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Population Pharmacokinetics (PK) Of Linezolid In Neonates And Young Infants

M. Vo[1], B.B. Cirincione[1], C.M. Rubino[1], and G. L. Jungbluth[2]

[1]Cognigen Corporation, Buffalo, NY and [2]Pharmacia Corporation, Kalamazoo, MI

Pharmacia Corporation
301 Henrietta Street
Kalamazoo, MI 49007-4940
Telephone: (616) 833-1359
Fax: (616) 833-1735

ABSTRACT

Background: Linezolid (LZD) is the first approved oxazolidinone antibiotic and has shown broad activity against gram-positive bacteria, including VRE and MRSA. Previous studies indicated LZD clearance was higher in pediatric patients than in adult patients. In order to characterize the impact of age-related changes in LZD PK, a population PK model was developed using data from neonates and young infants.

Methods: Patients aged birth to 3 months with varying gestational ages received a single dose of 10 mg/kg LZD as a one-hour intravenous infusion. Up to five blood samples were collected at 1.17, 2, 4, 6, and 12 hours after the start of infusion. Population PK parameters were estimated and the impact of patient covariates were evaluated using NONMEM® V. Individual AUC estimates were compared with those from a traditional compartmental analysis.

Results: A total of 199 LZD concentrations from 42 patients were evaluated. A one-compartment model with nonlinear elimination, interindividual (IIV) errors on volume of distribution (Vd) and maximum rate of elimination (Vm), and a log residual variability model best described the population PK of LZD. The population mean Vd and Michaelis constant (Km) were 0.67 L/kg and 20 mg/L. IIV in Vm and Vd was estimated to be 28% and 20%. The Vm increased rapidly during the first week after birth then leveled out. In addition, at any given postnatal age, term infants (>= 34 weeks gestation) had a higher Vm (mean = 21 mg/hr) than preterm infants (mean = 15 mg/hr). Individual estimates of AUC from the model were in agreement with those from the compartmental analysis.

Conclusions: Based on this model, elimination of LZD in neonates and young infants appears to be a concentration-dependent process. LZD Vd is highly correlated with weight regardless of gestational status, while elimination is dependent on both gestational and postnatal age. The greatest period of increase in Vm was seen in the first week after birth.

INTRODUCTION

Linezolid is the first oxazolidinone antibiotic approved for the treatment of adult patients with VRE, nosocomial pneumonia, skin and skin structure infections, and community acquired pneumonia. Data from Phase I studies in children have demonstrated that pediatric patients dosed with 10 mg/kg I.V. have a similar maximum plasma concentration but higher clearance when corrected by body weight, and shorter apparent elimination half-life than adults receiving 600 mg of linezolid. This analysis of a single-dose population pharmacokinetics study was conducted to further elucidate linezolid pharmacokinetics in neonates and young infants.

OBJECTIVES

- To develop a population pharmacokinetic model for linezolid in neonates and young infants,
- To evaluate the influence of patient demographic characteristics on the pharmacokinetic parameters,
- To compare the pharmacokinetic parameter estimates obtained from the population analysis with those obtained from traditional, compartmental analysis.

METHODS

Study Design

- Data were obtained from a multicenter, open-label, single dose, PK study
- Patients aged from birth to 3 months. Both term and preterm infants were enrolled.
- Each patient received a single dose of 10 mg/kg of linezolid as a 60-minute intravenous infusion.
- Samples for linezolid concentrations were drawn at pre-dose, and approximately 1.17, 2, 4, 6, and 12 hours after the start of infusion.

Data Management

- All concentrations recorded as being below the lower limit of quantification of assay were removed from the dataset.
- Body surface area (BSA) was calculated using the method of Gehan and George (Ref: Statistics in Medicine 1996;15: 1325-1332):
- BSA = 0.0235 * height(cm)$^{0.422}$ * weight(kg)$^{0.515}$

METHODS

Pharmacostatistical Model

- NONMEM version V was used to fit the model to the data
- Interindividual variability – exponential error model
- Residual variability – log residual variability model

Patient Covariate Analysis

- The following covariates were evaluated for their impact on the interindividual variability in linezolid pharmacokinetics: postnatal age (PNA), gestational age (GAGE), post-conceptional age, body weight (WTKG), BSA, race, and sex.

Statistical Analysis

- Statistical significance was 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.

Exposure Comparison

- Individual estimates of area under the concentration time curve (AUC_{0-12}) were obtained by generating a predicted concentration versus time profile for each patient using the individual post-hoc estimates of the PK parameter values and applying the trapezoid rule to that predicted profile.
- AUC_{0-12} values were compared to results obtained from traditional analysis results as a means of model validation.

RESULTS

Data

- 199 LZD concentrations from 42 patients were available for model development.
- The majority of patients contributed 5 concentration values.

TABLE 1. Demographic Characteristics of Patients

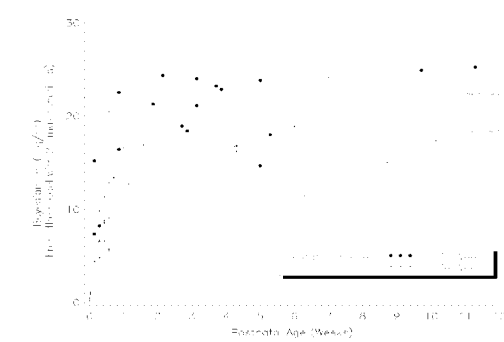
Variable	n (%)	Mean (SD)	Minimum	Median	Maximum
Postnatal Age (wks)	42	2.83 (3.07)	0.14	1.36	11.29
Gestational Age (wks)	42	35 (3.8)	25	34	40
Height (cm)	42	47.2 (5.75)	32	47	58
Weight (kg)	42	2.78 (1.24)	0.74	2.34	6.2
Body Surface Area (m^2)	42	0.2 (0.06)	0.09	0.18	0.32
Sex					
Males	28 (67)	----	----	----	----
Females	14 (33)				
Ethnicity					
Caucasian	35 (83)	----	----	----	----
Other	7 (17)				

RESULTS

Model Development

- A one-compartment model with Michaelis-Menten elimination.
- Parameter Estimates: Maximum rate of elimination (Vm), Michaelis constant (Km), and volume of distribution (Vd)
- Intervariability (IIV): Evaluated in Vm and V

FIGURE1. Scatterplot of individual Bayesian estimates of Vm versus postnatal age, stratified by gestational age – population mean curve from separate functions overlaid.



Final Pharmacokinetic Model

TABLE 2. Final Population Pharmacokinetic Model Developed Using the Single Dose LZD Data

Parameter	Population Mean		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
GAGE less than or equal to 34 weeks Max. PNA Effect on Vm	18.7	16.6	27.57	25.4
GAGE less than or equal to 34 weeks 50% of PNA Effect on Vm	0.490	23.5		
GAGE greater than 34 weeks Max. PNA Effect on Vm	22.4	13.8		
GAGE greater than 34 weeks 50% of PNA Effect on Vm	0.203	52.2		
Km	38.1	14.3	----	----
Vd WTKG coefficient	0.928	7.2	19.82	36.9
Vd WTKG power term	0.891	7.1		
Residual Variability (Log SD)	0.12	25.7	----	----

Minimum Value of the Objective Function = -390.808 Max. = Maximum value for Vm (mg/hr) EC50 = Age(weeks) when Vm is at 50% of maximum

The typical values of Vm, Km, and Vd can be calculated using the following equations:

For patients with gestational age ≤ 34 week: $Vm(mg/hr) = \frac{18.7 * PNA}{(0.490 + PNA)}$

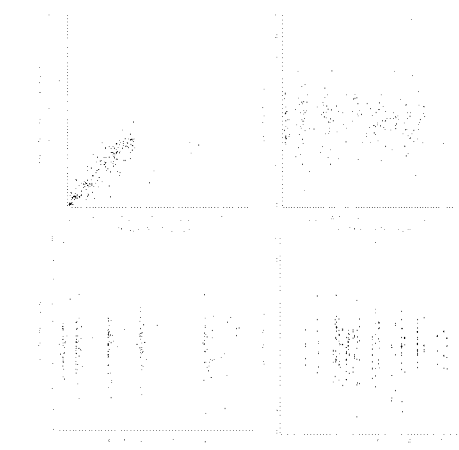
For patients with gestational age > 34 weeks: $Vm(mg/hr) = \frac{22.4 * PNA}{(0.203 + PNA)}$

$$Km\ (mg) = 38.1$$

$$Vd\,(L) = 0.928 * WTKG^{(0.891)}$$

RESULTS

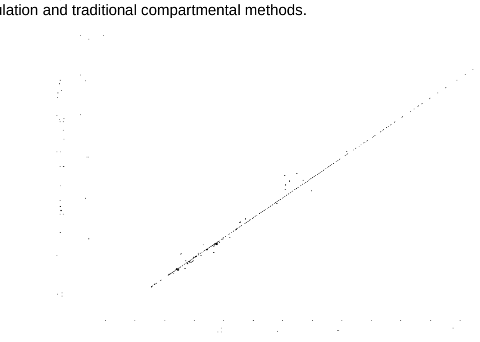
FIGURE 2. Scatterplots for the final population pharmacokinetic model: (upper left) predicted versus measured linezolid concentrations [ng/mL]; (upper right) weighted residuals versus predicted linezolid concentration [ng/mL]; (lower left) weighted residuals versus time since last dose [hrs]; (lower right) weighted residual versus linezolid dose [mg].



Exposure Comparison

- There was good agreement between the individual estimates of AUC_{0-12} from the population model and those from the traditional compartmental analysis.

FIGURE 3. Scatterplot of individual estimates of area under the concentration-time curve as calculated using population and traditional compartmental methods.



CONCLUSIONS

- **Based on this model, elimination of linezolid in neonates and young infants appears to be a concentration-dependent process.**
- **Linezolid Vd is highly correlated with weight regardless of gestational status, while elimination is dependent on both gestational and postnatal age.**
- **The greatest period of increase in Vm was seen in the first week after birth.**
- **This pharmacostatistical model has potential utility in the analysis of sparse sampling data obtained in future studies of linezolid for the treatment of infections in neonates and young infants.**