meropenem in different wards.

		Wards						
	Errors Number	**ICU (%)**	**Hematology-Oncology (%)**	**Pulmonary-endocrine (%)**	**Rheumatology (%)**	**Burn (%)**	**Infectious (%)**	**GI (%)**
Unapproved Indication	13	23.1%	61.5%	-	7.7%	7.7%	-	-
Inappropriate Dose	29	43.9%	31.7%	7.31%	2.44%	-	7.31%	7.31%
Inappropriate regimen based on tailoring culture results	12	75%	-	16.7%	8.3%	-	-	-
Inappropriate regimen tailoring based on clinical response	20	50%	25%	5%	10%	-	5%	5%

ICU: intensive care unit, GI: gastrointestinal.

One hundred patients, who received meropenem for more than 72 hours from March 2016 to October 2016 in selected wards, were recognized and one hundred cases were randomly chosen. This sample size chose based on time and human resource limitations. Random case selection performed by searching in HIS system by pharmacist.

Patient charts and hospital information system (HIS) were revised and required information for evaluation, were collected and recorded in predesigned questionnaires. This information included demographic data, diagnosis, vital signs and other clinical signs and symptoms, culture results, paraclinical tests like computed tomography (CT) scan and magnetic resonance imaging (MRI), biochemical tests, and also indication for meropenem prescription, its dose and duration and co-prescribed antibiotics.[8]

Data recruited from the standard forms were gathered and then analyzed with SPSS version 16.0 (Systat Software, Inc., Chicago, IL). We have shown the results as mean ± standard deviation or median continuous variables, respectively, and number (percentages) for nominal variables.

Results

This was a prospective study that was performed on 100 patients in Imam Reza hospital, Mashhad, Iran. Demographic information and laboratory tests are given in Table 1. Sepsis and fever and neutropenia were the most common diagnosis (30% and 17%, respectively). Most of patients admitted at ICU and hematology-oncology wards (36% and 33%, respectively).

In 13% of cases, meropenem administered without approved indication. Most of errors occurred in Hematology-oncology ward (61.5%).

Cultures were requested just for 18 patients out of 100 and only in 6 patients, empiric therapy properly changed based on culture results. As the evaluation shows, in ICU ward clinicians paid less attention to the culture results. The higher error rate belongs to the ICU ward (75%). Empiric meropenem was not tailored based on clinical improvement of patients in 20 patients, which half of them were admitted to the ICU wards.

Of these patients, 30 patients had renal failure. Despite the need for dose adjustment in these patients, it was properly done only in 30% cases. Also, infant aged below 3 months and patients with weight below 50 kg require dose adjustment based on body weight. Only in three patients out of 10 with this situation, dose adjustment was correct. Overall, in 29% of cases meropenen administered dose was inappropriate and 43.9% of these errors happened in ICU ward. Table 2 summarized the errors in indication and dose of meropenem in different wards.

In this study only 1 patient showed hypersensitivity reaction to meropenem, in hematology-oncology ward.

Overall, 196.2 vials underused based on patients requirements. In addition, 1751 vials administered more than patient's requirements. As each vial of meropenem 500mg costs 135000 Rials, the overall extra charge for these 100 patients was 236385000 Rials (≈62206.58 USD).

Discussion

This study conducted in order to evaluate the rate of appropriate use of meropenem in a teaching tertiary hospital. We found that in 13% cases, meropenem therapy was not necessary. A similar evaluation was carried out in Thailand by Sumret et al on 36 patients, retrospectively. They showed that 19.4% of patients did not need meropenem therapy (13). In Farzad et al., evaluation in a heart center in Tehran in 2016 on 136 post coronary artery bypass grafting (CABG) patients, retrospectively, 41.9% of meropenem prescriptions were inappropriate (14).

Mahini et al., performed a cross-sectional study on 68 patients admitted to the ICU wards of teaching hospital in Tehran in 2013. They found that 28% of patients received inappropriate carbapenem therapy (2). It seems that the rate of carbapenem use appropriateness is relatively higher in our center in comparison with other hospitals evaluated in Iran. This finding may be due to their concentration on a specific ward in contrast to our study. Studies which evaluated other antibiotics consumption appropriateness, show similar results. In Vessal et al., evaluation in Shiraz and in Erbay et al., study in Turkey, inappropriate antibiotic therapy was 30% and 45.3%, respectively (3,15).

Infectious specialists and clinical pharmacists have an important role in antibiotic therapy errors reduction. In Ozkurt et al., study in Turkey, after antibiotic restriction policy, inappropriate antibiotic usage reduction was 20% (16). In Pestotnic et al., evaluation, after guideline implementation, medication errors decreased by 20% (17). So, designing and implementing guideline for suitable antibiotic use may help to reduce errors in Iran hospitals.

Culture results have an important role to optimize antimicrobial regimen. In current study, only 18 patients had related culture and in six cases, physicians applied culture results. Fear of recurrence, unreliability of the culture results and laboratory kits are the most important reasons for ignoring culture results by physicians.

In Mahini et al., study 47% of culture results were not implemented (2). In Ozkurt et al., study in Turkey, after infectious specialist intervention, attention to culture results increased to 35.5% (16). Culture result are implemented in our center much less than other studies in Iran and other countries. Increasing culture result reliability could help to increase their application. Despite the same spectrum of meropenem and imipenem, in one patient imipenem regimen was changed to meropenem without a rational reason. In Salehifar et al., study in 2015, changing imipenem to meropenem was seen in 21% patients (18). Avoiding unnecessary changes of the antibiotics could be effective in reduction of antibiotic resistance occurrence.

A few days after initial regimen started, clinical signs should improve. Otherwise, the antibiotic regimen should be changed. In this study, in 20% of patients, antibiotic therapy was continued without paying attention to clinical signs. In Mahini et al., study, 20.5% of patients received appropriate antibiotic regimen but it was continued improperly. In Hecker et al., study, 30% of treatment duration seemed unnecessary (19). Our findings are in line with the other studies. Concerns about the recurrence of the disease may be the reason.

Meropenem has renal excretion and its dose adjustment is vital in renal failure (20). In our study, only in one third of the patients dose was adjusted properly. A similar study

in a teaching hospital in Mazandaran, Iran, carried out by Shiva et al., on 100 patients found that in 35% of patients (5 cases out of 14 patients with renal failure) renal dose adjustment was performed properly (8). In Farzad et al., study, 2.3% out of 33.8% of dosage errors were related to inappropriate dose adjustment in renal failure (14). In Mousavi et al., evaluation which was done on 263 patients who received imipenem or intravenous ciprofloxacin in a teaching hospital in Zabol, Iran, suitable dose adjustment based on creatinine clearance was done only in one case out of 15 patients with chronic kidney disease (21). Other studies in different countries also showed inappropriate dose adjustments in lots of cases. In Kabbara et al., study, meropenem dosage in 33 patients out of 100 patients was wrong that thirty of them had renal failure (5). In Sumret et al., evaluation, 91.7% dose adjustment was correct (13). Our results was similar to other researches in Iran.

Meropenem in infant below 3 months and patients, who weighted below 50 kg, require dose adjustment based on body weight. In this study, 30% of patients with this condition received meropenem in appropriate dosage. In Mahiniet al., study, thirteen patients (19%) needed dose adjustment due to low weight or increased serum creatinine, but none of them received the appropriate dose (2). According to these studies, it is concluded that meropenem dosage should be adjusted carefully, especially in patients with renal failure.

Seizure, hypersensitivity reaction and superinfection are the most important meropenem adverse reactions (9). In current study, meropenem hypersensitivity and in Kabbara et al., evaluation, seizure were observed both in 1 case (5). Another meropenem side effect is thrombocytopenia which in Khan et al. evaluation and in Norrby et al., study, was reported (22).

Antibiotic overuse not only cause antimicrobial resistance, but also imposes unnecessary costs on patients. In this study, 1751 meropenem vials were overused which costs 236385000 Rials (about 5630$). By specialist's comments implementation, antibiotic overuse and related costs can decrease; as seen in Pestotenic et al. study that after intervention, antibiotic costs per treated patient decreased from $122.66 per patient in 1988 to $51.90 per patient in 1994 (17).

In conclusion, it is observed that meropenem utilization in Imam Reza hospital of Mashhad, Iran, required modification. It is necessary to revise and implement standard guidelines to reduce inappropriate meropenem use, costs and consequently microbial resistance.

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