Monitoring of Effectiveness and Safety of Generic Formulation of Meropenem for Treatment of Infections at Siriraj Hospital

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Objective: *In Siriraj Hospital, generic meropenem (Monem®) has been available and was substituted for original meropenem, but the effectiveness and safety of using generic meropenem in a clinical setting are the main concern.*
Material and Method: *From July 2007 to June 2009, hospitalized patients aged 18 or older who received meropenem for 48 hours were identified from the pharmacy database of Siriraj hospital. A retrospective study was conducted. Three hundred patients in each of original and generic meropenem groups were required to demonstrate non-inferiority of generic to original meropenem.*
Results: *The mean age of all patients was 63 years. Most of the patients had co-morbidities. Approximately 90% of the infections were health-care associated. Drug-resistant gram-negative bacteria including ESBL producing E. coli and K. pneumoniae, P. aeruginosa and A. baumannii account for nearly 50% of all organisms. No significant difference was found regarding characteristics, type or site of infection and pathogen between generic and original groups but for more patients in the original group having cardiovascular disease and more patients in the generic group receiving immunosuppressive agents. Eighty-two to 85% received meropenem with one of appropriate indications. No statistically significant difference occurred either in an overall favorable outcome (63% vs.70.4%, p=0.07) or in overall mortality (38% vs. 32%, p=0.17), as well as adverse effects between the original and the generic groups.*
Conclusion: *Generic meropenem (Monem®) was not inferior to original meropenem for therapy of infections in the hospitalized patients at Siriraj Hospital.*

Keyword: *Meropenem, Effectiveness, Safety, Generic formulation*

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Meropenem is a broad spectrum antibiotic of the carbapenem family which has a good *in vitro* activity against many gram-positive and gram-negative pathogens, including extended-spectrum β-lactamase (ESBL) and Amp C-producing Enterobacteriaceae. The difference between meropenem and imipenem is the presence of a 1-β methyl constituent on the carbapenem nucleus of meropenem which increases its stability to renal dehydropeptidase-1(DHP-1); hence, it could be used alone without cilastatin. Meropenem also has a pyrrolidinyl substituent at the 2 position that increases its activity against gram-negative aerobic bacteria, especially to *P. aeruginosa*[1,2]. In 1996, meropenem was released and approved for use in complicated intra-abdominal infection, complicated skin and skin structure infection and bacterial meningitis (in pediatric patients aged < 3 months)[3]. In addition, it was used as empirical therapy of serious bacterial infection in hospitalized patients, or poly-microbial infection[4]. Although meropenem has been useful in a wide variety of infections, inappropriate use causes emergence of infection by multi-drug resistant organisms. The common inappropriate usages of meropenem are prescribing without appropriate indication and improper dosage[5]. Recommended dosage for patients who have normal renal function is 3 grams per day. Dosage should be adjusted for patients who have creatinine clearance

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less than 50 ml/min. To date, meropenem from innovator pharmaceutical company has been used for 13 years. Its patent has been expired; hence, the biosimilar from several generic manufacturers is now introduced.

Generally, the registration of a generic pharmaceutical product required only the same biopharmaceutical equivalence as the original product[6,7]. The demonstration of therapeutic equivalence through clinical studies is not necessary. In addition, most bioequivalence studies of the generic products were evaluated in healthy subject not in the patients who might have different pharmacokinetics depend on disease severity or co-morbidities[8,9]. Clinical efficacy and safety data of the generic products were allowed to rely on an innovator's studies according to scientific principles[10]. However, several studies revealed distinct differences in terms of clinical outcome and adverse events between a generic and the original product when used in clinical setting[11-13]. Meropenem from generic manufacturer (Monem® from Biopharm Chemical Limited) has been available in Siriraj Hospital since October 2008. The cost of generic meropenem is much less than that of the original product. Although the substitution of generic meropenem to original meropenem could reduce the healthcare budget, clinical effectiveness and the safety of using generic meropenem in clinical setting are still a main concern. Therefore, Siriraj Hospital has set the policy that any new generic drug in the hospital formulary needs to have drug use evaluation in order to ensure its effectiveness and safety.

The objective of the study was to compare effectiveness and safety of generic meropenem with original meropenem for treatment of infections in hospitalized patients at Siriraj Hospital.

Material and Method

Hospitalized patients aged 18 or older who received meropenem for 48 hours between July 2007 and June 2009 were identified from pharmacy database of Siriraj hospital. The eligible patients were selected by systematic random sampling. Medical records of the chosen patients were reviewed to obtain demographic data, underlying conditions, indications of prescribing meropenem, type and site of infection, causative organism, previous and concurrent antibiotic used, microbiological and clinical outcomes and adverse events.

This study was designed to demonstrate the non-inferiority of generic meropenem compared with original meropenem regarding favorable outcomes including cure and improvement at the end of treatment. It was expected that an overall favorable outcome of patients who received original meropenem would be 70%. Generic meropenem would not be inferior to original meropenem if an overall favorable outcome was more than 60%. A sample size of 300 patients in each of original and generic meropenem was required to test the non-inferiority of generic meropenem when the type I and type II errors were 5% and 20%, respectively.

Analyses were performed with SPSS 13.0. The data were analyzed by descriptive statistics. Categorical variables were compared using Chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test or Mann-Whitney U-test, as appropriate. A p-value of 0.05 or less was considered statistically significant.

Results

The characteristics of patients who received original and generic meropenem are shown in Table1. The mean age of all patients was 63 years. Nearly 50% of them were males. Approximately 60% of the patients were hospitalized at the Department of medicine. Most of the patients had co-morbidities such as diabetes mellitus, heart disease, hematologic malignancy, renal disease or cancer. Two-thirds of the patients had prior exposure to antibiotic before receiving meropenem. Most of the characteristics of the patients in both groups were not significantly different, except for heart disease which was found to be more common in the patients who received original product (33.3% vs. 25%, $p = 0.03$); those receiving immunosuppressive agents were found more often in those patients who received the generic product (6% vs.11%, $p = 0.04$).

The infections of the patients who received original and generic meropenem are shown in Table 2. Approximately 90% of infections were health-care associated. The common sites of infection were respiratory, genitourinary, intra-abdominal and wound or soft tissue. The microorganisms were isolated from two-thirds of the patients. The most common pathogen was gram-negative bacteria including extended-spectrum- beta-lactamase (ESBL) producing *E. coli* and *K. pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Susceptibility to meropenem of these isolates was available in 96% percent. All isolates of ESBL producing *E. coli* and *K. pneumoniae* were susceptible to meropenem. No significant difference in susceptibility to meropenem for *Pseudomonas aeruginosa* was found between original and generic group. For *Acinetobacter baumannii*, the

Table 1. Characteristics of patients

	Original Meropenem (n = 300)	Generic Meropenem (n = 300)	p-value
Mean age ± SD (year)	64.6 ±17.8	61.7 ± 19.8	0.06
Gender			
Male	145 (48.3%)	164 (54.7%)	
Female	155 (51.7%)	136 (45.3%)	0.12
Department			
Medicine	191 (63.7%)	176 (58.7%)	0.24
Surgery	95 (31.7%)	109 (36.3%)	0.26
Other	14 (4.6%)	15 (5%)	>0.99
Underlying disease	287 (95.7%)	280 (93%)	0.21
DM	103 (34.3%)	81 (27%)	0.06
Heart disease	100 (33.3%)	75 (25%)	0.03
Hematologic malignancy	54 (18%)	50 (16.7%)	0.75
Renal disease	51 (17%)	34 (11.3%)	0.06
Cancer	37 (12.3%)	29 (9.7%)	0.36
Pulmonary disease	28 (9.3%)	22 (7.3%)	0.46
Immunosuppressive agents	18 (6%)	33 (11%)	0.04
Liver disease	15 (5%)	17 (5.7%)	0.86
Previous use of antibiotic	211 (70.3%)	198 (66%)	0.29

isolates in the original group were more susceptible to meropenem than those in the generic group (30% vs.8.1%, p = 0.02). Eighty-two to 85% of meropenem usage was prescribed according to the following indications: 1) confirmed or suspected infection due to *P.aeruginosa*, 2) severe infection due to ESBL-producing pathogens, 3) empirical therapy for hospital-acquired infection not responding to cephalosporin, aminoglycoside, fluroquinolone, beta-lactam /beta-lactamase inhibitor,4) infection due to pathogen resistant to cephalosporin, aminoglycoside, fluroquinolone, beta-lactam/beta-lactamase inhibitor, 5) empirical therapy for febrile neutropenia, 6) infection due to pathogen susceptible to other antibiotic but the patient unable to receive such antibiotics. No significant difference for indications of meropenem was found between the original and the generic groups. The indications of meropenem usage in both groups are shown in Table 3.

The dosage and duration of meropenem are shown in Table 4. For all patients, the mean dose of meropenem was 2.2 grams per day and the median duration of treatment was 8 days. The dosage and duration of treatment with meropenem in the original and the generic groups had no significant difference.

The concurrent antibiotics are shown in Table 5. Forty percent of the patients who received meropenem also received other antibiotics. The commonly given antibiotics were glycopeptides, colistin, aminoglycoside and quinolone. There was no significant difference of concurrent antibiotics between the original and the generic groups.

The outcomes of meropenem therapy are shown in Table 6. There was no statistically significant difference in an overall favorable outcome between the original and the generic groups (63% vs.70.4%, p = 0.07). Regarding the microbiological outcome, no significant difference was found between the original and the generic groups. Mortality related to infection was similar between both groups. The overall mortality was 38% and 32% of the patients in the original and the generic groups respectively (p = 0.17). The adverse effects including antibiotic allergy and antibiotic associated diarrhea for patients who received generic or original meropenem were also similar.

Discussion

Nowadays, generic drugs are increasingly used and frequently substituted for innovator drugs due to cost savings. The more that additional generic drugs enter the market, the lower the cost of the generic drugs[14]. Since the development of a generic drug does not require extensive clinical study, the drug can be marketed after FDA approval, which requires only the

Table 2. Infections in the patients who received meropenem

	Original Meropenem (n = 300)	Generic Meropenem (n = 300)	p-value
Type of infection			
Community-acquired	33 (11%)	36 (12%)	0.79
Health-care associated	267 (89%)	264 (88%)	
Site of infection			
Respiratory	129 (43%)	135 (45%)	0.68
Genitourinary	60 (20%)	36 (12%)	0.09
Intra-abdominal	32 (10.7%)	32 (10.7%)	>0.99
Wound/soft tissue	22 (7.3%)	20 (6.7%)	0.88
CNS	9 (3%)	4 (1.3%)	0.26
Primary bacteremia	2 (0.7%)	8 (2.7%)	0.11
Others	10 (3.3%)	9 (3%)	>0.99
Evidence of infection			
No	18 (7%)	30 (10%)	0.09
Yes	282 (93%)	270 (90%)	
Microbiologically documented	197 (65.7%)	169 (56.3%)	0.09
Clinically documented	85 (28.3%)	101 (33.7%)	
Common causative organism			
E.coli (ESBL-ve)	19 (6.3%)	11 (3.7%)	0.19
E.coli (ESBL+ ve)	41 (13.7%)	41 (13.7%)	>0.99
K.pneumoniae (ESBL- ve)	22 (7.3%)	8 (2.7%)	0.01
K.pneumoniae (ESBL+ ve)	34 (11.3%)	37 (12.3%)	0.80
Pseudomonas aeruginosa	36 (12%)	49 (16.3%)	0.16
Acinetobacter baumannii	42 (14%)	38 (12.7%)	0.72
MSSA	14 (4.6%)	3 (1%)	0.01
MRSA	10 (3.3%)	12 (4%)	0.83
Enterococcus spp.	10 (3.3%)	10 (3.3%)	>0.99
Isolated pathogen susceptible to meropenem			
E.coli (ESBL+ ve)	37/37 (100%)	39/39 (100%)	>0.99
K.pneumoniae (ESBL+ ve)	34/34 (100%)	34/34 (100%)	>0.99
Pseudomonas aeruginosa	29/36 (80.6%)	33/47 (70.2%)	0.28
Acinetobacter baumannii	12/40 (30%)	3/37 (8.1%)	0.02

Each patient may have multiple causative organisms or multiple site of infections

same biopharmaceutical equivalence as innovator drug. Particularly for intravenous drugs, therapeutic equivalence, including effectiveness and safety, is based solely on biopharmaceutical equivalence; nevertheless, most of studies were evaluated in healthy subjects[8,9] or by *in vitro* microbiological assay[15]. Therefore, assuming therapeutic equivalence of generic as innovator drug in clinical practice should be cautious owing to heterogeneity of actual populations including co-morbidities or disease severity, particularly in critically ill patients. In addition, FDA observed significant violation of several pharmaceutical manufacturers facility from good manufacturing practice which effects to active pharmaceutical ingredient and finishing products[16,17]. There are several studies which demonstrated inferiority of a generic compared with the original drug in effectiveness. Mastoraki E, et al revealed a higher incidence of postoperative infection in adult patients undergoing CABG surgery who received generic cefuroxime compared to original drug as antimicrobial prophylaxis[18]. In addition, Rodriguez CA, et al also report treatment failure in a liver transplanted patient with MRSA peritonitis and bacteremia treated with generic vancomycin[19]. Meropenem, as a broad-spectrum antibiotic, has been widely used for treatment of critically ill patients with a variety of serious infections. The effectiveness and safety of using

Table 3. Indications of Meropenem

Indication	Original Meropenem (n = 300)	Generic Meropenem (n = 300)	p-value
No	44 (14.7%)	52 (17.3%)	
Yes	256 (85.3%)	248 (82.7%)	0.44
-Confirmed or suspected infection due to *P. aeruginosa*	106 (41.4%)	97 (39.1%)	0.49
-Severe infection due to ESBL-producing pathogens	62 (24.2%)	53 (21.4%)	0.41
-Empirical therapy for hospital-acquired infection not respond to cephalosporin, aminoglycoside, fluroquinolone, beta-lactam/ beta-lactamase inhibitor	48 (18.8%)	45 (18.1%)	0.82
-Infection due to pathogen resistant to cephalosporin, aminoglycoside, fluroquinolone, beta-lactam/ beta-lactamase inhibitor	25 (9.8%)	31 (12.5%)	0.48
-Empirical therapy for febrile neutropenia	14 (5.5%)	21 (8.5%)	0.30
-Infection due to pathogen susceptible to other antibiotic but the patient unable to receive such antibiotics	1 (0.4%)	1 (0.4%)	>0.99

Table 4. Dosage and duration of Meropenem

	All patients	Original Meropenem	Generic Meropenem	p-value
Mean Dosage (gram) per day (SD)*	2.23 (0.9)	2.16 (1)	2.30 (0.9)	0.06
Median Duration of Meropenem, day (IQR)**	8 (4-13)	7 (4-13)	9 (5-13)	0.05

*Compare mean by using Student's t-test, **Compare median by using Mann-Whitney U-test

Table 5. Concurrent antibiotics

	Original Meropenem (n = 300)	Generic Meropenem (n = 300)	p-value
No	177 (59%)	178 (59.3%)	>0.99
Yes	123 (41%)	122 (40.7%)	
Glycopepeptide	66 (22%)	62 (20.6%)	0.76
Colistin	18 (6%)	24 (8%)	0.42
Aminoglycoside	13 (4.3%)	11 (3.6%)	0.83
Quinolone	14 (4.6%)	9 (3%)	0.4
Beta-lactam	9 (3%)	6 (2%)	0.6

generic meropenem (Monem®) in clinical practice are the main concern. According to Siriraj Hospital policy, each new generic drug in the hospital formulary must be evaluated including generic meropenem; therapeutic

Table 6. Outcomes of Meropenem Therapy

	Original Meropenem (n = 300)	Generic Meropenem (n = 300)	p-value
Clinical outcome			
Favorable outcome (Cure + Improve)	189 (63%)	211 (70.4%)	0.07
Infection worse	32 (10.7%)	29 (9.7%)	0.79
Died of infection	65 (21.7%)	48 (16%)	0.09
Others	14 (4.7%)	12 (4%)	0.84
Microbiological outcome			
Eradicate	69 (23%)	89 (29.7%)	0.08
Persist	35 (11.7%)	25 (8.3%)	0.22
New organism	38 (12.7%)	29 (9.7%)	0.30
Undetermined	158 (52.7%)	157 (52.3%)	>0.99
Median length of hospital stay, day (IQR)	29 (15-47)	28.5 (14-50)	0.78
Discharge status			
Alive	181 (60.3%)	199 (66.3%)	0.15
Died of infection	67 (22.3%)	67 (22.3%)	>0.99
Died of other causes	47 (15.7%)	30 (10%)	0.05
Against advice	5 (1.6%)	4 (1.3%)	>0.99
Adverse effects			
Antibiotic allergy	2 (0.7%)	7 (2.3%)	0.09
Antibiotic-associated diarrhea	26 (8.7%)	18 (6%)	0.36
Overall mortality	114 (38%)	97 (32.3%)	0.17

equivalence of generic meropenem must also be evaluated in clinical setting and the clinical study is conducted to ensure its effectiveness and safety. Whenever generic meropenem was available in Siriraj Hospital, it would have been substituted for original meropenem. Therefore, most of original meropenem were prescribed from July 2007 to October 2008 and most of generic meropenem were prescribed from October 2008 to June 2009. The study was conducted retrospectively to demonstrate non-inferiority in effectiveness and safety of generic meropenem compared with original meropenem.

Most of characteristics of the patients in original and generic meropenem were comparable but more patients in original group had cardiovascular disease and more patients in generic group received immunosuppressive agents. Approximately 90% of infection was health-care associated. Drug-resistant gram-negative bacteria including ESBL producing *E. coli* and *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* account for nearly 50% of all organisms. Most of drug-resistant gram-negative bacteria were susceptible to meropenem except for *A. baumannii* for which more isolates in original group were susceptible to meropenem than those in generic group. Over 80% of patients received meropenem with one of the appropriate indications. The mean dose of meropenem in both generic and original group was quite lower than the recommended dose which might be the result from the older age of patients and their underlying diseases; ten to seventeen percent of patients had renal disease. However, no statistically significant difference between original and generic groups was found in term of dosage, duration and concurrent antibiotic. Regarding the outcome of meropenem therapy, generic meropenem had an overall favorable outcome 7 % higher than that of original group, but no statistically significant difference. Also no significant difference was found in terms of microbiological outcome, overall mortality and adverse events. However, only a few percent of the patients had infection of central nervous system. Thus, using generic meropenem for treatment of such infection may need further assessment. A limitation of this study is an inability to evaluate using two groups of carbapenems during the same period; therefore, an influence on treatment effect from potential confounding factor such as better supportive care over the time cannot be excluded.

From this study, generic meropenem (Monem®) showed non-inferiority in overall favorable outcome compared with original meropenem. Although this study is not a randomized controlled trial, it is

accurate enough to conclude that generic meropenem (Monem®) was not inferior to original meropenem for therapy of infections in the hospitalized patients at Siriraj Hospital.

Potential conflicts of Interest

None.

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การติดตามประสิทธิผล และความปลอดภัยของยาสามัญ meropenem ในการรักษาโรคติดเชื้อในโรงพยาบาลศิริราช

ณสิกาญจน์ อังคเศกวินัย, พีระวงษ์ วีรารักษ์, กุสุมา ไชยสูตร, วิษณุ ธรรมลิขิตกุล

วัตถุประสงค์*: โรงพยาบาลศิริราชได้มีการนำยาสามัญ meropenem (Monem®) มาใช้ทดแทนยาต้นแบบในการรักษาโรคติดเชื้อ อย่างไรก็ตามยังมีความไม่มั่นใจด้านประสิทธิผล และความปลอดภัยของยา*

วัสดุและวิธีการ*: ศึกษาข้อมูลแบบย้อนหลัง จากฐานข้อมูลยาระหว่างเดือนกรกฎาคม พ.ศ. 2550 ถึง เดือนมิถุนายน พ.ศ. 2552 โดยวิเคราะห์ข้อมูลผู้ป่วยที่มีอายุตั้งแต่ 18 ปี ขึ้นไปซึ่งถูกรับไว้รักษาในโรงพยาบาล และได้รับยา meropenem นานอย่างน้อย 48 ชั่วโมง โดยคัดเลือกผู้ป่วยที่เข้าตามเกณฑ์และได้รับยาสามัญ meropenem (Monem®) 300 ราย และยาต้นแบบ meropenem 300 ราย*

ผลการศึกษา*: ผู้ป่วยทั้งหมดมีอายุเฉลี่ย 63 ปี ส่วนใหญ่มีโรคประจำตัว โดยราวร้อยละ 90 เป็นการติดเชื้อที่เป็น health-care associated เกือบร้อยละ 50 มีการติดเชื้อแกรมลบดื้อยา ได้แก่ ESBL producing E. coli หรือ K. pneumoniae, P. aeruginosa หรือ A. baumannii โดยผู้ป่วยที่ได้รับยาต้นแบบ หรือยาสามัญ meropenem ไม่ได้มีความแตกต่างกันในด้านลักษณะพื้นฐาน ชนิดหรือตำแหน่งการติดเชื้อและเชื้อก่อโรค อย่างไรก็ตามพบว่าผู้ป่วยที่ได้รับยาต้นแบบมีโรคหัวใจและหลอดเลือดมากกว่า และผู้ป่วยที่ได้รับยาสามัญได้รับยากดภูมิคุ้มกันมากกว่าโดยผู้ป่วยที่ได้รับยา meropenem ร้อยละ 82 ถึง 85 มีข้อบ่งชี้การใช้ยาที่เหมาะสม สำหรับผลการรักษาไม่พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่มที่ได้รับยาต้นแบบและกลุ่มที่ได้รับยาสามัญ ทั้งในแง่อัตราการหายหรือดีขึ้น (ร้อยละ 63 เทียบกับ ร้อยละ 70.4, p = 0.07) อัตราการเสียชีวิต (ร้อยละ 38 เทียบกับร้อยละ 32, p = 0.17) รวมถึงผลข้างเคียงจากยา*

สรุป*: ยาสามัญ meropenem (Monem®) ไม่ด้อยกว่ายาต้นแบบ meropenem ในการรักษาโรคติดเชื้อในผู้ป่วยที่รับไว้ในโรงพยาบาลศิริราช*