

Pharmacokinetic and Pharmacodynamic Properties of Meropenem

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Pharmacokinetic and pharmacodynamic profiles of antibiotics are important in determining effective dosing regimens. Although minimum inhibitory concentration (MIC) data reflect microbial susceptibility to an antibiotic, they do not provide dosing information. The integration of pharmacokinetic and microbiological data, however, can be used to design rational dosing strategies. Meropenem is a broad-spectrum β -lactam antibiotic that penetrates most body fluids and tissues rapidly after intravenous administration. Meropenem undergoes primarily renal elimination; therefore, dosage adjustment is required for patients with renal impairment. Meropenem is indicated for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and bacterial meningitis. Meropenem has time-dependent bactericidal activity; thus, the percentage of time that free-drug concentrations are higher than the MIC (%T > MIC) best characterizes the drug's pharmacodynamic profile (bactericidal target of $\sim 40\%T > MIC$). Pharmacodynamic modeling can identify regimens with the greatest probability of attaining this target, and probabilities can be compared with clinical and microbiological responses in patients.

The efficacy of an antibiotic agent is dependent on its pharmacokinetic and pharmacodynamic properties. Serum concentrations of an agent reflect its absorption, distribution, metabolism, and excretion, as well as the magnitude of the dosing regimen. The pharmacodynamic profile is described as a function of the concentrations achieved in tissues, body fluids, and the infection site relative to the *in vitro* microbiological activity of a given agent. Because pharmacokinetic and pharmacodynamic profiles differ among antibiotics, an understanding of these characteristics for each agent is important in determining effective antibiotic dosing regimens [1, 2].

Some agents, such as the aminoglycosides and fluoroquinolones, exhibit concentration-dependent bactericidal activity, which requires an adequate maximum concentration (C_{max})/MIC ratio or area under the con-

centration-time curve (AUC)/MIC ratio for efficacy. In general, higher concentrations of these agents yield more-rapid and more-extensive bacterial killing [3, 4]. Other classes of antibiotics, such as the β -lactams, are characterized by time-dependent bactericidal activity, which means that free-drug concentrations higher than the MIC for an adequate percentage of time in a dosing interval (%T > MIC) must be maintained for efficacy. For these agents, increasing the concentration does not necessarily increase the rate or extent of killing; best results are achieved by optimizing the duration of exposure to effective concentrations [5–7].

Once an agent's pharmacodynamic profile has been established (i.e., C_{max} /MIC, AUC/MIC, or %T > MIC), studies then can be designed to identify the pharmacodynamic target associated with maximal bactericidal activity (e.g., 50%T > MIC). The use of mathematical modeling procedures that simulate population pharmacokinetic parameters and that use microbiological surveillance data to determine an agent's pharmacodynamic profile can assess the likelihood of pharmacodynamic target attainment with specific antibiotic dosing regimens [7].

This article summarizes the pharmacokinetic and pharmacodynamic characteristics of meropenem, a

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broad-spectrum β -lactam antibiotic indicated by the US Food and Drug Administration as single-agent therapy for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and bacterial meningitis in children aged ≥ 3 months (when infection is caused by susceptible isolates) [8]. Additional clinical uses of meropenem have regulatory approval in countries other than the United States, and clinical trials of meropenem for the treatment of a variety of conditions are ongoing. The optimization of meropenem dosing regimens also is discussed.

PHARMACOKINETIC PROPERTIES OF MEROPENEM

Penetration

Meropenem is administered intravenously as an infusion or bolus injection. The penetration of meropenem has been studied in a variety of tissues and body fluids and is rapid and substantial; in most cases, levels likely to be clinically effective are attained [9].

Several penetration studies have shown that meropenem provides adequate tissue concentrations for the treatment of intra-abdominal infections caused by susceptible bacteria. Adult patients scheduled for intra-abdominal surgery received a single 1-g dose of meropenem, administered as a 30-min infusion immediately before surgery. Tissue and body-fluid samples were collected $\sim 1, 2, 4,$ or 6 h after the start of the infusion. Results showed penetration of meropenem into intra-abdominal tissues and peritoneal fluid within 1 h and median peak concentrations in bile and muscle within 2–4 h after administration. Penetration into peritoneal fluid at ~ 1 h was $\sim 45\%$ of the median plasma concentration at that time. Meropenem levels in peritoneal fluid were $12.2 \mu\text{g/mL}$, which is higher than the MIC_{90} for common intra-abdominal pathogens ($0.03\text{--}4 \mu\text{g/mL}$). Sustained meropenem levels higher than the MIC_{90} also were observed in the colon, gall bladder, fascia, muscle, omentum, and skin [10]. In another pharmacokinetic study of patients with intra-abdominal infections, a 1-g dose of meropenem was administered as a 30-min infusion every 8 h; urine and blood samples were collected after surgery. This study showed that, although the pharmacokinetic parameters for these patients differed from those for healthy volunteers, serum concentrations were therapeutic with regard to susceptible organisms [11].

In patients undergoing gynecological surgery, the penetration of meropenem was assessed in gynecological tissue, peritoneal fluid, and plasma after a single 500-mg dose, administered as a 30-min infusion immediately before surgery. Meropenem showed rapid penetration of gynecological tissues (within ~ 1 h), with median peak concentrations at $14.3\%\text{--}63.9\%$ of the median plasma concentration at that time [12]. These meropenem concentrations ($1.9\text{--}8.5 \mu\text{g/mL}$) were higher than the MIC_{90} for common gynecological pathogens. In addition, the

concentration in peritoneal fluid at ~ 1 h was $8.8 \mu\text{g/mL}$, which was approximately two-thirds of the median plasma concentration at that time [12].

Meropenem also penetrates pulmonary tissues well. Patients scheduled for lung surgery received a single 1-g dose, administered as a 3-min infusion at 1–5 h before surgery. Peak concentrations of meropenem in lung, bronchial mucosal, and pleural tissues (mean, 3.9, 6.6, and $2.8 \mu\text{g/mL}$, respectively) usually were observed 1 h after administration. Between 1 and 5 h after administration, meropenem concentrations in lung and bronchial mucosal tissue were similar, whereas those in pleural tissue were lower. The ratio of mean tissue concentration to serum concentration ranged between 0.17 and 0.43 for lung tissue, 0.20 and 0.55 for bronchial mucosal tissue, and 0.18 and 0.26 for pleural tissue [13]. In another study, healthy subjects received 30-min infusions of 500 mg, 1 g, or 2 g of meropenem every 8 h, for 4 doses. Meropenem concentrations in the epithelial lining fluid (ELF) and alveolar cells (ACs) were measured by using samples obtained via bronchoalveolar lavage done at various times after infusion. As in the previously mentioned study, peak concentrations were observed at 1 h after the 1-g dose (ELF concentration, $5.3 \mu\text{g/mL}$; AC concentration, $1.0 \mu\text{g/mL}$). Although plasma pharmacokinetic properties were linear, the penetration of meropenem into ELF was less than proportional, and penetration into ACs was greater than proportional. At the 1-g dose, the ELF/plasma penetration ratios ranged between 32% and 53%, and the AC/plasma penetration ratios ranged from 26% to 34%. The $\%T > \text{MIC}_{90}$ for plasma, ELF, and ACs ranged from 64% to 100%, 38% to 100%, and 50% to 100%, respectively, suggesting that a dosing regimen of 1 g every 8 h should be effective for respiratory pathogens with MIC_{90} values of $0.12\text{--}2.0 \mu\text{g/mL}$ [14].

Meropenem penetration in cardiac muscle and valve tissue also was shown to be rapid and substantial. A single 1-g dose of meropenem over 5–10 min was administered to 33 patients, aged 39–75 years, before cardiac valve surgery. Meropenem concentrations were measured in plasma, atrial muscle, and cardiac valve tissue between 27 min and 3 h after the start of the injection. Plasma concentrations ($7.4\text{--}92.6 \text{ mg/L}$) in these patients were higher than those observed previously in healthy subjects who had received the same regimen, possibly owing to the effects of surgery, competition with coadministered antibiotics for excretory mechanisms, or a combination of these factors. These meropenem concentrations ($7.4\text{--}92.6 \text{ mg/L}$) were higher than the MIC_{90} for commonly occurring pathogens that cause infectious endocarditis. Meropenem concentrations in atrial muscle also were high ($0.43\text{--}25.5 \text{ mg/kg}$) and appeared to decrease over time in a pattern similar to that in plasma. Variable but high concentrations in valve tissue did not appear to be correlated with time. The ratio of valve concentration to simultaneous plasma concentration ranged from 15% to 66% [15].

Rapid and substantial penetration of meropenem also was observed in skin blister fluid. Before and at several time points after a single 1-g dose infused over 5 min, blister fluid from subjects with cantharidin-induced blisters was collected. The mean peak concentration in blister fluid (55.6 $\mu\text{g}/\text{mL}$) was determined for all subjects by 1 h after administration, and the mean percentage penetration was 110.7% [16]. In a multiple-dose study (3 doses of 500 mg infused every 8 h) of subjects with cantharidin-induced blisters, samples were collected before and at several time points after infusion of the third dose. The mean time to obtaining peak concentrations in plasma and blister fluid was 0.5 and 1.22 h, respectively. Mean peak concentrations were higher for plasma than for blister fluid (24.02 vs. 5.5 $\mu\text{g}/\text{mL}$) [17]. The AUC from 0 to 8 h also was higher for plasma than for blister fluid (28.6 vs. 18.9 $\mu\text{g} \times \text{h}/\text{mL}$), giving a mean percentage penetration into blister fluid of 67%. The investigators hypothesized that the difference in penetration between this study and the single-dose study previously described was related to the size of the blisters analyzed, because those in the single-dose study were smaller (1 cm^2) than those in the multiple-dose study (1.6 cm^2) [17]. Calculation of %T > MIC for blister fluid showed that 500 mg of meropenem infused every 8 h maintained concentrations higher than MIC₉₀ values for common skin pathogens for $\geq 70\%$ of the dosing interval [17].

Although many of the studies described above did not assess %T > MIC, they reported that the tissue and fluid concentrations achieved with the various doses of meropenem that were studied were higher than the MIC₉₀ for the relevant pathogens. Moreover, adequate tissue penetration in a variety of organs usually occurred within 1 h of dosing. Despite a lack of %T > MIC data in these studies, meropenem demonstrated rapid and effective penetration in a wide range of tissues, indicating that meropenem may be useful for the treatment of a variety of infectious conditions.

Special Populations

Patients with renal impairment. Meropenem undergoes predominantly renal excretion. Therefore, dosage adjustment is required for patients with renal impairment. Comparisons of meropenem pharmacokinetic properties after a single 30-min infusion of 500 mg in healthy subjects versus patients with renal impairment showed that the terminal half-life of meropenem increased in relation to the degree of impairment, with values ~ 10 -fold higher in patients undergoing hemodialysis [18–21]. In addition, the half-life of the open-ring metabolite of meropenem, which is present at very low levels in the plasma of healthy subjects, also increased as renal impairment increased [18, 21].

A linear relationship was found between total body clearance and renal clearance of meropenem and between renal clearance

of meropenem and creatinine clearance [18, 19]; therefore, creatinine clearance may be used as a guide for determining dosage for patients with renal impairment. The prescribing information states that meropenem doses should be reduced if creatinine clearance is <51 mL/min (administer the recommended dose every 12 h for creatinine clearance of 26–50 mL/min; one-half the recommended dose every 12 h for creatinine clearance of 10–25 mL/min; and one-half the recommended dose every 24 h for creatinine clearance of <10 mL/min).

The prescribing information also states that information on meropenem use by patients undergoing hemodialysis (i.e., patients with chronic renal failure) is inadequate [8]. Pharmacokinetic data are limited to studies that each included <10 patients undergoing hemodialysis. Nonetheless, these studies demonstrated that meropenem and its metabolite are cleared by hemodialysis, suggesting that a supplemental dose is required after this procedure [18–21].

Results of small pharmacokinetic studies of meropenem administration to critically ill patients receiving continuous venovenous (CVV) hemofiltration or CVV hemodiafiltration for acute renal failure suggest that a single dose of 1 g and multiple doses of 500 mg every 8 or 12 h or 1 g every 12 h were well tolerated [22–24]. The single-dose study demonstrated that patients with acute renal failure who were undergoing CVV hemofiltration had meropenem-elimination profiles comparable to those reported for patients without renal impairment [22]. In contrast, the multiple-dose study of 1 g every 12 h in patients undergoing CVV hemodiafiltration demonstrated that elimination was delayed, compared with that reported for subjects without acute renal failure [24]. A separate multiple-dose study of 500 mg every 8 or 12 h demonstrated that CVV hemofiltration increased total body clearance of meropenem in patients with acute renal failure, accounting for almost 50% of total body clearance of the administered dose of meropenem; thus, nearly twice the renal adjusted dose (recommended for patients with acute renal failure and creatinine clearance <10 mL/min) is needed for patients receiving CVV hemofiltration [23]. Results of an evaluation using pharmacokinetic and pharmacodynamic modeling techniques further suggest that a 1-g dose every 8 h is appropriate empirical therapy for patients undergoing CVV hemofiltration [25].

Patients with hepatic impairment. In contrast, no dosage adjustment is required for patients with hepatic impairment [8]. Results of a study comparing the pharmacokinetic profiles of meropenem and its metabolite in patients with cirrhosis and in subjects with normal liver function indicated no significant differences between groups after repeated dosing, and meropenem was well tolerated by both groups [26].

Geriatric patients. The effect of age on meropenem pharmacokinetic properties was assessed in a study comparing pharmacokinetic profiles for men aged 20–34 years with those for

men aged 67–80 years, after a single 500-mg dose infused over 30 min. Rates of renal excretion of meropenem and its metabolite were reduced in the elderly, reflecting a decline in renal function with aging [27]. The prescribing information for meropenem indicates that, for elderly patients, no dosage adjustment is required if creatinine clearance is >50 mL/min [8].

Pediatric patients. For pediatric patients aged ≥ 3 months who have normal renal function and weigh ≥ 50 kg, recommended doses of meropenem are 10, 20, and 40 mg/kg every 8 h, with a maximum dose of 2 g every 8 h, depending on the type of infection [8]. These doses were first investigated by Blumer et al. [28] in an escalating single-dose trial among hospitalized infants and children, and the pharmacokinetic profiles obtained after a 30-min infusion appeared to be similar to those reported for adults. When results were stratified by age (2–5 months, 6–23 months, 2–5 years, and 6–12 years), the elimination half-life was found to be longer in the 2–5-month age group than in the 6–12-year age group (1.7 h vs. 0.8 h; $P = .0003$) [28]. Calculations of $\%T > MIC$, based on the MIC_{90} , ranged from 7.8 to 17 h for various pathogens, indicating that a dose of 20 mg/kg every 8 h would be effective in these subjects [28].

Parker et al. [29] conducted population pharmacokinetic modeling with trial data from the Blumer et al. [28] study that included 300 plasma concentrations from various time points, fitted simultaneously with the nonlinear mixed-effects model (NONMEM) program. The effects of plasma creatinine level, creatinine clearance, weight, age, sex, race, body-surface area, and diagnosis on pharmacokinetic parameters were assessed. The investigators found that clearance of meropenem was related directly to creatinine clearance. Body weight was the most important determinant of the volume of distribution of meropenem. Weight was linearly related to volume in the central and peripheral compartments and nonlinearly associated with intercompartmental clearance [29]. Furthermore, age was correlated with clearance. After normalization for creatinine clearance, meropenem clearance was more appropriately modeled when age, rather than weight, was used. Thus, clearance of meropenem is lower in infants than in older children, which is expected given the physiological maturation process in infants and children [29]. Du et al. [30] subsequently constructed a similar model, improving on the methods used by Parker et al. [29] by accounting for interindividual variabilities. Data from 3 pediatric clinical trials (the trial by Blumer et al. [28] described above plus 2 other trials, providing a total of 425 plasma concentrations) were evaluated with the NONMEM program. As in the analysis by Parker et al. [29], results showed that creatinine clearance was significantly correlated with meropenem clearance and that weight was an important covariate for volume in the central and peripheral compartments [30]. In addition, analysis of pharmacodynamic data for 37 patients

with meningitis for whom MIC data for the causative pathogens were available was conducted to ascertain the relationship between $\%T > MIC$, C_{max}/MIC ratio, minimum concentration (C_{min})/MIC ratio, and microbiological outcomes. Because the causative pathogens were eradicated in all 37 patients with meningitis by the end of treatment, pharmacodynamic indices could not be correlated with a positive or negative influence; however, the median $\%T > MIC$ was 100% (range, 72%–100%). These 37 patients had received meropenem at a dose of 40 mg/kg; therefore, this dose was deemed to be adequate for pediatric patients with meningitis caused by organisms with MICs ≤ 0.6 $\mu\text{g/mL}$ [30].

PHARMACODYNAMIC PROPERTIES OF MEROPENEM

Several investigations of carbapenem (meropenem, ertapenem, and imipenem) bactericidal activity in animal models of infection have suggested that the pharmacodynamic target for maximal bactericidal activity is a $\%T > MIC$ of free drug of $\sim 40\%$ (figure 1) [31–33]. The corresponding target for a bacteriostatic effect (defined as no net change in bacterial density after 24 h of treatment) is a $\%T > MIC$ of $\sim 20\%$ [31, 32, 34]. These requirements did not appear to be influenced by the presence of extended-spectrum β -lactamase (ESBL)-producing strains of *Escherichia coli* and *Klebsiella pneumoniae* [34, 35] or of efflux pump-overexpressing strains of *Pseudomonas aeruginosa* [32].

This pharmacodynamic information has been used to help

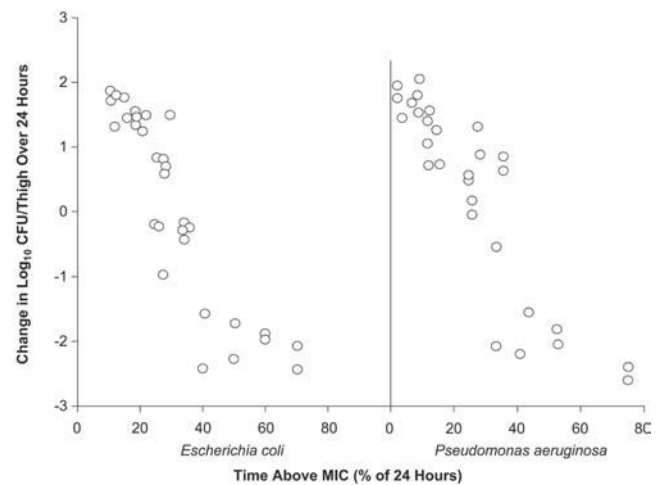


Figure 1. Meropenem pharmacodynamic data from a mouse model of thigh infection. In vivo bactericidal activity of meropenem against *Escherichia coli* and *Pseudomonas aeruginosa* is plotted as a function of the percentage of the dosage interval that drug concentrations remained higher than the MIC for each organism. CFU, colony-forming units. Reprinted from Mattoes HM, Kuti JL, Drusano GL, Nicolau DP. Optimizing antimicrobial pharmacodynamics: dosage strategies for meropenem. Clin Ther 2004;26:1189 [33], with permission from Excerpta Medica, Inc.

determine effective dosing regimens for humans. For example, the Optimizing Pharmacodynamic Target Attainment using the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) Antibiogram (OPTAMA) Program combines MIC information from an ongoing global surveillance study (MYSTIC Program) with information derived from Monte Carlo simulation. Monte Carlo simulation is a mathematical tool that accounts for interindividual variation in a population, thus enabling estimation of the dispersion of pharmacokinetic values that would occur in a larger population after antibiotic administration [7, 36]. The data produced from the OPTAMA Program are estimates based on experimental models that can be used to identify antibiotic regimens with the highest probability of achieving pharmacodynamic targets for specific infections and patient populations. It is important to note, however, that most estimates of pharmacokinetic parameters and their dispersion in OPTAMA Program studies are conservative estimates for most patient populations, because they are derived from pharmacokinetic data for healthy adult subjects, which are easier to acquire than are data for specific patient populations [36].

The OPTAMA Program evaluated the probability of pharmacodynamic target attainment with 5 broad-spectrum β -lactam antibiotics and 1 fluoroquinolone antibiotic against nosocomial pathogens of concern in North America (table 1) [37]. A 5000-subject Monte Carlo simulation was used. Results showed that optimal choices for antimicrobial therapy for the treatment of nosocomial infections caused by *E. coli* and *K. pneumoniae* were meropenem or imipenem at 1 g every 8 h and cefepime at 1 g every 12 h; for infections caused by *Acinetobacter baumannii*, the optimal choice was meropenem or imipenem at 1 g every 8 h. For infections caused by *P. aeruginosa*, cefepime at 2 g every 12 h had the highest pharmacodynamic target attainment. The lowest probabilities of target attainment for all pathogens were observed with ciprofloxacin at 400 mg every 8 or 12 h [37].

Because antibiotic susceptibility patterns and antibiotic dosing regimens vary among continents, separate OPTAMA Program analyses were done for other regions of the world. In Europe, the regimens assessed were meropenem at 500 mg or 1 g every 8 h, imipenem at 500 mg every 6 h, ceftazidime at 1 g every 8 h, cefepime at 1 or 2 g every 12 h, piperacillin/tazobactam at 4.5 g every 8 h, and ciprofloxacin at 400 mg every 12 h. Populations analyzed were from northern Europe (Sweden, Finland, Belgium, Germany, and the United Kingdom), southern Europe (Portugal, Spain, Italy, Malta, Greece, and Switzerland), and eastern Europe (Croatia, the Czech Republic, Poland, and Turkey) and Russia. Results showed that the optimal choices for the treatment of nosocomial infections caused by *E. coli* and *K. pneumoniae*, regardless of region, were the meropenem and imipenem regimens. In addition, the ce-

Table 1. Probability of pharmacodynamic target attainment for bactericidal response for various antibiotic regimens.

Regimen	Target attainment, %			
	EC	KP	AB	PA
Meropenem, 1 g q8h ^a	100	100	88	91
Imipenem, 1 g q8h ^a	100	99	92	89
Ceftazidime ^b				
1 g q8h	96	90	59	84
2 g q8h	NT	NT	69	89
Cefepime ^b				
1 g q12h	100	99	50	82
2 g q12h	NT	NT	67	93
Piperacillin/tazobactam ^b				
3.375 g q6h	95	89	56	70
3.375 g q4h	NT	NT	65	85
Ciprofloxacin ^c				
400 mg q12h	85	80	41	53
400 mg q8h ^c	NT	NT	46	59

NOTE. Data are from the Optimizing Pharmacodynamic Target Attainment using MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) Antibiogram Program, evaluating nosocomial pathogens of concern in North America. AB, *Acinetobacter baumannii*; EC, *Escherichia coli*; KP, *Klebsiella pneumoniae*; NT, not tested; PA, *Pseudomonas aeruginosa*; q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h. Adapted from [37], with permission from the American Society for Microbiology.

^a Bactericidal target assessed as free-drug concentration greater than the MIC for $\geq 40\%$ of the dosing interval.

^b Bactericidal target assessed as free-drug concentration greater than the MIC for $\geq 50\%$ of the dosing interval.

^c Bactericidal target assessed as total free-drug area under the concentration-time curve/MIC ratio of ≥ 125 .

fepime regimens had high probabilities of target attainment against these pathogens in southern and northern Europe. In comparison, probabilities and susceptibility levels were lower for all regimens against *A. baumannii* and *P. aeruginosa*, regardless of geographic region. The highest probabilities of target attainment against these pathogens were observed with the meropenem and imipenem regimens in northern Europe (range, 81%–95%) [38].

In South America (Brazil, Colombia, Peru, and Venezuela), the regimens assessed were meropenem or imipenem at 1 g every 8 h, ceftazidime at 1 or 2 g every 8 h, cefepime at 1 or 2 g every 12 h, piperacillin/tazobactam at 4.5 g every 8 h, and ciprofloxacin at 400 mg every 8 or 12 h. Results showed that the optimal choices for the treatment of nosocomial infections caused by all pathogens studied except *P. aeruginosa* were the meropenem and imipenem regimens, although they had much higher probabilities of target attainment against *E. coli* and *K. pneumoniae* (range, 98%–100%) than against *A. baumannii* (73%). Target attainment against *P. aeruginosa* was similar for the carbapenem regimens, cefepime at 2 g every 12 h, and ceftazidime at 2 g every 8 h (range, 60%–65%) [39]. In each of the 3 OPTAMA Program studies just described, the probability of target attainment did not always agree with the percent

susceptibility values, suggesting that over- or underestimation of clinical effectiveness may occur when relying on susceptibility rates for dosing decisions [37–39].

Another OPTAMA Program study evaluated the probabilities of success with meropenem and cefotaxime regimens against specific pathogens responsible for pediatric meningitis. This analysis used a 5000-subject Monte Carlo simulation for adolescents with meningitis who were 10 years of age. MIC data for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* were obtained from clinical trials for the treatment of pediatric meningitis; %T > MIC in CSF was determined for each agent (concentration in CSF was based on an average simulated CSF penetration of unbound drug of 13%). Results were expressed in terms of the cumulative fraction of response (CFR), which is the likelihood of target attainment against a population of bacteria. The meropenem regimen achieved a significantly higher CFR (range, 94.3%–96.1%) than did the cefotaxime regimen (range, 84.3%–91.6%) against each population of bacteria. Only meropenem had a CFR >90% against *S. pneumoniae* and *H. influenzae*. These findings suggest that meropenem has advantages over cefotaxime for the treatment of pediatric meningitis [40].

The Monte Carlo approach used in the OPTAMA Program studies also has utility in determining empirical therapy for specific disease states. When the pathogen responsible is unknown, MIC data for antibiotics used against likely causative pathogens, which are weighted by their prevalence in causing a specific infection, can be used to establish an MIC distribution against which various regimens can be evaluated via pharmacodynamic modeling. Application of this method has identified antibiotic regimens with optimal drug exposure for the treatment of skin and soft-tissue infections [41], secondary peritonitis [42], nosocomial bloodstream infections [43], and nosocomial pneumonia [44].

Although this methodology is valuable in determining regimens with a high probability of success, additional studies are needed to confirm that the ability to achieve a defined exposure is correlated with a clinical response (CR) or a microbiological response (MR). Whether CFR data obtained from pharmacokinetic/pharmacodynamic modeling could predict the CR and MR obtained with treatment was investigated among patients with complicated skin and skin-structure infections. A 1000-subject Monte Carlo simulation and available MIC and pharmacokinetic data from 96 patients given 500 mg of meropenem every 8 h were used to predict the probability of pharmacodynamic target attainment for bactericidal and bacteriostatic responses. The best agreement between prediction and response was between the probability of pharmacodynamic target attainment for bactericidal response and CR. Accordingly, the bactericidal CFR (92%) did not differ statistically from the CR (91.9%). Use of the bacteriostatic CFR slightly overesti-

mated the CR and MR, whereas use of the bactericidal CFR slightly overestimated the MR. Nonetheless, these results demonstrate the accuracy of the Monte Carlo simulation in predicting the CR to meropenem in patients with complicated skin and skin-structure infections [45]. In patients with febrile neutropenia and bacteremia, patient pharmacokinetic data, MIC₅₀ data from product literature, and the nonparametric expectation maximization modeling program were used to predict the probability of pharmacodynamic target attainment for 500 mg of meropenem administered every 6 h. Associations with clinical outcome were determined. The findings suggested that the pharmacodynamic target that translated into the best CR (80%) was a %T > MIC of at least 76% [46]. In patients receiving meropenem for lower respiratory tract infections, the best predictor of CR and MR was a C_{min}/MIC ratio >5; a %T > MIC of 54% and a C_{max}/MIC ratio >383 also were found to be significant predictors of MR [47].

OPTIMIZING ANTIBIOTIC DOSING REGIMENS ON THE BASIS OF PHARMACODYNAMIC PROPERTIES

Pharmacodynamic modeling also can be used to determine dosage modifications to improve bactericidal exposure. Alternative meropenem dosing regimens were explored with a population pharmacokinetic model developed by using data from clinical trials involving patients with intra-abdominal infections, community-acquired pneumonia, or ventilator-associated pneumonia and the NONMEM program. Results showed that, at an MIC of 4 µg/mL (susceptibility breakpoint for Enterobacteriaceae, *Acinetobacter* species, and *P. aeruginosa*), prolonging infusion time from 30 min to 3 h for 1 g of meropenem increased the probability of bactericidal target attainment (40%T > MIC) from 64% to 90% (figure 2) [48]. Monte Carlo simulation of the effects of other doses of meropenem administered as a 3-h infusion, compared with the standard 30-min infusion, showed that prolonged infusion increased the probability of conservative bactericidal target attainment (50%T > MIC) for *Acinetobacter* species and *P. aeruginosa*. For those pathogens, the highest target-attainment rates were obtained with a 3-h infusion of 2 g of meropenem every 8 h. For infections caused by *Enterobacter cloacae*, prolonging the infusion time allowed for the use of a lower total daily dose of meropenem (i.e., 500 mg every 8 h or 1 g every 12 h vs. 1 g every 8 h) [49]. In another study, a 3-h infusion of 1 g of meropenem every 8 h resulted in a higher probability of target attainment against *Acinetobacter* species and *P. aeruginosa*, compared with a 1-h infusion of 500 mg of imipenem every 6 h. In addition, a 3-h infusion of 500 mg of meropenem every 8 h achieved probabilities of bactericidal target attainment against *S. aureus* and *Klebsiella*, *Enterobacter*, and *Serratia* species similar to those

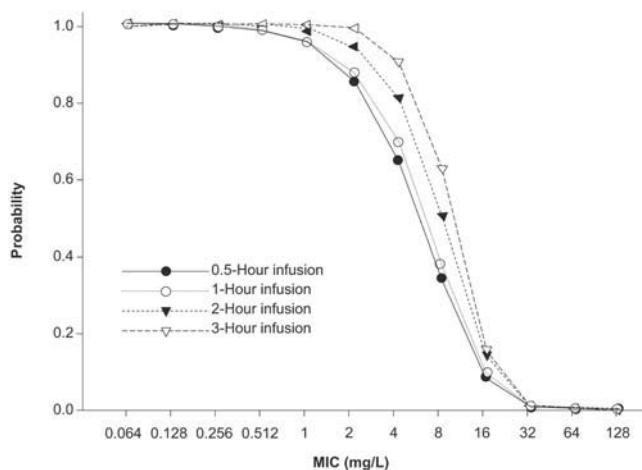


Figure 2. Probability of achieving the bactericidal target (free-drug concentration higher than the MIC for 40% of the dosing interval) at specific MICs, after administration of 1 g of meropenem every 8 h with infusion times of 0.5, 1, 2, and 3 h. Reprinted from [48], with permission from Sage Publications Inc.

reported for a 30-min infusion of 1 g of meropenem every 8 h [50].

The 3-h infusion schedule also was shown to provide benefits over bolus injection. In a single-dose study of healthy subjects, 3-h infusions of 1 g or 500 mg of meropenem achieved higher %T > MIC values (range, 47%–86%) for MICs of 1–4 mg/L than did a bolus injection of 1 g of meropenem (range, 43%–67%) [51]. In a 24-h assessment of patients with ventilator-associated pneumonia, results were similar, with a 3-h infusion of 1 or 2 g of meropenem every 8 h providing higher %T > MIC values than a bolus injection of 1 g of meropenem every 8 h [52]. However, dosing regimens using prolonged infusions of meropenem are not approved by any regulatory agency.

Monte Carlo simulation comparing low- and high-dose intermittent versus continuous infusion of meropenem in healthy subjects demonstrated that the probability of target attainment against *P. aeruginosa* was higher with continuous, versus intermittent, infusion and with high-dose, versus low-dose, continuous infusion. Against *K. pneumoniae* and *E. cloacae*, probabilities were similar with both types of dosing and both infusion schedules [53]. For critically ill patients, continuous infusion of meropenem was found to be equivalent to intermittent infusion, with a %T > MIC of 100% for common bacterial pathogens with both types of infusion [54].

The probability of pharmacodynamic target attainment also was used to determine an appropriate meropenem dosing regimen for patients receiving CVV hemofiltration. Pharmacokinetic data used for modeling were from literature reports of patients undergoing similar procedures, and MIC data for *P. aeruginosa* and *Acinetobacter* species were from the MYSTIC Program database (2003). The regimens tested were 1 g every

8 or 12 h and 500 mg every 6, 8, or 12 h. At the susceptibility breakpoint (MIC of 4 µg/mL), 1 g every 8 h and 500 mg every 6 h achieved >99% target attainment. Higher peak concentrations obtained with the 1-g dose enabled improved target attainment against strains with higher MICs [25]. Thus, the standard dosing regimen provides adequate pathogen coverage for patients undergoing CVV hemofiltration. Finally, pharmacodynamic modeling to determine the probability of target attainment with carbapenems and fluoroquinolones against ESBL-producing bacteria revealed that only imipenem and meropenem had a >90% likelihood of target attainment (table 2) [55].

Recently, these strategies have begun to be applied to the determination of pharmacodynamic breakpoints that may prevent the development of antimicrobial resistance. By identification of a pharmacodynamic target related to the prevention of amplification of resistant clones, dosing regimens can be designed to provide levels of drug exposure that minimize the development of resistance [56]. This is an area of ongoing investigation. For meropenem, in vitro data from a hollow-fiber model of *P. aeruginosa* infection treated with various doses of meropenem suggest that the meropenem C_{min} /MIC ratio could be optimized to suppress the emergence of resistance [57].

SUMMARY

Pharmacodynamic profiling is valuable in the design of rational dosing strategies for antibiotics. Moreover, the application of pharmacodynamic modeling is a useful tool for identifying

Table 2. Probability of pharmacodynamic target attainment for bactericidal response for carbapenems and fluoroquinolones against bacteria that do or do not produce extended-spectrum β-lactamases (ESBLs).

Regimen	Target attainment, %	
	Non-ESBL producers	ESBL producers
Meropenem, 1 g q8h ^a	98	97
Imipenem, 500 mg q6h ^a	98	98
Ertapenem, 1 g q24h ^a	94	78
Levofloxacin ^b		
500 mg q24h	88	11
750 mg q24h	91	13
Gatifloxacin, 400 mg q24h ^b	85	8
Ciprofloxacin, 400 mg q12h ^b	88	2

NOTE. q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h. Adapted from Moczygmba LR, Frei CR, Burgess DS. Pharmacodynamic modeling of carbapenems and fluoroquinolones against bacteria that produce extended-spectrum beta-lactamases. Clin Ther 2004;26:1802, 1804 [55], with permission from Excerpta Medica, Inc.

^a Bactericidal target assessed as free-drug concentration greater than the MIC for ≥40% of the dosing interval.

^b Bactericidal target assessed as total free-drug area under the concentration-time curve/MIC ratio of ≥125.

antibiotic regimens with the highest probability of achieving the desired pharmacodynamic targets for specific pathogens and for determining empirical therapy for the infected patient. In addition, modeling can be used to assess dosage modifications in order to improve bactericidal exposure and to delineate pharmacodynamic breakpoints that prevent the development of resistance. The broad-spectrum antibiotic meropenem shows a high probability of attaining its bactericidal and bacteriostatic pharmacodynamic targets in numerous applications, with standard dosing regimens. Clinical research and continued medical surveillance are necessary to demonstrate that these models support clinical outcomes. Finally, investigations of alternative dosing schedules to maximize drug exposure and to minimize the development of resistance are ongoing.

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