Experimental verification of the efficacy of optimized two-step infusion therapy with meropenem using an in vitro pharmacodynamic model and Monte Carlo simulation

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Abstract In this study we compared the efficacy of a theoretically optimized two-step infusion therapy (OTIT; rapid first-step infusion and slow second-step infusion) to the efficacies of prolonged infusion therapy (PIT) and traditional 0.5 h infusion therapy (TIT) with meropenem against Pseudomonas aeruginosa using an in vitro pharmacodynamic model and a Monte Carlo simulation. In the in vitro pharmacodynamic model, the bactericidal effect against P. aeruginosa was evaluated for 8 h, which is the usual dosing interval of meropenem. It was confirmed that the durability of the bactericidal effect of OTIT (0.25–1 g/0.5 h + 0.25–1 g/4 h t.i.d.) was almost equal to that of PIT and superior to that of TIT (0.5–2 g/0.5–4 h t.i.d.). In addition, the initial bactericidal effects of OTIT were superior to those of the prolonged 4 h infusion. In the Monte Carlo simulation study, the probability of target attainments (PTAs) of all dosing regimens of OTIT at MICs of 2–8 μg/ml were apparently superior to those of TIT and 4- and 6 h-PIT, when the target therapeutic condition for serious life-threatening infections was the achievement of both the percentage of the dosing interval at which the drug concentration exceeds the MIC (%T_MIC) ≥ 50% and the peak level divided by the MIC (C_max/MIC) ≥ 4. Especially, the PTAs of the dosing regimens of 0.25–1 g/0.5 h + 0.25–1 g/4–6 h were excellent at MICs of 2–8 μg/ml. Against recent clinical isolates of P. aeruginosa in Japan, the dosing regimens of OTIT provided higher PTAs compared with those of TIT and 4- and 6 h-PIT. These results suggested that OTIT with sufficient pharmacokinetic conditions could be useful for enhancing the therapeutic efficacy of meropenem against serious life-threatening infections.

Keywords Pseudomonas aeruginosa · Serious infections · Prolonged infusion therapy · Monte Carlo simulation · Pharmacokinetic–pharmacodynamic (PK–PD)

Introduction

Pseudomonas aeruginosa is one of the most important nosocomial pathogens, and it causes severe morbidity and mortality worldwide [1, 2]. Furthermore, the emergence of multidrug-resistant (MDR) P. aeruginosa is a growing problem. Surveillance of nosocomial P. aeruginosa infections has revealed trends of increasing antimicrobial resistance, including carbapenem resistance and multidrug resistance [3–6]. Considering that there are few candidates for new antibiotics in the pharmaceutical development
pipeline targeting \textit{P. aeruginosa}, the judicious use of currently available agents, along with optimal dosing conditions, will be crucial in maximizing microbiological outcomes and preventing the further development of resistance.

Meropenem is a parenteral carbapenem with excellent activity against various Gram-positive and -negative bacteria, including \textit{P. aeruginosa}, which makes it a good choice for empirical therapy situations, such as its use against serious life-threatening infections in intensive care units (ICUs) [7]. Like other \(\beta\)-lactams, the main pharmacokinetic–pharmacodynamic (PK–PD) parameter that correlates with the therapeutic efficacy of meropenem is the percentage of the dosing interval at which the drug concentration exceeds the MIC (\%\(T_{\geq \text{MIC}}\)). Therefore, administration by continuous infusion would most effectively allow for maximization and control of the \%\(T_{\geq \text{MIC}}\) in achieving a target of 100%. However, meropenem is only stable for approximately 6 h at room temperature and is thus an inappropriate agent for continuous infusion unless it is administered in a cold pouch [8]. Recently, another pharmacodynamically influenced dosing strategy; namely, prolonged infusion therapy (PIT, extending infusions to 3–4 h), has been adopted for meropenem. As compared with traditional 0.5 h infusion therapy (TIT), this dosing methodology increases the \%\(T_{\geq \text{MIC}}\), while remaining within the limits of the drug solution stability constraints [9–11]. In fact, it was reported that prolonged infusion (more than 3 h) of meropenem for the treatment of central nervous system infections resulted in adequate exposure at the site of infection and a successful clinical response [9, 12]. Furthermore, it was reported that prolonged (4 h) drip infusion of meropenem was useful for the improvement of clinical efficacy against life-threatening pneumonia [13].

Of note, \(\beta\)-lactams, including meropenem, also display some concentration-dependent activity, because maximum killing is usually achieved at greater than two to four times the MIC in in vitro killing-curve studies [14, 15]. So, it is considered that the initial bactericidal effect of PIT is reduced because of both the decrease in \(C_{\text{max}}\) and delay in \(T_{\text{max}}\). This prompted us to design a theoretically optimized two-step infusion therapy (OTIT; rapid first-step infusion and slow second-step infusion) with sufficient \%\(T_{\leq \text{MIC}}\) and \(C_{\text{max}}\) and short \(T_{\text{max}}\). It is expected that the therapeutic effect of meropenem, especially against serious life-threatening infections in ICUs, for which the initial treatment is considered to be important, will be further enhanced by OTIT in comparison with PIT. In this paper, we report our investigation of the efficacy of OTIT with meropenem against \textit{P. aeruginosa} using an in vitro pharmacodynamic model and Monte Carlo simulation in 0.5, 1, and 2 g t.i.d. models.

### Materials and methods

#### Organisms

Five clinical isolates of \textit{P. aeruginosa} (SP-18574, SP-18572, SP-11939, SP-11942, and SP-11994) collected in Japan were used in the in vitro pharmacodynamic model.

#### Antimicrobial agent

Meropenem (Dainippon Sumitomo Pharma, Osaka, Japan) was used in this study.

#### Susceptibility testing

MICs were determined by the agar dilution method, using Mueller–Hinton agar (MHA; Becton–Dickinson, Sparks, MD, USA) according to CLSI guidelines [16, 17]. The final inocula were approximately \(10^4\) cfu/spot.

#### In vitro pharmacodynamic model

Various human plasma concentration–time profiles of meropenem, based on the pharmacokinetic data from a phase I study [18], were simulated in the central compartment (200 ml), using a computer-associated autosimulation system (PASS-400; Dainippon Seiki, Kyoto, Japan). The central compartment of the model was inoculated with an exponential-phase culture of the respective bacterial strain tested (the initial inoculum size was approximately \(10^6\) cfu/ml) and the simulation was started. Mueller–Hinton broth (MHB; Becton–Dickinson) was used as bacterial growth medium and antibiotic dilution medium. Viable cell counts were determined serially during 8 h, which is the usual dosing interval of meropenem. A portion (1.3 ml) of the bacterial broth culture was removed 1, 2, 4, 6, and 8 h after the start of simulation, and aliquots of tenfold serial dilutions were plated on MHA.

Ten units of \(\beta\)-lactamase from \textit{Bacillus cereus} 569/H9 (EMD Chemicals, Darmstadt, Germany) was added to each sample before plating to inactivate the meropenem. The following 11 regimens were simulated in this model: 0.5 g t.i.d. model (0.5 g/0.5 h, 0.5 g/2 h, 0.5 g/4 h, 0.5 g/6 h, and 0.25 g/0.5 h + 0.25 g/4 h), 1 g t.i.d. model (1 g/0.5 h, 1 g/2 h, 1 g/4 h, and 0.5 g/0.5 h + 0.5 g/4 h), 2 g t.i.d. model (2 g/0.5 h, 2 g/2 h, 2 g/4 h, and 1 g/0.5 h + 1 g/4 h).

#### Determination of meropenem concentration

Concentrations of meropenem were determined by high-performance liquid chromatography (HPLC); 0.2 ml of the bacterial broth culture was taken during in vitro
pharmacodynamic model experiments. Samples were stored at −80°C until analysis. An aliquot of the sample (50 μl) was separated on a Puresil C18 column (4.6 mm × 150 mm; Waters, Milford, MA, USA) with PIC®. A low UV Reagent (Waters) solution-methanol (3:1, v/v) mobile phase delivered at 1.0 ml/min. The HPLC system (LC-2010C; Shimadzu, Kyoto, Japan) was controlled by a CLASS-VP workstation (Shimadzu) and the wavelength for the detection of meropenem was 300 nm.

Monte Carlo simulation

A 10,000-subject Monte Carlo simulation was performed to calculate the probability of target attainments (PTAs) for each dosing regimen, using Crystal Ball 7 (Kozo Keikaku Engineering, Tokyo, Japan). Both %T > MIC ≥ 50% and the peak level divided by the MIC (Cmax/MIC) ≥ 4 were set as target therapeutic conditions for serious life-threatening infections. The pharmacodynamic index of %T > MIC ≥ 50% was used because this is a requirement for the maximum bactericidal effect of carbapenems [19]. The pharmacodynamic index of Cmax/MIC ≥ 4 was used because it is considered that this is related to an earlier onset of bactericidal activity [14, 15]. The %T > MIC and Cmax/MIC were calculated using the following one-compartment intravenous infusion equation, modified from an equation reported previously [20]:

(A) If the meropenem concentration falls to the MIC level during the second step of infusion

\[
T_{\text{MIC}} = T_1 + \left( \frac{\ln R_0 (1 - \exp(-CLT_1/V)) - R_0}{CL \text{MIC} - R_0} \right) V CL \\
- \left( \ln \frac{R_0}{R_0 - CL \text{MIC}} \right) \frac{V}{CL} 
\]

(B) If the meropenem concentration falls to the MIC level after the second step of infusion is terminated

\[
T_{\text{MIC}} = T_1 + T_2 + \left( \frac{\ln R_0 + (R_0 - R_0) \exp(-CLT_2/V) - R_0 \exp(-CL(T_1 + T_2)/V)}{CL \text{MIC}} \right) \frac{V}{CL} \\
- \left( \ln \frac{R_0}{R_0 - CL \text{MIC}} \right) \frac{V}{CL} 
\]

\[
\%T_{\text{MIC}} = \frac{T_{\text{MIC}}}{100/DI} 
\]

\[C_{\text{max}}/\text{MIC} = (R_0/CL)(1 - \exp(-CLT_1/V))/\text{MIC},\]

where \(T_1\) is the infusion time of the first step of infusion (h), \(T_2\) is the infusion time of the second step of infusion (h), \(R_0\) is the first-step infusion rate calculated as first-dose/\(T_1\) (mg/h), \(R_0\) is the second-step infusion rate calculated as second-dose/\(T_2\) (mg/h), CL is the plasma clearance rate (l/h), V is the volume of distribution (l), exp is exponent, and DI is the dosing interval (h).

Pharmacokinetic variability derived from phase I data of meropenem (CL 15.58 ± 1.66 l/h, V 21.16 ± 2.62 l) was used [21]. During simulations, pharmacokinetic parameters were assumed to follow log-normal distribution. PTAs were determined for MICs between 0.25 and 16 μg/ml.

The following 21 regimens were investigated: 0.5 g t.i.d. model (0.5 g/0.5 h, 0.5 g/2 h, 0.5 g/4 h, 0.5 g/6 h, 0.25 g/0.5 h + 0.25 g/2 h, 0.25 g/0.5 h + 0.25 g/4 h, and 0.25 g/0.5 h + 0.25 g/6 h), 1 g t.i.d. model (1 g/0.5 h, 1 g/2 h, 1 g/4 h, 1 g/6 h, 0.5 g/0.5 h + 0.5 g/2 h, 0.5 g/0.5 h + 0.5 g/4 h, and 0.5 g/0.5 h + 0.5 g/6 h), 2 g t.i.d. model (2 g/0.5 h, 2 g/2 h, 2 g/4 h, 2 g/6 h, 1 g/0.5 h + 1 g/2 h, 1 g/0.5 h + 1 g/4 h, and 1 g/0.5 h + 1 g/6 h).

MIC data

The MICs of meropenem against 306 clinical isolates of P. aeruginosa collected in Japan during 2004 were obtained from nationwide surveillance in Japan [22]. These MIC data were used for the organism-specific PTA analysis. The PTAs were determined by Monte Carlo simulation under the same conditions as above except for the MICs used. During simulations, MICs were assumed to follow custom distributions.

Results

Theoretical PK–PD analysis

The concentration–time profile and PK–PD parameters of meropenem in each dosing regimen simulated by the in vitro pharmacodynamic model are shown in Fig. 1 and Table 1. It was considered that it was possible to obtain sufficient %\(T_{\text{MIC}}\) and \(C_{\text{max}}/\text{MIC}\) and short \(T_{\text{MIC}}\) by OTIT in comparison with TIT and PIT in all three dosing models against each target MIC.
In vitro pharmacodynamic model study

In the in vitro pharmacodynamic model experiments, the observed concentration–time profile of meropenem fitted satisfactorily to the target concentration–time profile of meropenem, as shown in Fig. 1, in all three dosing models (data not shown). The bactericidal activities of meropenem against *P. aeruginosa* under conditions simulating the pharmacokinetics at each dosing regimen are shown in Figs. 2, 3, 4.

In the 0.5 g t.i.d. model of the in vitro pharmacodynamic model study using a meropenem-susceptible strain of *P. aeruginosa* (SP-18574, MIC 2 µg/ml), the viable cell counts of the strain at 8 h after start of simulation decreased, but the initial killing rate was reduced by extending the infusion time, probably because of both the decrease in *C*<sub>max</sub> and the delay in *T*<sub>max</sub>, as expected (Fig. 2a). It was confirmed that the viable cell counts of the strain treated by OTIT at 8 h after start of simulation were lower than those of the strain treated by both the traditional 0.5 h infusion and prolonged 4 h infusion methods. Furthermore, the initial killing rate of OTIT was significantly higher than that of the prolonged 4 h infusion and was equivalent to that of the 0.5 h infusion (Fig. 2b).

In the 1 g t.i.d. model study using a meropenem-susceptible strain of *P. aeruginosa* (SP-18572, MIC 4 µg/ml), it was confirmed that the bactericidal effect of OTIT was greater than those of the 0.5 h infusion and the 2 or 4 h infusions at 8 h after the start of simulation. Furthermore, the initial killing rate of OTIT was significantly higher than those of the prolonged 2 and 4 h infusions (Fig. 3).

In the 2 g t.i.d. model studies using three strains of meropenem-intermediately resistant *P. aeruginosa* (MIC 8 µg/ml), the bactericidal effect of OTIT was equivalent to those of the other dosing regimens; however, the initial killing rate of OTIT in each test was superior to that of the prolonged 4 h infusion and equivalent to that of the 2 h infusion (Fig. 4).

**Table 1**

<table>
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<tr>
<th>Model</th>
<th>Dosing regimen</th>
<th>Target MIC (µg/ml)</th>
<th>%T &lt;sub&gt;MIC&lt;/sub&gt; (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th><em>C</em>&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sup&gt;a&lt;/sup&gt;</th>
<th><em>T</em>&lt;sub&gt;max&lt;/sub&gt; (h)</th>
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<tr>
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<td>14.4</td>
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</tr>
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<td>7.1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>0.5 g/4 h</td>
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<td>64.1</td>
<td>4.1</td>
<td>4</td>
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<tr>
<td></td>
<td>0.5 g/6 h</td>
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<td>6</td>
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<td>7.2</td>
<td>0.5</td>
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<td>38.4</td>
<td>14.4</td>
<td>0.5</td>
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<td></td>
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<td>48.3</td>
<td>7.1</td>
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<td>1 g/4 h</td>
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<td>64.1</td>
<td>4.1</td>
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<td>64.2</td>
<td>7.2</td>
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<td>2 g/0.5 h</td>
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<td>38.4</td>
<td>14.4</td>
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<td>2 g/2 h</td>
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<td>7.1</td>
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<td>64.1</td>
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<tr>
<td></td>
<td>1 g/0.5 h + 1 g/4 h</td>
<td></td>
<td>64.2</td>
<td>7.2</td>
<td>0.5</td>
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</tbody>
</table>

<sup>a</sup> %T <sub>MIC</sub> (percentage of the dosing interval at which the drug concentration exceeds the MIC) and *C*<sub>max</sub>/MIC (peak level divided by the MIC) were calculated from the pharmacokinetic data of healthy Japanese adults in a phase I study of meropenem.

**Fig. 1** Concentration-time profile of each dosing regimen of meropenem simulated in an in vitro pharmacodynamic model. **a** 0.5 g t.i.d. model, **b** 1 g t.i.d. model, **c** 2 g t.i.d. model.
Monte Carlo simulation study

The results of the Monte Carlo simulation with 10,000 simulated subjects for various dosing regimens of meropenem against target pathogens with each MIC are shown in Tables 2, 3, 4.

In the 0.5 g t.i.d. model, the PTAs of all dosing regimens were almost 100% at MICs of ≤1 μg/ml, except for the dosing regimen of the 0.5 h infusion, and the PTAs were 0% at MICs of ≥4 μg/ml. At an MIC of 2 μg/ml, the PTAs of the dosing regimens of the 0.5 h infusion and the prolonged 4 or 6 h infusions were 16.2, 29.3, and 0%, respectively. The PTAs of the dosing regimens of OTIT and the 2 h infusion were apparently superior to those of the above three regimens; especially, the PTAs of the dosing regimens of 0.25 g/0.5 h ? 0.25 g/4 h and 0.25 g/0.5 h ? 0.25 g/6 h were as high as 98.0% (Table 2).

In the 1 g t.i.d. model, the PTAs of all dosing regimens were almost 100% at MICs of ≤2 μg/ml, except for the dosing regimen of the 0.5 h infusion, and the PTAs were 0% at MICs of ≥8 μg/ml. At an MIC of 4 μg/ml, the PTAs of the dosing regimens of the 0.5 h infusion and the prolonged 4 and 6 h infusions were 16.2, 29.3, and 0%, respectively. The PTAs of the dosing regimens of OTIT and the 2 h infusion were apparently superior to those of the above three regimens; especially, the PTAs of the dosing regimens of 0.25 g/0.5 h + 0.25 g/4 h and 0.25 g/0.5 h + 0.25 g/6 h were as high as 98.0% (Table 2).

In the 2 g t.i.d. model, the PTAs of all dosing regimens were almost 100% at MICs of ≤4 μg/ml, except for the dosing regimen of the 0.5 h infusion, and the PTAs were 0% at an MIC of 16 μg/ml. At an MIC of 8 μg/ml, the PTAs of the dosing regimens of the 0.5 h infusion and the prolonged 4 h and 6 h infusions were 16.6, 30.1, and 0%,
respectively. The PTAs of the dosing regimens of OTIT and the 2 h infusion were apparently superior to those of the above three regimens; especially, the PTAs of the dosing regimens of 1 g/0.5 h + 1 g/4 h and 1 g/0.5 h + 1 g/6 h were as high as 98.1 and 98.0%, respectively (Table 4).

**Table 2** PTAs for various dosing regimens of meropenem (0.5 g t.i.d.) against target pathogens with each MIC

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>PTAs for each dosing regimen (%)</th>
<th>0.5 g/0.5 h</th>
<th>0.5 g/2 h</th>
<th>0.5 g/4 h</th>
<th>0.5 g/6 h</th>
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<th>0.25 g/0.5 h + 0.25 g/4 h</th>
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**Table 3** PTAs for various dosing regimens of meropenem (1 g t.i.d.) against target pathogens with each MIC

<table>
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<th>MIC (µg/ml)</th>
<th>PTAs for each dosing regimen (%)</th>
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<th>1 g/4 h</th>
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**Table 4** PTAs for various dosing regimens of meropenem (0.5 g t.i.d.) against target pathogens with each MIC

<table>
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<th>MIC (µg/ml)</th>
<th>PTAs for each dosing regimen (%)</th>
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**a** Target therapeutic condition: %T_{50\%\text{MIC}} \geq 50\% and \text{C}_{\text{max}/\text{MIC}} \geq 4

respectively.
The distribution of meropenem MICs against 306 clinical isolates of *P. aeruginosa* collected in Japan during 2004 is shown in Table 5. The PTAs for various dosing regimens of meropenem against these clinical isolates of *P. aeruginosa* are shown in Table 6.

In the 0.5 g t.i.d. model, the PTAs of the dosing regimens of OTIT and the 2 h infusion were superior to those of the 0.5 h infusion and prolonged 4 and 6 h infusions, but they were less than 80%.

In the 1 g t.i.d. model, the PTAs of the dosing regimens of OTIT and the 2 h infusion were superior to those of the 0.5 h infusion and the prolonged 4 and 6 h infusions, and exceeded 80%.

In the 2 g t.i.d. model, the PTAs of all dosing regimens exceeded 80% and the PTAs of the dosing regimens of OTIT and the 2 h infusion were almost as high as 90%, being superior to those of the 0.5 h infusion and the prolonged 4 and 6 h infusions.

### Discussion

Recently, as well as higher doses or increased daily frequency of administration, PIT has often been the preferred...
mode for carbapenem therapy in order to increase the $\%T_{>\text{MIC}}$ while remaining within the limits of the drug solution stability constraints [9–11, 23]. It was reported that prolonged infusion of meropenem for the treatment of central nervous system infections resulted in adequate exposure at the site of infection and a successful clinical response [9, 12]. Furthermore, it was reported that prolonged (4 h) drip infusion of meropenem was useful for the improvement of clinical efficacy against life-threatening infections in ICUs, for which the initial treatment is considered to be important, would be further enhanced by OTIT compared with that by PIT. So, we compared the efficacies of OTIT with the efficacies of PIT and TIT with meropenem against recent clinical isolates of $P$. aeruginosa in Japan, the dosing regimens of OTIT and the 2 h infusion provided higher PTAs compared with those of the other regimens in all three models. However, at 0.5 g t.i.d., which is usually prescribed as a high dose in Japan, the PTAs of the dosing regimens of OTIT and the 2 h infusion were, at most, about 75%, so it was suggested that even these regimens might be insufficient for the treatment of serious pseudomonal infections. By using doses greater than 0.5 g t.i.d., which are generally used for serious infections in many countries except Japan, the PTAs of the dosing regimens of OTIT exceeded 80%, so it was considered that OTIT with a high dose (≥1 g t.i.d.) could be a better therapeutic regimen for the treatment of serious life-threatening infections caused by $P$. aeruginosa. In addition, it was considered that the 2 h infusion was relatively proportionate for $\%T_{>\text{MIC}}$, $C_{\text{max}}$, and $T_{\text{max}}$ among PIT strategies that might produce therapeutic efficacy equivalent to that of OTIT.

In the present study, first, we evaluated the efficacy of PIT with meropenem using an in vitro pharmacodynamic model. We evaluated bacterial cell counts at 8 h after the start of simulation as the durability of the bactericidal effect, and we also evaluated the killing rate during the first 2 h as the initial bactericidal effect. The durability of the bactericidal effect of meropenem was improved by PIT, but the initial bactericidal effect was reduced, probably because of both the decrease in $C_{\text{max}}$ and delay in $T_{\text{max}}$. From this result, it was considered that the initial drug concentration after the start of dosing was important for the initial bactericidal effect. This finding prompted us to design the OTIT strategy with sufficient $\%T_{>\text{MIC}}$ and $C_{\text{max}}$, and short $T_{\text{max}}$. It was expected that the therapeutic effect of meropenem, especially against serious life-threatening infections in ICUs, for which the initial treatment is considered to be important, would be further enhanced by OTIT compared with that by PIT. So, we compared the efficacy of OTIT with the efficacies of PIT and TIT with meropenem against $P$. aeruginosa using an in vitro pharmacodynamic model and a Monte Carlo simulation. In the in vitro pharmacodynamic model, it was verified that it was possible to obtain sufficient $\%T_{>\text{MIC}}$ and $C_{\text{max}}$, and short $T_{\text{max}}$ using OTIT in comparison with TIT and PIT in all three dosing models. In these experiments, it was confirmed that the durability of the bactericidal effect of OTIT (0.25–1 g/0.5 h + 0.25–1 g/4 h t.i.d.) was almost equal to that of PIT and superior to that of TIT (0.5–2 g/0.5–4 h t.i.d.). With regard to the initial bactericidal effects, those of OTIT were superior to those of prolonged 4 h infusion. In all three models, it was considered that both the higher $C_{\text{max}}$ and shorter $T_{\text{max}}$ of OTIT contributed to the strong initial bactericidal effects.

In the Monte Carlo simulation study, we set both $\%T_{>\text{MIC}} \geq 50\%$ and $C_{\text{max}}/\text{MIC} \geq 4$ as the target conditions for the effective treatment of serious life-threatening infections. Pharmacokinetic parameters, calculated using a one-compartment model [21], were used in the simulation, because a one-compartment intravenous infusion equation was used for calculating $\%T_{>\text{MIC}}$ and $C_{\text{max}}/\text{MIC}$. In the analysis against target pathogens with each MIC, the PTAs of the dosing regimens of OTIT and the 2 h infusion were apparently superior to those of the traditional 0.5 h infusion and the prolonged 4 and 6 h infusions. In particular, the PTAs of the dosing regimens of 0.25–1 g/0.5 h + 0.25–1 g/4–6 h were excellent at MICs of 2–8 μg/ml. In addition, in the simulation based on the MIC distribution of meropenem against recent clinical isolates of $P$. aeruginosa in Japan, the dosing regimens of OTIT and the 2 h infusion were more effective for $\%T_{>\text{MIC}}$, $C_{\text{max}}$, and $T_{\text{max}}$ than that by PIT. So, OTIT may be a better therapeutic regimen for preventing resistance development compared to PIT.

In conclusion, from the results of the present study, it was suggested that OTIT with sufficient pharmacokinetic conditions could be useful for enhancing the efficacy of meropenem against serious life-threatening infections, such as infections in ICUs. In the near future, it will be desirable to evaluate the clinical efficacy of OTIT in patients.

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References

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