Pharmacokinetic/Pharmacodynamic Analysis of Data From a Phase III Trial of Linezolid IV/PO for the Treatment of Resistant Gram-Positive Bacterial Infections in Children

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ABSTRACT

Purpose: Linezolid (LZD), the first approved oxazolidinone antibiotic against Gram-positive cocci, was evaluated in a Phase III, randomized, blinded, comparator-controlled trial for the treatment of resistant Gram-positive infections. The study was designed to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of LZD in children aged 0 to 11 years. Methods: Samples were obtained from children aged 0 to 11 years, 2 to 11 years, and 12 to 18 years, respectively. The study population consisted of children aged 0 to 11 years, 2 to 11 years, and 12 to 18 years, respectively. The study population consisted of children aged 0 to 11 years, 2 to 11 years, and 12 to 18 years, respectively.

RESULTS

• LZD concentrations from 195 patients were available for the PK analysis. The mean predicted AUC 0-24 in patients aged 0 to 11 years (147 ± 62 mg·h/mL) was lower than that after intravenous administration. In contrast, the population mean predicted Cmin after IV infusion was lower than that after PO administration.

• The mean percent time above MIC90 after oral administration was higher than after intravenous administration (63% for oral and 54% for intravenous).

• No association was observed between exposure and safety indices.

• The pharmacokinetics between the linezolid oral formulation and the linezolid IV formulation were comparable.

CONCLUSIONS

• The pharmacokinetic and pharmacodynamic results of linezolid in children were comparable to those in adults, even when corrected for body weight and age. This was true for both oral and parenteral formulations.

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ABSTRACT

Purpose: Linezolid (LZD), the first approved oxazolidinone, is effective against Gram-positive infections. Population pharmacokinetic/pharmacodynamic (PK/PD) analyses of Phase III data were conducted to evaluate exposure-response relationships in children to support its multiple-dosing regimen.

Methods: Serum samples were obtained from patients aged 6 to 16 years (N=345) every 6 hours, and patients were administered a single 600 mg every-12-hour dose. The study was conducted in 3 countries in 30 centers. Modeling and simulation methods were used to develop population pharmacokinetic models and to predict individual (PK) pharmacokinetic parameters and measures by Bayesian (PBPK) analysis. Population PK/PD analysis was conducted to evaluate relationships between pharmacokinetics (PK) and pharmacodynamics (PD) in children. The MIC (minimum inhibitory concentration) of LZD for individual pathogens was determined using the Etest or broth dilution technique. Data were analyzed using NONMEM software. Exposures were defined as area under the concentration-time curve (AUC) and maximum concentration (Cmax).

Results: Mean Cmax was 147 mcg/mL (SD 87 mcg/mL) and mean AUC0-24 was 175 mcg*h/mL (SD 128 mcg*h/mL). Both Cmax and AUC were greater in children than in adults. Using PBPK model (Vd: volume of distribution; Km: Michaelis constant; PNA: time constant) and analysis of variance, children were found to have greater variability in PK parameters (CL and Vd) than adults. In children, 10 mg/kg IV was associated with lower variability in Cmax compared to 600 mg every 12 hours.

Conclusions: The pharmacokinetics between the linezolid oral formulation and the intravenous formulation were comparable. Exposure in children receiving 10 mg/kg linezolid every 8 hours is comparable to that in adults receiving 600 mg linezolid every 12 hours. No association was observed between exposure and safety indices. The pharmacokinetics of linezolid in children were similar to those of adults.

INTRODUCTION

The purpose of this study was to evaluate the pharmacokinetics and pharmacodynamics of linezolid (LZD) in children aged 0-16 years with suspected or proven resistant Gram-positive bacterial infections. The study was conducted as a Phase III, randomized (2:1 LZD to vancomycin), open-label, comparator-control, multicenter, PK/PD study. Patients were enrolled in the study if they had a documented or suspected resistant Gram-positive bacterial infection and were 6-16 years of age. The study population included patients with suspected or confirmed infection with E. faecium, S. aureus, or Enterococcus species. The study was conducted in 30 centers in 3 countries.

RESULTS

The exposure-response relationships were only evaluated graphically. No statistical analyses were performed.

EXPOSURE-RESPONSE ANALYSES

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CONCLUSIONS

The pharmacokinetics between the intravenous formulation and the intravenous formulation were comparable. Exposure in children receiving 10 mg/kg every 8 hours is comparable to that in adults receiving 600 mg every 12 hours.

METHODS

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The pharmacokinetics between the intravenous formulation and the intravenous formulation were comparable. Exposure in children receiving 10 mg/kg every 8 hours is comparable to that in adults receiving 600 mg every 12 hours.