Population Pharmacokinetic Analysis and Dosing Regimen Optimization of Meropenem in Adult Patients

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The objectives of this study were to develop a meropenem population pharmacokinetic model using patient data and use it to explore alternative dosage regimens that could optimize the currently used dosing regimen to achieve higher likelihood of pharmacodynamic exposure against pathogenic bacteria. We gathered concentration data from 79 patients (ages 18-93 years) who received meropenem 0.5, 1, or 2 g over 0.5- or 3-hour infusion every 8 hours. Meropenem population pharmacokinetic analysis was performed using the NONMEM program. A 2-compartment model fit the data best. Creatinine clearance, age, and body weight were the most significant covariates to affect meropenem pharmacokinetics. Monte Carlo simulation was applied to mimic the concentration-time profiles while 1 g meropenem was administrated via infusion over 0.5, 1, 2, and 3 hours. The 3-hour prolonged infusion improved the likelihood of obtaining both bacteriostatic and bactericidal exposures most notably at the current susceptibility breakpoints.

Keywords: *Meropenem; population pharmacokinetics; pharmacodynamics; dosing*

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Meropenem, an intravenous antibiotic of the carbapenem class, is indicated for the treatment of complicated intra-abdominal infections, complicated skin and skin structure infections, and bacterial meningitis in adults, as well as bacterial meningitis in pediatrics. Because of its broad-spectrum activity against both Gram-positive bacteria and Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Acinetobacter* species, it is also used for the treatment of other serious nosocomial infections, such as pneumonia and bacteremia, that are often caused by these multidrug-resistant pathogens. The pharmacokinetics of meropenem have been extensively studied in various subpopulations, including young and elderly healthy volunteers, pediatric and adult patients with different types of infections, and patients with renal or hepatic dysfunction.[1-7] As demonstrated, meropenem observes linear pharmacokinetics in the dose range from 0.25 to 2 g over a 0.5-hour infusion.[8] To date, there is limited information available regarding meropenem population pharmacokinetics in adult patients. Currently, one study used 12 febrile neutropenic patients to develop a patient covariate model to characterize meropenem population pharmacokinetics; however, the predictive performance of this model was not validated.[9] In addition, a covariate model in pediatric patients has been developed and validated, but this model cannot be applied to adults.[10]

Like penicillins and cephalosporins, meropenem demonstrates time-dependent killing at concentrations attained in humans. The percentage of the dosing interval that free drug antibiotic concentrations remain above the minimum inhibition concentration (MIC) of the pathogenic organism ($fT > MIC$) is the most important pharmacodynamic parameter to predict antimicrobial efficacy.[11] As a result, clinically used dosing regimens of meropenem have been modified in an

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effort to maximize its pharmacodynamic outcomes in some small trials and case series.[12,13] To overcome the limitation of small patient numbers in these studies and others, Monte Carlo simulation has been applied to predict the probability of attaining a specific pharmacodynamic target at various dosage regimens.[14-16] However, in the absence of patient pharmacokinetics, these studies used healthy volunteer pharmacokinetics or a mixture of the 2; thus, the prediction of pharmacodynamic attainment in patients may not be accurate, given greater variabilities of pharmacokinetic parameters in this population.

The objective of the present study was to develop a population pharmacokinetic model of meropenem in infected patients and to assess the impact of patient covariates on meropenem pharmacokinetics. In addition, based on the studied patients, clinical pharmacokinetic profiles were simulated to determine the optimal dosage regimen to achieve a high probability of target attainment at increasing MIC breakpoints.

MATERIALS AND METHODS

Data Assembly

The present population pharmacokinetic study was reviewed and approved by the Institutional Review Committee at Hartford Hospital (Hartford, Conn). Pharmacokinetic data of meropenem were obtained from 3 previously conducted clinical trials in patients with intra-abdominal infections, community-acquired pneumonia, or ventilator-associated pneumonia. Patients received 0.5, 1, or 2 g meropenem over a 0.5- or 3-hour infusion. Blood samples were collected at the third dose interval or steady state. Various sampling schedules were applied in these clinical trials. Meropenem concentrations were determined using a validated high-performance liquid chromatography assay with a UV detector.[17] The lower limit of quantification for this assay was 0.06 mg/L with inter- and intrarun coefficient of variability less than 10%. Baseline data of the patients included gender, age, weight, height, and serum creatinine concentration.

Pharmacokinetic Structural Model

Population pharmacokinetic analysis was performed using the first-order estimation method in the NONMEM program (version V, level 1.1, double precision).[18] One- and 2-compartment models with zero-order input and first-order elimination were evaluated as the pharmacokinetic structural model. The population pharmacokinetic parameters were assumed to follow log-normal distributions. A combination of additive and proportional error models was used to characterize the intraindividual variability. The selection of the base model was based on Akaike information criterion (AIC), a decrease in the residual errors, the scatter plots of the weighted residual versus the predicted concentration and time, and the scatter plot of the observed versus the predicted concentrations.

Covariate Model

Once the pharmacokinetic base model was selected, visual inspection was initially applied to assess the correlation of the individual pharmacokinetic parameter estimates and patient covariates, including categorical covariates (gender, disease) and continuous covariates (age, body weight, height, and creatinine clearance). Creatinine clearance was calculated according to the Cockcroft-Gault equation based on the patient ideal body weight.[19] A stepwise forward inclusion procedure (α = .05; ie, the decrease of objective function values larger than 3.84) was performed in NONMEM to build the full model; and a stepwise backward elimination procedure (α = .01; ie, the increase of objective function larger than 6.63) was applied to determine the final model.[20]

The final model was reevaluated using the first-order conditional maximum likelihood estimation method (FOCE). Continuous variables were normalized to their median values in a power function model. For example, meropenem clearance was modeled with creatinine clearance (CL_{CR}) as follows: $CL = \theta_1 \times (CL_{CR}/83)^{\theta_2}$, in which CL is the population value of meropenem clearance, θ_1 is meropenem clearance for a patient with the median creatinine clearance (83 mL/min), and θ_2 is the effect coefficient of the covariate. Categorical variables were modeled as $CL = \theta_1 \times \theta_2^{SEX}$, in which CL is the population value of meropenem clearance, θ_1 is meropenem clearance for female patients (setting SEX = 0 for female and SEX = 1 for male), and θ_2 is the fraction change of CL for male patients.

Model Validation

The nonparametric bootstrap resampling technique was performed to validate the reliability and stability of the model developed, as recommended by the Food and Drug Administration (FDA) guidance on population pharmacokinetics.[21] The program of Wings for

NONMEM (version 408b, N. Holford, Auckland, New Zealand) was used to create resampled new data sets. The means and 95% confidence intervals (CIs) of pharmacokinetic parameters from 1000 bootstrap replicates were compared with the estimates of the final model.

Dosing Regimen Optimization

To optimize the pharmacodynamic outcome, a prolonged infusion was simulated to determine the optimal dosing regimen to achieve a specific pharmacodynamic target at varying MIC breakpoints. For meropenem, exposure targets of 20% $fT > MIC$ and 40% $fT > MIC$ were used for bacteriostatic and bactericidal effects, respectively.[22-24] A Monte Carlo simulation was conducted using the final population pharmacokinetic model including the fixed- and random-effect parameters. To determine the probability of the target attainment at each MIC value, the concentration profile was simulated as 1 g meropenem every 8 hours administrated via infusions of 0.5, 1, 2, or 3 hours. For each dosing regimen, meropenem concentration-time profiles at steady state were generated for a total of 100 sets of simulated studied patients. The resultant probabilities of the bacteriostatic and bactericidal target attainment were estimated for each regimen against bacteria with various MIC values.

RESULTS

The final database consisted of 79 patients aged 18 to 93 years, including 61 men and 18 women. There were 52 patients with intra-abdominal infections, 21 patients with ventilator-associated pneumonia, and 6 patients with community-acquired pneumonia. Their demographic information is summarized in Table I. In total, 341 concentrations were used for population pharmacokinetic analysis, the number of concentrations per patient ranged from 1 to 12. Figure 1 presents the scatter plot of meropenem concentration versus time of all patients included in the present study.

After assessing the diagnostic plots and comparing AIC values, a 2-compartment model provided a better fit to the data and therefore was selected as the pharmacokinetic base model to build the covariate model. The following pharmacokinetic parameters were used to characterize the 2-compartment model: clearance (CL), intercompartmental clearance (Q), central volume of distribution (Vc), and peripheral volume of distribution (Vp). For the studied population, meropenem clearance was estimated to be 12.3 L/h, the intercompartmental clearance was 23.3 L/h, the central volume of distribution was 10.3 L, and the peripheral volume of distribution was 16.7 L. The relative standard error of these parameters ranged from 8.4% to 12.8%.

In step 1 of building the covariate model, all the covariates tested had significant effect on meropenem clearance, body weight and gender had significant effect on the central volume of distribution, body weight had significant effect on the intercompartmental clearance, and gender had significant effect on the peripheral volume of distribution. When compared to the base model, adding creatinine clearance to meropenem clearance resulted in a maximum decrease of objective function values ($\Delta OFV = -124.08$). After 5 steps of the forward inclusion procedure, creatinine clearance; age, gender, and body weight for meropenem clearance; and body weight for the central volume of distribution were included in the full covariate model.

Table I Summary of Demographic Characteristics of the Studied Patients

Covariate	Symbol	Mean (SD)	Median (Range)
Weight, kg	WT	73.0 (16.1)	70 (40.6-127)
Height, cm	HT	169.5 (8.7)	170 (147-185.4)
Sex, no. of male/female	SEX	61/18	—
Age, y	AGE	39.6 (18.2)	35 (18-93)
Serum creatinine, mg/dL	SCR	1.1 (0.8)	1.0 (0.4-6.9)

A total of 341 concentrations from 79 patients.

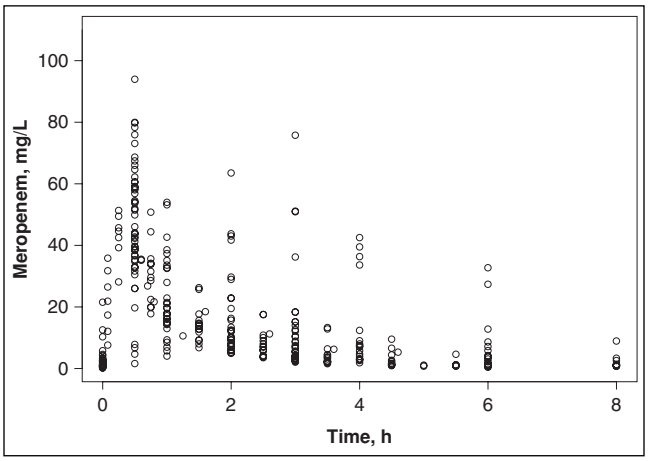

Figure 1. The scatter plot of meropenem concentration versus time sampled from 79 patients.

Table II Estimates of Population Pharmacokinetic Parameters in the Final Model

Parameter	Covariate Model		
	Population Estimate	**SE**	**Bootstrap (95% CI)**
$CL\ (L/h) = \theta_1 \times (CL_{CR}/83)^{\theta_2} \times (Age/35)^{\theta_3}$			
θ_1	14.60	0.93	12.61 to 16.46
θ_2	0.62	0.10	0.34 to 0.83
θ_3	–0.34	0.13	–0.04 to –0.57
ω_1^2	0.118	0.028	0.070 to 0.173
$V_1\ (L) = \theta_4 \times (WT/70)^{\theta_5}$			
θ_4	10.80	1.57	7.44 to 13.76
θ_5	0.99	0.34	0.09 to 2.04
ω_2^2	0.143	0.046	0.046 to 0.250
$Q\ (L/h) = \theta_6$			
θ_6	18.60	3.31	7.03 to 32.16
ω_3^2	0.290	0.140	0.050 to 1.120
$V_2\ (L) = \theta_7$			
θ_7	12.6	1.68	8.71 to 17.99
ω_4^2	0.102	0.085	0.002 to 0.383
	Residual Error Model		
σ_1^2	0.0352	0.0070	0.021 to 0.051
σ_2^2	0.220	0.165	0.004 to 0.639

CI, confidence interval; SE, standard error; ω^2, interindividual variance; σ_1^2, proportional residual variance; and σ_2^2, additive residual variance.

In the process of the stepwise backward deletion procedure, the exclusion of gender and body weight on meropenem clearance did not make significant change in the final model. Creatinine clearance and age (AGE) on meropenem clearance and body weight (WT) on the central volume of distribution made the most significant impact on meropenem pharmacokinetics in patients. Meropenem population pharmacokinetic parameter estimates are listed in Table II. The final model is summarized as follows: $CL\ (L/h) = 14.6 \times (CL_{CR}/83)^{0.62} \times (AGE/35)^{(-0.34)}$, $V_C\ (L) = 10.8 \times (WT/70)^{0.99}$, $Q\ (L/h) = 18.6$, $V_P\ (L) = 12.6$.

Figure 2 shows the diagnostic plots of the weighted residual versus the predicted concentration, the population predicted versus observed concentration, and the individual predicted versus observed concentration. These indicate that the model developed lacks bias and characterizes well meropenem pharmacokinetics in the studied patients. Moreover, all the population pharmacokinetic parameter estimates were in the range of the 95% CI of population estimates obtained from the bootstrap procedure (Table II), demonstrating the reliability and stability of the final model.

For each dosing regimen, a total of 7900 simulated patient concentration-time profiles were created based on the current studied patient population. The mean simulated free meropenem concentration for meropenem 1 g every 8 hours as a 0.5-hour infusion and 3-hour infusion at steady state (40-48 hours) are depicted in Figure 3. Figure 4A presents the probability of the target attainment versus MIC, indicating that similar bacteriostatic target attainments were achieved among the 4 simulated regimens. With regard to the susceptibility breakpoint of 4 μg/mL for Enterbacteriaceae, *Acinetobacter* species and *Pseudomonas aeruginosa*, the bactericidal target attainment rate increased from 64% to 90%, as the infusion time for a 1-g dose was prolonged from 0.5 to 3 hours.

DISCUSSION

The pharmacokinetic profile of meropenem has been described in healthy volunteers and in a limited number of patients; however, to date, a population model based on meropenem concentrations collected from an ample number of patients has not been described. There are 3 published studies involving meropenem that apply the nonparametric population pharmacokinetic approach.[9,15,16] A small number of subjects were used for the population pharmacokinetic analysis in 2 studies: 16 healthy volunteers in

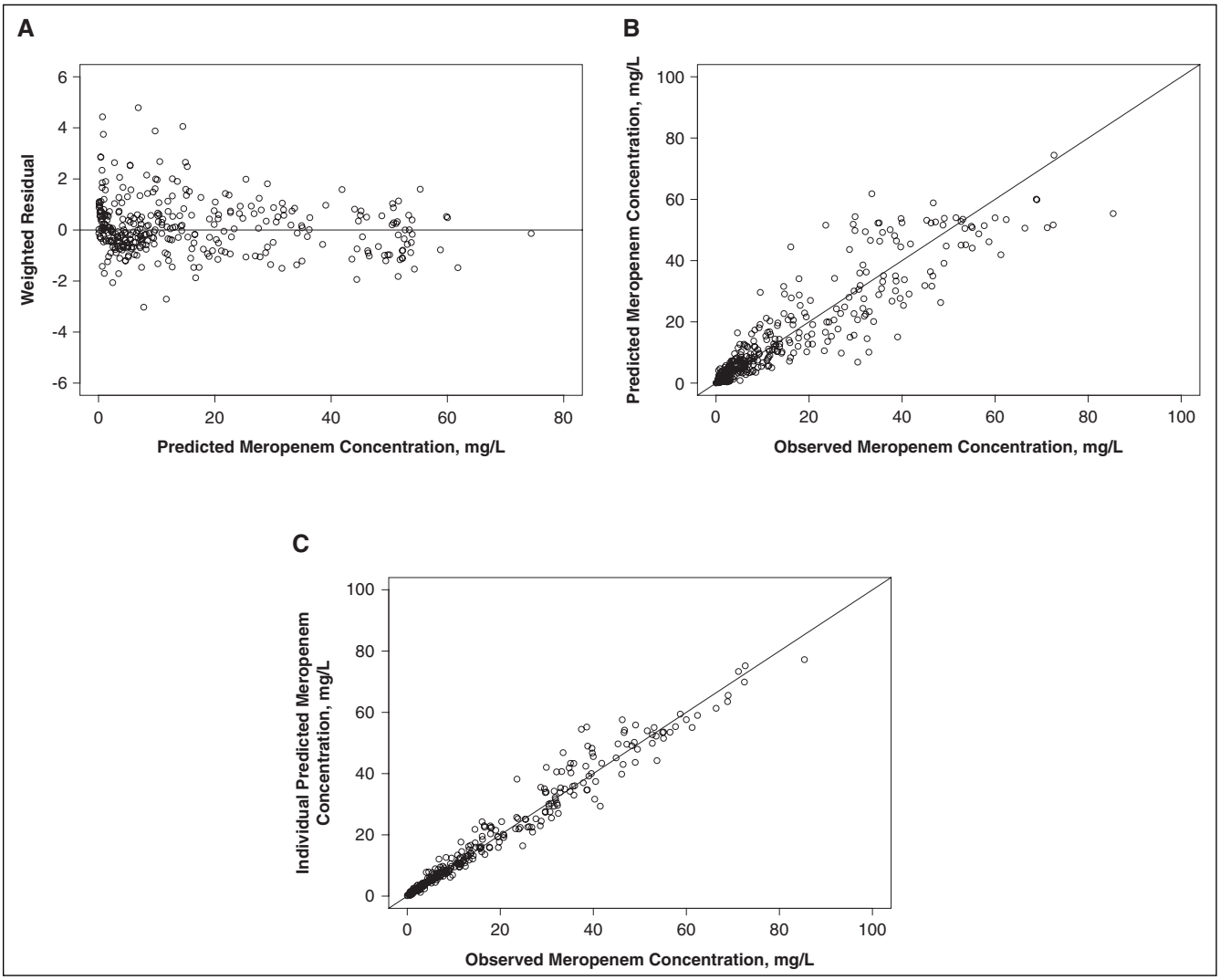

Figure 2. Diagnostic scatter plots of meropenem population pharmacokinetic model. (A) Weighted residual versus predicted concentration, (B) population predicted versus observed concentration, and (C) individual predicted versus observed concentration. The line of unity is included in (B) and (C).

one study[16] and 12 patients in another study.[9] Data from healthy volunteers and patients were mixed in the third study to perform the population pharmacokinetic analysis, but no statement was made whether there was any difference between healthy and infected subjects.[15] No validated covariate model was presented to profile meropenem population pharmacokinetics in these studies. Furthermore, the interindividual and intraindividual variabilities, the symbolic differences between population pharmacokinetics and traditional pharmacokinetics, were not presented to characterize meropenem population pharmacokinetics.

In the present study, a population pharmacokinetic model was developed to characterize meropenem pharmacokinetics in a large number of adult patients. Of the patient covariates evaluated, creatinine clearance was the most significant covariate to effect meropenem clearance, consistent with previous findings that 54% to 79% of unchanged meropenem was excreted in the urine.[25] Consequently, meropenem clearance can be altered depending on differing degrees of renal function in patients.[7,26] The population estimate of meropenem clearance in the studied patients was 12.3 L/h, larger than creatinine clearance in healthy volunteers, indicating that the renal elimination of meropenem

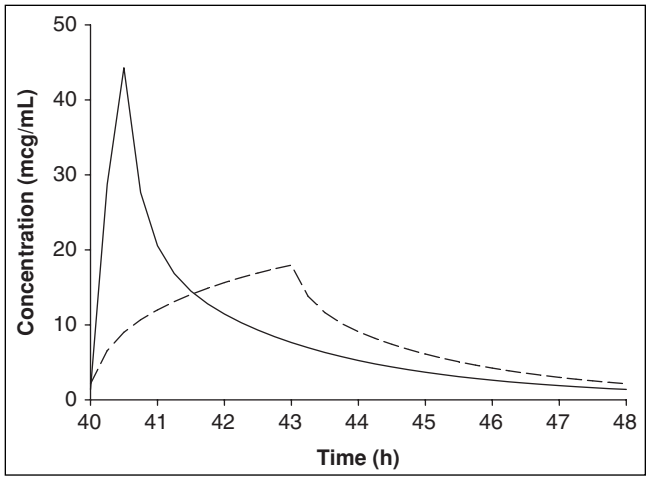

Figure 3. Mean simulated steady-state free meropenem concentration-time profile based on final population pharmacokinetic parameters for 1 g as a 0.5-hour infusion (solid line) and as a 3-hour infusion (dashed line).

involves glomerular filtration and tubular secretion and that there are other possible covariates affecting meropenem clearance.[27]

During the process of the model building, age was the second most important covariate to affect meropenem pharmacokinetics. Although age was one of the 4 covariates used to calculate creatinine clearance in the Cockcroft-Gault equation, the correlation coefficient (r^2) between creatinine clearance and age was .136 ($P < .001$), indicating no colinearity found between these 2 covariates in the studied patients. Therefore, these 2 covariates can be treated as 2 independent variables in the covariate model. The effect of age on meropenem pharmacokinetics has been observed in young (20-34 years old) and elderly (67-80 years old) healthy volunteers.[1] In elderly subjects, the clearance of meropenem and its metabolite were significantly decreased, and the areas under the curve were increased as a result of age-related declines in physiologic functions. Because meropenem is hydrolyzed to form 1 open-ring metabolite via renal dehydropeptidase-I, no significant change in meropenem pharmacokinetics has been observed in patients with hepatic impairment.[6,28] In addition, liver function data for these 79 patients were not available, so this variable was excluded during the model-building process.

In the final model, the central volume of distribution appeared linearly related to body weight, but no significant covariate was found to explain why interindividual variabilities were relatively high for the intercompartmental clearance and the peripheral volume of distribution. The variation of meropenem

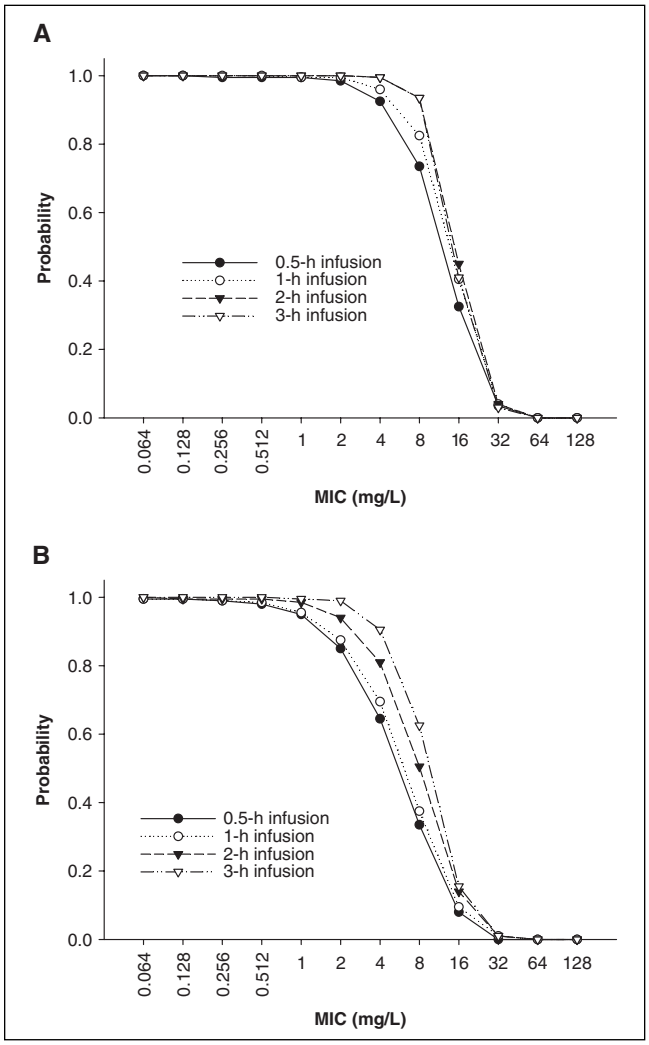

Figure 4. Probabilities of achieving (A) bacteriostatic (20% $fT >$ MIC) and (B) bactericidal (40% $fT >$ MIC) exposures at specific MICs after the administration of meropenem 1 g every 8 hours with varying infusion times of 0.5, 1, 2, and 3 hours. MIC, minimum inhibition concentration.

disposition in the peripheral compartment may be a result of physiologic changes due to the presence of infection or other unidentified causes.[29] Further study is needed to determine the source of the variation of meropenem disposition in the peripheral compartment.

As mentioned previously, Monte Carlo simulations in previous studies were totally or partly based on meropenem pharmacokinetics derived from healthy volunteers.[14-16] Compared to estimates of meropenem population pharmacokinetic parameters in healthy volunteers, the studied patients displayed a lower clearance and central volume of distribution. As a

time-dependent antibiotic, the T > MIC of meropenem against pathogens can be used as a surrogate marker to predict the pharmacodynamic outcome. Mattoes and colleagues extensively reviewed the dosage strategies to optimize meropenem antimicrobial pharmacodynamics and concluded that higher doses, increased dosing frequency, or prolonged duration of infusion resulted in improved pharmacodynamics.[30] Specifically, prolonged infusion has been suggested as an alternative method to optimize meropenem pharmacodynamics, especially considering the antibiotic is not stable at room temperature for a long enough time to justify a 24-hour continuous infusion. Our results agree with others that prolonging the infusion time from 0.5 hour to 3 hours increases the probability of target attainment at each MIC. Figure 4 demonstrates that the 3-hour infusion of meropenem 1 g every 8 hours achieved the bacteriostatic and bactericidal exposures with 99% and 93% likelihood at the susceptibility breakpoint of 4 μg/mL. According to the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program in 2002, the MIC_{90} of common pathogenic bacteria was less than 0.25 μg/mL with the exception of *Pseudomonas aeruginosa* (MIC_{90} 4 μg/mL) and *Acinetobacter* species (MIC_{90} 32 μg/mL).[31] Furthermore, the 3-hour infusion regimen of meropenem achieves a 62% probability of bactericidal target attainment against intermediate resistant pathogens with an MIC of 8 μg/mL without requiring extra drug. Overall, the highest target attainment rate was predicted with the 3-hour infusion of meropenem. Higher doses, along with prolonged infusion should increase the likelihood of targeted exposures at higher MICs even further.[30]

In summary, creatinine clearance, age, and body weight were the most significant covariates to affect meropenem pharmacokinetics. This population pharmacokinetic model adequately characterized the pharmacokinetic profile of meropenem in adult patients and should be further validated in an independent patient population. As predicted, the prolongation of the meropenem infusion to 3 hours can lead to improvements in meropenem pharmacodynamic exposure.

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