Population Pharmacokinetic/Pharmacodynamic Analyses of Cefidrofur in Subjects without Infection and Patients with Complicated Urinary Tract Infection and Acute Uncomplicated Pyelonephritis

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Abstract

Background: Cefidrofur (also known as S-648346) is a novel parenteral cephalosporin antibiotic discovered by Shinogu & Co., Ltd, which exhibits potent efficacy against various Gram-negative bacteria including carbapenem-resistant strains. The aim of this study is to perform a population pharmacokinetic (PK) analysis based on plasma concentrations of cefidrofur in subjects without infection and patients with complicated urinary tract infection (UTI) with or without pyelonephritis, or acute uncomplicated pyelonephritis (AUP) caused by Gram-negative pathogens, and evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship based on the fraction of time for which free drug concentration in plasma exceeds the MIC over dosing interval ($\theta_{MIC}$).

Methods: A population PK analysis was performed using a total of 2,317 cefidrofur concentrations in plasma from 93 phase 3 subjects with varying renal function and 328 patients with AUP or UTI. Covariates were explored from subjects’ background data. PK/PD analyses were performed to evaluate the relationship between $\theta_{MIC}$ and clinical, microbiological, and composite (clinical and microbiological) responses in the patients. Results: Plasma concentrations of cefidrofur were adequately described by the developed models. Renal function markers, body weight, and disease status (with or without infection) were significant covariates. Renal function markers were the most influential factors. The post-hoc analysis suggested that the effect of body weight on PK would not be clinically significant. Clearance and volume of distribution of cefidrofur were 26% and 35% higher in patients with WBCs, respectively, than those in subjects without infection, while $\theta_{MIC}$ values were more than 75% in all patients (100% $\theta_{MIC}$ in most patients). The dose required for PK/PD relationship was not identified for any efficacy responses. The PK/PD analysis was confirmed by high urine concentrations of cefidrofur.

Conclusions: Cefidrofur PK would be predictable with renal function markers. The exposure to cefidrof in patients with infection would be slightly lower than that in subjects without infection. A sufficient exposure to cefidrofur was provided to the tested dose regimens for the treatment of AUP and CAUTI caused by Gram-negative uropathogens.

Introduction and Purpose

Cefidrofur (also known as S-648346) is a novel parenteral cephalosporin antibiotic discovered by Shinogu & Co., Ltd, which exhibits potent efficacy against various Gram-negative bacteria including carbapenem-resistant strains. We have already reported the population pharmacokinetic (PK) analysis for healthy subjects and subjects with varying renal function [1]. The aim of this study is to perform a population PK analysis based on plasma concentrations of cefidrofur in subjects without infection and patients with complicated urinary tract infection (UTI) with or without pyelonephritis, or acute uncomplicated pyelonephritis (AUP) caused by Gram-negative pathogens, and evaluate the pharmacokinetic/pharmacodynamic (PK/PD) relationship based on the fraction of time for which free drug concentration in plasma exceeds the MIC over dosing interval ($\theta_{MIC}$).

Results

Population PK Analyses: The parameters are estimated in Table 2. The clear relationships of total clearance (CL) to eGFR, eGFRa, and body weight are demonstrated. The relationship of CL to eGFR is shown in Figure 3. All of the final models provided reasonable prediction for plasma cefidrofur concentrations in patients (Figure 4).

The daily AUC was similar among the renal function-adjusted dose regimens listed for the patients (Figure 5).

PK/PD Analyses: The median (range) of MICs to cefidrofur of the uropathogens isolated in patients included in the PK/PD analysis was 0.02 (4.0 to 80) $\mu$g/mL. The target AUC was set at 75% efficacy (125% in some patients). No clear PK/PD relationships were identified for any efficacy responses (Figure 7).

References


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