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Population Pharmacokinetics (PK) of Linezolid in Patients with Community-Acquired Pneumonia (CAP) and Skin and Soft Tissue (SST) Infections

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ABSTRACT

Background: A population PK analysis from 3 linezolid (LZD) trials was performed to estimate PK parameters in patients with CAP and SST infections, and evaluate patient covariate influence on LZD PK.

Methods: Sparse samples were obtained from patients administered low (750 mg/day) or high (1125-1250 mg/day) dosage LZD IV, then orally. A total of 3,238 LZD concentrations from 655 patients were available. Patient covariates were explored with univariate analysis and significant findings were combined into a full multivariable model using forward selection and backward elimination in NONMEM.

Results: The most robust model that could be adequately fit was a one compartment model with first-order absorption (Ka) and parallel linear (Ke) and non-linear (Km, Vm) elimination. The mean parameter estimates (% SEM) were: 0.802 (30.7) hr^{-1} for Ka, 75.5 (11.7) mg/hr and 378 (16.7) mg for Vm and Km. Although the linear elimination process was 111% higher in non-whites compared to other races, there was no significant effect on total clearance. For a 52-year-old white male weighing 84.4 kg, clearance was estimated to be 6.96 and 4.51 L/hr at usual steady-state concentrations for the low and high dose groups. The non-linear clearance component represented 88.5 and 82.3 percent of total clearance, but significant accumulation is not expected based on 60 day simulations. Men have a 12% higher Vd than women. The Vd increased by a factor of 0.351 for total body weight and decreased by a factor of 0.21 for age.

Conclusions: A one-compartment model with linear and non-linear elimination adequately describes lzd PK. Covariate effects were small and not sufficient to require dosage adjustment. At doses expected in clinical use, extensive accumulation is not expected.

INTRODUCTION

Linezolid (LZD) is an oxazolidinone that selectively inhibits bacterial protein synthesis through interruption of bacterial RNA translation. This agent has been effective in the treatment of staphylococcal and streptococcal skin and soft tissue infections (SST) including infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and community-acquired pneumonia (CAP), including infections caused by penicillin-resistant *Streptococcus pneumoniae*. LZD pharmacokinetics were investigated in Phase I studies. The compound has an elimination half-life of 5-7 hours. Approximately 35% of an administered dose of LZD appears in the urine as the parent compound, and approximately 50% appears as two inactive metabolites. Nonrenal clearance of LZD is mediated by nonenzymatic chemical oxidation, and approximately 31% of the administered drug is bound to proteins. This study was undertaken to further elucidate LZD pharmacokinetics in patients with CAP and SST infections, and to examine the influence of patient covariates (eg, age, gender, body weight, race, renal function) on LZD pharmacokinetics.

METHODS

Data

- Data was obtained from the 3 Phase II linezolid clinical trials described in **Table 1**.

Pharmacostatistical Model

- NONMEM version V used to fit the model to the data
- Interindividual variability – exponential error model
- Residual variability – combination additive plus constant coefficient of variation error model
- One compartment model with first order absorption and parallel linear and non-linear elimination

METHODS (continued)

TABLE 1: Phase II Linezolid Clinical Trials Included in the Population Pharmacokinetic Analysis

Indication	Study Description	Doses Administered	# of Patients Enrolled	# of Blood Samples per Patient
Community Acquired *S. pneumononiae* Pneumonia (CAP)	An open-label, dose comparative Phase II study of IV therapy with optional oral continuation	250 mg TID 375 mg BID or TID 625 mg BID	178	9
Skin & Soft Tissue Infections (SST)	An open-label, dose comparative Phase II study of IV therapy with optional oral continuation	250 mg TID 375 mg BID or TID 625 mg BID	339	9
Skin & Soft Tissue Infections	An open-label, randomized, dose comparative Phase II study of low dose linezolid	100 mg BID 200 mg BID	189	4

Patient Covariate Analysis

- ***Covariates***: age, total body weight, creatinine clearance (estimated by the Cockcroft & Gault method), gender and race (white, black or other)

Statistical Analysis

- Statistical significance assessed by the change in the log likelihood value obtained from the NONMEM objective function
- For univariate analyses, statistical significance was defined as a change in the minimum value of the objective function of at least 3.84 (α = 0.05, 1 degree of freedom) for the addition of a single parameter; for multivariable backward elimination, a change of at least 6.63 (α = 0.01, 1 degree of freedom) was used for the deletion of a single parameter.

RESULTS

Data

- 3,205 linezolid concentrations from 655 patients were available for model development

TABLE 2: Demographic Data from Phase II Linezolid Clinical Trials Included in the Population Pharmacokinetic Analysis

Patient Characteristics	All Studies Combined* n mean (SD)
Weight (Kg)	655 82.2 (24.0)
Age	655 50.1 (17.7)
CrCl	655 87.2 (37.6)
Gender n (%) Males Females	 409 (62.4) 246 (37.6)
Race n (%) White Black Asian Other	 482 (73.6) 129 (19.7) 2 (0.3) 42 (6.4)

*The combined patient population included patients with CAP (25%), and SST infections (48% and 27% from the 2 studies)

RESULTS (continued)

Final Pharmacokinetic Model

TABLE 3: Final Pharmacokinetic Model of Linezolid Applied to the Dataset with all Concentrations Associated with Absolute Weighted Residuals >8 Included – Final Parameter Estimates and Standard Errors

Parameter	Population Mean		Magnitude of Interindividual Variability (% CV)	
	Final Estimate	% SEM	Final Estimate	% SEM
$Ka(1/hr)$	0.802	30.7	101.00	49.7
$Km(mg)$	378	16.7	56.83	23.3
$K^{int}(1/hr)$	0.0135	42.8	65.88	54.8
K^{race}	1.11	55.0		
$V^{int}(L)$	23.4	16.8	18.38	23.1
$V^{WTKG}(L/Kg)$	0.351	17.6		
$V^{frac}_{Age}(L/yrs)$	-0.0088	35.0		
V^{gender}	0.124	40.5		
$Vm(mg/hr)$	75.5	11.7		
Bioavailability	1.24	3.2		

Min. value of obj. function = 10300.965

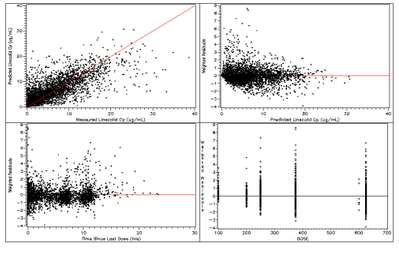
$$K(1/hr) = K^{int} \bullet \left(1 + K^{race} \bullet RACEN\right)$$

where RACEN=0 for white, 1 for all others

$$V(L) = \left[V^{int} + \left(V^{WTKG} \bullet WTKG\right) + \left(V^{int} \bullet V^{frac}_{Age} \bullet (Age - 50)\right)\right] \bullet \left(1 + V^{gender}(1 - GENDER)\right)$$

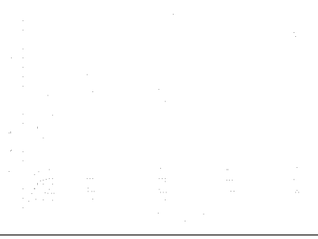
- Residual variability ranged from 5754.3% CV to 28.0% CV for concentrations ranging from 0.03 to 30.7 ug/ml
- Goodness-of-fit plots shown below (**Figure 1**)
- No accumulation because of non-linear pathway is anticipated based on simulations to 60 days (**Figure 2**)

FIGURE 1. Scatterplots for the final pharmacokinetic model applied to the datasets with all concentrations associated with absolute weighted residuals >8 included: (upper left) predicted linezolid concentrations (ug/mL) versus measured linezolid concentrations (ug/mL), (upper right) weighted residuals versus predicted linezolid concentration (ug/mL), (lower left) weighted residuals versus time since last dose (hrs), (lower right) weighted residuals versus dose.



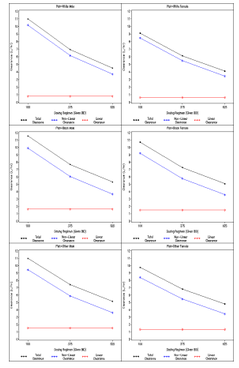
RESULTS (continued)

FIGURE 2. Boxplots of simulated peak and trough concentrations associated with BID Oral dosing to 60 days.



- Based on the parameter estimates for the from the final model, the total clearance for a 52 year old white male patient weighing 84.4 kg was estimated to be 10.99, 6.96, and 4.51 at steady-state concentration values of 1.02, 5.86, and 13.94. The non-linear component of clearance represented 92.73, 88.53, 82.30 percent of the total clearance. (**Figure 3**)

FIGURE 3. Lineplots of linear clearance, total clearance for a given Css versus dose stratified by patient demographic characteristics.



CONCLUSION

- **The most robust model that could be fit to the current database was a one compartment model with first-order absorption and parallel linear and non-linear elimination.**
- **Covariate analysis indicated that the first-order elimination process was influenced by race, however no changes in total clearance were identified and dosage adjustment is not required. Weight, age and gender also were significant covariates of volume of distribution**
- **Although non-linear clearance is a substantial component of linezolid total clearance, significant accumulation is not anticipated even at the higher dose level based on 60 day simulations.**