Comparison of the Pharmacodynamics of Meropenem in Patients with Ventilator-Associated Pneumonia following Administration by 3-Hour Infusion or Bolus Injection

Sutep Jaruratanasirikul,* Somchai Sriwiriyajan, and Jarurat Punyo

Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, Thailand

Received 7 September 2004/Returned for modification 11 October 2004/Accepted 7 December 2004

The time that concentrations in serum are above the MIC (T>MIC) is the pharmacokinetic/pharmacodynamic parameter that correlates with efficacy of β-lactam antibiotics. The aim of this study was to demonstrate the T>MIC of meropenem when administered by a 3-h infusion compared with that when administered by bolus injection. The study was conducted with nine patients with ventilator-associated pneumonia. Each subject received meropenem in three regimens consecutively: (i) bolus injection of 1 g every 8 h for 24 h; (ii) 3-h infusion of 1 g every 8 h for 24 h; and (iii) 3-h infusion of 2 g every 8 h for 24 h. Following bolus injection, the percentages of the T>MICs of 16, 8, 4, and 1 μg/ml were 28.33% ± 11.67%, 45.89% ± 22.90%, 57.00% ± 24.82%, and 74.67% ± 17.94% of an 8-h interval, respectively. For the 3-h infusion of 1 g of meropenem, the percentages of the T>MICs of 16, 8, 4, and 1 μg/ml were 37.78% ± 20.57%, 58.11% ± 24.38%, 72.67% ± 21.97%, and 93.56% ± 6.84% of an 8-h interval, respectively. For the 3-h infusion of 2 g of meropenem, the percentages of the T>MICs of 16, 8, 4, and 1 μg/ml were 57.89% ± 24.26%, 72.89% ± 22.40%, 85.56% ± 16.42%, and 98.56% ± 3.28% of an 8-h interval, respectively. In conclusion, a 3-h infusion resulted in greater T>MICs than those after a bolus injection. For the treatment of infections caused by pathogens with intermediate resistance, a 3-h infusion of 2 g of meropenem every 8 h can provide concentrations in serum above the MIC of 16 μg/ml for almost 60% of an 8-h interval.

Pharmacodynamic analyses have been used in the development of antibiotic administration regimens that maximize antibacterial effects. Aminoglycosides, for example, exhibit concentration-dependent bacterial killing. Thus, increasing the peak serum drug concentration can enhance the bactericidal activity of these agents (12). On the other hand, β-lactam antibiotics exhibit primary time-dependent killing. Therefore, the time that concentrations in tissue and serum are above the MIC (T>MIC) is the pharmacokinetic/pharmacodynamic parameter that correlates with efficacy (3, 16), and the optimal method to maintain such serum drug concentrations would be to administer the agent by continuous infusion (2, 10, 11).

Meropenem is a carbapenem antibiotic agent with a broad spectrum of activity against several pathogens (17). In common with other β-lactams, the main pharmacokinetic/pharmacodynamic parameter that correlates with the therapeutic efficacy is the T>MIC, and administration by continuous infusion is the preferred route to maximize this parameter. However, in tropical countries the stability of meropenem is an important consideration when continuous infusion is to be used.

We recently conducted a study to compare the pharmacokinetics and pharmacodynamics of meropenem in normal volunteers when it was administered by a 3-h infusion or bolus injection regimen. The study revealed that a 3-h infusion of either 0.5 or 1 g of meropenem gives greater values for T>MIC than a 1-g bolus injection. We have therefore suggested that a 3-h infusion every 8 h may be a useful mode of administration in tropical countries (8). For the treatment of most serious infections, including ventilator-associated pneumonia (VAP), this drug should be administered at a dosage of 1 g intravenously every 8 h; if necessary, this dosage can be increased to a maximum of 2 g every 8 h (7). The aim of this study was to elucidate the pharmacodynamic parameter, T>MIC, of 1 and 2 g of meropenem when administered by a 3-h infusion compared with that of bolus injection regimens in these patients.

MATERIALS AND METHODS

Subjects. The study was conducted with patients who were intubated and receiving mechanical ventilation. The patients were eligible for the study if they met the following criteria: (i) older than 18 years and (ii) clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography associated with at least one of the following—purulent tracheal secretions, temperature of 38.3°C or higher, or a leukocyte count higher than 10,000/mm³. Patients were excluded from the study if they were pregnant or in circulatory shock (which was defined as a systolic blood pressure of <90 mm Hg and poor tissue perfusion) or had documented hypersensitivity to meropenem or an estimated creatinine clearance (determined by the Cockcroft-Gault method [1]) of <60 ml/min. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital, and written informed consent was obtained from each subject.

Drugs and chemicals. Meropenem was donated by AstraZeneca, and cefepime (internal standard) was donated by Bristol-Myers Squibb. All of the solvents were high-performance liquid chromatography grade.

Study design. The study was a randomized three-way crossover study. Meropenem was reconstituted according to the manufacturer’s guidelines. It was then diluted into two preparations: 1 g in 50 ml of normal saline solution and 2 g in 50 ml of normal saline solution. Each subject received meropenem in three regimens at room temperature (32 to 37°C) consecutively: (i) bolus injection of 1 g of meropenem over 10 min every 8 h for 24 h; (ii) 3-h infusion of 1 g of meropenem via an infusion pump at a constant flow rate every 8 h for 24 h; and (iii) 3-h infusion of 2 g of meropenem via an infusion pump at a constant flow rate every 8 h for 24 h. After completion of meropenem therapy for 3 days, all patients were appropriately treated with other antibiotics for 10 days.

* Corresponding author. Mailing address: Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand. Phone: 66-074-429385. Fax: 66-074-429385. E-mail: sutepj@psu.ac.th.

The study was a randomized three-way crossover study. Meropenem was donated by AstraZeneca, and cefepime (internal standard) was donated by Bristol-Myers Squibb. All of the solvents were high-performance liquid chromatography grade.

Study design. The study was a randomized three-way crossover study. Meropenem was reconstituted according to the manufacturer’s guidelines. It was then diluted into two preparations: 1 g in 50 ml of normal saline solution and 2 g in 50 ml of normal saline solution. Each subject received meropenem in three regimens at room temperature (32 to 37°C) consecutively: (i) bolus injection of 1 g of meropenem over 10 min every 8 h for 24 h; (ii) 3-h infusion of 1 g of meropenem via an infusion pump at a constant flow rate every 8 h for 24 h; and (iii) 3-h infusion of 2 g of meropenem via an infusion pump at a constant flow rate every 8 h for 24 h. After completion of meropenem therapy for 3 days, all patients were appropriately treated with other antibiotics for 10 days.
The mobile phase was 15 mM KH₂PO₄–acetonitrile–methanol (84:12:4, vol/vol) (pH 2.8) at a flow rate of 1 ml/min. The column effluent was monitored by UV detection (Waters 486 UV detector) at 308 nm. The peaks were recorded and integrated on a Waters 746 Data Module. The limit of detection of meropenem was 70 μg/liter.

**Blood sampling.** Meropenem pharmacokinetic studies were carried out during administration of the third dose of each regimen (16 to 24 h after the start of each regimen). Blood samples (approximately 5 ml) were obtained by direct venipuncture at the following times: before (time zero) and 10 and 30 min and 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 5, 6, and 8 h after the third dose of each regimen.

**Meropenem assay.** The concentrations of meropenem were determined by reverse-phase high-performance liquid chromatography. Ceftazidime (100 μg/ml) was used as the internal standard, and the samples were extracted by the method of Ozkan et al. (13). An aliquot of the extracted sample (50 μl) was injected, using an automated injection system (Waters 717 plus Autosampler; Waters Associates, Milford, Mass.), onto a Nova-Pak C₁₈ column (Waters Associates). The mobile phase was 15 mM KH₂PO₄-acetonitrile–methanol (84:12:4, vol/vol/vol) (pH 2.8) at a flow rate of 1 ml/min. The column effluent was monitored by UV detection (Waters 486 UV detector) at 308 nm. The peaks were recorded and integrated on a Waters 746 Data Module. The limit of detection of meropenem was 70 μg/liter.

The intraassay reproducibility values characterized by coefficients of variation 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 coefficients of variation, were 3.21, 2.98, and 3.74% for samples containing 2, 32, and 128 μg/ml, respectively.

**Pharmacokinetic and statistical analysis.** The elimination half-life was calculated as $t_{1/2} = \frac{\ln 2}{k_e}$, where $k_e$ is the elimination rate constant as published previously (14). The area under the concentration curve from 0 to 8 h (AUC₀–₈) was determined by the trapezoidal rule over 8 h. The total clearance (CLtot) was estimated as $CL_{tot} = \frac{\text{dose (mg)}}{\text{AUC₀–₈}}$, and the volume of distribution (V) was estimated as $V = CL_{tot}/k_e$. The maximum plasma concentration ($C_{max}$) and the minimum plasma concentration ($C_{min}$) were determined by visual inspection of the individual plasma concentration-time profiles. From the individually fitted concentration-time curves, the $T > $MICs were calculated for MICs of 16, 8, 4, and 1 μg/ml. Results were expressed as mean values ± standard deviations, and statistical comparisons were made using the Wilcoxon signed-rank test. P values of <0.05 were considered significant.

**RESULTS**

The mean serum meropenem concentrations for bolus injection and 3-h infusion are shown in Fig. 1. The pharmacokinetic parameters for bolus injection and 3-h infusion of meropenem are presented in Table 1. Nine patients were enrolled in the study. Six were male, and three were female. Their mean age was 39.56 ± 15.73 years (range, 16 to 62 years), and their mean weight was 54.19 ± 11.59 kg (range, 37 to 70 kg). *P. aeruginosa* was isolated from all patients for whom the MIC was 0.125 μg/ml for three isolations, 0.25 μg/ml for one isolation, 0.5 μg/ml for three isolations, and 6 μg/ml for two isolations. *Acinetobacter* sp. was isolated from two of nine patients for whom the MIC was 4 μg/ml. Both bolus injection and 3-h infusion were well tolerated, and there were no reported adverse events.

**FIG. 1.** Mean serum meropenem concentration-time data for nine patients with VAP following administration of 1 g by bolus injection (filled squares), 1 g by a 3-h infusion (open circles), and 2 g by a 3-h infusion (filled triangles).

**TABLE 1.** Pharmacokinetic parameters for meropenem administered by 3-h infusion and bolus injection

<table>
<thead>
<tr>
<th>Parametera</th>
<th>Bolus injection</th>
<th>3-h infusionb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 g</td>
<td>2 g</td>
</tr>
<tr>
<td>$C_{max}$ (μg/ml)</td>
<td>112.52 ± 34.33$^b$</td>
<td>30.24 ± 10.71$^a$</td>
</tr>
<tr>
<td>$C_{min}$ (μg/ml)</td>
<td>1.00 ± 1.78</td>
<td>2.28 ± 3.05</td>
</tr>
<tr>
<td>$AUC_{0–₈}$ (μg · h/ml)</td>
<td>136.27 ± 58.49</td>
<td>186.16 ± 79.51</td>
</tr>
<tr>
<td>$CL_{tot}$ (liter/h)</td>
<td>8.52 ± 3.20</td>
<td>6.39 ± 2.77</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.44 ± 0.56</td>
<td>1.02 ± 0.30</td>
</tr>
<tr>
<td>$k_e$ (h⁻¹)</td>
<td>0.53 ± 0.15</td>
<td>0.73 ± 0.18a</td>
</tr>
<tr>
<td>$V$ (liter)</td>
<td>15.99 ± 3.72</td>
<td>9.26 ± 2.43a</td>
</tr>
<tr>
<td>%T &gt; MIC ($μg/ml$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>28.33 ± 11.67</td>
<td>37.78 ± 20.57</td>
</tr>
<tr>
<td>8</td>
<td>45.89 ± 22.90</td>
<td>58.11 ± 24.38</td>
</tr>
<tr>
<td>4</td>
<td>57.00 ± 24.82</td>
<td>72.67 ± 21.97</td>
</tr>
<tr>
<td>1</td>
<td>74.67 ± 17.94</td>
<td>93.56 ± 6.84a</td>
</tr>
</tbody>
</table>

a $C_{max}$, maximum plasma concentration; $C_{min}$, minimum plasma concentration; $AUC_{0–₈}$, area under the concentration-time curve from 0 to 8 h; $CL_{tot}$, total clearance; $t_{1/2}$, half-life in serum; $k_e$, elimination rate constant; $V$, volume of distribution; $T > $MIC, time that the serum drug concentration was above the MIC.

b Mean ± standard deviation.

$^a$ P < 0.05 versus bolus injection; $^b$ P < 0.05 versus 3-h infusion of 1 g of meropenem.

**DISCUSSION**

Over the last decade, several investigators have attempted to establish the most appropriate administration techniques to optimize the bactericidal activity of parenteral antibiotics for the treatment of infections (2, 17). For $β$-lactams, it is generally accepted that the bactericidal effect of these agents is determined by the $T > $MICs for the pathogens (3, 16). Following manufacturers’ instructions, $β$-lactams are usually administered by intermittent injection; however, with this mode of administration, the high peak concentrations do not enhance the bactericidal activity of these agents, and during the dosing interval, drug concentrations may fall below the MIC for the pathogen. A previous study of critically ill patients proposed that meropenem serum concentrations from a 3-g continuous infusion over 24 h remained above the MIC for most common bacterial pathogens (15). However, meropenem, reconstituted in normal saline solution, is unstable when stored at room temperature in a tropical country (32 to 37°C) for 8 h. Drug concentrations decreased only 4% when this agent was stored at room temperature for 3 h (9). Animal infection model studies have shown that for most $β$-lactams, concentrations do not need to exceed the MIC for 100% of the dosing interval to achieve a significant antibacterial effect. Bacteriostatic effects of carbapenems are observed when serum drug concentrations are above the MIC for 20 to 26% of the dosing interval, whereas the $T > $MICs required for static effects of penicillins...
and cephalosporins are 29 to 34% and 35 to 53% of the dosing interval, respectively (5). Moreover, the mortality in animals infected with Streptococcus pneumoniae and treated with β-lactams is very low when levels of antibiotics exceed the MIC for 40 to 50% of the dosing interval (4). A previous study of healthy volunteers revealed that a 3-h infusion of 1 g of meropenem can maintain serum drug concentrations above the MIC for most pathogens in patients for 60% of an 8-h dosing interval (8). Thus, a 3-h infusion has been proposed as an appropriate mode of administration in tropical countries.

In this study, the serum drug concentration estimates for bolus injection of 1 g of meropenem in patients with VAP were higher than estimates in previous studies (7, 17). This may have been due to the low body weight of our patients when compared with that of patients in previous studies. We used the susceptibility breakpoint value for our pharmacodynamic analysis. The nonsusceptible microbiologic breakpoints of meropenem established by the National Committee for Clinical Laboratory Standards for most isolated pathogens are greater than 4 μg/ml. In this study, the mean serum concentrations after a 3-h infusion of 1 g of meropenem were above 4 μg/ml for approximately 72% of an 8-h dosing interval. Even when a bolus injection of 1 g of meropenem was used, the percentages of the T>MIC for 4 μg/ml were still almost 60% of the dosing interval. Therefore, from these data it appears that either a 3-h infusion or a bolus injection of 1 g of meropenem every 8 h can provide serum concentrations above the MIC of 4 μg/ml for 60% of the dosing interval. However, a 3-h infusion seems to result in greater T>MICs than those seen after bolus injection. In addition, in patients infected with pathogens for which the MIC is lower than 1 μg/ml, the required meropenem dosage may be reduced by one-half.

The MICs for P. aeruginosa isolated from two patients in our study were greater than 4 μg/ml. According to pharmacokinetic simulations with MICs for the pathogens, the mean serum drug concentrations obtained from a 3-h infusion of 1 g of meropenem were above 8 μg/ml for approximately 58% of an 8-h period. Meanwhile, the mean serum drug concentrations when administration was by a 3-h infusion of 2 g of meropenem were above 8 and 16 μg/ml for 72 and 57% of an 8-h period, respectively. In a previous study with healthy volunteers, a 3-h infusion of 2 g of meropenem could maintain serum drug concentrations above the MICs of 4 and 16 μg/ml for 73 and 48% of an 8-h period, respectively (6). Thus, for the treatment of infections caused by isolated pathogens with intermediate resistance, the meropenem dosage administered by a 3-h infusion should be increased to a maximum of 2 g every 8 h.

The outcomes of meropenem treatment by 3-h infusion and bolus injection could not be evaluated due to the small number of patients and the short duration of the treatment. However, during meropenem administration, no major adverse events related to the use of a 3-h infusion or bolus injection were observed.

In conclusion, a 3-h infusion results in greater T>MICs than those seen after bolus injection, indicating that intermittent infusion may be an appropriate mode of administration of meropenem in tropical countries. Moreover, for the treatment of infections caused by isolated pathogens with intermediate resistance, a 3-h infusion of 2 g of meropenem every 8 h can provide serum concentrations above the MIC of 16 μg/ml for almost 60% of the 8-h interval.

ACKNOWLEDGMENTS

Meropenem was generously donated by AstraZeneca, and ceftazime was generously donated by Bristol-Myers Squibb. This work was supported by a faculty grant from the Faculty of Medicine, Prince of Songkla University. We thank David Patterson for checking our English.

REFERENCES