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The Development of a Population Pharmacokinetic (PK) Model for Linezolid

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ABSTRACT

Introduction: Linezolid (lzd) is an oxazolidinone antibiotic under development for infection due to gram-positive bacteria. It is rapidly and extensively absorbed following oral administration and initial PK studies have suggested non-linear elimination.

Purpose: To develop a PK model using Phase I data for application to Phase II data.

Methods: Full profile blood samples following single- and multiple-doses of lzd and interval trough samples were collected from healthy volunteers in an open-label, three-way crossover study evaluating oral doses; 125 mg, 375 mg, 625 mg of lzd. Samples were pooled with full profile samples from volunteers enrolled in an open-label study of 375 mg given via oral and intravenous administration. A total of 1937 lzd concentrations (cps) collected from 31 subjects were analyzed using a one compartment model with first-order absorption (Ka). Elimination was modeled as a first-order (Ke) plus a Michaelis Menten (MM) (Km, Vm) pathway with competitive inhibition from a hypothetical factor (Kf).

Results: The combined linear and MM model adequately fit the single- and multiple- dose data across lzd doses. The parameter (% SEM) estimates were as follows: Mean Vd was 0.672 (2.2) L/kg, mean Ka was 4.52 (13.6) hr^{-1}, mean Vm and Km were 38.0 (45.3) mg/hr and 466 (45.9) mg respectively, Ke was 0.0745 (9.0) hr^{-1}, the equilibrium rate constant (Kf) for the hypothetical factor was 0.00781 (19.5) hr^{-1} and the inverse equilibrium constant of the enzyme-factor complex was 0.01 (54.3) mg factor. Modest interindividual variability was noted for Ka, Km, K, V, and Kf. A mean prediction error of -4.8%, indicating a trend to overpredict the cps, was noted when these estimates were used to predict the lzd cps obtained in Phase II trials. Simulations of the predicted peak and trough cps over 60 days of lzd BID dosing suggest that steady-state is achieved after 3 days with no evidence of excessive accumulation.

Conclusion: A one compartment PK model with combined linear and non-linear elimination adequately describes the PK of lzd. The non-linearity is not expected to result in excessive accumulation with dosing to SS.

INTRODUCTION

The oxazolidinones are a new class of antibiotics that show in vitro and in vivo activity against gram-positive organisms, including *Streptococcus pneumoniae* resistant to penicillin and other classes of antibiotics. Linezolid is an oxazolidinone that has shown bactericidal effects against *S pneumoniae* in preclinical studies and clinical and microbiological efficacy against *S pneumoniae* in Phase II clinical trials in adults with community acquired pneumonia.

METHODS

Data

A Phase I Assessment of Absolute Bioavailability
- single-dose, open-label, two-way crossover study (compressed tablets given while fed and fasted) of 375 mg linezolid
- an added third phase (intravenous) of 375 mg linezolid to healthy subjects
- a seven-day washout between each treatment period
- detailed pharmacokinetic monitoring performed at baseline and specified times over 48 hours following the administration of the single-dose
- samples associated with the doses of linezolid administered in the presence of food were excluded for this analysis

A Phase I Single- and Multiple-Dose Pharmacokinetic Evaluation of Dose Proportionality
- randomized, open-label, single- and multiple-dose study conducted as a three-way crossover, evaluating doses of 125 mg, 375mg and 625 mg of linezolid in healthy subjects
- a 14-to-16 day washout interval between periods
- subjects received a single oral dose of linezolid on day one of each treatment
- intense pharmacokinetic monitoring performed at specified times over the next 24 hours
- at the end of this 24 hour period, subjects received multiple-doses of linezolid every 12 hours on day 2, day 3 and day 4
- on the morning of Day 5, all subjects received their last dose of linezolid with intense pharmacokinetic sampling performed over the next 48 hours

Phase II Clinical Trials
- A total of 5213 linezolid concentrations collected from 687 patients enrolled in selected linezolid Phase II clinical trials evaluating pneumonia and skin and soft tissue infections were available for analyses.
- Doses included in the data set were 100, 200, 375, 600, and 625 mg BID and 250 and 375 mg TID.
- Both oral and IV administration were employed.

Pharmacostatistical Model

As series of linear and non-linear models were evaluated, all models presented were fit to the data using version V of the NONMEM computer program.

Statistical Analysis
- Statistical significance was assessed by the change in the log likelihood value obtained for various models (the NONMEM objective function). When alternative models could not be cast as hierarchical, the change in the objective function was only used as a qualitative measure of statistical significance.
- In order to evaluate model bias, the percent prediction errors were calculated using the following equation:

$$\% \text{ Prediction error} = \frac{(\text{Measured Cp} - \text{Predicted Cp})}{\text{Predicted Cp}} \times 100$$

The mean percent prediction error was calculated by taking the average of all percent prediction errors across all observations.

RESULTS

Noncompartmental Analyses

A small degree of nonlinearity was observed in linezolid pharmacokinetics at higher concentrations of drug - achieved either through higher doses or with multiple dosing. Total clearance of linezolid was about 30% lower after a 625- mg dose than would be expected based on a 125- mg dose. This decrease in clearance was due to a decrease in both the renal and nonrenal clearance components of linezolid elimination. This small degree of dose- dependency was observed after single or multiple doses. Upon multiple dosing, the total clearance decreased about 10% relative to the single- dose estimates. Renal elimination of linezolid accounted for about one- third of the elimination of linezolid, and remained constant, as does the elimination half-life, with increasing dose and with multiple dose.

TABLE 1. Pharmacokinetic Parameters and Statistical Comparison of Linezolid After Oral Single and Multiple Doses n=19 Mean ± SD (%CV) (Range)

	Day 1 Treatment				Day 5 Treatment			
Parameter	A- 125 mg	B- 375 mg	C- 625 mg	p-value	A- 125 mg	B- 375 mg	C- 625 mg	p-value
Cmax, µg/mL	2.3* ± 0.6 (28%) (1.3 to 3.7)	7.7* ± 2.1 (27%) (4.9 to 12.0)	13.2* ± 3.1 (23%) (8.8 to 21.0)	0.0001 A B C	3.2* ± 1.3 (38%) (1.4 to 5.5)	10.8* ± 4.4 (41%) (6.1 to 22)	20.0* ± 6.8 (34%) (13 to 36)	0.0001 A B C
Tmax, hours	1.2 ± 0.9 (0.5 to 3)	1.2 ± 0.8 (0.5 to 3)	1.0 ± 0.4 (0.5 to 2)	NS	1.1 ± 0.6 (0.5 to 3)	1.2 ± 0.6 (0.5 to 3)	1.1 ± 0.9 (0.5 to 4)	NS
CL/F, mL/min (43%)	147 ± 75 (51%) (55 to 360)	118 ± 54 (45%) (29 to 269)	103* ± 39 (38%) (52 to 198)	0.0004 A B C	160 ± 100 (63%) (42 to 420)	113 ± 50 (44%) (53 to 210)	88* ± 35 (40%) (33 to 156)	0.0001 A B C
% of Dose in Urine as Linezolid	33.4 ± 14.7 (9.8 to 70.2)	33.1 ± 12.0 (16% (10.6 to 63.2)	32.6 ± 11.0 (34%) (18.4 to 52.4)	NS	34.9 ± 20.5(59%) (6.4 to 73)	28.4 ± 17.8(50%) (4.7 to 75.8)	36.2 ± 15.6 (43%) (11.7 to 71.2)	NS

* Difference is statistically significant between Day 1 and Day 5 by paired t-test. AUC = AUC0- for Day1 and AUC0-12 for Day5. AUC norm and Cmax norm are dose-normalized parameters to a 125 mg dose. NS = not statistically different among treatments by ANOVA. A = NOT Statistically different among treatments on either Day 1 or Day 5 by ANOVA.

FIGURE 1. Mean plasma linezolid concentrations after a single oral dose and at steady-state.

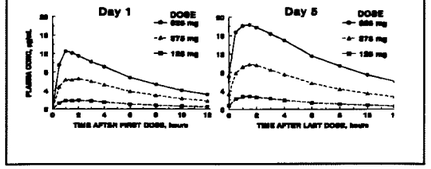
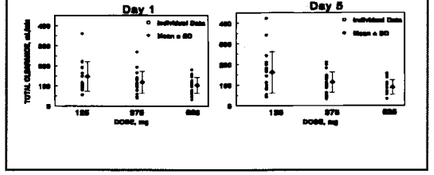


FIGURE 2. Linezolid clearance as a function of oral dose and day.



Compartmental Analysis

In order to develop a model for the Phase II data, data from the bioavailability and dose proportionality studies were pooled. Previous data suggests that samples collected at least 24 hours following the dose may have been influenced by multi compartmental disposition. Given that there was a small number of concentrations collected during this time period, and the inability of the data to support a two-compartment model, they were excluded from the analysis. In addition, concentrations collected during IV infusion, and intervening trough concentrations were also excluded.

After the above data exclusions, there were 1937 concentrations from 31 patients available for analysis.

Model Development
- Previous noncompartmental analyses, described above, suggest that a small amount of non-linearity was observed.
- An initial anlaysis using a one-compartment linear model applied to the oral data from the dose proportionality study resulted in significant bias, thus a non-linear model for oral administration was explored.

Step 1: Michaelis-Menten Model – Oral Data
A Michaelis-Menten model was applied to the single and multiple dose data separately, but evidence of model misfit still remained.

Step 2: Michaelis-Menten and Linear Elimination Applied to Single Dose Oral Data
A one compartment model with linear and Michaelis-Menten elimination with a proportional error model was applied to the single dose data. The addition of the linear component to the elimination model reduced the minimum value of the objective function by 26 units and slightly reduced the bias seen in the goodness of fit plots.

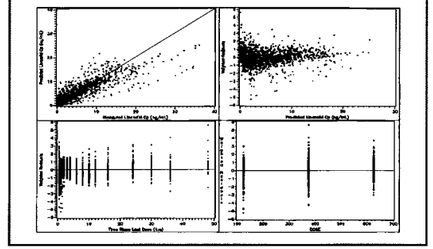
Step 3: Michaelis-Menten and Linear Elimination Applied to Single and Multiple Dose Oral Data Combined
- Applying the Michaelis-Menten plus linear elimination model with an additive plus proportional error model to the combined single and multiple dose data. The Km value for the combined data was 1210 versus a value of 402 for the single dose data. This large change in the Km value between single dose and multiple dose data had also occurred when evaluating the standard Michaelis-Menten elimination model (Km = 1070 and Km = 1800, respectively). Because all of the concentrations after multiple dosing are much smaller than the estimated Km for the models with multiple dose data, this change in the Km value suggests that the structural model is approaching linearity after multiple dosing (with an elimination rate of (Vm/Km + K).
- Based upon the change in behavior of the models for the single dose versus multiple dose data, it was hypothesized that a factor might be acting as a competitive inhibitor. Therefore, it was decided to test this hypothesis by introducing a hypothetical factor compartment to the model.

Step 4: Linear plus Michaelis-Menten Elimination with Competitive Inhibition – Oral Data
- The hypothetical factor was modeled by adding one compartment to the model with an equilibration rate constant of Kf (similar to Keo for a hypothetical effect compartment in PD analysis).
- Compartment #1 = Depot, Compartment #2 = Central Compartment, and Compartment #3 = Hypothetical Factor Compartment.
- The Michaelis-Menten elimination pathway with competitive inhibition from the hypothetical factor was modeled as -Vm*A(2)/(Km*(1+ (1/Kp)*A(3)) + A(2)).
- Parameter Definitions:
  - Kf is the equilibration rate constant for the hypothetical factor compartment.
  - Kp is the equilibrium constant for the enzyme-metabolite (product) complex.
  - Inverse Kp is 1/Kp.
- Results:
  - Residual variability ranged from 1104.71 to 19.34%CV for concentrations ranging from 0.01 to 40 ug/mL.
  - The addition of the inhibition from the hypothetical metabolite compartment noticably improved the fit of the data. Many of the curved patterns and other trends previously noted in goodness of fit plots were no longer present and all parameters were estimated more accurately. The residual variability for concentrations less than 0.5 was also greatly reduced. Given that this model appeared to explain the behavior of the Phase I oral dosing data fairly well, it was decided that this model should serve as the base structural model for the analysis of the Phase II data.

TABLE 2. Parameter Estimates and Standard Errors for the Pharmacokinetic Model with Michaelis-Menten Plus Linear Elimination, with Competitive Inhibition from a Hypothetical Factor Applied to the Data from the Dose Proportionality Study

Parameter	Final Estimates		Magnitude of Interindividual Variability	
	Population Mean	%SEM	%CV	%SEM
Ka	5.86	20.1	245.76	65.1
Vm	30.3	47.5		
Km	341	56.3	95.60	46.0
K	0.0764	8.0	49.70	34.7
V (L/kg)	0.670	2.8	12.88	46.1
Kmet	0.00679	13.5	175.50	39.9
1/kp	0.0145	59.1		
Prop. Err.	0.0374	11.4		
Add. Err.	0.0122	30.8		

FIGURE 3. Goodness of fit plots for the Michaelis-Menten plus linear elimination model and competitive inhibition from a hypothetical factor applied to the data from the dose proportionality study.

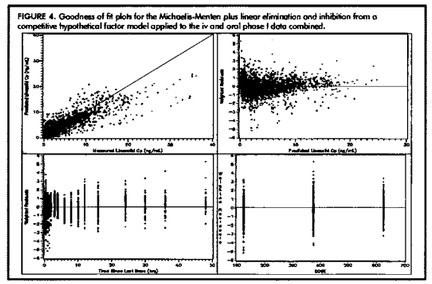


Step 5: Final Phase I model - Michaelis-Menten plus Linear Elimination with Hypothetical Factor applied to IV and Oral Administration Data Combined
- Because the Phase II data consists of IV and oral administration with single and multiple dose regimens, it was decided to test the model on a combination of IV and oral data from Phase I before returning to the analysis of the Phase II data.
- Results:
  - The addition of the IV data from Phase I did not alter the fit of the model. Km increased slightly but the estimate was still reasonable. The goodness of fit plots did not show any biases. Thus, this model will be applied to the Phase II data.

TABLE 3. Final Parameter Estimates and Standard Errors for the Michaelis-Menten plus Linear Elimination and Inhibition from a Hypothetical Factor Applied to the IV and Oral Phase I Data Combined

Parameter	Final Estimates		IIV	
	Population Mean	%SEM	%CV	%SEM
Ka	4.52	13.6	154.92	27.3
Vm	38.0	45.3		
Km	466	45.9	80.00	24.5
K	0.0745	9.0	51.87	35.1
V (L/kg)	0.672	2.2	12.92	36.6
Kmet	0.00781	19.5	194.94	33.9
1/kp	0.0100	54.3		
Prop. Err.	0.0370	9.5		
Add. Err.	0.0153	33.4		

FIGURE 4. Goodness of fit plots for the Michaelis-Menten plus linear elimination and inhibition from a competitive hypothetical factor model applied to the iv and oral phase I data combined.

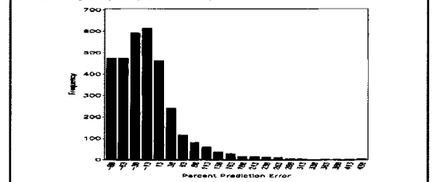


Applications To Phase II

The final Phase I model was used to predict the linezolid concentrations collected from selected Phase II clinical trials evaluating patients with pneumonia and skin and soft tissue infections.

Percent prediction errors were calculated for a measure of model bias.
- The mean (SD) percent prediction error was -4.7 (134.2).
- Further evaluation of the percent mean prediction error showed that the median value (- 20.9). Indicating that the trend for the model to overpredict was more reflective of model performance. Because the model does not incorporate covariate effects, and the Phase II population was composed of a more diverse group of patients, these results were considered adequate for a basic Phase II model.

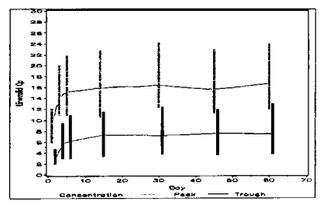
FIGURE 5. Histogram of percent prediction errors for phase II clinical data.



18 observation with percent mean predictions greater than 500 were excluded for graphical purposes

- In order to evaluate the model for evidence of accumulation over time, 200 patients receiving oral 600 mg BID were simulated using weights representative of the Phase II patient population. Peak and trough concentrations were simulated on days 1, 3, 5, 14, 30 and 45. From figure 6 below, it can be seen that steady-state is achieved after 3 days with no evidence of excessive accumulation.

FIGURE 6. Boxplots of simulated peak and trough concentration in patients receiving linezolid 600 mg , orally, BID.



Boxes range from the 25 to 75 percentile with the median from each box joined.
Peak concentrations were simulated 1 hr following the dose.
Trough concentrations were simulated 11.9 hrs after the dose.

CONCLUSIONS

Noncompartmental
- Overall, the pharmacokinetics of linezolid are dose- dependent, but only to a minor degree (30% decrease in clearance with a 5- fold increase in dose).
- Although the pharmacokinetics of linezolid have been shown to be statistically dependent on dose, the degree of nonlinearity is small relative to the overall degree of variability among subjects such that dose-adjustments in the clinical use of the drug are not considered necessary.

Compartmental
- A one-compartment pharmacokinetic model with combined linear and non-linear elimination and inhibition from a hypothetical factor adequately describes the pharmacokinetics of linezolid.
- The non-linearity is not expected to result in excessive accumulation with dosing to steady- state.
- Because all of the concentrations after multiple dosing are much smaller than the estimated Km for the models with multiple dose data, this change in the Km value suggests that the structural model is approaching linearity after multiple dosing (with an elimination rate of (Vm/Km + K).