Clinical Pharmacodynamics of Meropenem in Patients with Lower Respiratory Tract Infections[▽]

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Studies of β -lactam pharmacodynamics in infected patients are sparse. In this study, classification and regression tree (CART) and logistic regression analyses were used to identify which pharmacodynamic indices and magnitudes were significant predictors of meropenem efficacy for 101 adult patients with lower respiratory tract infections (LRTI). Using demographic data, a validated population pharmacokinetic model was employed to predict pharmacokinetic parameters and free serum concentrations in the studied patients. Pharmacodynamic indices [percentage of the dosing interval that free drug concentrations remain above the MIC ($\% fT > MIC$), f (maximum concentration of drug in serum) (fC_{max})/MIC, fC_{min} /MIC, and f (area under the concentration-time curve) ($fAUC$)/MIC] were calculated based on the baseline pathogen with the highest drug MIC for each patient. The median (range) of percent $fT > MIC$, fC_{max} /MIC, fC_{min} /MIC, and $fAUC$ /MIC were 100% (0 to 100%), 728.8 (0.8 to 15,777), 19.9 (0.01 to 278), and 3,605.4 (2.7 to 60,865.9), respectively. CART identified the following breakpoints as significant predictors for microbiological response: $>54\% fT > MIC$, a $fC_{max}/MIC > 383$, and a $fC_{min}/MIC > 5$; $fC_{min}/MIC > 5$ was the only significant predictor of clinical response. Due to 100% $fT > MIC$ achieved in the majority of LRTI patients, fC_{min}/MIC was the statistically significant parameter associated with meropenem clinical and microbiological response in the adults with LRTI. The findings for LRTI patients can be applied to optimize meropenem dose regimens to achieve clinical success and microbiological eradication in clinical practice.

Meropenem, a carbapenem antimicrobial agent, has potent in vitro activity against gram-positive and gram-negative pathogenic bacteria (7, 11). As a result, meropenem has been investigated in numerous clinical trials to treat intra-abdominal infections, febrile neutropenia, meningitis, lower respiratory tract infections, urinary tract infections, skin and skin structure infections, etc. (20). Like other β -lactams, meropenem demonstrates time-dependent bactericidal activity against gram-positive and -negative bacteria in animal studies (5, 19). Consequently, the percentage of the dosing interval that free drug concentrations remain above the MIC ($\% fT > MIC$) is the most important parameter for predicting meropenem antibacterial efficacy. This pharmacodynamic parameter has also been linked to clinical cure in patients treated with meropenem (2, 9).

The majority of data regarding meropenem pharmacodynamics, as well as other β -lactams, were derived from in vitro or in vivo animal models of infection (18, 19). Due to the difficulty of simultaneously collecting data on meropenem concentrations for a large number of homogenous patients who have had pathogens isolated and the difficulty of combining those data with MIC results, there is a lack of published studies available to explore the correlation of β -lactam pharmacokinetics and pharmacodynamics with successful response. In the absence of concentration data, population pharmacokinetic models can be employed to estimate exposures for clinically evaluable patients whose bacterial infections have been iden-

tified and whose MIC data have been collected (1, 2, 6). Using this approach, meropenem data are available only from adult patients with neutropenic fever and pediatric patients with meningitis; the data available for the latter group could not identify a pharmacodynamic relationship due to small numbers of patients and a 100% eradication rate (2, 6). The objective of this study was to utilize demographic data and a population pharmacokinetic model to predict meropenem exposure to pathogens isolated from patients with lower respiratory tract infections (LRTI) and characterize the relationship of pharmacodynamic indices to clinical and microbiological response.

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MATERIALS AND METHODS

Patients. This analysis was approved by the institutional review board at Hartford Hospital (Hartford, CT). Patients recruited into four previously conducted multicenter, randomized, open-label clinical trials were used to generate the population for the present pharmacodynamic analysis. These included trial 194660/0200, which was an unpublished study of patients with community-acquired LRTI, trial 194660/0401, an unpublished study of patients with severe nosocomial infections, trial 194660/0402, which included hospitalized patients with severe bacterial infections (3), and trial 3591US/0008, a study of patients with hospital-acquired LRTI (15). All four studies used similar enrollment criteria with respect to previous antibiotic exposure, and all used standard definitions for LRTI. Data for adult patients (>17 years of age) with a diagnosis of LRTI, including pneumonia, bronchitis, or other severe LRTI, were extracted. In these clinical trials, patients received meropenem (500 mg or 1 g) as a 0.5-h infusion every 8 or 12 h, depending on renal function status. Patients who had baseline pathogens identified and had meropenem MICs available were eligible for the pharmacodynamic analysis. For the purpose of predicting individual pharmacokinetic profiles, only patients with available covariate data (i.e., body weight, age, and creatinine clearance) were included.

Clinical and microbiological response. All clinical trials used the same definitions for clinical and microbiological response at the end of treatment. Clinical

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TABLE 1. Demographic characteristics and outcomes of the studied 101 adult patients with LRTI

Characteristic	No. (%), unless otherwise specified
Gender	
Male	63 (62%)
Female	38 (38%)
Race	
Black	6 (6%)
Caucasian	80 (79%)
Hispanic	3 (3%)
Other	12 (12%)
Age, yr [median (range)]	67 (29–98)
Body weight, kg [median (range)]	70.2 (42.7–105)
Creatinine clearance, ml/min [median (range)]	65.3 (14–150)
Serum creatinine, mg/dl [median (range)]	1.1 (0.5–6.7)
Infection type	
Pneumonia	89 (88.1%)
Bronchitis	11 (10.9%)
Other LRTI	1 (0.99%)
Common pathogens ^a	
<i>Streptococcus pneumoniae</i>	27 (26.7%)
<i>Staphylococcus aureus</i>	14 (13.9%)
<i>Haemophilus influenzae</i>	11 (10.9%)
<i>Klebsiella pneumoniae</i>	9 (8.9%)
<i>Escherichia coli</i>	8 (7.9%)
<i>Pseudomonas aeruginosa</i>	7 (6.9%)
Clinical success	89 (88.1%)
Microbiological success ^b	82 (86.3%)

^a Most common bacteria isolated; defined according to the pathogen with the highest meropenem MIC.

^b Ninety-five of the 101 patients were microbiologically evaluable.

response was categorized as either clinical success or failure, with success defined as cure or improvement of all signs and symptoms caused by the infection and no additional antibiotic therapy required. Clinical failure was defined as a persistent or worsening condition for any one of the clinical symptoms, new clinical signs and symptoms of infection, or the requirement for other systemic antimicrobial therapy at the end of meropenem therapy. Microbiological response was graded as representing success (including eradication and presumed eradication) or failure (including persistence and presumed persistence).

Derivation of pharmacodynamic indices. Meropenem pharmacokinetic parameters for each individual patient were estimated based on a validated covariate population pharmacokinetic model derived from studies of adult patients (10). Briefly, data from 79 infected patients with pneumonia or intra-abdominal infections were included to develop a meropenem population pharmacokinetic model. Population pharmacokinetic analysis was performed using the NONMEM program (version V, level 1.1, double precision). A two-compartment model was selected as the pharmacokinetic structural model; in this approach, exponential error models were used to characterize interindividual variabilities and a combination error model was used to characterize the residual error. The following pharmacokinetic parameters were used to characterize the two-compartment model: clearance (CL), intercompartmental clearance (Q), central volume of distribution (V_c), and peripheral volume of distribution (V_p). Creatinine clearance (CL_{cr} [in milliliters per minute]), age (AGE [in years]), and body weight (WT [in kilograms]) were the most significant covariates to affect meropenem pharmacokinetics. The final model was calculated using first-order conditional maximum likelihood estimation methods and are summarized as follows: CL (in liters per hour) = $14.6 \times (\text{CL}_{\text{cr}}/83)^{0.62} \times (\text{AGE}/35)^{(-0.34)}$, V_c (in liters) =

$10.8 \times (\text{WT}/70)^{0.99}$, Q (in liters per hour) = 18.6, and V_p (in liters) = 12.6. This population pharmacokinetic model was validated using the bootstrap (1,000 replicates) procedure via the program Wings for NONMEM (version 408b; N. Holford, Auckland, New Zealand), as recommended by the Food and Drug Administration (8). All estimates of population pharmacokinetic parameters were in the range of the 95% confidence interval (CI) of mean population estimates obtained from the bootstrap procedure, indicating that the final model was fairly robust.

Patient covariates were utilized to estimate pharmacokinetic parameters for the LRTI patients, which were then applied to simulate steady-state concentration-time profiles for each patient based on the dose received during the trial (WinNonlin, version 3.3; Pharsight Corp., Mountain View, CA). All drug concentrations were corrected for protein binding based on the assumption that 92% of meropenem was unbound (4). The drug MIC for the isolated pathogen was integrated with free drug exposure data to calculate the following pharmacodynamic indices: percent $fT > \text{MIC}$, the ratio of maximum free drug concentration to MIC ($fC_{\text{max}}/\text{MIC}$), the ratio of minimum free drug concentration to MIC ($fC_{\text{min}}/\text{MIC}$), and the ratio of the free drug area under the concentration curve to MIC ($fAUC/\text{MIC}$). For patients with polymicrobial infections, the organism with the highest meropenem MIC was used to calculate the pharmacodynamic indices.

Statistical analysis. Recursive partitioning was conducted using Classification and Regression Tree (CART) analysis (version 5.0; Salford Systems, San Diego, CA) to identify partitioning breakpoints for each of the pharmacodynamic indices on the basis of (i) clinical and (ii) microbiological response. The robustness of the classification tree was tested using 10-fold cross-validation in which all data were divided into 10 equal parts and the last part of the data acted as the “validation” sample. Statistical significance of the identified breakpoints was validated by Fisher’s exact test. Logistic regression was conducted to further corroborate CART-identified breakpoints as predictors for clinical and microbiological response. During regression analyses, pharmacodynamic indices were reclassified as binary variables (i.e., values greater than the breakpoint or less than or equal to the breakpoint) as well as being treated as continuous variables (both normal and log transformed). Stepwise backward multivariable regression was performed using all pharmacodynamic indices as well as patient characteristics (age, gender, weight, renal function, causative pathogen, and meropenem MIC) to identify significant predictors of clinical and microbiological response. Causative pathogens were analyzed independently by species and additionally when grouped as gram positive versus gram negative. During regression, a probability model designed to predict clinical and microbiological responses over a range of exposures was built based on each patient’s pharmacodynamic indices. All statistical analyses were conducted using SAS software (version 9.1; SAS Institute, Cary, NC). A P value less than or equal to 0.05 was considered statistically significant.

RESULTS

Patient characteristics and clinical-microbiological response. Of the eligible patients from the clinical trials, a total of 101 LRTI patients were evaluable for clinical and/or microbiological outcome and had the covariate data required to estimate pharmacokinetic parameters. A detailed summary of patient characteristics and outcomes is presented in Table 1. Thirty-nine patients were included from trial 194660/0200 and thus had community-acquired pneumonia or bronchitic infections. The remainder of the patients (15 from trial 194660/0401, 11 from trial 194660/0402, and 36 from trial 3591US/0008) had nosocomial pneumonia. The overall clinical and microbiological success rates were 88.1% and 86.3% for these

TABLE 2. Pharmacokinetic and pharmacodynamic statistics of 101 adult patients receiving meropenem for a LRTI

Statistic	fC_{max} (μg/ml)	fC_{min} (μg/ml)	$fAUC$ (μg · h/ml)	% $fT > \text{MIC}$	$fC_{\text{max}}/\text{MIC}$	$fC_{\text{min}}/\text{MIC}$	$fAUC/\text{MIC}$
Median	27.3	0.62	131.7	100	728.8	19.9	3605.4
Range	18.9–62.3	0.05–3.67	66.5–348.1	0–100	0.8–15,777.1	0.01–278.0	2.7–60,865.9
Mean	32.27	0.91	157.43	91.0	1,427.66	34.24	6,683.38
SD	11.38	0.77	67.95	23.9	2,125.83	50.51	9,225.04

evaluable LRTI patients. Of the patients with bronchitis who were clinically and microbiology evaluable, 9 of 11 had a positive clinical response and 8 of 9 had a positive microbiological response, respectively. Of the evaluable patients with pneumonia, 79 of 89 and 73 of 85 experienced a positive clinical and microbiological response, respectively. Most patients were infected with *Streptococcus pneumoniae*, methicillin-susceptible *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*. These bacteria accounted for 75% of infections. The median (range) of meropenem MICs for these pathogens was 0.06 (0.002 to 64) mg/liter. Microbiological responses among the infections caused by gram-positive and gram-negative bacteria were 44 of 49 (90%) and 40 of 46 (87%), respectively.

Pharmacodynamic measurements. The summary of estimated steady-state pharmacokinetics and drug exposure is listed in Table 2. Due to the range of MICs, $fC_{\min}/\text{MIC}$, $fC_{\max}/\text{MIC}$, and $f\text{AUC}/\text{MIC}$ varied widely from 0.01 to 278, 0.8 to 15,777, and 2.7 to 60,865, respectively. However, 82% of the patients achieved 100% $fT > \text{MIC}$. Moreover, plateaus at 100% $fT > \text{MIC}$ were observed in the plots of $fT > \text{MIC}$ versus $fC_{\max}/\text{MIC}$, $fC_{\min}/\text{MIC}$, and $f\text{AUC}/\text{MIC}$ (Fig. 1), indicating that the values of percent $fT > \text{MIC}$ for these studied patients were not evenly distributed over the range of 0 to 100%. Despite this, a range of exposures for the pharmacodynamic indices was observed among patients when the results were divided by response (Fig. 2).

Breakpoint determination. The breakpoints partitioning success or failure for both clinical and microbiological response are included in Table 3. For clinical response, only an $fC_{\min}/\text{MIC}$ ratio > 5 ($P = 0.048$) was found to be a statistically significant predictor of clinical success. Breakpoints for the other pharmacodynamic indices were calculated by CART, but these were not found to be statistically significant. For microbiological response, $fC_{\min}/\text{MIC} > 5$ ($P = 0.022$), $fC_{\max}/\text{MIC} > 383$ ($P = 0.029$), and $> 54\% fT > \text{MIC}$ ($P = 0.05$) were found to be significant predictors of microbiological success; $f\text{AUC}/\text{MIC}$ was not statistically significant. The significance of these CART-defined breakpoints was confirmed in univariate logistic regression analyses (Table 3). In multivariate logistic regression (including patient characteristics), only an $fC_{\min}/\text{MIC}$ ratio > 5 was predictive of clinical and microbiological response. Continuous variables for pharmacodynamic indices, including log-transformed variables, were not significant. Additionally, there was no statistical significant connection between clinical-microbiological responses and patient covariates (e.g., weight, age, gender, creatinine clearance, bronchitis versus pneumonia diagnosis, causative pathogens, and meropenem MICs).

Probability of clinical-microbiological success. For these LRTI patients, Fig. 3 shows the predicted probability curve of microbiological outcome based on percent $fT > \text{MIC}$, $fC_{\min}/\text{MIC}$, $fC_{\max}/\text{MIC}$, and $f\text{AUC}/\text{MIC}$ derived from the logistic regression model.

DISCUSSION

Pharmacodynamic studies of humans are needed to determine whether exposure targets determined for β -lactams from in vitro and in vivo animal infection models predict clinical and

FIG. 1. The percentage of free time above MIC (% $fT > \text{MIC}$) versus the ratio of free meropenem maximum concentration to MIC ($fC_{\max}/\text{MIC}$) (A), the ratio of free meropenem minimum concentration to MIC ($fC_{\min}/\text{MIC}$) (B), and the ratio of free meropenem AUC over MIC ($f\text{AUC}/\text{MIC}$) (C) for 101 patients with LRTI.

FIG. 2. Scatter plots of individual patient microbiological responses (0 = failure, 1 = success) versus achieved % $fT > MIC$ (A), fC_{max}/MIC (B), fC_{min}/MIC (C), and $fAUC/MIC$ (D).

TABLE 3. Results from CART and univariate logistic regression analyses to determine which pharmacodynamic indices significantly predicted clinical and microbiological response and the associated breakpoint for predicted success

Response category and parameter	CART analysis result			Logistic regression	
	% Breakpoint ^a	% Response rate (above, below)	P	Odds ratio (95% CI)	P
Clinical					
% $fT > MIC$	24	87.4, 100	1.0	1.0 (0.001–2.83)	0.970
fC_{max}/MIC	302	92.3, 80.6	0.109	2.90 (0.85–10.54)	0.090
fC_{min}/MIC	5	92.8, 78.1	0.048	3.58 (1.05–13.13)	0.043
$fAUC/MIC$	1,189	92.5, 79.4	0.099	3.22 (0.94–11.04)	0.064
Microbiological					
% $fT > MIC$	54	88.6, 57.1	0.05	5.85 (1.14–30.03)	0.034
fC_{max}/MIC	383	93.1, 75.7	0.029	4.34 (1.23–15.34)	0.023
fC_{min}/MIC	5	92.3, 73.3	0.022	4.36 (1.32–15.82)	0.018
$fAUC/MIC$	6,355	96.8, 81.3	0.054	6.92 (0.86–55.9)	0.070

^a Percentages of error for misclassification of clinical success during CART were 70.8%, 44.9%, 28.1%, and 28.1% for percent $fT > MIC$, fC_{max}/MIC , fC_{min}/MIC , and $fAUC/MIC$ breakpoints, respectively. Percentages of error for misclassification of microbiological success during CART were 8.5%, 46.3%, 61.0%, and 57.3% for % $fT > MIC$, fC_{max}/MIC , fC_{min}/MIC , and $fAUC/MIC$ breakpoints, respectively.

microbiological responses. In the present study, a population pharmacokinetic model was used to estimate meropenem pharmacokinetic parameters for patients receiving meropenem therapy to treat lower respiratory tract infections in order to predict achieved exposure and impact on clinical and microbiological response. For the 101 patients in this study, an fC_{min}/MIC ratio > 5 was found to be the most significant predictor of successful clinical and microbiological responses. Furthermore, 54% $fT > MIC$ and an $fC_{max}/MIC > 383$ were also found to be significant predictors of microbiological response in univariate analyses.

Unlike studies of fluoroquinolones, where human pharmacodynamic target data appear to agree largely with that from in vitro and in vivo animal infection models (1, 14), the pharmacodynamic target predicting success for meropenem was somewhat different in this analysis. Early murine infection experiments identified time above the MIC as the parameter correlating with survival and decrease in bacterial counts; furthermore, approximately 40% $fT > MIC$ was defined as the maximum bactericidal exposure (5, 19). In the current analysis, while 54% $fT > MIC$ was found to be a predictor of at least

FIG. 3. The estimated probability of microbiological eradication curve (solid line) with bounding 95% CIs (dashed lines) for % fT > MIC (A), $fC_{\max}/MIC$ (B), $fC_{\min}/MIC$ (C), and $fAUC/MIC$ (D) for these LRTI patients. Corresponding *P* values of the maximum likelihood ratio test were 0.11, 0.10, 0.13, and 0.10, respectively.

microbiological response, $fC_{\min}/MIC$ provided the most significant prediction for both clinical and microbiological success. We speculate that this finding stemmed from the nature of the pharmacodynamic indices and their colinearity for these 101 patients (Fig. 1). Of the population studied, only 14 patients were infected by causative pathogens for which the meropenem MIC was larger than 1 $\mu\text{g}/\text{ml}$. As a result, 100% fT > MIC was achieved in 82% of the patients, and the power of sample size was dramatically lost while evaluating the significance of this pharmacodynamic parameter with respect to outcome. In addition, 100% fT > MIC was achieved in 11 of 17 clinical and/or microbiological failures due to low creatinine clearance and low MICs. Nevertheless, bacterial eradication occurred in 88.6% of these patients when the fT > MIC was above 54%, which is compatible with pharmacodynamic targets derived from animal infection models (5). These observations are also similar to those of a study evaluating meropenem exposure with clinical cure of febrile neutropenic patients, where Ariano and colleagues documented a clinical response rate of 80% when total drug concentrations exceeded the MIC for 75% of the dosing interval (2).

In this population of LRTI patients, greater than 90% achieved clinical and microbiological success when the meropenem $fC_{\min}/MIC$ was greater than 5. To some extent, this finding supports results from previously published in vitro and in vivo studies of β -lactams in general; i.e., the bactericidal activity of β -lactams can be maximized when drug concentrations are maintained at four to six times the MIC throughout the dosing interval (12, 13, 16). Specifically, Tam and colleagues found that microbiological success was significantly correlated with the proportion of the dosing interval that cefepime concentrations exceeded $4.3 \times$ the MIC for gram-negative infections in 20 patients (16). Moreover, the results of an in vitro study demonstrated that resistance emergence could be suppressed in *P. aeruginosa* when the meropenem $fC_{\min}/MIC$ was larger than 6.2 (17). While our objective was not to determine a parameter that would predict suppression of resistance, these data taken together suggest that the values for β -lactam pharmacodynamic targets may be greater than otherwise predicted by in vitro and animal infection studies. Further in vivo study is needed to confirm this observation.

There are several limitations to our study. First, although we

began with data from four separate randomized clinical trials and over 800 patients receiving meropenem, we only identified 101 subjects who met inclusion criteria for this analysis; therefore, the number of events (i.e., failures at specific exposures) in this analysis became small. This was the most likely explanation for our having observed a more powerful relationship between $fC_{\min}/\text{MIC}$ and outcome instead of time above the MIC and is also the likely reason for the relatively high response rates predicted by our model, even in the absence of drug exposure (Fig. 3). This reiterates the difficulty in performing such studies and exemplifies the utility of covariate population models. Secondly, no actual patient concentration data were present for this cohort. As such, a population pharmacokinetic model based on patient demographics and renal function was utilized to estimate individual pharmacokinetic parameters and predict exposure. While this model could not be validated for this specific population of patients with LRTI, the demographics and infections in this current study were actually very similar to those of the patients used to develop the original model, including the ranges of body weight, age, serum creatinine levels, creatinine clearance, and diseases (10). In this case, it was suitable to extrapolate the validated model to another similar patient population for the purposes of predicting meropenem exposure without blood sampling. Nevertheless, future antibiotic clinical trials should require sparse blood sampling in all participants for the purposes of applying population models and conducting pharmacodynamic analyses. Lastly, we were limited by the number of independent variables provided in the database, which restricted our ability to control for other important variables (e.g., severity of illness, comorbidities, intensive care unit stay, etc.) in the multivariable model.

In summary, this pharmacodynamic analysis demonstrates a relationship between free drug exposure to meropenem and clinical and microbiological response in this population of patients with lower respiratory tract infections. $fC_{\min}/\text{MIC}$ was the most significant pharmacodynamic index to predict clinical and microbiological efficacy.

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