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

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ABSTRACT

Background: Linezolid (LZD) is the first approved oxazolidinone antibiotic and has shown broad activity against gram positive infections, 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 12 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®. 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 non-linear elimination, inter-individual (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 Vm and Michaelis constant (Km) were 0.67 L/hr and 20 mg/L, respectively. Vm and Vd were estimated to be 25% and 25%. The Vm increased rapidly during the first week after birth and then leveled off. In addition, at any given postnatal age, term infants (>24 weeks gestation) had a higher Vm (mean = 21 mg/hr) than preterm infants (mean = 15 mg/hr). Individual estimates of the PK parameter values 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 infections, 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 LZD 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. The analysis of a single-dose population pharmacokinetic 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

Data

199 LZD concentrations from 42 patients were available for model development.

The majority of patients contributed 5 or more concentrations.

RESULTS

TABLE 1. Demographic Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Minimum</th>
<th>Median</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal Age (days)</td>
<td>62 (25.6)</td>
<td>11.0</td>
<td>31.5</td>
<td>112.0</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>62 (25.6)</td>
<td>26.0</td>
<td>30.5</td>
<td>63.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>62 (25.6)</td>
<td>91.5 (5.6)</td>
<td>82</td>
<td>107</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62 (25.6)</td>
<td>2.34 (2.08)</td>
<td>0.96</td>
<td>3.96</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>62 (25.6)</td>
<td>0.59 (0.12)</td>
<td>0.49</td>
<td>0.81</td>
</tr>
<tr>
<td>Sex</td>
<td>28 (67)</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Gender</td>
<td>14 (33)</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Race</td>
<td>28 (67)</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>28 (67)</td>
<td>----</td>
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</tbody>
</table>

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

For patients with postnatal age < 24 weeks:

Vm = 0.435 * weight (kg) + 0.14
Km = 0.025 * weight (kg)
Vd = 0.025 * weight (kg)

For patients with postnatal age ≥ 24 weeks:

Vm = 0.422 * weight (kg)0.515
Km = 0.155 * weight (kg)0.355
Vd = 0.025 * weight (kg)0.515

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 pharmacokinetic 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.