A-19

Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, December 16-19, 2005

Population Pharmacokinetics of Tigecycline in Patients with Complicated Skin and Skin-Structure and Intra-Abdominal Infections

Scott A. Van Wart,[1] Joel S. Owen,[1,2] Alison K. Meagher,[1] and Brenda B. Cirincione[1]

[1]Cognigen Corporation, Buffalo, NY and [2]Auburn University, Auburn, AL

For more information, please contact:
Scott Van Wart, MS
Assistant Director, PK/PD
Cognigen Corporation
395 Youngs Road
Buffalo, NY, 14221
(716) 633-3463, ext. 241
Scott.VanWart@cognigencorp.com

ABSTRACT

Purpose. Tigecycline is a novel glycylcycline antibiotic with expanded broad-spectrum *in vitro* activity, including emerging multidrug-resistant pathogens. The goal of this analysis was to develop a PPK model for tigecycline in patients with complicated skin and skin-structure infections (cSSSI) or complicated intra-abdominal infections (cIAI) in Phase 2 studies and generate steady-state $AUC_{0\text{-}12}$ values for use in exposure-response analyses of safety and efficacy.

Methods. A population PK model was developed using pooled data from two Phase 2 studies in patients with cSSSI or cIAI. Tigecycline was infused over 1 hr as either a 100-mg or 50-mg loading dose followed by either 50 or 25 mg every 12 hr for up to 14 days. Serial blood samples were collected to determine steady-state serum tigecycline concentrations using LC/MS/MS. Both 2- and 3-CMT models were evaluated using NONMEM®. Patient covariates were evaluated to explain interindividual variability in PK using stepwise forward selection (α = 0.05) and backward elimination (α = 0.001). The final model was used to generate individual tigecycline steady-state $AUC_{0\text{-}12}$ values, which were assessed for bias (PE%) and precision (|PE|%) relative to noncompartmental estimates.

Results. A 2-CMT model with zero-order input and first-order elimination best described the steady-state tigecycline concentration-time data. Tigecycline clearance was increased with creatinine clearance, weight, and for male gender. Mean (SD) steady-state $AUC_{0\text{-}12}$ values for the 25-mg and 50-mg dose groups were 1.34 (0.5) and 2.70 (0.8) mg·hr/L, respectively. Creatinine clearance had the largest apparent impact on the PK of tigecycline; $AUC_{0\text{-}12}$ values were 31% to 48% higher across dose groups in patients with moderate or severe renal impairment relative to normal values. $AUC_{0\text{-}12}$ was unbiased (median PE% ± 2%) and acceptably precise (median |PE|% < 10%).

Conclusions. A population PK model was developed to characterize steady-state tigecycline concentration-time data and to determine the impact of various patient covariates on the PK of tigecycline. Steady-state tigecycline exposures were obtained in the current Phase 2 patient population, and the model is available to estimate steady-state $AUC_{0\text{-}12}$ in future Phase 3 trials.

BACKGROUND

- Tigecycline (Tygacil™) is a first-in-class glycylcycline that exhibits a broad spectrum of activity against many aerobic and anaerobic gram-positive and gram-negative organisms, as well as atypical pathogens, including many multiple-drug resistant organisms.
- Pharmacokinetic/pharmacodynamic (PK/PD) analyses in experimental animal models of infection have indicated that serum AUC:MIC ratio is the index that is most likely to correlate with the efficacy of tigecycline (AAC 44:943-9, 2000).
- Results from Phase 2/3 clinical trials demonstrated that tigecycline was efficacious and well tolerated in the treatment of complicated skin and skin-structure infections (cSSSI) and complicated intra-abdominal infections (cIAI).
- The Food and Drug Administration approved tigecycline for the treatment of these infections in June 2005, including cSSSI due to methicillin-resistant *Staphylococcus aureus*.
- This report describes the development of a population PK model for tigecycline in Phase 2/3 patients with cSSSI or cIAI.

METHODS

Data

- Data were pooled from two Phase 2 studies, one conducted in patients with cSSSI and the other in patients with cIAI (**Table 1**).
- Blood (5 mL) was collected prior to dosing, at the end-of-infusion (~1 hr), and at 3 and 6 hr post-start of infusion on the day before or day of hospital discharge (Days 3 to 14 of dosing). Tigecycline concentrations in serum were determined using an LC/MS/MS assay (LLOQ = 10 ng/mL).

METHODS (Continued)

Table 1: Tigecycline Study Designs, Dosing Regimens, and Number of Patients Included in the PK Analysis

Study	Description	No. of Patients	Dosage Regimen(s)[a]	Infusion Duration (hr)
1	Multicenter, randomized, open-label, Phase 2 study of tigecycline safety and efficacy in hospitalized patients with cSSSI	43	50 mg+25 mg q12h	1
		35	100 mg+50 mg q12h	
2	Multicenter, open-label, Phase 2 study of tigecycline safety and efficacy in hospitalized patients with cIAI	68	100 mg+50 mg q12h	1

[a] Tigecycline was administered for up to 14 days

Statistical Analysis

- PK analysis was performed using NONMEM® version 5 Level 1.1 using the first-order conditional estimation method with interaction. For each analysis, the minimum value of the objective function (MVOF) was computed.
  - 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 the precision of PK parameter estimates (%SEM), changes in both the IIV and RV, and scatterplots of:
  - population and individual predicted concentrations versus measured concentrations;
  - weighted residuals versus predicted concentrations and time since last dose; and
  - individual weighted residuals and the absolute values versus individual predicted concentrations.

Structural Model Development

- A 2-CMT model with zero-order input and first-order elimination was used to describe steady-state tigecycline data in Phase 2 patients with cSSSI or cIAI.
  - IIV of clearance (CL), distributional clearance (Q), and both the central and peripheral volume of distribution (Vc and Vp) were described with exponential error models; and
  - RV was described using a proportional error model.

Covariate Analyses

- Patient covariates evaluated were:
  - demographics (age, weight, gender, and race);
  - alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and creatinine clearance (CrCL); and
  - potential drug binding factors (albumin, hematocrit, hemoglobin, and red blood cell count).
- Stepwise forward selection (α = 0.05) and backward elimination (α = 0.001) procedures were used.

Relationship Between Patient Covariates and Tigecycline Exposure

- Bayesian PK parameters were obtained using the final model, and steady-state tigecycline concentrations were predicted every five minutes to calculate individual predicted $AUC_{0\text{-}12}$ values using the mixed trapezoidal rule.
- Statistically significant covariates were categorized into populations based upon physiologically-based criteria, and the magnitude of the differences in steady-state $AUC_{0\text{-}12}$ values between populations were compared.

Assessment of Predictive Performance

- Bayesian PK parameters from the final model were used to predict tigecycline concentrations at the sparse-sampling times for patients who:
  - contributed at least four samples;
  - had a sample collected at 1 ± 0.25 hr of termination of the infusion; and
  - had a trough sample collected at 12 ± 0.5 hr following a dose (trough concentration was duplicated for use as an estimate of the 12-hr tigecycline concentration).
- Steady-state $AUC_{0\text{-}12}$ values were calculated for both the observed and individual predicted concentrations (mixed trapezoidal rule) and assessed graphically for bias.
- Prediction error percents (PE% = [observed $AUC_{0\text{-}12}$ - predicted $AUC_{0\text{-}12}$] · 100/observed $AUC_{0\text{-}12}$) and |PE|% were also evaluated as measures of bias and precision, respectively.

RESULTS

Data

- A total of 530 steady-state tigecycline concentrations from 146 Phase 2 patients were included in the PK analysis.
- The Phase 2 population for all studies combined was:
  - 71% male, and was 43% White, 14% Black, 41% Hispanic, and 2% Other
  - mean age = 46 yr (ranged from 18 to 82 yr)
  - mean weight = 84 kg (ranged from 47 to 227 kg)
  - mean CrCL = 92 mL/min (ranged from 24 to 278 mL/min)

PK Analysis

- A 2-CMT model with zero-order input and first-order elimination adequately described the data.
- Population mean PK parameter estimates for both the base structural model and the final model are provided in **Table 2**.
- A semilog plot of the population mean predicted serum tigecycline concentration-time profile for the final model, stratified by tigecycline dosing regimen, is shown in **Figure 1**.
- Population mean and individual predicted versus observed tigecycline concentrations for the final model are shown in **Figure 2**.
- Tigecycline CL was shown to increase with increasing weight, CrCL, and male gender ($P < 0.001$).
  - The equation for computing the population mean CL is provided in **Table 2**.
  - The population mean CL is shown graphically in **Figure 3** for both a male and a female patient, varying either weight or CrCL over the studied range while the other covariate is held at the median value.
- Examination of individual predicted $AUC_{0\text{-}12}$ values (**Table 3**) revealed that:
  - patients with moderate/severe renal impairment had moderately higher mean $AUC_{0\text{-}12}$ values relative to patients with normal renal function (~31 and 48% for patients given 25 or 50 mg q12h, respectively); and
  - patients weighing ≥ 80 kg had a slightly higher mean $AUC_{0\text{-}12}$ value relative to patients weighing < 80 kg (~30 and 9% for patients given 25 or 50 mg q12h, respectively).
- Steady-state $AUC_{0\text{-}12}$ computed using individual predicted concentrations were unbiased (median PE% = 1.6) and very precise (median |PE|% = 2.94) relative to $AUC_{0\text{-}12}$ computed using observed concentrations, as shown graphically in **Figure 4**.

Figure 1: Measured and Population Mean Predicted Steady-State Serum Tigecycline Concentration-Time Profile, Stratified by Dose Group, for the Final Population PK Model

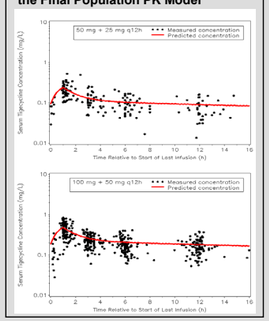

Figure 2: Population Mean (top) and Individual Predicted (bottom) Versus Observed Tigecycline Concentrations for the Final Population PK Model

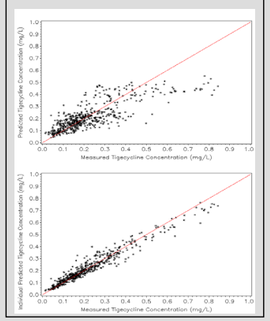

Figure 3: Population Mean CL Computed Over the Range of Each Significant Covariate Studied

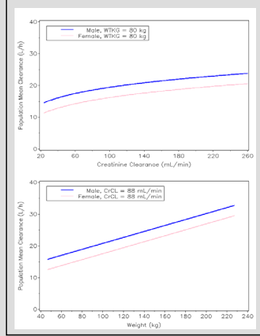

Figure 4: Individual Predicted Versus Observed Steady-State Tigecycline $AUC_{0\text{-}12}$ Values for the Final Model

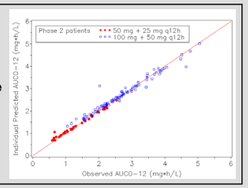

Table 2: Population Mean (%SEM) of the PK Parameters for Select Models

Parameter	Base Structural Model	Final Model[a,b]
CL (L/hr)	18.6 (6)	15.7 (8)
CL-WTKG slope	NE[c]	0.0943 (28)
CL-CrCL power	NE	0.250 (38)
Shift on CL for Males (L/hr)	NE	3.23 (37)
Vc (L)	100 (9)	115 (7)
Q (L/hr)	73.5 (9)	70.9 (7)
Vp (L)	554 (37)	644 (20)
IIV of CL (%CV)	36.2 (22)	35.1 (19)
IIV of Vc (%CV)	43.7 (33)	43.2 (27)
IIV of Q (%CV)	55.1 (39)	49.3 (35)
IIV of Vp (%CV)	NE	NE
RV (%CV)	22.2 (15)	21.0 (13)

[a] Population mean CL_i (L/hr)=15.7 · $(CrCL_i/88.3)^{0.250}$ + 0.0943 · $(WTKG_i\text{-}80)$+3.23 · MALE; $CrCL_i$ is the creatinine clearance (mL/min) of the i^{th} patient, $WTKG_i$ is the weight (kg) of the i^{th} patient, and MALE is 1 if the i^{th} patient is male and 0 if the i^{th} patient is female.
[b] Covariances between η_{CL},η_{Vc} (r^2 = 0.385), η_{CL},η_Q (r^2 = 0.095), and η_Q,η_{Vc} (r^2 = 0.666) were estimated.
[c] NE: not estimated

Table 3: Mean (SD) of the Individual Predicted Steady-State $AUC_{0\text{-}12}$ Estimates for Selected Populations, Stratified by Dose Group

Covariate	Population	Dose (mg)	No. of Patients	Mean (SD), mg·hr/L	%Diff[a]
Gender	Males*	25	26	1.20 (0.43)	—
	Females	25	17	1.55 (0.53)	28.8
	Males*	50	77	2.60 (0.80)	—
	Females	50	26	3.02 (0.70)	16.5
Renal Function[b]	Normal*	25	24	1.20 (0.48)	—
	Mild Impairment	25	11	1.47 (0.55)	22.1
	Moderate/Severe Impairment	25	8	1.58 (0.38)	31.1
	Normal*	50	67	2.56 (0.67)	—
	Mild Impairment	50	28	2.73 (0.91)	6.67
	Moderate/Severe Impairment	50	8	3.78 (0.47)	47.6
Body Weight	≥ 100 kg	25	10	1.11 (0.34)	-32.1
	90-100 kg	25	7	1.17 (0.40)	-28.4
	80-90 kg	25	9	1.17 (0.30)	-28.5
	< 80 kg*	25	17	1.73 (0.63)	—
	≥ 100 kg	50	18	2.56 (0.11)	-8.50
	90-100 kg	50	12	2.55 (0.79)	-8.90
	80-90 kg	50	17	2.65 (0.82)	-5.33
	< 80 kg*	50	56	2.82 (0.59)	—

[a] Percent difference was calculated, stratified by dose group, between each population and a designated reference population (*).
[b] Normal: CrCL ≥ 80 mL/min; mild impairment: 50 mL/min ≤ CrCL < 80 mL/min; moderate and severe impairment: CrCL< 50 mL/min

CONCLUSIONS

- A 2-CMT model with zero-order input and first-order elimination provided an adequate fit to the steady-state tigecycline concentration-time data in Phase 2 patients with cSSSI or cIAI.
- Tigecycline was estimated to have a large steady-state volume of distribution (Vc + Vp = 759 L), indicating extensive tissue distribution.
- Tigecycline CL was higher for males and increased with both weight and CrCL.
- Differences in $AUC_{0\text{-}12}$ between various populations created using combinations of these covariates were consistent with previous findings reported in healthy subjects and did not warrant dose adjustment.
- The results of these analyses verify that the model is adequate for generating accurate and unbiased estimates of steady-state $AUC_{0\text{-}12}$.
- This model will have important future application for estimating patient exposures for use in exposure-response analyses for safety and efficacy outcomes for tigecycline.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of Dr. Sarapee Hirankarn (Cognigen Corporation) during model development, as well as Dr. Gopal Muralidharan, Dr. EJ Ellis-Grosse, and Mr. Steven Troy of Wyeth Research.