

Bioequivalence Study with Comparative Antibacterial Activity of a Generic Meropenem

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ABSTRACT

Bioequivalence with antibacterial activity was comparatively studied with a generic meropenem (Enem[®]) and an original Meronem[®], employing a randomized, open-label, crossover study, in twenty-six healthy males recruited at Siriraj Hospital, Thailand. The duration of one-gram intravenous infusion was 30 minutes, and the washout period was one week. Fourteen blood samples were collected before and at prescheduled intervals after meropenem infusion. Blood samples were coded and separated into plasma and serum samples for blind analyses. Plasma concentrations were determined by validated method using high-pressure liquid chromatography-ultraviolet (HPLC-UV) detector. Serum inhibition test was used to indicate antibacterial activity using *Escherichia coli* ATCC 25922, and the results were measured in term of the inhibitory zone size. The statistical analysis of the means and 90-percent confidence interval of geometric mean ratio of peak concentration (C_{max}), area under concentration curve (AUC_{0-t}), and AUC_{0-inf} were 95.1401 (88.7502-101.9902%), 97.8434 (94.1017-101.7340%), and 97.3817 (93.6596-101.2517%), respectively. The results were within the standard range of bioequivalence acceptance criteria (80-125%). Serum inhibitory zone sizes of both generic and original meropenems were similar with respect to the times of blood collections and their widths, and exhibited a curvature relation with the corresponding plasma levels. We concluded from this study that the generic meropenem (Enem[®]) exhibited similar antibacterial activity and pharmacokinetic equivalence, compared to the original meropenem. (*J Infect Dis Antimicrob Agents* 2008;25:63-72.)

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INTRODUCTION

Meropenem is a highly potent carbapenem antibiotic with a broad-spectrum activity against most Gram-positive and Gram-negative bacteria.¹ Its antibacterial activity also expands to cover almost all clinically relevant aerobic, nutritionally fastidious, and anaerobic bacteria. Therefore, meropenem is commonly used for empirical therapy of serious or drug-resistant infections, most notably bacterial meningitis in pediatric patients with a relatively good safety profile.² In addition, the drug molecule is not significantly destroyed by renal dehydropeptidase enzyme, hence a coadministration with a renal dehydropeptidase-1 inhibitor is not necessary.

The generic version of meropenem is now available in Thai market. Although bioequivalence study is not required by law for a generic, intravenous meropenem, it is prudent for the company to perform the pharmacokinetic study as those drugs with other administration routes³, as the last step of quality assurance before launching in Thai market. Since a randomized double-blinded control trial to demonstrate a "clinical equivalence" is impossible to perform with a generic meropenem, we sought a proxy study which is additional to the bioequivalence study, to compare the "antibacterial equivalence" of the generic with the original meropenem. The method we choose is to perform the serum inhibition test using the same blood samples for bioequivalence study after the drug has been infused intravenously. The antibacterial activity exhibited by an *in vitro* serum inhibition test would be the result of drug potency and stability after the drug went through the preparation process, and was diluted and infused patient's into the circulation. We also aimed to correlate serum concentrations and inhibitory zone sizes of the same blood samples collected at each period of time in order to show if any relationship can be established for either generic or original meropenem.

MATERIALS AND METHODS

A generic meropenem from MacroPhar Co. Ltd. lot EN001 Mfg. date 06/2006 (Enem[®], MacroPhar Co., Ltd.) was used as the generic or test product and compared with Meronem[®] of AstraZeneca Ltd. lot DV826 Mfg. date 02/2006 as the original or reference product. The study protocol was approved by the Ethics Committee (SiEC protocol no. 403/2549), and written informed consent was obtained from each volunteer prior to participation in the study.

An open-label, randomized, crossover, single-dose study, using two periods, two sequences, with a washout period of 7 days, was carried out.⁴ Twenty-six Thai male volunteers, age between 20 and 40 years were recruited at Siriraj Hospital, Thailand. Their healthy conditions were assessed by medical history, clinical examination, and blood chemistry analysis. All subjects were randomly assigned to firstly receive either generic or original one-gram, single-dose of meropenem, intravenously infused for 30 minutes with an infusion pump and vice versa for the second period. Serial 10 milliliters of blood samples were collected from each volunteer at before; and 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 470, and 480 minutes after the initial infusion. Blood samples were kept in the heparinized and ordinary tubes, coded and separated into plasma and serum specimens and stored at -80°C until analysis. The determination of plasma concentration was performed at Faculty of Pharmacy, Department of Pharmacy, Mahidol University, according to the method described by Ozkan and colleagues.⁵ In brief, plasma samples were extracted by the protein precipitation method, using cold methanol and evaporating until dry. Then, they were reconstituted by the mobile phase of 15 mM KH₂PO₄/acetonitrile/methanol (8:12:4 v/v/v) at pH of 2.8. Then, plasma samples were injected into the reversed-phase high-pressure liquid chromatography system, using the mobile phase of 15 mM KH₂PO₄/

acetonitrile/methanol (8:12:4 v/v/v) pH of 2.8, with the flow rate of 1.0 mL/minute. The separation was achieved on an ODS C18 analytical column. Meropenem was quantitated by measuring the ultraviolet (UV) absorbance at 296 nm. This bioanalytical method was validated for specificity, linearity, precision/accuracy, and recovery based on the United States Food and Drug Administration (FDA) Guidance for Industry Bioanalytical Method Validation before testing.⁴ The noncompartmental analysis will be applied for the pharmacokinetic analysis to determine the peak concentration (C_{max}), time to peak concentration (T_{max}), area under concentration curve (AUC_{0-inf}), and AUC_{0-t} . The parameter values were log transformed for the statistical analysis, and 90-percent confidence interval (CI) of difference or ratio (log transformed parameter) of the parameters were calculated for comparison under nonequivalence null hypothesis. In order to achieve the pharmacokinetic bioequivalence criteria, the 90-percent CI of the ratio of the log transformed parameters should be contained in the range of 80.00-125.00 percent.

Serum inhibition bioassay was blindly performed indicate to active ingredient's activity of both the generic and original meropenems. In brief, three milliliters of Muller Hinton broth (Difco) containing meropenem-susceptible *Escherichia coli* ATCC 25922 at concentration of 1×10^8 colony-forming units (CFUs) per milliliter was mixed thoroughly with 300 milliliters of Muller Hinton agar at 50°C. Then, 15 milliliters of the mixture were poured over sterile petri dish with a diameter of 90 millimeters. The dish was left to cool down and form agar at room temperature for 30 minutes. Then, a cox borer with 7 millimeters in internal diameter was used to punch holes with 28 millimeters apart in one agar plate. Then, 50 microliters of serum samples collected at the same time point from the same volunteer either receiving

generic or original meropenem, were added in triplicate into the alternative wells on the same dish. The dishes were incubated for 18 hours at 37°C. Then, they were inverted, and the diameters of inhibitory zones were read with a vernier caliper through the back of the dish to the nearest 0.1 millimeter. Then, the serum inhibitory zone sizes exhibited by serum samples from generic or original meropenem at the same period of collections were averaged and compared to show the level of similarity of potency. The correlation between serum meropenem levels and the inhibitory zone sizes of the same generic or original samples collected at each interval was determined to indicate the level of causal strength and direction of a linear relationship between the two variables.

RESULTS

All twenty-six Thai healthy male volunteers, age between 20 and 40 years completed the open-label, randomized, crossover, single-dose study without any notable adverse reaction. The non-compartmental analysis for pharmacokinetic study revealed that the values for average geometric means of AUC_{0-inf} , AUC_{0-t} , C_{max} , half life ($T_{1/2}$), and terminal elimination rate constant (λ_z) of serum samples from the volunteers receiving the original (reference, R) product were 82.2 mg/L.hr (9.47%), 80.4 mg/L (9.44%), 49.5 mg/L (28.4%), 0.920 hr (27.2%), and 0.753 hr⁻¹ (27.2%), respectively. The values for average geometric mean (CV%) of AUC_{0-inf} , AUC_{0-t} , C_{max} , $T_{1/2}$, and terminal elimination rate constant (λ_z) of serum samples from the volunteers receiving the generic (test T) product were 80.0 mg/L (12.4%), 78.7 mg/L (12.6%), 47.1 mg/L (23.3%), 0.952 hr (23.7%), and 0.728 hr⁻¹ (23.7%), respectively. The details of other parameters are shown in Table 1. The average plasma concentrations over time profile are plotted (normal and semi-log plots) and shown with their standard errors in Figure 1. The ANOVA of the cross-

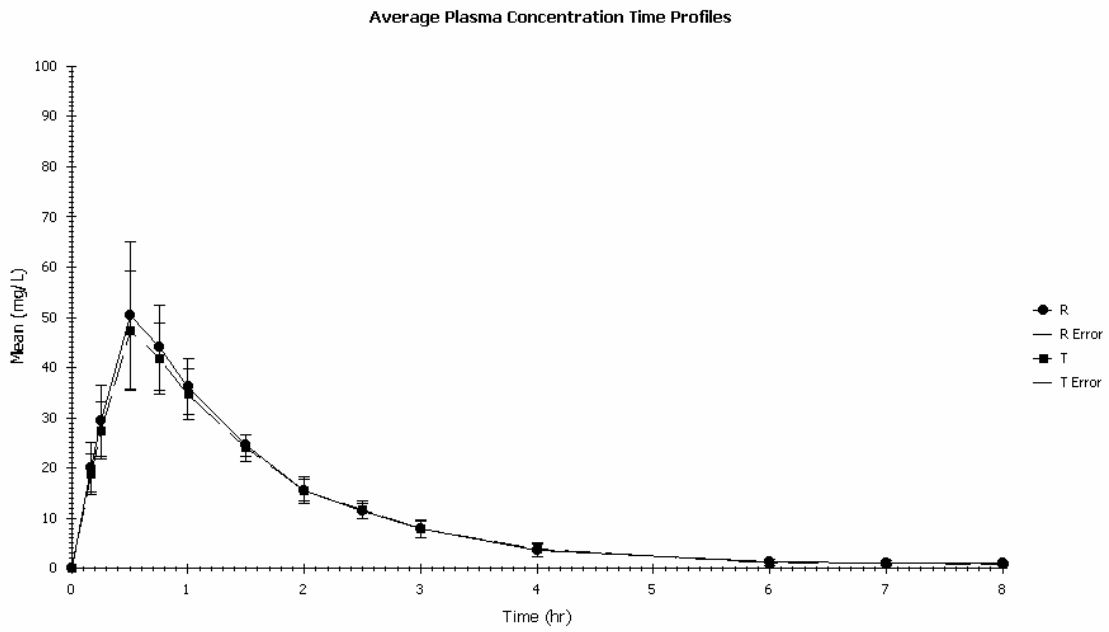
Table 1. Comparison of pharmacokinetic (PK) parameters after one gram, intravenous infusion in 26 volunteers between the generic (Enem®) and original meropenems (Meronom®).

| | Enem® | | | | Meronom® | | | |
|-----------------------|-----------------------------|----------------------------|--------------------------------------|--|-----------------------------|----------------------------|--------------------------------------|--|
| | C _{max} (µg/ml) | T _{max} (hour) | AUC _{0-t} (µg.mintue/mL) | AUC _{0-inf} (µg.minute/mL) | C _{max} (µg/mL) | T _{max} (hour) | AUC _{0-t} (µg.minute/mL) | AUC _{0-inf} (µg.minute/mL) |
| Mean | 48.3 | 0.538 | 79.3 | 80.6 | 51.4 | 0.538 | 80.7 | 82.5 |
| SD | 11.0 | 0.092 | 9.78 | 9.78 | 13.8 | 0.092 | 7.56 | 7.74 |
| SE | 2.16 | 0.018 | 1.92 | 1.92 | 2.70 | 0.018 | 1.48 | 1.52 |
| Min | 28.5 | 0.50 | 57.4 | 58.5 | 28.7 | 0.50 | 65.2 | 66.2 |
| Median | 47.2 | 0.50 | 80.1 | 81.2 | 50.2 | 0.50 | 80.2 | 82.1 |
| Max | 71.1 | 0.75 | 99.3 | 99.9 | 78.1 | 0.75 | 94.7 | 97.8 |
| CV (%) | 22.8 | 17.1 | 12.3 | 12.1 | 26.8 | 17.1 | 9.36 | 9.37 |
| Geometric mean | 47.1 | 0.532 | 78.7 | 80.0 | 49.5 | 0.532 | 80.4 | 82.2 |
| CV (%) geometric mean | 23.3 | 15.0 | 12.6 | 12.4 | 28.4 | 15.0 | 9.44 | 9.47 |

C_{max}: peak concentration, T_{max}: time to peak concentration, AUC: area under concentration curve, SD: standard deviation,

MIN: minimum, CV: coefficient variance, SE: standard error

A. Normal plot



B. Semilog plot

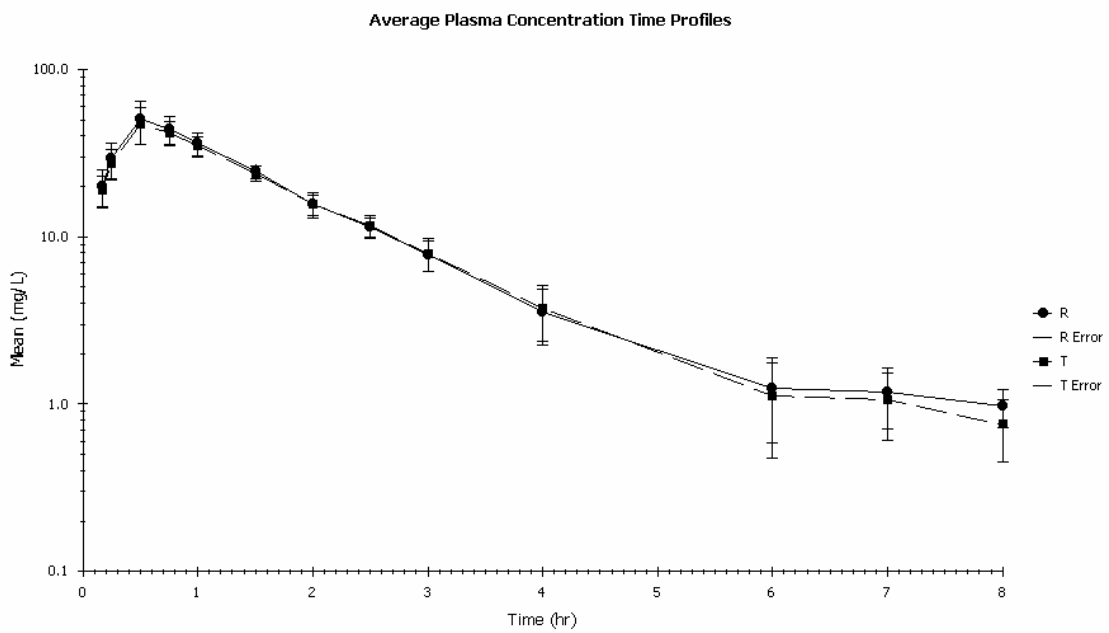


Figure 1. Average \pm standard error of plasma concentrations over time profile of meropenems in the study for all 26 volunteers.

over study revealed non-significant difference between the two groups in terms of the sequence, period, and treatment, with the exception of the subject nested in sequence which is not unusual in a study with small sample size. The ratio and 90-percent CI of the means and geometric means of C_{max} , $AUC_{0 \rightarrow \infty}$, and $AUC_{0 \rightarrow t}$ between the generic and original meropenems were 0.9514 (0.887502-1.019902), 0.9738 (0.936596-1.012517), and 0.9784(0.941017-1.017340), respectively; and fell in the range of 0.80-1.25 or 80.00-125.00 percent. Therefore, the two products were bioequivalent, according to the standard criteria.

The diameters (milliliter) of the inhibitory zone sizes exhibited by the generic and original meropenems are shown in details in Table 2. The comparison of the diameters between both groups at the same time points revealed almost the identical average values, and the minute differences were not statistically significant by a paired T-test. The homogeneity of the variance for each pair of serum samples was demonstrated, using Levene's test for equality of variances. Therefore, the antibacterial activities of the generic and original meropenems were comparable at least up to eight hours after intravenous infusion.

DISCUSSION

Although the bioequivalence study must be performed for a new generic antimicrobial in every formulation except the intravenous formulation, it would be prudent for the local manufacturer of generic antimicrobial to provide physicians with the results of the bioequivalence study of a new generic antimicrobial if it is being launched for the first time in the market. The study that shows the bioequivalence between the generic and original products can assure prescribers the quality of the generic product prescribed to their patients, especially for the treatment of serious infections. This point is well illustrated in this study.

All volunteers completed the whole study without any adverse reaction. Plasma concentrations at each interval and pharmacokinetic parameters of the generic and original meropenems were comparable without the significant difference. In addition, the antibacterial activity of the generic meropenem was also determined and compared with that of the original meropenem, using the inhibitory zone sizes as the parameters for the comparison. The results of the assessment of antibacterial activity together with the bioequivalence study help confirm the similarity of biological activity of active ingredients containing in both meropenems. Although meropenem is not the drug that must be given in very precise amount or less likely to be interchangeable with other brands of the same product, we were indeed satisfied with the small non-significant difference of the pharmacokinetic parameters and antimicrobial and antibacterial activities between the two studied drugs. Legally, the bioequivalence of different companies of an antimicrobial can vary by up to 20 percent, because for most antimicrobials, such variation does not noticeably alter the effectiveness or safety. However, we believe that the actual differences between the generic and original antimicrobials should be made much smaller than the allowable 20 percent if the quality of a generic product is of paramount concern by the local manufacturer. This study showed that the actual differences are typically only about or less than 5 percent on average, and rarely exceed 10 percent when pharmacokinetic parameters and antibacterial activities were taken into account. We acknowledge that a bioequivalence study can not substitute for a clinical trial since that type of study aims to prove that the drug is safe and effective in the real world. A clinical study of a new drug is much more complex and requires a large number of participants and is more expensive and time-consuming to perform, hence we try to gain more informations by studying the antibacterial activity

Table 2. Serum concentrations ($\mu\text{g/mL}$) and the inhibitory zone sizes (mm) exhibited by serum samples of Enem[®] and Meronem[®] at each period of sample collections.

| Minutes after infusion | Concentration of Enem [®] | | Inhibitory zone size of Enem [®] | | Concentration of Meronem [®] | | Inhibitory zone size of Meronem [®] | |
|------------------------|---|-------------------------|---|-------------------------|---|-------------------------|--|--|
| | ($\mu\text{g/mL}$) (mean \pm SD) | (mm) (mean \pm SD) | ($\mu\text{g/mL}$) (mean \pm SD) | (mm) (mean \pm SD) | ($\mu\text{g/mL}$) (mean \pm SD) | (mm) (mean \pm SD) | | |
| 0* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 10 | 18.82 \pm 4.00 | 25.36 \pm 3.63 | 20.11 \pm 4.94 | 25.44 \pm 3.94 | 20.11 \pm 4.94 | 25.44 \pm 3.94 | 25.44 \pm 3.94 | |
| 15 | 27.48 \pm 5.71 | 30.27 \pm 4.30 | 29.33 \pm 7.12 | 30.83 \pm 3.06 | 29.33 \pm 7.12 | 30.83 \pm 3.06 | 30.83 \pm 3.06 | |
| 30 | 47.38 \pm 11.95 | 31.20 \pm 3.85 | 50.34 \pm 14.68 | 31.96 \pm 2.89 | 50.34 \pm 14.68 | 31.96 \pm 2.89 | 31.96 \pm 2.89 | |
| 45 | 41.81 \pm 7.03 | 31.04 \pm 2.64 | 44.01 \pm 8.44 | 31.55 \pm 2.46 | 44.01 \pm 8.44 | 31.55 \pm 2.46 | 31.55 \pm 2.46 | |
| 60 | 34.74 \pm 4.99 | 29.82 \pm 3.38 | 36.21 \pm 5.65 | 29.42 \pm 3.61 | 36.21 \pm 5.65 | 29.42 \pm 3.61 | 29.42 \pm 3.61 | |
| 90 | 23.97 \pm 2.58 | 24.62 \pm 2.33 | 24.53 \pm 2.15 | 25.18 \pm 2.24 | 24.53 \pm 2.15 | 25.18 \pm 2.24 | 25.18 \pm 2.24 | |
| 120 | 15.58 \pm 2.71 | 24.86 \pm 2.69 | 15.57 \pm 2.11 | 24.87 \pm 2.94 | 15.57 \pm 2.11 | 24.87 \pm 2.94 | 24.87 \pm 2.94 | |
| 150 | 11.58 \pm 1.77 | 22.28 \pm 3.41 | 11.49 \pm 1.46 | 23.28 \pm 3.69 | 11.49 \pm 1.46 | 23.28 \pm 3.69 | 23.28 \pm 3.69 | |
| 180 | 7.97 \pm 1.75 | 21.40 \pm 2.97 | 7.80 \pm 1.59 | 22.14 \pm 3.54 | 7.80 \pm 1.59 | 22.14 \pm 3.54 | 22.14 \pm 3.54 | |
| 240 | 3.75 \pm 1.37 | 20.53 \pm 2.82 | 3.55 \pm 1.30 | 21.59 \pm 3.01 | 3.55 \pm 1.30 | 21.59 \pm 3.01 | 21.59 \pm 3.01 | |
| 360 | 1.11 \pm 0.64 | 18.31 \pm 2.85 | 1.24 \pm 0.66 | 19.69 \pm 2.67 | 1.24 \pm 0.66 | 19.69 \pm 2.67 | 19.69 \pm 2.67 | |
| 470 | 1.07 \pm 0.46 | 15.87 \pm 2.90 | 1.18 \pm 0.47 | 16.64 \pm 3.16 | 1.18 \pm 0.47 | 16.64 \pm 3.16 | 16.64 \pm 3.16 | |
| 480 | 0.75 \pm 0.30 | 14.89 \pm 2.36 | 0.97 \pm 0.25 | 14.97 \pm 2.65 | 0.97 \pm 0.25 | 14.97 \pm 2.65 | 14.97 \pm 2.65 | |

0*: within 5 minutes before starting the antibiotic infusion

SD: standard deviation

in addition to bioequivalence determination in only one study to assure that the two drugs have virtually the same effect in humans.

A significant relationship between plasma concentrations of meropenem and the corresponding inhibitory zone sizes of the same specimen, was observed in this study. However, the relationship was not linear and the inhibitory zone sizes were not highly sensitive to the change, compared with plasma concentrations. In other words, the variation in diameters of the inhibitory zone size was relatively small which was in the range of 15-31 mm; while plasma concentrations could vary from 0.75 to 50 µg/mL. At the highest concentration of 47-50 µg/mL, the widths of the diameter of the inhibitory zone size were 31-32 mm, and when the plasma levels declined to 24-25 µg/mL, the widths of the diameter were also at 24-25 mm. The widths of the diameter were still at 15-18 mm, while plasma levels fell to 0.75-1.24 g/mL. However, since the determination of serum inhibition is simple and cheap, we propose that this method can be used with less frequency of blood collection and still yields the antibacterial activity results for comparison. The hospitals can do the test by themselves if there are microbiologists who are accustomed to the method of serum inhibition test. The test can be made simple for a hospital that is going to have a generic meropenem in the stock and wants to assess the antibacterial activity of the generic drug. Blood samples for the test could be reduced to four samples per one infusion per drug, and should be drawn just before the next infusion; and then 30, 180, and 360 minutes after the initial infusion which takes 30 minutes. In order to compare with the original meropenem, the intravenous administration must employ an infusion pump to accurately infuse the antimicrobial for 30 minutes. If the patient was initially given a generic meropenem, one can draw four blood samples on day 3 or day 5 and substitutes the generic

with the original meropenem for two consecutive infusions in the next day, and blood samples should be collected during the second infusion. Then eight serum samples from the two products of meropenem could be determined for the pharmacokinetics, and the inhibitory zone sizes of corresponding samples are compared at each interval. Such a test will generate more informations about the quality of the generic meropenem after the drug has been bought and kept in the hospital pharmacy. Physicians in the hospitals will have the informations of the tests, and the patients can decide for themselves whether to use a generic or original drug.

Theoretically, a generic drug that is proven bioequivalent to its original counterpart may be interchanged for it in any prescription. However, the National Health Care Scheme does not open up a choice for a consumer to choose between an original drug and a bioequivalent generic version. Even if the doctor has written on the prescription that no substitution can be made, many hospital directors have overruled the prescription and automatically let the pharmacy substitutes with the one in the hospital's stock. The consumer's choice may also be limited by an insurance plan or a managed care organization, which may require that the generic drugs should be prescribed and dispensed whenever possible to save the money. This study opened up a choice of a generic meropenem with the good quality, and both the doctors and patients should be well informed of the quality of the products. We hope that one day, the National Health Care Scheme Plans will allow the consumers to choose whether they would like to use the original meropenem or a generic meropenem, providing that the patients are also willing to pay the difference in cost.

Many classes of antimicrobial drugs have limited activities against currently circulating strains of Gram-negative bacteria due to the emergence of resistance.

Clinicians are increasingly concerned about multidrug-resistant Gram-negative bacterial infections, as an infectious threat in the hospital and now in the community. For many decades, third- and fourth-generation cephalosporins as well as piperacillin have been the drugs of first choice for the empirical treatment of serious Gram-negative infections. Due to their superior bactericidal activity and penetrating ability into various organs with fewer toxicity, most guidelines recommend the beta-lactams as the starting regimens. A recent emergence of resistance to the workhorse antimicrobials including the third- and fourth-generations cephalosporins, piperacillin, or advanced-generation of fluoroquinolones is becoming widespread and is of a great concern in critically ill patients who are at greatest risk of acquiring serious infections due to the multidrug-resistant Gram-negative bacteria. Among the beta-lactams that are still active against extended-spectrum β -lactamase (ESBL)-producing enterobacteria, carbapenem is the antimicrobial with the most reliable bactericidal activity.⁶⁻⁸ The administration can be the intermittent or continuous infusion to maximize the time above the minimal inhibitory concentration (MIC).⁹ However, its activity against *Pseudomonas aeruginosa* is becoming deteriorated¹⁰, and is even more disturbing when considering current resistance profiles of *Acinetobacter baumannii*.¹¹ Though the generic meropenem is cheaper than the original meropenem, we hope that physicians will continue to use carbapenem rationally in order to avoid the development of antimicrobial resistance among most pathogenic bacteria. Currently, there is the poor interest but urgency in the development of new antimicrobials that can be effectively implemented for the treatment of multidrug-resistance pathogenic bacteria. However, the new effective antimicrobials in the pipeline development are scarce, and we need to make the best use of existing antimicrobials especially the antimicrobials with the

availability of generic products in order to prolong their usefulness in fighting serious infections.

In conclusion, this study revealed a bioequivalence and similarity of the antibacterial activity between the generic and original meropenems. We propose the simple way to assess the antimicrobial activity of a generic version if its quality is in doubt. The result of this study should open up a choice for consumers to select a quality product, whether it is the original or generic antimicrobials according to their preferences.

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