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Optimization of meropenem dosage in the critically ill population based on renal function

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Abstract *Purpose:* To develop a meropenem population pharmacokinetic model in critically ill patients with particular focus on optimizing dosing regimens based on renal function. *Methods:* Population pharmacokinetic analysis was performed with creatinine clearance (CrCl) and adjusted body weight to predict parameter estimates. Initial modeling was performed on 21 patients (55 samples). Validation was conducted with 12 samples from 5 randomly selected patients excluded from the original model. A 5,000-patient Monte Carlo simulation was used to ascertain optimal dosing regimens for three CrCl ranges. *Results:* Mean ± SD age, APACHE, and CrCl were 59.2 ± 16.8 years, 13.6 ± 7, and 78.3 ± 33.7 mL/min. Meropenem doses ranged from 0.5 g every 8 h (q8h)–2 g q8h as 0.5–3 h infusions. Median estimates for volume of the central compartment, K_{12}, and K_{21} were 0.24 L/kg, 0.49 h^{-1}, and 0.65 h^{-1}, respectively. K_{10} was described by the equation: $K_{10} = 0.3922 + 0.0025 \times \text{CrCl}$. Model bias and precision were −1.9 and 8.1 mg/L. R^2, bias, and precision for the validation were 93%, 1.1, and 2.6 mg/L. At minimum inhibitory concentrations (MICs) up to 8 mg/L, the probability of achieving 40% $fT > \text{MIC}$ was 96, 90, and 61% for 3 h infusions of 2 g q8h, 1 g q8h, and 1 g q12h in patients with CrCl ≥50, 30–49, and 10–29, respectively. Target attainment was 75, 65, and 44% for these same dosing regimens as 0.5 h infusions. *Conclusions:* This pharmacokinetic model is capable of accurately estimating meropenem concentrations in critically ill patients over a range of CrCl values. Compared with 0.5 h infusions, regimens employing prolonged infusions improved target attainment across all CrCl ranges.

Keywords Meropenem · Population pharmacokinetics · Prolonged infusion · Creatinine clearance · Monte Carlo simulation

Introduction

Meropenem is a carbapenem antibiotic that is commonly used to treat a variety of pathogens in critically ill patients. Meropenem is approved by the Food and Drug Administration (FDA) for a number of indications [1]; however, recent studies have cautioned that FDA-approved doses may exhibit less than optimal exposures against pathogens considered susceptible by the Clinical and Laboratory Standards Institute (CLSI), especially for patients with normal renal function [2–5]. Meropenem microbiological efficacy, as with all β-lactams, is predicated by the percentage of the dosing interval in which free drug concentrations remain above the minimum

inhibitory concentration (MIC) of the infecting organism ($fT > MIC$) [6]. For the carbapenem class, antimicrobial activity is optimized when the $fT > MIC$ is $\geq 40\%$ [7]. For patients with normal renal function, the probability of meropenem 1 g q8h (0.5 h infusion) achieving this target against isolates with MICs of 2 or 4 μg/mL is only 85 and 65%, respectively [2].

The potential inadequacies noted for standard doses of meropenem may be further compounded in the intensive care unit (ICU) as they typically harbor the most resistant pathogens within a given population [8]. Further, the pharmacokinetics of the critically ill may differ from non-critically ill patients, often resulting in a reduction in exposure [9]. For these reasons, higher empiric doses may be required to adequately achieve pharmacodynamic targets against pathogens encountered within the ICU.

With the availability of institution- or, optimally, unit-specific susceptibility patterns, informed decisions can be made towards the selection of empiric doses exhibiting the most optimal pharmacodynamics for a given population [10]. In a number of institutions, the development of clinical dosing pathways derived from eloquent pharmacodynamic analyses aid clinicians in optimal empiric dose and drug selection [11]. The predictability of these pharmacodynamic studies relies heavily on the availability of robust population pharmacokinetic data derived from the patient population of interest. Unfortunately, although meropenem is widely used in the critical care population, pharmacokinetic data gathered solely in that patient population are sparse [12]. As when developing our clinical dosing pathway, we utilized parameter data from a population pharmacokinetic model derived from both critically ill and non-critically ill patients.

In an attempt to ensure optimal regimens are given to critically ill patients in our hospital, the objectives of this study are to create a relatively robust population pharmacokinetic model for meropenem derived from patients within the ICU and to use this model to select dosing regimens for critically ill patients that optimize pharmacodynamics across various ranges of renal function.

Materials and methods

Patients and setting

Patients residing in the 12-bed medical, 12-bed surgical, 12-bed cardiothoracic, or 18-bed neurotrauma ICU at Hartford Hospital, Hartford, CT, receiving meropenem, were identified via a daily pharmacy-generated report from April 2007 to October 2008. Patients were included in the analysis if they were at least 18 years of age and had received at least 3 consecutive doses of meropenem. Patients were excluded if they were deemed poor candidates for blood collection or required hemodialysis during meropenem therapy. The protocol was reviewed and approved by Hartford Hospital's Institutional Review Board and a waiver of consent was granted because these data were collected as part of an ongoing quality assurance assessment of the previously described clinical dosing pathway and the risk to participants (i.e., blood draws) were minimal [11]. Namely, the meropenem pharmacokinetic data used to develop our ICU-specific clinical dosing pathway were derived from a population of both critically ill and non-critically ill patients. While these pharmacokinetic data were the most applicable of those available when our dosing pathway was designed, the data collected herein were used to validate predicted exposures in our critically ill patients to optimize patient care.

Pharmacokinetic sampling

A maximum of three blood samples were collected over the dosing interval from each patient after at least three consecutive doses of meropenem (i.e., steady-state). After collection, blood samples were immediately centrifuged, serum separated, and stored at −80°C until drug analysis.

Concentration determination

Meropenem concentrations were determined by using a previously published validated high-performance liquid chromatography assay [13]. The interday coefficients of variation for high (30 μg/mL) and low (0.5 μg/mL) check samples were 2.4 and 5.9%, respectively; whereas, intraday coefficients of variation were 1.6 and 2.1%, respectively.

Population pharmacokinetic model

Population modeling of meropenem was performed by the non-parametric adaptive grid (NPAG) method using a two-compartment pharmacokinetic model with zero-order input and first-order intercompartmental transfer and elimination [14]. The demographic variables age, gender, ethnicity, adjusted body weight (AdjBW), APACHE II score, and creatinine clearance (CrCl) were examined for potential correlation with pharmacokinetic parameters. CrCl was calculated by using the Cockcroft–Gault equation: $CrCl = (140 - age) \times IBW/(serum\ creatinine \times 72)$ (multiplied by 0.85 for females), where ideal body weight (IBW) = 50 kg + 2.3 kg for each inch over 5 feet for males and 45.5 kg + 2.3 kg for each inch over 5 feet for females. If the serum creatinine was less than 0.9 mg/dL and the patient was at least 65 years old, it was adjusted to 0.9 mg/dL for calculations. AdjBW, determined only for patients whose weight exceeded their IBW by more than

20%, was calculated by the equation: AdjBW = IBW + 0.4(actual weight − IBW). The elimination rate constant (K_{10}) was defined as a function of CrCl by the equation $K_{10} = K_i + (K_S \times \text{CrCl})$, where K_i is the intercept and K_S is the slope parameter. Volume of distribution of the central compartment (V_1) was defined as a function of AdjBW or actual body weight for patients who did not meet the above criteria.

An assay variance model with a gamma function (γ) was determined by fitting a polynomial to the plot of the assay standard deviations (SD) versus the measured meropenem concentrations on a between-day basis generating the following formula: $SD = \gamma(0.48 - 0.00013C + 0.00027C^2)$ where C was the meropenem concentration and γ was identified to be 1.32. Individual concentrations in serum were weighted by the reciprocal of the assay variance pattern, applying more weight to the more precisely measured concentrations. Goodness of fit was assessed by the coefficients of determination of the observed-predicted plot. Predictive performance was evaluated from this plot on the basis of the coefficient of determination, weighted mean error, and the root mean squared error. Concentration data from five randomly selected patients were withheld from the initial model building process to independently validate the model.

Monte Carlo simulation

A 5,000-patient Monte Carlo (Crystal Ball, Decisioneering Inc., Denver, CO, USA) simulation was performed as previously described [15]. Briefly, meropenem steady-state concentration–time profiles for a number of dosing regimens were simulated by using the median pharmacokinetic parameter estimates derived from the population pharmacokinetic model described above. All input variables were assumed to follow log distribution except for fraction unbound (85–98%) and CrCl, which were assumed to follow a uniform distribution over the specified ranges. Simulations were run over three CrCl ranges: 50–120, 30–49, and 10–29 mL/min.

From the simulated concentration–time profiles, the probability of pharmacodynamic target attainment (PTA) was calculated over a range of doubling MICs from 0.008 to 64 μg/mL, assuming a pharmacodynamic target of 40% $fT >$ MIC [7]. Regimens with PTAs of at least 90% were considered optimal.

Results

Patient population

A total of 67 samples were collected from 26 critically ill patients. Of these, 7 (26.9%) resided in the medical ICU, 2 (7.7%) were in the cardiothoracic ICU, 12 (46.2%) were in the surgical ICU, and 5 (19.2%) were in the neurotrauma ICU. Fifty-five meropenem samples from 21 patients were included in the model building group, whereas the validation group consisted of 12 samples from 5 patients. The characteristics of patients in both groups are shown in Table 1. The majority of patients received high dose prolonged infusions of meropenem (2 g every 8 h as a 3 h infusion). This was consistent with the observation that only 23% of patients had calculated CrCls of less than 50 mL/min.

Population pharmacokinetic model

The population pharmacokinetic parameters derived for meropenem are listed in Table 2. The covariance matrix of these parameters is available as Online Resource 1. The median parameter estimates resulted in the most predictable model. Using these estimates, we obtained the following equations: $K_{10} = 0.392 + 0.003 \times \text{CrCl}$ and $V_1 = \text{AdjBW (kg)} \times 0.239$ L. Aside from CrCl and AdjBW, none of the other potential covariates were found to correlate with any of the pharmacokinetic parameters. The coefficient of determination, bias, and precision of the population model were 52%, −1.9, and 8.1 μg/mL, respectively (Fig. 1). These same predictive performance measures determined after completion of the Bayesian step were 96%, −0.49, and 2.39 μg/mL, respectively. Concentration data of the validation group were predictable using the population model, with a coefficient of determination, bias, and precision of 93%, 1.1, and 2.6 μg/mL, respectively (Fig. 2).

Table 1 Comparative characteristics of ICU patients receiving meropenem between the modeling and validation groups

Characteristic	Modeling group (n = 21)	Validation group (n = 5)
Age (years), mean ± SD	60.0 ± 17.5	59.2 ± 17.5
Infection type, n (%)		
VAP	17 (81)	5 (100)
Other[a]	4 (19)	–
Weight (kg), mean ± SD	88.9 ± 22.3	94.3 ± 27.2
APACHE II, median (range)	12 (4–40)	11.6 (7–16)
Male gender, n (%)	12 (57.1)	3 (60)
CrCl (ml/min), median (range)	70 (35–201)	68 (51–111)
Meropenem regimen, n (%)		
2 g every 8 h (3 h INF)	8 (38.1)	3 (60)
2 g every 8 h (1 h INF)	1 (4.8)	–
1 g every 8 h (1 h INF)	3 (14.3)	–
1 g every 8 h (0.5 h INF)	4 (19.0)	–
0.5 g every 8 h (0.5 h INF)	2 (9.5)	–
0.5 g every 6 h (0.5 h INF)	3 (14.3)	2 (40)

VAP ventilator associated pneumonia, *CrCl* creatinine clearance, *INF* length of infusion

[a] Urinary tract infection, sepsis, intra-abdominal infection, skin and skin structure infection

Table 2 Population model pharmacokinetic parameters derived from ICU patients

Parameter	K_i (h^{-1})	K_S (h^{-1})	K_{12} (h^{-1})	K_{21} (h^{-1})	V_1 (L/kg)
Mean	0.348	0.007	0.503	0.580	0.210
Median	0.392	0.003	0.487	0.647	0.239
SD	0.212	0.011	0.223	0.332	0.115

K_i ordinate intercept constant, K_S slope constant, K_{12} intercompartmental transfer rate constant from central to peripheral compartments, K_{21} intercompartmental transfer rate constant from peripheral to central compartments, V_1 volume of the central compartment

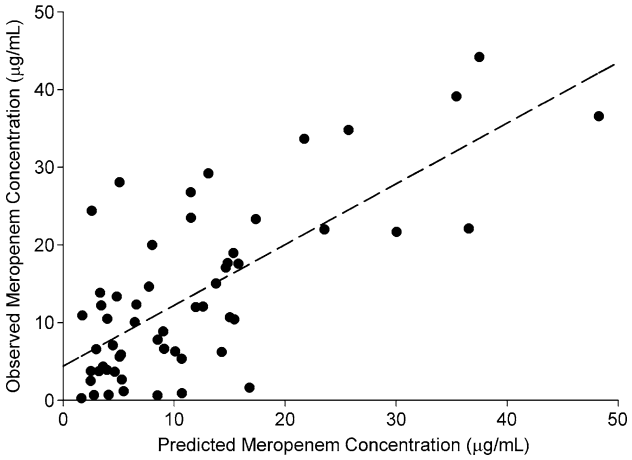

Fig. 1 Scatter plot of observed versus predicted meropenem concentrations using the population pharmacokinetic model

Monte Carlo simulation

The results of the PTA analyses are shown in Fig. 3. For simulated patients with normal renal function (CrCl 50–120 mL/min), only 3 h prolonged infusions of 2 g every 8 h resulted in optimal target attainments at MICs >2 μg/mL. The observed PTAs were 99.6, 95.9, and 73.0% at MICs of 4, 8, and 16 μg/mL, respectively. In comparison, the respective PTAs for standard 0.5 h infusions of 2 g every 8 h at these same MICs were 89.2, 74.8, and 40.7%. For patients within the CrCl range of 30–49 mL/min, meropenem doses of 1 g every 8 h given as either 0.5 or 3 h infusions were optimal (≥92.9 and ≥99.8%, respectively) at MICs up to 4 μg/mL. However, at a MIC of 8 μg/mL, only the prolonged infusion regimen remained optimal (89.6 vs. 65.4%). At a CrCl range of 10–29 mL/min, PTAs for doses of 500 mg every 6 h (0.5 h infusion) and 1 g every 12 h (3 h infusion) were similar across the MIC range (Fig. 3c) and were optimal against MICs ≥4 μg/mL (i.e., ≥95.1 and ≥96.0%, respectively). Similarly to the other CrCl ranges studied, a standard 0.5 h infusion of 1 g every 12 h resulted in a reduction in PTA when compared with a 3 h prolonged infusion of the same dose; while remaining optimal at an MIC 2 μg/mL (98%), the PTA dropped below the threshold at a MIC of 4 μg/mL (84.0%).

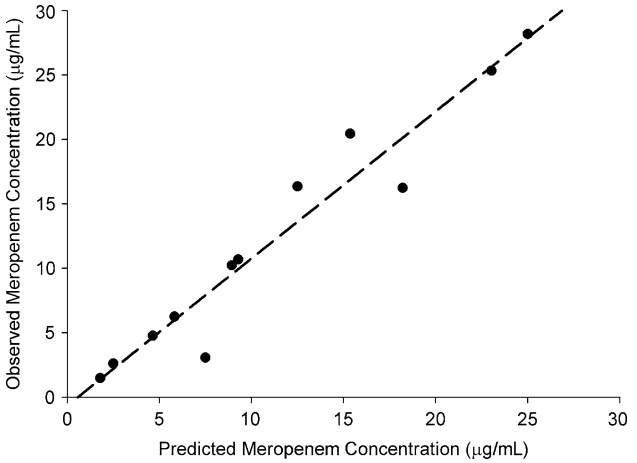

Fig. 2 Scatter plot of observed and predicted meropenem concentrations of the validation group applying the median parameter values of the population pharmacokinetic model

Table 3 shows the median (25%, 75%) area under the concentration–time profile for the dosing interval ($AUC_{0-\tau}$) and the maximal concentration (C_{max}) attained by each of the doses simulated during Monte Carlo analyses. As expected, prolonging the length of the infusion resulted in a reduction in C_{max} when compared with standard infusions and had no effects on total exposure. For simulated patients with impaired renal function, reduced total daily doses were able to achieve similar pharmacodynamic targets while maintaining a reduction in AUC_{0-24} and C_{max} when compared with the highest doses in patients with normal renal function.

Discussion

As antimicrobial agents traverse the road from development to market, a number of pharmacokinetic analyses are completed, often in healthy volunteers and non-critically ill patients. Although these studies garner insight into a large percentage of patients, the pharmacokinetics of critically ill patients may differ from the non-critically ill. For β-lactams such as meropenem, these alterations may lead to considerable differences in pharmacokinetic exposure [9]. Herein, we described meropenem pharmacokinetics in a population of critically ill patients and used these data to determine optimal meropenem dosing regimens for patients with various degrees of renal function.

A number of other pharmacokinetic studies of meropenem were recently published with considerable variability surrounding their results. This discordance is

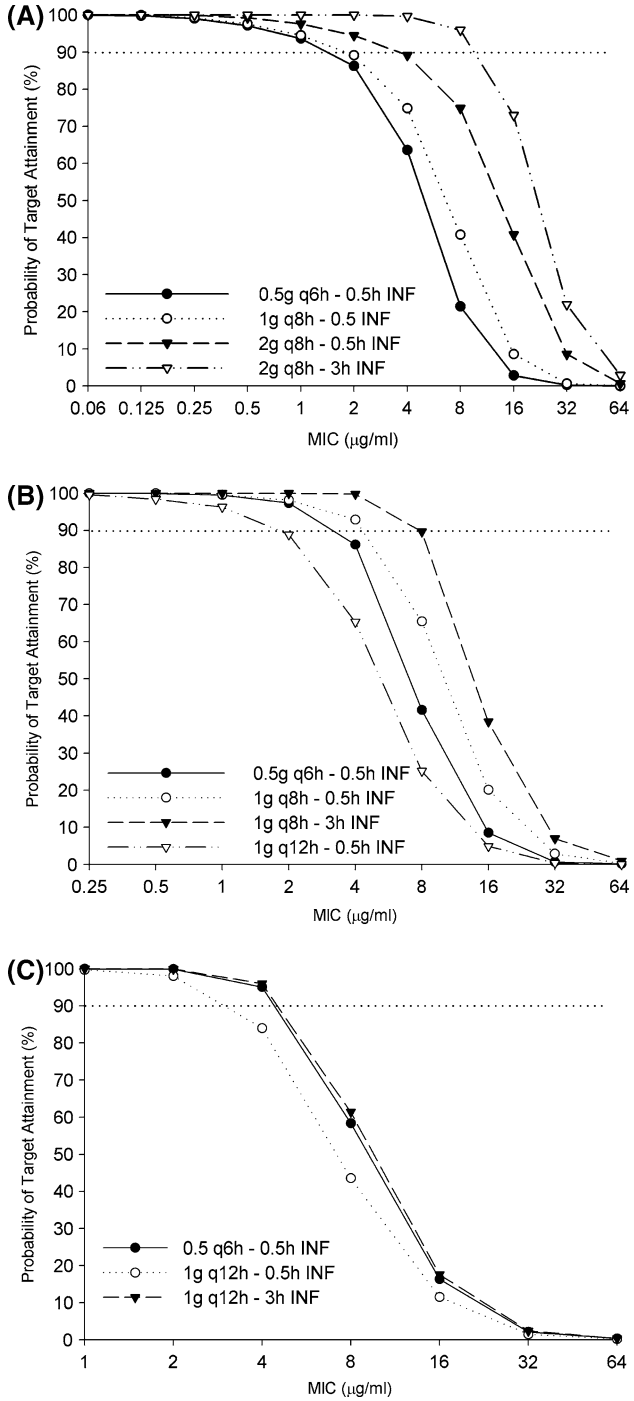

Fig. 3 Probability of meropenem regimens achieving 40% $fT > MIC$ at CrCl ranges of **a** 50–120 mL/min, **b** 30–49 mL/min, **c** 10–29 mL/min

likely due to a number of factors including the characteristics of the patient population studied, the approach taken towards pharmacokinetic modeling (i.e., population vs. standard 2-stage pharmacokinetic analyses), and the modeling software. The mean meropenem total body clearance reported for the populations studied ranged from 7.7 to 15.4 L/h and V_1 ranged from 7.9 to 14.6 L [2, 12, 16–20]. Of these studies, only one analyzed a population of solely critically ill patients by population pharmacokinetic methods [12]. In comparison with their results, our patients had a greater V_1 and reduced total body clearance (CL_T) (17.5 vs. 7.9 L and 9.87 vs. 13.6 L/h, respectively). Given that the primary route of elimination of meropenem is renal [1], the reduction of CL_T noted in our patients is not unexpected as the previous analysis was performed in a relatively young population of patients and excluded those with renal dysfunction [12].

Table 3 Comparative steady-state area under the concentration time profile for the dosing interval ($AUC_{0-\tau}$) and maximal concentration (C_{max}) for the various simulated doses and renal function ranges

	$AUC^{a}_{0-\tau}$ (μg h/mL)	C^{a}_{max} (μg/mL)
CrCl 50–120 mL/min		
0.5 g q6h (0.5 h INF)	38 (27.1, 54.1)	21.6 (16.8, 29.5)
1 g q8h (0.5 h INF)	76.3 (54.3, 108.5)	41.6 (32, 57.3)
2 g q8h (0.5 h INF)	152.7 (108.6, 217.1)	83.1 (64.1, 114.6)
2 g q8h (3 h INF)	152.7 (108.6, 217)	37.4 (28.2, 51.2)
CrCl 30–49 mL/min		
1 g q12h (0.5 h INF)	99.2 (73.2, 142.0)	43.2 (33.1, 60.3)
0.5 g q6h (0.5 h INF)	49.5 (36.6, 70.6)	24.0 (18.6, 33.0)
1 g q8h (0.5 h INF)	99.1 (73.2, 141.5)	45.5 (35.1, 62.5)
1 g q8h (3 INF)	99.1 (73.2, 141.5)	22.8 (17.5, 31.6)
CrCl 10–29 mL/min		
0.5 g q6h (0.5 h INF)	58.9 (43.3, 85.6)	25.8 (19.7, 35.9)
1 g q12h (0.5 h INF)	118.2 (86.9, 173.3)	36.9 (28.1, 51.2)
1 g q12h (3 h INF)	118.2 (86.9, 173.3)	20.5 (15.6, 28.6)

CrCl creatinine clearance, *INF* length of infusion
[a] Reported as median (25%, 75%)

Given this correlation between renal function and meropenem clearance, we evaluated the PTA for many doses across subsets of creatinine clearance. As expected, following an equivalent dose across the creatinine clearance ranges showed that as renal function improved, a decrease was noted in the highest MIC at which optimal PTAs were attained. Recent reports measuring CrCl in otherwise healthy ICU patients reported values in excess of 120 mL/min [21, 22]. As such, we reexamined the 2 g q8h (3 h infusion) with a fixed CrCl of 144 mL/min (20% higher than the expected maximum); in doing so, we found that while an optimal PTA was lost at 8 μg/mL, target attainments remained optimal against MICs ≤4 μg/mL (data not shown).

To assess patient exposure we included a comparison of the median $AUC_{0-\tau}$ and C_{max} for all simulated doses across the CrCl ranges (Table 3). Although the interpretation of these data is difficult given an incomplete understanding of the pathogenesis of β-lactam-induced adverse events, most notably seizures, 24 h steady-state AUC and C_{max} for pharmacodynamically similar doses were less in patients with reduced renal function as

compared with those in the normal renal function group. Given data from animal models suggesting that β-lactam-induced seizures are related to drug concentrations in brain tissues, it seems reasonable to assume that measures of serum exposure are practical correlates for brain concentrations and thus risk [23]. Further, although the highest meropenem dose simulated in this analyses was 2 g every 8 h (3 h infusion), we recently published a case report of a patient with cystic fibrosis that tolerated meropenem 3 g every 8 h (3 h infusion) [24]. Taken collectively, it is possible that the maximum tolerable exposure is even greater than suggested by Table 3.

Given that MIC data are not always readily available to clinicians in the hospital setting, it is important to assess the implications of pharmacodynamics relative to identified susceptibility breakpoints. Currently the European Committee on Antimicrobial Susceptibility Testing defines susceptibility for all Gram negative organisms as no more than 2 μg/mL and the CLSI sets breakpoints for Enterobacteriaceae at no more than 1 μg/mL. Assuming these criteria, all approved regimens achieved optimal exposures against isolates classified as susceptible. However, for *P. aeruginosa* and *Acinetobacter baumannii* isolates, CLSI currently defines meropenem susceptibility as no more than 4 μg/mL, a target that no approved regimen was able to obtain.

Despite the availability of susceptibility criteria to aid in empiric therapy decisions, within the ICU it is not uncommon to have MICs at or slightly above these breakpoints (i.e., 4–16 μg/mL). In these cases, empiric therapeutic options designed to eradicate organisms above these criteria are necessary. The pharmacodynamic optimized regimens provided herein offer clinicians the opportunity to achieve therapeutic exposures against these most difficult pathogens, regardless of patient renal function.

While evaluating the results of this or any other pharmacokinetic study and its potential applicability to another practice site, it is essential to consider the similarities of the studied population to that in one's clinical practice. Further, although we included a relatively diverse population of critically ill patient in our analysis, no patients had CrCl less than 30 mL/min; therefore, further study of patients with severe renal dysfunction is required to validate our findings in that population. It should also be noted that although the widely accepted pharmacodynamic target of 40% $fT > MIC$ was adopted for Monte Carlo simulations in this analysis, use of a more conservative target of 54% [25] yielded similar results for patients with normal and moderately impaired renal function.

Conclusions

We described a validated meropenem population pharmacokinetic model of critically ill patients that predicted concentration data based on minimal demographic information. Using this model, we found that for ICU patients with normal renal function, meropenem doses of 2 g every 8 h (3 h infusion) were required to achieve predictable PTA against MICs $\leq$8 μg/mL and further identified regimens required to achieve similar targets for patients with impaired renal function. Regardless of renal function, 3 h infusions improved target attainments when compared with standard 0.5 h infusions. These data, coupled with local susceptibility trends, offer clinicians the tools necessary to best select empiric meropenem therapy.

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