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Intrapulmonary pharmacokinetic profile of cefiderocol in mechanically ventilated patients with pneumonia

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Objectives: Lung penetration of cefiderocol, a novel siderophore cephalosporin approved for treatment of nosocomial pneumonia, has previously been evaluated in healthy subjects. This study assessed the intrapulmonary pharmacokinetic profile of cefiderocol at steady state in hospitalized, mechanically ventilated pneumonia patients.

Methods: Patients received cefiderocol 2 g (or ≤1.5 g if renally impaired), administered IV q8h as a 3 h infusion, or 2 g q6h if patients had augmented renal function (estimated CL_{CR} > 120 mL/min). After multiple doses, each patient underwent a single bronchoalveolar lavage (BAL) procedure either at the end of the infusion or at 2 h after the end of infusion. Plasma samples were collected at 1, 3, 5 and 7 h after the start of infusion. After correcting for BAL dilution, cefiderocol concentrations in epithelial lining fluid (ELF) for each patient and the ELF/unbound plasma concentration ratio ($R_{C,\ E/P}$) were calculated. Safety was assessed up to 7 days after the last cefiderocol dose.

Results: Seven patients received cefiderocol. Geometric mean ELF concentration of cefiderocol was 7.63 mg/L at the end of infusion and 10.40 mg/L at 2 h after the end of infusion. $R_{C,\ E/P}$ was 0.212 at the end of infusion and 0.547 at 2 h after the end of infusion, suggesting delayed lung distribution. There were no adverse drug reactions.

Conclusions: The results suggest that cefiderocol penetrates the ELF in critically ill pneumonia patients with concentrations that are sufficient to treat Gram-negative bacteria with an MIC of ≤4 mg/L.

Introduction

Antibiotic penetration to the infection site is critical for optimizing clinical outcome in patients with ventilator-associated pneumonia.[1] Epithelial lining fluid (ELF) is a surrogate for extracellular penetration and is used to measure unbound drug concentration in the alveolar space; therefore, evaluation of ELF penetration is recommended for estimating antibiotic efficacy for pneumonia.[1,2] Cefiderocol is a novel siderophore cephalosporin with potent activity against Gram-negative bacteria, including carbapenem-resistant strains.[3] Using bronchoalveolar lavage (BAL) in healthy adult subjects, we previously reported geometric mean concentration ratios over 6 h ranging from 0.0927 to 0.116 mg/L for ELF and total plasma after a single IV dose of cefiderocol (2 g) infused over 1 h.[4] The recently conducted APEKS-NP study demonstrated that cefiderocol was non-inferior to high-dose, extended-infusion meropenem in the primary outcome of Day 14 all-cause mortality and that clinical and microbiological outcomes were comparable between treatment arms in critically ill patients with nosocomial pneumonia caused by Gram-negative pathogens.[5]

This study aimed to estimate the steady-state ELF concentration and the degree of penetration of IV cefiderocol in infected lung of hospitalized patients with bacterial pneumonia requiring mechanical ventilation.

Patients and methods

Ethics

The study protocol (#1713R2117) was approved by the Institutional Review Board (Table S1, available as Supplementary data at *JAC* Online) at each participating centre and complied with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of

Helsinki. All patients or legal guardians provided written informed consent according to local guidelines.

Study design

This single-arm, multicentre, open-label Phase 1b study assessed intrapulmonary concentrations of cefiderocol at steady state in hospitalized adult male or female patients with known or suspected bacterial pneumonia on treatment with standard-of-care (SOC) antibiotics and requiring mechanical ventilation (ClinicalTrials.gov: NCT03862040).

Study drug

Patients received cefiderocol 2 g (or 1.5 g if renally impaired) IV q8h as a 3 h infusion, or q6h for patients with augmented renal function (estimated CL_{CR} > 120 mL/min). Cefiderocol was administered for a minimum of three doses and up to a total of six doses in patients with normal, augmented renal function or mild/moderate renal impairment, and for a minimum of six doses and up to a total of nine doses in patients with severe renal impairment. Doses were adjusted for emergent changes in renal function as they occurred.

Sample collection

A single bronchoscopic BAL procedure of the affected lobe per patient was conducted after steady state of cefiderocol was achieved to determine its concentration in ELF. BAL was performed at the end of the 3 h infusion or 2 h after the end of infusion; collection at 4 h after the end of infusion was also planned but not carried out (see Figure S1).

A total of four blood samples (i.e. 1 h after the start of infusion, at the end of infusion, and at 2 and 4 h after the end of infusion; Figure S1) were collected after multiple doses of cefiderocol for determination of plasma concentrations. An additional blood sample for urea assessment was collected as part of the plasma sample collection within 30 min prior to the BAL procedure.

Further details of the study design, bioanalytical measurements and pharmacokinetic (PK) assessments are provided in the Supplementary methods.

Sample size

No formal calculations were performed to determine sample size for the study. A minimum of three subjects at a single timepoint, then a minimum of three additional subjects at another timepoint (up to approximately 18 patients) were deemed sufficient to provide a summary of cefiderocol concentrations in the ELF in this study.

PK assessments

For each subject, the concentration of cefiderocol in ELF was calculated and determined as follows: $C_{ELF} = C_{BAL} \times Urea_{serum}/Urea_{BAL}$.

The % coefficient of variation (CV%) of the geometric mean was calculated according to a formula: CV% geometric mean = $[\exp(SD^2) - 1]^{1/2} \times 100$, where SD is the standard deviation for natural log (ln)-transformed data. ELF/unbound plasma concentration ratio ($R_{C,\ E/P}$) was also calculated and summarized descriptively for each patient. The unbound plasma concentration of cefiderocol was calculated based on the *in vitro* unbound fraction of 0.422.[4]

Statistical analysis

Individual ELF and plasma concentrations of cefiderocol were summarized descriptively by nominal sampling time. Adverse events were classified by system organ class and preferred term using Version 21.1 of the Medical Dictionary for Regulatory Activities. Due to the small number of patients enrolled in the study, all safety data were listed by patient and timepoint. All statistical analyses were performed using SAS 9.2 or higher.

Results

Patients

Seven eligible patients received cefiderocol and completed the study as scheduled and provided safety and adequate PK data. Table S2 shows the demographic and baseline characteristics of the study patients.

PK results

Concentration profiles of cefiderocol in plasma and ELF for the seven patients are displayed in Figure 1. The geometric mean (range) of total plasma concentration of cefiderocol was 60.3 (25.2–104.0) mg/L at 1 h after the start of the infusion, 80.8 (43.6–116.0) mg/L at the end of the infusion (3 h after the start of infusion), 56.3 (20.7–102.0) mg/L at 2 h after the end of the infusion and 44.6 (12.9–99.3) mg/L at 4 h after the end of the infusion.

The geometric mean (range) ELF concentration of cefiderocol was 7.63 (3.10–20.7) mg/L at the end of the infusion ($n = 4$) and 10.4 (7.19–15.9) mg/L at 2 h after the end of the infusion (5 h after the start of the infusion) ($n = 3$). The geometric mean (range) ratios of cefiderocol in the ELF to total plasma concentration were 0.0893 (0.0379–0.178) at 3 h after the start of infusion and 0.231 (0.187–0.347) at 2 h after the end of infusion. Data were not collected at 4 h after the end of infusion. The geometric mean (range) $R_{C,\ E/P}$ for cefiderocol was estimated to be 0.211 (0.090–0.422) at the end of the infusion and 0.547 (0.443–0.822) at 2 h after the end of the infusion (Figure 2).

Safety

All seven patients in the safety population reported at least one treatment-emergent adverse event (TEAE). All TEAEs were mild or

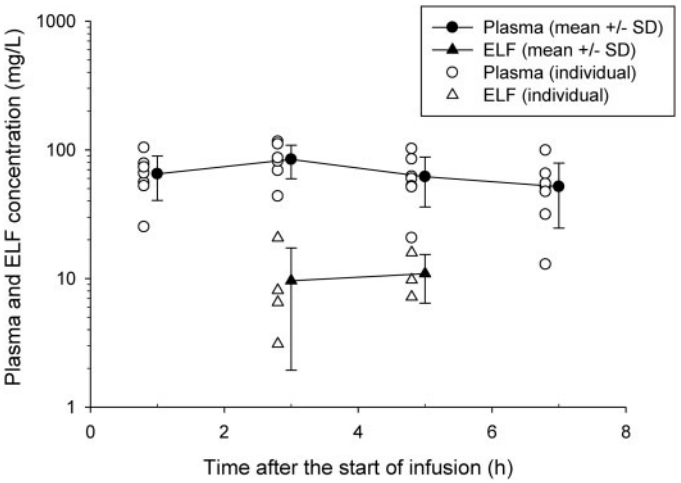

Figure 1. Individual and mean (SD) total plasma and ELF concentration profiles of cefiderocol in pneumonia patients. Filled circles, mean plasma concentrations; filled triangles, mean ELF concentrations; open circles, individual patient plasma concentrations; open triangles, individual patient ELF concentrations.

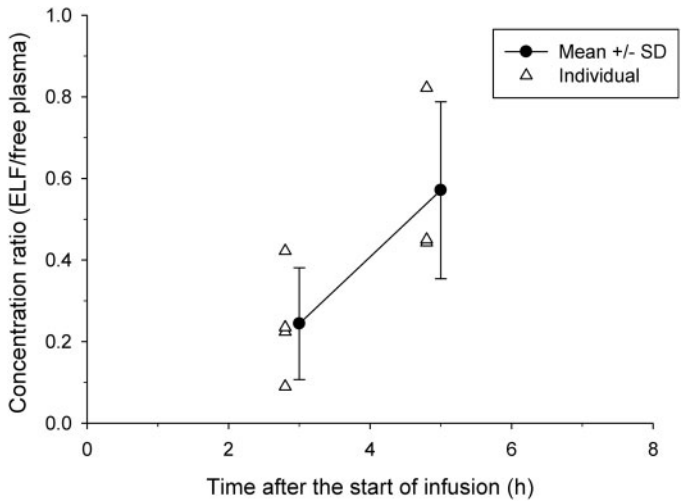

Figure 2. Individual and mean (SD) concentration ratio of cefiderocol in ELF to unbound plasma ($R_{C,\ E/P}$) in pneumonia patients. Filled circles, mean concentration ratio; open triangles, individual patient concentration ratios.

moderate in severity and were considered not related to cefiderocol. No deaths, serious AEs or AEs led to study withdrawal.

Discussion

Our study demonstrated that IV cefiderocol 2 g infused over 3 h, or renally adjusted doses, not only attained therapeutically relevant concentrations in the plasma but also in the extracellular/interstitial target site of the lungs in mechanically ventilated patients with pneumonia. Historically, plasma concentrations of antibiotics were considered as a surrogate to establish adequate exposures without direct measurements in the lung.[6,7] Geometric mean plasma concentrations of cefiderocol in this study were consistent with the PK parameters obtained in patients with nosocomial pneumonia enrolled in Phase 3 clinical studies,[8] suggesting that the actual concentrations are clinically sufficient to treat pathogens with MICs of ≤4 mg/L. Cefiderocol was well tolerated in the study.

Variation in penetration for parenteral cephalosporins in critically ill patients, $R_{C,\ E/P}$ ranging between 0.07 and 0.36, has been reported.[9] In critically ill patients, parenteral cefepime and ceftazidime $R_{C,\ E/P}$ were reported as >1 and 0.21, respectively;[9,10] however, in healthy adults, $R_{C,\ E/P}$ for cefepime has been reported as 0.39.[11]

In the current study with ventilated pneumonia patients, the ELF concentrations at the end of infusion [geometric mean (range): 7.63 (3.10–20.7) mg/L] were comparable with those in the previous ELF study in healthy subjects [13.8 (11.2–21.0) mg/L], while the ELF concentrations at 2 h after the end of infusion [geometric mean (range): 10.4 (7.19–15.9) mg/L] were greater than those observed at 1 h [6.69 (5.45–8.87) mg/L] and 3 h [2.78 (1.71–4.40) mg/L] after the end of infusion in healthy subjects.[4] The differences in ELF concentrations between the current study and the study in healthy subjects were partially due to differences in study drug administration (multiple doses versus single dose), infusion time (3 versus 1 h) and CL_{CR} in participants [median (range): 78 (43–256) and 124 (95–148) mL/min for the patients and healthy subjects, respectively]. Covariate analysis to look at the influence of age, body weight, BMI and CL_{CR} were not feasible to conduct due to limited data.

In the current study with ventilated pneumonia patients, the geometric mean (range) ratio of ELF concentration to plasma at 2 h after the end of infusion [0.231 (0.187–0.347)] was two-fold greater than that at the end of infusion [0.0893 (0.0379–0.178)], while the ratios in healthy subjects were consistent (0.0927 to 0.116) throughout the sampling period from the end of infusion to 5 h after the end of infusion.[4] A similar penetration profile in ELF (i.e. delayed distribution and sustained exposure) was also observed for ceftolozane/tazobactam or vancomycin in critically ill pneumonia patients.[12,13]

Multiple explanations for this finding are possible. To be measured in ELF, an IV drug must cross both the pulmonary endothelial and alveolar epithelial barriers, while simultaneously undergoing active clearance from the intervening interstitial space through pulmonary lymphatics.[13] Lymphatic clearance returns the drug to the serum pool, replenishing blood levels. A prolonged infusion maintains the concentration gradients across both membranes for a longer period of time, while minimizing the effect of lymphatic clearance.[13] Felton and colleagues[14] hypothesized that pulmonary protein permeability and/or organic anion transporters may also affect the slower diffusion of β-lactams out of the lungs of critically ill patients. Additionally, pneumonia results in increased permeability of the endothelial membranes, especially early in the course of treatment.[15] In addition, lymphatic clearance may be decreased by the use of positive intrathoracic pressures in mechanically ventilated patients. Since the relative role of positive intrathoracic pressure is unknown, whether higher ELF to plasma levels occur in non-ventilated pneumonia patients cannot be predicted from our data.

Previous PK studies showed that cefiderocol provided >90% PTA for 75% of the time during the dosing interval, where the unbound drug concentration in plasma exceeds the MIC of ≤4 mg/L for healthy individuals with normal renal function.[16] Recent clinical studies in seriously ill patients, including pneumonia patients, have demonstrated a higher plasma exposure than in healthy subjects and an improved pharmacodynamic profile with a >95% PTA of 75% $fT_{>MIC}$ and a >90% PTA of 100% $fT_{>MIC}$ for MICs of ≤4 mg/L.[8] Additionally, an intrapulmonary population PK model developed by using ELF concentration data from seven pneumonia patients enrolled into the current study and 20 healthy subjects showed >95% PTA in ELF for 100% $fT_{>MIC}$ against MICs ≤2 mg/L and >85% PTA for 100% $fT_{>MIC}$ against MICs ≤4 mg/L, regardless of renal function.[8,17] Furthermore, surveillance studies of more than 20 000 isolates show that cefiderocol is active against >99% of pathogens with MICs ≤4 mg/L.[18,19]

Our results revealed high target ELF concentrations in patients with pneumonia and lend further support to the efficacy of cefiderocol in pneumonia patients, as demonstrated in the APEKS-NP[5] and CREDIBLE-CR[20] studies.

The limitation of the current study was that only a limited number of samples could be collected (i.e. one single lavage procedure per patient). Our study evaluated only seven patients, including four patients at the end of the 3 h infusion and three patients 2 h after the end of the infusion. However, as we had 20 cefiderocol ELF concentrations based on the use of BAL samples collected in healthy subjects,[17] we were able to successfully integrate the ELF PK data collected in the current study and continued with

modelling of ELF exposure in patients with nosocomial pneumonia (Kawaguchi N, Katsube T, Echols R, Wajima T, Nicolau DP, unpublished data, prepared for submission).

Conclusions

Cefiderocol was distributed in ELF of the lung in pneumonia patients and provided exposures supporting its use for the treatment of nosocomial pneumonia caused by susceptible Gram-negative pathogens.

Data in this manuscript were presented at IDWeek™, 21–25 October 2020, virtual conference at www.idweek.org, as Katsube T, Wajima T, Echols R *et al*. Abstract 1311. Intrapulmonary pharmacokinetics of cefiderocol in hospitalized and ventilated patients receiving standard of care antibiotics for bacterial pneumonia. *Open Forum Infect Dis* 2020; **7** Suppl 1: S668. https://doi.org/10.1093/ofid/ofaa439.1493.

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Transparency declarations

D.P.N. is a consultant, speaker bureau member and has received other research grants from Shionogi, the sponsor for the study. K.A.R. has served as a consultant and is a speaker bureau member for Shionogi, the sponsor for the study. R.G.W. has served as a consultant for Shionogi and Merck. T.K. and T.W. are employees of Shionogi & Co., Ltd., Osaka, Japan. Y.M., A.M. and S.P. are employees of Shionogi Inc., Florham Park, NJ, USA. R.E. is a consultant for Shionogi and has received consultancy fees from Shionogi Inc., USA.

Supplementary data

Supplementary methods, references, Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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