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Evaluation by Monte Carlo Simulation of the Pharmacokinetics of Two Doses of Meropenem Administered Intermittently or as a Continuous Infusion in Healthy Volunteers

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Meropenem is a broad-spectrum carbapenem antibacterial agent. In order to optimize levels in plasma relative to the MICs, the ideal dose level and dosage regimen need to be determined. The pharmacokinetics of meropenem were studied in two groups, each comprising eight healthy volunteers who received the following doses: 500 mg as an intravenous infusion over 30 min three times a day (t.i.d.) versus a 250-mg loading dose followed by a 1,500 mg continuous infusion over 24 h for group A and 1,000 mg as an intravenous infusion over 30 min t.i.d. versus a 500-mg loading dose followed by a 3,000-mg continuous infusion over 24 h for group B. Meropenem concentrations in plasma and urine were determined by liquid chromatography-mass spectrometry/mass spectrometry and high-performance liquid chromatography with UV detection, respectively. Pharmacokinetic calculations were done by use of a two-compartment open model, and the data were extrapolated by Monte Carlo simulations for 10,000 simulated subjects for pharmacodynamic evaluation. There were no significant differences in total clearance and renal clearance between group A and group B or between the intermittent treatment and the continuous infusion. The analyses of the probability of target attainment by MIC for the high- and low-dose continuous infusions were robust up to MICs of 4 mg/liter and 2 mg/liter, respectively. The corresponding values for intermittent infusions were only 0.5 mg/liter and 0.25 mg/liter. When these observations were correlated with MICs obtained from the MYSTIC database, intermittent infusion results in adequate activity against two of the most common nosocomially acquired pathogens, *Klebsiella pneumoniae* and *Enterobacter cloacae*. However, against *Pseudomonas aeruginosa*, the evaluation shows a clear advantage of high-dose therapy administered as a continuous infusion. We believe that in the empirical therapy situation, the continuous-infusion mode of administration is most worth the extra efforts. We conclude that clinical trials for evaluation of the continuous infusions of meropenem in critically ill patients are warranted.

Considerable evidence demonstrates that the amount of time that free drug concentrations exceed the MIC is the measure of drug exposure most closely linked to the ability of a regimen of β-lactam antibiotics to kill the target organisms (9, 17, 19, 48). This linkage is likely due to the fact that the rate of organism killing is maximized rapidly with the concentration and maximal killing is attained at drug concentrations of four to six times the MIC (6). Among the β-lactam agents, there are differences in the fraction of the dosing interval in which the drug concentration needs to be in excess of the MIC to attain organism stasis or to attain maximal killing of the organism population. Generally, β-lactams have some postantibiotic effects against gram-positive cocci but only limited postantibiotic effects against gram-negative rods (4, 8, 18, 22, 48). This means that the duration of plasma levels above the MIC is the most critical value for treatment of infections caused by members of the family *Enterobacteriaceae* and nonfermenters, which are targeted by acylamino-penicillins, expanded-spectrum cephalosporins, and carbapenems. For penicillins, cephalosporins, and carbapenems, stasis against *Enterobacteriaceae* is achieved when approximately 30%, 35 to 40%, and 20% of the dosing interval has free drug concentrations in excess of the MIC, respectively. For maximal cell killing, these percentages are circa 50%, 60 to 70%, and 40%, respectively (15).

When the clinician is treating seriously ill patients, particularly patients with ventilator-associated pneumonia, a number of investigators have indicated that choosing the antimicrobial therapy that is effective against the pathogen at the earliest possible moment has an important impact on ultimate survival as well as on other end points, such as the length of stay in the intensive care unit (ICU) and the hospital, the duration of intubation, as well as the amount of resources expended on the patient's therapy (26, 27, 38).

A number of clinical studies addressed the pharmacokinetic and pharmacodynamic relationships of β-lactam antibiotics. Ceftazidime has most extensively been studied during continuous infusion (32, 35, 37), which was proven to be safe and effective in neutropenic (11) and critically ill (2) patients. Limited data are also available for piperacillin-tazobactam (21) and meropenem (45). However, the intermittent mode of administration is still the clinical standard. Besides the instabili-

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ties of some drugs at room temperature, the drawback of continuous infusion is that there is a need for an additional intravenous line in order to prevent physicochemical incompatibilities with other drugs. Furthermore, the patients are limited in their mobility by the presence of an infusion pump. Thus, there is still a need to define the possible advantages of continuous infusions for the treatment of specific infections or for infections caused by specific pathogens.

Meropenem is a carbapenem antibiotic with a very broad spectrum of activity that makes it a good choice for the empirical therapy situation. It also possesses an excellent safety profile, so that doses as high as 6.0 g/day have been safely administered (25, 40). Because of its potency against gram-negative bacteria, lower doses (e.g., 500 mg every 8 h) may provide optimal therapy for pathogens commonly encountered in the ICU, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter* species. For more resistant pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter* species, larger doses would likely be more appropriate. Given that the time above the MIC is most closely linked to organism killing, we wished to examine the pharmacokinetics of meropenem when it was administered to volunteers at different doses (1.5 and 3.0 g/day) and with different modes of administration (intermittent administration every 8 h as a 30-min infusion versus a continuous infusion after the administration of a small loading dose).

MATERIALS AND METHODS

Subjects. Sixteen volunteers participated in the study after written informed consent was obtained. All study subjects were shown to be healthy by physical examination and electrocardiography and by laboratory tests, including urinalysis and screening for drugs of abuse. Drugs other than the study drug were not taken by any of the volunteers from 2 weeks before the start of the study until the end of the study. Food and fluid intakes were strictly standardized and were exactly scheduled during all study periods. The consumption of alcohol or methylxanthines in any form was forbidden from 48 h before the first dosing and during the study.

The volunteers were randomly assigned to group A (low dose) or group B (high dose). Group A consisted of four female and four male volunteers aged 18 to 27 years (mean age ± SD, 21 ± 3 years; median age, 20 years) with body weights of 53.0 to 92.0 kg (mean body weight, 67.1 ± 14.0 kg; median body weight, 62.5 kg). Group B comprised four female and four male volunteers aged 19 to 29 years (mean age, 24 ± 4 years; median age, 23 years) with body weights of 42.5 to 80.1 kg (mean body weight, 66.1 ± 12.4 kg; median body weight, 67.0 kg).

All volunteers were closely observed by physicians for the occurrence of adverse events during the period of drug administration. They were asked to immediately report any discomfort and to answer questionnaires on their health status on a daily basis. The study protocol was approved by the Ethics Committee of the Bavarian Physicians Chamber (Bayerische Landesärztekammer), Munich, Germany.

Study design. The study had a single-center, open, randomized, two-way crossover design. After assignment to group A or group B, four subjects in each group were randomly chosen to be started on the intermittent-dosing regimen, whereas the remaining subjects in each group were started on the regimen of a loading dose followed by continuous infusion. After a washout period of 14 days, the volunteers were crossed over within each subject group and received the other regimens.

Drug administration and dosage. Volunteers in group A received 500 mg of meropenem (AstraZeneca, Wedel, Germany) dissolved in 100 ml of sterile 0.9% NaCl solution exactly over 30 min every 8 h for 24 h in study period I and a loading dose of 250 mg (dissolved in 50 ml of saline) as a 5-min short-term infusion (starting time, −5 min) followed by three doses of 500 mg as continuous infusions of 62.5 mg/h in a volume of 3× 100 ml for 24 h in study period II, or vice versa. Volunteers in group B received doses exactly two times higher than those administered to group A, with otherwise identical conditions. All infusions were administered with exactly adjustable motor syringes. The instruments were checked on a daily basis by weighing defined volumes delivered by the syringe. Each dose was dissolved in sterile 0.9% NaCl solution immediately before administration. For the continuous infusions, half of each dose was stored at 4°C until administration in order to reduce the time of exposure to room temperature. The infusions were administered through indwelling venous catheters, which were placed in the forearms.

Sampling schedule. All blood samples were drawn via an intravenous catheter from a forearm vein contralateral to the one used for drug administration and placed in 5-ml NH_4-heparinate tubes (Sarstedt, Nümbrecht, Germany). During intermittent infusion, blood samples were drawn immediately before the start of the first infusion; at 7.5, 15, 22.5, 30, 35, 40, 45, 60, 75, 90, 120, 150, 180, 240, 360, 470, and 480 min after the start of the first and the third doses; and at 30, 60, 120, 180, 360, and 480 min after the start of the second intermittent infusion. During continuous infusion, blood samples were drawn immediately before the start of the loading dose (−5 min); at the end of the loading dose (0 min); at 5, 15, 30, 45, 60, 90, 120, 180, 360, 420, 460, 470, and 480 min after the start of the first dose; and at 180, 360, 420, 460, 470, and 480 min after the start of the second and the third continuous infusions. All blood samples were immediately placed in an ice-water bath for approximately 10 min before centrifugation at 4°C for 10 min. The plasma samples were then frozen on dry ice and stored at −70°C until analysis. Urine was collected before drug administration and at 0 to 4 h, 4 to 6 h, and 6 to 8 h after the start of each infusion. The urine samples were stored at 4°C during the collection period. Then, the amount was measured and aliquots were frozen on dry ice and stored at −70°C until analysis.

Determination of meropenem concentrations in plasma by LC-MS/MS. Meropenem concentrations in plasma were determined by high-performance liquid chromatography (HPLC) coupled with mass spectrometry (LC-MS/MS; PE SCIEX API III Plus). All sample handling and thawing of frozen plasma samples were done at +4°C. Plasma samples (0.1 ml) were deproteinized by addition of 0.2 ml of acetonitrile containing the internal standard. Since less than 2% of meropenem is bound to plasma proteins (10), we did not differentiate between protein-bound and unbound fractions. After the samples were thoroughly mixed, they were centrifuged at 3,600 rpm for 5 min at approximately +4°C, and the supernatant was diluted after centrifugation with ammonium acetate buffer. A volume of 50 μl of each sample was chromatographed on a reversed-phase column (Spherisorb Phenyl, 5 μm, 40 by 4.6 mm) eluted with an isocratic solvent system consisting of 0.005 M ammonium acetate buffer and acetonitrile (78:22; vol/vol) and monitored by LC-MS/MS by an SRM method, as follows: precursor → product ion for meropenem, m/z 384 → m/z 68; precursor → product ion for the internal standard, m/z 518 → m/z 143. Both analyses were performed in the positive mode. Under these conditions meropenem and the internal standard were eluted after approximately 0.9 min and 1.5 min, respectively. Mac Quan software (version 1.4-noFPU, 1991–1995; Perkin-Elmer, Toronto, Ontario, Canada) was used for evaluation of the chromatograms.

The limit of quantification for plasma samples was 0.019 mg/liter, as determined by analysis of spiked quality control samples. The response from the calibration standards was linear from 0.01968 to 40.6 mg/liter, and the coefficient of correlation for all measured sequences was at least 0.9991. The interday precision and relative error {defined as [1 − (mean analyzed concentration/nominal concentration)]} of the meropenem assay during samples analysis ranged from 3.8 to 6.4% and from −1.9 to 0.2%, respectively.

Determination of meropenem concentrations in urine by high-performance liquid chromatography with UV detection. Meropenem concentrations in urine were determined by high-performance liquid chromatography with UV detection. All sample handling and thawing of frozen plasma samples were done at +4°C. Urine samples (0.02 ml) were diluted by addition of 0.05 M NaH_2PO_4/Na_2HPO_4 buffer (pH 7.0) containing the internal standard. After thorough mixing of each sample, 120 μl of each diluted sample was chromatographed on a reversed-phase column (Spherisorb ODS2 column, 5 μm, 250 by 4.6 mm) eluted with an isocratic solvent system (0.05 M sodium dihydrogen phosphate buffer and acetonitrile [85:15; vol/vol]). The retention times of meropenem and the internal standard were 12.2 and 14.9 min, respectively. The eluent was monitored by determination of UV absorption at 296 nm. Turbochrom 3 (version 3.2, 1991; PE Nelson, Cupertino, CA) software was used for evaluation of the chromatograms.

The limit of quantification for the urine samples was 2.81 mg/liter. The response of the calibration standards was linear from 2.81 to 2,010 mg/liter, and the coefficient of correlation for all measured sequences was at least 0.9992. The interday precision and relative error of the meropenem assay during sample analysis ranged from 1.9 to 4.6% and −2.9 to −0.7%, respectively.

Pharmacokinetic calculations. Each of the modes of drug administration was initially analyzed separately. The Non-Parametric Adaptive Grid with adaptive γ (NPAG) program of Leary et al. (R. Leary, R. Jelliffe, A. Schumitzky, and M.

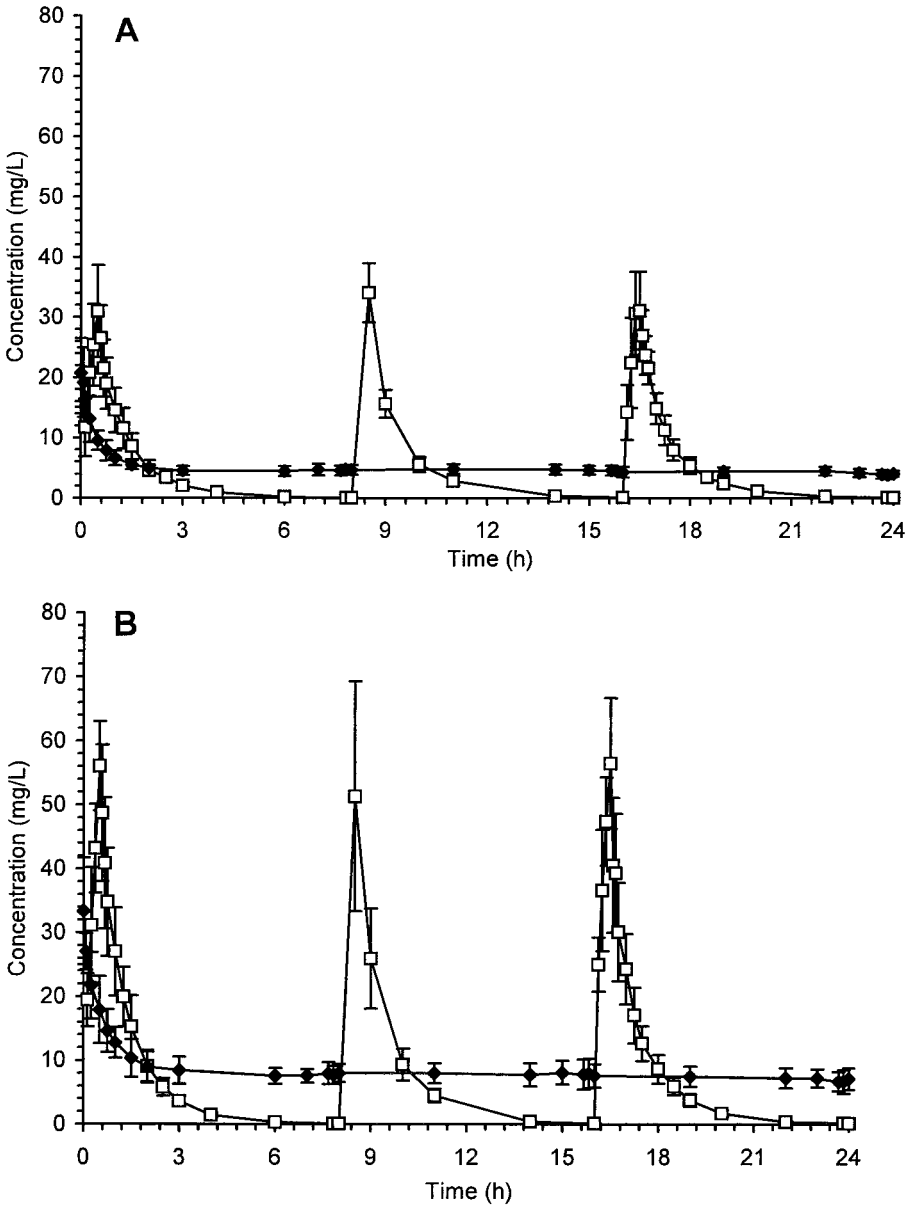

FIG. 1. (A) Plasma concentrations of meropenem (mean ± standard deviation) following intermittent dosing of 500 mg three times a day (open squares) versus a 250-mg loading dose (from −5 min to 0 min), followed by a continuous infusion of 62.5 mg/h over 24 h (filled diamonds) in eight healthy volunteers; (B) plasma concentrations of meropenem (mean ± standard deviation) following intermittent dosing of 1,000 mg three times a day (open squares) versus a 500-mg loading dose (from −5 min to 0 min), followed by a continuous infusion of 125 mg/h over 24 h (filled diamonds) in eight healthy volunteers.

Van Guilder, 2001) was used for the analysis. An adaptive-grid nonparametric approach to the pharmacokinetic and pharmacodynamic models (Proceedings of the 14th IEEE Symposium on Computer-Based Medical Systems, IEEE Computer Society, Bethesda, Md., 2001, p. 389–394) was used. Because of prior data relating to meropenem pharmacokinetic modeling (1, 14, 33, 42), a two-compartment open model with a time-delimited zero-order input (intermittent administration) or a short (5-min [see above]) intravenous infusion followed by a continuous drug infusion was used. In both instances, first-order elimination was used in the model. The initial choice of weights was determined to be proportional to the inverse of the assay variance. Briefly, the nominal concentrations and their between-day standard deviations were modeled as one-, two-, three-, or four-parameter polynomials. The polynomial chosen was identified by the Akaike information criterion (49). This polynomial was multiplied by a scalar value, γ, which was iteratively determined with each cycle. In this way, a good approximation to the homoscedastic assumption was obtained. Maximal a posteriori probability (MAP) Bayesian estimates were obtained by using the population-of-one utility within the NPAG model. Model fit was examined by regression analysis after the MAP Bayesian step and by visual examination of the estimates for each subject. The weighted mean error was used as a measure of bias, and the bias-adjusted weighted mean squared error was used as a measure of precision. Estimates of clearance were examined for difference by mode of administration by Student's *t* test.

Urinary clearance was calculated as the amount of the parent compound recovered in urine divided by the meropenem area under the plasma concentration-time curve (AUC) from time zero to infinity. The AUCs were calculated from the MAP Bayesian estimates of clearance for each patient.

Pharmacodynamics. The final mean parameter vector and full covariance matrix were inserted into the PRIOR subroutine of the ADAPT II package of

TABLE 1. Pharmacokinetic parameter values and their dispersions as calculated from all 32 drug administrations by two modes of administrations and two doses in 16 healthy volunteers[a]

Parameter	V_c (liters)	K_{cp} (h^{-1})	K_{pc} (h^{-1})	CL (liters/h)
Mean	12.4	1.21	4.03	16.3
Median	12.0	0.552	1.48	16.0
SD	3.51	1.79	8.18	3.08

[a] Abbreviations: V_c, volume of distribution of the central compartment; K_{cp}, first-order intercompartmental transfer rate constant from the central to the peripheral compartment; K_{pc}, first-order intercompartmental transfer rate constant from the peripheral to the central compartment; CL, total clearance; SD, standard deviation.

the programs of D'Argenio and Schumitzky (D. Z. D'Argenio and A. Schumitzky, ADAPT II. A program for simulation, identification, and optimal experimental design. User manual, Biomedical Simulations Resource University of Southern California, Los Angeles, 1992). Monte Carlo simulations (for 10,000 simulated subjects) were performed for both modes of administration for both doses. Normal and log-normal distributions were evaluated. The choice of distribution was determined by the fidelity with which the original mean parameter vector and the variances of the parameter values was recapitulated by the simulations with the different distributions.

The pharmacodynamic target chosen was maximal bacterial cell killing. Given the data from animal experiments (9), we chose the time above the MIC of meropenem for 40% of the dosing interval to represent attainment of the target.

Target pathogen MIC distributions were obtained from the MYSTIC database (31, 39, 47). A weighted average (expectation) over the MIC distribution and the target attainment rates was taken to obtain an estimate of the population probability of target attainment for a specific pathogen for a specific mode of administration and a specific dose. As the lowest MIC tested in the MYSTIC database was 0.25 mg/liter and as the intermittent mode of drug administration had probabilities of target attainment less than unity at this value, the target attainment probability used for this MIC was the average of the target attainment probabilities from 0.0156 mg/liter to 0.25 mg/liter.

RESULTS

Drug concentrations. After intermittent dosing, peak levels of meropenem in plasma were reached by the end of the infusions (30 min). All values are provided as arithmetic means ± standard deviations. For subjects in group A, they amounted to 31.0 ± 7.64 mg/liter, 34.0 ± 4.89 mg/liter, and 32.5 ± 6.55 mg/liter after the first, second, and third doses, respectively. The trough levels were 0.0509 ± 0.0177 mg/liter, 0.0778 ± 0.0375 mg/liter, and 0.0676 ± 0.0249 mg/liter (Fig. 1A). The corresponding values for the peak levels for subjects in group B were 56.1 ± 7.00 mg/liter, 51.3 ± 18.0 mg/liter, and 56.5 ± 10.2 mg/liter; and trough levels were 0.0871 ± 0.0313 mg/liter, 0.129 ± 0.0505 mg/liter, and 0.125 ± 0.0413 mg/liter (Fig. 1B). Steady-state plasma concentrations after continuous infusion amounted to 4.34 ± 0.79 mg/liter (group A) and 7.58 ± 1.63 mg/liter (group B) (Fig. 1A and B).

Pharmacokinetic parameter values. There was no significant difference between the modes of administration for total clearance (16.1 ± 3.20 liter/h versus 16.4 ± 2.95 liter/h). Renal clearance and the fraction of intact drug excreted in urine also did not differ (data not shown). Because of this, an analysis in which all the plasma data were simultaneously comodeled was performed, and the derived pharmacokinetic parameters were used for the Monte Carlo simulations.

The overall mean and median parameter values and their standard deviations are presented in Table 1, and the full covariance matrix is presented in Table 2. The volume of distribution and the plasma clearance values are concordant with those from previous volunteer studies of meropenem (14, 16, 24, 36). The overall fit of the model to the data was good, with the line of best fit for the regression after the MAP Bayesian step being observed value = (1.022 × predicted value) + 0.288 ($r^2 = 0.949$; $P \ll 0.001$). Measures of bias and precision were acceptable at −0.558 mg/liter and 13.9 $(\text{mg/liter})^2$, respectively. The plot is presented in Fig. 2. The renal clearances were 9.75 ± 1.84 liter/h and represented 60.3% ± 6.3% of the total clearance. Again, these values are concordant with previously reported values.

TABLE 2. Covariance matrix[a]

Parameter	V_c	K_{cp}	K_{pc}	CL
V_c	12.3			
K_{cp}	−2.97	3.22		
K_{pc}	6.58	−1.90	66.9	
CL	2.95	1.35	−0.830	9.51

[a] See footnote *a* of Table 1 for the definitions of the abbreviations.

Monte Carlo simulation evaluation. The results of the analyses of the probability of target attainment by MIC for the high- and low-dose continuous infusions are displayed in Fig. 3A and B. It is apparent by inspection that the high-dose continuous infusion has a robust probability of target attainment up to an MIC of 4 mg/liter. The lower-dose probability of target attainment is still robust up to an MIC of 2 mg/liter.

The results the analyses of the probability of target attainment by MIC for the high- and low-dose intermittent administration are presented in Fig. 4A and B. Here, it is again obvious by inspection that high (>0.9) target attainment rates are maintained up to 0.5 mg/liter for the high-dose group and up to 0.25 mg/liter for the low-dose group.

In order to put these observations into perspective, we ob-

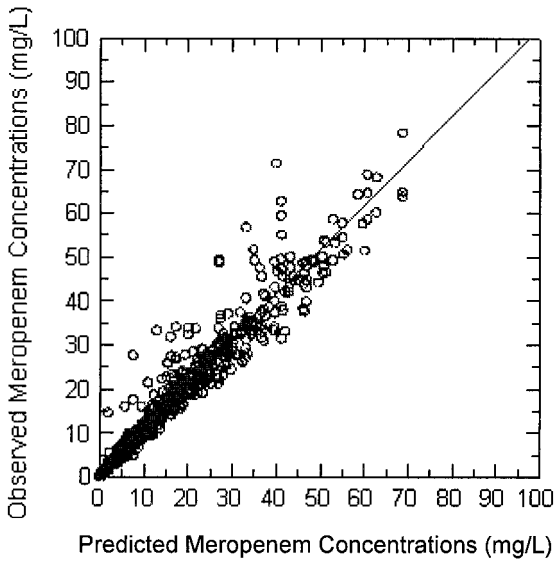

FIG. 2. Meropenem population model regression shown as an observed-predicted plot for all doses and modes of administration. The line of best fit was observed value = (1.022 × predicted value) + 0.288 ($r^2 = 0.949$; $P \ll 0.001$).

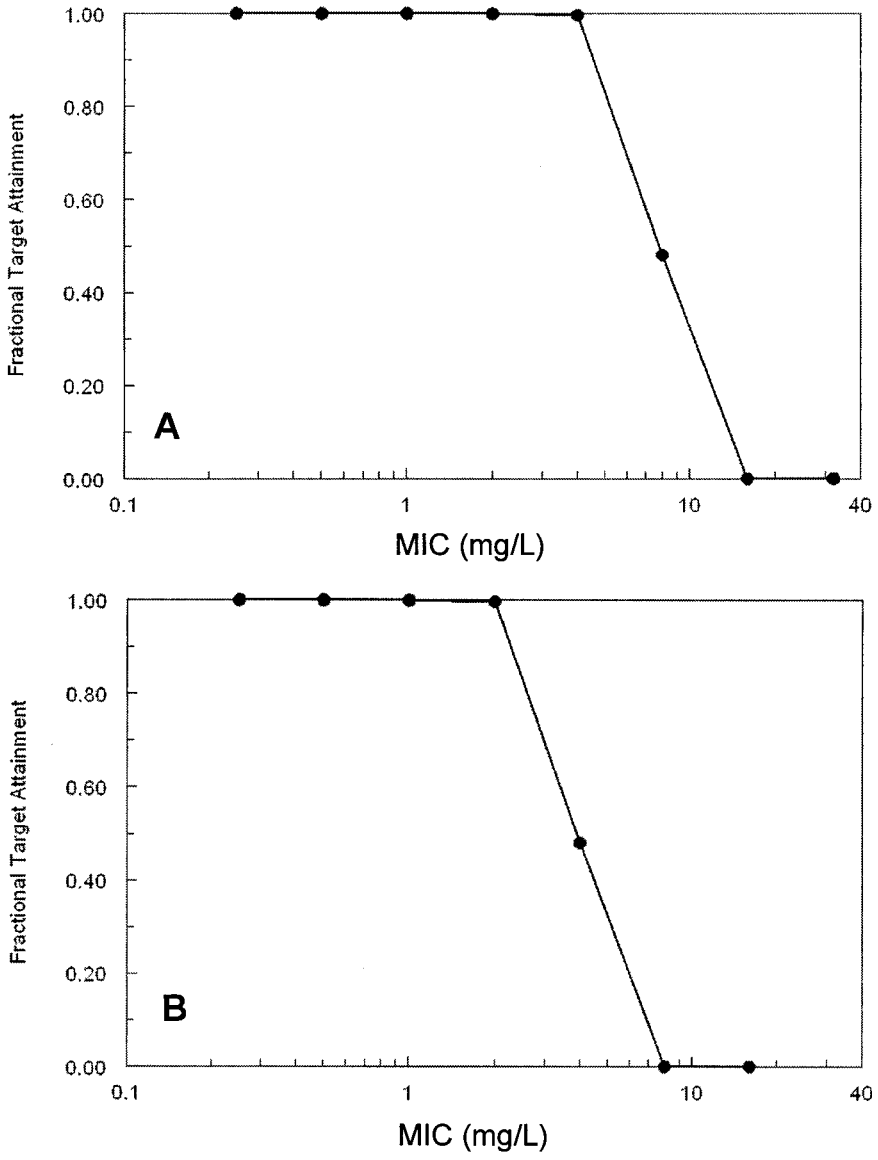

FIG. 3. Probability of target attainment for 10,000 simulated subjects for meropenem administered as continuous intravenous infusions in high-dose (3-g/day; A) and low-dose (1.5-g/day; B) regimens. A time for the plasma concentration of meropenem above the MIC exceeding 40% of the dosing interval was chosen as the target for the analysis.

tained meropenem MIC distributions for common gram-negative nosocomial pathogens (*K. pneumoniae*, *Enterobacter cloacae*, and *P. aeruginosa*) from the MYSTIC database (31, 39, 47). Weighted averages were calculated over the MIC distributions, and the probabilities of target attainment by dose and mode of administration and are presented in Table 3.

Toxicity evaluation. All volunteers completed the study. Some mild adverse events, such as diarrhea, headache, and very mild skin reactions, were reported. No vein reactions were observed during the continuous infusion of meropenem.

DISCUSSION

Optimal outcomes for patients are obtained when the antimicrobial chemotherapy administered is correct at the time of initiation of therapy. Meropenem has an exceedingly broad spectrum of activity and, consequently, represents a good choice for an empirical therapy regimen (25, 34, 40). Such an empirical therapy regimen may be monotherapy or combination therapy, depending upon the incidence of methicillin-resistant *Staphylococcus aureus* infections and *P. aeruginosa* or *Acinetobacter* sp. infections at the site where the regimen is to be used (5).

Given that the time above the MIC is the pharmacodynamically linked variable for β-lactam antibiotics, it stands to reason that continuous infusions (7) or prolonged infusions (30) of drug would increase the time above the MIC. Carbapenem antibiotics achieve maximal killing of organisms at the primary infection site when the free drug concentration exceeds the MIC of the infecting pathogen for about 40% of the dosing

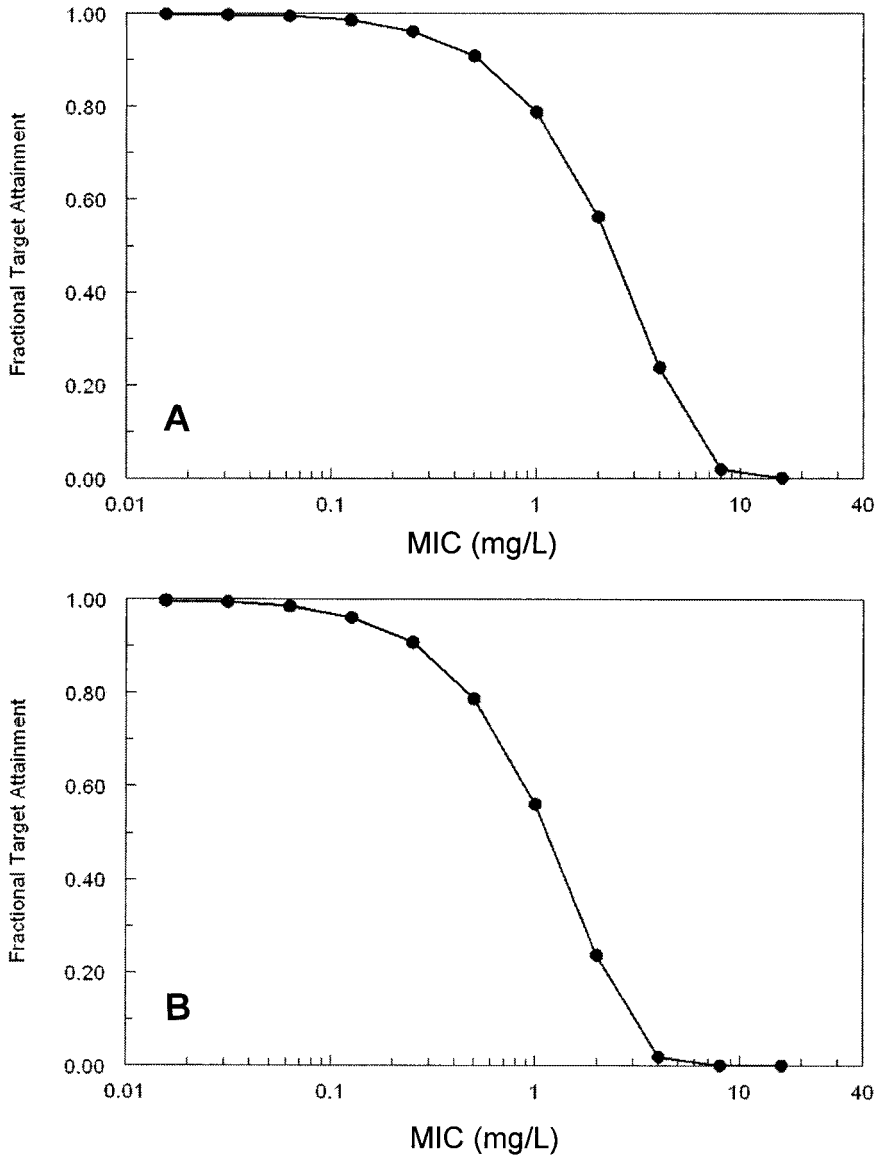

FIG. 4. Probability of target attainment for 10,000 simulated subjects for meropenem administered as intermittent intravenous infusions given three times a day for high-dose (3-g/day; A) and low-dose (1.5-g/day; B) regimens. A time for the plasma concentration of meropenem above the MIC exceeding 40% of the dosing interval was chosen as the target for the analysis.

interval (9). In this evaluation we examined the probability of attainment of this target for two different doses (1.5 g/day versus 3.0 g/day) and two modes of administration (continuous infusion after a small loading dose versus intermittent administration as a short intravenous infusion) of meropenem.

It also needs to be appreciated that there is true between-patient variability in clearance and other pharmacokinetic parameters. Such variability will have a major impact upon the probability at which the administration of a fixed dose of drug will attain the desired target (maximal bacterial cell killing) that the free drug concentration remains above the MIC for at least 40% of the dosing interval. It also needs to be understood that as the MIC of the pathogen to be treated increases, there will be a lower probability that a fixed drug dose will attain the desired target. It is vital to evaluate the variability in pharmacokinetic parameter values as well as examine the impact that the distribution of MICs for target pathogens has on the probability of target attainment. Furthermore, one must consider local susceptibility patterns of infecting the organisms and the widespread distributions of MICs for the organisms.

In this evaluation, we examined the pharmacokinetics of meropenem in healthy volunteers. This represents a serious challenge for the drug. In the vast majority of instances, populations of ill patients have lower drug clearances, larger volumes of distribution, and, consequently, longer terminal half-lives than those seen in healthy volunteer populations (20, 28, 29, 44). Consequently, the conclusions that emerge from an analysis of volunteer data are quite conservative with regard to the probability of target attainment.

Indeed, the clearance of drug observed in the overall pop-

TABLE 3. Population probability of target attainment for common gram-negative pathogens for two different modes of administration and two different doses of meropenem

Type of administration and dose	Probability of target attainment for:		
	K. pneumoniae	*E. cloacae*	*P. aeruginosa*
Continuous infusion			
High dose (3 g/day)	0.996	0.997	0.834
Low dose (1.5 g/day)	0.994	0.993	0.758
Intermittent administration			
High dose (3 g/day)	0.971	0.968	0.637
Low dose (1.5 g/day)	0.942	0.937	0.520

ulation pharmacokinetic analysis was larger than that seen in patients with ventilator-associated pneumonia treated with meropenem (16.3 liter/h in our volunteers versus 11.0 liter/h in patients with ventilator-associated pneumonia [13]). Again, this makes the overall conclusions conservative. On the other hand, the distribution of antimicrobials to infected tissues might be lower, especially in critically ill patients. This might be due to increased third spaces in septic patients, which is caused by the loss of endothelial barrier function, as well as by compromised tissue perfusion caused by decreased cardiocirculatory function (12). Data for the related carbapenem antibiotic imipenem show that both the rate and the extent of tissue penetration may be decreased in critically ill patients compared to those in healthy volunteers (43). Furthermore, the penetration of meropenem into infected lung tissue shows significantly lower areas under the curve of the free, unbound concentration for infected lung tissue compared to those for serum (46). Thus, the conservative estimates derived from our study with healthy volunteers seem more realistic, given that the target site concentrations may be lower than the plasma concentrations in a clinical setting.

Besides altered pharmacokinetic parameters between healthy volunteers and patients, a larger variability of pharmacokinetic parameters is often observed in patients than in healthy volunteers (3; P. F. Laterre, N. Baririan, H. Spapen, et al., Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1402, 2002). We found a relatively low variability for meropenem, with coefficients of variation of 19% for total clearance and 28% for the volume of distribution of the central compartment in this study with healthy volunteers (Table 1). In severely ill patients, a considerably higher variability of meropenem pharmacokinetics may be observed (28, 29). It should be noted that the low variability in pharmacokinetic parameters observed in this study may lead to conclusions that are not conservative enough, especially for the treatment of severely ill patients.

The overall fit of the model to the data was quite acceptable, as were the measures of bias and precision (Fig. 2). The resulting Monte Carlo simulations can then be viewed with a measure of confidence. The low variability observed in this study with healthy volunteers may lead to confidence intervals too narrow in comparison to the clinical situation. The organism MIC distributions in the MYSTIC database represent data for a large collection of current pathogens, and the data were collected in Europe and the United States (31, 39, 47). Figure 5 demonstrates that *K. pneumoniae* and *E. cloacae* both have MIC distributions in which >90% of the isolates examined have meropenem MICs ≤0.25 mg/liter. *P. aeruginosa*, on the other hand, is a much more challenging pathogen for this (or any other) agent, and <30% of the isolates have meropenem MICs < 0.25 mg/liter.

The target attainment rates for the continuous-infusion mode of administration (Fig. 3) demonstrate >99% probability of target attainment for both high and low doses of meropenem for both *Klebsiella* and *Enterobacter* species. For *P. aeruginosa*, the probability of target attainment is still quite good at 83% for the high dose and 76% for the low dose. For this mode of administration, the probability of target attainment falls precipitously from >99% to about 50% and then to almost 0%. The MIC with circa 50% probability of target attainment represents most clearly the impact of between-patient variability in drug clearance, as at a twofold higher MIC, approximately half the patients will have a drug clear-

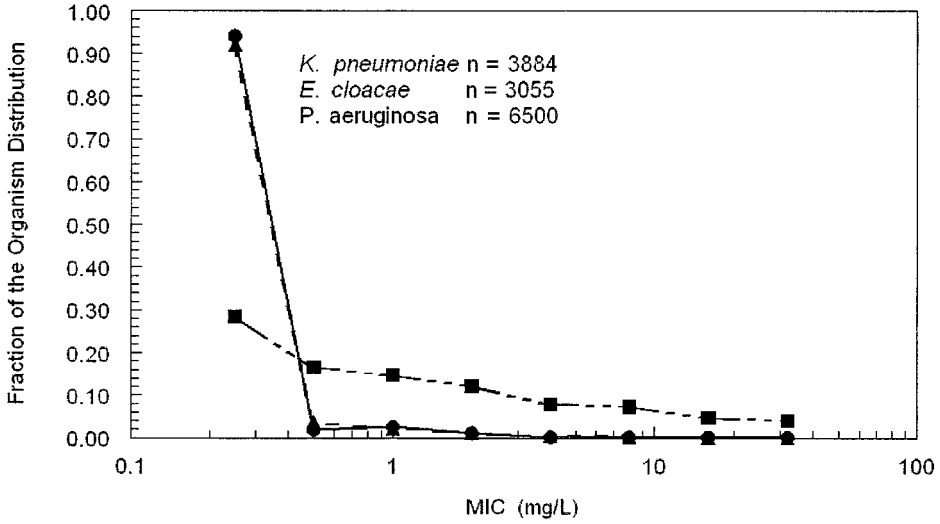

FIG. 5. Distributions of meropenem MICs for three gram-negative pathogens: *K. pneumoniae* (●), *E. cloacae* (♦), and *P. aeruginosa* (■).

ance that drops their steady-state drug concentration to below (if only barely) the MIC.

Intermittent administration as a short infusion demonstrates that the probability of target attainment declines more slowly, but the probability of target attainment for maximal bacterial cell killing decreased below 90% earlier, at 0.5 mg/liter for the 3-g/day group and at 0.25 mg/liter for the low-dose (1.5-g/day) group.

Given the expected organism distributions, it is demonstrated that the continuous-infusion mode of administration has advantages over the intermittent mode of administration. Every contrast by dose and organism shows that the continuous-infusion mode is superior. However, determination of where the superiority is most important is also important. For *K. pneumoniae* and *E. cloacae*, even the low-dose intermittent administration group had probabilities of target attainment that exceeded 93%. While the continuous-infusion groups had target attainments that were higher, it should be recognized that continuous (or even prolonged) infusions are not without a price. The need to use a line continuously means that drug incompatibilities may surface, necessitating the placement of a separate line, with all the implications for infection attendant to the placement of an intravenous access.

It is in *P. aeruginosa* where the advantage of continuous infusion is most clearly made manifest. Here, the probabilities of target attainment are 83% and 76% for the high- and low-dose continuous-infusion regimens, respectively; but they are 64% and 52% for the high- and low-dose intermittent administration regimens, respectively. In the empirical therapy situation, the infecting pathogen is, by definition, unknown. We believe that it is in this circumstance that the continuous-infusion mode of administration is most clearly worth the extra efforts. Once the pathogen and its meropenem MIC are known, it may be possible to reduce the dose to 1.5 g/day and to use an intermittent mode of administration, for convenience. Likewise, Bhavani and coworkers (S. M. Bhavnani, J. P. Hammel, B. B. Cirincioni, et al., Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr A-11, 2003) applied Monte Carlo simulations for the currently investigated but not yet clinically available carbapenem doripenem and studied the target attainment probability for different lengths of infusions at different doses. They suggested that prolonged infusions could be applied for infections caused by pathogens with higher MICs with little or no increase in dose exposure (Bhavnani et al., 43rd ICAAC). Doripenem is slightly more active against problematic pathogens like *P. aeruginosa* (23) and might therefore be an important treatment option for the future. However, in the current situation, we propose that continuous infusion of meropenem is the most feasible method for the treatment of infections caused by such pathogens.

In the empirical treatment setting, in which, as Kollef et al. (26) and other investigators have demonstrated, it is vital to have appropriate antimicrobial chemotherapy present from the beginning; the continuous infusion of high doses of meropenem will demonstrate considerable advantages. In this way, it is possible to minimize mortality, morbidity, and the durations of intubation and ICU and hospital stays by using larger doses of meropenem administered by continuous infusion. When the infecting pathogen becomes identified, it is likely that the intermittent administration of lower doses will be adequate. For the cases in which a pathogen is not identified, it is important to recall the data of Singh et al. (41) and recognize that it is possible to identify clinically patients for whom the early cessation of therapy is safe.

In conclusion, when meropenem was administered either intermittently or as a continuous infusion at either a high or a low dose (3.0 and 1.5 g/day, respectively), it had robust activity against two of the most common nosocomially acquired gram-negative pathogens, *K. pneumoniae* and *E. cloacae*, with a probability of target attainment always exceeding 93%. Against *P. aeruginosa*, the results of the evaluation make clear the advantage of high-dose therapy administered as a continuous infusion. As new pharmacodynamic information becomes available, we should evaluate its application to the clinical arena so that we can optimize antimicrobial therapy for critically ill patients.

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REFERENCES

1. **Bedikian, A., M. P. Okamoto, R. K. Nakahiro, J. Farino, P. N. R. Heseltine, M. D. Appleman, A. E. Yellin, T. V. Berne, and M. A. Gill.** 1994. Pharmacokinetics of meropenem in patients with intra-abdominal infections. Antimicrob. Agents Chemother. **38:**151–154.
2. **Benko, A. S., D. M. Cappelletty, J. A. Kruse, and M. J. Rybak.** 1996. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. Antimicrob. Agents Chemother. **40:**691–695.
3. **Buijk, S. L. C. E., I. C. Gyssens, J. W. Mouton, A. Van Vliet, H. A. Verbrugh, and H. A. Bruining.** 2002. Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections. J. Antimicrob. Chemother. **49:**121–128.
4. **Bustamante, C. I., G. L. Drusano, B. A. Tatem, and H. C. Standiford.** 1984. Postantibiotic effect of imipenem on *Pseudomonas aeruginosa*. Antimicrob. Agents Chemother. **26:**678–682.
5. **Campbell, G. D., M. S. Niederman, W. A. Broughton, D. E. Craven, A. M. Fein, M. P. Fink, K. Gleeson, D. B. Hornick, J. P. Lynch, L. A. Mandell, C. M. Mason, A. Torres, and R. G. Wunderink.** 1996. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement. Am. J. Respir. Crit. Care Med. **153:**1711–1725.
6. **Craig, W., and S. C. Ebert.** 1992. Continuous infusion of beta-lactam antibiotics. Antimicrob. Agents Chemother. **36:**2577–2583.
7. **Craig, W. A.** 2003. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect. Dis. Clin. N. Am. **17:**479–501.
8. **Craig, W. A.** 1995. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad spectrum cephalosporins. Diagn. Microbiol. Infect. Dis. **22:**89–96.
9. **Craig, W. A.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing in mice and men. Clin. Infect. Dis. **26:**1–12.
10. **Craig, W. A.** 1997. The pharmacology of meropenem, a new carbapenem antibiotic. Clin. Infect. Dis. **24**(Suppl. 2)**:**S266–S275.
11. **Daenen, S., Z. Erjavec, D. R. A. Uges, H. G. De Vries-Hospers, P. De Jonge, and M. R. Halie.** 1995. Continuous infusion of ceftazidime in febrile neutropenic patients with acute myeloid leukemia. Eur. J. Clin. Microbiol. Infect. Dis. **14:**188–192.
12. **Dellinger, R. P., J. M. Carlet, H. Masur, H. Gerlach, T. Calandra, J. Cohen, J. Gea-Banacloche, D. Keh, J. C. Marshall, M. M. Parker, G. Ramsay, J. L. Zimmerman, J. L. Vincent, and M. M. Levy.** 2004. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. **30:**536–555.
13. **de Stoppelaar, F., L. Stolk, F. H. van Tiel, A. J. Beysens, S. van der Geest, and P. W. de Leeuw.** 2000. Meropenem pharmacokinetics and pharmacodynamics in patients with ventilator-associated pneumonia. J. Antimicrob. Chemother. **46:**151–153.
14. **Dreetz, M., J. Hamacher, J. Eller, K. Borner, P. Koeppe, T. Schaberg, and H. Lode.** 1996. Serum bactericidal activities and comparative pharmacokinetics of meropenem and imipenem-cilastatin. Antimicrob. Agents Chemother. **40:**105–109.
15. **Drusano, G. L.** 2004. Antimicrobial pharmacodynamics: critical interaction of "bug and drug." Nat. Rev. Microbiol. **2:**289–300.

16. **Drusano, G. L., and M. Hutchison.** 1995. The pharmacokinetics of meropenem. Scand. J. Infect. Dis. Suppl. **96:**11–16.
17. **Eagle, H., R. Fleischman, and M. Levy.** 1953. "Continuous" vs. "discontinuous" therapy with penicillin; the effect of the interval between injections on therapeutic efficacy. N. Engl. J. Med. **248:**481–488.
18. **Eagle, H., R. Fleischman, and A. D. Musselman.** 1950. The bactericidal action of penicillin in vivo: the participation of the host, and the slow recovery of the surviving organisms. Ann. Intern. Med. **33:**544–571.
19. **Flückiger, U., C. Segessenmann, and A. U. Gerber.** 1991. Integration of pharmacokinetics and pharmacodynamics of imipenem in a human-adapted mouse model. Antimicrob. Agents Chemother. **35:**1905–1910.
20. **Giles, L. J., A. C. Jennings, A. H. Thomson, G. Creed, R. J. Beale, and A. McLuckie.** 2000. Pharmacokinetics of meropenem in intensive care unit patients receiving continuous veno-venous hemofiltration or hemodiafiltration. Crit. Care Med. **28:**632–637.
21. **Grant, E. M., J. L. Kuti, D. P. Nicolau, C. H. Nightingale, and R. Quintiliani.** 2002. Clinical efficacy and pharmacoeconomics of a continuous-infusion pipercillin-tazobactam program in a large community teaching hospital. Pharmacotherapy **22:**471–483.
22. **Hanberger, H., L. E. Nilsson, M. Nilsson, and R. Maller.** 1991. Post-antibiotic effect of beta-lactam antibiotics on gram-negative bacteria in relation to morphology, initial killing and MIC. Eur. J. Clin. Microbiol. Infect. Dis. **10:**927–934.
23. **Jones, R. N., H. K. Huynh, D. J. Biedenbach, T. R. Fritsche, and H. S. Sader.** 2004. Doripenem (S-4661), a novel carbapenem: comparative activity against contemporary pathogens including bactericidal action and preliminary *in vitro* methods evaluations. J. Antimicrob. Chemother. **54:**144–154.
24. **Kelly, H. C., M. Hutchison, and S. J. Haworth.** 1995. A comparison of the pharmacokinetics of meropenem after administration by intravenous injection over 5 min and intravenous infusion over 30 min. J. Antimicrob. Chemother. **36**(Suppl. A)**:**35–41.
25. **Klugman, K. P., R. Dagan, and The Meropenem Meningitis Study Group.** 1995. Randomized comparison of meropenem with cefotaxime for treatment of bacterial meningitis. Antimicrob. Agents Chemother. **39:**1140–1146.
26. **Kollef, M. H., G. Sherman, S. Ward, and V. J. Fraser.** 1999. Inadequate antimicrobial treatment of infections. Chest **115:**462–474.
27. **Krueger, W. A., F.-P. Lenhart, G. Neeser, G. Ruckdeschel, H. Schreckhase, H.-J. Eissner, H. Forst, J. Eckart, K. Peter, and K. E. Unertl.** 2002. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients. A prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. Am. J. Respir. Crit. Care Med. **166:**1029–1037.
28. **Krueger, W. A., G. Neeser, H. Schuster, T. H. Schroeder, E. Hoffmann, A. Heininger, H.-J. Dieterich, H. Forst, and K. Unertl.** 2003. Correlation of meropenem plasma levels with pharmacodynamic requirements in critically ill patients receiving continuous veno-venous hemofiltration. Chemotherapy (Basel) **49:**280–286.
29. **Krueger, W. A., T. H. Schroeder, M. Hutchison, E. Hoffmann, H.-J. Dieterich, A. Heininger, C. Erley, A. Wehrle, and K. Unertl.** 1998. Pharmacokinetics of meropenem in critically ill patients with acute renal failure treated by continuous hemodiafiltration. Antimicrob. Agents Chemother. **42:** 2421–2424.
30. **Kuti, J. L., P. K. Dandekar, C. H. Nightingale, and D. P. Nicolau.** 2003. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. J. Clin. Pharmacol. **43:**1116–1123.
31. **Kuti, J. L., C. H. Nightingale, and D. P. Nicolau.** 2004. Optimizing pharmacodynamic target attainment using the MYSTIC antibiogram: data collected in North America in 2002. Antimicrob. Agents Chemother. **48:**2464–2470.
32. **Lemmen, S. W., I. Engels, and F. D. Daschner.** 1997. Serum bactericidal activity of ceftazidime administered as continuous infusion of 3 g over 24 h versus intermittent bolus infusion of 2 g against *Pseudomonas aeruginosa* in healthy volunteers. J. Antimicrob. Chemother. **39:**841–842.
33. **Lovering, A. M., C. J. Vickery, D. S. Watkin, D. Leaper, C. M. McMullin, L. O. White, D. S. Reeves, and A. P. MacGowan.** 1995. The pharmacokinetics of meropenem in surgical patients with moderate or severe infections. J. Antimicrob. Chemother. **36:**165–172.
34. **Mehtar, S., E. P. Dewar, D. J. Leaper, and E. W. Taylor.** 1997. A multi-center study to compare meropenem and cefotaxime and metronidazole in the treatment of hospitalized patients with serious infections. J. Antimicrob. Chemother. **39:**631–638.
35. **Mouton, J. W., A. M. Horrevorts, P. G. H. Mulder, E. P. Prens, and M. F. Michel.** 1990. Pharmacokinetics of ceftazidime in serum and suction blister fluid during continuous and intermittent infusions in healthy volunteers. Antimicrob. Agents Chemother. **34:**2307–2311.
36. **Mouton, J. W., and M. F. Michel.** 1991. Pharmacokinetics of meropenem in serum and suction blister fluid during continuous and intermittent infusion. J. Antimicrob. Chemother. **28:**911–918.
37. **Nicolau, D. P., C. H. Nightingale, M. A. Banevicius, Q. Fu, and R. Quintiliani.** 1996. Serum bactericidal activity of ceftazidime: continuous infusion versus intermittent injections. Antimicrob. Agents Chemother. **40:**61–64.
38. **Rello, J., M. Gallego, D. Mariscal, R. Sonora, and J. Valles.** 1997. The value of routine microbial investigation in ventilator-associated pneumonia. Am. J. Respir. Crit. Care Med. **156:**196–200.
39. **Rhomberg, P. R., R. N. Jones, and The MYSTIC Program (USA) Study Group**, 2003. Antimicrobial spectrum of activity for meropenem and nine broad spectrum antimicrobials: report from the MYSTIC Program, 2002, in North America. Diagn. Microbiol. Infect. Dis. **47:**365–372.
40. **Sieger, B., S. J. Berman, R. W. Geckler, S. A. Farkas, and The Meropenem Lower Respiratory Infection Study Group.** 1997. Empiric treatment of hospital-acquired lower respiratory infections with meropenem or ceftazidime with tobramycin: a randomized study. Crit. Care Med. **25:**1663–1670.
41. **Singh, N., P. Rogers, C. W. Atwood, M. M. Wagener, and V. L. Yu.** 2000. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. Am. J. Respir. Crit. Care Med. **162:**505–511.
42. **Tegeder, I., F. Neumann, F. Bremer, K. Brune, J. Lötsch, and G. Geisslinger.** 1999. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. Clin. Pharmacol. Ther. **65:**50–57.
43. **Tegeder, I., A. Schmidtko, L. Brautigam, A. Kirschbaum, G. Geisslinger, and J. Lotsch.** 2002. Tissue distribution of imipenem in critically ill patients. Clin. Pharmacol. Ther. **71:**325–333.
44. **Thalhammer, F., P. Schenk, H. Burgmann, I. El Menyawi, U. M. Hollenstein, A. R. Rosenkranz, G. Sunder-Plassmann, S. Breyer, and K. Ratheiser.** 1998. Single-dose pharmacokinetics of meropenem during continuous venovenous hemofiltration. Antimicrob. Agents Chemother. **42:**2417–2420.
45. **Thalhammer, F., F. Traunmüller, I. El Menyawi, M. Frass, U. M. Hollenstein, G. J. Locker, B. Stoiser, T. Staudinger, R. Thalhammer-Scherrer, and H. Burgmann.** 1999. Continuous infusion versus intermittent administration of meropenem in critically ill patients. J. Antimicrob. Chemother. **43:**523–527.
46. **Tomaselli, F., A. Maier, V. Matzi, F. M. Smolle-Juttner, and P. Dittrich.** 2004. Penetration of meropenem into pneumonic human lung tissue as measured by in vivo microdialysis. Antimicrob. Agents Chemother. **48:**2228–2232.
47. **Unal, S., R. Masterton, and H. Goossens.** 2004. Bacteraemia in Europe—antimicrobial susceptibility data from the MYSTIC surveillance programme. Int. J. Antimicrob. Agents **23:**155–163.
48. **Vogelman, B., S. Gudmundsson, J. Leggett, J. Turnidge, S. Ebert, and W. A. Craig.** 1988. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J. Infect. Dis. **158:**831–847.
49. **Yamaoka, K., T. Nakagawa, and T. Uno.** 1978. Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J. Pharmacokinet. Biopharm. **6:**165–175.