Population pharmacokinetics and Monte Carlo dosing simulations of meropenem during the early phase of severe sepsis and septic shock in critically ill patients in Intensive Care Units


aDepartment of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand.
bDepartment of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand.
cDepartment of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Pathumwan, Bangkok 10330, Thailand.

Running title: PK/PD of meropenem in severe sepsis and septic shock

*Corresponding author:
Sutep Jaruratanasirikul
Department of Medicine, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkla 90110, Thailand.
Tel: +66-74-451452, Fax: +66-74-429385
E-mail: jasutep@medicine.psu.ac.th
Abstract

Pathophysiologica changes during the early phase of severe sepsis and septic shock in critically ill patients resulting in altered pharmacokinetics (PK) of antibiotics are important factors for influencing the therapeutic success. The aims of this study were to i) reveal the population PK, and ii) assess the probability of target attainment (PTA) of meropenem. The PK studies were carried out following administration of 1 g every 8 h (q8h) of meropenem during the first 24 h of severe sepsis and septic shock in nine patients and a Monte Carlo simulation was performed to determine the PTA of achieving 40% $f_{T>MIC}$ and 80% $f_{T>MIC}$. The volume of distribution ($V_d$) and total clearance (CL) of meropenem in these patients were 23.7 L and 7.82 L/h, respectively. For pathogens with a MIC of 4 μg/mL, the PTAs of 40% $f_{T>MIC}$ following administration of a 1-h infusion of 1 g q8h and a 4-h infusion of 0.5 g q8h of meropenem were 92.52% and 90.29%, respectively. For pathogens with a MIC of 2 μg/mL in immunocompromised hosts, the PTAs of 80% $f_{T>MIC}$ following administration of a 1-h and a 4-h infusion of 2 g q8h of meropenem were 84.32% and 94.72%, respectively. These findings indicated that the $V_d$ of meropenem was greater, and the CL of meropenem was lower than the values obtained from a previous study in healthy subjects. The maximum recommended dose, 2 g q8h of meropenem may be required for treatment of life-threatening infections in this patient population.

Key words: pharmacodynamics, population pharmacokinetics, meropenem, severe sepsis, septic shock
Introduction

Severe sepsis and septic shock are one of the most important reasons for admitting a critically ill patient to an Intensive Care Unit (ICU), and remain a major cause of high rates of morbidity and mortality (1). Early and appropriate antimicrobial therapy has been shown to be the crucial factor for therapeutic success, leading to reduction of the mortality rate in these patients (2-4). However, during the early phase of severe sepsis and septic shock in critically ill patients, pathophysiological changes resulting in altered pharmacokinetic (PK) patterns, including volume of distribution ($V_d$) and total clearance (CL), have been found with several antimicrobial agents that may affect therapeutic plasma concentrations and the achieving of pharmacodynamic (PD) targets for antimicrobial therapy (5, 6).

Meropenem, a broad-spectrum carbapenem effective against Gram-negative bacilli, Gram-positive cocci and anaerobic bacteria, is commonly prescribed for empirical treatment of highly resistant pathogens in patients with life-threatening severe sepsis or septic shock in ICUs (7). In common with other β-lactams, this agent exhibits primarily time-dependent antimicrobial activity and the PK/PD index that best predicts the in vivo antimicrobial activity is the exposure time during which the plasma concentration remains above the minimum inhibitory concentration (T$_{MIC}$) of the pathogen (8, 9). However, standard dosage recommendations of antibiotics for treatment of infections are obtained from PK data from patients with less severe sepsis (10, 11), and standardized dosage regimens for critically ill patients with severe sepsis or septic shock, particularly during the early phase, have not to date been determined. Therefore, the aims of this study were i) to reveal the population PK of meropenem; and ii) to assess the probability of target attainment (PTA) of meropenem during the early phase of severe sepsis or septic shock in critically ill patients in order to be able to optimize dosing recommendations.
Materials and methods

Subjects

The study was conducted during the initial 24 h of severe sepsis or septic shock in nine patients admitted into the ICU of Songklanagarind Hospital, the largest tertiary-care center in southern Thailand, from January through December 2013. 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 PaCO₂ 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 associated 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 resuscitation (12). Patients were excluded from the study if they were pregnant or had documented hypersensitivity to carbapenems or had a history of chronic kidney disease. The severity of illness of each patient was assessed at the time of enrolment into the study using the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Sepsis-related Organ Failure Assessment (SOFA) scores. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital. Written informed consent was obtained from each subject’s legally acceptable representative before enrolment.

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 chromatography (HPLC) grade.

Study design

Following the manufacturer’s instructions, the dosage recommendation of meropenem was administered in a 1-h infusion of 1g diluted in 100 mL of normal saline solution via infusion pump at a constant flow rate every 8 h (q8h) for 14 days. A Monte Carlo simulation (MCS) was performed to assess the efficacy of standard dosage regimens of meropenem. Each patient received meropenem at room temperature (32-37°C).

Blood sampling

Meropenem PK studies were carried out during the administration of the first and second doses of meropenem (0-16 h after the start of administration of meropenem) during the initial 24 h of severe sepsis and septic shock. Blood samples (ca. 3 mL) were obtained by direct venipuncture at the following times: shortly before (time 0) and then at 0.25, 0.5, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 8, 8.5, 9, 9.5, 10, 12, 14 and 16 h after the start of administration of meropenem. All blood samples were added to a heparinized tube, immediately stored on ice and centrifuged at 2000 × g at 4°C for 10 min within 5 min. All plasma samples were stored at -80°C until analysis within 1 week.

Meropenem assay

Blood concentrations of meropenem were determined by reverse-phase HPLC. The samples were prepared by the modified method of Ozkan et al. (13). 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 KH$_2$PO$_4$–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 μg/mL and the limit of quantitation was 0.08 μg/mL. 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 μg/mL, respectively. The interassay reproducibility precision values, calculated by CVs, were 3.21%, 2.98% and 3.74% for samples containing 2, 32 and 128 μg/mL, 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 μg/mL, respectively.

**Pharmacokinetics analysis**

**Model building**

The concentration versus time data for meropenem in plasma were analyzed by a nonlinear mixed-effects modeling approach using NONMEM® version 7.2 (ICON Development Solutions, Ellicott city, MD, USA). The NONMEM® runs were executed by PDx-Pop® version 5.1 (ICON Development Solutions, Ellicott city, MD, USA). Data were analyzed using the first-order conditional estimation with interaction (FOCE-I) method. The plasma meropenem concentrations were fitted to one-, two- and three-compartment models using subroutines from the NONMEM library to obtain the appropriate base model.
Covariate exploration

After obtaining the appropriate base model, the fifteen covariates including age, body weight, body mass index, systolic blood pressure, diastolic blood pressure, fluid intake (per day), fluid output (per day), arterial blood pH, blood urea nitrogen, SOFA score, APACHE II score, serum creatinine, serum albumin, creatinine clearance estimated by Cockcroft–Gault equation and by modification of diet in renal disease formula (MDRD-CLc(r)) were analyzed. Individual parameters were plotted against covariate values to assess relationships. If a trend between a covariate and a PK parameter was found, then it was considered for inclusion in the base model. Covariates were kept in the model if there was significant improvement in the fit over the base model. Based on a $\chi^2$ test, a decrease in the minimum objective function value (MOFV) of 3.84 units was considered significant ($P < 0.05$) for addition step and a more stringent criterion ($P < 0.01$) was used in backward deletion to avoid any possible false positives.

Covariate model diagnostics

Statistical comparisons of models were based on differences in the MOFV. Goodness-of-fit of models were evaluated by visual inspection of diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual error versus time and weighted residual error versus predicted concentrations.

Model validation

One thousand bootstrap runs were performed to assess the robustness of all PK parameter estimates in the final model. Model stability was indicated by a condition number of less than 1,000. In addition, a visual predictive check was performed by simulating 100 subjects to assess the predictive performance of the final model. The visual checks and representative percentiles (5th, 10th, 50th (median), 90th and 95th percentiles) were visually assessed.
Pharmacodynamic assessment using Monte Carlo simulation

The MCS of concentration-time profiles was performed using Box-Muller Transform to simulate the log-normal PK parameters of the population (14). The covariate was included in the MCS, therefore, the behavior of these simulated parameters of the population still retained the characteristics of the parameters obtained from the actual patients. Additionally, for more reliable MCS, 10,000 iterations were simulated to calculate $\% T > \text{MIC}$ at 40% and 80% target attainment. The MCS code was written in the Basic language, using Runge-Kutta order 4 as the algorithm for solving differential equations, and compiled by a Quick Basic compiler.
Results

Nine patients were enrolled in the study (eight males and one female). Their mean age was 57.22±16.10 years (range 33-83 years) and their mean weight was 62.88±11.64 kg (range 49–80.5 kg). The characteristics of all patients are shown in Table 1.

PK modeling was performed using the data from the 171 plasma concentration samples. The PK data were best described by a one-compartment model with a combined additive and proportional residual variability (the minimum objective function value of 717.728). The two-compartment model provided an insignificant decrease in the objective function compared to the one-compartment model while the three-compartment model seemed to be over-parameterized for our data as the minimization did not terminate successfully or the model was not stable. The Akaike information criterion (AIC) for the one-, two-, and three-compartment models were 729.728, 735.508 and 744.287, respectively. The values of the parameters for the one-compartment model used in this study are given in Table 2.

Only MDRD-CLCr was a significant covariate describing the CL of meropenem (MOFV decreased by 5.063) and reduced the estimated interindividual variability of clearance from 64% to 48%. There was no significant covariate that explained the \( V_d \). The final model was represented by:

\[
\begin{align*}
CL &= TVCL \times e^{\eta_1} \\
TVCL &= [\theta_1 + \theta_2 \times \text{MDRD-CLCr}] \\
V_d &= TVV \times e^{\eta_2}
\end{align*}
\]

where \( TVCL \) and \( TVV \) are the typical values of CL and \( V_d \),
\( \eta_1 \) and \( \eta_2 \) are the interindividual random effects of CL and \( V_d \), and
\( \theta_1 \) and \( \theta_2 \) are shape parameters.
Goodness-of-fit plots for the final model were evaluated and showed no apparent visual bias for the predictions as shown in Figure 1. From 1,000 bootstrap runs, the 95% confidence interval for the parameters from the final model is presented in Table 3. It shows that all parameter estimates were in the range of the 95% confidence interval from 1,000 bootstrap runs, indicating the robustness of the final model. The condition number for the final model was 172.6. A visual predictive check also confirmed the predictive performance of the model. There was a resemblance between observed and simulated data. The observations outside the percentile range were randomly scattered, not aggregated at a particular time point. These findings imply that the final model had an adequate predictive ability to describe the measured meropenem concentrations.

The PTAs for all meropenem regimens achieving 40% $fT_{>MIC}$ and 80% $fT_{>MIC}$ at specific MICs are shown in Table 4 and Figure 2.
Discussion

In critically ill patients with severe sepsis and septic shock, PK changes, including \( V_d \) and \( CL \), of antimicrobial agents can occur as a result of the patient’s altered pathophysiological conditions (15). The presence of extensive fluid extravasation and tissue edema, associated with increased capillary leakage and the use of inotropes during septic shock, can induce a larger \( V_d \) than the values obtained from healthy subjects. Moreover, increased cardiac output during the initial hyperdynamic state of severe sepsis leading to increased renal blood flow and an increased free fraction of antibiotics as observed with hypoalbuminemia can result in increased renal clearance, particularly for highly protein-bound hydrophilic antimicrobial agents, and on the other hand, with end-organ dysfunctions that can occur with severe sepsis and septic shock, the renal clearance may be decreased (12, 15, 16). As a consequence of these alterations in \( V_d \) and \( CL \), the half-life \( (t_{1/2}) \) of antimicrobial agents can be affected, leading to undesirable therapeutic outcomes. In the current study, an alteration of the PK of meropenem was found when compared to an earlier study in healthy volunteers (17). The \( V_d \) of meropenem was greater whereas the \( CL \) of meropenem was lower than the values obtained from a previous study in healthy volunteers (17), resulting in a more than 2-fold prolongation of the \( t_{1/2} \) of this agent. A possible explanation for the PK changes in this study is that the study was undertaken in seriously ill patients with life-threatening infections and more than half of the recruited patients were experiencing renal dysfunction as defined by MDRD-CL\(_{Cr}\), of ≤60 mL/min. All enrolled patients were in very seriously ill condition with four patients with severe sepsis and five with septic shock. The majority of the patients had an APACHE II score ≥18 and a SOFA score ≥8. However, the current study was not conducted to compare PK changes of meropenem between early and late phases during antimicrobial therapy in order to characterize the PK of meropenem when the patients were recovered from severe sepsis and septic shock. A previous study in septic critically ill patients
ill patients for assessment of PK changes during meropenem therapy found that the PK of this
agent had large inter-patient variability and the mean value of $V_d$ decreased from 18.5 L during
the early phase to 17.3 L during the late phase of severe sepsis and the mean value of CL
increased from 7.2 L/h during the early phase to 8.10 L/h during the late phase of severe sepsis,
but the PK changes between these two phases were not statistically significantly different (18).
In addition, we compared the PK of meropenem during the early phase therapy between the
current study and a previous study (18) and found that the $V_d$ and CL of meropenem from our
study was still greater than the values in the other study obtained from septic critically ill
patients, while the $t_{1/2}$ was similar. Therefore, the altered PK of meropenem found in the current
study may have affected the achievement of the PD targets associated with maximal
antimicrobial efficacy.

Carbapenems, including meropenem, are one of the most important and commonly
prescribed drugs for coverage of highly resistant nosocomial infections in critically ill patients in
an ICU. The PK characteristic of meropenem, a hydrophilic antimicrobial agent, is primarily
distributed to extracellular compartments, such as the pulmonary epithelial lining fluid (ELF) in
ventilator-associated pneumonia (VAP). The ability of this agent to penetrate the infected site for
achieving the exposure targets is altered by the primary infection site and drug concentrations in
extracellular compartments are difficult to determine, thus correlations between the PK/PD index
in the tissue and antimicrobial effects are less well understood (19). Therefore, plasma drug
concentrations are most commonly used as a surrogate measure for determining the PK/PD
indices, and $T_{>MIC}$ is the best parameter that correlates with the bactericidal activity of $\beta$-lactams.
High peak concentrations do not enhance the bactericidal activity of these agents and bacterial
growth resumes rapidly when the level of antibiotics decreases to below the MIC (8, 9). Studies
in animal infection models have shown that for most $\beta$-lactams, concentrations do not need to
exceed the MIC for 100% of the dosing interval to achieve a significant antibacterial effect (8, 9) and bactericidal effects of carbapenems against *Escherichia coli* and *P. aeruginosa* in a murine thigh infection model are observed when plasma drug concentrations are above the MIC for 40% of the dosing interval (20). Moreover, optimum killing properties have been observed in critically ill patients when concentrations are maintained at 4×MIC, with higher concentrations providing little added benefit (21, 22). However, there is no consensus about which strategy between $T\text{_}^{>\text{MIC}}$ and $T\text{_}^{>4\times\text{MIC}}$ is better.

A previous PD study of a first dose of 1 g of meropenem administration during the early phase of severe sepsis and septic shock in critically ill patients found that serum concentrations of this agent remained above 4 times the MIC of 2 μg/mL for 57% of the dosage interval and concluded that the standard dosage regimen of meropenem is sufficient to be empirically used for coverage of less susceptible pathogens in the early phase of severe sepsis and septic shock in this patient population (5). In the current study, we conducted a study to examine the population PK of meropenem during the first 24 h of severe sepsis and septic shock in patients in an ICU, and performed a Monte Carlo dosing simulation to determine the probability of attaining a specific PD target using various regimens, including 0.5 g q8h, 1 g q8h and 2 g q8h of meropenem. A prolonged 4-h infusion regimen for achieving PTAs of 40% $f\text{_}\text{>MIC}$ and 80% $f\text{_}\text{>4\times\text{MIC}}$ was a more effective strategy to achieve optimal PD exposure for pathogens with higher MICs than a 1-h infusion regimen. The high PTAs (≥90%) achieving 40% $f\text{_}\text{>MIC}$ for MIC of 4 μg/mL were observed when meropenem was administered by either a 1-h infusion of 1 g q8h or a 4-h infusion of 0.5 g q8h regimen. For pathogens with a MIC of 8 μg/mL, the high PTAs were achieved when the dosage of meropenem was increased to either a 1-h infusion of 2 g q8h or a 4-h infusion of 1 g q8h regimen, moreover, the 4-h infusion of 2 g q8h regimen achieved the high PTA of 40% $f\text{_}\text{>MIC}$ for a MIC of 16 μg/mL. These data indicate that a prolonged infusion of 1 g
q8h of meropenem can provide good coverage for pathogens with MICs of ≤8 μg/mL and for less susceptible pathogens with MICs >8 μg/mL, the dosage regimen should be increased to a 4-h infusion of 2g q8h regimen for achieving the optimal antimicrobial activity. Therefore, the standard manufacturer’s dosage recommendation of 0.5g to 1 g q8h of meropenem is sufficient to use for empirical coverage of the pathogens normally encountered in the early phase of severe sepsis and septic shock. A previous clinical study in immunocompromised patients with febrile neutropenia found that the optimal clinical response of meropenem for the treatment of bacteremia was achieved when the percentages of $T_{\geq \text{MIC}}$ of meropenem were greater than 75% of the dosing interval (23). The current study examining the treatment of life-threatening infections during the early phase of severe sepsis and septic shock found the high PTAs of achieving 80% of $f_{T>MIC}$ for MICs of 1 μg/mL and 2 μg/mL were obtained when the meropenem was administered by 4-h infusions of 1 g q8h and 2 g q8h, respectively. Therefore, the results from this study indicate that for treatment during the early phase of a life-threatening infection in an immunocompromised host, the high dosage regimen of a 4-h infusion of 2 g q8h may be required in order to achieve the optimal pharmacodynamic targets. In the current study, four critically ill patients had pneumonia, 3 with VAP and 1 with community-acquired pneumonia. An adequate penetration of antimicrobial agents to the site of infections is a crucial factor for achieving a successfully therapeutic outcome in a critically ill patient. The determination of drug concentrations in the ELF for extracellular respiratory tract pathogens provided the best estimate of antibiotic exposure in this patient population (24). A previous study of PK of meropenem in plasma and ELF among seriously ill patients with VAP found the mean plasma CL of meropenem to be variable due to the differing physiological statuses across the patient population, leading to the variability of the penetration of this agent into the ELF, with the 10th-90th-percentile range of penetration being 3.67% to 177.90%, and inadequate drug exposure at
the primary infection site of some patients (25). Another previous study in a murine pneumonia model with *P. aeruginosa* for determining the penetration of meropenem into the ELF of mice also had varying levels of penetration (26). The exposure targets developed in the murine model to ascertain how well a 2 g of meropenem dose administered as a 3-h infusion could achieve those targets were simulated. The target attainment of this dosage regimen for achieving a 2 log₁₀ (CFU/g) cell kill was <80% at a MIC of 2 µg/mL, while a 3 log₁₀ (CFU/g) cell kill and for resistance suppression were <90% at a MIC of 0.25 µg/mL and <75% at a MIC of 1 µg/mL (25, 26). These findings indicate that PD targets may not be achieved even when the largest licensed dose of meropenem administered as a prolonged infusion is prescribed for critically ill patients being treated for VAP because of the variability of the penetration, as well as, the high exposure targets of meropenem in ELF in the lungs in this patient population.

This study had a few limitations that must be considered. First, the results of this study could be difficult to extrapolate to other situations because the low body weight of the patients could have had an effect on *Vd* and CL. Second, the small number of patients could be considered a potential limitation. However, in the absence of data from a larger sample size, a MCS based on a small number of patients such as in this study can be instructive in illuminating the effects of different dosing approaches.

In conclusion, our current population PK study during the early phase of severe sepsis and septic shock in critically ill patients in ICUs found that the *Vd* of meropenem was greater, and the CL of meropenem was lower than the values obtained from a previous study in healthy subjects. In addition, the *Vd* and CL of meropenem in the current study was greater than the values obtained from a previous study in the early phase of septic critically ill patients. In our study, we found that prolonged 4-h infusion regimens were a more effective strategy for achieving optimal PTAs of 40% *fT>MIC* and 80% *fT>MIC* than a 1-h infusion regimen. The
maximum recommended dose, 2 g q8h of meropenem administered as a prolonged 3-h infusion may be required to maintain an adequate PK for treatment of life-threatening infections in critically ill patients with severe sepsis and septic shock in an ICU. However, further well-defined and large clinical trials in this patient population are required to confirm these findings.
Acknowledgements

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We declare that we have no conflicts of interest related to this work.
References


Figure 1 legend

Basic goodness-of-fit plots: (A) plot between observations and population predictions, (B) plot between observations and individual predictions, (C) plot between conditional weighted residuals and time and (D) plot between conditional weighted residuals and individual predictions.

Figure 2 legend

Probability of target attainment (PTA) for meropenem regimens achieving (A) 40% \( f_{T>MIC} \) and (B) 80% \( f_{T>MIC} \) at specific minimum inhibitory concentrations (MICs) during the early phase of severe sepsis and septic shock in 9 patients after administration of a 1-h infusion of 0.5 g every 8 h (▲), a 4-h infusion of 0.5 g q8h (Δ), a 1-h infusion of 1 g q8h (■), a 4-h infusion of 1 g q8h (□), a 1-h infusion of 2 g q8h (●) and a 4-h infusion of 2 g q8h (○). The broken line represents 90% PTA. \( T_{>MIC} \), time that concentrations in tissue and serum are above the MIC.
Table 1. Characteristics of 9 critically ill patients with severe sepsis and septic shock in the ICU.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>BW (kg)</th>
<th>MDRD-CLcr (mL/min)</th>
<th>Comorbidity</th>
<th>Source of infection</th>
<th>Pathogen</th>
<th>APACHE II score</th>
<th>SOFA score</th>
<th>Concomitant medication</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>F</td>
<td>51</td>
<td>142.46</td>
<td>Meningioma, High dose steroid therapy</td>
<td>VAP</td>
<td>GNB</td>
<td>25</td>
<td>5</td>
<td>Cefotaxime, dexamethasone, omeprazole, metocloplamide</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>58</td>
<td>31.89</td>
<td>DM</td>
<td>CAP with septic shock</td>
<td>GNB</td>
<td>21</td>
<td>14</td>
<td>Atrapid, dopamine, doxycycline, levofloxacin, morphine, omeprazole</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>M</td>
<td>49</td>
<td>79.78</td>
<td>DM</td>
<td>Bacteremia with septic shock</td>
<td>Escherichia coli and Streptococcus bovis</td>
<td>25</td>
<td>8</td>
<td>Ceftazidime, levofloxacin, norepinephrine, oseletamivir</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>M</td>
<td>56</td>
<td>59.43</td>
<td>PV</td>
<td>UTI with septic shock</td>
<td>E. coli, Klebsiella pneumoniae and Pseudomonas aeruginosa</td>
<td>33</td>
<td>9</td>
<td>Dopamine, norepinephrine, omeprazole</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>M</td>
<td>80</td>
<td>48.10</td>
<td>COPD, MI</td>
<td>VAP with septic shock</td>
<td>K. pneumoniae</td>
<td>17</td>
<td>6</td>
<td>Dicloxacillin, vancomycin, isosorbide dinitrate, norepinephrine, metoprolol, nifedipine, omeprazole, prednisolone</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>60</td>
<td>214.55</td>
<td>DM, AA</td>
<td>Bacteremia</td>
<td>Salmonella spp.</td>
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<td>12</td>
<td>Cardipine, ceftriaxone, metoprolol, nifedipine, omeprazole, simvastatin</td>
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<tr>
<td>7</td>
<td>33</td>
<td>M</td>
<td>70.8</td>
<td>52.09</td>
<td>Thalassemia</td>
<td>Severe leptospirosis with septic shock</td>
<td>NA</td>
<td>29</td>
<td>8</td>
<td>Dopamine, doxycycline, norepinephrine, morphine, omeprazole, hydrocortisone</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>80.5</td>
<td>12.37</td>
<td>NF</td>
<td>Bacteremia</td>
<td>β-streptococcus group A</td>
<td>18</td>
<td>14</td>
<td>Clindamycin, omeprazole</td>
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<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>60.6</td>
<td>65.08</td>
<td>ASD, PH</td>
<td>VAP</td>
<td>GNB</td>
<td>16</td>
<td>9</td>
<td>Cloxacillin, morphine, omeprazole, lorazepam</td>
</tr>
</tbody>
</table>

BW, Body weight; MDRD-CLcr, Modification of diet in renal disease formula; DM, Diabetes mellitus; PV, Polysytemia vera; COPD, Chronic obstructive pulmonary disease; MI, Myocardial infarction; AA, Aortic aneurism; NF, Necrotizing fasciitis; ASD, Atrial septal defect; PH, Pulmonary hypertension; VAP, Ventilator associated pneumonia; CAP, Community acquired pneumonia; UTI, Urinary tract infection; GNB, Gram negative bacilli; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organic Failure Assessment; NA, Not available.
Table 2. Population pharmacokinetic (PK) parameters of meropenem in 9 critically ill patients.

<table>
<thead>
<tr>
<th>Population PK parameter</th>
<th>Estimate (%RSE)</th>
<th>Interindividual variability (%)</th>
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<tbody>
<tr>
<td>$V_d$ (L)</td>
<td>23.7 (12.6)</td>
<td>35</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>7.82 (22.1)</td>
<td>64</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>2.54 (68.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

$V_d$, volume of distribution; CL, total clearance; %RSE, percentage of relative standard error; $t_{1/2}$, elimination half-life
Table 3. Parameter estimates, standard errors, and bootstrap confidence intervals.

<table>
<thead>
<tr>
<th>Population PK parameter</th>
<th>Estimate (%RSE)</th>
<th>Interindividual variability (%)</th>
<th>Bootstrap confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (L)</td>
<td>23.7 (12.6)</td>
<td>35</td>
<td>(18.80, 30.90)</td>
</tr>
<tr>
<td>$CL$ (L/h) - $\theta_1$</td>
<td>3.01 (47.5)</td>
<td>48</td>
<td>(0.07, 8.11)</td>
</tr>
<tr>
<td>- $\theta_2$</td>
<td>0.07 (32.9)</td>
<td></td>
<td>(0.01, 0.14)</td>
</tr>
</tbody>
</table>

$V_d$, volume of distribution; $CL$, total clearance; $\theta_1$ and $\theta_2$, shape parameters; \%RSE, percentage of relative standard error.
Table 4. Probability of target attainment (PTA) for meropenem regimens achieving 40% and 80% $\text{fT}_{\text{MIC}}$ in 9 critically ill patients in the ICU following administration by a 1-h and a 4-h infusions.

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>1-h infusion 0.5 g</th>
<th>1-h infusion 1 g</th>
<th>1-h infusion 2 g</th>
<th>4-h infusion 0.5 g</th>
<th>4-h infusion 1 g</th>
<th>4-h infusion 2 g</th>
<th>1-h infusion 0.5 g</th>
<th>1-h infusion 1 g</th>
<th>1-h infusion 2 g</th>
<th>4-h infusion 0.5 g</th>
<th>4-h infusion 1 g</th>
<th>4-h infusion 2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.125</td>
<td>99.69</td>
<td>99.76</td>
<td>99.90</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>93.23</td>
<td>95.26</td>
<td>96.80</td>
<td>98.61</td>
<td>99.29</td>
<td>99.57</td>
</tr>
<tr>
<td>0.25</td>
<td>99.40</td>
<td>99.65</td>
<td>99.81</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>89.73</td>
<td>92.91</td>
<td>95.20</td>
<td>97.41</td>
<td>98.58</td>
<td>99.23</td>
</tr>
<tr>
<td>0.5</td>
<td>98.73</td>
<td>99.33</td>
<td>99.65</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>84.01</td>
<td>89.46</td>
<td>93.11</td>
<td>94.41</td>
<td>97.19</td>
<td>98.53</td>
</tr>
<tr>
<td>1</td>
<td>97.28</td>
<td>98.77</td>
<td>99.37</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>75.22</td>
<td>83.89</td>
<td>89.73</td>
<td>88.55</td>
<td>94.49</td>
<td>97.31</td>
</tr>
<tr>
<td>2</td>
<td>92.75</td>
<td>97.02</td>
<td>98.77</td>
<td>99.59</td>
<td>100.00</td>
<td>100.00</td>
<td>60.47</td>
<td>74.43</td>
<td>84.32</td>
<td>74.69</td>
<td>88.49</td>
<td>94.72</td>
</tr>
<tr>
<td>4</td>
<td>79.38</td>
<td>92.52</td>
<td>97.04</td>
<td>90.29</td>
<td>99.59</td>
<td>100.00</td>
<td>37.44</td>
<td>59.51</td>
<td>75.19</td>
<td>45.36</td>
<td>74.63</td>
<td>88.64</td>
</tr>
<tr>
<td>8</td>
<td>43.56</td>
<td>79.05</td>
<td>92.66</td>
<td>43.46</td>
<td>90.45</td>
<td>99.63</td>
<td>11.04</td>
<td>36.54</td>
<td>60.13</td>
<td>9.02</td>
<td>45.49</td>
<td>75.08</td>
</tr>
<tr>
<td>16</td>
<td>5.51</td>
<td>43.18</td>
<td>79.65</td>
<td>3.72</td>
<td>43.28</td>
<td>90.24</td>
<td>0.72</td>
<td>11.31</td>
<td>37.27</td>
<td>0.11</td>
<td>8.79</td>
<td>45.95</td>
</tr>
<tr>
<td>32</td>
<td>0.06</td>
<td>5.73</td>
<td>43.51</td>
<td>0.02</td>
<td>3.61</td>
<td>43.88</td>
<td>0.01</td>
<td>0.67</td>
<td>11.83</td>
<td>0.00</td>
<td>0.10</td>
<td>8.70</td>
</tr>
<tr>
<td>64</td>
<td>0.00</td>
<td>0.07</td>
<td>5.98</td>
<td>0.00</td>
<td>0.01</td>
<td>3.54</td>
<td>0.00</td>
<td>0.00</td>
<td>0.66</td>
<td>0.00</td>
<td>0.00</td>
<td>0.09</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration; $\text{T}_{\text{MIC}}$, time that concentration in tissue and serum are above the MIC; q8h, every 8 h