ORIGINAL ARTICLE

Pharmacokinetic–pharmacodynamic target attainment analysis of meropenem in Japanese adult patients

**Kazuro Ikawa · Norifumi Morikawa ·
Hiroki Ohge · Kayo Ikeda · Taijiro Sueda ·
Masafumi Taniwaki · Kaoru Kurisu**

Abstract This study was a pharmacokinetic (PK)–pharmacodynamic (PD) target attainment analysis of meropenem in Japanese adult patients. Plasma drug concentration data (265 samples from 42 patients) were used for population PK modeling and Monte Carlo simulation to assess the probability of attaining the PK–PD target (40% of the time above the MIC for the bacterium). The final population PK model identified creatinine clearance (Cl_{cr}, ml/min) and body weight (BW, kg) as the most significant covariates: Cl (l/h) = $0.0905 \times Cl_{cr} + 2.03$, V_c (l) = $0.199 \times BW$, Q (l/h) = 4.02, and V_p (l) = 4.55, where Cl is the clearance, V_c and V_p are the volumes of distribution of the central and peripheral compartments, respectively, and Q is the intercompartmental clearance. The Monte Carlo simulation developed the PK–PD breakpoints (the highest MIC values at which the probabilities of target attainment in plasma are 80% or more) for meropenem regimens, the values of which varied with the Cl_{cr} and BW of the patient. The simulation also demonstrated that 0.25 g every 12 h (0.5-h infusion) achieved a target attainment probability of 82.4–100% against *Escherichia coli*, methicillin-susceptible *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* isolates. However, against *Pseudomonas aeruginosa* isolates, 0.5 g every 8 h or 1 g every 8 h was required to achieve 80% or more probability in most typical patients. These results provide a PK–PD-based strategy for tailoring a meropenem regimen according to Cl_{cr} and BW of a Japanese adult patient and susceptibility of the causative bacteria.

Keywords Meropenem · Pharmacokinetics–pharmacodynamics (PK–PD) · Monte Carlo simulation

Introduction

Meropenem is a commonly used carbapenem for the treatment of various infections such as pneumonia, sepsis, urinary-tract infections, and intra-abdominal infections in adult patients [1]. The approved regimen for intravenous meropenem in Japan is 0.5–2 g daily in two to three divided doses. Antibacterial regimens should be tailored and optimized on a case-by-case basis to maximize the agent's microbiological effects and clinical outcomes, and potentially provide a cost-effective medical benefit. However, information is limited on choosing the appropriate meropenem dosage for Japanese adult patients. This choice necessitates actively considering such factors as patient characteristics and susceptibility to meropenem of the bacteria involved.

Integration of pharmacokinetic (PK) and pharmacodynamic (PD) targets derived from both PK data and

K. Ikawa (✉) · N. Morikawa · K. Ikeda
Department of Clinical Pharmacotherapy, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
e-mail: ikawak@hiroshima-u.ac.jp

H. Ohge · T. Sueda
Department of Surgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

M. Taniwaki
Department of Hematology and Oncology, Kyoto Prefectural University of Medicine, Kyoto, Japan

K. Kurisu
Department of Neurosurgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

exposure–response data can be utilized to support anti-bacterial dosage choice and optimize the dosing regimen. This PK–PD target attainment analysis [2, 3], particularly using a statistical technique called the Monte Carlo simulation, has also been applied to meropenem. However, earlier analyses [4–9] had several problems. Drug concentration data were obtained from a small number of healthy subjects. In the Monte Carlo simulations, the mean ± standard deviations of individual pharmacokinetic parameters (the standard two-stage method) were used, although the method yields a large bias toward their interindividual variability [10]. Moreover, covariates to affect the drug pharmacokinetics were ignored. For an appropriate PK–PD target attainment analysis of meropenem, it is necessary to use the mean population PK parameters, their variability, and potential covariates in adult patients.

The aim of this study was thus to perform a PK–PD target attainment analysis of meropenem in Japanese adult patients. We first developed a population PK model to accurately describe the drug disposition in adult patients. Incorporating the developed model into a Monte Carlo simulation, we then estimated the probabilities of target attainment for meropenem regimens and assessed their expected population probabilities against the MIC distributions for common bacterial isolates.

Patients, materials, and methods

Study subjects

This study was approved by the ethics committees of the study institutes and conducted in compliance with the Declaration of Helsinki, and all subjects provided written informed consent. Forty-two Japanese adults (including febrile neutropenic patients, surgical patients, and patients with pneumonia or urinary-tract infections) received 0.25, 0.5, or 1 g meropenem (0.5- or 1-h infusion) every 8 or 12 h. Four to ten samples of blood were drawn in heparinized tubes. After centrifugation, each plasma sample was removed, stabilized with an equal volume of 1 mol/l MOPS buffer (pH 7.0), and frozen until assay. Demographic and physiopathological parameter data, such as sex, age, body weight, blood urea nitrogen, serum creatinine, and creatinine clearance, were recorded for all subjects.

Meropenem assay

The total concentrations of meropenem in plasma were determined using our high-performance liquid chromatography method, as reported previously [11]. In brief, plasma sample (400 µl) was transferred to an ultrafiltration device and centrifuged. Then, the filtered solution (20 µl) was injected onto a chromatograph with a C18 column at 40°C and an ultraviolet absorbance detector at 300 nm. The mobile phase was a mixture of 10 mM phosphate buffer (pH 7.4) and acetonitrile (90:10). The limit of quantification was 0.05 µg/ml, the accuracy was 97.7–106.3%, and the precision was <7.2%.

Population pharmacokinetic (PK) modeling

Population PK modeling was performed using the first-order conditional estimation (FOCE) method in the NONMEM program (version 6.2.0; ICON Development Solutions, Ellicott, MD, USA). Both one- and two-compartment models were fitted to the data when choosing the basic structural PK model. Model discrimination was assessed using Akaike information criterion (AIC) values. The interindividual variability was modeled exponentially:

$$\theta_i = \theta \times \exp(\eta_i)$$

where θ_i is the fixed-effects parameter for the ith subject, θ is the mean value of the fixed-effects parameter in the population, and η is a random interindividual variable, which is normally distributed with mean 0 and variance ω^2. The residual (intraindividual) variability was modeled with a proportional error model:

$$C_{\mathrm{obs},ij} = C_{\mathrm{pred},ij} \times (1 + \varepsilon_{ij})$$

where $C_{\mathrm{obs},ij}$ and $C_{\mathrm{pred},ij}$ denote the jth observed and predicted concentrations for the ith subject, and ε is a random intraindividual error which is normally distributed with mean 0 and variance σ^2.

The influences of the patient characteristics on the individual PK parameters obtained from the basic structural model were explored graphically. The covariates showing a correlation with the PK parameters were introduced into the model. The significance of the influence of the covariates was evaluated by the changes of −2 log likelihood (the minimum value of the objective function: OBJ). An OBJ decrease of more than 3.84 from the basic structural model ($P < 0.05$; χ^2 test) was considered statistically significant during the forward inclusion process. The full model was built by incorporating the significant covariates, and the final model was developed by a backward elimination method. The covariates in the full model were excluded from the model one at a time, and an OBJ increase of more than 6.63 from the full model ($P < 0.01$; χ^2 test) was considered statistically significant. Goodness of fit was evaluated by checking the plots of observed, predicted, and individual predicted concentrations, and weighted residual.

A nonparametric bootstrap resampling technique was performed to validate the reliability and stability of the population PK model developed. The program Wings for NONMEM (version 612; Holford NH, University of Auckland, Auckland, New Zealand) was used to create resampled new data sets. The 95% confidence intervals of PK parameters from 1,000 bootstrap replicates were compared with the estimates of the final model.

Microbiological data

Five common types of pathogenic bacteria were selected, and the MIC distribution data of their clinical isolates were derived from recent susceptibility surveillance in Japan, including the study institutes: [12] *Pseudomonas aeruginosa* ($n = 322$ isolates; range 0.06–128 μg/ml; $MIC_{50} = 1$ μg/ml; $MIC_{90} = 16$ μg/ml), *Haemophilus influenzae* ($n = 252$; range 0.015–2 μg/ml; $MIC_{50} = 0.12$ μg/ml; $MIC_{90} = 0.5$ μg/ml), *Streptococcus pneumoniae* ($n = 181$; range 0.06–1 μg/ml; $MIC_{50} = 0.06$ μg/ml; $MIC_{90} = 0.5$ μg/ml), *Escherichia coli* ($n = 141$; range 0.03–0.06 μg/ml; $MIC_{50} = 0.03$ μg/ml; $MIC_{90} = 0.03$ μg/ml), and methicillin-susceptible *Staphylococcus aureus* (MSSA) ($n = 58$; range 0.06–0.12 μg/ml; $MIC_{50} = 0.12$ μg/ml; $MIC_{90} = 0.12$ μg/ml).

Probability of target attainment analysis using a Monte Carlo simulation

A Monte Carlo simulation was conducted using the final population PK model to estimate the probability-of-target-attainment profile for each meropenem regimen (0.5-h infusion)–MIC combination. The following process was repeated 10,000 times with Crystal Ball 2000 software (Oracle, Redwood Shores, CA, USA). A set of fixed-effects parameters was generated randomly according to each mean estimate (θ) and interindividual variance (ω) of the final population PK model. The steady-state unbound drug concentration versus time curve was simulated using the fixed-effects parameters, where a value of 2.4% protein binding in humans [13] was employed. The time point at which the free drug concentration coincided with a specific MIC value was determined, and the time for which the free drug concentration remained above the MIC ($fT > MIC$) was finally calculated as the cumulative percentage of a 24-h period [14]. The probability of target attainment (%) was determined as the fraction that achieved at least 40% $fT > MIC$ (the bactericidal target [1, 6, 8, 9, 15–17]) of 10,000 estimates.

For each meropenem regimen, the highest MIC at which the probability of target attainment achieved 80% or more probability was defined as the PK–PD breakpoint (μg/ml) [18]. For each bacterium, the probability at a specific MIC

was multiplied by the fraction of the population of bacterium in each MIC category, and the sum of individual products was defined as the expected population probability of target attainment (%) [14].

Results

The demographic and physiopathological parameters of the study subjects (26 men and 16 women) were as follows: age 62.2 ± 19.6 years (mean $\pm$ SD) (range 23.0–88.0 years); body weight 56.0 ± 10.4 kg (38.5–84.6 kg); blood urea nitrogen 15.5 ± 7.2 mg/dl (5.8–36.1 mg/dl); serum creatinine 0.87 ± 0.41 mg/dl (0.46–2.30 mg/dl); and creatinine clearance (Cl_{cr}) 77.7 $\pm$ 32.3 ml/min (15.5–137.7 ml/min). A total of 265 plasma drug concentration data (Fig. 1) were used for the population PK modeling.

Because AIC values indicated that the two-compartment model (AIC, 516) described the data better than the one-compartment model (AIC, 763), the two-compartment model was chosen as the basic structural model. Therefore, the PK parameters were clearance (Cl, l/h), volume of distribution of the central compartment (V_c, l), intercompartmental clearance (Q, l/h), and volume of distribution of the peripheral compartment (V_p, l).

As the scatter plots (Fig. 1) showed that the drug elimination was slower in patient group with Cl_{cr} of <50 ml/min than in patient group with Cl_{cr} of >100 ml/min, incorporation of creatinine clearance (Cl_{cr}) into Cl caused the largest OBJ change (ΔOBJ, −40.8) in the forward inclusion process to build the covariate model. Age and body weight (BW) each also had a significant effect on Cl, but neither of them was additionally incorporated into Cl to avoid a collinearity effect, because age and BW each
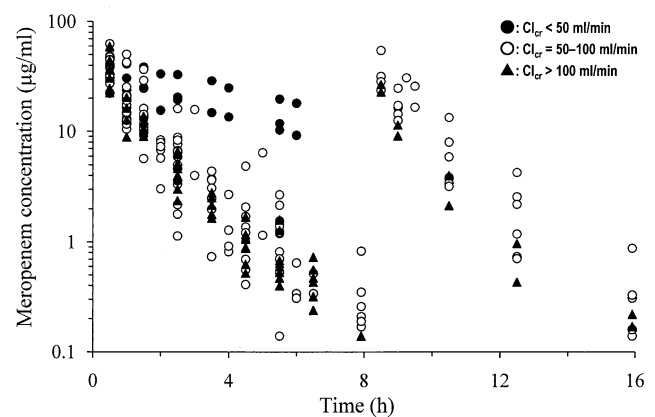

Fig. 1 Scatter plots of plasma meropenem concentration versus time in patient groups with creatinine clearance (Cl_{cr}) of <50 ml/min ($n = 7$ patients), 50–100 ml/min ($n = 24$), and >100 ml/min ($n = 11$)

**Table 1** Estimates of population PK parameters in the final model

Parameter	Population estimate	Standard error (covariance step)	95% Confidence interval (bootstrap procedure)
Fixed-effects parameter			
$Cl\ (l/h) = \theta_1 \times Cl_{cr}\ (ml/min) + \theta_2$			
θ_1	0.0905	0.0267	0.0525–0.1248
θ_2	2.03	0.940	0.14–4.19
$V_c\ (l) = \theta_3 \times BW\ (kg)$			
θ_3	0.199	0.0159	0.167–0.231
$Q\ (l/h) = \theta_4$			
θ_4	4.02	0.783	2.57–5.48
$V_p\ (l) = \theta_5$			
θ_5	4.55	0.424	3.93–5.29
Interindividual variability			
η_{Cl}	0.156 ($\omega_{Cl} = 41.1\%$)	0.0452	0.068–0.228
η_{V_c}	0.147 ($\omega_{V_c} = 39.8\%$)	0.0420	0.061–0.239
η_{Q}	0.102 ($\omega_{Q} = 32.8\%$)	0.0459	0.031–0.180
η_{V_p}	0.0854 ($\omega_{V_p} = 29.9\%$)	0.0406	0.001–0.148
Residual variability			
ε	0.0121	0.00405	0.0044–0.0199

Standard error determined via covariance step in the NONMEM modeling; 95% confidence interval determined from 1,000 bootstrap replicates using the program Wings for NONMEM
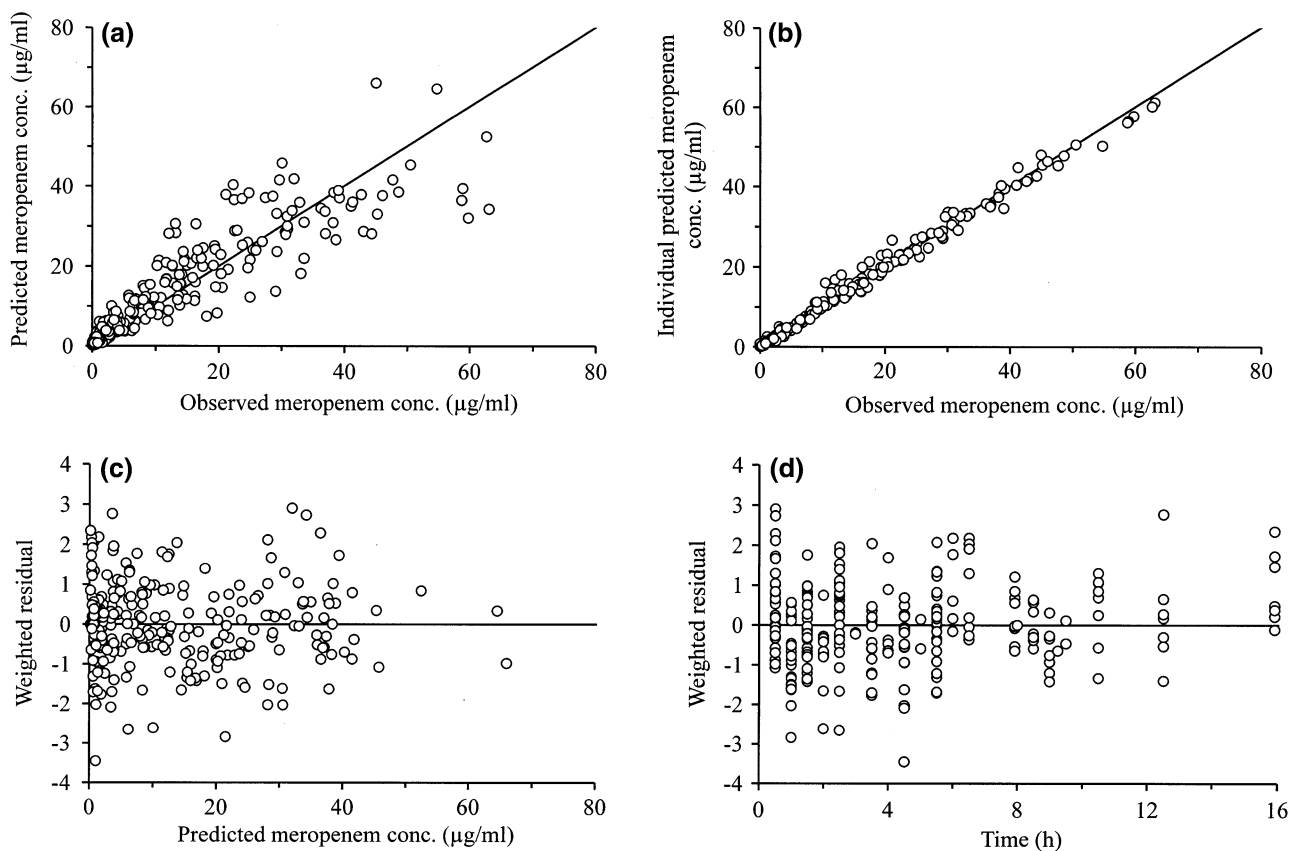
Fig. 2 Diagnostic plots of the final population pharmacokinetic model for meropenem ($n = 265$ plots) **a** Predicted versus observed concentration (*conc.*), **b** individual predicted versus observed concentration, **c** weighted residual versus predicted concentration, **d** weighted residual versus time
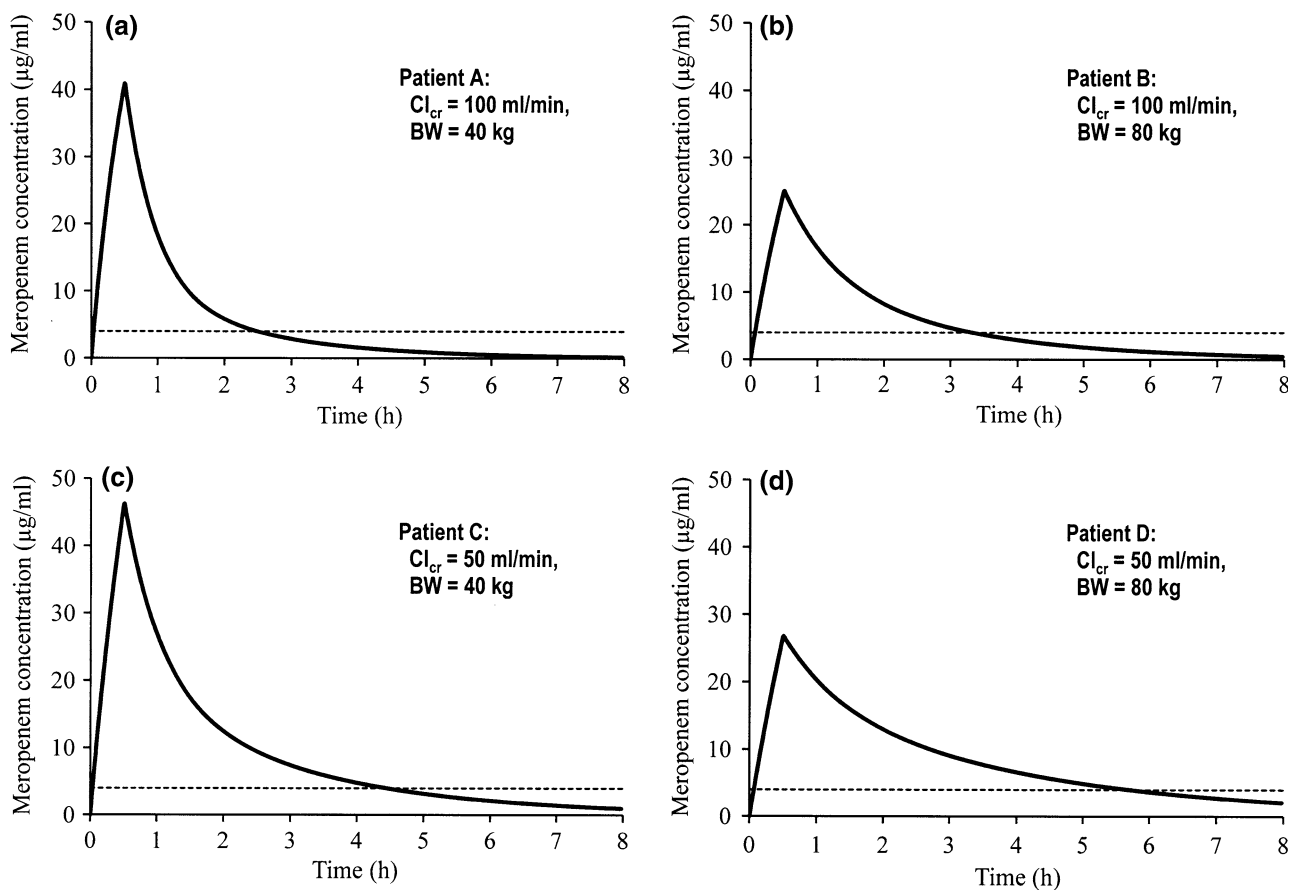
Fig. 3 Simulation curves in four typical patients (**a–d**) after a 0.5-h infusion of 0.5 g meropenem. Each simulation curve was drawn using the mean fixed-effects parameters given in Table 1. The *dotted line* represents 4 µg/ml. Cl_{cr} creatinine clearance; *BW* body weight

showed a high correlation with Cl_{cr}. Meanwhile, incorporation of BW into V_c caused the largest OBJ change (ΔOBJ, -17.6). However, none of the examined covariates had a significant effect on V_p and Q. During the backward deletion process, every covariate and coefficient remained in the model, causing significant OBJ increase. Therefore, the final model was as follows:

$$Cl (l/h) = 0.0905 \times Cl_{cr} + 2.03,$$

$$V_c \ (l) = 0.199 \times BW, Q \ (l/h) = 4.02, V_p(l) = 4.55.$$

The mean and variability of the final population PK parameters and 95% confidence interval estimated from bootstrap replicates are summarized in Table 1. Diagnostic plots indicated that the final model accurately reflected the data (Fig. 2).

Based on the final model, four typical patients were supposed with Cl_{cr} (50 or 100 ml/min) and BW (40 or 80 kg) combinations. Figure 3 illustrates the influences of Cl_{cr}–BW combinations on meropenem pharmacokinetics and pharmacodynamics. Given a 0.5-h infusion of 0.5 g meropenem and MIC = 4 µg/ml, the mean values of

$fT > MIC$ (percentage of an 8-h period) were: 30.7% in patient A (Cl = 11.1 l/h and V_c = 7.96 l given in Table 1); 40.8% in patient B (Cl = 11.1 l/h, V_c = 15.9 l); 55.3% in patient C (Cl = 6.56 l/h, V_c = 7.96 l); and 70.5% in patient D (Cl = 6.56 l/h, V_c = 15.9 l).

Consequently, the probability of target attainment versus MIC profiles (Fig. 4) and the PK-PD breakpoints (Table 2) for meropenem regimens were changed by Cl_{cr} and BW. In the case of 0.5 g every 8 h, the BW increase from patient A (40 kg) to patient B (80 kg) raised the PK–PD breakpoint from 1 to 2 µg/ml, and then the Cl_{cr} decrease from patient B (100 ml/min) to patient D (50 ml/min) raised the PK–PD breakpoint from 2 to 4 µg/ml.

Table 3 shows the expected population probabilities of target attainment against common pathogenic bacteria. In all patients, the probability values for 0.25 g every 12 h were >82% against *E. coli*, MSSA, *H. influenzae*, and *S. pneumoniae* isolates. However, the values were lower against *P. aeruginosa* isolates. The minimum regimens required to achieve 80% or more probability were 0.5 g every 8 h for patients C and D, and 1 g every 8 h for patient B.
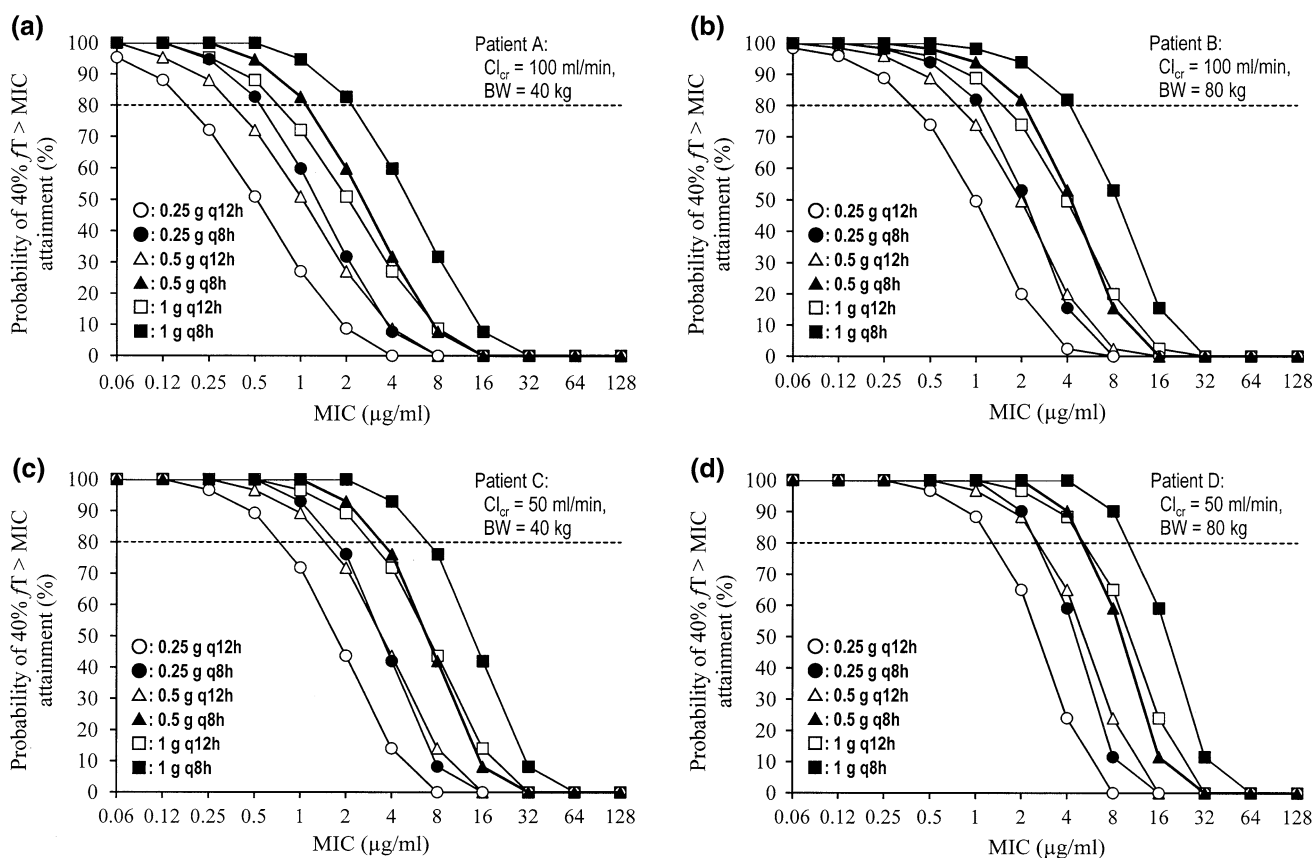
Fig. 4 Probabilities of 40% fT > MIC attainment in four typical patients (**a–d**) using every 12 h (q12 h) and every 8 h (q8 h) meropenem regimens (0.5-h infusions). Cl_{cr} Creatinine clearance, *BW* body weight

Table 2 Pharmacokinetic (PK)–pharmacodynamic (PD) breakpoints (the highest MIC values at which the probabilities of 40% fT > MIC attainment are 80% or more) for meropenem regimens in four typical patients

Meropenem regimen (0.5-h infusion)	PK–PD breakpoint (µg/ml)			
	Patient A	Patient B	Patient C	Patient D
0.25 g every 12 h	0.12	0.25	0.5	1
0.25 g every 8 h	0.5	1	1	2
0.5 g every 12 h	0.25	0.5	1	2
0.5 g every 8 h	1	2	2	4
1 g every 12 h	0.5	1	2	4
1 g every 8 h	2	4	4	8

Patient A, Cl_{cr} = 100 ml/min, BW = 40 kg; patient B, Cl_{cr} = 100 ml/min, BW = 80 kg; patient C, Cl_{cr} = 50 ml/min, BW = 40 kg; patient D, Cl_{cr} = 50 ml/min, BW = 80 kg

Discussion

The population PK model developed for meropenem in Japanese adult patients identified Cl_{cr} and BW as the most significant covariates affecting the pharmacokinetics. Based on the developed model, the Monte Carlo simulation determined the PK–PD breakpoints for meropenem regimens, the MIC values of which varied with the Cl_{cr} and BW of the patient. The simulation also demonstrated that

0.25 g every 12 h (0.5-h infusion) achieved a target attainment probability of >82% against *E. coli*, MSSA, *H. influenzae*, and *S. pneumoniae* isolates. However, against *P. aeruginosa* isolates, 0.5 g every 8 h or 1 g every 8 h was required to achieve 80% or more probability in most typical patients.

Earlier PK studies of meropenem found that meropenem followed a two-compartment model [19, 20]: the drug was eliminated renally with a 12-h urinary recovery of

Table 3 Expected population probabilities of 40% fT > MIC attainment in four typical patients against *Escherichia coli*, methicillin-susceptible *Staphylococcus aureus* (MSSA), *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Pseudomonas aeruginosa* isolates using different meropenem regimens

Meropenem regimen (0.5-h infusion)	Probability of 40% fT > MIC attainment (%)			
	Patient A	Patient B	Patient C	Patient D
E. coli				
0.25 g every 12 h	99.9	100	100	100
MSSA				
0.25 g every 12 h	90.1	96.6	100	100
H. influenzae				
0.25 g every 12 h	83.8	92.5	97.3	99.3
0.25 g every 8 h	96.0	98.3	99.7	100
S. pneumoniae				
0.25 g every 12 h	82.4	91.8	97.3	99.3
0.25 g every 8 h	95.7	98.4	99.9	100
P. aeruginosa				
0.25 g every 12 h	35.3	48.5	60.2	68.0
0.25 g every 8 h	54.9	64.0	72.8	76.9
0.5 g every 12 h	49.4	61.5	71.7	77.9
0.5 g every 8 h	67.4	74.5	82.0	85.7
1 g every 12 h	62.4	72.6	81.3	86.6
1 g every 8 h	77.9	83.7	89.6	92.6

Patient A, Cl_{cr} = 100 ml/min, BW = 40 kg; patient B, Cl_{cr} = 100 ml/min, BW = 80 kg; patient C, Cl_{cr} = 50 ml/min, BW = 40 kg; patient D, Cl_{cr} = 50 ml/min, BW = 80 kg

62.2–78.2% [19, 21], and the drug clearance was lowered according to the degree of renal dysfunction [22, 23]. In earlier population PK analyses, body weight was the most significant covariate affecting volume of distribution in both Caucasian adult patients [16] and Korean febrile neutropenic patients [17]. The results of the population PK modeling (Table 1) are consistent with these earlier findings. The two-compartment model described the current data better than did the one-compartment model. Although age often plays an important role in pharmacokinetics, renal function (Cl_{cr}) had a more direct effect than age on meropenem pharmacokinetics. The mean renal clearance was estimated as 77.6% of the total clearance [(0.0905 × Cl_{cr})/(0.0905 × Cl_{cr} + 2.03) using the mean Cl_{cr} of 77.7 ml/min].

The final population PK model lacked bias, regardless of the drug concentration (Fig. 2c) and time (Fig. 2d), and the observed drug concentration was almost identical to the individual predicted concentration after the Bayesian step (Fig. 2b). In addition, all relative standard error (standard error/estimate, %) values via the covariance step in the NONMEM modeling were <48%, and all parameter estimates were in the range of the 95% confidence interval using the bootstrap method (Table 1), indicating the reliability and stability of the final model. Therefore, we consider the final model to have a good predictive performance for PK–PD assessment use.

The Monte Carlo simulation demonstrated that the probabilities of target attainment for 0.25 g every 8 h (0.75 g/day) and 0.5 g every 8 h (1.5 g/day) were comparable to those for 0.5 g every 12 h (1 g/day) and 1 g every 12 h (2 g/day), respectively (Fig. 4), suggesting that the dosing interval is a more important point than the daily dose in the dosing strategy for meropenem, which exhibits time-dependent killing. From the viewpoint of cost-effective benefit, every 8 h regimens would be preferable to every 12 h regimens, unless frequent administration is unacceptable due to the increase in the patient's burden and the medical workload.

The differences in the PK–PD target attainment among the bacteria resulted from their varying specific susceptibilities to meropenem (Table 3). A regimen of 0.25 g every 12 h would be sufficient against high-susceptibility bacteria such as *E. coli*, MSSA, *H. influenzae*, and *S. pneumoniae* ($MIC_{90} \le 0.5$ μg/ml). However, when there is a suspicion of infection with meropenem-resistant bacteria such as *P. aeruginosa* (MIC_{90} = 16 μg/ml), we recommend 0.5 g every 8 h to a patient with low Cl_{cr} and 1 g every 8 h to a patient with high Cl_{cr}, although 1 g every 8 h is higher than the maximal 2 g/day in Japan (but the dosage is equal to 3 g/day for intra-abdominal infections [24] and is within 6 g/day for bacterial meningitis [25] in other countries). Otherwise, when the MIC of the patient's causative pathogen including *P. aeruginosa* is determined,

the newly developed PK–PD breakpoints (Table 2) can help us to choose a more appropriate meropenem regimen based on the MIC value.

In an effort to provide an overview of the population pharmacokinetics and pharmacodynamics of meropenem in adult patients, the analysis employed only four typical patients and five common pathogenic bacteria. However, we can estimate the PK parameters of a patient from their Cl_{cr} and BW values (Table 1), and the probability of target attainment versus MIC profiles (Fig. 4) can be useful when the MIC value for a bacterium is given, regardless of its susceptibility pattern.

In conclusion, Cl_{cr} and BW were the most significant factors affecting the population pharmacokinetics of meropenem in Japanese adult patients, and consequently the PK–PD breakpoints for meropenem regimens varied with the Cl_{cr} and BW of the patient. A regimen of 0.25 g every 12 h (0.5-h infusion) achieved a target attainment probability of >82% against E. coli, MSSA, H. influenzae, and S. pneumoniae isolates. However, against P. aeruginosa isolates, 0.5 g every 8 h or 1 g every 8 h was required to achieve a high probability. The results of the analysis are considered to provide a PK–PD-based strategy for tailoring a meropenem regimen according to the Cl_{cr} and BW of a Japanese adult patient and susceptibility of the causative bacteria (suspected because of the patient's symptoms or identified with the MIC data). The implications of our findings and proposals need to be confirmed in clinical settings.

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