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Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol in Critically Ill Patients

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Abstract

Background : Cefiderocol (CFDC), a novel siderophore cephalosporin, has demonstrated potent antibacterial activity against a wide range of Gram-negative bacteria including carbapenem-resistant strains. We aimed to evaluate relationships between drug exposure and outcomes in critically ill patients.
Materials/Methods : Sparse pharmacokinetic (PK) samples at steady state from critically ill patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection receiving CFDC in two Phase 3 studies were analyzed. Percent time of dosing interval of free drug concentration exceeding the minimum inhibitory concentration (MIC) in plasma and epithelial lining fluid (ELF) (% $fT_{>MIC}$ and % $fT_{>MIC,ELF}$, respectively) were determined for 60 (CREDIBLE-CR; NCT02714595) and 97 patients (APEKS-NP; NCT03032380), using a 3-compartment population PK model. The % $fT_{>MIC,ELF}$ was calculated for 125 pneumonia patients based on an intrapulmonary PK model. Relationships between % $fT_{>MIC}$, % $fT_{>MIC,ELF}$ and clinical and microbiological outcomes at test of cure (TOC), or mortality at Day 28 were assessed.
Results : The median (90th percentile) MICs of Gram-negative pathogens in the PK/pharmacodynamic (PD) analyses were 0.25 (4) μg/mL (CREDIBLE-CR) and 0.25 (2) μg/mL (APEKS-NP), respectively. Individual plasma % $fT_{>MIC}$ was 100% in ≥ 95% of patients in each study, and estimated % $fT_{>MIC,ELF}$ was 100% in 89.3% (25/28 pneumonia patients; CREDIBLE-CR) and 97.9% (95/97 pneumonia patients; APEKS-NP). Clinical cure rates and survival rates in patients with 100% $fT_{>MIC}$ or % $fT_{>MIC,ELF}$ were similar between the two studies (Table). No PK/PD relationships between % $fT_{>MIC}$, % $fT_{>MIC,ELF}$ and clinical cure, microbiological eradication, or survival were identified in either study because high % $fT_{>MIC}$ or % $fT_{>MIC,ELF}$ was achieved in all patients.
Conclusions : PK/PD relationship was not identified between CFDC plasma or ELF exposure and clinical or microbiological outcomes, or mortality as high % $fT_{>MIC}$ and % $fT_{>MIC,ELF}$ were achieved, suggesting the recommended dosing regimen of 2 g q8h or renally adjusted dosage (including augmented renal clearance), infused over 3 hours, provides sufficient exposure to CFDC in critically ill patients.

Table. Clinical cure and survival rates in patients with 100% $fT_{>MIC}$ or % $fT_{>MIC,ELF}$ in CREDIBLE-CR and APEKS - NP studies

Study and outcome	% $fT_{>MIC}$		% $fT_{>MIC,ELF}$	
	<100%	100%	<100%	100%
CREDIBLE -CR, % (n/N)				
Clinical cure rate	0 (0/2)	62.1 (36/58)	0 (0/3)	64.0 (16/25)
Eradication rate	0 (0/2)	33.3 (25/75)	0 (0/3)	20.5 (8/39)
Survival rate	0 (0/2)	81.0 (47/58)	0 (0/3)	84.0 (21/25)
APEKS -NP, % (n/N)				
Clinical cure rate	100 (2/2)	65.3 (62/95)	100 (2/2)	65.3 (62/95)
Eradication rate	100 (2/2)	44.2 (53/120)	100 (2/2)	44.2 (53/120)
Survival rate	100 (2/2)	82.1 (78/95)	100 (2/2)	82.1 (78/95)

n = number achieving clinical cure, eradication, or survival; N = total number of patients for clinical outcome and mortality or total number of causative pathogens for microbiological outcome.
CREDIBLE-CR: n=60 (Median [Range] APACHE II score: 14 [2-29]). APEKS-NP: n=97 (Median [Range] APACHE II score: 15 [3-31])

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 and 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].
- Two prospective, randomized Phase 3 clinical studies were conducted to investigate the efficacy and safety of cefiderocol in critically ill patients with pneumonia, blood stream infection (BSI)/sepsis, or cUTI [4, 5]. In animal infection models, the percentage of the dosing interval during which free drug concentration exceeds the minimum inhibitory concentration (MIC) in plasma (% $fT_{>MIC}$) was determined as a primary pharmacokinetic/pharmacodynamic (PK/PD) index [6].
- The purpose of this study was to examine relationships between PK/PD parameters of cefiderocol and outcomes in critically ill patients.

Methods

Data
- Plasma concentrations of cefiderocol at steady state from sparse samples and MICs of causative pathogens were available from 60 patients in the CREDIBLE-CR study (NCT02714595) [4] and 97 patients in the APEKS-NP study (NCT03032380) [5].
- MICs were determined by IHMA, Inc (Schaumburg, IL, USA) using iron depleted, cation-adjusted Mueller Hinton broth.

PK/PD analyses
- In plasma, % $fT_{>MIC}$ was estimated for 60 (CREDIBLE-CR) and 97 (APEKS-NP) patients using a 3-compartment population PK model [7]. In epithelial lining fluid (ELF), % $fT_{>MIC,ELF}$ was calculated for 28 (CREDIBLE-CR) and 97 (APEKS-NP) pneumonia patients based on an intrapulmonary PK model developed using data from healthy subjects and pneumonia patients. AUC ratio of ELF to free plasma in pneumonia patients was estimated to be 0.340 [7].
- Relationships between % $fT_{>MIC}$ or % $fT_{>MIC,ELF}$ and microbiological outcome at TOC, clinical outcome at TOC or vital status at Day 28 were assessed.
- Relationships between % $fT_{>MIC}$ for 4-fold MIC (% $fT_{>4\times MIC}$), maximum plasma concentration (C_{max}) divided by MIC (C_{max}/MIC), daily area under plasma concentration–time curve (AUC) divided by MIC (AUC/MIC), or minimum plasma concentration (C_{min}) divided by MIC (C_{min}/MIC) and the above outcomes were also assessed to explore clinically relevant indices for efficacy of cefiderocol.

Software
- NONMEM (version 7.3) [8] and Perl-speaks NONMEM (version 4.2.0) [9] were used to estimate the PK parameters in each patient. R (version 3.5.1) [10] was used to calculate the PK/PD parameters.

Result

- The demographic characteristics in patients for the PK/PD analyses are shown in **Table 1**.
- The median and 90th percentile MICs of Gram-negative pathogens were 0.25 and 4 μg/mL, respectively, in the CREDIBLE-CR study, and 0.25 and 2 μg/mL, respectively, in the APEKS-NP study for the PK/PD analyses. The MIC ranges were ≤0.03 to 64 μg/mL in both studies.
- Individual % $fT_{>MIC}$ in plasma was 100% in ≥95% of patients in each study, and estimated % $fT_{>MIC,ELF}$ in ELF was 100% in 89.3% (CREDIBLE-CR) and 97.9% (APEKS-NP) (**Figures 1 and 2**).
- For patients with 100% $fT_{>MIC}$ or 100% $fT_{>MIC,ELF}$, clinical cure rates were 62% to 65%, and survival rates were 81% to 84% in both studies (**Figures 1**). Microbiological eradication rates for patients with 100% $fT_{>MIC}$ were 21% in CREDIBLE-CR and 44% in APEKS-NP and those for patients with 100% $fT_{>MIC,ELF}$ were 33% in CREDIBLE-CR and 44% in APEKS-NP. Microbiological persistence rates were 18% to 23% in both studies.
- No PK/PD relationships between % $fT_{>MIC}$ or % $fT_{>MIC,ELF}$ and microbiological eradication, clinical cure or survival were identified in either study because high % $fT_{>MIC}$ and % $fT_{>MIC,ELF}$ were achieved (**Figures 1 and 2**).
- Even % $fT_{>4\times MIC}$ in plasma was 100% in 83% of patients in CREDIBLE-CR and 89% of patients in APEKS-NP. Therefore, due to high % $fT_{>4\times MIC}$, no PK/PD relationships between % $fT_{>4\times MIC}$ and microbiological eradication, clinical cure or survival were identified (**Figure 3**).
- The median values of C_{max}/MIC, AUC/MIC and C_{min}/MIC were slightly lower in patients with microbiological eradication or clinical cure than in patients with persistence or clinical failure in the CREDIBLE-CR study, indicating no positive correlation between PK/PD parameters and efficacy. The PK/PD parameters were comparable between patients who survived and those who died (**Figure 4**).

Table 1. Demographics in PK/PD analysis population

Background characteristics	CREDIBLE -CR (N=60)	APEKS -NP (N=97)
	Mean (range)	Mean (range)
Age (years)	59.9 (21 –92)	66.6 (18 –91)
Body weight (kg)	69.3 (25 –156)	74.7 (28.9 –130)
eGFR (mL/min/1.73 m^2)	100 (15 –507)	76 (6 –225)
CrCL (mL/min)	101 (10 –540)	79.2 (5 –306)
Albumin (g/dL)	2.7 (1.6 –4.2)	3.01 (1.2 –4.5)
APACHE II score	14.2 (2 –29)	16 (3 –31)
Sex (male : female)	41 (68.3%) : 19 (31.7%)	64 (66.0%) : 33 (34.0%)
Race (Asian : White : the others)	19 (31.7%) : 34 (56.7%) : 7 (11.7%)	28 (28.9%) : 68 (70.1%) : 1 (1.0%)
Infection sites		
HAP/VAP/HCAP	28 (46.7%)	97 (100.0%)
BSI/sepsis	17 (28.3%)	---
cUTI	15 (25.0%)	---
Ventilation status (with : without) in HAP/VAP/HCAP patients	17 : 11	47 : 50
Ventilation status (with : without) in non-HAP/VAP/HCAP patients	8 : 24	---
ICU admission (yes : no)	37 : 23	70 : 27

APACHE II = Acute Physiology And Chronic Health Evaluation II; CrCL = creatinine clearance calculated by Cockcroft – Gault equation; eGFRabs = estimated glomerular filtration rate; ICU = intensive .care unit
Data are mean (range), or n (%).

Figure 1 Relationships of % $fT_{>MIC}$ with Microbiological Outcomes, Clinical Outcomes, or Vital Status in CREDIBLE-CR and APEKS-NP Studies

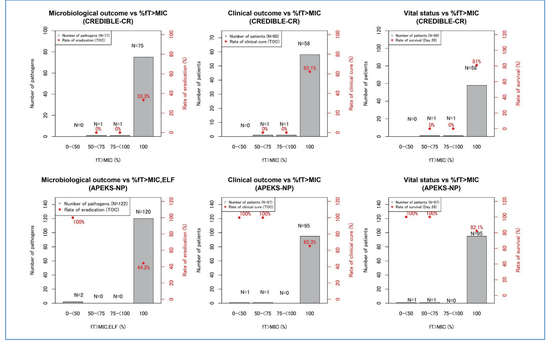


Figure 2 Relationships of % $fT_{>MIC,ELF}$ with Microbiological Outcomes, Clinical Outcomes, or Vital Status in CREDIBLE-CR and APEKS-NP Studies

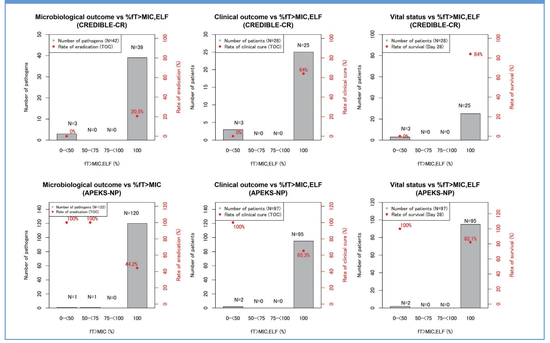


Figure 3 Relationships of % $fT_{>4\times MIC}$ with Microbiological Outcomes, Clinical Outcomes, or Vital Status in CREDIBLE-CR and APEKS-NP Studies

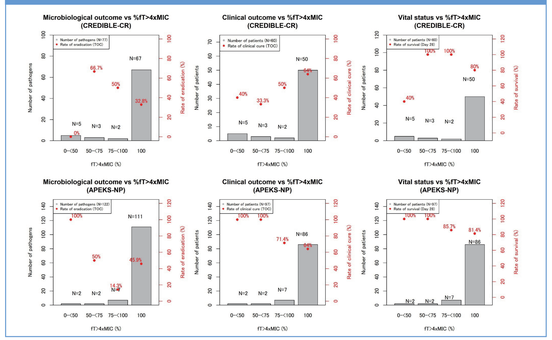
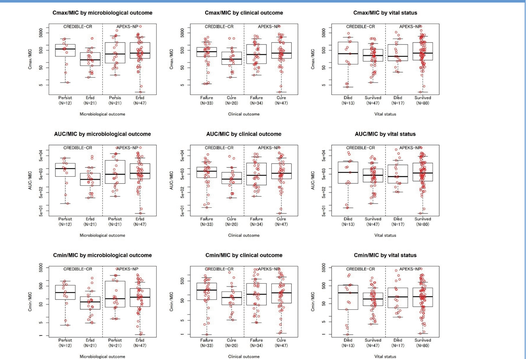


Figure 4 Comparisons of C_{max}/MIC, AUC/MIC, or C_{min}/MIC by Microbiological Outcomes, Clinical Outcomes, or Vital Status in CREDIBLE-CR and APEKS-NP Studies



Y-axis: logarithmic scale. Persist = Persistence; Erad = Eradication

Conclusion

- As high % $fT_{>MIC}$ and % $fT_{>MIC,ELF}$ were achieved, PK/PD relationships were not identified between exposure of cefiderocol and microbiological outcomes, clinical outcomes or vital status.
- There was no positive correlation between other PK/PD parameters (% $fT_{>4\times MIC}$, C_{max}/MIC, AUC/MIC and C_{min}/MIC) and efficacy.
- It is suggested that the recommended dosing regimen of 2 g q8h or renally adjusted dosage including augmented renal clearance, infused over 3 hours, provides sufficient exposure to cefiderocol in critically ill patients.

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