

Intrapulmonary pharmacokinetics of cefiderocol, a novel siderophore cephalosporin, in healthy adult subjects

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Background: Cefiderocol, a novel siderophore cephalosporin, has shown potent activity against Gram-negative bacteria, including MDR pathogens. Cefiderocol is under clinical investigation for the treatment of serious Gram-negative infections including nosocomial pneumonia.

Objectives: This study assessed intrapulmonary penetration after a single intravenous dose of cefiderocol (2000 mg infused over 60 min) in healthy adult males.

Materials and methods: Each subject underwent one bronchoscopy with bronchoalveolar lavage (BAL) to collect BAL fluid (BALF). Fifteen subjects were assigned to one of three collection timepoints (1, 2 or 4 h from start of infusion). Five additional subjects were assigned to a collection timepoint at 6 h, which was added based on concentration data between 1 and 4 h predicting measurable BALF cefiderocol concentrations at 6 h.

Results: Cefiderocol concentrations in plasma, epithelial lining fluid (ELF) and alveolar macrophages (AMs) were calculated for each subject. The ELF concentration of cefiderocol was 13.8, 6.69, 2.78 and 1.38 mg/L at 1, 2, 4 and 6 h after single intravenous dosing, respectively. Over 6 h, geometric mean concentration ratios ranged from 0.0927 to 0.116 for ELF to total plasma and from 0.00496 to 0.104 for AMs to total plasma. AUC ratios of ELF and AMs to plasma were 0.101 and 0.0177 based on total drug in plasma, respectively, and 0.239 and 0.0419 based on free drug in plasma, respectively. There were no major drug-related adverse events.

Conclusions: Results of this study indicate that cefiderocol penetrates into ELF, and ELF and plasma concentrations appear to be parallel.

Introduction

The treatment of infections caused by MDR Gram-negative bacteria, including Enterobacteriaceae and the non-fermenting bacteria *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, is an important unmet medical need.¹

Cefiderocol, a novel siderophore cephalosporin, has shown potent *in vitro* activity against Gram-negative bacteria [Enterobacteriaceae, *P. aeruginosa*, *A. baumannii* and *Stenotrophomonas maltophilia*, including MDR pathogens (MIC₉₀, 0.5 to 4 mg/L)].^{2–4} Efficacy in a rat pneumonia model where cefiderocol exposures reproduced the human free drug plasma concentrations of a 2 g dose every 8 h infused over 3 h has been demonstrated against carbapenem-resistant Gram-negative

pathogens.⁵ Cefiderocol is currently under clinical investigation for the treatment of serious Gram-negative infections, including nosocomial pneumonia (ClinicalTrials.gov: NCT02714595, NCT03032380).^{6,7} A dose adjustment of 2 g every 8 h based on renal function was predicted to provide adequate exposure to cefiderocol in pharmacokinetic/pharmacodynamic (PK/PD) modelling and simulation.⁸ Bronchoalveolar lavage (BAL) of human subjects is known to offer information on drug distribution in the lower respiratory tract.⁹ By using the BAL method, this study was designed to assess the intrapulmonary penetration after a single intravenous dose of cefiderocol in healthy adult male subjects in order to support the utility of cefiderocol for the treatment of respiratory infections.

Materials and methods

Ethics

The clinical study was conducted in compliance with International Conference on Harmonisation Guidelines and Good Clinical Practice. The protocol was approved by institutional review boards (approval reference number: 12–14). Subjects were able to understand the study and comply with all study procedures, and provided written informed consent prior to screening.

Study design and subjects

This was a Phase I, single-centre, open-label study in healthy adult male subjects 20 to 40 years of age, with body weight from 50.0 to 80.0 kg, and BMI from 18.5 to <25.0 kg/m². Cefiderocol was administered by a single intravenous infusion over 60 min at a dose of 2000 mg.

PK assessments

Each subject underwent one bronchoscopy with BAL to collect BAL fluid (BALF), and blood was collected prior to the beginning of the bronchoscopy for measurements of urea and red blood cell counts. Fifteen subjects were assigned to one of the three BALF collection timepoints: 1 (just after the completion of the infusion), 2 or 4 h from the start of the infusion. After the study started, it was determined that the BALF concentrations of cefiderocol were predicted to be measurable at 6 h from the start of the infusion based on the concentration data available between 1 and 4 h from the start of the infusion. Taking this into consideration, the BALF collection at 6 h was added, and five subjects were assigned to the additional BALF collection timepoint. BAL was carried out by the infusion of four 50 mL volumes of sterile saline into the subsegmental bronchus of the right middle lobe, and each specimen was immediately aspirated.⁹ The BAL procedure was performed within 1 min. The first aliquot recovered was discarded and the last three were pooled. Alveolar macrophages (AMs; cell pellet) were separated from BALF via centrifugation (400 g for 5 min at 4°C). Each subject underwent blood sampling pre-dose (0 h) and then 1 (just before completion of infusion), 1.5, 2, 3, 4, 6 and 8 h from the start of the infusion. Analyses of cefiderocol in plasma were performed using a validated LC/MS/MS method.¹⁰ This analytical method was applied to determine cefiderocol concentrations in BALF and AMs after preparing samples with the process reported previously.⁹ The lower limit of quantification for cefiderocol was 0.1 mg/L in plasma and 0.005 mg/L in both BALF and AMs. Urea concentrations in serum and BALF were measured using a spectrophotometer based on a previous report.¹¹ The precision and accuracy of the urea assay were 1.3% to 12.0% and –12.0% to 15.0%, respectively.

PK analyses

Individual plasma cefiderocol concentrations were summarized by nominal sampling time. For each subject, concentrations of cefiderocol in epithelial lining fluid (ELF) and AMs were calculated according to the procedures reported previously.⁹

The PK parameters for plasma, ELF and AMs were calculated by the non-compartmental method using WinNonlin (Version 6.2.1). The PK parameters for ELF and AMs were estimated from the geometric mean concentrations in ELF and AMs. Concentration ratios in ELF and AMs to total plasma and AUC ratios in ELF and AMs to total or free plasma were also calculated.

Safety assessments

Safety and tolerability assessments included adverse events (AEs), adverse drug reactions, vital signs, 12-lead ECG and standard clinical laboratory

safety tests (haematology and blood chemistry tests and urinalysis). The number and percentage of subjects reporting AEs were summarized.

Results

PK assessments

All 20 subjects who received cefiderocol were included in the PK evaluations. Subject demographic and baseline characteristics are shown in Table S1 (available as [Supplementary data](#) at JAC Online). The mean dilution factor calculated by Urea_{BALF}/Urea_{SERUM} was 0.018.

Mean total plasma and ELF or AM concentration profiles following a single intravenous infusion of cefiderocol are shown in Figure 1. The ELF concentration profile appeared to be parallel to the total plasma concentration profile. Individual and mean total plasma, ELF or AM concentrations at BALF collection time are presented in Figure S1.

The geometric mean concentrations of cefiderocol in ELF and AMs and the concentration ratios of ELF and AMs to total plasma ($R_{C, E/P}$ and $R_{C, A/P}$) are summarized in Table S2. The geometric mean ELF concentrations were 13.8, 6.69, 2.78 and 1.38 mg/L at 1, 2, 4 and 6 h from the start of the infusion, respectively. The concentration ratios of ELF to total plasma over 6 h ranged from 0.0927 to 0.116. The concentration ratios of AMs to total plasma over 6 h ranged from 0.00496 to 0.104. A summary of the plasma, ELF and AM PK parameters is presented in Table 1. The AUC ratios in ELF and AMs to total plasma ($R_{AUC, E/P}$ and $R_{AUC, A/P}$) were 0.101 and 0.0177, respectively, and 0.239 and 0.0419 based on free plasma, respectively, using a plasma protein unbound fraction of 0.422 (protein-binding study sponsored by Shionogi & Co., Ltd and tested by Sekisui Medial Co., Ltd; study number: R-649266-PF-037-L; date of report: 31 January 2012).

Safety assessments

All 20 subjects who received a dose of cefiderocol were included in the safety evaluations. The incidence of AEs is summarized in Table S3. In total, 14 of the 20 subjects (70.0%) reported 27 AEs. All of the AEs were judged to be due to the BAL procedure and not considered drug related, except for one AE (vomiting), which occurred just after drug administration. All AEs were mild in severity, except for one moderate AE (respiratory tract infection). All AEs resolved by the end of the study.

Discussion

Cefiderocol was discovered by modifying the C-3 side chain from cefepime and the C-7 side chain from ceftazidime, and it is expected that the cefiderocol intrapulmonary PK profile is similar to that of cefepime or ceftazidime. The cefepime concentration ratio in ELF to total plasma in healthy subjects was 0.39.¹² Cefepime ELF concentrations administered by continuous infusion in critically ill patients were similar to the total plasma concentrations.¹³ The ratios of ELF to the total plasma ceftazidime concentrations were 0.31 and 0.21 in healthy volunteers and patients with infection, respectively.^{14,15} The physiological condition is different between healthy subjects and critically ill patients with pulmonary infections, and there have been reports of both higher and

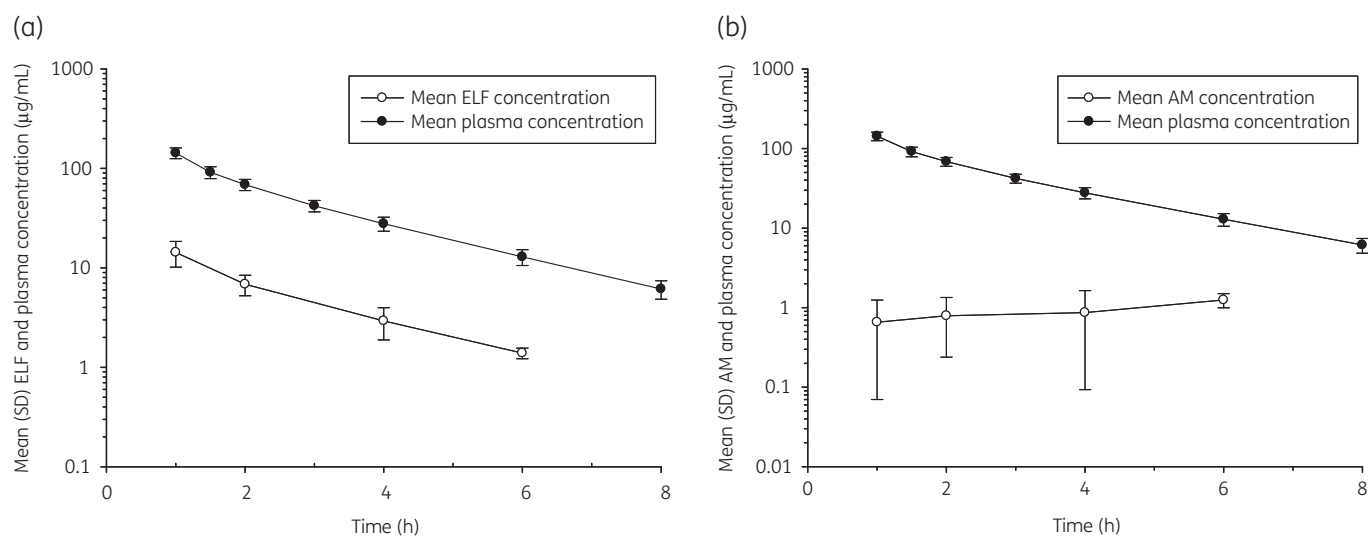


Figure 1. (a) Mean (SD) total plasma and ELF cefiderocol concentration profiles following a single intravenous infusion of 2000 mg of cefiderocol. (b) Mean (SD) total plasma and AM cefiderocol concentration profiles following a single intravenous infusion of 2000 mg of cefiderocol. Arithmetic mean concentrations of cefiderocol in plasma, ELF and AMs were calculated by nominal sampling time. $N=20$ at each timepoint for plasma; $N=5$ at each timepoint for ELF and AMs. Logarithmic y-axis.

Table 1. Cefiderocol pharmacokinetic parameters following single intravenous infusion of 2000 mg of cefiderocol

Specimen	C_{max} (mg/L)	T_{max} (h)	AUC_{0-6} (mg·h/L)	$AUC_{0-\infty}$ (mg·h/L)	$t_{1/2, z}$ (h)	AUC ratio (total) ^a	AUC ratio (free) ^b
Plasma	142	1.0	294.5	328.5	1.79	NA	NA
ELF	13.8	1.0	29.62	33.12	1.76	0.101	0.239
AM	1.23	6.0	5.203	NE	NE	0.0177	0.0419

Geometric mean pharmacokinetic parameters in plasma are shown except for median T_{max} .

AUC_{0-6} , area under the concentration–time curve over the last nominal sampling time (i.e. 6 h); NA, not applicable; NE, not estimated; $t_{1/2, z}$, terminal elimination half-life.

^aAUC ratio in ELF or AMs to total plasma AUC ($R_{AUC, E/P}$ or $R_{AUC, A/P}$) was calculated as AUC_{0-6} in ELF or AM/ AUC_{0-6} in total plasma.

^bAUC ratio in ELF or AMs to free plasma AUC was calculated as AUC_{0-6} in ELF or AM/ AUC_{0-6} in free plasma using a plasma protein unbound fraction of 0.422.

similar intrapulmonary PK of cephalosporins in the infected condition compared with the uninfected condition.^{12–17}

The ELF concentrations of cefiderocol were 13.8, 6.69, 2.78 and 1.38 mg/L at 1, 2, 4 and 6 h after single intravenous dosing, respectively. These ELF concentrations of cefiderocol were similar to those of other β -lactams that are used for respiratory infections.¹⁸ The ELF concentration appears to be parallel to the total plasma concentration, suggesting that cefiderocol was distributed rapidly from plasma to ELF. The AUC ratios of ELF were 0.101 to total plasma and 0.239 to free plasma. The penetration ratio of cefiderocol into ELF was comparable with that of ceftazidime in critically ill patients (0.229 based on free plasma using a protein unbound fraction of 0.9).^{15,19}

The fraction of time during the dosing interval where free concentration exceeded the MIC ($fT_{>MIC}$) for a PD target was reported to be 75%.⁸ This study assessed ELF concentrations after a single intravenous dose over 60 min, which was different from a 3 h infusion time for severe infections, including nosocomial pneumonia.^{6,7} The 3 h infusion is expected to extend $fT_{>MIC}$ in ELF and have

more potency. PK modelling for ELF concentrations would be useful to consider cefiderocol exposure in ELF with the 3 h infusion.

Although BALF concentrations would be measurable at 8 h, it was determined that no further timepoints for BALF sampling were added. The parallel PK in plasma and ELF was observed over 6 h, and we presumed that ELF concentrations should be predictable based on plasma concentrations.

This study revealed that cefiderocol penetrates into ELF, and the ELF concentration appears to be parallel to the plasma concentration. The results of this study and animal studies may support the further investigation of cefiderocol in nosocomial pneumonia, including Phase III clinical studies.

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Transparency declarations

T. Katsube and Y. Saisho are employees of Shionogi & Co., Ltd. T. Katsube owns stock in Shionogi & Co., Ltd. All other authors: none to declare.

Supplementary data

Tables S1–S3 and Figure S1 are available as [Supplementary data](#) at JAC Online.

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