Microbiological Equivalence of Serum Bacteriostatic and Bactericidal Activities of the Sera from Healthy Volunteers Receiving Original Meropenem (Meronem^{R}) and Generic Meropenem (Mero^{R})

Visanu Thamlikitkul MD*,
Surapee Tiengrim MSc*, Chalobol Chalermsri MD**,
Pornsiri Chinsawangwatanakul MSc**, Siriluk Suddhichupaiboon MSc***

** Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Office for Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
**** Siriraj Hospital, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Several generic meropenem formulations have been approved by Thai Food and Drug Administration, Ministry of Public Health since 2008. Meropenem is a parenteral drug. Therefore, a study demonstrating a biological equivalence of generic meropenem is not required for drug registration in Thailand. The objective of the study was to determine microbiological equivalence of serum bacteriostatic and bactericidal activities of the sera from healthy volunteers receiving original meropenem (Meronem^{R}) and generic meropenem (Mero^{R}).*

Material and Method: *This was a randomized crossover study in 16 adult healthy volunteers. Each subject received one gram of Meronem^{R} and Mero^{R} in 50 ml of normal saline via intravenous infusion for 30 minutes. The blood samples were drawn at baseline prior to receiving the study drug, at 30 minutes after initiating infusion, and at 8 hours after initiating infusion. The serum bacteriostatic activity against E. coli ATCC 25922, K. pneumoniae, P. aeruginosa ATCC 27853 and A. baumannii was performed by disk diffusion The serum bactericidal activity against E. coli ATCC 25922 was performed by Serum Bactericidal Titre.*

Results: *The average inhibition zone diameter of the serum samples from the subjects while receiving Mero^{R} against each tested organisms was < 1 mm smaller than that while receiving Meronem^{R} and such difference was not significantly different. All serum samples taken at 30 minutes after initiating Meronem^{R} and Mero^{R} had bactericidal titres against E. coli ATCC 25922 $\geq$ 1:256. Only 3 serum samples taken from the subjects while receiving Mero^{R} at 8 hours had less bactericidal titre for 1-fold dilution when compared with that of Meronem^{R}.*

Conclusion: *The sera from healthy volunteers receiving Meronem^{R} and Mero^{R} had microbiological equivalence in terms of serum bacteriostatic and bactericidal activities.*

Keywords: *Microbiological Equivalence, Generic Drug, Meropenem*

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Meropenem is antibacterial agent of the carbapenems[1]. Meropenem has a broad spectrum of in vitro activity against Gram-positive and Gram-negative pathogens, including extended-spectrum beta-lactamase (ESBL)- and Amp C-producing Enterobacteriaceae, *Pseudomonas aeruginosa* and anaerobes. Meropenem is indicated in complicated intra-abdominal infection, complicated skin and skin structure infection, bacterial meningitis, nosocomial pneumonia, septicaemia, febrile neutropenia, complicated urinary tract infection, obstetric and gynaecological infections

Correspondence to: Thamlikitkul V, Division of Infectious Disease, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. E-mail sivth@mahidol.ac.th

as well as empiric therapy of gram negative nosocomial infections and febrile neutropenia. Meropenem is a member drug in category D of the national drug list of Thailand. At Siriraj Hospital, meropenem is approved to be used for 1) confirmed or suspected infection due to *P. aeruginosa*, 2) infection due to pathogen resistant to cephalosporins, aminoglycosides and fluoroquinolones, 3) empiric therapy for febrile neutropenia, 4) infection due to the pathogen susceptible to other antibiotics but when the patient is unable to receive such antibiotics, 5) empiric therapy of nosocomial infection not responding to other antibiotics, 6) infection due to pathogen resistant to a combination of beta-lactam and beta-lactamase inhibitor and 7) severe infection due to extended spectrum beta-lactamase (ESBL)-producing pathogens.

The original product of meropenem is Meronem^{R} from an innovator pharmaceutical company that has been used in Siriraj Hospital for many years. The cost of the original meropenem in Thailand is still high. In 2008, several generic products of meropenem were approved by Thai Food and Drug Administration (FDA), Ministry of Public Health and became available in many hospitals. Meropenem is a parenteral drug. Therefore, a study demonstrating a biological equivalence of generic meropenem is not required for drug registration in Thailand. Although several generic formulations of meropenem had shown biological equivalence to original formulation of meropenem[2,3], both original and generic formulations may not have microbiological equivalence in terms of bacteriostatic and bactericidal activities.

The objective of the study was to determine microbiological equivalence of bacteriostatic and bactericidal activities of the sera from healthy volunteers receiving original meropenem (Meronem^{R}) and generic meropenem (Mero^{R}).

Material and Method

The study was approved by Siriraj Institutional Review Board and it was conducted at Siriraj Clinical Research Center and Microbiology Laboratory of Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital.

Study Population

The study was conducted in the volunteers aged 18 to 45 years who had a body mass index of 18 to 25 kg/m^2. All subjects were healthy, had no history of beta-lactam allergy and had not received any medications over the past 14 days prior to receiving the study drugs. It was estimated that 16 subjects were needed, based on the assumptions that the difference in the average inhibition zone diameters of the sera from healthy volunteers receiving original meropenem and generic meropenem was within 2 mm; a standard error of inhibition zone diameter was 2 mm with 5% type I and 20% type II error.

Study Medications

The original meropenem was Meronem^{R} (AstraZeneca Co Ltd) and the generic meropenem was Mero^{R} (Swiss Parenteral Co Ltd). Each subject received one gram of Meronem^{R} and Mero^{R} in 50 ml of normal saline via intravenous infusion for 30 minutes.

Study Procedures

Clinical Study

This was a randomized crossover study with a wash-out period of 7 days. Each subject had 20 ml of blood samples drawn at baseline prior to receiving the study drug, at 30 minutes after initiating meropenem infusion and at 8 hours after initiating meropenem infusion. The sera were separated and kept at -70°C before microbiological testing. Each subject was asked about any new symptoms experienced while receiving the study drugs.

Microbiological Study: Serum Bacteriostatic Activity by Disk Diffusion

The test was undertaken on the plate containing 10 ml of Mueller Hinton agar (Oxoid, UK) with 10^5 CFU/ml of *E. coli* ATCC 25922, *Klebsiella pneumoniae* (clinical isolate), *Pseudomonas aeruginosa* ATCC 27853 and *Acinetobacter baumannii* (clinical isolate). All bacterial isolates were susceptible to meropenem with minimum inhibitory concentration (MIC) of meropenem of 0.012, 0.016, 0.094 and 0.19 mg/l for *E. coli* ATCC 25922, *K. pneumoniae*, *P. aeruginosa* ATCC 27853 and *A. baumannii* respectively. Four blank paper disks with diameter of 6 mm were placed on Mueller Hinton agar plate. Twenty-five microlitres of the sera taken from the same subject at the same blood drawing point were inoculated on the blank paper disks on the same plate. The plate was incubated at 35□C for 16 to 18 hours. The inhibition zone diameter was measured by vernier caliper and recorded.

Microbiological Study : Serum Bactericidal Activity by Serum Bactericidal Titre

Each serum sample was diluted with the pool

serum samples taken from all subjects prior to receiving the study drug in order to achieve the final dilution titres from 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128 and 1:256. Each test tube contained 0.5 ml of the diluted serum sample and it was inoculated with 0.5 ml of *E. coli* ATCC 25922 at 10^5 CFUs/ml. The tube containing serum sample and bacteria was incubated at 35°C for 16 to 18 hours. Then, 10 microlitre of the inoculated serum sample was inoculated onto blood agar plate and the plate was incubated at 35°C for 16 to 18 hours. A serum bactericidal activity was present if ≤ 5 bacterial colonies were found on the blood agar plate (≥ 99.5% bacterial killing).

Data Analysis

The inhibition zone diameters were compared by student t-test.

Results

Serum Bacteriostatic Activity

The average inhibition zone diameters of the serum samples from the subjects while receiving Meronem^R and Mero^R against *E. coli* ATCC 25922, *K. pneumoniae*, *P. aeruginosa* ATCC 27853 and *A. baumannii* are shown in Table 1 to 4. The average inhibition zone diameters of the serum samples from the subjects while receiving Mero^R against each tested bacteria was ≤ 1 mm smaller than that from the subjects while receiving Meronem^R. The difference of the average inhibition zone diameters of the serum samples from the subjects while receiving Meronem^R and Mero^R was not significantly different.

Serum Bactericidal Activity

Bactericidal activity of the serum samples from the subjects while receiving Meronem^R and Mero^R against *E. coli* ATCC 25922 are shown in Table 5 and 6. All serum samples collected at 30 minutes after initiating Meronem^R and Mero^R had bactericidal titres ≥1:256. Only 3 serum samples taken from the subjects while receiving Mero^R at 8 hours had less bactericidal titre for 1-fold dilution when compared with that of Meronem^R.

Adverse Events

Five subjects had adverse events (back pain, dizziness, headache, pain at injection site) while receiving Meronem^R. Two subjects had adverse events (dizziness, hypotension) while receiving Mero^R. All adverse events were mild and transient without any specific treatments.

Discussion

An ideal generic drug product is one that is chemically equivalent, bioequivalent and therapeutically equivalent to an innovator or first version of the

Table 1. Serum bacteriostatic activity against *E. coli* ATCC 25922

Drug	Mean (standard deviation) of inhibition zone (mm)		
	Baseline	30 min after initiating infusion	8 h after initiating infusion
Meronem^R	no zone	29.4 (3.2)	10.6 (2.6)
Mero^R	no zone	29.2 (3.0)	10.1 (3.1)
p		0.88	0.62

Table 2. Serum bacteriostatic activity against *Klebsiella pneumoniae*

Drug	Mean (standard deviation) of inhibition zone (mm)		
	Baseline	30 min after initiating infusion	8 h after initiating infusion
Meronem^R	no zone	16.0 (1.3)	7.8 (1.9)
Mero^R	no zone	15.6 (0.9)	7.7 (2.1)
p		0.36	0.85

Table 3. Serum bacteriostatic activity against *Pseudomonas aeruginosa* ATCC 27853

Drug	Mean (standard deviation) of inhibition zone (mm)		
	Baseline	30 min after initiating infusion	8 h after initiating infusion
Meronem^{R}	no zone	33.8 (1.9)	no zone
Mero^{R}	no zone	33.1 (1.7)	no zone
p		0.33	

Table 4. Serum bacteriostatic activity against *Acinetobacter baumannii*

Drug	Mean (standard deviation) of inhibition zone (mm)		
	Baseline	30 min after initiating infusion	8 h after initiating infusion
Meronem^{R}	no zone	22.7 (1.9)	no zone
Mero^{R}	no zone	22.5 (1.7)	no zone
p		0.82	

Table 5. Serum bactericidal titre against *E. coli* ATCC 25922 from the subjects receiving Meronem^{R}

Subject	Baseline	30 min after initiating infusion	8 h after initiating infusion
1	< 1 : 2	> 1 : 256	1 : 4
2	< 1 : 2	> 1 : 256	1 : 8
3	< 1 : 2	> 1 : 256	1 : 8
4	< 1 : 2	> 1 : 256	1 : 4
5	< 1 : 2	> 1 : 256	1 : 4
6	< 1 : 2	> 1 : 256	1 : 8
7	< 1 : 2	> 1 : 256	1 : 2
8	< 1 : 2	> 1 : 256	1 : 4
9	< 1 : 2	> 1 : 256	1 : 4
10	< 1 : 2	> 1 : 256	1 : 8
11	< 1 : 2	> 1 : 256	1 : 8
12	< 1 : 2	> 1 : 256	1 : 2
13	< 1 : 2	> 1 : 256	1 : 2
14	< 1 : 2	> 1 : 256	1 : 4
15	< 1 : 2	> 1 : 256	1 : 4
16	< 1 : 2	> 1 : 256	1 : 8

drug product approved by the FDA. If a generic drug is clearly shown to be chemically equivalent, bioequivalent and therapeutically equivalent to an original drug, it can be substituted for the original product with much lower cost. Although the randomized controlled trial of generic meropenem is ideal for assessing a therapeutic equivalence, it is not feasible because the study needs a large number of patients, has a very high cost and requires a long duration of study. Moreover, the data on therapeutic equivalence of generic drug from randomized controlled trials are not required for drug registration with Thai FDA. Neither is bioequivalence study of a generic intravenous drug required for drug registration. Bioequivalence study of an oral generic drug is mandatory for drug registration in Thailand. Measurement of serum levels or a

Table 6. Serum bactericidal titre against *E. coli* ATCC 25922 from the subjects receiving Mero^{R}

Subject	Baseline	30 min after initiating infusion	8 h after initiating infusion
1	< 1 : 2	> 1 : 256	1 : 4
2	< 1 : 2	> 1 : 256	1 : 8
3	< 1 : 2	> 1 : 256	1 : 4*
4	< 1 : 2	> 1 : 256	1 : 4
5	< 1 : 2	> 1 : 256	1 : 4
6	< 1 : 2	> 1 : 256	1 : 4*
7	< 1 : 2	> 1 : 256	1 : 2
8	< 1 : 2	> 1 : 256	1 : 2*
9	< 1 : 2	> 1 : 256	1 : 4
10	< 1 : 2	> 1 : 256	1 : 8
11	< 1 : 2	> 1 : 256	1 : 8
12	< 1 : 2	> 1 : 256	1 : 2
13	< 1 : 2	> 1 : 256	1 : 2
14	< 1 : 2	> 1 : 256	1 : 4
15	< 1 : 2	> 1 : 256	1 : 4
16	< 1 : 2	> 1 : 256	1 : 8

* serum bactericidal titre was 1-fold dilution less than that while receiving Meronem^{R}

bioequivalence study of non-antibiotic generic drugs is logical since their activity is quite difficult to determine. However, antimicrobial activity of generic antibiotics can be easily determined and their antimicrobial activity can be compared with that of the original antibiotic. This type of study could be called microbiological equivalence. Zuluaga AF et al reported an application of microbiological assay to determine pharmaceutical equivalence of generic intravenous antibiotics[4]. The proposed method was based on the concentration-dependent variation of the inhibitory effect of antibiotics on reference bacteria (*B. subtilis* ATCC 6633, *S. aureus* ATCC 6538p and *S. epidermidis* ATCC 12228) in a seeded agar, producing a concentration-response linear relationship with two parameters: y-intercept (concentration) and slope (potency). The proposed method allowed rapid, cost-saving, precise, and accurate determination of pharmaceutical equivalence of drugs in pharmaceutical dosage-form, and may be used as a technique for testing generic antibiotics prior to their approval for human use. However, such a proposed method is still an in vitro test and its results may not reflect microbiological activity in vivo. The method used in our study should be more valid because 1) we used the serum samples collected from the subjects who received original and generic antibiotics instead of using the original and generic drugs for direct testing, 2) we used the organisms that were the target of the study drug, and 3) we determined bactericidal activity in addition to bacteriostatic activity. We proposed serum bactericidal activity assay as a method to determine microbiological equivalence because the serum bactericidal titres were found to be associated with microbiological and clinical outcomes of treatment of several bacterial infections in some other studies[5-10].

The methodology for determining serum bacteriostatic activity by disk diffusion was simple and more practical than the method that made a hole on agar for inoculating the serum[3]. The inhibition zone of meropenem against *E. coli* ATCC 25922 from the serum at 30 minutes and 8 hours after initiating meropenem infusion in our study was smaller because the volume of the serum sample used in our study was only 50% of that from another study[3]. For more resistant organisms, *i.e. P. aeruginosa* and *A. baumannii*, we were unable to detect the inhibition zone because the amount of the serum sample was too small. Therefore, a larger blank paper disk as well as more volume of serum would be needed in order to determine the inhibition zone at 8 hours after initiating meropenem infusion. However, the detected inhibition zones of Meronem^{R} and Mero^{R} were not statistically or clinically different.

The methodology for determining serum bactericidal activity by serum bactericidal titre was also simple and practical. Since we used a very susceptible organism (*E. coli* ATCC 25922 with meropenem MIC of 0.012 mg/l), we were able to detect very high serum bactericidal titres at 30 minutes after initiating mero-

penem infusion (≥ 1:256) and lower titres (1:2 to 1:8) at 8 hours after initiating meropenem infusion. The exact serum bactericidal titres were not observed because we did not prepare the serum samples with more dilution than 1:256. Therefore, one should be aware of this observation and should prepare the serum samples for at least 2 more dilutions, *i.e.* 1:512 and 1:1,024 for future testing. However, it was observed that serum bactericidal titre ≥1:8 was sufficient to achieve a favourable treatment outcome[5-10]. We observed that three serum samples taken from the subjects while receiving Mero^{R} at 8 hours had lower bactericidal titre when compared with that of Meronem^{R}. This should be considered as a non-significant difference since a difference was only 1-fold dilution and it could be simply due to a technical problem from diluting the sample. However, several serum samples taken from the subjects while receiving Meropenem at 8 hours had serum bactericidal titre of only 1:2 and such titre could be less than this if the organism was more resistant. Therefore, if one wants to have a higher trough serum bactericidal titre, the dose of meropenem should be more than 1 gram, or the dosage interval should be less than 8 hours, or meropenem should be given as prolonged infusion or continuous infusion. It should be mentioned that prolonged infusion of meropenem or continuous infusion of meropenem was associated with better pharmacodynamics and better clinical outcomes when compared with a conventional dose of meropenem given as intermittent intravenous injection[11,12].

We found that the methodology used for determining microbiological equivalence of a generic antibiotic was more relevant, simpler, less expensive and less time consuming than a conventional bioequivalence study. Therefore, microbiological equivalence of generic antibiotics in terms of bacteriostatic and bactericidal activities should be substituted for bioequivalence study when a therapeutic equivalence study is not feasible.

In conclusion, the sera from healthy volunteers receiving Meronem^{R} and Mero^{R} had microbiological equivalence in terms of serum bacteriostatic and bactericidal activities.

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ความเท่าเทียมกันของฤทธิ์ยับยั้งเชื้อและฤทธิ์ทำลายเชื้อแบคทีเรียโดยซีรั่มของอาสาสมัครที่ได้รับยาต้นแบบเมอโรพีเนม (เมอโรเนม) และยาสามัญเมอโรพีเนม (เมอโร)

วิษณุ ธรรมลิขิตกุล, สุรภี เทียนกริม, ชโลบล เฉลิมศรี, พรสิริ ชินสว่างวัฒนกุล, ศิริลักษณ์ สุทธิชูไพบูลย์

***บทนำ**: ยาสามัญ meropenem หลายขนานได้รับการรับรองจากคณะกรรมการอาหารและยา กระทรวงสาธารณสุข ตั้งแต่ พ.ศ. 2551 ยา meropenem เป็นยาฉีดเข้าหลอดเลือดดำ ดังนั้น การขึ้นทะเบียนยาดังกล่าวจึงไม่ต้องมีข้อมูลชีวสมมูลของยา การศึกษานี้มีวัตถุประสงค์เพื่อทราบความเท่าเทียมกันทางจุลชีววิทยาของยาต้นแบบ meropenem (Meronem^{R}) กับยาสามัญ meropenem (Mero^{R}) ในการยับยั้งและทำลายแบคทีเรีย*

***วิธีการศึกษา**: การศึกษานี้เป็นการศึกษาชนิด randomized crossover ในอาสามัครสุขภาพแข็งแรงจำนวน 16 คน อาสาสมัครแต่ละคนได้รับยา Meronem^{R} และ Mero^{R} ขนาด 1 กรัมผสมในน้ำเกลือ 50 มล หยดเข้าหลอดเลือดดำนาน 30 นาที ซีรั่มจากอาสามัครเก็บก่อนได้รับยา ที่ 30 นาทีหลังเริ่มยา และที่ 8 ชั่วโมงหลังเริ่มยานำไปทดสอบฤทธิ์ยับยั้งเชื้อ E. coli ATCC 25922, K. pneumoniae, P. aeruginosa ATCC 27853 และ A. baumannii ด้วยวิธี disk diffusion และฤทธิ์ทำลายเชื้อแบคทีเรีย E. coli ATCC 25922 ด้วยวิธี Serum Bactericidal Titre*

***ผลการศึกษา**: ขนาดเฉลี่ยของ inhibition zone diameter ของซีรั่มจากอาสาสมัครขณะได้รับ Mero^{R} ต่อเชื้อแบคทีเรียทุกชนิดมีขนาดเล็กกว่าณะที่ได้รับ Meronem^{R} น้อยกว่า 1 มม และความแตกต่างนี้ ไม่มีนัยสำคัญทางสถิติ ซีรั่มที่เก็บจากอาสาสมัครทุกรายที่ 30 นาทีหลังเริ่มยามีฤทธิ์ทำลายเชื้อแบคทีเรีย E. coli ATCC 25922 ≥ 1:256 มีซีรั่มที่เก็บจากอาสาสมัคร 3 ราย ขณะได้รับ Mero^{R} ที่ 8 ชั่วโมง มีฤทธิ์ทำลายเชื้อแบคทีเรีย E. coli ATCC 25922 น้อยกว่าขณะได้รับ Meronem^{R} 1 ความเจือจาง*

***สรุป**: ซีรั่มจากอาสาสมัครขณะได้รับ Meronem^{R} และ Mero^{R} มีความเท่าเทียมกันทางจุลชีววิทยาในการยับยั้งเชื้อและทำลายเชื้อแบคทีเรีย*