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Population Pharmacokinetics of Doripenem

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ABSTRACT (REVISED)

Background: Doripenem is a broad-spectrum carbapenem currently in development for treatment of bacterial infections. Previously, we presented a population pharmacokinetic (PK) model for doripenem in healthy subjects (ICAAC 2003, A-11). A refined PK model was developed to describe doripenem data in patients and assess the impact of subject characteristics on PK variability.

Methods: A population PK model was developed using data from Phase 1 subjects (n = 44) and Phase 2 patients (n = 107). Doripenem (250 - 1000 mg) was infused over 30 or 60 min as a single dose or either BID/TID for 7 days. Serial blood samples were collected on Days 1 and 7. Two- and three-compartment models with zero-order input and first-order elimination were evaluated. Subject demographics were evaluated as predictors of PK variability using stepwise forward selection and backward elimination.

Results: Doripenem data were similar for subjects and patients and were best described using a two-compartment model. Interindividual variability of clearance (CL), distribution clearance (Q), and the central (Vc) and peripheral (Vp) volumes were described using an exponential error model and were estimated to be 30, 61, 35, & 100 %CV, respectively. A log error model best described the residual variability. The model estimated CL to increase 11% for Days 2-7 relative to Day 1. Significant relationships were identified between CL and creatinine clearance, Vc and age, Q and weight, and Vp with both age and gender. Predicted mean $C_{max,ss}$ and $AUC_{0-\tau,ss}$ for a 500-mg dose infused over 1 hr were 20.2 µg/mL and 44.1 mg·hr/L, respectively. $AUC_{0-\tau}$ was ~1.5-fold and 2-fold higher for individuals with mild and moderate renal impairment, respectively, compared to young adults with normal renal function.

Conclusions: A population PK model was developed for doripenem and the impact of subject covariates was evaluated. Identification of measurable factors that significantly influence PK variability provides a predictive tool for estimating doripenem exposures and can be used for exposure-response evaluations of safety and efficacy to support Phase 3 dose selection.

INTRODUCTION

- Doripenem is a synthetic, parenteral carbapenem with a broad spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria.
- The PK properties of doripenem are similar to those reported for other parenteral carbapenems. Doripenem is renally eliminated from the body, via a combination of active tubular secretion and glomerular filtration, as either unchanged drug (~75%) or as a by-product resulting from other non-renal mechanisms.
- A population PK model was previously developed for doripenem (ICAAC 2003, A-11). This work demonstrated that a two-compartment (CMT) model adequately characterized full-profile plasma concentration-time data in healthy subjects.
- The goal of this analysis was to develop a population PK model to describe doripenem plasma concentrations following administration of various short-term infusion regimens to both:
  - Phase 1 subjects with varying degrees of renal function; and
  - Patients with complicated lower urinary tract infections (cUTIs) or pyelonephritis.

MATERIALS AND METHODS

Data

- The data for the population PK analysis were collected from Phase 1 subjects with varying degrees of renal function and from patients with cUTIs or pyelonephritis.
- **Table 1** contains doripenem dosing regimens and blood sampling strategies.
- Plasma samples were separated by centrifugation and frozen at -80°C until analyzed using a validated LC/MS/MS method with an LLOQ of 0.2 µg/mL.

Statistical Analysis

- PK analyses were performed using NONMEM®, version 5.1.1, using the first-order conditional estimation method (FOCE) with interaction.
- For each analysis, NONMEM® computed the minimum value of the objective function (MVOF).
  - MVOF is proportional to minus twice the log likelihood of the data.
  - The change in MVOF is asymptotically distributed as χ^2 for hierarchical models.
- Goodness-of-fit (GOF) of each NONMEM® analysis was assessed by examining:
  - scatterplots of population and individual predicted concentrations versus measured concentrations;
  - scatterplots of weighted residuals versus predicted concentrations;
  - scatterplots of individual weighted residuals and absolute values versus predicted concentrations;
  - %SEM (standard error / parameter estimate • 100%) of the PK parameter estimates; and
  - changes in the estimates of interindividual variability (IIV) and residual variability.

Structural Model Development

- Both 2- and 3-CMT models with zero-order input and first-order elimination were evaluated.
- IIV for each PK parameter was described using an exponential error model.
- Residual variability was described using a proportional error model, however, other error models were also tested (e.g., log error model).
- Following multiple dosing, a modest decrease in doripenem exposure has been observed across studies. To determine the significance of this change, an additive shift in CL was tested separately for each day of dosing (i.e., Days 2-7).

Assessment of Subject Descriptor Covariates

- Age, weight, race, gender, and creatinine clearance were evaluated.
- Stepwise forward selection and stepwise backward elimination procedures were used. To determine statistical significance, a change in the MVOF of:
  - ≥ 3.84 (α = 0.05, 1 *df*) was used for forward selection; and
  - ≥ 10.83 (α = 0.001, 1 *df*) was used for backward elimination.

Assessment of the Relationship Between Subject Covariates and Doripenem Exposures

- Individual Bayesian PK parameter estimates from the final model were used to calculate C_{max} and area under the curve from 0 to infinity ($AUC_{0-\infty}$) for a single IV infusion of 500 mg over 1 hr.
- Statistically significant covariates were categorized based upon 0-25th, 25-75th, and 75-100th percentiles of the data or by using physiologically-based categories (e.g., renal function).
- Summary statistics of C_{max} and $AUC_{0-\infty}$ were calculated for sub-populations.
- The magnitude of the differences in C_{max} and $AUC_{0-\infty}$ between populations was then assessed to better understand the impact of these covariates on doripenem exposure.

Table 1: Dosing and PK Sampling for Studies Included in the Population PK Analysis

Study	Study Design & Population	# of Subjects	Dosing Regimen(s)	PK Sample Collection Times
1	Phase 1, double-blind, dose-escalation study of safety, tolerability and PK in healthy subjects	N = 24 (6 group)	500 mg over 30 min q8hr for 7 days	Day 1: Pre-dose, midpoint of the infusion, end of infusion (EOI), and at 5, 15, 30, 45, and 60 min and 3, 5, 8, and 12 hrs post-EOI Days 4-6: Pre-dose and 5 min post-EOI Day 7: Pre-dose, midpoint of the infusion, EOI, and at 5, 15, 30, 45, and 60 mins and 3, 5, 8, 12, and 24 hrs post-EOI
			1000 mg over 1 hr q8hr for 7 days	
			1000 mg over 30 min q12hr for 7 days	
2	Phase 1, open-label study of safety, tolerability, and PK in subjects with renal impairment	N = 20	500 mg over 30 min	Pre-infusion and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, 18, 24, 36, and 48 hrs post-start of infusion
3	Phase 2, double-blind, dose-finding study in patients with cUTIs or pyelonephritis	N = 60	250 mg over 30 min q8hr for 5 days	Days 1 and 7: Pre-dose, EOI, and at 1, 2, 3, 4, and 6 hr post-EOI
		N = 47	500 mg over 30 min q8hr for 5 days	

RESULTS

Data

- A total of 1614 doripenem plasma concentrations collected from 151 individuals (44 healthy subjects and 107 patients) were available for PK analysis.
- Summary statistics of the subject descriptors are provided in **Table 2**.
- Plots of doripenem concentrations versus time (**Figure 1b**) show PK data from patients were within the same range as Phase 1 subjects over the dosing interval.

Final Model

- A 2-CMT model with zero-order input and first-order elimination, plus an additive shift for CL on Days 2 to 7, best described the doripenem data.
- Equations for computing the typical values of each parameter (**Eq. 1-4**) are shown below.

$$TVCL_i\ (L/hr) = 13.1 \bullet (CRCL_i/84)^{0.817} + 1.94 \bullet MD_i \quad \textbf{(Eq. 1)}$$

$$TVVc_i\ (L) = 17.3 \bullet (AGE_i/50)^{0.531} \quad \textbf{(Eq. 2)}$$

$$TVQ_i\ (L/hr) = 3.32 + 0.0999 \bullet (WT_i - 71) \quad \textbf{(Eq. 3)}$$

$$TVVp_i\ (L) = (10.9 \bullet (AGE_i/50)^{1.969}) \bullet (1 + 0.802 \bullet SEX_i) \quad \textbf{(Eq. 4)}$$

Where:

TVX_i = the typical value of the X^{th} parameter for the i^{th} subject;
WT_i = the weight (kg) of the i^{th} subject;
AGE_i = the age (yr) of the i^{th} subject;
$CRCL_i$ = the creatinine clearance (mL/min) of the i^{th} subject;
SEX_i = gender for the i^{th} subject (male=0, female=1);
MD_i = dosing for i^{th} subject on the i^{th} day (Day 1=0, Days 2-7=1).

- Parameter estimate statistics and GOF plots are shown in **Table 3** and **Figure 2**.

Relationships Between Significant Subject Covariates and Doripenem Exposures

- Compared to young adults with normal renal function, the predicted $AUC_{0-\tau}$ was ~1.5-fold and 2-fold higher for individuals with mild or moderate renal impairment, respectively (**Table 4**). Age, weight, and gender did not substantially impact $AUC_{0-\tau}$ after renal function was considered.
- Within each renal function category, the predicted C_{max} generally decreased as age and weight increased; when compared to young adults with normal renal function these differences were < 27% (**Table 4**).

44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy
October 30 – November 2, 2004
Washington, DC

Table 2: Summary Statistics of the Subject Covariates Included in the PK Analysis

Covariates	Study 1 (N = 24)	Study 2 (N = 20)	Study 3 (N = 107)	Total Combined (N = 151)
Age (yr) Mean (SD) Min – Max	26.6 (4.5) 18.0 – 36.0	47.7 (12.8) 25.0 – 69.0	53.3 (18.8) 18.0 – 88.0	48.2 (20.0) 18.0 (88.0)
Weight (kg) Mean (SD) Min – Max	72.2 (10.3) 55.5 – 89.0	76.3 (15.7) 51.6 – 104	72.1 (16.0) 45.0 – 142	72.7 (15.2) 45.0 – 142
CrCl (mL/min) Mean (SD) Min – Max	104 (17.9) 68.4 – 136	74.8 (29.3) 35.9 – 132	81.4 (26.8) 30.2 – 186	84.1 (27.3) 30.2 – 186
Gender, n (%) Male Female	18 (75) 6 (25)	15 (75) 5 (25)	46 (43.0) 61 (57.0)	79 (52.3) 72 (47.7)
Ethnicity, n (%) White Black Asian Hispanic	24 (100) 0 (0) 0 (0) 0 (0)	16 (75) 4 (25) 0 (0) 0 (0)	91 (85.0) 0 (0) 1 (0.9) 15 (14.0)	131 (86.8) 4 (2.6) 1 (0.7) 15 (9.9)

FIGURE 1: Scatterplots of Doripenem Concentration-Time Data

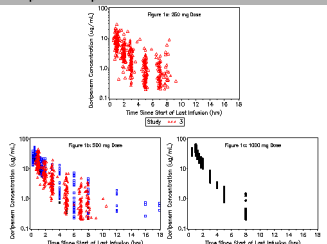

Table 3: Population PK Parameter Estimates and Standard Errors for the Final Model

Parameter	Population Mean	
	Final Estimate	%SEM
CL coeff. (L/hr) on Day 1	13.1	2.8
Additive Shift for CL on Days 2-7 (L/hr)	1.94	15.5
CL-CrCL power	0.817	8.3
Vc coeff. (L)	17.3	4.6
Vc-Age power	0.331	19.5
Q intcpt. (L/hr)	3.32	9.5
Q/Weight slope	0.100	19.8
Vp coeff. (L)	10.9	19.2
Vp-Age power	0.963	27.2
Proportional Shift on Vp for Females	0.802	56.2
IIV of CP (%CV)	30.5%	13.7
IIV of Vc[a] (%CV)	34.9%	21.7
IIV of Q[a] (%CV)	61.5%	32.3
IIV of Vp[a] (%CV)	100%	21.3
Residual Variability (Log, SD)	0.32	15.5

[a] Covariance$_{Vc,Vp}$ = 0.0935 (SEM= 19.0%); Correlation between CL and Vc: r^2 = 0.721
[b] Covariance$_{Q,Vp}$ = 0.542 (SEM= 28.0%); Correlation between Q and Vp: r^2 = 0.777

FIGURE 2: Goodness-of-Fit Plots for the Final Model

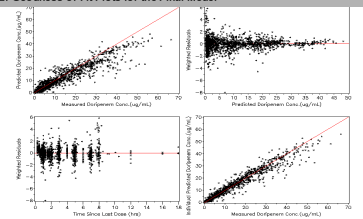

Table 4: Mean (SD) Values for the Predicted Doripenem Exposures for Sub-Populations for a Single 500 mg Infusion over 1 hr

Renal Function Category[a]	Age or Weight Category	n	Doripenem Exposures			
			$AUC_{0-\tau}$ (mg•hr/L)	% Diff[c]	C_{max} (µg/mL)	% Diff
Normal	Young Adults	49	34.4 (4.94)	Ref.	20.5 (4.22)	Ref.
	Middle-Aged	29	32.5 (10.7)	-5.5%	17.0 (4.81)	-17.1%
Mild Impairment	Young Adults	7	48.8 (9.19)	36.0%	25.8 (2.97)	25.9%
	Middle-Aged	26	49.6 (19.0)	44.2%	22.0 (7.71)	7.3%
	Elderly	21	49.6 (18)	44.2%	18.0 (5.97)	-12.2%
Moderate Impairment	Elderly	10	75.0 (30.1)	118%	20.9 (6.23)	2.0%
Normal	Low	12	34.3 (7.21)	0.0%	20.4 (4.46)	3.6%
	Middle	39	34.3 (7.24)	Ref.	19.7 (4.71)	Ref.
	High	31	32.0 (10.3)	-6.7%	17.3 (4.81)	-12.2%
Mild Impairment	Low	13	48.1 (14.4)	40.2%	24.2 (5.57)	22.8%
	Middle	27	51.4 (18.7)	49.9%	21.4 (7.47)	8.6%
	High	13	46.0 (18)	34.1%	16.6 (5.62)	-15.7%
Moderate Impairment	Low	5	81.0 (35.8)	136%	25.0 (9.10)	26.9%
	Middle	7	73.6 (15.6)	115%	22.2 (7.13)	12.7%

[a] Renal function categories: Normal (CrCL ≥ 80 mL/min), Mild Impairment (50 ≤ CrCL < 80 mL/min), and Moderate Impairment (30 ≤ CrCL < 50 mL/min)
[b] Age categories: Young Adults (< 40 yr), Middle-Aged (40 ≤ age < 65 yr), and Elderly (age ≥ 65 yr)
[c] Weight categories: Low (45 ≤ WT < 60 kg, Middle (60 ≤ WT < 80 kg), and High (WT ≥ 80 kg)
[d] The percent difference in the PK parameter for all sub-populations relative to the reference (Ref.) group

CONCLUSIONS

- This population PK model characterized the doripenem concentration-time data in both Phase 1 subjects and patients with cUTIs or pyelonephritis.
- The PK of doripenem were best described using a 2-CMT model with zero-order input and first-order elimination.
- A modest increase in CL (~11%) was observed following multiple-dose administration of doripenem; while the mechanism of this increase is not well understood, similar findings have been reported in multiple-dose studies of other carbapenems.
- The following statistically significant relationships with subject covariates were identified:
  - CL decreased as CrCL decreased;
  - Q increased as weight increased;
  - Vc and Vp increased as age increased; and
  - Vp was also higher for females.
- CrCL had the greatest impact on the PK of doripenem. Compared to young adults with normal renal function, the predicted $AUC_{0-\tau}$ was ~1.5-fold and 2-fold higher for individuals with mild or moderate renal impairment, respectively.
- This model may be utilized to predict doripenem exposures in patients with sparse PK data for the investigation of exposure-response analyses of safety and efficacy in future Phase 2/3 clinical trials.