Research Article

Evaluation of Meropenem Use Among Septic Patients at Hua Hin Hospital, Thailand

Wandee Sumret[1], Wichai Santimaleeworagun[2*], Kamonphop Saowakul[2], Thirawan Haephruek[2], Penprapa Pengsombat[2] and Witchuda Kwanmuang[2]

[1]*Pharmacy Department, Huahin Hospital, Prachuap Khiri Khan, Thailand*
[2]*Department of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand*
[*]*Corresponding author. E-mail: swichai1234@gmail.com*

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Abstract

Antimicrobial-resistant bacteria are an important medical concern. This problem might be resulted from an inappropriate use of antibiotics. The review of antibiotic drug use could help understanding the cause of drug resistance and eventually resolve the problem. Our retrospective cohort study aimed to review meropenem use at Hua-hin hospital, Prachuap Khiri Khan, including therapeutic indications, dosage regimens and duration of sepsis treatment. Data were gathered from patients admitted in the hospital during January to December 2013. The sources of data included patient medical records, patient database from computer program and in-house form of meropenem evaluation. A total of thirty-six cases were evaluated, 17 cases (47.2%) were male, and the average age was 58.3 (±19.9) years. There were 22 cases (61.1%) and 14 cases (38.9%) receiving meropenem as empirical and definitive therapy, respectively. According to meropenem use evaluation, there were 29 (80.6%), 33 (91.7%) and 24 (85.7%) cases that met the criteria for indication, dosage regimen, and treatment duration, respectively. Only 17 cases (60.7%; n=28) met all three criteria for appropriate meropenem use. Thus, with our finding, the role of healthcare professionals in reducing the inappropriate use of antibiotics for the entire course of treatment should be encouraged.

***Key Words*:** Evaluation; Meropenem

Introduction

Currently, the antimicrobial resistance is a world-wide medical and public health problem (Balode et al., 2013; Molton et al., 2013). The 6-year period (2000-2005) of antimicrobial resistance surveillance data from the National Antimicrobial Resistance Surveillance Thailand reported that the rate of carbapenem resistance against *Acinetobacter baumannii* (CR-AB) infection increased from 2.1% in 2000 to 46.7% in 2005 (Dejsirilert et al., 2009). Unfortunately, while the rate of infection and pathogen resistance are increasing, the therapeutic choice for treatment of *Pseudomonas aeruginosa* and *A. baumannii* were limited.

The antibiotic resistance era does not only affect the antimicrobial option, but also leads to unfavorable clinical outcomes and increased medical cost. Lemos et al. (2014) found that patients with CR-AB infection had significantly higher risk of 30-day mortality than those with carbapenem-susceptible *A. baumannii* (CS-AB). Moreover, the average cost of hospitalization among patients with CR-AB (US$ 11,359) was significantly higher than that among patients with CS-AB (US$7,049). Similar to the study by Lautenbach et al. (2010) patients with carbapenem-resistant *P. aeruginosa* (CR-PA) had a higher in-hospital mortality rate than those with carbapenem-susceptible *P. aeruginosa* (CS-PA) (17.4% vs 13.4%, respectively). Moreover, CR-PA was associated with a longer hospital stay and a higher hospital cost. In addition, prior to the carbapenems use, patients were significantly associated with CR-PA infection or colonization.

Medication-use evaluation (also called medication use review) is a performance improvement method to evaluate and improve medication-use processes with the goal of

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favorable patient outcomes (Nadzam, 1991). This process has been implemented worldwide, including Thailand, to evaluate carbapenems use, (Sirinavin et al., 1998; Ayuthya et al., 2003; Rattanaumpawan et al., 2010). However, it is often done in medical schools. Thus, the use of carbapenems in general hospitals might have a different situation.

The problem of antimicrobial resistance at Hua Hin Hospital, a general hospital in Prachuap Khiri Khan Province, has been increasing. In 2010, only one percent of multi-drug resistant *A. baumannii* (MDR-AB; resistant to ceftazidime, ciprofloxacin and aminoglycoside) was sensitive to carbapenems when antimicrobial susceptibility was tested (P. Preechachuawong, Hua-Hin Hospital, personal communication, October 18, 2014). This phenomenon should be considered as an urgent problem. Moreover, meropenem was ranked number one in the total cost of antimicrobial uses in 2012 (O. Hongchumpae, Hua-Hin Hospital, personal communication, October 18, 2014). Therefore, the objective of the present study was to retrospectively collect the data of patients receiving meropenem treatment, as well as to review the appropriateness of indication, dosage regimen and duration of sepsis treatment. Our results will be useful for planning the effective strategy to regulate the meropenem use in the antibiotic resistant era.

Materials and Methods

This study was a retrospective cohort study that gathered the patients' data from electronic medical record database and the meropenem-use form completed by on-site clinical pharmacists in the medical ward. The study included patients receiving meropenem during January to December 2013, who were admitted to the medical ward at Hua Hin Hospital, a 400-bed general hospital located in Prachuap Khiri Khan Province, Thailand. The protocol was approved by research ethics committee with a waiver for informed consent. [No. 8/2557; issued date 19th December 2014]

Participants

This study was to evaluate the meropenem use according to the hospital protocols of therapeutic indication. Moreover, this study also assessed the dosage regimen and the duration of sepsis treatment. The inclusion criteria for septic participants consisted of (1) age > 18 years old (2) patients treated with intravenous meropenem as empirical or documented therapy (3) showing clinical signs of infection, such as systemic inflammatory syndrome (SIRS) for at least 2 of 4 signs (body temperature > 38 ºC or < 36 ºC, respiratory rate > 20 breaths/min, heart rate > 90 beats/min, leukocytosis > 12,000 cells/cm or < 4,000 cells) with suspected source of infections (Levy et al., 2003; Calandra and Cohen, 2005). Patients who had bacterial growth in the specimen without any sign and symptom (also called colonization), and patients with incomplete data either from medical records or meropenem utilization form were excluded.

Definitions

The criteria of appropriate meropenem indication for empirical therapy were defined as a cases when patients were suspected with MDR-pathogen infection with at least one of the following criteria: (1) prior treatment with third- or fourth generation cephalosporins in the previous 90 days, (2) history of more than 2 days of hospitalization in the previous 90 days, (3) patients staying in the intensive care unit more than 2 days, (4) hospitalized patients having severe sepsis/septic shock for more than 2 days, (5) history of ESBLproducing bacteria infection in the previous 90 days, (6) patients who had severe sepsis/ septic shock with suspected *Burkholderia pseudomallei* infection. *The criteria of appropriate indication for documented therapy* were meant for meropenem treatment without other narrower spectrum antimicrobial agents (such as third or fourth generation cephalosporins, aminoglycosides, fluoroquinolone, β-lactam/β-lactamse inhibitors (cefoperazone/sulbactam, piperacillin/tazobactam), or ertapenem) after reporting the susceptibility of pathogens. Additionally, the de-escalation strategy was not applied within 48 hours after reporting the susceptibility. This situation was also classified as a discordance for the criteria of appropriate indication for documented therapy. De-escalation was defined as change of antibiotic to one with a narrower spectrum once culture results were available. For example of de-escalation: a patient with documented therapy showing the causative pathogens susceptible to the narrower spectrum of antimicrobials and also had a stable/or good clinical symptoms, could switch from meropenem to other classes of antimicrobial agents (such as aminoglycoside, third generation cephaloporins, beta-lactam/betalactamase inhibitors or fluoroquinolones), which can sufficiently penetrate into the infectious source or organ.

The criteria of appropriate meropenem dosage in this study was adapted from generally recommended doses studied in clinical data (Mouton and van den Anker, 1995; Baldwin et al., 2008). Among septic patients with normal renal function received one gram intravenously every 8 hours for intra-abdominal infection, urinary tract infection, bacteremia, lower respiratory tract infection, skin and soft tissue infections, bone and joint infections or febrile

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neutropenia. Up to 2 grams of meropenem every 8 hours was used for central nervous system infection. These criteria were applied to patients with creatinine clearance (CLcr) > 50 mL/min. For patients with CLcr <50 mL/min (based on Cockcroft-Gault equation), an adjustment to the dosing regimen was required, including: CLcr 26-50 mL/min; one unit dose based on indication every 12 hours, CLcr 10-25 mL/min; one-half unit dose based on indication every 12 hours, CLcr <10 mL/min; one-half unit dose based on indication every 24 hours.

The criteria of appropriate treatment duration followed a specific type of organ/system infection. The treatment duration for intra-abdominal infection, urinary tract infection, bacteremia, lower respiratory tract infection, skin and soft tissue infections, septic joint infection and unidentified source of infection were usually within 7-14 days. However, a longer period of treatment might be considered appropriate in certain cases based on their clinical responses to the therapy. For instance, up to 21 days and 3-6 months were treatment duration for meningitis and osteomyelitis (Baldwin et al., 2008). For patients with febrile neutropenia, if the neutrophil count was > 1,000 cells/μL and the patient had been asymptomatic, afebrile and had negative blood cultures, the antibacterials could be discontinued (de Naurois et al., 2010). *Febrile neutropenia* is defined as a body temperature >38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count < 500 cells/μL, or expected to fall below < 500 cells/μL within 48 hours (de Naurois et al., 2010).

Data collection

Both medical records from computer database and meropenem use report were reviewed to gather clinical information, including age, gender, underlying diseases, clinical ward, shock and immunocompromized status, antimicrobial regimen (date of start, dosage, administration and duration), antimicrobial susceptibility, source of infection, and vital sign. The primary outcome was percentage of meropenem use accrording to the three setting criteria (therapeutic indication, either empirical or documented therapy, dosage regimen and treatment duration).

Statistical analysis

Descriptive statistics were used for explanation of the percentage of appropiate meropenem use accrording to the criteria. Analysis and data interpretation were processed via PSPP for windows data analysis.

Results

During the study, 36 patients met the inclusion criteria. Among them, 17 patients (47.2%) were male, the average age (SD) was 58.3 (19.9) years (range, 18-89 years), and average duration of meropenem use (SD) was 13 (9.6) days. According to renal function assessment, 7, 9, 3 and 17 cases had CLcr of >50, 26-50, 10-25 and <10 mL/min, respectively. The four most common sites/sources of infection were nosocomial pneumonia (30.6%), intra-abdominal infection (19.4%), urinary tract infection (16.7%) and bacteremia (16.7%), respectively (n=11, 7, 6, and 6). (Table 1)

Table 1 Summary of characteristics of patients treated with meropenem (n=36)

Characteristics	Number (%)
Sex ; male	17 (47.2)
Age (years; Mean ±SD)	58.3 ± 19.9
Creatinine clearance (mL/minute)	
> 50	7 (19.4)
26-50	9 (25.0)
10-25	3 (8.3)
< 10	17 (47.2)
Duration of meropenem use (days; Mean ±SD)	13.0 ± 9.6
Source of infection	
Nosocomial pneumonia	11 (30.6)
Intra-abdominal infection	7 (19.4)
Urinary tract infection disease	6 (16.7)
Bacteremia	6 (16.7)
Skin and soft tissue infection	3 (8.3)
Bacterial meningitis	2 (5.6)
Febrile neutropenia	1 (2.8)

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Meropenem use evaluation

Of the 36 septic patients, 22 (61.1%) received meropenem as empirical therapy. The others were treated as documented therapy (38.9%; n=14). Twenty nine cases (80.6%; n=36) were in accordance with appropriate indication criteria, including 21 (95.5%; n=22) and 8 (57.1%; n=14) patients with empirical and documented therapy, respectively. Among patients with documented therapy, meropenem in six patients was not de-escalated to the narrower spectrum such as the third generation cephalosporins (n=2), ertapenem (n=2) or both of them (n=2), even they had stable/or good clinical symptoms.

For the remaining domains, dosage regimen of 33 (91.7%; n=36) cases (19 and 14 cases in empirical and documented therapy group, respectively) and duration of treatment of 24 (85.7%; n=28 excluding death or transfer-out) cases (15 and 9 cases in empirical and documented therapy group, respectively) were in accordance with appropriate criteria. Among three cases with inappropriate dosage regimen, one of them received higher than recommended dose based on patients' renal function, whereas the others were given lower dose. Furthermore, three out of four cases with inappropriate duration of treatment were treated with meropenem longer than the recommended treatment duration although the patients had good clinical symptoms. The remaining cases stopped meropenem before completing recommended treatment duration. Focusing on the 3 criteria, seventeen cases (60.71%; n=28; excluding death or transfer out) totally met all criteria. (Table 2)

Discussion

Medication use evaluation, or drug use review, is a process to ensure the appropriate drug use. Moreover, this is also a method for obtaining information to improve rational drug therapy in the clinical setting (Nadzam, 1991; World Health Organization, 2003). Drug use review could assess the entire process of medication use, including indications, dose, route of administration, treatment duration and drug interactions (World Health Organization, 2003). Thus, the evaluated domains in our study were adapted from concept of WHO to assess the dosage regimen and duration of treatment beyond therapeutic indication. Our results showed that more than eighty percents of meropenem indication, dosage regimen and duration of treatment among patients appropriately met the criteria. Similar results were found in a study by Sumitsawan et al. (2012), patients were given meropenem with appropriate indication and dosing at 78 and 90%, respectively. However, when we assessed overall criteria, only 60.7% met all three-criteria of meropenem use. Thus, evaluation of some domains of medication use did not represent the real situation of rational drug use.

According to our result, the rate of appropriate use was higher in patients treated as empirical therapy. Not surprisingly, in the absence of a microbiologic documentation, the physicians empirically treated patients either on the basis of sign and symptoms or available laboratory data. While, documented therapy was the treatment with known causative pathogens and/or source of infections. This situation could make it easier to retrospectively validate all three

Table 2 The meropenem use according to each appropriate criteria including indication, dosage regimen, and treatment duration.

Domain	Empirical therapy n (%)	Documented therapy n (%)	Total n (%)
Indication (n=36)			
Accordant with criteria	21 (95.5)	8 (57.1)	29 (80.6)
Discordant with criteria	1 (4.5)	6 (42.9)	7 (19.4)
Dosage regimen (n=36)			
Accordant with criteria	19 (52.8)	14 (38.9)	33 (91.7)
Discordant with criteria	3 (8.3)	0 (0)	3 (8.3)
Too low dose	2 (5.6)	-	2 (5.6)
Too high dose	1 (2.78)	-	1 (2.78)
Treatment duration (n=28)†			
Accordant with criteria	15 (53.6)	9 (32.1)	24 (85.7)
Discordant with criteria	4 (14.3)	0 (0)	4 (14.3)

† Eight cases were excluded due to death and transferring during hospital treatment.

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setting criteria therefore, the higher rate of inappropriate use was found in patients with documented therapy.

Antimicrobial de-escalation is a practical technique used for changing the initial antibiotic treatment to the narrow spectrum of antimicrobials in order to reduce unnecessary antibiotic use that might promote the drug resistant problem (Masterton, 2011). Owing to the result, 6 of 14 cases (42.9%) of documented therapy did not use de-escalation technique. This number was higher than the finding from a previous study (25.6%), which had pharmacist intervention on physicians's de-escalation criteria (Sumitsawan et al., 2012). Oxman et al. (2014) indicated that a decision support by ward unit pharmacists could significantly improve the rate of appropriate antibiotic use, particularly, in the cases of culture-positive suspected ventilator associated pneumonia. However, in our study, pharmacists only had a role in initial treatment evaluation based on hospital policy. Thus, antibiotic de-escalation should be incorporated into a routine antimicrobial management.

Previously, the appropriate antimicrobial use remained a favorable factor. Certain studies indicated that appropriate antimicrobial agents for treatment of *Acinetobacter* infections could significantly reduce mortality (Falagas et al., 2006; Deris et al., 2009; Santimaleeworagun et al., 2011). However, the present study did not compare the clinical outcomes between patients receiving appropriate and inappropriate antimicrobial therapy according to the criteria. These outcomes of treatment (e.g. cured disease or improved clinical parameter) were monitoring parameters for drug use review.

Another limitation of this study is that the authors did not evaluate the cost of treatment, adverse drug reactions and drug interactions which are in fact crucial in drug evaluation process (Sumitsawan et al., 2012). Moreover, due to the fact that our findings were based on recorded evidence, there may be a situation of incomplete data. For instance, the actual rate of inappropriate use of meropenem may be lower than what we found because the reasons of drug use were not completely documented in the medical records. Therefore, it is possible that there may be a misclassification between appropriate and inappropriate meropenem use. Moreover, we included thirty-six participants for meropenem use evaluation. This number seems like a small sample group. However, owing to the fact that this study was set in the general hospital, the small number of patients may not fully reflect the appropriateness of meropenem use in a larger group or a different setting. Nevertheless, this information are definitely useful for the antimicrobial management in the similar settings.

Conclusion

The antimicrobial treatment should be throughout assessed for indication, dosage and treatment. With our result, the de-escalation for documented therapy should be applied to all patients having clinically stable condition in order to decrease the antimicrobial resistant problem. A further study with a larger population should be done to assess which process is at risk for the inappropriate antimicrobial use. Eventually, these data will help improving the medication guidance or strategy for antimicrobial use in a hospital.

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