Journal of Pharmaceutical Care
jpc.tums.ac.ir

Drug Utilization Evaluation of Two Broad-Spectrum Antimicrobials: Cefepime and Piperacillin/Tazobactam in a Teaching Hospital in Tabriz, Iran

Parviz Saleh[1], Hadi Hamishekar[2, 3], Farnaz Naeimzadeh[3], Sara Mikaili[3], Hamid Owaysee Osquee[4], Haleh Rezaee[1, 3]*

[1]Infectious and Tropical Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Department of Clinical Pharmacy, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.
[4]Department of Infectious Diseases, School of Medicine, Tabriz university of Medical Sciences, Tabriz, Iran.

Received: 2019-06-07, Revised: 2019-07-26, Accept: 2019-07-27, Published: 2019-08-0

ARTICLE INFO

Article type:
Original article

Keywords:
Piperacillin/tazobactam;
Cefepime;
Drug Utilization Evaluation

ABSTRACT

Background: The inappropriate use of antibiotic leads to microbial resistance, nosocomial infections and increased hospital costs. The present study was designed to evaluate DUE (Drug utilization evaluation) of cefepime and piperacillin-tazobactam drugs consumption patterns.

Methods: This study was a descriptive and cross–sectional which performed 2014 on 140 hospitalized patients in Sina hospital Tabriz, Iran. Demographic data, duration of prescription, dose, dosage adjustment in renal impairment and accompanied prescribed antibiotics were extracted from medical files. UpToDate and American Hospital Formulary Service (AHFS) drug information 2012 were considered as standards of rational prescribing. Data analysis was performed by SPSS 18 software.

Results: In 77.4% and 90% of the prescribed doses of cefepime and piperacillin-tazobactam for patients with guideline. The most common antibiotic administered with cefepime was ciprofloxacin (37 cases). In 21 patients, cefepime dosage should have been adjusted according to renal impairment, whereas it has done only in 16 (22.9%) patients. Culture was done in 60 (85.8%) cases. In 22(31.4%) patients, the result of culture was negative. Drug dosage and indication were appropriate in 34 (48%). The most common antibiotic administered with Piperacillin/tazobactam was vancomycin (45 cases). In 9 patients, Piperacillin/tazobactam dosage should have been adjusted according to renal impairment and it has done. Culture was done in 53 (75.8%) cases. In 9(12.8%) patients, the result of culture was negative.

Conclusion: The results showed that there was an injudicious use of cefepime and piperacillin/tazobactam at our hospital, evidenced by the significant number of inappropriate empiric prescriptions and drug modifications.

J Pharm Care 2019; 7(1-2): 21-25.

► Please cite this paper as:
Saleh P, Hamishekar H, Naeimzadeh F, Mikaili S, Owaysee Osquee H, Rezaee H. Drug Utilization Evaluation of Two Broad-Spectrum Antimicrobials: Cefepime and Piperacillin/Tazobactam in a Teaching Hospital in Tabriz, Iran. J Pharm Care 2019; 7(1-2): 21-25.

Introduction

Inappropriate use of antibiotics is related to which affects treatment outcome (1). 23,000 deaths/year in the United States of America (USA) were estimated by the Centers for Disease Control and Prevention due to infections by antibiotic-resistant pathogens (2). The increased prevalence of known resistant organisms have delayed in effective therapy, increased the length of hospitalization and treatment cost for patients. Therefore, evaluation of the appropriate utilization of antibiotic is the first step to reduce

*Corresponding Author: Dr Haleh Rezaie
Address: Department of Clinical Pharmacy, School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran. Tel:+984133372250, Fax:+984133344798.
E-mail: Rezaeeha@tbzmed.ac.ir

of antibiotic resistance (3).

Five criteria guide for the appropriate use are: clinical evidence-based therapy, therapeutic benefits, safety, cost-effectiveness and optimal drug dose with suitable duration (4).

Antibiotics are the most frequent prescribed drugs in hospitals. About one-third of hospitalized patients receive antimicrobial therapy (5). The important role of the broad-spectrum antibiotics, such as fourth-generation cephalosporins and piperacillin/tazobactam, in the empiric therapy of serious infections has been proven (6). Cefepime is a fourth generation cephalosporin antimicrobial with a wide spectrum of antimicrobial activity, high penetration, and stability against most β –lactamases (7). It is common for the treatment of infections and is widely used to treat severe nosocomial pneumonia, empirical treatment of febrile neutropenia, uncomplicated and complicated urinary tract infections, uncomplicated skin and soft tissue infections, and complicated intra- abdominal infections (8). Piperacillin/tazobactam is a β-lactam/ β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against most Gram-positive and Gram-negative aerobic bacteria and anaerobic bacteria. Piperacillin/tazobactam is effective and well tolerated in patients with lower respiratory tract infections, intra-abdominal infections, skin and soft tissue infections, and febrile neutropenia (9).

One of the studies that focus on the appropriateness and rational use of various drugs is Drug Utilization Evaluation (DUE). The DUE is an ongoing and systematic process to promote the appropriate and effective use of drugs which detect, potential problems and improve drug use. The DUE includes qualitative measures and emphasizes the outcomes and cost-effectiveness of drug therapy (10). Traditionally, DUE programs have focused on drugs with narrow therapeutic indices, high price tags, complicated dosage schedules and regular side effects (11).

Due to lack of information about cefepime and piperacillin/tazobactam prescription in Sina hospital; this study was designed to evaluate the rational use of these drugs in this center. Considering the importance of these drugs in treatment of infectious diseases and the consequences of irrational use, the present DUE study can help to identify defects related to the drug use, and develop rational antibiotic implementation protocols to prevent emerging resistance.

Methods

This study was a descriptive and cross–sectional which performed over a 6-month period from May to October 2014 in all wards of Sina teaching hospital affiliated to Tabriz University of Medical Sciences, Iran. The study protocol was approved by the Ethical Committee of Tabriz University of Medical Sciences. All patients who received one of the study drugs were reviewed and entered on data collection forms.

The data included patient demographic information, diagnosis, antibiotic therapy received (agents, doses, initiation times, and durations of administration) emphasizing on cefepime and Piperacillin/tazobactam (initiation times, doses, dose intervals, and routes of administration, number of doses, dosage adjustments in renal failure, durations of administration, other concomitant antibiotics, samples site and results of culturing and antibiogram test).Compliance with the recommendations and defined standards by the Up to Date and American Hospital Formulary Service (AHFS) drug information 2012 was assessed for every aspect of these drugs use (12-14). SPSS18 software was used for statistical analysis. The qualitative variables were presented by their frequency and percentage.

.

Results

During the study, the total of 140 patients received one of the antibiotics. 70 patients received cefepime in which 54.3% were male and mean age of patients was 62.2± 19.3 years (9-90years). Pneumonia and urinary tract infections were the most frequent cause of antibiotics prescribing including 40% and 27.2% of the diagnosis, respectively. Cefepime was prescribed frequently in infectious disease ward (60%) and infectious disease intensive care unit (21.4%). Demographic and clinical data are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients who received cefepime.

Gender	
Male	38 (54.3%)
Femal	32 (45.7%)
Age* (years)	62.2± 19.3
Length of stay* (days)	7.61± 4.17
Diagnosis	
Skin and soft tissue structure	10 (14.3%)
Pneumonia	28 (40%)
Urinary tract infections	19 (27.2%)
Febrile neutropenia	5 (7.1%)
Sepsis	4 (5.7%)
Intra-abdominal infections	3 (4.3%)
Brain abscess	1 (1.4%)
Wards	
Infectious disease	42 (60%)
Infectious disease Intensive Care Unit	15 (21.4%)
Internal	8 (11.4%)
Surgery	3 (4.3%)
Burn	1 (1.4%)

*: Values are presented based on mean ± standard deviation (SD).

The most common prescribed antibiotics concomitantly with cefepime were ciprofloxacin (52.9%) and vancomycin (27.1%). With regard to the dosing, 16 patients (22.9%) received inappropriate doses based on with the recommendations and guidelines. Six patients (8.6%) received doses lower than the recommended dose and 10 (14.3%) patients received doses more than the recomme nded dose. Treatment duration with cefepime was appropriate for 41.4% of patients. However, 7 patients (10%) received cefepime longer than periods justified by guidelines and recommendations. 21 patients (30%) needed a dosage adjustment due to renal failure. However, 16 patients (22.9%) were received correctly. In overall, 22.8% of hospitalized patients (n=16) of this center received correct dose of cefepime for proper duration (Table 2).

Table 2. Evaluation of cefepime use in Sina hospital.

Indices	Inappropriate	Appropriate
Dose(n=70)	16(22.9%)	54 (77.4%)
Duration of therapy (n=70)	41(58.5%)	29(41.4%)
Dose + Duration of therapy (n=70)	54(77.4%)	16(22.8%)

64 patients (91.4%) received cefepime as an empiric treatment. 60 patients (85.7%) were ordered for microbiology culture. Culture results were negative in 22 samples (31.4%). 23 samples (32.8%) were sensitive and 6 samples (8.5%) were resistant to cefepime. Mean age of 70 patients who received piperacillin/tazobactam was 31.2±30.1 years (Range 2-89 years). Skin and soft tissue structure and pneumonia were the most frequent cause of antibiotics prescribing including 74.3% and 15.7% of the diagnosis respectively. Piperacillin/tazobactam was prescribed frequently in burn unite (51.4%) and infectious disease ward (38.6%). Demographic and clinical data are shown in Table 3.

Table 3. Demographic and clinical characteristics of the patients who received piperacillin/tazobactam.

Gender	
Male	43 (61.4%)
Female	27 (36.8%)
Age* (years)	31.2±30.1
Length of stay* (days)	10.15± 5.25
Diagnosis	
Skin and soft tissue structure	52 (74.3%)
Pneumonia	11 (15.7%)
Intra-abdominal infections	4 (5.7%)
Febrile neutropenia	2 (2.9%)
Sepsis	1 (1.4%)
Wards	
Burn	36 (51.4%)
Infectious disease	27 (38.6%)
Internal	4 (5.7%)
Surgery	2 (2.9%)
Infectious disease Intensive Care Unit	1 (1.4%)

***: Values are presented based on mean ± standard deviation (SD).**

The most common prescribed antibiotics concomitantly with Piperacillin/tazobactam were vancomycin (64.3%) and ceftazidime (7.1%). With regard to the dosing, 63 (90%) patients received appropriate doses based on the recommendations and guidelines. The dosing in 7 (10%) patients was inappropriate in which 3 (4.3%) patients received doses lower than the recommended dose. and 4 (5.7%) patients received more than the recommended dose. Treatment duration with Piperacillin/tazobactam was appropriate 67.1% (n=47) for consistent accordance with the recommendations. 11 patients received Piperacillin/tazobactam longer than periods justified by guidelines and recommendations.9 patients needed a dosage adjustment due to renal failure which was done correctly. In overall, 48.4% of hospitalized patients of this center received correct dose of Piperacillin/tazobactam for proper duration (Table 4).

Table 4 . Evaluation of piperacillin/tazobactam use in sina hospital.

Indices	Inappropriate	Appropriate
Dose(n=70)	7 (10%)	63 (90%)
Duration of therapy (n=70)	23 (32.8%)	47 (67.1%)
Dose + Duration of therapy (n=70)	36 (51.5%)	34 (48.4%)

51 (72.8%) patients received Piperacillin/tazobactam as an empiric treatment. 53 patients (75.7%) were ordered for microbiology culture. Culture results were negative in 9 samples (12.8%) but drug was discontinued only in 2 patients (2.8%). 15 samples (21.4%) were sensitive and 4 samples (5.7%) were resistant to Piperacillin/tazobactam but drug discontinuation was seen in none of the patients.

Discussion

The results showed that cefepime and Piperacillin/tazobactam was used frequently in this center for the treatment of pneumonia and skin and soft tissue structure disease, respectively. For 77.4% of patients (n=54) who received cefepime and 90% of patients (n=63) who received Piperacillin/tazobactam. The dose of drug was appropriate. In 41.4% of patients (n=29) who received cefepime and 67.1% of patients (n=67) who received Piperacillin/tazobactam, duration of treatment was appropriate. The majority (91.4% cefepime (n=64) and 72.8% Piperacillin/tazobactam (n=51)) of our broad-spectrum antibiotic treatment was initiated empirically. Raveh et al., showed that 77% of patients received antibiotic empirically (6). Inadequate initial antibiotic therapy in nosocomial is associated with emergence of antibiotic resistance which is increased morbidity and mortality (15). Therefore, the appropriate antibiotic selection, the appropriate dose and duration of treatment play an important role for the improvement of patient outcomes and the effectiveness of antibiotics in future infections (16). The recommended dose and duration for cefepime in brain abscess is 2g every 8 h, in febrile neutropenia is 2g every 8 h for 7 days, in intra-abdominal infections is 2g every 12 h for 7-10 days, in pneumonia is 1-2g every 8-12

h for 7-21days, in skin and soft tissue structure is 2g every 12 h for 10 days and in urinary tract infections is 0.5-2 g every 12 h for 7-10 days. With regard to the dosing, 54 (77.4%) patients received appropriate doses whereas dosing in 16 (22.9%) cases was inappropriate. 6 (8.6%) patients received doses lower than the recommended dose and 10 (14.3%) patients received doses more than the recommended dose. Treatment duration with cefepime was 41.4% appropriately in accordance with the recommendations. Among 41 individuals with improper duration of treatment, 7 patients received cefepime longer than periods justified by guidelines and recommendations. Most of the inadequate dose prescribing occurred in infectious disease ward (30.9%). The highest rate of inappropriate therapy duration was occurred in internal ward (87.5%). 22.8% of patients received the correct dose of cefepime for proper duration.

The usual dosage range for Piperacillin/tazobactam is 3.375g every 6 h or 4.5g every 6-8 h, maximum 18g/day. 63 (90%) patients received appropriate doses and 7 (10%) patients received inappropriate. 3 (4.3%) patients received doses lower than the recommended dose and 4 (5.7%) patients received doses more than the recommended dose. Treatment duration with Piperacillin/tazobactam was 67.1% appropriately in accordance with the recommendations. Among 23 individuals with improper duration of treatment, 11 patients received Piperacillin/tazobactam longer than justified period by guidelines and recommendations. The wards in which inappropriate prescription patterns were most frequently observed included the infectious disease ward (46.6%) and burn unit (36.1%). 48.4% of patients received the correct dose of Piperacillin/tazobactam for proper duration.

Both cefepime and Piperacillin/tazobactam required dosage adjustment in renal impairment (12, 13). In 21 patients, cefepime dosage should have been adjusted according to renal insufficiency, whereas it has done only in 16 (22.9%) patients.

One way to ensure the effectiveness of antibiotic selection is sampling, culture and antibiogram, to modify initial empiric therapy based on culture and antibiogram results (17). 60 (85.7%) patients received cefepime and 53 patients (75.7%) received Piperacillin/tazobactam which were ordered for microbiology culture. Discontinuation once culture data showed resistant organism was not seen in none of the patients received Piperacillin/tazobactam and one patient (12.8%) received cefepime. Discontinuation once culture data were negative for only 2 patients (of 9 patients, 2.8%) who received Piperacillin/tazobactam and 6 patients (of 22 patients, 8.5%) who received cefepime. The reasons for medicine continuation in our study despite negative cultures were physician distrust of the results reported by the hospital laboratory, physicians concerning for not having complete treatment of the patient in the event of drug discontinuation, difference in the effectiveness of antibiotics in the laboratory and the patient's body and finally, routine treatment with the desired drug.

In a study that was done in Hamad General Hospital during a period of three months in 2008, the appropriateness of Piperacillin/tazobactam usage was evaluated. During this period, 610 prescriptions were ordered for 596 patients. Among cultured negative cases (265/610; 43%), Piperacillin/tazobactam was continued in most cases (160/265; 60%) without any clear reason. Discontinuation once culture data were negative and once culture data showed resistant organism were seen in 105/265 (40%) and 27/30 (90%) prescriptions, respectively. 73.6% of positive-culture cases were suitable for modification to narrow-spectrum antimicrobials, but 22% of them remained unchanged these rates are higher than our results (17).

In the study of Raveh et al., a drug utilization evaluation program was carried out over two 3-month periods in 2001. During the first survey, 102 patients received 143 courses with at least one of these three antibiotics, cefepime, piperacillin-tazobactam and meropenem. The results showed that 90 (of 110) appropriately initiated, empirically-chosen antibiotic courses in phase 1 of the study, 54 (60%) were continued: 7 (13%) according to culture results, of which 5 (71%) were deemed appropriate. The remaining 47 (87%) were continued empirically (of which100% were deemed appropriate) (6). In this study, 115 patients (of 140 patients 82.1%) received cefepime and Piperacillin/tazobactam as empiric administration. 76 patients (54.28%) received the appropriate dose. Unfortunately, there was no other study in Iran regarding cefepime or Piperacillin/tazobactam to compare the results.

In summary, the results showed the high rate of empiric prescription, inadequate dosing in considerable percentage of patients, and initiation of antibiotics in the first day of hospitalization for the high percentage of patients. Strategies that can be used to remove the observed defects in this DUE study include:

1- Establishment of a central committee for DUE studies by the Ministry of Health, which coordinates, summarizes and evaluates all information and allocates the national budget for the ongoing implementation of DUE studies in hospitals as well as appropriate software facilities.
2- The presence of a clinical pharmacist in the wards.
3- Announcing the results of DUE studies in hospitals to physicians.
4-Performing microbial culture before prescribing cefepime and piperacillin-tazobactam.
5- Avoiding the simultaneous use of antibiotics with the same effect spectrum.
6-Measure the weight of patients to determine the correct dose for each patient, the attention to the interval between the doses, and the pharmacokinetics of the drug.

References

1. Shoaei S, Bagherzadeh A, Haghighi M, Shabani M. Vancomycin and Five Broad-spectrum Antibiotic Utilization Evaluation in an Educational Medical Center in One Year. J Pharm Care 2015;2(4):154-61.
2. Vaughan L., Wise K., Holmes-Maybank K., Charity P. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention. 2013.
3. Ayinalem GA, Gelaw BK, Belay AZ, Linjesa JL. Drug use evaluation of ceftriaxone in medical ward of Dessie Referral Hospital, North East Ethiopia. Int J Basic Clin Pharmacol 2017;2(6):711-7.
4. Slama T, Amin A, Brunton S. A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Am J Med 2005;118(7A):1S-6S.
5. Erbay A, Çolpan A, Bodur H, Çevik MA, Samore MH, Ergönül Ö. Evaluation of antibiotic use in a hospital with an antibiotic restriction policy. Int J Antimicrob Agents. 2003;21(4):308-12.
6. Raveh D, Muallem-Zilcha E, Greenberg A, Wiener-Well Y, Schlesinger Y, Yinnon AM. Prospective drug utilization evaluation of three broad-spectrum antimicrobials: cefepime, piperacillin-tazobactam and meropenem. QJM 2006;99(6):397-406.
7. Lei J, Wang Y. Cefepime. World Pharm 1996;17:354–8.
8. Lu H, Weng X, Pang M. Phase IV trials of cefepime in treat-ment of various moderate or severe bacterial infections. Chin J New Drugs Clin Remedies 2002;21:268-70.
9. Young M, Plosker G. Piperacillin/tazobactam: a pharmacoeconomic review of its use in moderate to severe bacterial infections. Pharmacoeconomics 2001;19(11):1135-75.
10. Brodie D, Smith W, Hlynka J. Model for drug usage review in a hospital. Am J Hosp Pharm 1977;34:251.
11. Terry AK, Draugalis JR, Bootman JL. Drug-use evaluation programs in short-term-care general hospitals. Am J Hosp Pharm 1993;50(5):940-4.
12. Cefepime: Drug information [Available from URL: http://www.uptodate.com/contents/cefepime-drug-information?source=search_result&search=cefepime&selectedTitle=1~75.
13. Piperacillin and tazobactam sodium: Drug information [Available from URL: http://www.uptodate.com/contents/piperacillin-and-tazobactam-sodium-drug-information?source=search_result&search=tazocin&selectedTitle=1~81.
14. Hossain DM, Panda AK, Chakrabarty S, et al. MEK inhibition prevents tumour-shed transforming growth factor-beta-induced T-regulatory cell augmentation in tumour milieu. Immunology 2001; 144:561-73.201.
15. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. Clin Infect Dis 2000;31(S131-S138).
16. Meakins M, Jonathan L, Byron J, Masterson R. Prevention of postoperative infection. ACS Surgery: Principles and Practice 2004:26-35.
17. Khan FY, Elhiday A, Khudair IF, et al. Evaluation of the use of piperacillin/tazobactam (Tazocin) at Hamad General Hospital, Qatar: are there unjustified prescriptions? Infect Drug Resist 2012;5:17-21.