No. 1311

IDWeek 2020
21-25 October, 2020

Intrapulmonary Pharmacokinetics of Cefiderocol in Hospitalized and Ventilated Patients Receiving Standard of Care Antibiotics for Bacterial Pneumonia

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Abstract(revised)

Background : Cefiderocol (CFDC), a novel siderophore cephalosporin, has potent in vitro activity against Gram-negative bacteria causing nosocomial pneumonia (NP). The non-inferiority of CFDC to meropenem in Day 14 all-cause mortality in NP was previously demonstrated. In this study, we assessed the intrapulmonary pharmacokinetics of CFDC in hospitalized and ventilated patients with bacterial pneumonia receiving standard of care (SOC) antibiotics.

Methods : A multicenter, single-arm, open-label study was conducted to assess epithelial lining fluid (ELF) and plasma concentrations of CFDC at steady state in mechanically ventilated patients with bacterial pneumonia receiving SOC antibiotics (NCT03862040). Seven patients received 2 g doses of CFDC (or renally adjusted doses), infused over 3 hours, q8h, or q6h for patients with augmented renal function (creatinine clearance estimated by Cockcroft-Gault equation >120 mL/min). One bronchoalveolar lavage (BAL) sample per patient was collected to determine ELF concentration at 3 or 5 hours after at least 3 CFDC doses (or ≥6 doses in patients with severe renal impairment). Four blood samples were collected per patient for plasma concentrations at 1, 3, 5, and 7 hours after the start of the infusion used for BAL sampling. Urea concentrations in blood and BAL were measured to calculate CFDC concentrations in ELF.

Results : Geometric mean (minimum, maximum) ELF concentration of CFDC was 7.63 (3.10, 20.7) μg/mL at the end of infusion (3 h after the start of infusion) (N=4) and 10.4 (7.19, 15.9) μg/mL at 2 hours after the end of infusion (5 h after the start of infusion) (N=3). ELF/free plasma concentration ratios were estimated to be 0.212 at the end of infusion and 0.547 at 2 hours after the end of infusion based on the in vitro unbound fraction of 0.422.

Conclusions : The individual ELF concentrations of CFDC were close to, or higher than, 4 μg/mL in pneumonia patients. Compared with the ELF/free plasma area under the curve ratio in healthy subjects (0.239), the ELF/free plasma concentration ratio at the end of infusion (0.212) was comparable, and at 2 hours after the end of infusion (0.547) was higher in pneumonia patients. These findings suggest delayed distribution and sustained exposure of CFDC in the ELF of pneumonia patients.

Introduction

- Cefiderocol, a novel siderophore cephalosporin, has demonstrated potent antibacterial activity against a wide range of Gram-negative bacteria including carbapenem-resistant strains [1].
- Cefiderocol was approved in the USA for the treatment of complicated urinary tract infection (cUTI) including pyelonephritis hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by Gram-negative pathogens in adults [2]. Cefiderocol was also approved by the European Medicines Agency for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options [3].
- In APEKS-NP study (NCT03032380) [4], the non-inferiority of cefiderocol to 2 g 3-hour infusion of meropenem in Day 14 all-cause mortality was demonstrated in critically-ill patients with pneumonia.
- In this study, we assessed the intrapulmonary pharmacokinetics of cefiderocol in hospitalized and ventilated patients with bacterial pneumonia receiving standard of care (SOC) antibiotics.

Methods

Study design
- A multicenter, single-arm, open-label study was conducted to assess epithelial lining fluid (ELF) and plasma concentrations of cefiderocol at steady state in mechanically ventilated patients with bacterial pneumonia receiving SOC antibiotics (NCT03862040).
- Seven patients received 2 g q8h doses of cefiderocol or renally adjusted doses based on creatinine clearance by Cockcroft-Gault equation (CrCL), infused over 3 hours (1 g q8h for CrCL 15 to < 30; 1.5 g q8h for CrCL 30 to < 60; 2 g q8h for CrCL 90 to < 120; 2 g q6h for CrCL ≥ 120 mL/min).
- One bronchoalveolar lavage (BAL) sample per patient was collected to determine ELF concentration 3 or 5 hours after at least 3 cefiderocol doses (or ≥ 6 doses in patients with severe renal impairment).
- BAL was carried out by the infusion of one 20 mL and two 50 mL volumes of sterile saline into the subsegmental bronchus under sedation and anesthesia, and each specimen was aspirated. The first aliquot recovered was discarded and the last two were pooled. Cell pellet was separated from BAL fluid via centrifugation (400 g at 4°C for 5 min), and the supernatant was used for measuring cefiderocol concentrations in BAL.
- Four blood samples were collected per patient for plasma concentrations 1, 3, 5, and 7 hours after the start of the same infusion for BAL sampling.
- Urea concentrations in blood and BAL were measured to calculate cefiderocol concentrations in ELF.

PK analyses
- Concentration ratios in ELF to free plasma were calculated using unbound fraction of 0.422 in plasma.
- The ELF concentrations and concentrations ratios were summarized.

Safety assessments
- All safety data (adverse events [AEs], physical examination findings, vital sign results, chest x-ray findings, and clinical laboratory parameter values) were examined by subject and time point.

Result

Pharmacokinetics:
- The demographic characteristics in patients are shown in **Table 1**.
- Plasma and ELF concentration profiles were presented in **Figure 1**. Geometric mean (minimum, maximum) ELF concentration of cefiderocol was 7.63 (3.10, 20.7) μg/mL at the end of infusion (3 hours after the start of infusion) (N=4) and 10.4 (7.19, 15.9) μg/mL 2 hours after the end of infusion (5 hours after the start of infusion) (N=3).
- Mean concentration ratios in ELF to free plasma are presented in **Figure 2**. The concentration ratios were estimated to be 0.212 at the end of infusion and 0.547 2 hours after the end of infusion.

Safety:
- All 7 subjects (100%) reported at least 1 AE. All of the AEs were mild or moderate in severity, and all were considered not related to cefiderocol.
- There were no AEs reported in the categories of *C. difficile*-related AEs, rash/hypersensitivity reactions, liver-related AEs, seizures/epilepsy, or iron transport/metabolism.

Table 1. Baseline demographics and clinical characteristics

N	7
	Median (range)
Age (years)	70 (19–78)
Body weight (kg)	88.1 (69.4 -113)
BMI (kg/m^2)	33.5 (21.3–47.1)
CrCL (mL/min)	78 (43–256)
	n (%)
Sex	
Male	3 (42.9 %)
Female	4 (57.1 %)
Race	
White	5 (71.4 %)
Black/African American	1 (14.3 %)
Other	1 (14.3 %)
Diagnosis	
HAP	4 (57.1 %)
VAP	1 (14.3%)
CAP	2 (28.6 %)

BMI = body mass index; CrCL = creatinine clearance calculated by Cockcroft–Gault equation; CAP = community acquired pneumonia; HAP = healthcare associated pneumonia; VAP = ventilator associated pneumonia

Figure 1. Individual and mean (SD) plasma (total) and ELF concentration profiles of cefiderocol in pneumonia patients

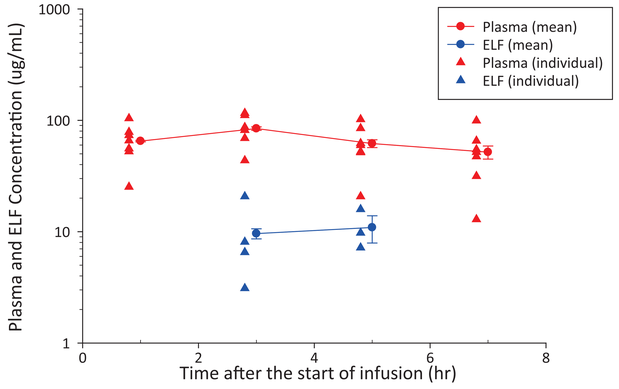
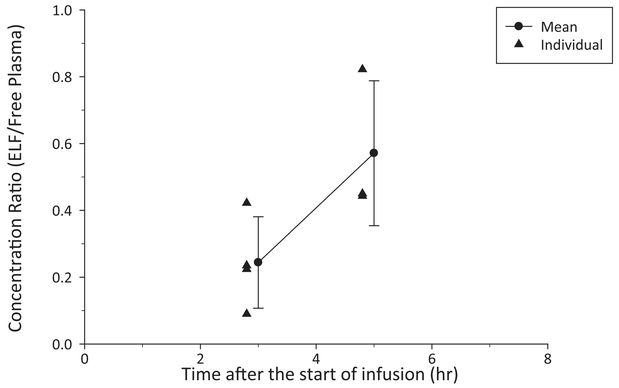


Figure 2. Individual and mean (SD) concentration ratio of cefiderocol in ELF to free plasma in pneumonia patients



Conclusion

- The individual ELF concentrations of cefiderocol were close to, or higher than, 4 μg/mL in pneumonia patients. This study may support cefiderocol effectiveness in nosocomial pneumonia caused by pathogens with MIC of 4 μg/mL or less.
- Compared with the ELF/free plasma AUC ratio in healthy subjects (0.239) [5], the ELF/free plasma concentration ratio at the end of infusion (0.212) was comparable, and 2 hours after the end of infusion (0.547) was higher in pneumonia patients.
- The PK profiles in ELF suggest delayed distribution and sustained exposure of cefiderocol in the ELF of pneumonia patients.

References

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