

Drug utilization evaluation of meropenem: an important broad-spectrum antibiotic for the treatment of serious bacterial infections in hospitalized patients

Farzaneh Foroughinia¹, Seyed Mohammadreza Hashemian², Fanak Fahimi^{3,4*}

¹ Department of Clinical Pharmacy, School of pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran.

² Nursing and Respiratory Health Management Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

³ Department of Clinical Pharmacy, School of pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

⁴ Chronic Respiratory Disease Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Increasing trend in the development of antibiotic resistance is one the major concerns of health care systems throughout the world. Several factors are responsible of the emergence of this problem of which frequent inappropriate uses of antimicrobial agents plays an important role. Therefore, in this study we aimed to assess the appropriateness of the usage of meropenem, a broad-spectrum antibiotic, in a teaching affiliated hospital. This study is an observational prospective research on drug utilization. All patients admitted to Masih Daneshvari hospital that had received meropenem during June to July 2011 were enrolled in the study. To evaluate the appropriate use of meropenem, an institutional standard guideline was designed by pharmacy and therapeutic committee using evidence-based guidelines. Prescriptions were considered appropriate if they were compliant with the guideline. The total number of meropenem vials used during this period was 2153 vials. Most prescriptions started empirically (85.9%). Of these, 16.9% of prescriptions continued according to lab results whereas 69% of meropenem courses remained empirical. Our results showed that meropenem was started appropriately in 64.8% of patients whereas just 74.3% of patients received the drug for an adequate duration. In conclusion, our study and several other surveys detected various areas of inappropriate use of broad-spectrum antibiotics such as meropenem. With regard to the important role of these drugs in the treatment of serious nosocomial infections, a combination of both restrictive and educational measures appears to be necessary to improve rational antibiotic usage as well as to decrease in the frequency of antibiotic resistant.

Keywords: : Antibiotic resistance, Drug utilization evaluation, Meropenem.

1. Introduction

Increasing trend in the development of antibiotic resistance is one the major concerns of

Corresponding Author: Fanak Fahimi, Department of Clinical Pharmacy, School of pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: fahimi@nritld.ac.ir

health care systems throughout the world. Several factors are responsible of the emergence of this problem of which frequent inappropriate uses of antimicrobial agents plays an important role (1).

The broad-spectrum antibiotics such as carbapenems, are essential for the empiric therapy

of serious nosocomial infections. Concern about escalating rates of multi-drug-resistant occurrence to broad-spectrum antimicrobials has forced most researchers to evaluate the pattern of administration of these drugs worldwide (2). Therefore, studies such as Drug Utilization Evaluation (DUE) are increasingly used to assess the appropriateness of the usage of these antibiotics. Generally, the purpose of a DUE is to detect possible problems with drug use and if possible to recommend a way to decrease improper usage of medications (3).

According to the pharmacy database, about 11423 vials of meropenem were administered during a year in Masih Daneshvari hospital (an educational tertiary lung care hospital, Tehran, Iran). Doing ABC analysis (the 80/20 rule) in this hospital, it was revealed that meropenem is widely used and is categorized in class A (4). Since meropenem has both high prescription vol-

ume and significant economical impact in Masih Daneshvari hospital, this study was conducted to evaluate the pattern of meropenem usage in the mentioned hospital.

2. Methods

This study is an observational prospective DUE that was done in all wards of Masih Daneshvari hospital for the duration of two months (June to July 2011). The hospital includes 13 wards with 320 active beds. All patients receiving the study drug were identified on daily review of the patients' drug records in inpatient pharmacy database. To qualify for inclusion, they must have received at least 3 doses of meropenem. This study has been approved by the ethics committee of hospital.

The required data were retrieved from the pharmacy chart and the patients' records by two clinical pharmacy residents using a standard

Part 1: Indication

Meropenem should be reserved for the most serious and life threatening infections as follows:

- Documented Gram negative infections involving **multiple resistant organisms** where other agents are either ineffective due to resistance or cannot be used due to intolerance.
- Empiric therapy for **severe, life threatening infections** where multiple resistant organisms may be suspected, such as:
 - o Severe sepsis
 - o Cystic fibrosis
 - o Febrile neutropenia
- For patients with suspected nosocomial pneumonia, initial empirical therapy with broad-spectrum antibiotics is recommended until culture results are obtained

Note:

- Antimicrobial therapy for all serious infections should be administered without delay and reassessed within 2-3 days to determine if step down to narrower regimen is possible.
- For patients with normal renal function, the approved dosage of meropenem for the treatment of complicated skin and skin structure infections is 500 mg every 8 h for adults ¹.
- For severe gastrointestinal or any serious post surgical infections consider using other effective antibiotics such as Piperacillin/tazobactam or combination regimens.

Part 2: Meropenem Dosing (Adults)

| Estimated GFR (ml/min) | >50 ² | 26-50 | 10-25 | <10 |
|------------------------|------------------|-----------|------------|------------|
| Dose | 1gr q8h | 1gr q12 h | 500mg q12h | 500mg q24h |

¹ Skin and skin-structure infections are considered to be complicated when deep structures (e.g., fascia or muscle) are involved, when surgical intervention is necessary, and when significant comorbidities, such as diabetes mellitus, are present.

² EXCEPTIONS:

- Cystic Fibrosis (1g IV q6h)
- Meningitis or CNS infections (may use 1g IV q6H or maximum 2 g IV q8H)

Figure 1. Conditions where administration of meropenem is appropriate.

questionnaire. To evaluate the appropriateness of meropenem use, an institutional standard guideline was designed by pharmacy and therapeutic committee using evidence-based guidelines (5, 6) (Figure 1). Prescriptions were considered appropriate if they were compliant with the guideline.

Collected data were analyzed using the SPSS version 17 (SPSS INC, Chicago, IL, USA). For continuous variables, mean and standard deviation were provided. The appropriate usage of meropenem was reported by number and percentages of correct prescriptions with regard to the standard guideline.

3. Results

During the study, 71 patients received meropenem. Among these, 46(64.8%) patients were men. The patients' demographic data and number of patients studied per ward are listed in Table 1.

The total number of meropenem vials used during this time was 2153 vials ranging from 3 to 105 vials for each patient. The most distributions of meropenem usage were observed in the internal ward with 38% of total prescriptions.

Most of prescriptions were started empirically (85.9%). Of these, 16.9% continued according to lab results whereas 69% of meropenem courses remained empirical, regardless of their initial appropriateness. Only 14.1% of patients initially received antibiotic therapy based on documented microbial lab data.

Using standard guideline, the initial administration of meropenem was appropriate in

only 64.8% of patients.

All patients were followed during the course of the study. Only four patients could not be re-evaluated because of early discharge or transfer to another hospital. The remaining were re-evaluated 3-5 days after initiation of therapy. Follow up data were inconclusive for 12 patients, therefore; it was impossible to make decision around the adequacy of continuing therapy with meropenem for them. Among the remaining patients, it was revealed that 25.7% received meropenem for improper duration.

4. Discussion

This study was conducted to evaluate the pattern of meropenem prescription, a broad-spectrum and restricted antibiotic, in the various wards of a tertiary care teaching hospital in Tehran, Iran. Our major findings were as follows. First, the rate of meropenem consumption differed significantly among departments of the studied hospital and more usage was detected in the internal ward. Second, most of prescriptions were started empirically (85.9%), of which the majority continued without any relevant culture result (69%). Third, the appropriateness rate for meropenem use was relatively low (64.8%) in this study.

The broadest-spectrum antibiotics, such as carbapenems, play an important role in the empiric therapy of serious nosocomial infections. Nowadays, the development of bacterial resistance to antibiotics, especially last-line wide-spectrum agents, has been become a major concern in the

Table 1. Demographic characteristics and sites of care of patients.

| Variables (N=71) | Results |
|--|------------|
| Age (years, mean±SD, range) | 50.8±21.2 |
| Gender: male (%) | 46 (64.8) |
| Admission ward, n (%) | |
| Internal | 818 (38) |
| Intensive Care Unit | 609 (28.3) |
| Surgery | 364 (16.9) |
| Emergency | 151 (7) |
| Cardiac Care Unit/post Cardiac Care Unit | 121 (5.6) |
| Transplant | 90 (4.2) |
| Total number of vials used | 2153 |
| Duration of therapy (days, mean±SD) | 9.1±6.4 |

treatment of infectious diseases across the world (7). It has revealed that resistant organisms may emerge as a result of several factors mainly inappropriate widespread usage of antibiotics (8). A 10-year study investigating the correlation between antimicrobial consumption and antimicrobial resistance, demonstrated a significant increase in resistance to meropenem in patients with more irrational use of this antibiotic (9).

Concern about the increasing rates of multi-drug-resistant organisms and the cost of these antibiotics has induced some investigators to implement several DUE surveys. Previous studies have shown that up to 50% of antibiotic prescriptions can be inappropriate in hospitals (10). A retrospective survey evaluated the use of 11-restricted antibiotics, indicated that of the total of 285 prescriptions, 42.92% of them were inappropriate (11). Another study investigated the adequacy of therapy with broad spectrum antibiotics including piperacillin-tazobactam, meropenem, and imipenem. Results of this study revealed that empirical treatment with piperacillin-tazobactam, imipenem, and meropenem were inappropriate in 43%, 40% and 21% of such cases. It has also showed that the majority (77%) of the prescriptions was initiated empirically (12). On the other hand, some other studies showed a better pattern in the appropriateness of antibiotic administration. 102 patients received three restricted antibiotics of cefepime, piperacillin-tazobactam and meropenem were included in the two-phase drug utilization survey. In phase 1, 79% of meropenem utilization was appropriate whereas 89% was correct in phase 2 demonstrated the positive effect of educational interventions (13).

Several meropenem DUE studies were also performed in Iran. In a retrospective observational study conducted in a teaching hospital affiliated to Mazandaran University of Medical Sciences, 100 patients were included. All patients received meropenem as an empiric therapy. Among these, appropriate meropenem use obtained in only 41% of the patients (14). Another DUE survey was performed on 68 patients in three Intensive Care Units (ICU; surgical, medical, neurosurgical) of Shariati Teaching Hospital (affiliated to Tehran University of Medi-

cal Sciences). This study mentioned that although the empiric initial therapy with meropenem was justified in most cases (78%), the continuation of treatment was unjustified in 47% of patients (15).

Results of these studies indicated that the majority of antibiotic prescriptions are empirically initiated and continued worldwide (12, 16, 17) and most importantly, they revealed that the rate of appropriate treatment with empiric antibiotics was significantly lower than that of treatment based on a relevant culture results (11, 13).

Although several attempts have been made in order to decrease the inappropriate administration of these drugs, improving antibiotic usage still remains a challenging task. Therefore; different approaches were introduced to decrease this problem such as operating educational programs, development of a restrictive hospital formulary, and development of automatic stop-orders for specific antimicrobial agents (18, 19). One study evaluated antimicrobial stewardship programme-guided de-escalation of carbapenems suggested that this approach could lead to comparable clinical success, fewer adverse effects and a lower incidence of the development of resistance compared to non de-escalation program (20). Another survey investigated the effect of an antibiotic stewardship program (ASP) by carbapenems restriction on gram-negative antimicrobial resistance in ICU. Results of this study showed a 64% decrease in carbapenem administration during the post-restriction phase and importantly a significant increase in the sensitivity of pseudomonas to imipenem 6 months after implementation of restriction policy. Therefore; it concluded that restriction of carbapenems can increase the sensitivity of *P. aeruginosa* to imipenem (21).

In conclusion, our results and other mentioned studies detected various areas of inappropriate use of broad-spectrum antibiotics such as meropenem. With regard to the important role of these drugs in the treatment of serious nosocomial infections, a combination of both restrictive and educational measures such as the implementation of standard guidelines, performing ongoing education of hospital staff regarding proper antibiotic prescription, strict controlled use of broad-spectrum antibiotics, in conjunction with formal in-

fectious disease consultation are essential in order to promote more rational drug use as well as to decrease in the frequency of antibiotic resistance. This multifaceted approach should involve pharmacists, clinical microbiologists, physicians, and infectious diseases experts.

Study limitations

Our study has several limitations. First, the study period was limited and hence seasonal variations in prescribing patterns were not completely revealed. Second, appropriateness was evaluated as adherence with defined institutional guideline, rather than as an objective fact. This, however, is the case with most drug utilization evaluations.

Third, in this study, we mainly focused on the appropriate use of meropenem, therefore; issues such as appropriateness of dose, route of administration, drug monitoring, and drug dose adjustment remained uninvestigated.

Acknowledgement

We thank Dr. Elchin Barzegar for providing some data of this article and also Dr. roodabeh haghgoo, Dr. maryam habibi and Dr. masoomeh karimi for their assistance in the finalization of the proposal.

Conflict of Interest

None declared.

5. References

- Marcus EL, Clarfield AM, Moses AE. Ethical issues relating to the use of antimicrobial therapy in older adults. *Clin Infect Dis*. 2001; 33:1697-705.
- Roark MK, Reed WE Jr. Econotherapeutics. *Diagn. Microbiol. Diagn Microbiol Infect Dis*. 1995;22:209-17.
- Yinnon AM, Skorohod Y, Schlesinger Y, Greenberg A. Cefuroxime utilization evaluation: impact of physician education on prescribing patterns. *Isr Med Assoc J*. 2000;2:187-91.
- Gupta LC, Gupta CK, Jain BB, Garg MG. ABC and VED analysis in medical stores inventory control. *Med J Armed Forces India*. 2007;63:325-7.
- Mohr JF 3rd. Update on the efficacy and tolerability of meropenem in the treatment of serious bacterial infections. *Clin Infect Dis*. 2008;47:S41-51.
- McEvoy GK, ed in chief, Snow ED, ed. AHFS: Drug Information. Bethesda, MD: American Society of Health-System Pharmacists; 2008:1125-6.
- Balderson BJ, Yates ME, Patil NP, Suda KJ. Evaluation of doripenem utilization and susceptibilities at a large urban hospital. *Int J Clin Pharm*. 2011;33:958-63.
- Kollef M, Niederman M. Antimicrobial resistance in the ICU: The time for action is now. *Crit Care Med*. 2001;29:N63.
- Mladenovic-Antic S, Kocic B, Velickovic-Radovanovic R, Dinic M, Petrovic J, Randjelovic G, et al. Correlation between antimicrobial con-

- sumption and antimicrobial resistance of *Pseudomonas aeruginosa* in a hospital setting: a 10-year study. *J Clin Pharm Ther*. 2016;41:532-7.
- Gould IM, Jappy B. Trends in hospital antibiotic prescribing after introduction of an antibiotic policy. *J Antimicrob Chemother*. 1996;38:895-904.
- TarceaBizo P, Dumitras D, Popa A. Evaluation of restricted antibiotic use in a hospital in Romania. *Int J Clin Pharm*. 2015;37:452-6.
- Thuong M, Shortgen F, Zazempa V, Girou E, Soussy CJ, Brun-Buisson C. Appropriate use of restricted antimicrobial agents in hospitals: the importance of empirical therapy and assisted re-evaluation. *J Antimicrob Chemother*. 2000;46:501-8.
- 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;99:397-406.
- Salehifar E, Shiva A, Moshayedi M, Kashi TS, Chabra A. Drug use evaluation of Meropenem at a tertiary care university hospital: A report from Northern Iran. *J Res Pharm Pract*. 2015;4:222-5.
- Mahini Sh, Hayatshahi A, Torkamandi H, Gholami K, Javadi MR. Carbapenem Utilization in Critically Ill Patients. *J Pharm Care*. 2013;1:141-4
- Khan MU, Yousuf RI, Shoaib MH. Drug utilization evaluation of meropenem and correlation of side effects with renal status of

patients in a teaching based hospital. *Pak J Pharm Sci.* 2014;27:1503-8.

17. Mousavi S, Behi M, Taghavi MR, Ahmadvand A, Ziaie S, Moradi M. Drug utilization evaluation of imipenem and intravenous ciprofloxacin in a teaching hospital. *Iran J Pharm Res.* 2013;12:161-7.

18. Anglim AM, Klym B, Byers K. E, Scheld WM, Farr BM. Effect of a vancomycin restriction policy on ordering practices during an outbreak of vancomycin-resistant *Enterococcus faecium*. *Arch Intern Med.* 1997;157:1132-6.

19. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, *et al.*

Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA.* 1996;275:234-40.

20. Lew KY, Ng TM, Tan M, Tan SH, Lew EL, Ling LM, *et al.* Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an ES-BL-endemic setting. *J Antimicrob Chemother.* 2015;70:1219-25.

21. Sistanizad M, Kouчек M, Miri M, Goharani R, Solooki M, Ayazkhoo L, *et al.* Carbapenem restriction and its effect on bacterial resistance in an intensive care unit of a teaching hospital. *Iran J Pharm Res.* 2013;12:503-9.