Optimal Dosage Regimen of Meropenem for Pediatric Patients Based on Pharmacokinetic/Pharmacodynamic Considerations

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Summary: A population pharmacokinetic (PK) model for meropenem in Japanese pediatric patients with various infectious diseases was developed based on 116 plasma concentrations from 50 pediatric patients. The population PK parameters developed in this analysis are useful for calculation of the percent time above minimum inhibitory concentration (%T >MIC) and for optimal dosing of meropenem in pediatric patients. After dosing at 20 mg/kg t.i.d. by 0.5-h infusion (approved standard dose for pediatric patients in Japan), the target value of 50%T >MIC was achieved, indicating that 20 mg/kg t.i.d. by 0.5-h infusion is effective for susceptible bacteria. In contrast, for bacteria with higher MICs such as Pseudomonas aeruginosa (MIC ≥ 2 µg/mL), the probability of target attainment of 50%T >MIC was 60.7% at a dose of 40 mg/kg t.i.d. by 0.5-h infusion (highest dose approved for pediatric patients in Japan). The simulations described in this article indicated that 40 mg/kg t.i.d. with a longer infusion duration (e.g., 4 h) is more effective against bacteria with a MIC higher than 2 µg/mL. The predicted probability of target attainment for 50%T >MIC (97.0%) was well correlated not only to the microbiological efficacy rate (97.0%) but also to the clinical efficacy rate (95.9%) in the present phase 3 study.

Keywords: meropenem; %T >MIC; PK/PD; pediatrics; Monte Carlo simulation

Introduction

Meropenem is a widely used carbapenem antibiotic with a broad spectrum of activity that covers most gram-positive and gram-negative bacteria. Many pharmacokinetic (PK)/pharmacodynamic (PD) simulations (Monte Carlo simulation) for meropenem have been reported, and such simulations are considered to be an important approach for predicting antibacterial efficacy of various dosages. 1-9 All simulations considered the percent time above minimum inhibitory concentration (%T >MIC) as the important PD index for meropenem. Levels of 20–30%T >MIC were proposed to achieve bacteriostatic effects and 40–50%T >MIC to achieve bactericidal outcomes. 1-9 Some of these reports estimated target attainment rates of bacteriostatic exposures and/or bactericidal exposures at various dosage regimens against various values of MIC, 1,3-6 and some estimated target attainment rates against various strains of bacteria based on MIC distribution data from surveillance studies. 1,2,5-9 Additionally, relationships of target attainment rates with clinical effectiveness were also reported. 4,10,11

For PK/PD simulation, both MIC distribution profiles as PD data and the population PK parameters, including population mean and inter-individual variability, are required. PK/PD simulations of meropenem for Japanese populations have been reported based on PK parameters obtained from healthy subjects. 7 One population PK analysis of meropenem was performed for pediatric patients in the USA, 12 but it did not predict PK/PD target attainment

Received; April 2, 2011, Accepted; June 24, 2011
J-STAGE Advance Published Date: July 12, 2011, doi:10.2133/dmpk.DMPK-11-RG-027

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against various MICs or various bacterial species based on their model.

The aim of this study was to investigate effective dosage regimens in Japanese pediatric patients. First, a population PK model of meropenem for Japanese pediatric patients was developed. Based on the developed population PK model, %T>MIC values of meropenem against various bacteria with various MICs were simulated. The target attainment of %T>MIC values for various dosage regimens were simulated to consider effective dosage strategy.

Methods

Study protocol: An open-labeled phase 3 study in pediatric patients was conducted in Japan from April 2001 through May 2002. The purpose of this phase 3 study was to evaluate the efficacy, safety, and PK profile of meropenem in the treatment of hospitalized infants and children with various infections. The phase 3 study was conducted in accordance with the Declaration of Helsinki and domestic regulations on clinical trials (Japanese Good Clinical Practice (GCP) guidance) and with Ethical Committee approval. The parents or legal guardians of all subjects gave written informed consent allowing participation in this study.

Study subjects were patients in need of treatment with carbapenem; the age requirement was from 29 days to 16 years and the subjects’ body weights had to be ≥3.9 kg (boys) and ≥3.7 kg (girls). The clinical response at the end of the treatment was mainly categorized into five groups: excellent, good, fair, poor, or unable to evaluate. The microbiological response during the treatment was classified into four groups: eradicated, presumed eradicated, decreased, or unable to evaluate.

Subjects: A total of 50 pediatric patients were enrolled in the phase 3 study for evaluation of PK profile. The subjects suffered from respiratory tract infection, meningitis, presumed sepsis, urinary tract infection, sepsis, or other infections. The subjects ranged in age from 0 to 13 years (mean ± S.D. 3.1 ± 3.2) years, and their mean weight (± S.D.) was 14.8 ± 8.1 kg.

Meropenem dosage: Meropenem was administered intravenously every 8 h at a dose of 10 mg/kg (n = 6), 20 mg/kg (n = 36), or 40 mg/kg (n = 8) t.i.d. by 0.5 h or longer infusion duration. The meropenem dose for each patient was determined according to the disease severity or symptoms of the patient by the physicians in charge.

Blood sampling: Plasma concentrations and patient data were obtained from the phase 3 study. Plasma samples were collected for meropenem assay at 15–25 min after the start of infusion or at 15 min to 6 h after end of infusion. Because full-screen sampling from the same pediatric patients was not appropriate, sampling was conducted as many times as possible during the phase 3 study. Two to four samples of blood were drawn from each patient in heparinized tubes. After centrifugation, plasma samples were frozen and stored until assay.

Analytical procedure: Plasma concentrations of meropenem (116 data points) were determined using high-performance liquid chromatography (HPLC). All plasma samples collected in the clinical study were analyzed at Mitsubishi Chemical BCL, Inc. (Tokyo, Japan). Each plasma sample was mixed with an equal volume of 1 M 3-morpholinopropanesulfonic acid (MOPS) buffer solution as a stabilizer and transferred to an ultrafiltration device and centrifuged at 12000 rpm (approximately 8000 g) for 5 min. Filtrate was injected into the HPLC system for analysis and chromatographically separated on a reversed-phase column (Hypersil C18, 4.6 mm Φ × 10 cm, 3 µm). The detector wavelength was set to 300 nm. The mobile phase consisted of PIC A (tetrabutylammonium phosphate) solution and methanol (5/1, v/v). The flow rate was 1.0 mL/min. The correlation of the regression line was greater than 0.98. Meropenem in the plasma samples was quantified using the peak area of standard samples for calibration; the lower quantitation limit was 0.05 µg/mL. This analytical method was validated for selectivity (no peak interfering with peak of meropenem, n = 6), linearity (r = 0.999), accuracy (intra-day assay: −4.4% to 3.4%, n = 5, inter-day assay: −5.7% to 0.9%, n = 5), precision (intra-day assay: −2.9% to 4.5%, n = 5, inter-day assay: 3.6% to 7.4%, n = 5), recovery (97.2% to 103.6% at 0.05, 10, and 200 µg/mL), calibration curve (0.05–200 µg/mL), and stability (stored first at −20°C for 96 h, and then at −80°C for 60 days).

Bacteriological tests: Blood from patients was collected and examined. The samples were collected prior to the drug treatment, at the middle of the treatment, and on the last day. Isolation and identification of causative bacteria were performed by standard procedures. The MICs of each antibacterial drug against the isolated strains were measured in accordance with the Clinical Laboratory Standards Institute guidelines.

Population PK model development: Analysis of data was carried out using the computer software package NONMEM (double-precision, version V, level 1.1, GloboMax, LLC, a division of ICON, USA) for nonlinear mixed-effects modeling with an Intel Visual Fortran Compiler (version 9.1 or later, Intel Corporation, USA) on a Microsoft Windows XP Professional operation system (version 2002, Microsoft Corporation, USA). The NONMEM companion interface used was PDx-POP (version 2, Globo-Max, LLC, a division of ICON, USA). Output files for the population analysis results were produced using SAS (version 8.2, SAS Institute, Japan) or Microsoft Office Excel 2003 (Microsoft Corporation, USA). Figures were drawn using Origin (version 7.5, OriginLab Corporation, USA).

The first-order conditional estimation with interaction (FOCE-INTER) method was adopted for PK model development. An exponential model was used to describe the inter-individual variability, as described below using total body clearance (CL) as an example:
\[ \text{CL}_j = \text{TVCL} \times \exp(\eta_{\text{CL}}) \]

where \( \eta_{\text{CL}} \) is a random variable that represents the difference between individual clearance of the \( j \)th individual (\( \text{CL}_j \)) and the population mean value (\( \text{TVCL} \)). The random variable \( \eta_{\text{CL}} \) is normally distributed with an expectation of zero and a variance of \( \omega_{\text{CL}}^2 \).

Similarly, a log-normal distribution was modeled as described for the intra-individual (residual) variability as follows:

\[ C_j = C_{\text{pred},j} \times \exp(\epsilon_j) \]

where \( C_j \) is the \( j \)th observed plasma concentration of meropenem for the \( j \)th individual, \( C_{\text{pred},j} \) is the concentration predicted by the population PK model and \( \epsilon_j \) is a randomly distributed variable with mean of zero and variance of \( \sigma^2 \).

The effects of the patient characteristics and clinical laboratory test values on meropenem PK parameters were investigated graphically using post hoc estimates of \( \eta \), and these covariate candidates were used for the first screening. For covariate candidates showing high correlation with \( \eta \), the covariate models for PK parameters were basically described according to a power function, as described below for CL as an example:

\[ \text{CL} = \text{TVCL} \times \left( \frac{\text{WT}}{\text{WT}_{\text{geomean}}} \right)^{\theta_{\text{CL,WT}}} \]

where WT is body weight as an example of a covariate candidate. WT_{geomean} is the geometric mean (15 kg) of WT and \( \theta_{\text{CL,WT}} \) is the influence factor. TVCL reveals a typical value of clearance, which describes CL when WT is equal to the geometric mean of WT in the population.

Model selection was based on an extended least-squares method (the maximum likelihood objective function). The minimum value of the NONMEM objective function (OBJ) was used as a statistic for choosing suitable models during the model-building process. The difference in OBJ approximates a \( \chi^2 \) distribution with degrees of freedom equal to the number of added or reduced parameters. At first, a forward inclusion procedure was performed in NONMEM to build the full model, and then a backward deletion procedure was applied to the final model candidate. For the forward inclusion process, a decrease in OBJ of at least 3.84 (\( P = 0.05 \), 1 degree of freedom) was used to incorporate a covariate into the model. For the backward deletion process, an increase in OBJ of at least 6.63 (\( P = 0.01 \), 1 degree of freedom) was required to retain the covariate.

Model validation: The model was evaluated by goodness of fit with graphical displays. The observed concentrations versus the predicted concentrations were investigated to determine if the model described the data accurately.

The reliability and stability of the final population PK parameters were confirmed by a bootstrap technique. One thousand datasets were reconstructed by resampling from the original data set and 1000 sets of population PK parameters were estimated, using the same model structure. Non-parametric, empirical 95% confidence intervals were calculated by the 2.5th and 97.5th percentiles of the resulting parameter distributions from the bootstrap runs.

**PK/PD simulation:** Plasma concentrations of meropenem at doses of 20 mg/kg t.i.d. and 40 mg/kg t.i.d. (basically 0.5-h infusion) were simulated for 1000 virtual subjects with a body weight of 15 kg at each dose. The virtual plasma concentration data set with a grid interval of 0.01 h was generated by SAS and NONMEM using $\text{SIMULATION}$ mode. Individual CL values were generated from a log-normal distribution based on the population PK mean value as the mean and the inter-individual variability as the variance.

Calculating \%T>MIC at MICs of 0.06–16 µg/mL for each plasma meropenem profile on the 4th day (steady state) in 1000 simulated subjects, mean and 95% prediction intervals of \%T>MIC were obtained for each MIC and each dose. Target attainment rates for bacteriostatic exposures (target: 30\%T>MIC) or bactericidal exposures (target: 50\%T>MIC) at each MIC were also predicted. The target attainment rate against each strain, including *Escherichia coli* (E. coli), methicillin-susceptible *Staphylococcus aureus* (MSSA), and *Pseudomonas aeruginosa* (P. aeruginosa), were predicted using the reported MIC distribution data of meropenem against clinically isolated strains in 2006.\(^{16}\) *E. coli* and MSSA were selected as typical gram-negative and gram-positive organisms, respectively. *P. aeruginosa* was selected as a representative example commonly associated with more severe infections. To investigate the effect of infusion duration, target attainment rates were simulated with infusion durations of 0.5, 2, 3, 4, or 6 h against pathogens at various MIC breakpoints.

### Results

**Subjects:** Table 1 shows the characteristics of the subjects in the phase 3 study. Their ages ranged from 0 to 13 years, weights from 6.5 to 50.0 kg, and 20 of the patients were female. The weights of two children were heavier than 30 kg. The data for serum creatinine was not obtained from one patient. The mean serum creatinine (± S.D.) and

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Gender (male:female)</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
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</tbody>
</table>

*\( n = 49 \).
creatinine clearance of 49 patients were 0.30 ± 0.12 mg/dL and 90 ± 34 mL/min, respectively.

**Population PK analysis:** In total, 116 plasma concentrations from 50 patients (2–4 concentrations from each) were used for population PK analysis; they are plotted in Figure 1 as dose-normalized concentrations against time after dosing. The major investigated models are listed in Table 2.

A two-compartment model with zero-order infusion (ADVAN3 and TRANS4) was used as a basic model. Inter-individual variability could be modeled for CL. An exponential model was appropriate for the inter-individual variability and intra-individual (residual) variability.

![Figure 1. Observed plasma meropenem concentrations and 95% predictive intervals equivalent to 20 mg/kg dose](image)

**Fig. 1.** Observed plasma meropenem concentrations and 95% predictive intervals equivalent to 20 mg/kg dose

The open circles (○) represent observed values from 50 patients. The broken lines show 2.5th and 97.5th percentile of the simulated plasma concentrations obtained from a Monte Carlo simulation of 1000 virtual patients using parameter estimates from the final population PK model. The solid line shows population mean plasma concentration profile.

For the covariate search, WT, age, and creatinine clearance ($CL_{CR}$) showed correlation with CL, but WT was the best covariate to improve the fitting (model 2 in Table 2). After the incorporation of the correlation of WT with CL into the model, WT showed correlation with Vc, and the goodness of fit of the model was improved by the incorporation of the correlation of WT with Vc into the model (model 5 in Table 2). $\theta_{CLWT}$ and $\theta_{VcWT}$ were not significantly different from 1. The covariate models for CL and Vc were then described according to a proportional function (model 6 in Table 2) as follows:

$$CL = TVCL \times WT, Vc = TVVc \times WT.$$  

As the difference of the OBJ (1.298, $P > 0.05$) between model 5 and 6 was not significant, the proportional function model (model 6) was applied to the covariate model for CL and Vc. By the forward selection step, the goodness of fit of the model was improved by incorporation of the correlation of WT with CL, Vc, Q, and Vp into the model (model 7 in Table 2). No significant covariance was found for Vc, Q, or Vp (data not shown). During the backward deletion process to build the final model, it was found that all coefficients should remain in the model. The final population PK parameters for pediatric patients were as follows:

$$CL(L/h) = 0.428 \times WT, Vc(L) = 0.287 \times WT,$$
$$Q(L/h) = 0.0452 \times WT, Vp(L) = 0.0537 \times WT.$$  

The parameter estimates in the final population PK model are presented in Table 3. Inter-individual variability was modeled only for CL. The inter-individual variability ($\omega^2$) for CL was 0.0229 and 15.2% as a coefficient of variation (CV, %) for CL. The residual error was 0.0975 (32.0% as CV). An exponential model was appropriate for the inter-individual variability because $\eta$ for each patient was distributed normally (data not shown).

### Table 2. Major investigated models during population PK analysis

<table>
<thead>
<tr>
<th>Model</th>
<th>Equations</th>
<th>OBJ</th>
<th>$\Delta$OBJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CL = $\theta_2$, Vc = $\theta_3$, Q = $\theta_4$, Vp = $\theta_4$</td>
<td>368.278</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>CL = $\theta_1 \times (WT/15)^{\omega}$</td>
<td>333.216</td>
<td>—35.062</td>
</tr>
<tr>
<td>3</td>
<td>CL = $\theta_1 \times (CL_{CR}/88.7)^{\omega}$</td>
<td>347.767</td>
<td>—20.511</td>
</tr>
<tr>
<td>4</td>
<td>CL = $\theta_1 \times (AGE/37)^{\omega}$</td>
<td>343.548</td>
<td>—24.730</td>
</tr>
<tr>
<td>5</td>
<td>CL = $\theta_1 \times (WT/15)^{\omega}$, Vc = $\theta_2 \times (WT/15)^{\omega}$</td>
<td>296.792</td>
<td>—36.424</td>
</tr>
<tr>
<td>6</td>
<td>CL = $\theta_1 \times WT$, Vc = $\theta_2 \times WT$</td>
<td>298.090</td>
<td>—35.126 1.298</td>
</tr>
<tr>
<td>7</td>
<td>CL = $\theta_1 \times WT$, Vc = $\theta_2 \times WT$, Q = $\theta_3 \times WT$, Vp = $\theta_4 \times WT$</td>
<td>295.249</td>
<td>—37.967</td>
</tr>
<tr>
<td>8</td>
<td>CL = $\theta_1 \times WT \times (CL_{CR}/88.7)^{\omega}$, Vc = $\theta_2 \times WT$, Q = $\theta_3 \times WT$, Vp = $\theta_4 \times WT$</td>
<td>293.907</td>
<td>—1.342</td>
</tr>
</tbody>
</table>

WT: body weight (kg), geometric mean = 15 kg; CL<sub>CR</sub>: creatinine clearance (mL/min) calculated by Cockcroft and Gault equation, geometric mean of CL<sub>CR</sub> = 88.7 mL/min; AGE: age (months), geometric mean = 37 months.

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As seen in Figure 2, the final model adequately described the data except for three outliers. One of these outliers was obtained during an infusion period. During infusion, concentrations change dramatically with time, and small deviations of time for dosing and/or sampling can result in a large concentration deviation. The other two outliers came from the same patient. Even after excluding this patient, the parameter estimates changed little, and therefore the data for all patients were included in the calculations of the final parameters.

In the final model, only WT was retained as a covariate for CL, Vc, Q and Vp. Figure 3 shows the WT distribution of the present pediatric population and the good correlation between WT and individual CL values, which is well approximated by the estimated equation of $CL = 0.428 \times WT$.

### Table 3. Final estimates of population PK parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Final estimates, mean ± SE</th>
<th>Bootstrap validation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.428 ± 0.0151</td>
<td>0.428</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>0.287 ± 0.0181</td>
<td>0.285</td>
</tr>
<tr>
<td>Q (L/h/kg)</td>
<td>0.0452 ± 0.0203</td>
<td>0.0458</td>
</tr>
<tr>
<td>Vp (L/kg)</td>
<td>0.0537 ± 0.0127</td>
<td>0.0575</td>
</tr>
<tr>
<td>$\omega_u^2$</td>
<td>0.0229 ± 0.00812</td>
<td>0.0200</td>
</tr>
<tr>
<td>(CV%)</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.0975 ± 0.0214</td>
<td>0.0924</td>
</tr>
<tr>
<td>(CV%)</td>
<td>32.0</td>
<td></td>
</tr>
</tbody>
</table>

*All 1000 computations completed successfully.

CI: confidence intervals. 95% CI was calculated by a percentile method.

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**Model validation:** As shown in Table 3, the parameter estimates obtained based on the original data set were close to the geometric means of parameter estimates obtained from the bootstrap resampled data sets, and fell within the 95% confidence intervals of these parameter estimates.

The observed plasma concentrations normalized by the dose of 20 mg/kg t.i.d. and 95% prediction intervals of predicted plasma concentration profiles are presented in Figure 1. The prediction intervals of model-predicted concentration, including inter-individual variability of virtual patients (IPRED), included most of the observed values evenly, which suggested that the simulated plasma concentrations of meropenem based on the final population PK model were adequate.

**PK/PD simulation for various MICs:** Mean and 95% prediction intervals of %T>MIC for various MIC values were estimated for four dosing conditions with 8-h dose intervals, including 20 mg/kg t.i.d. by 0.5-h infusion and 40 mg/kg t.i.d. by 0.5-, 2-, 3-, 4-, or 6-h infusion (Fig. 4, Table 4; 3-h and 6-h infusion data not shown). Target attainment rates for achieving 30%-T>MIC and 50%-T>MIC at each MIC were also predicted (Fig. 5). For sensitive bacteria (MIC ≤ 2 µg/mL), mean values of %T>MIC were more than 36.3% at 20 mg/kg t.i.d. by 0.5-h infusion and more than 45.8% at 40 mg/kg t.i.d. by 0.5-h infusion (Table 4). For intermediate resistant bacteria (MIC = 4 or 8 µg/mL) and resistant bacteria (MIC ≥ 16 µg/mL), mean values of %T>MIC were more than 30.0% at 40 mg/kg t.i.d. by 2- to 4-h infusion (Table 4). After dosing of 20 mg/kg t.i.d., a high target attainment rate (>ca 80%) for 30%-T>MIC was achieved for a MIC of 2 µg/mL or lower, and a high target attainment rate for 50%-T>MIC was achieved for a MIC of 0.5 µg/mL or lower (Fig. 5). With dose escalation from 20 to 40 mg/kg t.i.d.,...
A Histogram of WT of 50 patients

Fig. 3. Histogram for body weight (WT) distribution of the 50 pediatric patients (A) and the relationship between WT and individual CL values (B)

Open circles (○) represent individual data of 50 patients. The line shows a linear equation of CL = 0.428 × WT estimated by the present population PK analysis.

target attainment rates for 30%T>MIC (e.g., at a MIC of 4 µg/mL) and 50%T>MIC (e.g., at MIC of 1 µg/mL) were increased from 30.6% to 87.7% and from 26.7% and 79.0%, respectively (Fig. 5). Prolonged infusion duration (4 h) increased target attainment rates at higher MICs (Fig. 5).

PK/PD simulation for *E. coli*, *MSSA*, and *P. aeruginosa*: Target attainment rates at 30%T>MIC and at 50%T>MIC against *E. coli* and those against MSSA were nearly 100% even at a dose of 20 mg/kg t.i.d. by 0.5-h infusion (data not shown). Target attainment rates at 30%T>MIC and 50%T>MIC against *P. aeruginosa* were 73.4% at 20 mg/kg t.i.d. by 0.5-h infusion and 60.7% at the 40 mg/kg t.i.d. by 0.5-h infusion, respectively (Fig. 6). To achieve a high target attainment rate (>80%) against *P. aeruginosa*, 40 mg/kg t.i.d. by 0.5 h or longer infusion duration was required for 30%T>MIC, and 40 mg/kg t.i.d. by 3- to 6-h infusion was required for 50%T>MIC (Fig. 6).

Table 4: Prediction of %T>MIC of meropenem for various MICs and various dosing regimens

<table>
<thead>
<tr>
<th>MIC of bacteria (µg/mL)</th>
<th>%T&gt;MIC (%), mean (95% prediction intervals**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/kg t.i.d.</td>
<td></td>
</tr>
<tr>
<td>0.5-h infusion</td>
<td>13.6 (10.1–17.3)</td>
</tr>
<tr>
<td>0.5-h infusion</td>
<td>20.7 (15.3–26.6)</td>
</tr>
<tr>
<td>2-h infusion</td>
<td>28.1 (20.4–36.7)</td>
</tr>
<tr>
<td>4-h infusion</td>
<td>36.3 (25.9–47.9)</td>
</tr>
<tr>
<td>40 mg/kg t.i.d.</td>
<td></td>
</tr>
<tr>
<td>0.5-h infusion</td>
<td>20.7 (15.3–26.6)</td>
</tr>
<tr>
<td>2-h infusion</td>
<td>36.3 (25.9–47.9)</td>
</tr>
<tr>
<td>4-h infusion</td>
<td>45.8 (32.3–60.1)</td>
</tr>
<tr>
<td><strong>95% prediction intervals</strong></td>
<td></td>
</tr>
</tbody>
</table>

* A total of 1000 virtual pediatric patients were simulated at each regimen.

** 95% prediction intervals were calculated by a percentile method.
Clinical efficacy and bacteriological efficacy:
The clinical efficacy rate, that is, the rate of excellent or good was 95.9% (47/49 patients) in the present phase 3 study at the end of treatment. Clinical responses of two patients were judged as fair and poor because of their underlying diseases, i.e., cellulitis and lung suppuration, respectively. Both patients were administered 20 mg/kg t.i.d. The causative pathogen of the patient who suffered from lung suppuration was *Haemophilus influenzae* with a MIC value of 0.25µg/mL. At their follow-up visits, the clinical efficacy rate had reached 100%.

The causative pathogen was identified in 33 of 49 patients. The microbiological response, i.e., the rate of eradicated or presumed eradicated for all identified causative pathogens, was 97.0% (32/33 patients). In the 33 patients for whom the causative pathogens were identified, 49 bacterial strains were isolated as follows: 16 strains of *Streptococcus pneumoniae*, 1 of *Streptococcus pyogenes*, 8 of *Moraxella catarrhalis*, 2 of *E. coli*, 1 of *P. aeruginosa*, and 21 of *H. influenzae*. MIC values of each isolate were 0.5µg/mL or less.

Discussion
This article reports a population PK model and PK/PD simulation of meropenem with various dosage regimens in Japanese pediatric patients. The most important determinants of PK parameters were WT in the pediatric patients in the present analysis. The previous population PK study on meropenem in pediatrics reported that CLCR and WT were the most important determinants of clearance. In their report, CLCR was calculated using the Cockcroft and Gault equation and the range of serum creatinine was 0.10–3.40 mg/dL, indicating that their population included patients with renal impairment. In the population of the present analysis, the range of serum creatinine was in the range 0.1–0.7, suggesting that no patients with renal impairment were included. CL showed a marginal, but statistically insignificant correlation to CLCR in this analysis, suggesting that body weight is the major determinant for PK parameters of meropenem in pediatric patients with normal renal function.

As previously reported, %T>MIC was considered as the important PD index for meropenem, and 20%–30%T>MIC has been proposed to achieve bacteriostatic effects and 40%–50%T>MIC has been proposed to achieve bactericidal outcomes. As the predictors of bacteriostatic and bactericidal effects, some reports used 20%T>MIC and 40%T>MIC, respectively, and others used 30%T>MIC and 50%T>MIC, respectively. For clinical effectiveness, the target attainment rates for 40%T>MIC (92%) were not statistically different from the clinical response (91%) with 95% confidence intervals of the difference of −7.7% to 4.2% in one report, and 54%T>MIC was found to be a significant predictor of microbiological response in another. Considering this
information, as predictors of effect, means and 95% confidence intervals of %T>MIC, target attainment rates for 30%>MIC (for bacteriostatic effect) and those for 50%>MIC (for bactericidal effect) were predicted against various MICs in the present study. Not only larger doses but also longer infusion durations resulted in higher %T>MIC, which is consistent with previous reports.\(^3,4,5\) However, for 40 mg/kg t.i.d. by 6-h infusion, the value of %T>MIC at high MIC was lower than that by 4-h infusion. As longer infusion durations result in lower peak plasma concentrations, the peak concentration after 40 mg/kg t.i.d. by 6-h infusion was close to MIC = 16 µg/mL (data not shown). Prolonged infusion durations up to 4 h increased target attainment rates at higher MICs. These results demonstrated that there is an optimal infusion duration depending on the dose and the MIC of the infectious organism.

The MICs of meropenem against \(E. \ coli\) (141 strains) and MSSA (58 strains) were below or equal to 0.12 µg/mL in clinically isolated strains in Japan in 2006.\(^6\) After dosing at 20 mg/kg t.i.d. by 0.5-h infusion (approved standard dose for pediatric patients in Japan), complete target attainment rates (100%) were achieved at MIC values of 0.5 µg/mL or lower. As considered above, the optimal dosage regimen against bacteria with lower MICs, such as \(E. \ coli\) and MSSA, for meropenem was 20 mg/kg t.i.d. by 0.5-h infusion. Against bacteria with higher MICs, such as some strains of \(P. \ aeruginosa\) (especially if MIC is above or equal to 2 µg/mL), dose escalation from 20 to 40 mg/kg t.i.d. (highest dose approved for pediatric patients in Japan) and/or prolonged infusion duration were effective for achieving higher target attainment rates. The target attainment rate at 50%>MIC against \(P. \ aeruginosa\) was 60.7% at 40 mg/kg t.i.d. by 0.5-h infusion. Target attainment rates at 50%>MIC against \(P. \ aeruginosa\) increased to 89.9% by 4-h infusion, suggesting that 40 mg/kg t.i.d. by longer infusion duration is more effective for bacteria against which meropenem shows relatively higher MICs. For this latter regimen, almost all of the cases in which the target was not attained (about 10% of cases) seemed to result from insusceptible bacteria, as MIC\(_{90}\) of meropenem against \(P. \ aeruginosa\) was 16 µg/mL,\(^6\) and the target attainment rate for 50%>MIC at the MIC of 16 µg/mL was 1.7% by 4-h infusion.

According to the microbiological tests, MIC values of 49 strains in 33 patients were below or equal to 0.5 µg/mL. The probability of achieving 50%>MIC in the above 33 patients was calculated as 97.0% in this clinical trial. These predicted PK/PD parameters were well correlated to not only the microbiological efficacy rate (97.0%, 32 of 33 patients) but also to the clinical efficacy rate (95.9%, 47 of 49 patients). The current analysis revealed that PK/PD parameters were helpful to predict both microbiological efficacy and clinical efficacy in patients.

In conclusion, this is the first report of population pharmacokinetics of meropenem in pediatric patients based on a GCP clinical study conducted in Japan. The optimal dosage regimen was discussed based on PK/PD target (%T>MIC) attainment simulations for various pathogens with different MICs. The standard dosage regimen of meropenem, 20 mg/kg t.i.d. with 0.5-h infusion (approved standard dose for pediatric patients in Japan) was effective for bacteria against which meropenem shows low MICs, such as \(E. \ coli\) and MSSA. Furthermore, 40 mg/kg t.i.d. with a longer infusion duration (highest dose approved for pediatric patients in Japan) was suggested to be more effective for bacteria with higher MICs, such as some strains of \(P. \ aeruginosa\) (MIC ≥ 2 µg/mL).

References


