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Drug Utilization Evaluation of Cefepime and Meropenem Based on the Infectious Disease Society of America and Defined Daily Dose Guidelines at the Payambare-Azam Bandar Abbas Hospital: A Retrospective Study

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Abstract

Background: Given the significant consumption of antibiotics in hospitals and the likelihood of resistance, this study was designed to determine the pattern of meropenem and cefepime administration and prescription dose, according to Infectious Disease Society of America (IDSA) and WHO Defined Daily Dose guidelines, at Payambare-Azam Hospital in Bandar Abbas, Iran.

Methods: A Retrospective study was performed from August 2016-March 2017, on 200 patients (100 patients receiving cefepime and 100 patients received meropenem) hospitalized in different wards of the hospital. A total of 189 patients were enrolled in the study, with was with consideration of the patients receiving the two antibiotics concurrently.

Results: Of the examined patients, 58 (31%) were female and 131 (69%) male. In the group receiving meropenem and cefepime, 62% and 60% of the patients were above 50 years old, respectively. In terms of prescriptions, 85% cases of meropenen and 49% cefepime were performed according to the defined daily dose (DDD)'s guideline. Prescribing antibiotics for 170 (90%) of patients was empirical. Also, in the 176 (93%) patients, the dose was adjusted according to the creatinine clearance.

Conclusions: Increasing the number of empirical therapy, regardless of microbial cultures and susceptibility profiles, suggests further prospective studies to evaluate the reason for this finding.

Keywords: Meropenem, Cefepime, Drug Utilization Evaluation

1. Background

Today it is well-known that bacterial species with multidrug resistance are increasingly common in hospital settings. Bacterial resistance is a major problem facing practitioners in the treatment of microbial infections. An increase in the use of antibiotics and sometimes inappropriate treatment has led to an increase in the incidence of antibiotic resistance. This, coupled with an increase in the number of patients with immunodeficiency, which means that the need for proper use of antibiotics, careful clinical care, and microbiological studies has never been so necessary (1). Cefepime, a fourth-generation cephalosporin and meropenem, a carbapenem, are widely used in the treatment of a variety of infections (2, 3). Over time, resistance to these antibiotics was increased among bacteria. According to studies conducted on the intensive care unit (ICU) bacterial isolates in the United States between 1987 and 1991, approximately 48% of *Enterobacter* species were resistant to ceftazidime (4). The prevalence of cefepime resistance *Escherichia coli* in Iran (53.4%), is higher than the mean rate reported in most countries (5). In the studies conducted up to 2018, in burn patients, resistance of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* against cefepime was reported as 98% and 87%, respectively. This study, also revealed high resistance to meropenem in comparison with other antibiotics, while resistance in *A. baumannii* and *P. aeruginosa* has been reported 91% and 60% (6). Resistance to meropenem among *A. baumannii* isolates from ICU wards has been reported up to 100% (7). Given the wide-spectrum nature of these two antibiotics, there is a potential risk for their uncontrolled and experimental use in hospitals (8, 9). Today, medication use evaluation

(MUE) studies are in an evolving era. Drug utilization study is a method for determining, defining, and improving the quality of drug use, which examines the stages of prescribing, delivery, and use of drugs. This method is particularly valuable for drugs with limited therapeutic indices, expensive drugs and for use in particular cases (10). Therefore, the principal aim of drug utilization research is to evaluate the health care system (11). According to WHO for the rational use of drugs, it should be accordance with the following rules "right drug, right patient, right dosage, right cost" and SANE criteria "safety, affordability, need, efficacy" (12). Increasing the prevalence of pathogens resistant to antimicrobials in hospitals is often due to the selective pressure of administration of antibiotics in hospitalized patients (13).

2. Objectives

Considering the significant consumption of cefepime and meropenem in hospitals and the probability of resistance as well as the need for extensive studies to determine prescribing pattern of these antimicrobials, we designed a retrospective study to evaluate the pattern of administration cefepime and meropenem in the Payambare-Azam Hospital of Bandar Abbas, Iran in 2017.

3. Methods

The present cross-sectional retrospective study was conducted during one year at Payambare-Azam Hospital in 2017. Payambare-Azam Hospital is the educational referral hospital with 450 bed and 21 specialized wards including ICU and burn wards, in the Bandar Abbas and Hormozgan province in the south of Iran (14). Firstly, by referring to the pharmacy of the hospital, 100 patients who were treated with meropenem and 100 patients who received parenteral cefepime from April 2017 to March 2018, were selected. Eleven patients received cefepime and meropenem concurrently; therefore, total of 189 patients were enrolled in the study.

By referring to the medical files of these patients in the medical records department of the hospital, the required information including age, sex, weight, length of hospital stay, duration of treatment, the cause of admission, final diagnosis, reported adverse drug effects, treatment outcome, fever, microbiological culture and antibiogram results, and dose adjustment of cefepime and meropenem based on creatinine clearance, was extracted and the checklist was completed (15, 16).

This information was then reviewed by an infectious disease specialist in accordance with the Infectious Diseases Society of America (IDSA) and Defined Daily Dose (DDD) guidelines (17, 18). The DDD is a measurement unit that is defined as the usual daily dose for a particular drug (19).

The diagnosis of an infection and the response of an antibiotic to infections take more than three days; therefore, patients who were admitted for less than three days were excluded from this study. The data were analyzed by SPSS software version 18 (Chicago, IL, USA) by descriptive statistics and chi-square test.

4. Results

Of the 189 examined patients, 58 (31%) were female and 131 (69%) male. Sixty-two percent of the patients who received meropenem and 60% of those who received cefepime were over the age of 50. Most of the patients were in the infectious ward 90 (48%), internal 37 (20%), and ICU 33 (17%), respectively. Fifty-four and 65% of patients receiving meropenem and cefepime, respectively, had no history of any underlying disease. As indicated in Table 1, the immune deficiency was the most underlying disease in meropenem, 30 (30%) and cefepime 23 (23%) recipients.

In the group receiving meropenem, 66 (66%) took antibiotics previously, 28 (28%) had no history of antibiotic use, and 6 (6%) were unclear. In the cefepime recipient group, 67 (67%) received antibiotics, 26 (26%) had no history of use and 7 (7%) were unclear.

Thirteen (7%) of the patients in the first line of treatment received cefepime and 43 (23%) of patients received meropenem. However, 45 patients (24%) received cefepime and 53 (28%) patients received meropenem within 48 hours after hospitalization. After two days, antibiotic use increased so that 95 patients (50%) took cefepime and 78 (41%) meropenem.

A total of 150 (79%) patients showed community-acquired infection, and the rest were afflicted with nosocomial infections. Of these, exactly 150 (79%) had infectious specialist counseling.

Of the 189 patients examined, only 41 (22%) were requested for antibiogram (Table 2), of which 6 (15%) were tested before starting antibiotic treatment. Out of the 189 patients, only 3% were tested before starting treatment. Of the 41 patients who were tested for culture and antibiogram, in 30 patients, a broad range of bacteria were isolated. *Acinetobacter* spp. 12 (40%), *E. coli* 4 (13%) and *P. aeruginosa* 3 (10%) were predominant. Susceptibility data showed that 8 (27%) and 11 (37%) of different bacterial isolates were resistant to cefepime and meropenem, respectively. However, in about 20 (67%) and 14 (47%) of isolates, there was no sensitivity data of cefepime and meropenem in antibiogram results.

Table 1. Comparison of Meropenem and Cefepime Consumption and Prescriptive Dosage Based on Age and Sex, Hospital Wards, Underlying Disease, History of Hospitalization and History of Antibiotic use in Hospitalized Patients in Payambare-Azam Hospital of Bandar Abbas in 2017[a]

Variable	Meropenem			Cefepime		
	Appropriate	Inappropriate	P Value	Appropriate	Inappropriate	P Value
Gender			0.006			0.02
Female	26 (30)	9 (69)		8 (17.4)	21 (37.5)	
Male	61 (70)	4 (31)		38 (82.6)	35 (62.5)	
Age			0.97			0.84
16 - 50	33 (38)	5 (38)		18 (39.1)	23 (41.1)	
Above 50	54 (62)	8 (61)		28 (60.9)	33 (58.9)	
Ward			0.47			0.03
Infectious	38 (44)	6 (46)		17 (37)	34 (60.7)	
Internal	21 (24)	5 (38)		5 (10.9)	6 (10.7)	
Surgery	9 (10)	0		10 (21.7)	6 (10.7)	
ICU	19 (22)	2 (15.4)		13 (28.3)	6 (10.7)	
Burn	0	0		1 (2.2)	4 (7.1)	
Underlying disease			0.69			0.55
Kidney	10 (11)	0		4 (8.7)	3 (5.4)	
Liver	1 (1)	0		0	1 (1.8)	
Immune deficiency	25 (29)	5 (38.5)		9 (19.6)	14 (25)	
None	47 (54)	7 (53.7)		30 (65.2)	37 (66.1)	
Kidney and immune deficiency	4 (5)	1 (7.7)		3 (6.5)	1 (1.8)	
History of admission			0.79			0.53
Yes	68 (78)	11 (84.6)		31 (67.4)	38 (67.9)	
No	19 (22)	2 (15.4)		15 (32.6)	18 (32.1)	
History of antibiotic use			0.03			0.08
Yes	55 (63)	11 (84.6)		28 (60.9)	40 (71.4)	
No	29 (33)	0		17 (37)	10 (17.9)	
Unknown	3 (3)	2 (15.4)		1 (2.2)	6 (10.7)	

[a]Values are expressed as No. (%).

Table 2. Antimicrobial Examination in Hospitalized Patients in Payambare-Azam Hospital of Bandar Abbas in 2017, Who Received Meropenem and Cefepime

Request Time for Antibiogram Test	No. (%) of Patients
On arrival to hospital	2 (1)
Up to 48 hours of hospitalization	8 (4)
After 48 hours of hospitalization	31 (16)
Antibiogram test not performed	148 (78)

Prescribing antibiotics for 170 (90%) of patients was empirical, 8 (4%) were based on a antibiogram test and 11 (6%) on experience and antibiogram test. Therefore, 19 (10%) patients continued their treatment based on antibiogram.

Of 85 febrile patients, 81 (43%) appeared with reduced fever, and the remaining were found to have a fever despite the treatment they received.

A total of 155 patients (82%) had normal renal function and 33 (17%) experienced renal failure, where antibiotic dosage adjustment was based on renal function for 178 people (94%).

The duration of the treatment is shown in Table 3. Of the patients who received meropenem, 86 patients (86%) had an appropriate course of treatment. In patients treated with cefepime, 92 (92%) showed an appropriate course of treatment, this relationship was statistically significant (P value > 0.000001).

There was an appropriate interval between drug

Table 3. Comparison of Meropenem and Cefepime Defined Daily Dose in Payambare-Azam Hospital of Bandar Abbas in 2017

Antibiotic	No. (%)	Duration of Treatment
Meropenem	47 (47.5)	Less than 5 days
	28 (28)	Between 5 - 10 days
	24 (24)	More than 10 days
Cefepime	44 (40)	Less than 5 days
	29 (26)	Between 5 - 10 days
	38 (34)	More than 10 days

dosage in the 86 (86%) patients receiving meropenem, and 46 patients (46%) receiving cefepime. In the majority of patients, 176 (93%) drug dosage was based on creatinine clearance.

Of the patients receiving meropenem, 13 (13%) had no indications for this antibiotic, and 16 (16%) of the patients taking cefepime had no indication either.

Based on the data collected, 79% of the people receiving meropenem, as well as 80% of the cefepime recipients, recovered and were discharged from the hospital.

In Table 1, the relationship between drug dosages and different variables such as gender, age, ward of hospital, underlying disease, history of hospitalization, and history of antibiotic use have been shown.

The majority of people with abnormal renal function were in the age range above 50 (82%), which was statistically significant (P = 0.04).

It should also be noted that no adverse effects, including neurotoxicity, were reported for both meropenem and cefepime.

5. Discussion

The present study was conducted to investigate the proper prescribing of cefepime and meropenem in the referral hospital of Bandar Abbas, over a one-year period. This study generally determined that 85% of meropenem and 49% of cefepime prescriptions were performed based on DDD's guideline, which was in accordance with the previous study about meropenem (86%), however, less than that reported about cefepime (86%). In the study of Zarezade et al. in 2015, about 69% of the antibiotics were administered, based on the guidelines (20). In a study conducted in Brazil in 2003, prior to the implementation of the prophylaxis, indication of the administration of antibiotics was altered in 56.4% of patients (21). Another study by Askarian et al. in Iran (22) and a couple of other studies conducted in Spain (23) and Jordan (24), suggested that between 0% to 0.9% of the prescriptions for antibiotics have been based on instructions and in Nicaragua, only 7% of the cases were in accordance with the guidelines (25). In the study of Bull et al. antibiotics in 72% of cases were not consistent with the guidelines (26). In a study by Yeap et al. in Malaysia, none of the patients had a prescription for antibiotics, according to the instructions (27) and in the study of Khoshdel and Panahandeh in Shahrekord, Iran, about 37% of antibiotic use was incorrect (28).

Treatment continued in less than five days in 47.5% of meropenem and 40% of cefepime cases, which was not appropriate in comparison to the other study where 60% of case treatment was continued for five days or more (29). In the present study, the highest age distribution was over 50. In a Chinese study, the median age was 40.2 ± 15.3 years (30). This age difference is justifiable since one of the main uses of this drug is for the treatment of endocarditis and these patients frequently comprise the middle-age group.

In the present study, for the majority of patients (78%), no antibiogram was performed. However, the choice of antibiotic or its change based on laboratory results and consultation with a microbiologist can be one of the most reliable methods of antibiotic administration.

Considering the difference in the number of people who received empirical treatment (90%), and those whose antibiogram test was not performed (78%), indicates that 12% of patients, despite the availability of their antibiogram results, treatment started regardless those results. Furthermore, in about 47% - 67% of bacterial isolates there was no data of cefepime or meropenem susceptibility. In addition, in the Taleghani Hospital, in 2005, about 23% of prescriptions were based on laboratory results, of which about 2% were also inappropriate due to the culture response (31).

Despite the poor laboratory data, in the current study, 87% of cases of meropenem and 85% of cases of cefepime were prescribed based on the opinion of an infectious disease specialist.

Paying attention to renal function based on creatinine clearance is important for b-lactam antibiotics, as well as other antibiotics such as vancomycin (32). In our study, dose adjustment, according to the creatinine clearance was conducted on 176 (93%) patients, which was less than the Tehran study where 96% of patients were evaluated for renal functions (33).

Since the present study was retrospective, lack of access to all information in patients' medical records, including patient weight and a wide range of reasons for hospitalization, made it difficult to analyze the results considering these items.

It should be noted that the rational use of antibiotics in hospital needs multi-disciplinary coordination and should be based on the results of the laboratory an-

timicrobial susceptibility test and consulting with infectious specialist along with hospital pharmacist.

5.1. Conclusions

The present data suggest that microbiological results and susceptibility profiles are not fully considered in the process of antibiotic therapy. Further prospective studies to evaluate the reason for this finding are suggested. In order to further improve the use of antibiotics in Payambare-Azam Hospital, preventive measures including the publication of standardized guidelines, training courses, the requirement to obtain permission from an infectious disease specialist before the onset or continuation of certain drugs, as well as full attention to the results of antimicrobial tests is recommended.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design: Afsaneh Karmostaji and Parivash Davoodian. Analysis and interpretation of data: Parivash Davoodian. Drafting of the manuscript: Afsaneh Karmostaji and Mahshid Hadad. Critical revision of the manuscript for important intellectual content: Parivash Davoodian. Statistical analysis: Daniel Morabbi.

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