Reappraisal of the Optimal Dose of Meropenem in Critically Ill Infants and Children: a Developmental Pharmacokinetic-Pharmacodynamic Analysis

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ABSTRACT Data of developmental pharmacokinetics (PK) of meropenem in critically ill infants and children with severe infections are limited. We assessed the population PK and defined the appropriate regimen to optimize treatment in this population based on developmental PK-pharmacodynamic (PD) analysis. Blood samples were collected from pediatric intensive care unit patients with severe infection treated with standard dosage regimens for meropenem. Population PK data were analyzed using NONMEM software. Fifty-seven patients (mean age, 2.96 years [range, 0.101 to 14.4]; mean body weight, 15.8 kg [range, 5.0 to 65.0]) were included. A total of 135 meropenem concentrations were obtainable for population PK modeling. The median number of samples per patients was 2 (range, 1 to 4). A two-compartment model with first-order elimination was optimal for PK modeling. Weight and creatinine clearance (estimated by the Schwartz formula) were significantly correlated with the PK parameters of meropenem. The probabilities of target attainment for pathogens with low MICs of 1 and 2 $\mu\text{g/ml}$ were 87.5% and 68.6% following administration of 40 mg/kg/dose (every 8 h [q8h]) as a 4-h infusion and 98.0% and 73.3% with high MICs of 4 and 8 $\mu\text{g/ml}$ following administration of 110 mg/kg/day as a continuous infusion in critically ill infants and children under 70% $fT_{>MIC}$ (the free time during which the plasma concentration of meropenem exceeds the MIC), respectively. The standard dosage regimens for meropenem did not meet an appropriate PD target, and an optimal dosing regimen was established in critically ill infants and children. (This study has been registered at ClinicalTrials.gov under identifier NCT03643497.)

KEYWORDS population pharmacokinetics, meropenem, children, critically ill

Meropenem is a carbapenem antibacterial of the β -lactam family. It is used frequently as an empirical and definitive treatment of severe infections in children because of its broad antimicrobial spectrum (including against multidrug-resistant bacteria) and favorable safety profile (1, 2). Meropenem is characterized by a low

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volume of distribution (V_d) and a low ($\sim 2\%$) level of protein binding (3). Meropenem is excreted primarily by the kidneys through glomerular filtration, with 54% to 79% remaining unchanged in urine (4).

However, the pharmacokinetics (PK) of meropenem in critically ill adult patients are different from those in the general population of adult patients with bacterial infection, and the interpatient disposition varies widely (5, 6). The pathophysiologic or iatrogenic changes (e.g., polytrauma; drainage after surgery and fluid therapy) that occur commonly during critical illness can affect fluid balance and intravascular perfusion. This scenario can increase the V_d and decrease the peak concentration, which would result in subtherapeutic concentrations of meropenem (7–9). Critically ill patients often have sepsis-induced decreases or increases in cardiac output, which lead to hypoperfusion or hyperperfusion of the kidneys and alterations in drug clearance (CL) (7).

Meropenem has time-dependent bactericidal activity. Hence, efficacy is determined by the free time during which the plasma concentration of meropenem exceeds the MIC ($fT_{>MIC}$) (8). Optimum antibacterial activity occurs when the $fT_{>MIC}$ value is $\geq 40\%$ of the dosage interval, but a higher level (70% to 80%) is required in critically ill patients (7, 10). In addition, critically ill children are affected disproportionately by multidrug-resistant bacteria, which show a higher meropenem MIC and decreased $fT_{>MIC}$ and require intensified dosing strategies (11, 12). The standard dosing regimen for meropenem administered as 10 to 40 mg/kg of body weight/dose every 8 h (q8h) infused for 0.5 h has been shown to achieve the pharmacodynamic (PD) target of 40% $fT_{>MIC}$ in clinically stable children (13). However, it does not meet an appropriate PD target in critically ill children and should be optimized (7, 14, 15). Two studies have assessed the PK to explore the appropriate dose in critically ill children (7, 14), but no covariates were identified due to the small number of children enrolled. The PK data for meropenem are limited, and no optimal dosing regimen for this population has been recommended.

Therefore, we aimed to assess the PK and PD of meropenem in critically ill infants and children using a population approach. In addition, we attempted to establish an evidence-based optimal dosing regimen in this vulnerable population based on developmental PK-PD.

RESULTS

Study population. Fifty-seven patients were included from 2018 to 2019: 35 had sepsis, 15 had bacterial meningitis, and 7 had severe pneumonia. The dose (mean $\pm$ standard deviation [SD]) received by the 57 children was 23.7 ± 8.59 mg/kg of body weight/dose (range, 9.6 to 40). The weight and age (mean $\pm$ SD) at the sampling time were 15.8 ± 12.6 kg (range, 5.0 to 65) and 2.96 ± 3.7 years (range, 0.101 to 14.4), respectively. The characteristics of patients at baseline are presented in Table 1.

Model building. For population modeling, 135 meropenem concentrations were obtainable. The median number of samples per patients was 2 (range, 1 to 4). The range of meropenem concentrations of PK samples was 0.2 to 67.9 $\mu\text{g/ml}$. Thirty-one samples have a concentration below the limit of quantitation (LOQ). The concentration versus time profile is shown in Fig. 1. A two-compartment model with first-order elimination fitted the data best. The two-compartment structure model had a lower objective function value (OFV) (95.454) and lower residual variability value (42.7%) ($\Delta\text{OFV} = 71.965$) than the one-compartment structure model (OFV, 167.419; residual variability, 55.9%). The model was parameterized in terms of central volume of distribution (V_1), peripheral volume of distribution (V_2), intercompartment clearance (Q), and CL of meropenem. An exponential model was used to represent the interindividual variability and estimates for V_1 and CL. Residual variability was described best by an exponential model.

Covariate analysis. Weight was the most important covariate on CL and was associated with a decline in the OFV of 31.9 units. A further decrease in the OFV of 10.3 units was achieved by implementing creatinine clearance (CRCL) on CL. For V_1 , weight also was the most important covariate and caused a significant drop in the OFV of 11.0 units ($P < 0.01$). Covariate analysis results are shown in Table 2. No further decrease in

TABLE 1 Baseline characteristics of the 57 children^a

Characteristic	Values	
	Mean (SD)	Median (range)
Patients		
Age (yrs)	2.96 (3.70)	1.44 (0.101–14.4)
Weight (kg)	15.8 (12.6)	11.0 (5.00–65.0)
CREA ($\mu\text{mol/liter}$)	25.9 (7.76)	24.7 (16.5–38.1)
CRCL (ml/min/1.73 m^2)	163 (49.0)	155 (57.9–279)
ALT (U/liter)	19.0 (10.1)	15.2 (6.94–42.4)
AST (U/liter)	28.7 (15.4)	23.60 (11.3–70.4)
BUN (mmol/liter)	3.68 (0.91)	3.51 (2.00–4.87)
ALP (U/liter)	208 (78.4)	178.9 (96.9–338)
GGT (U/liter)	37.4 (45.4)	19.2 (11.3–154)
ALB (g/liter)	36.8 (4.95)	37.7 (28.3–44.5)
Meropenem treatment		
Vol		
mg/dose	349 (261)	250 (100–1,000)
mg/kg/dose	23.7 (8.59)	20.0 (9.6–40)

^aAll 57 of the subjects were Chinese. CREA, serum creatinine concentration; CRCL, creatinine clearance; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; ALB, albumin.

the OFV was achieved by implementing another covariate. The final population PK parameters are given in Table 3. The median (range) values of estimated weight-normalized CL and V under steady-state conditions (sum of V_1 and V_2) were 0.43 (range, 0.12 to 0.72) liters/h/kg and 0.51 (range, 0.13 to 1.03) liters/kg, respectively. Meropenem CL increased allometrically with current weight in children.

Model evaluation. Reliable goodness of fit for the final model of meropenem was reflected by model diagnostics. The predictions were unbiased (see Fig. S1A and B in the supplemental material). No trends were observed in the diagnostic plots of conditional weighted residuals (CWRES) versus population prediction (PRED) and time (Fig. S1C and D). Bootstrap analysis presented the result corresponding to the reliability and stability of the final model. The respective values from the final population model were found to be in accordance with the estimated values of median parameters obtained from bootstrap analysis. Normalized prediction distribution errors (NPDEs) are shown in Fig. S1E and F. The distribution and histogram of NPDEs followed the normal distribution of $N(0, 1)$ and density, indicating a good fit of the model to the individual data. The mean and variance values for the NPDEs were -0.043 and 1.04 , respectively. Results of a visual predictive check performed to evaluate the predictive performance of the model to reproduce the observed data are presented in Fig. S2.

FIG 1 Meropenem concentrations versus time. LG, $\log_{10}$.

TABLE 2 Covariate analysis^a

Process and effect	OFV	ΔOFV
Forward selection		
Structure model	95.533	
Weight impact on CL	63.598	−31.935
Weight impact on V	52.638	−10.960
CRCL impact on CL	42.364	−10.274
Backward elimination		
Full model	42.364	
CRCL impact on CL	52.638	+10.274
Weight impact on V	53.454	+11.090
Weight impact on CL	75.754	+33.390

^aΔOFV represents changed value of OFV in the model compared with the value in the model with addition or elimination of covariate. Weight data refer to subject weight.

Evaluation and optimization of the dosing regimen. The probability of target attainment (PTA) values corresponding to the standard regimen (20 mg/kg, q8h) for meropenem therapy were 18.7%, 5.8%, and 1.1% (MIC = 1, 2, and 4 μg/ml) with 70% $fT_{>MIC}$, respectively. The PTA for simulated dosage regimens using 70% $fT_{>MIC}$ PD thresholds is shown in Fig. 2. The PTA values for pathogens with low MICs (1 and 2 μg/ml), i.e., *S. pneumoniae* and *N. meningitidis*, were 87.5% and 68.6% following administration of meropenem at 40 mg/kg (q8h) as a 4-h infusion, respectively (Fig. 2A).

TABLE 3 Population pharmacokinetic parameters of meropenem and bootstrap analysis^a

Parameter	Value(s)			
	Full dataset		Bootstrap	
	Final estimate	RSE (%)	Median	Range (5 th –95 th)
CL (liter/h)				
CL = $\theta_1 \times F_{\text{weight-1}} \times \text{RF}$				
θ_1	4.79	7.30	4.85	4.41–5.34
V_1 (liters)				
$V_1 = \theta_2 \times F_{\text{weight-2}}$				
θ_2	3.68	11.4	3.77	3.07–4.51
V_2 (liters)				
$V_2 = \theta_3$				
θ_3	1.67	27.7	1.74	1.22–2.82
Q (liters/h)				
$Q = \theta_4$				
θ_4	0.216	18.3	0.221	0.172–0.279
$F_{\text{weight-1}} = (W/11)^{\theta_5}$				
θ_5	0.365	12.0	0.358	0.285–0.436
$F_{\text{weight-2}} = (W/11)^{\theta_6}$				
θ_6	0.435	24.8	0.421	0.263–0.612
$\text{RF} = (\text{CRCL}/155.6)^{\theta_7}$				
θ_7	0.317	28.3	0.300	0.115–0.500
Interindividual variability (%)				
CL	12.5	39.2	12.8	6.62–18.6
V_1	43.4	24.5	39.0	18.2–54.7
Residual variability (%)	38.1	9.3	37.1	31.8–43.0

^aRSE, relative standard error; CL, clearance; V_1 , central volume of distribution; V_2 , peripheral volume of distribution; Q, intercompartment clearance; W, weight (in kilograms); CRCL, creatinine clearance (in ml/min/1.73 m²); RF, renal function. In our population, 11 kg and 155.6 ml/min/1.73 m² were the median weight (day of the study) and creatinine clearance values, respectively.

FIG 2 Probability of target attainment (PTA) for meropenem with MICs of 1, 2, 4, and 8 $\mu\text{g/ml}$ as a 4-h infusion (A) and MICs of 4 and 8 $\mu\text{g/ml}$ as continuous (24-h) infusion (B) (70% $fT_{>\text{MIC}}$).

The PTA values for pathogens with high MICs (4 and 8 $\mu\text{g/ml}$), i.e., *Enterobacteriaceae* and *P. aeruginosa*, were 98% and 73.3% following administration of 110 mg/kg/day as a continuous infusion, respectively (Fig. 2B).

DISCUSSION

We enrolled critically ill infants and children (57 patients) and found that a two-compartment model with first-order elimination was optimal for modeling of PK data. Weight and CRCL were significant covariates that correlated with the PK parameters of meropenem in this population.

The median estimated weight-normalized CL and V levels at steady-state were 0.43 liters/h/kg of body weight and 0.51 liters/kg, respectively. They seem to be identical to the values reported previously. Cies et al. (7) reported that the median total CL from the body was 0.39 liters/h/kg, whereas the mean V_d was 0.78 ± 0.73 liters/kg, in 9 critically ill young children. Kongthavongsakul and colleagues (14) suggested the CL to be 0.33 liters/h/kg and estimated the volumes of V_1 and V_2 to be 1.93 liters and 2.13 liters, respectively, in 14 critically ill children. Two studies reported no significant correlation between weight, age, or CRCL and CL in the covariate analysis, data which are different from our results. A possible reason for the differences may be the small study cohort evaluated in those two studies. However, CRCL correlated weakly with the PK parameters of meropenem in this population (14). Du et al. (16) evaluated 99 children and found that CRCL and weight were the most significant covariates explaining variabilities in the PK of meropenem among children and reported that the mean values of CL, V_1 , and V_2 were 0.33 liters/h/kg, 3.3 liters, and 2.6 liters, respectively. Our data showed a larger V and faster CL for meropenem than had been reported previously, which could be explained by the fact that critical illness necessitates administration of resuscitative fluids, inotropes, vasopressors, and diuretics. Such administration can cause enhanced blood flow to the kidneys and increased glomerular filtration, which result in increased CL and subtherapeutic concentrations of the drug (7, 17).

The larger V and faster CL decreased $fT_{>\text{MIC}}$ as a measure of the efficacy of the PK-PD index of meropenem (9, 18). In addition, critically ill children are usually infected by multiresistant bacteria (e.g., *Actinobacter* spp. and *Enterobacteriaceae*) (12) with higher drug MICs. Those phenomena decrease the $fT_{>\text{MIC}}$ (9, 18). Critically ill infants and children are immunodeficient, so 70% $fT_{>\text{MIC}}$ was selected as the PD target (19, 20). That is, the PTA values were 18.7% (MIC = 1 $\mu\text{g/ml}$) and 5.8% (MIC = 2 $\mu\text{g/ml}$) for the regimen of standard doses of meropenem in our study, similar to those noted by Hassan and colleagues (15) (the PTA value was 68.4% in children with 40% $fT_{>\text{MIC}}$ [MIC = 2 $\mu\text{g/ml}$]). Certainly, the regimen of standard doses of meropenem could not achieve the PD target for susceptible and multiresistant organisms.

Therefore, we increased the frequency of administration or prolonged the infusion time and hypothesized that a dosage regimen of 20 and 30 mg/kg/dose (q6h) as a 4-h infusion could achieve 70% $fT_{>\text{MIC}}$ in 99.7% and 83% of simulated patients with normal

renal clearance and in 97.7% and 81.5% of those with augmented renal clearance, at MICs of 2 and 8 $\mu\text{g/ml}$, respectively. However, the difference between these two populations in their PTA values was indistinctive. The CRCL of almost of 57 critically ill patients was $>100 \text{ ml/min/1.73 m}^2$ (43 patients had $\geq 130 \text{ ml/min/1.73 m}^2$). Then, we simulated the general optimal regimen and demonstrated that prolonging infusion to 4 h and 24 h with a lower dose (110 mg/kg/day) than those used previously by Cies et al. (120 and 160 mg/kg/day as a continuous infusion against all susceptible Gram-negative bacteria [7]) would be efficacious and would reduce the overuse of meropenem. Hassan et al. (15) illustrated that a 40 mg/kg/dose (q8h), 20 mg/kg/dose (q6h), or 20 mg/kg/dose (q8h) administered as a 3-h infusion should be efficacious. However, they did not enroll children with abnormal renal function or target critically ill children only.

Our study had three main limitations. First, we did not assess the clinical efficiency and safety of the recommended regimen for meropenem. However, we are currently carrying out a multicenter, double-blind randomized controlled clinical trial. Second, the population PK estimates showed large interindividual variability for V_d and CL. Thus, our simulation results should be interpreted with caution. Third, the recommended dosage regimen of prolongation of to continuous infusion may affect the compliance and quality of life of critically ill children.

Conclusions. The dosage regimen of meropenem must be optimized. For critically ill infants and children, 40 mg/kg/dose (q8h) with 4-h infusion can achieve therapeutic concentrations for bacteria with a low ($\leq 2 \mu\text{g/ml}$) meropenem MIC. We suggest that a dosing strategy of 110 mg/kg/day with continuous infusion could be more efficacious against bacteria with a high (2 to 8 $\mu\text{g/ml}$) meropenem MIC.

MATERIALS AND METHODS

Study design. We conducted a multicenter prospective, open-label PK-PD study of meropenem in Beijing Children's Hospital, Baoding Children's Hospital, and Guizhou Provincial People's Hospital. Patients admitted to pediatric intensive care unit were included if they (i) were aged from 1 month to 15 years; (ii) met the criteria for bacterial meningitis (21), sepsis (7), or severe pneumonia (22), and (iii) had received meropenem as part of empirical or definitive therapy for $>48 \text{ h}$. Patients who were enrolled in another clinical trial and had received metronidazole or who were hypersusceptible to carbapenems were excluded. The study protocol was approved by the Ethics Committee of each participating hospital (2019-k-185) and is registered on clinicalTrials.gov (ClinicalTrials registration no. NCT03643497). Written informed consent was obtained from the parents or guardians of patients.

Dosing regimen and PK sampling. Meropenem (Dainippon Sumitomo Pharma, Osaka, Japan) was administered as an intravenous infusion over 0.5 to 1 h at 40 mg/kg of body weight/dose or 10 to 20 mg/kg/dose (q8h) in patients with bacterial meningitis or other severe infections, respectively. If the weight of the child was $>50 \text{ kg}$, the adult dosing regimen (1 g, q8h) was employed. An opportunistic sampling design was chosen to collect PK samples. Blood samples were obtained from the blood remaining after blood-gas or biochemical analyses (23, 24). Infusion and sample times were recorded precisely. Only samples with identified sampling information were included. Plasma samples were obtained from blood specimens after 10 min of centrifugation at 3,000 rpm at 4°C and were stored at -80°C immediately after addition of a stabilizer [3-(*N*-morpholino)propanesulfonic acid (MOPS)]. Subsequently, samples were transported on dry ice to the Department of Clinical Pharmacy at Shandong Provincial Qianfoshan Hospital (Shandong, China) for storage at -80°C before analyses were performed.

Analytical method for meropenem. Plasma concentrations of meropenem were quantified using high-performance liquid chromatography (HPLC) with a UV detector (Shimadzu, Kyoto, Japan). The chromatographic separation was performed with an InertSustain C_{18} column (Shimadzu, Tokyo, Japan) (5- μm pore size, 4.6 by 250 mm). The UV detection was performed at 300 nm. The mobile phase consisted of acetonitrile (10%) and 0.015 M MOPS buffer (pH 7.00) (90%) with isocratic elution at a flow rate of 0.8 ml/min. The temperatures of the autosampler and column oven were 4°C and 35°C , respectively. The internal standard (IS) was metronidazole prepared in acetonitrile at a concentration of 50 $\mu\text{g/ml}$. The acetonitrile (100 μl)-containing IS was added into the plasma samples (100 μl) for deproteinization. The supernatant (175 μl) was immediately extracted by the use of dichloromethane (100 μl). The mixture was subjected to vortex mixing and centrifuged at 10,000 rpm for 5 min at room temperature. Then, the mixture delaminated into two layers; the lower layer was a mixture of acetonitrile and dichloromethane, and the upper layer was water in which meropenem was dissolved. Subsequently, a 10- μl volume of the supernatant placed in the autosampler at 4°C was injected into the HPLC system within 4 h. A weighted ($1/\times 2$) linear regression analysis was used to establish a standard curve for meropenem within a linear range of 0.2 to 50 $\mu\text{g/ml}$, and the correlation coefficient (*R*) was ≥ 0.995 . The accuracy and intraday and interday precision were evaluated by calculation of the lower limit of quantification (LLOQ) using quality control samples at three concentrations (0.5, 20, and 40 $\mu\text{g/ml}$). Intra-assay accuracy ranged from 91.22% to 100.12%, and the precision was less than 5.75%. Interassay

accuracy ranged from 94.93% to 97.59%, and the precision was less than 4.54%. The lower limit of quantification was 0.2 µg/ml. If samples were outside the upper limit of determination on the standard curve, then a 1:2 dilution or 1:5 dilution was made until the sample was within the standard curve. If a sample was below the LLOQ on the standard curve, the value was reported as <0.2 µg/ml.

Population PK modeling of meropenem. A nonlinear mixed-effects modeling program (NONMEM v7.2.0; Icon Development Solutions, Dublin, Ireland) was used to carry out PK analysis. In this study, double-sided LN transformation was not used in data analysis. To estimate PK parameters and their variability, a first-order conditional estimation method with interaction was applied.

Interindividual variability of PK parameters was estimated using an exponential model expressed as follows:

$$\theta_i = \theta_{\text{mean}} \cdot \exp(\eta_i) \quad (1)$$

where θ_i represents the individual parameter value of the i^{th} subject, θ_{mean} represents the typical value of the parameter in the population, and η_i represents the variability between participants (which is assumed to follow a normal distribution with a mean of 0 and variance of ω^2). The residual variability was evaluated with additive, proportional, exponential, and combined residual error models, respectively.

In forward-selection and backward-elimination processes, covariates were considered in various rounds, with a single covariate added at the conclusion of each step. The likelihood ratio test was used to test the effect of each variable on model parameters. Weight and age data and levels of alanine transaminase, aspartate aminotransferase, creatinine clearance (CRCL; estimated using the Schwartz formula), blood urea nitrogen, glutamyl transpeptidase, alkaline phosphatase, and albumin (PK samples were collected within 48 h) were investigated as potential variables affecting PK parameters and added to the model. During the first step of building of the covariate model, if the objective function value (OFV) decreased >3.84 compared with the base model, the covariate was considered to have had a significant impact ($P < 0.05$). Then, all of the significant covariates were added simultaneously to the model. Subsequently, in the backward-elimination step, each covariate was removed independently from the full model. If the increase in the OFV was >6.635 ($P < 0.01$), the covariate was considered to be correlated significantly with the PK parameter and was, finally, retained in the final model.

Model validation. Model validation was based on graphical and statistical criteria. A scatterplot of observed (dependent variable [DV]) values versus population prediction (PRED) and individual prediction (IPRED) data was constructed to compare the population and individual-specific predicted values with the measured values, respectively. A plot of conditional weighted residuals (CWRES) versus PRED and time identifies poorly fitting values and illustrates potential patterns of misfit across the range of predicted values and time, respectively (25).

A nonparametric bootstrap analysis performed with resampling and replacement was done to evaluate the stability and performance of the final model. Resampling was repeated 1,000 times, and the parameter values obtained from the bootstrap procedure were compared with those determined from the original data set. Normalized prediction distribution errors (NPDEs) were used to further assess the final model (26, 27). A total of 1,000 data sets were simulated using the final parameters for the population model. NPDE results, the Q-Q plot (where Q is quantile), and a histogram of NPDEs were summarized graphically by default as provided by R (R Foundation for Statistical Computing, Vienna, Austria) (28). The values corresponding to the NPDEs were expected to follow the N (0, 1) distribution.

Evaluation and optimization of the dosing regimen. Monte Carlo simulations were undertaken using the final model to define the optimal dosing regimen capable of attaining the target 70% $fT_{>\text{MIC}}$ level (19). According to the European Committee on Antimicrobial Susceptibility Testing (29) and the Clinical and Laboratory Standards Institute (30), meropenem MICs for the most common pathogens (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) range from 0.25 to 1.0 µg/ml in meningitis. Non-meningitis-related *S. pneumoniae* and *H. influenzae* strains are sensitive to meropenem, with a MIC of 2 µg/ml. *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. have a MIC of 4 to 8 µg/ml. For severe infection caused by various pathogens, a non-species-related MIC of 8 µg/ml was selected as the PK-PD breakpoint value. The pediatric dose of meropenem was simulated on the basis of mg/kg data. The unbound fraction of meropenem was defined as 0.98 (7). The original data set was simulated 100 times, and the time above the MIC was calculated for each original patient. Data from the original patients were used in the simulations in order to make sure that the population distribution characteristics were the same. If the current dosing regimen showed underdosing in >50% of patients, the optimal dosing regimen with an increased dose and/or frequency was given to the “virtual patient.” Thus, various dosing regimens (20, 30, 40, 50, and 60 mg/kg/dose; q6h, q8h, and q12h) were simulated as a prolonged infusion (2 to 4 h) and continuous infusion in this group. The probability of target attainment (PTA) was calculated for each dosing regimen. A PTA value of $\geq 70\%$ was defined as “optimal.”

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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