Steady-State Pharmacokinetics and Pharmacodynamics of Meropenem in Hospitalized Patients

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Study Objective. To evaluate the steady-state pharmacokinetics and pharmacodynamics of meropenem 500 mg every 6, 8, and 12 hours, based on renal function, in hospitalized patients.

Design. Prospective, open-label, steady-state pharmacokinetic study.

Setting. One tertiary care medical center and one community hospital.

Patients. Twenty adult patients (12 men, 8 women) with suspected or documented bacterial infections requiring antimicrobial therapy.

Intervention. Patients received 30-minute infusions of meropenem 500 mg every 6 hours (group 1), every 8 hours (group 2), or every 12 hours (group 3) based on estimated creatinine clearances greater than 60, 40–60, or 10–39 ml/minute, respectively.

Measurements and Main Results. Serial blood samples were collected after 2 or more days of therapy. Meropenem concentrations were determined by high-performance liquid chromatography, and pharmacokinetic data were analyzed by noncompartmental methods. Monte Carlo simulations (10,000 patients) were performed to calculate the cumulative fraction of response (CFR) for a percentage of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration ($fT>MIC$) of 40% by using pharmacokinetic data for each group and MIC data for seven gram-negative pathogens from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC, 2004–2005) database. Maximum and minimum serum concentrations (mean ± SD) were 29.2 ± 9.8 and 2.4 ± 1.1 µg/ml, 33.2 ± 8.5 and 3.8 ± 2.7 µg/ml, and 33.5 ± 4.7 and 4.9 ± 1.6 µg/ml for groups 1, 2, and 3, respectively. The half-life values were 2.5 ± 0.9, 3.4 ± 1.3, and 6.1 ± 1.4 hours, and the values for volume of distribution at steady state were 29.3 ± 8.7, 23.8 ± 8.1, and 28.7 ± 8.6 L for groups 1, 2, and 3, respectively. For all three groups, the CFR was greater than 90% for the enteric pathogens and *Pseudomonas aeruginosa* and 82.4–85.2% for *Acinetobacter* species.

Conclusion. Pharmacodynamic analyses suggest that regimens of meropenem 500 mg every 6, 8, or 12 hours, adjusted for renal function, are acceptable for treatment of infections caused by enteric gram-negative pathogens and *P. aeruginosa*. However, more aggressive dosing or alternative dosing strategies may be necessary for *Acinetobacter* species.

Key Words: meropenem, pharmacokinetics, pharmacodynamics, Monte Carlo simulation, bacterial infection.

Meropenem, a broad-spectrum carbapenem antibiotic, is approved by the United States Food and Drug Administration (FDA) for the treatment of complicated skin and skin structure infections,

complicated intraabdominal infections, and bacterial meningitis.[1] In addition, meropenem is recommended and frequently used for the treatment of other serious infections in patients with risk factors for multidrug-resistant bacteria, such as hospital-acquired and ventilator-associated pneumonia.[2] The FDA-approved dosing regimens for meropenem in patients with normal renal function are 500 mg every 8 hours for skin and skin structure infections and 1 g every 8 hours for more serious infections.[1] Dosage adjustment is required for patients with renal impairment.[1]

Meropenem, like other β-lactam antibiotics, exhibits time-dependent bactericidal activity, and the pharmacodynamic parameter predicting clinical and bacteriologic outcomes is the percentage of the dosing interval that free drug concentrations remain above the minimum inhibitory concentration (fT>MIC) of the infecting pathogen.[3, 4] For carbapenems, bacteriostatic activity is observed when the fT>MIC is approximately 20%, and bactericidal activity is observed when the fT>MIC is 40% or longer.[5] To maximize exposures or to reduce drug acquisition costs while maintaining appropriate exposures, the FDA-approved dosing regimens for meropenem may be modified by changing the dose, dosing frequency, or duration of the infusion.[6, 7] One common approach has been to administer meropenem at a dose of 500 mg every 6 hours in patients with normal renal function.[6, 8] Pharmacodynamic analyses have shown that the T>MIC for 500 mg every 6 hours is comparable to that of 1 g every 8 hours, while reducing the daily dose from 3 g to 2 g.[9, 10] Another study found that the probability of attaining a target T>MIC of 30% and 50% for meropenem 500 mg every 6 hours was comparable to that of imipenem 500 mg every 6 hours.[11] Of note, the Monte Carlo simulations in these studies used pharmacokinetic

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data from healthy volunteers.[9–11]

The pharmacokinetics of meropenem have been studied in several patient populations at various doses, dosing intervals, and infusion times.[12–19] However, we found no published studies on the pharmacokinetics of 500 mg every 6 hours in hospitalized patients with normal renal function. At our institutions, we have adopted a meropenem dosing protocol in which patients receive 500 mg every 6, 8, or 12 hours, depending on their renal function. The purpose of this study was to evaluate the steady-state pharmacokinetics and pharmacodynamics of meropenem in hospitalized patients by using the dosing protocol from our institutions.

Methods

Patients

Adult patients who were hospitalized at Methodist Hospital, Clarian Health Partners, Inc. (Indianapolis, IN) or St. Francis Hospital (Beech Grove, IN) were eligible for the study. All patients were 18 years of age or older and required antimicrobial therapy for a suspected or documented bacterial infection. Exclusion criteria were allergy to any β-lactam antibiotic, history of drug or alcohol abuse, pregnancy, history of any seizure disorder, acute or chronic renal failure, and dialysis of any type. The study was approved by the institutional review board at each study site, and written informed consent was obtained from each patient or a first-degree relative if the patient was unable to give informed consent due to his or her medical condition before initiation of any study procedures.

Study Design

Patients received meropenem 500 mg, infused intravenously over 30 minutes, every 6 hours (group 1), every 8 hours (group 2), or every 12 hours (group 3) based on estimated creatinine clearances greater than 60, 40–60, or 10–39 ml/minute, respectively. Creatinine clearance was estimated by using the Cockcroft-Gault equation, ideal body weight, and the actual serum creatinine concentration for each patient.[20] After 2 or more days of therapy, blood samples were collected from an indwelling intravenous catheter at the following times for each group: immediately before drug administration, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 3, 4, 5, and 6 hours after the start of the infusion. Additional blood samples were collected at 8 hours for group 2 and

at 8 and 12 hours for group 3. All blood samples were collected in nonanticoagulant (red-top) tubes and immediately placed on ice. After allowing the blood to coagulate, the samples were centrifuged, and the serum was stored at -70°C. Samples were shipped on dry ice by overnight carrier to the Center for Anti-Infective Research and Development at Hartford Hospital (Hartford, CT) for determination of serum meropenem concentrations.

Determination of Meropenem Concentrations

Serum meropenem concentrations were determined by using a validated high-performance liquid chromatography assay, as previously described.[21] The assay was linear over a range of 0.25–50 µg/ml (r^2=0.99), and the intraday coefficients of variation for the high (40 µg/ml) and low (2 µg/ml) quality control standards were less than 3%.

Pharmacokinetic Analysis

Serum meropenem concentration versus time data were evaluated by noncompartmental methods.[22] The maximum observed concentration (C_{max}) occurred at the end of the infusion, and the minimum observed concentration (C_{min}) occurred at 6, 8, and 12 hours after the start of the infusion for groups 1, 2, and 3, respectively. The elimination rate constant (k) was calculated by least-squares linear regression of the log-linear portion of the serum concentration–time curves, and terminal elimination half-life ($t_{1/2}$) was calculated as 0.693/k. The area under the serum concentration–time curve (AUC) and area under the first moment of the serum concentration–time curve (AUMC) were calculated by using the linear trapezoidal rule. Mean residence time at steady state (MRT_{ss}) was calculated as [$AUMC_{0-\tau}$ + $\tau(C'/k)]/AUC_{0-\tau}$, where $AUC_{0-\tau}$ and $AUMC_{0-\tau}$ correspond to the AUC and AUMC for one dosing interval, and C' is the predicted concentration at time τ.[22] The MRT equivalent for intravenous bolus administration, MRT_{iv}, was calculated as MRT_{ss} – (T/2), where T is the infusion time, 0.5 hour. Systemic clearance (Cl_s) was calculated as dose/$AUC_{0-\tau}$, and the steady-state volume of distribution (V_{ss}) was calculated as MRT_{iv} x Cl_s.[23]

Statistical analyses were performed using Statview for Windows, version 5.0 (SAS Institute Inc., Cary, NC). Descriptive statistics were used to summarize the pharmacokinetic parameters for each patient group. Differences in the pharmacokinetic parameters among the groups were evaluated by the Kruskal-Wallis test. For the post hoc test, a Mann-Whitney test was used, and the Bonferroni adjustment was applied. Statistical significance was defined as p<0.017. Simple linear regression was used to describe the relationship between the systemic clearance of meropenem and creatinine clearance.

Pharmacodynamic Analysis

The pharmacodynamic profile of meropenem was evaluated by performing a 10,000-patient Monte Carlo simulation (Crystal Ball 2000.2.2 software; Decisioneering, Inc., Denver, CO) for each patient group against *Escherichia coli* (1214 isolates), *Klebsiella pneumoniae* (703 isolates), *Enterobacter* species (274 isolates), *Serratia marcescens* (244 isolates), *Citrobacter* species (228 isolates), *Pseudomonas aeruginosa* (1277 isolates), and *Acinetobacter* species (267 isolates). The MIC distributions were obtained for organisms isolated in the United States in 2004–2005 by using the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) database.[24–26] The ƒT>MIC (%) was calculated for each group by using the following equation:

$$ƒT>MIC = \ln[(\text{dose x } f)/(V_\beta \text{ x MIC})] \text{ x } (t_{1/2}/0.693) \text{ x } (100/\text{dosing interval})$$

where *f* is the fraction of unbound drug, ln is the natural logarithm, V_β is the volume of distribution calculated during the β elimination phase, and $t_{1/2}$ is the terminal elimination half-life.[27] The parameter V_β was calculated as Cl_s/β. The fraction of unbound meropenem used in the analysis was 0.98.[1, 28]

The cumulative fraction of response (CFR) was calculated for each patient group and organism by using the pharmacodynamic targets of 40% and 60% ƒT>MIC.[5, 29] The 40% ƒT>MIC target was chosen because it represents maximum bactericidal activity in animal and in vitro studies.[5] The 60% ƒT>MIC target was chosen because a recent study in patients with lower respiratory tract infections found a significant relationship between microbiologic response and an ƒT>MIC of 54%.[29] Therefore, the target was rounded up to 60%. In addition, the probability of attaining 40% and 60% ƒT>MIC targets was calculated for each patient group at specific MIC values ranging from 0.5–16 µg/ml. The dosing regimens were considered optimum if the CFR and probability of target attainment (PTA) were 90% or greater.[30]

Table 1. Baseline Demographic Characteristics of the 20 Study Patients

Characteristic	Group 1, Meropenem 500 mg q6h (n=8)	Group 2, Meropenem 500 mg q8h (n=8)	Group 3, Meropenem 500 mg q12h (n=4)
	No. (%) of Patients		
Sex			
Male	6 (75)	4 (50)	2 (50)
Female	2 (25)	4 (50)	2 (50)
	Mean ± SD		
Age (yrs)	46.4 ± 14.6	64.4 ± 8.2	74.8 ± 3.7
Height (in.)	67.6 ± 4.1	66.9 ± 1.5	67.8 ± 3.0
Weight (kg)	90.4 ± 21.4	87.9 ± 15.8	76.4 ± 10.2
Creatinine clearance (ml/min)	91.5 ± 17.3	52.1 ± 8.0	35.1 ± 11.6

Table 2. Meropenem Pharmacokinetic Parameters

Parameter	Group 1, Meropenem 500 mg q6h (n=8)	Group 2, Meropenem 500 mg q8h (n=8)	Group 3, Meropenem 500 mg q12h (n=4)
C_{max} (µg/ml)	29.2 ± 9.8	33.2 ± 8.5	33.5 ± 4.7
C_{min} (µg/ml)	2.4 ± 1.1	3.8 ± 2.7	4.9 ± 1.6
$t_{1/2}$ (hrs)[a]	2.5 ± 0.9	3.4 ± 1.3	6.1 ± 1.4
$AUC_{0-\tau}$ (µg•hr/ml)[b]	49.1 ± 11.7	86.2 ± 28.5	140.2 ± 25.0
MRT_{iv} (hrs)[a]	2.78 ± 0.79	4.10 ± 2.16	7.89 ± 2.28
Cl_s (L/hr)[b]	10.7 ± 2.6	6.4 ± 2.2	3.7 ± 0.7
V_{ss} (L)	29.3 ± 8.7	23.8 ± 8.1	28.7 ± 8.6
V_{ss} (L/kg)	0.33 ± 0.10	0.27 ± 0.09	0.38 ± 0.15

Data are mean ± SD.
C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; $t_{1/2}$ = terminal elimination half-life; $AUC_{0-\tau}$ = area under the serum concentration-time for one dosing interval; MRT_{iv} = mean residence time for intravenous bolus administration; Cl_s = systemic clearance; V_{ss} = steady-state volume of distribution.
[a]p=0.007 for group 1 vs group 3.
[b]p=0.009 for group 1 vs group 2; p=0.007 for group 1 vs group 3.

Results

Twenty patients completed the study. Eight patients received 500 mg every 6 hours (group 1), eight patients received 500 mg every 8 hours (group 2), and four patients received 500 mg every 12 hours (group 3). Baseline patient demographics are shown in Table 1. Sixteen patients were hospitalized in an intensive care unit, and four patients were hospitalized on a general medical ward. The primary infection-related diagnosis was pneumonia in 12 patients, sepsis in five patients, and osteomyelitis, necrotizing pancreatitis, and peritonitis in one patient each. No adverse events related to meropenem therapy were reported during the study.

Meropenem pharmacokinetic parameters for the three patient groups are shown in Table 2, and the serum concentration–time curves are shown in Figure 1. No statistically significant differences were noted in C_{max}, C_{min}, or V_{ss} among the patient groups. For group 3, the mean C_{min} was greater than the meropenem susceptibility breakpoint of 4 µg/ml.[31] Half-life and MRT_{iv} were significantly different between groups 1 and 3 (p=0.007). The $AUC_{0-\tau}$ and Cl_s were significantly different between groups 1 and 2 (p=0.009) and groups 1 and 3 (p=0.007). The statistically significant relationship between Cl_s and creatinine clearance is shown in Figure 2.

Meropenem MIC data from the MYSTIC database are shown in Table 3. The CFR results for meropenem at 40% and 60% fT>MIC against the gram-negative pathogens are shown in Table 4. For all three groups, the CFR at both pharmacodynamic targets was optimum (> 90%) for *E. coli*,

Table 3. Meropenem Minimum Inhibitory Concentration Data

Organism	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	Susceptibility (%) Susceptible	Intermediate	Resistant
Escherichia coli	0.008	0.06	0.008–2	100.0	0	0
Klebsiella pneumoniae	0.06	0.06	0.008–64	97.1	0.3	2.6
Enterobacter sp	0.06	0.12	0.008–16	99.6	0	0.4
Serratia marcescens	0.06	0.12	0.008–32	99.6	0	0.4
Citrobacter sp	0.06	0.12	0.008–4	100.0	0	0
Pseudomonas aeruginosa	0.5	8.0	0.008–64	89.0	4.7	6.3
Acinetobacter sp	0.5	16.0	0.008–64	80.5	7.1	12.4

Data were collected during the 2004–2005 Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) surveillance programs in the United States.[25, 26]
MIC_{50} and MIC_{90} = minimum inhibitory concentration for 50% and 90% of tested strains, respectively.

K. pneumoniae, *Enterobacter* species, *S. marcescens*, and *Citrobacter* species. For *P. aeruginosa*, the CFR at 40% ƒT>MIC was optimum for all three patient groups, but the CFR at 60% ƒT>MIC was optimum for group 3 only. Of the organisms evaluated, the CFR was lowest for *Acinetobacter* species. None of the regimens was optimum against *Acinetobacter* species, although the highest CFRs were seen in group 3.

The PTA results for meropenem at specific MIC values are shown in Figure 3. At 40% ƒT>MIC, the PTA was 90.2%, 95.6%, and 99.5% for groups 1, 2, and 3, respectively, at the meropenem susceptibility breakpoint of 4 µg/ml.[31] At the higher pharmacodynamic target, the PTA was optimum for groups 1 and 2 at MICs of 2 µg/ml or lower and for group 3 at MICs of 4 µg/ml or lower.

Discussion

With the constant concern for bacterial resistance and the diminishing development of novel agents active against gram-negative pathogens, it is imperative that clinicians optimize antimicrobial exposures of available agents with the goals of maximizing patient outcomes and minimizing the potential for further resistance. Monte Carlo simulations have been used to determine the likelihood that an antibiotic regimen will achieve specific pharmacodynamic targets against a variety of clinically relevant bacterial pathogens.[7, 8] By incorporating mean pharmacokinetic data, variability in parameter estimates, and MIC distributions, a variety of doses, dosing intervals, and infusion times may be simulated to determine an optimum dosing strategy for a given antibiotic. It is, therefore, important to have pharmacokinetic parameter estimates, as well as their variability, from a target population of patients (e.g., critically ill) rather than healthy volunteers.[8]

Meropenem pharmacokinetics have been studied in a variety of patient populations.[12–19] In critically ill patients with pneumonia and/or sepsis and creatinine clearances greater than 60
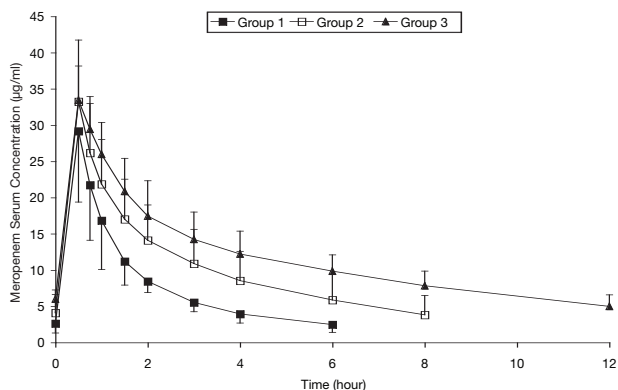
Figure 1. Mean ± SD serum concentration–time profiles for meropenem 500 mg every 6 hours (group 1 [n=8]), every 8 hours (group 2 [n=8]), and every 12 hours (group 3 [n=4]).
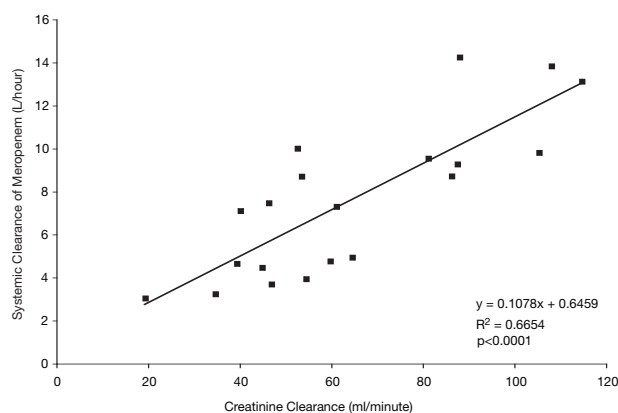
Figure 2. Relationship between systemic clearance of meropenem and creatinine clearance in the 20 patients.

Table 4. Cumulative Fraction of Response for Meropenem at 40% and 60% ƒT>MIC Against Gram-Negative Pathogens

Organism	Group 1, Meropenem 500 mg q6h		Group 2, Meropenem 500 mg q8h		Group 3, Meropenem 500 mg q12h	
	40% ƒT>MIC	60% ƒT>MIC	40% ƒT>MIC	60% ƒT>MIC	40% ƒT>MIC	60% ƒT>MIC
Escherichia coli	100.0	100.0	100.0	100.0	100.0	100.0
Klebsiella pneumoniae	97.3	97.2	97.4	97.3	100.0	97.2
Enterobacter sp	99.6	99.6	99.7	99.7	100.0	100.0
Serratia marcescens	99.6	99.6	99.6	99.6	100.0	100.0
Citrobacter sp	100.0	99.7	100.0	99.9	100.0	100.0
Pseudomonas aeruginosa	90.3	87.4	92.4	89.5	92.5	90.4
Acinetobacter sp	82.4	78.0	84.5	80.3	85.2	82.3

Data are percentages.
MIC = minimum inhibitory concentration; ƒT>MIC = percentage of the dosing interval that free drug concentrations remain above the MIC.

ml/minute, the mean meropenem half-life ranged from 1.4–3.1 hours, the mean volume of distribution ranged from 16.0–34.4 L, and the mean systemic clearance ranged from 8.5–13.0 L/hour.[13–15, 17, 18] In these studies, patient demographics were similar to that of group 1 of our study, and the mean half-life (2.5 hrs), V_{ss} (29.3 L), and Cl_s (10.7 L/hr) for group 1 were within the reported ranges of these previous studies. However, these parameters are different from those of healthy volunteers and other patient populations. Healthy volunteers have a shorter half-life (1 hr), a smaller volume of distribution (12–22 L), and a faster drug clearance (16 L/hr) than those parameters in critically ill patients.[7, 32, 33] Patients with intraabdominal infections or febrile neutropenia were also found to have faster half-lives and drug clearances.[12, 16]

We compared the actual Cl_s and V_{ss} values from the patients in our study with the values predicted by using a published population pharmacokinetic model.[19] In general, the population pharmacokinetic model overpredicted Cl_s, and the predicted Cl_s was at least 1.5-fold greater than the actual Cl_s in 13 of the 20 patients. The mean ± SD for predicted Cl_s was 14.2 ± 1.7, 8.9 ± 0.9, and 6.5 ± 1.4 L/hour for groups 1, 2, and 3, respectively, which was substantially greater than the actual values (Table 2). The population model also performed poorly when predicting V_{ss}. The predicted V_{ss} values ranged from 21.5–30.9 L, whereas the actual V_{ss} values ranged from 10.8–40.0 L. The patient populations in the two studies were different, which may explain, at least in part, these findings. Therefore, clinicians should be cautious when using this population pharmacokinetic model to predict Cl_s and V_{ss} in all patient populations.

Several published studies support the use of meropenem 500 mg every 6 hours in patients with normal renal function. Monte Carlo simulations using pharmacokinetic data from healthy volunteers have shown comparable target attainment rates for T>MIC with meropenem 500 mg every 6 hours and 1 g every 8 hours.[9, 10] Comparable T>MIC values were also observed with these regimens with use of pharmacokinetic data from patients with febrile neutropenia.[16] Target attainment rates for 30% and 50% ƒT>MIC were comparable for meropenem 500 mg every 6 hours and imipenem 500 mg every 6 hours, when using pharmacokinetic data from healthy volunteers.[11] In a retrospective review of 85 patients treated with meropenem, the clinical success rate was 78% for patients receiving 500 mg every 6 hours and 82% for patients receiving
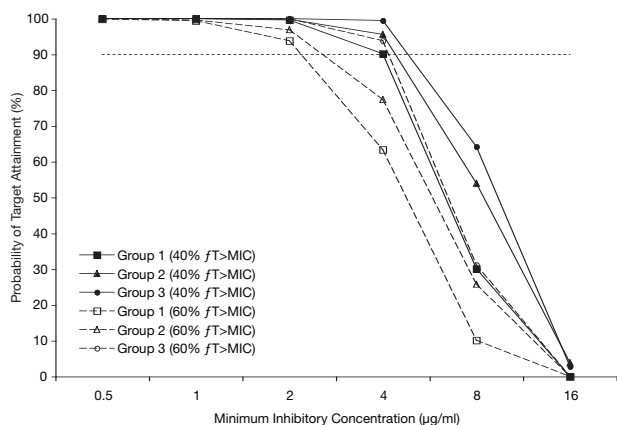

Figure 3. Probability of target attainment (PTA) for meropenem at specific minimum inhibitory concentration (MIC) values in group 1 (500 mg every 6 hrs), group 2 (500 mg every 8 hrs), and group 3 (500 mg every 12 hrs). The dotted line indicates which dosing regimens at PTA 90% or greater were considered optimum. ƒT>MIC = percentage of the dosing interval that free drug concentrations remain above the MIC.

1 g every 8 hours.[34] There were no significant differences in rate of response, microbiologic success, or length of stay between the two groups. In a larger retrospective cohort study, 100 patients received meropenem 1 g every 8 or 12 hours and 192 patients received meropenem 500 mg every 6 or 8 hours, based on renal function.[35] Duration of therapy, concomitant antimicrobial therapy, clinical success rates, length of stay, and in-hospital mortality rates were similar between the two groups. However, the median time to resolution of symptoms was significantly shorter (p<0.0001) and the median cost of antibiotic therapy was significantly lower (p<0.0001) in the group who received 500 mg every 6 or 8 hours.

At our institutions, meropenem 500 mg is administered every 6, 8, or 12 hours in patients with estimated creatinine clearances greater than 60, 40–60, or 10–39 ml/minute, respectively. With use of the pharmacokinetic data from this study, the pharmacodynamic parameters of these dosing regimens were optimum for most gram-negative pathogens evaluated. The CFR for 40% *f*T>MIC was greater than 90% for *E. coli*, *K. pneumoniae*, *Enterobacter* species, *S. marcescens*, *Citrobacter* species, and *P. aeruginosa* for all three patients groups. At 60% *f*T>MIC, a target associated with microbiologic response in patients with lower respiratory tract infections,[29] the CFR was optimum for the enteric pathogens in all three groups and for *P. aeruginosa* in group 3 only. The CFR was 87.4% and 89.5% for *P. aeruginosa* in groups 1 and 2, respectively. Therefore, it may be prudent to add an additional agent (e.g., tobramycin) to meropenem when treating systemic infections caused by *P. aeruginosa*, although this issue is very controversial. The CFR was not optimum for any of the dosing regimens against *Acinetobacter* species, and combination therapy may be appropriate for treatment of infections caused by these organisms.

The PTA for 40% *f*T>MIC was greater than 90% for all three patient groups at MICs of 4 µg/ml or lower (Figure 3). Based on the Clinical and Laboratory Standards Institute susceptibility breakpoints, bacterial strains are susceptible to meropenem at MICs of 4 µg/ml or lower.[31] Therefore, this dosing protocol provides optimum exposures for all meropenem-susceptible strains. At higher pharmacodynamic targets, PTA was higher with use of pharmacokinetic data from group 1 of the present study when compared with a study that used data from healthy volunteers.[11] At the susceptibility breakpoint of

4 µg/ml, the PTA for 50% *f*T>MIC was less than 20% using data from volunteers compared with 77% using patient data from group 1. At an MIC of 1 µg/ml, the PTA for 100% *f*T>MIC was less than 10% using volunteer data and 86% using patient data. Although some investigators have reported similar exposures using pharmacokinetic data from healthy volunteers and patients,[6, 32] our study suggests substantial differences in PTA between volunteers and patients.

A limitation of our study is the relatively small number of patients enrolled, especially those who received 500 mg every 12 hours (group 3). Recruitment of patients in this group was difficult, and only four patients were studied. Inclusion of these patients in the pharmacokinetic study strengthened the relationship between systemic clearance of meropenem and creatinine clearance. However, pharmacodynamic results based on the pharmacokinetic data from this group should be interpreted with caution.

Conclusion

Based on pharmacokinetic data in hospitalized patients and pharmacodynamic analyses using Monte Carlo simulations, meropenem 500 mg every 6, 8, or 12 hours, adjusted for renal function, provides optimum exposures and should be appropriate for treatment of infections caused by meropenem-susceptible pathogens. In all three groups, antimicrobial exposures were optimum for the enteric pathogens and *P. aeruginosa*. However, more aggressive dosing or alternative dosing strategies may be necessary for *Acinetobacter* species.

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