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Research Article

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

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Abstract

Pathophysiological 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 were compared to the mean values obtained from healthy subjects. Fourteen patients were enrolled in this study and the 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) occur 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[1-3]. The pathophysiological 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[4,5]. 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 changes[6]. Meropenem, a carbapenem antibacterial 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 infections[7]. 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 pathogen[8,9]. 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 ºC or <36 ºC; 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/mm^3, <4,000 cell/mm^3 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[10]. 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 representative 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 chromatography (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 KH_2PO_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 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 1. Summary of the characteristic of 14 critically ill patients with life-threatening infections

	Number of cases (%)
Life-threatening conditions	
Severe sepsis	6 (42.86)
Septic Shock	8 (57.14)
Source of infections	
Bacteremia	4 (28.57)
Pneumonia	6 (42.86)
Diarrheae	1 (7.14)
Urinary tract infection	3 (21.43)
APACHE II score	
≥ 18	10 (71.43)
< 18	4 (28.57)
SOFA score	
≥ 8	9 (64.29)
< 8	5 (35.71)
Use of inotropic drugs	
Norepinephrine or dopamine	8 (57.14)
None	6 (42.86)
Positive fluid balance	
0-2.l	4 (28.57)
2.1-4.l	7 (50)
4.1-6.l	3 (21.43)
Serum albumin (normal range, 4.1-5.3 g%)	
< 3 g%	12 (85.71)
≥ 3 g%	2 (14.29)
CLcr	
≥ 60 mL/min	6 (42.86)
< 60 mL/min	8 (57.14)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis-related Organic Failure Assessment; Positive fluid balance, fluid intake minus fluid output during initial 24 h of administration of meropenem; CL_{cr}, the creatinine clearance

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

PK Parameter	Patients with severe sepsis[a]	Healthy Volunteers[b]
C_{max} (mg/L)	46.95 ± 15.40	24.95 ± 6.85[c]
C_{min} (mg/L)	4.77 ± 6.01	0.47 ± 0.23[c]
$AUC_{0-\infty}$ (mg.h/L)	172.73 ± 137.05	-
AUC_{0-8} (mg.h/L)	121.64 ± 56.79	80.06 ± 21.86[c]
$t_{1/2}$ (h)	3.30 ± 3.45	0.61 ± 0.14[c]
k_e (h^{-1})	0.38 ± 0.24	1.21 ± 0.38[c]
V (L)	26.36 ± 13.37	11.72 ± 2.22[c]
CL (L/h)	9.39 ± 6.67	14.46 ± 5.88

C_{max}, the maximum serum concentrations; C_{min}, the minimum serum concentrations; $AUC_{0-\infty}$, the areas under the concentration-time curve between 0 to infinity hour; AUC_{0-8}, the areas under the concentration-time curve between 0 to 8 hour; $t_{1/2}$, the elimination half-life; k_e, the elimination rate constant; V, the volume of distribution; CL, the total clearances; a, patients with severe sepsis received a 1-h infusion of 1 g of meropenem every 8 h; b, healthy volunteers received a 3-h infusion of 1 g of meropenem single dose; c, $p<0.05$ versus patients with severe sepsis

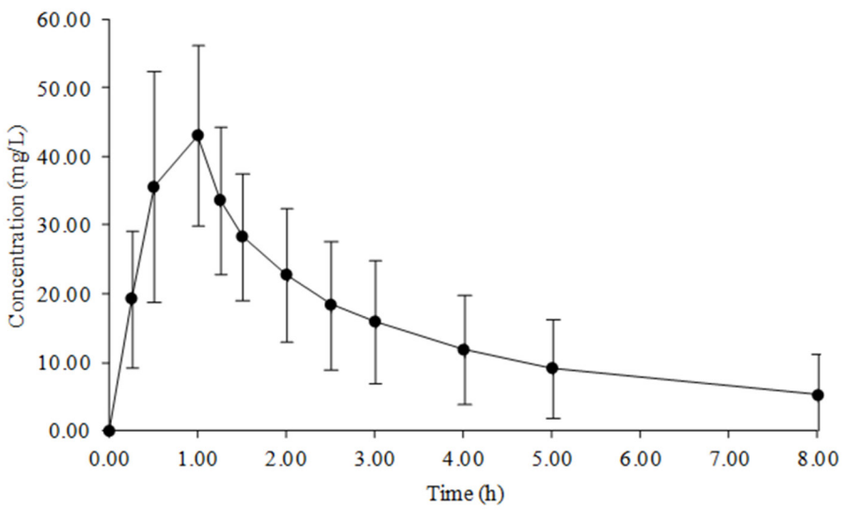

Figure 1. Mean plasma meropenem concentration-time data in fourteen critically ill patients

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

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 AUC_{0-8} of meropenem were significantly increased, whereas the CL was decreased although the difference was not significant[12]. The comparisons of C_{max} and C_{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 AUC_{0-8} 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.

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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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