Therapeutic Effectiveness of a Generic versus Original Meropenem in Serious Infections

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Background: *Meropenem plays a significant role in the current antimicrobial treatment of serious infections. Recently, generic meropenems have become widely available in Thailand.*
Objective: *Compare the effectiveness and safety of a generic meropenem (Mapenem®) with the original meropenem (Meronem®) in clinical practice.*
Material and Method: *A retrospective cohort study was conducted in hospitalized patients with serious infections that had been treated with either the generic or the original meropenem in nine secondary- and tertiary-care hospitals nationwide. The treatment outcomes at days 3, 7, and 14 after the use of meropenem between the two groups were compared.*
Results: *Three hundred ninety seven patients with a mean (SD) age of 66.4 ± 16.9 years were included. There were 228 (57.4%) males and 169 (42.6%) females. Two hundred and seven (52.1%) and 190 (47.9%) cases fell into the generic and original groups respectively. There were no significant differences regarding age, gender, history of underlying disease, body weight, and ward of admission between the two groups. The majority of patients had presented with the respiratory tract (48.6%) and blood stream infections (29.5%). The three most common causative bacteria were Pseudomonas aeruginosa, Acinetobacter baumannii, and extended-spectrum beta-lactamase (ESBL) producing Escherichia coli. The distribution of the sites of infection, causative microorganisms, the dosage of meropenem, and duration of treatment were similar between the two groups. The distribution of patients with complete resolution, improvement, stable, worse, died from infection, and died from other causes were similar between the two groups at day 3, 7, and 14 of meropenem use ($p > 0.05$). The drugs were well-tolerated, and less than 2% of patients in both groups discontinued meropenem due to the adverse drug effects.*
Conclusion: *The generic meropenem has a similar effectiveness in the treatment of serious bacterial infections when compared with original meropenem. Both formulations are well tolerated among patients with substantial comorbidities. Adverse drug effects that lead to drug discontinuation are uncommon.*

Keywords: *Meropenem, Effectiveness, Carbapenems, Generic, Original*

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In the era of gram-negative bacterial resistance, carbapenems play a significant role since they provide better gram-negative coverage than other beta-lactams and are stable against extended-spectrum beta-lactamases (ESBL) and AmpC beta-lactamases where third generation cephalosporins are not effective[1-6].

Meropenem is a carbapenem that is more active against Gram-negative bacteria. A recent study showed that a generic meropenem is pharmaceutical equivalent and fulfills the requirements of the US Pharmacopoeia (XXVIII) in relation to their activities[7]. This generic meropenem has been

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approved by the Thai Food and Drug Administration after it demonstrated indifferent bioequivalence and antibacterial activity[8], as well as safety, and tolerability. In the present study, the authors aimed to compare the effectiveness and safety of the generic with original meropenem in the real-life clinical practice setting after it has been available in many hospitals in Thailand for more than a year.

Material and Method

A retrospective cohort study was conducted in hospitalized patients who had been treated with either the generic or the original meropenem in nine secondary- and tertiary-care hospitals nationwide. These included King Chulalongkorn Memorial Hospital, Lerdsin Hospital, Police General Hospital, Somdej Phrapinklao Hospital and Vajira Hospital at Bangkok, Buddhachinnaraj Hospital at Phitsanulok, Chiang Mai University Hospital at Chiang Mai, Narathiwas Hospital at Narathiwas, and Udon Thani Hospital at Udon Thani, Thailand. The present study was conducted between April 1, 2007 and February 28, 2010.

Inclusion criteria were hospitalized adults ($\geq$ 15 years old) with serious bacterial infections, such as lower respiratory tract infection, necrotizing skin/soft tissue infection, nosocomial or health-care associated intra-abdominal infection and sepsis. Etiologic agents of these infections were mostly multi-drug resistant Gram-negative bacilli or ESBL-producing Enterobacteriaceae, with or without anaerobic bacteria. The patients received either a generic meropenem (Mapenem®) or an original meropenem (Meronem®).

Baseline data were collected from the medical records. They including demographic data, underlying diseases, date and duration of hospitalization, site of infections, clinical specimens for microbiological cultures, antimicrobial agents used prior and during the hospitalization, duration of meropenem used, laboratory results, adverse drug effects, and outcomes of treatment at days 3, 7, and 14 after the use of the meropenem. The present study was approved by the institutional review board and/or ethical clearance committee of the Ministry of Public Health.

Data analysis

Continuous data with normal distribution were shown as mean and standard deviation (SD) and those with non-normal distribution as median and interquartile range (IQR). Categorical data were shown as frequency and percentage. Study patients were categorized into generic or original meropenem groups. Continuous data were compared between the two groups using independent t-test or the Mann-Whitney U test. Chi-square test or Fisher's exact test was used for categorical data analysis where appropriate. Clinical outcomes at days 3, 7 and 14 after meropenem use were compared. All analysis was performed using the SPSS version 14.0. A p-value of < 0.05 was considered statistical significance.

Results

Three hundred ninety seven patients from nine hospitals were included in the present study (Buddhachinnaraj Hospital 80 patients, Police General Hospital 80 patients, Somdej Phrapinklao Hospital 80 patients, Chiang Mai University Hospital 78 patients, King Chulalongkorn Memorial Hospital 21 patients, Vajira Hospital 20 patients, Narathiwas Hospital 20 patients, Lerdsin Hospital 11 patients, and Udon Thani Hospital 7 patients). The age (mean $\pm$ SD) was 66.4 $\pm$ 16.9 years. Two hundred and twenty-eight (57.4%) patients were male and 169 (42.6%) were females. Of 397 patients, 272 (68.5%) were hospitalized in the intensive care units. Two hundred and seven (52.1%) cases were in the generic meropenem group and 190 (47.9%) patients were in the original meropenem group. Table 1 shows the comparison of baseline characteristics between the two groups. There were no significant differences of age, gender, history of underlying disease, body weight, and ward of admission.

The sites of infection in the majority of patients were the respiratory tract (48.6%) and blood stream (29.5%) infections. The rest were urinary tract, skin and soft tissue, intra-abdominal cavity, central nervous system and bone and joints. The three most common causative microorganisms were *Pseudomonas aeruginosa, Acinetobacter baumannii,* and ESBL-producing *Escherichia coli*. The distribution of the sites of infections and causative microorganisms are shown in Table 2. There were no statistical differences of the distribution of the sites of infection and causative microorganisms between the two groups, except for ESBL-producing *E. coli*, which was significantly higher in the generic meropenem group. The baseline laboratory results including complete blood counts, liver function tests, blood urea nitrogen and serum creatinine were similar between the two groups (data not shown).

More than eighty percent of patients in both groups had previously used other antimicrobial agents

Table 1. Baseline characteristics of 397 study patients

Variables	Generic meropenem group (n = 207)	Original meropenem group (n = 190)	p-value
Age, years, mean (SD)	65.7 (16.9)	67.2 (17.0)	0.399
Male gender, number (%)	124 (59.9)	104 (54.7)	0,309
History of underlying disease, number (%)	191 (92.3)	174 (91.6)	0.939
Hypertension	90 (43.5)	84 (44.2)	0.919
Diabetes mellitus	59 (28.5)	64 (33.7)	0.277
Chronic kidney disease	41 (19.8)	37 (19.5)	0.954
Ischemic heart disease	32 (15.5)	23 (12.1)	0.384
Chronic lung disease	18 (8.7)	27 (14.2)	0.084
Chronic liver disease	9 (4.3)	17 (8.9)	0.070
Cancer	27 (13.0)	23 (12.1)	0.880
Body weight, kg, mean (SD)	51.8 (10.3)	54.3 (10.0)	0.151
Ward of admission			0.536
General ward	144 (69.6)	128 (67.4)	
Intensive care unit	63 (30.4)	62 (32.6)	

Table 2. Clinical features of the 397 study patients by sites of infection and micro-organism

Variables	Generic meropenem group (n = 207)	Original meropenem group (n = 190)	p-value
Site of infections*, number (%)			0.196
Respiratory tract	95 (45.9)	98 (51.6)	
Blood stream	59 (28.5)	58 (30.5)	
Urinary tract	56 (27.1)	42 (22.1)	
Skin and soft tissue	28 (13.5)	16 (8.4)	
Intra-abdominal	17 (8.2)	14 (7.4)	
Central nervous system	2 (1.0)	4 (2.1)	
Bone and joints	1 (0.5)	1 (0.5)	
Multiple sites of infection, number (%)	51 (24.6)	41 (21.6)	0.924
Causative microorganisms**, number (%)			
P. aeruginosa	46 (22.2)	44 (23.2)	0.487
A. baumannii	48 (23.2)	37 (19.5)	0.319
E. coli	5 (2.4)	8 (4.2)	0.401
ESBL-p *E. coli*	44 (21.3)	22 (11.6)	0.010
K. pneumoniae	5 (2.4)	6 (3.2)	0.764
ESBL-p *K. pneumoniae*	29 (14.0)	24 (12.6)	0.768
Enterobacter cloacae	10 (4.8)	3 (3.9)	0.887
Enterococcus sp.	5 (2.4)	4 (1.2)	0.653
Others	31 (15.0)	26 (13.7)	0.258

* Some patients had more than one site of infection
** Some patients had more than one microorganism
ESBL-p = extended spectrum beta-lactamase producing

for other episodes of infection prior to the use of meropenem in the same hospitalization (84.5% vs. 81.1%, p = 0.424). Ceftriaxone and ceftazidime were such antimicrobials frequently used in both groups. There was no difference of the median durations of prior antimicrobial therapy between the two groups (6 vs. 5 days, p = 0.617).

The median and IQR of daily dose of meropenem were 2.0 (1.5-3.0) grams in both groups. The median duration of meropenem use was not

different between the two groups (9 vs. 10 days, p = 0.285). In addition to meropenem, other antimicrobial agents were concomitantly used in 44.0% of generic meropenem group and 54.7% of original meropenem group (p = 0.035). The common concomitant antimicrobial agents used were cefoperazole/sulbactam, ciprofloxacin, colistin, vancomycin and metronidazole. Table 3 shows the comparison of clinical outcomes of 397 study patients. The distribution of patients with complete resolution, improved, stable, worse, died from infection, and died from other causes between the two groups were similar at days 3, 7 and 14.

The rate of total adverse drug effects was slightly higher in the original meropenem group but the difference was not significant. Common adverse drug effects in both groups were rashes and acute renal failure (Table 4). Less than 2% of patients in both groups discontinued meropenem due to its adverse drug effects.

Discussion

The results from the current study demonstrated the similarity of effectiveness of the generic and original meropenem therapy in both fixed-time points at 3, 7, and 14 days of meropenem use. In addition, patients in both groups tolerated meropenem well, with minimal adverse drug effects that lead to drug discontinuation. Of note, patients in the present study were very old, had a high proportion of underlying diseases, and the majority of them needed to be hospitalized in intensive care units.

Respiratory tract infection was the major entity of clinical presentations in the present study. Previous clinical trials had shown that meropenem is effective and well tolerated by patients with hospital-acquired pneumonia, including a subgroup of patients with ventilator-associated pneumonia[9-11]. In addition, meropenem had also proved to effectively useful in patients with bloodstream infections and infections of urinary tract, skin and soft tissue, intra-abdominal, central nervous system, and bone and joints[4-6]. In the present study, the three most common causative microorganisms were *Pseudomonas aeruginosa, Acinetobacter baumannii,* and ESBL producing *Escherichia coli*. Meropenem has a good activity against *P. aeruginosa,* and ESBL-producing *E. coli*[4-6,12].

Table 3. Clinical outcomes of the 397 study patients

Outcomes	Generic meropenem group (n = 207)	Original meropenem group (n = 190)	p-value
Clinical outcomes at day 3, number (%)			0.059
Complete resolution	6 (2.9)	4 (2.1)	
Improved	101 (48.8)	78 (41.1)	
Stable	92 (44.3)	83 (43.7)	
Worse	2 (1.0)	8 (4.2)	
Died from infection	2 (1.0)	10 (5.3)	
Died from other causes	2 (1.0)	2 (1.1)	
Missing data	2 (1.0)	5 (2.5)	
Clinical outcomes at day 7, number (%)			0.284
Complete resolution	42 (20.3)	24 (12.6)	
Improved	96 (46.4)	84 (44.2)	
Stable	24 (11.6)	29 (15.3)	
Worse	6 (2.9)	11 (5.8)	
Died from infection	8 (3.9)	15 (7.9)	
Died from other causes	8 (3.9)	8 (4.2)	
Missing data	23 (11.0)	19 (10.0)	
Clinical outcomes at day 14, number (%)			0.089
Complete resolution	64 (30.9)	44 (23.2)	
Improved	87 (42.0)	78 (41.1)	
Stable	7 (3.4)	11 (5.8)	
Worse	5 (2.4)	5 (2.6)	
Died from infection	12 (5.8)	21 (11.1)	
Died from other causes	10 (4.8)	13 (6.8)	
Missing data	24 (11.7)	18 (9.4)	

Table 4. Adverse drug reaction (ADR) and discontinuation of meropenem in 397 study patients

Outcomes	Generic meropenem group (n = 207)	Original meropenem group (n = 190)	p-value
Total ADR, number (%)	6 (2.9)	13 (6.8)	0.097
Rashes	4 (1.9)	4 (2.1)	
Pancytopenia	0	1 (0.5)	
Thrombocytopenia	0	1 (0.5)	
Acute renal failure	2 (1.0)	7 (3.7)	
Seizure	0	0	
Discontinuation of meropenem due to ADR, number (%)	4 (1.9)	3 (1.6)	0.579
Rashes	3 (1.4)	2 (1.1)	
Acute renal failure	1 (0.5)	0	
Pancytopenia	0	1 (0.5)	

However, activity of meropenem against *A. baumannii* in Thailand may be compromised[13,14]. Recent studies reported that addition of cefoperazone/sulbactam to meropenem might be useful for infections caused by MDR *A. baumannii*[14,15]. However, the addition of other antimicrobials during meropenem use, could contribute to successful therapy or adverse effect as well.

The overall mortality rate at 14 days of meropenem use was 14.1%, which is lower than the previous open-label study[16]. However, the mortality rate could be underestimated due to missing data in some patients. Thus, the nature of retrospective study is a limitation of the present study. Other limitations include the limited data of *in vitro* susceptibility of causative bacteria, and APACHE score. Nevertheless, this multicenter cohort study provides an important clinical data in real-life practice and to the authors' best knowledge, is the first comparative study of generic and original meropenem.

In conclusion, therapy of the generic meropenem has similar effectiveness in the treatment of serious infections when compared to the original meropenem. Both formulations are well tolerated among patients with substantial comorbidities. Adverse drug effects that lead to drug discontinuation are uncommon.

Potential conflicts of interest

None.

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ประสิทธิผลของยาสามัญเมโรพีเนมเปรียบเทียบกับยาต้นแบบในการรักษาการติดเชื้อรุนแรง: การศึกษาสหสถาบัน

สมบูรณ์ ตันสุภสวัสดิกุล, ทรงชัย สิมะโรจน์, สมชาย จันทโรธร, นนทกานต์ นันทจิต, กมลวรรณ จุติวรกุล, วรางคณา มั่นสกุล, ขนิษฐา ยอมเต็ม, ฐิติรัตน์ ตั้งก่อสกุล, ศุภฤษณ์ วรรณสุนทรไชย

ภูมิหลัง: *ยาปฏิชีวนะเมโรพีเนม มีบทบาทสำคัญในการรักษาโรคติดเชื้อรุนแรงซึ่งในปัจจุบันมียาสามัญใช้ในประเทศไทย แต่ยังขาดข้อมูลเกี่ยวกับประสิทธิผลและความปลอดภัยในการใช้เปรียบเทียบกับยาต้นแบบ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาประสิทธิผลและความปลอดภัยในการใช้ยาสามัญเมโรพีเนมในการรักษาผู้ป่วยโรคติดเชื้อรุนแรง*

วัสดุและวิธีการ: *รูปแบบการศึกษาที่ใช้ คือ การศึกษาแบบวิเคราะห์ข้อมูลย้อนหลังผู้ป่วยที่ได้รับการรักษาด้วยยาต้นแบบ หรือยาสามัญเมโรพีเนมใน 9 โรงพยาบาล ทำการประเมินผลการตอบสนองทางคลินิก ณ วันที่ 3, 7, 14 ภายหลังการใช้ยาทั้ง 2 กลุ่ม และใช้ค่าทางสถิติ Kaplan-Meier ในการวิเคราะห์ข้อมูล*

ผลการศึกษา: *ผู้ป่วยในการศึกษาทั้งหมด 397 ราย ค่าอายุเฉลี่ย 66.4 ปี ผู้ป่วยชายคิดเป็น 57.4% แบ่งเป็นกลุ่มที่ได้รับยาสามัญ 207 ราย (52.1%) และยาต้นแบบ 190 ราย (47.9%) ซึ่งอายุ เพศ โรคประจำตัว น้ำหนัก ของผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกัน ผู้ป่วยส่วนใหญ่เป็นการติดเชื้อทางเดินหายใจ (48.6%) และกระแสโลหิต (29.5%) เชื้อก่อโรคส่วนใหญ่ได้แก่ Pseudomonas aeruginosa, Acinetobacter baumannii และ (ESBL)-producing Escherichia coli ตำแหน่งที่ติดเชื้อ เชื้อที่เป็นสาเหตุ ขนาดยาและระยะเวลาการได้รับยาของทั้งสองกลุ่มไม่แตกต่างกัน ผลการรักษาผู้ป่วย หายเป็นปกติ มีอาการดีขึ้น มีอาการคงที่ มีอาการแย่ลง ตายจากการติดเชื้อ และตายจากสาเหตุอื่น ๆ ณ วันที่ 3, 7 และ 14 ไม่มีความแตกต่างกันทางนัยสำคัญทางสถิติ ($p > 0.05$) จากการวิเคราะห์ด้วย Kaplan-Meier พบว่าผู้ป่วยที่ได้รับยาสามัญมีความน่าจะเป็นของการรอดชีวิตสูงกว่าเล็กน้อย แต่ไม่มีความแตกต่างกันทางนัยสำคัญทางสถิติ (log-rank test, $p = 0.12$) ยาทั้ง 2 กลุ่ม มีความปลอดภัยและมีผู้ป่วยน้อยกว่า 2% ที่ต้องหยุดยาจากอาการข้างเคียง*

สรุป: *ยาสามัญเมโรพีเนม (Mapenem) มีประสิทธิผลในการรักษาโรคติดเชื้อรุนแรงไม่แตกต่างจากยาต้นแบบ ยาทั้ง 2 สูตร มีความปลอดภัยในการใช้และอาการข้างเคียงที่ส่งผลให้ต้องหยุดยาพบน้อย*