Population Pharmacokinetics of Doripenem Based on Data from Phase 1 Studies with Healthy Volunteers and Phase 2 and 3 Studies with Critically Ill Patients^{∇†}

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A population pharmacokinetic model of doripenem was constructed using data pooled from phase 1, 2, and 3 studies utilizing nonlinear mixed effects modeling. A 2-compartment model with zero-order input and first-order elimination best described the log-transformed concentration-versus-time profile of doripenem. The model was parameterized in terms of total clearance (CL), central volume of distribution (V_c), peripheral volume of distribution (V_p), and distribution clearance between the central and peripheral compartments (Q). The final model was described by the following equations (for j th subject): CL_j (liters/h) = $13.6 \cdot (CL_{CRj}/98 \text{ ml/min})^{0.659} \cdot (1 + CL_{racej} [0 \text{ for Caucasian}])$; V_{cj} (liters) = $11.6 \cdot (\text{weight}_j/73 \text{ kg})^{0.596}$; Q_j (liters/h) = $4.74 \cdot (\text{weight}_j/73)^{1.06}$; and V_{pj} (liters) = $6.04 \cdot (CL_{CRj}/98 \text{ ml/min})^{0.417} \cdot (\text{weight}_j/73 \text{ kg})^{0.840} \cdot (\text{age}_j/40 \text{ years})^{0.307}$. According to the final model, population mean parameter estimates and interindividual variability (percent coefficient of variation [% CV]) for CL (liters/h), V_c (liters), V_p (liters), and Q (liters/h) were 13.6 (19%), 11.6 (19%), 6.0 (25%), and 4.7 (42%), respectively. Residual variability, estimated using three separate additive residual error models, was 0.17 standard deviation (SD), 0.55 SD, and 0.92 SD for phase 1, 2, and 3 data, respectively. Creatinine clearance was the most significant predictor of doripenem clearance. Mean Bayesian clearance was approximately 33%, 55%, and 76% lower for individuals with mild, moderate, or severe renal impairment, respectively, than for those with normal renal function. The population pharmacokinetic model based on healthy volunteer data and patient data informs us of doripenem disposition in a more general population as well as of the important measurable intrinsic and extrinsic factors that significantly influence interindividual pharmacokinetic differences.

Doripenem is a parenteral carbapenem with *in vitro* microbiological activity against a broad spectrum of clinically important Gram-positive and Gram-negative pathogens (9, 14, 23). It is approved for complicated intra-abdominal and complicated urinary tract infections (UTI) in the United States and in Europe, where it is also approved for nosocomial pneumonia (15). All carbapenems (except for ertapenem) have very similar pharmacokinetics, including half-life (1 h), protein binding (2 to 20%), distribution properties (0.23 to 0.35 liters/kg of body weight), and temporal plasma profiles (3, 29).

The value of dose individualization based on pharmacokinetic principles was recognized early in doripenem's development and was integral to its clinical development. Using doripenem dosing regimens intended for clinical use, Bhavnani et al. developed a population pharmacokinetic model from limited intensively sampled data from a phase 1 study of 24 healthy volunteers with normal renal function (3). Simulation results based on this model predicted that 500 mg of doripenem infused over 1 h, administered every 8 h, would be

effective against bacterial strains with MICs up to 2 $\mu\text{g/ml}$ and that less susceptible strains could be treated with a more prolonged infusion. Subsequently, Ambrose et al. incorporated data from an additional phase 1 study of subjects with various degrees of renal impairment into the population pharmacokinetic model to refine dose regimen forecasts (1). More recent analyses by the same research group, which included phase 2 data, formed the basis for doripenem dosing during phase 3 studies (27). A logical next step in dose optimization is refinement of the population pharmacokinetic model after phase 2 and 3 patient pharmacokinetic data have become available.

This report describes population pharmacokinetics of doripenem based on a comprehensive model incorporating all currently available phase 1, 2, and 3 data and all significant covariate effects. Initially, a (original) population pharmacokinetics model was developed using data collected from healthy subjects and patients (from phase 2 studies) with complicated UTI or pyelonephritis. This model was then used to evaluate the pharmacokinetics of doripenem in a cohort of patients with nosocomial pneumonia. Pharmacokinetic parameters were then reestimated using doripenem concentration data pooled from phase 1, 2, and 3 studies. Finally, the relationships between key covariates and pharmacokinetic parameters that explain interindividual variability in doripenem pharmacokinetics were confirmed. The objective of this work was not only to provide a better understanding of doripenem disposition in a more general population but also

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to assess important measurable factors that significantly influence interindividual pharmacokinetic differences that affect drug exposure.

MATERIALS AND METHODS

Study design. The studies of doripenem, as described in this report, were performed in compliance with the standards of the Institutional Review Board, Independent Ethics Committee, and the Code of Federal Regulations and the principles of the Declaration of Helsinki and its amendments.

The phase 1 studies included one trial of subjects with renal impairment who received a single 500-mg dose of doripenem infused over 30 min and five trials of healthy subjects who received multiple doses of doripenem for up to 10 days. Across these five studies, doripenem was administered as a 500-mg intravenous (i.v.) infusion over 30 to 60 min, administered every 8 to 12 h; a 500-mg i.v. infusion over 4 h, administered every 8 h; a 1,000-mg i.v. infusion over 60 min, administered every 8 to 12 h; a 1,000-mg i.v. infusion over 6 h, administered every 12 h; and a 1,000-mg i.v. infusion over 4 h, administered every 8 h. In the phase 2 study of patients with complicated UTI or pyelonephritis, doripenem at 250 to 500 mg was infused over 60 min every 8 h. In the two phase 3 studies of patients with nosocomial pneumonia, doripenem at 500 mg was infused over either 1 or 4 h every 8 h.

Pharmacokinetic methods. Blood samples for the determination of doripenem concentrations were scheduled to be collected predose and at multiple time points during and following the completion of doripenem infusion in the phase 1 studies. In the phase 2 study, blood samples were to be collected on days 1 and 7 at predose, at the end of infusion, and at 1, 2, 4, and 6 h after the end of infusion. In the phase 3 studies, pharmacokinetic sampling was to be performed on day 2, or alternatively on day 3, with samples collected immediately prior to infusion and at 5 to 6 time points over the 8-hour dosing interval.

Covariates. The patient covariates evaluated in the original model analyses included sex, race/ethnicity (i.e., white, black, Hispanic/Latino, Asian, Native Hawaiian/other Pacific islander, other), age, body weight, height, lean body mass, body mass index (BMI), body surface area, health status (e.g., healthy subject, complicated UTI/pyelonephritis), and renal impairment status (normal [creatinine clearance (CL_{CR}) > 80 ml/min], mild [$50 \leq$ creatinine clearance ≤ 80 ml/min], moderate [$30 \leq$ creatinine clearance < 50 ml/min], or severe [$10 <$ creatinine clearance < 30 ml/min]). The laboratory indices evaluated included serum creatinine, estimated creatinine clearance (based on the Cockcroft-Gault formula [6]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total protein, gamma glutamyl transferase, and lactate dehydrogenase (LDH). Other covariates included study phase, treatment (according to dose, infusion duration, and dosing frequency), concomitant medications used in the phase 2 study (i.e., heparin, metamizole, ciprofloxacin, paracetamol, acetylsalicylic acid, metoclopramide, enalapril, metformin, and clonixin), and occasion number (1, 2, or 3, consistent with the sampling period).

Doripenem assay. Plasma samples were assayed for doripenem concentration by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay, with a lower limit of quantitation of 0.2 μ g/ml (5).

Population pharmacokinetics: stage 1 structural model development. Nonlinear mixed effects modeling of the pooled data from healthy subjects with various degrees of renal function and patients with complicated UTI/pyelonephritis was conducted using NONMEM version V, level 1.1 (2). Several structural models were tested using both untransformed and log-transformed data. A 2-compartment model with zero-order input and first-order elimination best described the concentration-versus-time profile of doripenem. The model was parameterized in terms of total clearance (CL), central volume of distribution (V_c), peripheral volume of distribution (V_p), and the distribution clearance between the central and peripheral compartments (Q). Interindividual variability for CL, V_c , and V_p was described using an exponential error model. Since the plasma concentrations of doripenem were log transformed, an additive error model was used to describe the residual variability. The final selection of the optimal model was based on goodness-of-fit criteria: the agreement between the observed and predicted doripenem concentrations; the pattern of weighted population and individual residuals compared to predicted population and individual concentrations, respectively, as well as compared to time since administration of the last dose; the distribution of the observed versus predicted concentrations across the identity line; smaller value of Akaike's information criterion (AIC) or reduction in minimum value of the objective function (MVOF); and decrease in the residual error variance.

Covariate analyses. Plots of Bayesian estimates of the pharmacokinetic parameters versus each covariate and individual weighted residuals were examined for observable trends. Certain other covariate relationships were tested based on prior knowledge or on the basis of physiological findings. The graphical covariate search was complemented by generalized additive modeling (GAM) analysis (11, 18), and the covariate choices from this analysis were confirmed by bootstrap GAM. The final significance of each fixed effect was assessed by a stepwise univariate backward elimination analysis of the covariate. If the exclusion of a fixed effect resulted in an increase in MVOF of < 7.88 ($P < 0.005$, χ^2 , 1 df), the covariate was removed from the model (2, 8, 17).

Final model. The final model, including all significant patient covariates, was then evaluated for any remaining biases, and modifications were made to the model, including optimization of the covariance matrix.

Model validation. The final pharmacokinetic model, including all statistically significant covariates, was validated using the predictive check (28).

Application of the model to phase 3 data. Finally, the ability of the original population pharmacokinetic model (here called stage 1 population pharmacokinetic model) to predict doripenem plasma concentrations in a small external data set comprised of sparse ($n = 89$) pharmacokinetic samples from 18 patients with nosocomial pneumonia enrolled in two phase 3 studies was assessed. Diagnostic plots, including standard goodness-of-fit plots, were employed to establish whether or not the pharmacokinetic model was adequate for describing the phase 3 data. This was accomplished by computing prediction errors. Prediction errors provide a measure of bias and precision by assessing the differences between the measured and population mean predicted doripenem concentrations. The prediction error percents (PE%) were computed for each pharmacokinetic sample using the following equation: $PE\%_{ij} = (C_{pij} - PRED_{ij})/PRED_{ij} \times 100$, where $PE\%_{ij}$ is the percent prediction error between the measured value of the i th plasma concentration in the j th subject and the predicted value of the i th plasma concentration in the j th subject, C_{pij} is the measured value of the i th plasma concentration in the j th subject, and $PRED_{ij}$ is the population mean predicted value of the i th plasma concentration in the j th subject.

The absolute prediction error percents (IPE%) were computed as the absolute value of the PE%. Summary statistics for individual prediction error percentage (IPE%) and absolute individual PE% (IPE%) were computed as measures of overall accuracy and precision, respectively, in the model-predicted individual concentrations relative to the observed individual concentrations of doripenem when interindividual variability was incorporated. Following validation of the model, including the significant covariates, as appropriate for characterizing pharmacokinetics in this new population of patients, data from phases 1, 2, and 3 were pooled into a combined data set. The pharmacokinetic model was then applied to the combined data set, and population pharmacokinetic parameters were reestimated, resulting in the final model (here called the stage 2 population pharmacokinetic model).

RESULTS

A total of 4,543 valid concentration time points from 285 subjects (176 healthy volunteers and 109 patients) were utilized for the development of the stage 1 population pharmacokinetic model. More than half of the subjects were male (58%), and 81% were Caucasian. Their median (range) age was 38 (18 to 88) years, weight was 72.1 (45 to 142) kg, and creatinine clearance was 97.6 (15.6 to 215.6) ml/min.

Goodness-of-fit plots for measured versus predicted concentrations from the stage 1 model are presented in Fig. 1. The population mean parameter estimates and interindividual variability (percent coefficient of variation [% CV]), described using an exponential error model, for CL (liters/h), V_c (liters), V_p (liters), and Q (liters/h) were 13.6 (19%), 11.5 (19%), 5.8 (24%), and 4.6 (41%), respectively. The residual errors were estimated to be 0.17 standard deviation (SD) and 0.55 SD for phase 1 and phase 2 studies, respectively. Model improvement efforts (e.g., to one 2×2 variance-covariance matrix; a full 4×4 block) did not result in measurable improvement. An assessment of subject covariates showed that CL was related to both creatinine clearance and race, while V_c and Q were related to and increased with body weight and V_p was related to age, body

FIG. 1. Goodness-of-fit plots for the final doripenem pharmacokinetic model.

weight, and creatinine clearance. Distributions of weighted residuals and the interindividual variability of the pharmacokinetic parameters showed a log-normal distribution.

Bayesian estimates of the pharmacokinetic parameters were generated for each individual included in the population pharmacokinetic analysis using the stage 1 model. Mean (SD) individual Bayesian clearance (in liters/h) was 14.09 (4.46) and 13.93 (4.25) for male and female subjects/patients, respectively, and ranged from 13.72 (4.22) in Caucasian to 17.79 (6.16) in Hispanic/Latino subjects/patients. The relationships between the individual Bayesian estimates of clearance and corresponding covariates were plotted, with those for renal function and health status shown in Fig. 2 and 3, respectively. Of the statistically significant subject covariates identified, creatinine clearance was the most significant predictor of doripenem clearance. Compared to individuals with normal renal function, mean doripenem clearance was approximately 29%, 55%, and 77% lower for individuals with mild, moderate, or severe renal impairment, respectively. Although disease state was not identified as a statistically significant predictor of doripenem clearance, the mean clearance of doripenem was slightly lower in patients with complicated UTI (20%) or pyelonephritis (7%) than in healthy subjects. There was substantial overlap in drug

FIG. 2. Estimated Bayesian clearance (liters/h) by renal function. The solid line in the box is the median. The lower boundary of the box represents the 25th percentile, and the higher boundary of the box represents the 75th percentile. The whiskers are the nearest values within 1.5 times the interquartile range below and above the 25th and 75th percentiles, respectively. Any points beyond these values are possible outliers and drawn individually.

clearance between patients and healthy subjects (Fig. 3), suggesting similarity between the two groups.

With regard to other associations between subject covariates and drug clearance, the model indicated a 15% increase in mean clearance in subjects/patients of Hispanic or Latino ancestry, compared to Caucasians, whereas negligible differences were observed for subjects/patients of African American, Asian, or other ancestry. Gender did not affect doripenem clearance. No significant difference in estimated mean clearance of doripenem was observed in subjects/patients between 18 and 65 years of age or in those between 65 and 75 years, whereas clearance was reduced by approximately 16% in those over 75 years, possibly due to age-related decrease in renal function (data not shown).

FIG. 3. Estimated Bayesian clearance (liters/h) by health status. The solid line in the box is the median. The lower boundary of the box represents the 25th percentile, and the higher boundary of the box represents the 75th percentile. The whiskers are the nearest values within 1.5 times the interquartile range below and above the 25th and 75th percentiles, respectively. Any points beyond these values are possible outliers and drawn individually.

FIG. 4. Scatter plot of doripenem plasma concentration versus time since last dose in nosocomial pneumonia patients overlaid on data from phase 1 and 2 studies.

Application of the stage 1 population pharmacokinetic model to phase 3 data. A semilogarithmic scatter plot of doripenem concentration-versus-time values since last dose for nosocomial pneumonia patients was overlaid on these data from phase 1 and 2 studies (used in developing the stage 1 population pharmacokinetic model) in Fig. 4. The vast majority of phase 3 data were located within the same range of doripenem concentrations in samples collected from healthy subjects and from patients with complicated UTI, although several concentrations from nosocomial pneumonia patients were located near the lower and upper spectra of the phase 1 and 2 data.

The cohort of 18 nosocomial pneumonia patients used in the external validation of the stage 1 population pharmacokinetic model was comprised primarily of male (16 [89%]) Caucasian (15 [83%]) patients. Their median (range) age was 54 (40 to 80) years, and creatinine clearance was 139.3 (22.0 to 357.0) mL/min. The population mean Bayesian clearance of doripenem was similar between patients with nosocomial pneumonia (15.30 L/h) and healthy volunteers (15.36 L/h).

A strong correlation between measured and individual predicted doripenem concentrations was observed in a goodness-of-fit plot (linear scale) for the stage 1 pharmacokinetic model applied to the phase 3 validation data set (Fig. 5). The median IPE% was 0.71% (very close to 0), suggesting that when interindividual and interoccasion variabilities are accounted for, the pharmacokinetic model is fairly accurate in predicting subject-specific doripenem concentrations from phase 3 studies (Table 1). The median absolute IPE% was 21.3%, which also suggests that the model exhibits reasonable precision in individual predictions. On this basis, the phase 3 data were pooled with the phase 1 and 2 data, the stage 1 pharmacokinetic model was applied to the pooled data, and population pharmacokinetic parameters were then reestimated.

Final population pharmacokinetic model (stage 2 model). The final analysis data set was comprised of a total of 4,630 pharmacokinetic observations collected from 303 individuals. Their median age was 40 years, median weight was 73 kg, and median creatinine clearance was 98 mL/min. The population mean pharmacokinetic parameter estimates and % CV values for the stage 2 model are summarized in Table 2. The reesti-

FIG. 5. Individual predicted doripenem concentrations based on stage 1 population pharmacokinetic model versus measured concentrations in nosocomial pneumonia patients enrolled in a phase 3 study.

mated population mean parameter estimates and interindividual variability (% CV) for CL (L/h), V_c (L), V_p (L), and Q (L/h) were 13.6 (19%), 11.6 (19%), 6.0 (25%), and 4.7 (42%), respectively. Residual variability, estimated using three separate additive residual error models, was 0.17 SD, 0.55 SD, and 0.92 SD for phase 1, 2, and 3 data, respectively. The linear goodness-of-fit plot (of measured versus predicted concentrations) for the stage 2 (final) model is presented in Fig. 6.

The relationships between pharmacokinetic parameters and relevant covariates, as observed in the stage 1 (pooled phase 1 and 2) model, were confirmed. A direct relationship was observed between doripenem clearance and creatinine clearance. Drug clearance was also mostly affected by Hispanic/Latino race. Compared to Caucasians, the model indicated a 16% increase in mean clearance in subjects/patients of Hispanic or Latino ancestry, whereas minor differences were estimated for those of African American (2.0% increase) or Asian/other (4.5% decrease) ancestry. The % CV values associated with these later estimates were high (Table 2). Doripenem clearance was unaffected by gender (14.04 and 13.71 L/h in male and female subjects/patients, respectively). In the stage 2 model, mean doripenem clearances were approximately 33%, 55%, and 76% lower for individuals with mild, moderate, or severe renal impairment, respectively, than for individuals with normal renal function.

DISCUSSION

A two-compartment model with zero-order input and first-order elimination best described the pharmacokinetics of doripenem following i.v. administration. The model was parameterized in terms of CL, V_c , V_p , and Q , with interindividual variability in each described using exponential error models. Parameter estimates of the final (stage 2) model were similar to those obtained from the stage 1 model developed using data from only phase 1 and 2 studies, a finding that is consistent with our expectations. Pharmacokinetic variability of doripenem was relatively low in the population of volunteers and patients who were studied.

Consistent with findings from earlier models (developed from limited, phase 1 and 2 data) (1, 3, 26, 27), creatinine

TABLE 1. Summary statistics of the individual prediction error and absolute individual prediction error for the stage 1 population pharmacokinetic model from phase 1 and 2 data applied to phase 3 data

Variable	Mean (SD)	Minimum	5th percentile	25th percentile	Median	75th percentile	95th percentile	Maximum
Individual prediction error %	13.0 (72.4)	-87.1	-62.6	-19.7	0.71	22.4	140.2	382.5
Absolute individual prediction error %	39.9 (61.7)	0.41	3.06	8.59	21.2	44.0	140.2	382.5

clearance was the most statistically significant predictor of doripenem clearance, which is not surprising since renal elimination is the predominant route for doripenem clearance (~75% and up to 90% in some studies [4]). Clearance was generally lower in elderly subjects/patients, probably due to age-related reduction in renal function. The extent of reduc-

tion in doripenem clearance due to age-related renal impairment is probably somewhat offset by decreases in plasma and tissue binding of the drug (12), which would increase doripenem clearance. The magnitude of the decline in doripenem clearance in the elderly was minor; therefore, no dosage adjustments are recommended for elderly patients with age-appropriate renal function (21).

Doripenem clearance was estimated to be modestly increased (~16%) in individuals of Hispanic or Latino ancestry compared to Caucasians, although the interpretation of this finding is complicated by large standard errors around the means for race. While ethnic differences in doripenem clearance should not be dismissed, the clinical significance of the difference in clearance for the Hispanic/Latino ethnic group may be due, at least in part, to potential confounding from sources such as study design (only 3 of 9 studies enrolled Hispanic/Latino subjects, 81% of subjects were Caucasian, and the total number of subjects in each of the other race categories was relatively small), sampling schedule, and/or dosing regimens.

Mean clearance for the population used for modeling was estimated to be 13.6 liters/h (227 ml/min) for Caucasian subjects/patients, with a population median creatinine clearance of 98 ml/min. Based upon the range of creatinine clearance values measured within this population (15.6 to 215.6 ml/min), estimated mean clearance of doripenem for Caucasian individuals can range from 4.1 liters/h (68 ml/min) in a renally impaired patient to 22.9 liters/h (382 ml/min) in a subject with normal renal function.

Regarding the other terms used in the model, a direct relationship was observed between body weight and V_c , V_p , and Q . Based upon the observed distribution of body weight within this analysis population (45 to 142 kg), the model-predicted range for V_c was

TABLE 2. Final parameter estimates and standard errors—stage 2 population pharmacokinetic model from phase 1, 2 and 3 data^a

Parameter	Population mean		Magnitude of interindividual variability	
	Final estimate	(% CV) ^a	Final estimate of % CV ^f	(% CV) ^a
CL (liters/h) ^b	13.6	1.86	19.24	17.6
V_c (liters) ^c	11.6	2.6	19.13	37.2
Q (liters/h) ^d	4.74	6.4	41.59	27.4
V_p (liters) ^e	6.04	4.2	24.82	31.2
Power				
CL-CL _{CR}	0.659	7.4		
V_c -wt	0.596	15.4		
V_p -wt	0.840	25.0		
Q -wt	1.06	28.2		
V_p -age	0.307	32.3		
V_p -CL _{CR}	0.417	34.5		
Proportional shift in CL for race				
African American/black	0.0204	144.6		
Hispanic/Latino	0.163	29.3		
Asian and other combined	-0.0445	207.6		
Residual variability (SD) for phase				
1	0.17	14.7		
2	0.55	18.6		
3	0.92	32.3		
Interoccasion variability (% CV)				
CL	14.90	16.6		
V_c	18.55	20.9		
V_p	30.18	38.7		

^a (% CV) represents precision of parameter estimate.

^b Typical value for CL_j (TV_{CL}) (liters/h) = $13.6 \cdot (\text{CL}_{\text{CRj}}/98)^{0.659} \cdot (1 + \text{CL}_{\text{racej}})$; CL_{race} = 0 (Caucasian), 0.0204 (African American), 0.163 (Hispanic/Latino), and -0.0445 (others).

^c TV_{V_{cj}} (liters) = $11.6 \cdot (\text{wtj}/73)^{0.596}$

^d TV_{Qj} (liters/h) = $4.74 \cdot (\text{wtj}/73)^{1.06}$

^e TV_{V_{pj}} (liters) = $6.04 \cdot (\text{CL}_{\text{CRj}}/98)^{0.417} \cdot (\text{wtj}/73)^{0.840} \cdot (\text{agej}/40)^{0.307}$, where TV_{xj} is the typical value of the xth parameter for the jth subject, wtj is the weight (kg) of the jth subject (centered around a median weight of 73 kg), agej is the age (yr) of the jth subject (centered around a median age of 40 years), CL_{CRj} is the CL_{CR} (ml/min) of the jth subject (centered around a median CL_{CR} of 98 ml/min), and CL_{racej} is the indicator variable of the jth subject with a value of 0 for Caucasians.

^f Off-diagonal elements of covariance matrix are as follows: covariance_{CL,V_c} = 0.0349 (CV = 26.1%); correlation between CL and V_c , $r = (\text{covariance}_{\text{CL},V_c} / [\omega_{\text{CL}} \cdot \omega_{V_c}]) = 0.948$ and $r^2 = 0.899$; covariance_{Q,V_p} = 0.0924 (CV = 29.4%); correlation between Q and V_p , $r = (\text{covariance}_{\text{CL},V_p} / [\omega_{\text{CL}} \cdot \omega_{V_p}]) = 0.895$ and $r^2 = 0.801$.

^g Minimum value of the objective function = -6765.485.

FIG. 6. Predicted doripenem concentrations based on stage 2 population pharmacokinetic model versus measured concentrations.

8.7 to 17.2 liters and that for Q was 2.8 to 9.6 liters/h. At a median age of 40 years and a median creatinine clearance of 98 ml/min, the predicted values for V_p ranged from 4.0 to 10.6 liters. Thus, even for individuals with greater body weight (with normal creatinine clearance and ~40 years of age), it appears that the distribution of doripenem is mainly confined to plasma, extravascular fluid, and highly perfused tissues and organs (e.g., kidneys) (20), as is the case for other carbapenems (22).

In addition to body weight, both age and creatinine clearance had a positive effect on V_p . Although creatinine clearance decreases with advancing age and these two covariates were somewhat correlated, both covariates were necessary to account for the observed interindividual variability. A reduction in creatinine clearance in renally impaired subjects is often associated with altered protein and/or tissue binding (10, 24), thereby changing V_p . A similar phenomenon was observed with digoxin (25), which, like doripenem, has low plasma protein binding (~22%) (13). Since inherent inverse correlations exist between age and creatinine clearance, as well as between age and body weight, the collective impact of these three covariates upon V_p is likely to be minimal.

The significant relationships between pharmacokinetic parameters of doripenem and covariates, as reported in this paper, have been observed by others in population pharmacokinetic models for meropenem and imipenem (7, 16, 19, 21). By way of example, the important impact of creatinine clearance on carbapenem clearance was reported by Dailly et al., who found that among the tested covariates (e.g., age, gender, body weight, height, and serum creatinine), serum creatinine (creatinine clearance) substantially affected the pharmacokinetic parameters of imipenem (7). Similarly, in a population pharmacokinetic analysis of meropenem, which included concentration data gathered from 79 adult patients (aged 18 to 93 years), Li et al. determined that creatinine clearance, age, and body weight were the most significant covariates to affect meropenem pharmacokinetics. The estimates of imipenem CL and V_c were higher in burn patients (who have higher glomerular filtration rates and creatinine clearance) than in healthy subjects (16).

In summary, the population pharmacokinetic model that was developed from phase 1, 2, and 3 data adequately characterized the pharmacokinetics of doripenem in both normal volunteers and patients and has allowed identification of intrinsic and extrinsic factors that significantly influence pharmacokinetic variability. The model provides a predictive tool for estimating pharmacokinetic exposure in individuals and in groups of patients.

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