Critical Care

CORRESPONDENCE

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Cefiderocol pharmacokinetics in critically ill patients undergoing ECMO support

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To the Editor,

Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a rescue therapy for severe acute respiratory distress syndrome or severe circulatory failure. Nosocomial infections are common in ECMO patients; therefore, antibiotics are frequently used [1]. However, preliminary evidence suggests that ECMO support could alter antibiotic serum concentrations. Both subtherapeutic and elevated serum concentrations of commonly used antimicrobial agents have been reported [2]. New antimicrobials, especially novel β-Lactams and β-Lactam/β-Lactamase inhibitors, have been commercialized after a thorough pharmacokinetic (PK) assessment. However, new molecule PK changes have again been reported in critically ill patients, especially in those on ECMO support [3]. Circuit adsorption and sequestration are added to critical illness PK derangements, yet the specific weight of each of these factors is not clear [2, 3]. Cefiderocol is a siderophore cephalosporin active against gram-negative bacteria, including carbapenemase-producing strains, with promising positioning for difficult-to-treat infections. Scarce data has been published about its pharmacokinetics in patients with ECMO support [2, 3]. Therefore, we performed an observational and prospective study including adult critically ill patients treated with cefiderocol between January 2022 and December 2023 at a tertiary university hospital. Total plasma concentrations (Cp) at trough (C_{min}) and at the end of the 3 h infusion (C_{max}) were determined using UPLC-MS/MS after at least 72 h of treatment were completed. Free plasma concentrations (fC_{min}, fC_{max}) were corrected using the average protein binding from clinical pharmakocinetic studies [4]. The minimum inhibitory concentration (MIC) of cefiderocol on the antibiogram was determined by the microdilution technique (UMIC® Cefiderocol BMD test). The established therapeutic objective (Pk/Pd) was when Cp was at least four times above the MIC ($100\%fT > 4 \times MIC$). The calculation of the pharmacokinetic parameters was performed from the plasma concentrations obtained and Pmetrics version 1.5.2 software package for R was used (1) [5]. A 3-compartment model with a proportional error model for the intraindividual variability was used (2) [6]. Hyperfiltration was considered when creatinine clearance (ClCr) exceeded 130 ml/min. Clinical response was defined as the resolution of the signs and symptoms present at the time of the infection. The study protocol was approved by the local Ethics Committee, and written informed consent was obtained from the patient or their legal representatives, and. A Student's t-test or Mann–Whitney test was used to compare quantitative variables and Pearson's chi-square or Fisher's exact test for qualitative variables according to normality, using STATA v.14.2. Statistical significance was considered if $p \leq 0.05$.

Ten caucasian patients were included: four of them were treated with veno-venous ECMO, and one of them

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Table 1 Individual clinical and pharmacokinetic characteristics

Patient	Sex	Age	BMI	ECMO	ClCr	Microorganism	Hours on ECMO circuit before analysis[1]	ECMO blood/ gas flow l/min	Days on treatment	*f*Cmin (µg/ml)	*f*Cmax (µg/ml)	MIC (mg/l)	%time > MIC	Vd (L)	CL (l/h)	Half-life (hrs)
1	M	60	36, 7	Yes	108	*Stenotrophomona maltophilia*	48	3.9/5	9	26	30	0.25	100%	6, 13	3, 72	14.53
2	F	20	16, 3	Yes	CRRT	*Pseudomonas aeruginosa*	888	2.8/7	7	86	140			6, 12	2, 92	4.27
3	F	67	32, 7	Yes	45	*Serratia marcenses*	312	4.1/7	3	64	152	0.25	100%	9, 87	2, 62	2.4
4	F	27	17.2	Yes	130	*Pseudomonas aeruginosa*	24	3.9/3	3	8	104	1.00	100%	8, 12	3, 74	0.81
5	M	68	18, 4	No	111	*Acinetobacter baumannii*			5	68	194	0.125	100%	6, 56	1, 24	1.98
6	F	36	24, 7	No	108	*Stenotrophomona maltophilia*			3	56	102	0.25	100%	11, 91	2, 88	3.47
7	M	64	25,4	No	107	*Acinetobacter baumannii*			3	64	116	0.25	100%	9, 82	2, 28	3.5
8	F	59	30, 9	No	102	*Acinetobacter baumannii*			3	8	76			9, 93	3, 84	0.92
9	F	65	31, 1	No	102	*Acinetobacter baumannii*			3	20	88	0.5		9, 92	3, 64	1.42
10	F	66	45, 7	No	100	*Pseudomonas aeruginosa*			3	68	142			11, 91	2, 08	2.82
Healthy subjects (clinical trials I/II) (n = 54)[2]	M	30.55	22.05	No	138.6					7.32 (± 4.3)	156 (± 7.9)			18 (± 3.36)	5.13 (± 9.0)	2.74 (± 10.2)

BMI body mass index, *IMV* invasive mechanical ventilation, *CRRT* continuous renal replace treatment, *ECMO* extracorporeal membrane oxygenation, *CrCl* creatinine cleareance, *Pk* pharmacokinetic measure, *MIC* minimum inhibitory concentration, *Vd* volumen of distribution, *CL* Clearance from compartment

[1] Hours on the same ECMO circit previous to cefiderocol asessment, [2][16]

additionally underwent continuous renal replacement therapy (CRRT). The demographic and clinical characteristics of patients are depicted in Table 1. Patients under ECMO support were managed with a peripheral femoro-jugular venovenous configuration. ECMO Cardiohelp HLS system (Maquet Cardiopulmonary ®, Rastaat, Germany) was used in all cases. The circuit comprises a polymethylpentene membrane oxygenator, a centrifugal pump, a heat exchanger and polyvinil chloride tubing. All components of the circuit were treated with heparin (Bioline coating ®, Maquet). Physiological saline solution was used to prime the circuit.

All patients received 2 g/8 h in a 3-h infusion for a mean duration of 10 (4.03) days. Hyperfiltration was present in two ECMO patients. Treated infections were nosocomial pneumonia in nine cases (90%) and nosocomial bloodstream infection in one (10%). All microorganisms involved in the treated infections were multidrug resistant strains, but sensitive to cefiderocol [MIC 0.56 (0.39) mg/L]. No patient received combined therapy, and no adverse effects associated with cefiderocol were observed. Serum cefiderocol measurements for the entire cohort were fC_{min} 25.2 (8.4–28.5) µg/mL and fC_{max} 46.2 (36.9–59.6) µg/mL. No differences in fC_{min} or fC_{max} were found between the ECMO group and the non-ECMO group (Table 2 supplementary material). All patients achieved the 100%$fT > 4 \times$MIC objective. ECMO patients were sampled after a median time of 31 days (10–29) of ECMO treatment. ECMO membranes had not been replaced before cefiderocol assessment (previous duration in all cases of at least 96 h). Individual PK parameters are shown in Table 1. Our critically ill patients had lower Vd and CL compared to healthy patients. Important variations in Vd, CL, and especially in half-life were present in our population showing heterogeneity of our patient sample and the presence of multiple factors affecting cefiderocol PK. Apparently the presence of ECMO treatment did not result in any specific pharmacokinetic behavior of cefiderocol.

Previous cefiderocol serum concentrations studies performed in critically ill patients had presented heterogeneous results. Suboptimal $fT\% > MIC$ due to low fC_{min} has been described in two studies (50% and 23% of patients, respectively), and this was associated with microbiological failure in *A baumannii* infection in the later one [7, 8]. However, the potential factors associated with these alterations were not studied. Conversely, 100%$fT > 4 \times$MIC was achieved in another two studies including 12 patients with difficult to treat infections by multidrug resistant gram-negative bacteria [9, 10]. Katsube et al. studied seven patients with pneumonia in whom the Pk/Pd target was attained in plasma and also in epithelial lining fluid when treated with a standardized cefiderocol dosage [9]. The cefiderocol dosage recommendation for CRRT should be adjusted to the effluent rates and presence of residual renal function. These two factors were evaluated to indicate a full dosage (2 g/8 h) in two studies including six patients, achieving accurate plasma concentrations and without detecting adverse events [11, 12].

Cefiderocol PK in ECMO patients have been assessed successfully in two ex vivo studies suggesting no loss due to sequestration or adsorption [13, 14]. These results were corroborated in one critically ill patient under ECMO therapy due to COVID19 [15]. To our knowledge, this is the first time that critically ill patients with and without ECMO support have been pharmacokinetically studied and presented together. Our results suggest that the pharmacokinetic profile of cefiderocol in critically ill patients is adequate, even in the presence of ECMO treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05126-4.

Additional file1 (DOCX 19 KB)

Author contributions

MMC and PR wrote the main manuscript text. JRR, RML, MJB, JF and MG prepared Table 1. AC and SGC reviewed the manuscript to assess concordance with the literature. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interest

The authors declare no competing interests.

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