Meropenem Pharmacokinetics During the Initial Phase of Life-Threatening Infections in Critically Ill Patients in Intensive Care Units

Sutep Jaruratanasirikul¹, Krittimeth Trerayapiwat¹, Monchana Nawakitrangson¹, Maseetoh Samaeng¹, Somchai Sriwiriyajan²

¹ Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand
² Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand

Abstract

Pathophysiologic changes during life-threatening infections have an influence on alteration of pharmacokinetics (PK) of antimicrobial agents. The aim of this study was to characterize meropenem PK during the initial phase of life-threatening infections in critically ill patients. The PK studies were conducted during the first dose of a 1-h infusion of 1 g of meropenem every 8 h in critically ill patients with life-threatening infections in the intensive care unit. The mean PK parameters of meropenem in this group were found to be variable. The volume of distribution, half-life and the area under the concentration-time curve between 0-8 h (AUC0-8) were 26.36 ± 13.37 L, 3.30 ± 3.45 h, and 121.64 ± 56.79 mg.h/L, respectively, which were significantly increased, whereas, total clearance was 9.39 ± 6.67 L/h which was decreased but not significantly different from the values obtained from healthy subjects. PK changes of meropenem can occur during the initial phase of life-threatening infections, resulting in variability and unstable plasma concentrations and thus affecting the antimicrobial efficacy of this agent.

1. INTRODUCTION

A critical illness in an intensive care unit (ICU) occurs frequently in patients with multiple severe underlying diseases and organ failure. This condition is usually a crucial risk factor for developing life-threatening infections due to the extensive use of invasive devices for diagnostic and therapeutic interventions. Appropriate choice of antibiotic as well as optimal dosage regimens are required in these already difficult ICU circumstances to maximize the antimicrobial activity, minimize the emergence of drug resistance and avoid adverse events, and reduce the morbidity and mortality rates for these severe infections. The pathophysiologic changes that occur during these severe infections can lead to pharmacokinetic (PK) changes of antibiotics, resulting in the unstable blood concentrations of drugs and affecting the achievement of PK/pharmacodynamic (PD) targets. Moreover,
hydrophilic antibiotics with a small volume of
distribution (V) and excretion unchanged by
the kidneys have been found to be highly affected by
these PK changes6. Meropenem, a carbapenem antibiotic agent, is a broad spectrum of activity
against several pathogens, including Gram-negative bacilli, Gram-positive cocci, and anaerobic bacteria.
This agent is commonly used for the treatment of multidrug-resistant microorganisms in patients
with life-threatening infections7. In common with other β-lactams, the PK/PD parameter that best
predicts the in vivo antimicrobial activity is the exposure time during which the plasma concentration
remains above the MIC (T >MIC) of the pathogen8,9.
The objective of this study was to characterize
the meropenem PK during the initial phase of life-
threatening sepsis in critically ill patients admitted
into the ICU of Songklanagarind Hospital, Songkla,
Thailand.

2. MATERIALS AND METHODS
2.1. Subjects
The PK studies were undertaken during the
first dose of a 1-h infusion of 1 g of meropenem
every 8 h in fourteen patients who were diagnosed
with life-threatening infections with severe sepsis
or septic shock in the ICU. Therefore, all patients
received a large volume of intravascular fluid for
resuscitation of severe sepsis or septic shock and
nothing per oral was allowed during the study. A
patient was eligible for the study if they met the
following criteria: (i) >18 years of age, and (ii) a
diagnosis of severe sepsis or septic shock, either
at admission or during the ICU stay. Sepsis is the
systemic response to an infection defined by two or
more of the following conditions: body temperature
>38 °C or <36 °C; heart rate of >90 beats per min;
respiratory rate of >20 breaths per min or a PaCO
2 of <32 mmHg; and leucocyte count >12,000 cell/
mm³, <4,000 cell/mm³ or 10% immature (band)
forms. Severe sepsis is defined by sepsis associ-
ated with organ dysfunction, hypoperfusion, or
hypotension (systolic blood pressure <90 mmHg,
mean arterial pressure <70 mmHg or a reduction of
≥40 mmHg from baseline). Septic shock is defined
by severe sepsis associated with hypotension despite
adequate fluid resuscitation10. Patients were excluded
from the study if they were pregnant or had
documented hypersensitivity to carbapenems or had
a history of chronic kidney disease. Acute Physiology
and Chronic Health Evaluation (APACHE) II and
Sepsis-related Organ Failure Assessment (SOFA)
scores were used for assessment of the severity of illness of each patient at the time of enrollment.
The present study was reviewed and approved by
the Ethics Committee of Songklanagarind Hospital
(Ethical approval: REC 56-065-14-1) and written
informed consent was obtained from a representa-
tive of each subject before recruitment. Blood samples (~3 mL) were collected via an intravascular
catheter at 0, 0.25, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5
and 8 h after the first dose of meropenem was given.

2.2. Drugs and chemicals
Meropenem (Meronem®) was donated by
AstraZeneca (Bangkok, Thailand). Meropenem
standard powder was donated by AstraZeneca
(Macclesfield, UK) and cefepime standard powder
(internal standard) was donated by Bristol-Myers
Squibb (Sermoneta, Italy) as pure powder. All
solvents were of high-performance liquid chroma-
tography (HPLC) grade.

2.3. Meropenem assay
Blood concentrations of meropenem were
determined by reverse-phase HPLC. The samples
were prepared by the modified method of Ozkan
et al.11. Briefly, 500 µL of plasma was applied
to ultrafiltration, using a Nanosep® 10K (Pall
Corporation, Northborough, MA). The devices
were centrifuged at 13,000 × g for 30 min at 4°C.
A 50 µL aliquot of the sample was injected onto
a μBondapak C18 column (Waters Associates;
3.9×300 mm) using an automated injection system
(Waters 717 Plus Autosampler; Waters Associates,
Milford, MA). The mobile phase was 15 mM
KH₂PO₄–acetonitrile–methanol (84:12:4, v/v/v),
PH 2.8, at a flow rate of 1 mL/min. The column
effluent was monitored by a Photodiode Array
detector (Waters 2996; Waters Associates, Milford,
MA) at 308 nm. Peaks were recorded and integrated
on a Waters 746 Data Module (Waters Associates).
The limit of detection of meropenem was 0.05 mg/L
and the limit of quantitation was 0.08 mg/L. The
intra-assay reproducibility values characterized by
coefficients of variation (CVs) were 2.58%, 1.77%
and 3.45% for samples containing 2, 32 and 128
mg/L, respectively. The interassay reproducibility
precision values, calculated by CVs, were 3.21%, 2.98% and 3.74% for samples containing 2, 32 and 128 mg/L, respectively. The accuracy values were 102.91%, 105.49% and 108.08% and the recovery values were 117.85%, 103.37% and 109.15% for samples containing 2, 32 and 128 mg/L, respectively.

2.4. Pharmacokinetic analysis

Non-compartment model PK parameters were determined by using the WinNonlin Version 1.1 program (Scientific Consulting Inc, NC, USA). The results were expressed as mean values ± standard deviation and the mean PK parameters of meropenem of all patients were compared to values obtained from healthy subjects who received a 3-h infusion of 1 g of meropenem single dose\(^{12}\), using the \(t\)-test. The \(p\)-values of <0.05 were considered to be significant.

3. RESULTS

Fourteen patients were enrolled in the study (twelve male and two female). The mean age of study subjects was 58.64 ± 18.55 years, the mean weight was 58.44 ± 11.25 kg and the mean BMI was 21.73 ± 3.42 kg/m\(^2\). A summary of the important characteristics of the patients is shown in Table 1. The comparisons of the mean PK parameters of meropenem in our study and values obtained from healthy subjects are shown in Table 2. The mean plasma concentration-time data are shown in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Summary of the characteristic of 14 critically ill patients with life-threatening infections</th>
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<tbody>
<tr>
<td><strong>Life-threatening conditions</strong></td>
</tr>
<tr>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Septic Shock</td>
</tr>
<tr>
<td><strong>Source of infections</strong></td>
</tr>
<tr>
<td>Bacteremia</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td><strong>APACHE II score</strong></td>
</tr>
<tr>
<td>(\geq 18)</td>
</tr>
<tr>
<td>(&lt; 18)</td>
</tr>
<tr>
<td><strong>SOFa score</strong></td>
</tr>
<tr>
<td>(\geq 8)</td>
</tr>
<tr>
<td>(&lt; 8)</td>
</tr>
<tr>
<td><strong>Use of inotropic drugs</strong></td>
</tr>
<tr>
<td>Norepinephrine or dopamine</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td><strong>Positive fluid balance</strong></td>
</tr>
<tr>
<td>0-2.1</td>
</tr>
<tr>
<td>2.1-4.1</td>
</tr>
<tr>
<td>4.1-6.1</td>
</tr>
<tr>
<td><strong>Serum albumin (normal range, 4.1-5.3 g%)</strong></td>
</tr>
<tr>
<td>(&lt; 3\ g%)</td>
</tr>
<tr>
<td>(\geq 3\ g%)</td>
</tr>
<tr>
<td><strong>CLcr</strong></td>
</tr>
<tr>
<td>(\geq 60\ mL/min)</td>
</tr>
<tr>
<td>(&lt; 60\ mL/min)</td>
</tr>
</tbody>
</table>

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment; Positive fluid balance, fluid intake minus fluid output during initial 24 h of administration of meropenem; CL\textsubscript{cr}, the creatinine clearance
4. DISCUSSION

During the initial phase of life-threatening infections, the shifting of a large volume of fluid resuscitation from intravascular into extravascular space, as well as endothelial damage, and subsequently enhanced capillary permeability, can induce a larger $V$ than the values obtained from healthy volunteers. Peripheral effusion or edema from fluid retention can affect the distribution of antimicrobial agents. Moreover, the hyperdynamic state of severe infections during this period is associated with a high cardiac output and increased renal blood flow, resulting in enhancement of renal clearance of antimicrobial agents eliminated by glomerular infiltration. Hypoalbuminemia can occur in critically ill patients with multiple comorbidities due to decreased protein synthesis in the liver, resulting in an increased unbound form of drugs and, thus, increased renal clearance of antibiotics. Therefore, increased $V$ and renal clearance of antimicrobial agents result in lower plasma drug concentrations. Contrarily however, decreased renal clearance may occur with severe sepsis and septic shock due to decreased organ perfusion, leading to the development of end-organ dysfunction.3,13,14

Antibiotic concentration at the infection sites is

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Patients with severe sepsis</th>
<th>Healthy Volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>46.95 ± 15.40</td>
<td>24.95 ± 6.85&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (mg/L)</td>
<td>4.77 ± 6.01</td>
<td>0.47 ± 0.23&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (mg.h/L)</td>
<td>172.73 ± 137.05</td>
<td>-</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-8&lt;/sub&gt; (mg.h/L)</td>
<td>121.64 ± 56.79</td>
<td>80.06 ± 21.86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>3.30 ± 3.45</td>
<td>0.61 ± 0.14&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>$k_e$ (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.38 ± 0.24</td>
<td>1.21 ± 0.38&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>$V$ (L)</td>
<td>26.36 ± 13.37</td>
<td>11.72 ± 2.22&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>9.39 ± 6.67</td>
<td>14.46 ± 5.88</td>
</tr>
</tbody>
</table>

$c$, $p<0.05$ versus patients with severe sepsis

Table 2. The mean pharmacokinetic parameters of meropenem in 14 critically ill patients with life-threatening infections compared to healthy volunteers

![Figure 1. Mean plasma meropenem concentration-time data in fourteen critically ill patients](image-url)
also one of the contributing factors for determining the success of therapeutic outcomes. For beta-lactams, the penetration of these agents into the infection sites has been found to be limited, leading to inadequate concentrations. In the current study, we found that the mean PK parameters of this agent were variable and different from the parameters found in healthy subjects. The \( V \), \( t_{1/2} \), and \( \text{AUC}_{0-\text{8}} \) of meropenem were significantly increased, whereas the CL was decreased although the difference was not significant\(^{12}\). The comparisons of \( \text{C}_{\text{max}} \) and \( \text{C}_{\text{min}} \) of meropenem in both studies were difficult to be made due to different dosage regimens. The explanation of our findings is that all of our patients had life-threatening infections, with eight patients having septic shock and six severe sepsis, and they had multiple underlying diseases with high APACHE II and SOFA scores. Most had received a large volume of fluid resuscitation for their life-threatening infections and had hypoalbuminemia due to severe sepsis and the multiple underlying diseases. Moreover, the majority of the enrolled patients had renal impairment, resulting in decreased renal clearance of meropenem and subsequently increased \( \text{AUC}_{0-\text{8}} \) of meropenem as compared to healthy volunteers. Therefore, during the initial phase of life-threatening infections, the PK of meropenem were found to be changed, resulting in undesirable PD and therapeutic outcome of antimicrobial agents.

5. CONCLUSION

The PK changes of meropenem during the initial phase of treatment of life-threatening infections in critically ill patients can lead to fluctuation of plasma concentrations and the adjustment of dosage regimens may be required for achieving the PK/PD targets.

6. ACKNOWLEDGEMENTS

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Conflict of interest

we have no conflicts of interest related to this work

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Ethical approval

This study was reviewed and approved by the Ethics Committee of Songklanagarind Hospital (Ethical approval: REC 56-065-14-1)

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