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CLINICAL THERAPEUTICS

Dose Optimization of Cefpirome Based on Population Pharmacokinetics and Target Attainment during Extracorporeal Membrane Oxygenation

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ABSTRACT To obtain the optimal dosage regimen in patients receiving extracorporeal membrane oxygenation (ECMO), we developed a population pharmacokinetics model for cefpirome and performed pharmacodynamic analyses. This prospective study included 15 patients treated with cefpirome during ECMO. Blood samples were collected during ECMO (ECMO-ON) and after ECMO (ECMO-OFF) at predose and 0.5 to 1, 2 to 3, 4 to 6, 8 to 10, and 12 h after cefpirome administration. The population pharmacokinetic model was developed using nonlinear mixed effects modeling and stepwise covariate modeling. Monte Carlo simulation was used to assess the probability of target attainment (PTA) and cumulative fraction of response (CFR) according to the MIC distribution. Cefpirome pharmacokinetics were best described by a two-compartment model. Covariate analysis indicated that serum creatinine concentration (SCr) was negatively correlated with clearance, and the presence of ECMO increased clearance and the central volume of distribution. The simulations showed that patients with low SCr during ECMO-ON had lower PTA than patients with high SCr during ECMO-OFF; so, a higher dosage of cefpirome was required. Cefpirome of 2 g every 8 h for intravenous bolus injection or 2 g every 12 h for extended infusion over 4 h was recommended with normal kidney function receiving ECMO. We established a population pharmacokinetic model for cefpirome in patients with ECMO, and appropriate cefpirome dosage regimens were recommended. The impact of ECMO could be due to the change in patient status on consideration of the small population and uncertainty in covariate relationships. Dose optimization of cefpirome may improve treatment success and survival in patients receiving ECMO. (This study has been registered at ClinicalTrials.gov under identifier NCT02581280.)

KEYWORDS ECMO, beta-lactams, cephalosporin, pharmacodynamics, population pharmacokinetics

Extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory support for patients with profound cardiogenic shock (1, 2). ECMO has a critical role in the treatment of cardiogenic shock refractory to conventional medical management (3). As ECMO involves the use of a percutaneously inserted invasive device that uses large-diameter catheters and critically ill patients are generally vulnerable to infection,

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TABLE 1 Demographic information and baseline characteristics of all enrolled patients

Patient no.	Sex	Age (yrs)	Wt (kg)[a]		Indication of ECMO[b]	Duration of ECMO (h)	SCr[a,b] (mean, mg/dl)		Use of CRRT[a,b]		APACHE II score[b]	Length of hospital stay (days)
			ECMO-ON	ECMO-OFF			ECMO-ON	ECMO-OFF	ECMO-ON	ECMO-OFF		
1	Male	34	92.9	84.9	ARVD	209.5	2.46	2.31	Yes	Yes	32	102
2	Male	69	72	69.4	AMI	152.4	2.55	2.3	No	Yes	30	54
3	Female	52	49.2	48.4	AMI	171.8	3.41	1.56	No	Yes	37	74
4	Male	72	69.6		AMI	361.8	2.06		No		36	44
5	Male	63	81.7		AMI	166.1	3.11		Yes		46	7
6	Male	82	61.8	58.8	AMI	86.2	1.65	1.24	Yes	Yes	32	92
7	Male	75	98.3		AMI	421.5	0.44		Yes		36	20
8	Female	27	60.5		Myocarditis	720.2	0.40		No		36	53
9	Male	76		54.3	AMI	34.6		2.11		Yes	40	74
10	Male	52	76.3	72.5	AMI	89.8	1.37	2.26	Yes	No	31	12
11	Female	62	60.5	58.3	AMI	113.8	0.61	0.85	No	No	32	24
12	Male	67	75	65.7	PTE	285.4	1.55	1.56	No	No	24	26
13	Male	51	71		AMI	222.7	1.14		No		26	35
14	Male	66	65.5		AMI	134.6	1.61		No		14	22
15	Male	42	60		AMI	163.8	0.95		No		28	31
Median		63	70.3	62.25		166.1	1.58	1.84			32	35
IQR		51.5–70.5	60.8–76.0	57.3–70.2		124.2–254.0	0.99–2.36	1.48–2.27			29–36	23–64

[a]The data were collected during sampling.
[b]ARVD, arrhythmogenic right ventricular dysplasia; AMI, acute myocardial infarction; PTE, pulmonary thromboembolism; ECMO, extracorporeal membrane oxygenation; SCr, serum creatinine concentration; CRRT, continuous renal replacement therapy; APACHE II, acute physiology and chronic health evaluation II.

broad-spectrum antibiotics are required for prophylaxis and the treatment of infection during ECMO (4, 5).

Several studies have suggested changes in drug pharmacokinetics (PK) during ECMO. Typically, owing to drug sequestration in ECMO circuits, hemodilution, and the inherent physiological changes associated with ECMO and critical illness, the volume of distribution is increased, whereas clearance (CL) is generally decreased owing to renal and hepatic hypoperfusion and hypoxia (6–8). However, the PK changes of a drug in the ECMO device are dependent on the physiochemical properties of the drug; therefore, exact prediction is difficult (9).

Third- and fourth-generation cephalosporins, as broad-spectrum antibiotics, are usually recommended for patients receiving ECMO (5, 10, 11). Cefpirome, a fourth-generation cephalosporin, is used to treat hospitalized patients with moderate to severe infections (12, 13). Beta-lactam antibiotics are relatively hydrophilic with varying protein binding ratios; therefore, ECMO-associated PK changes in beta-lactams also vary (9, 14, 15). The risk of a subtherapeutic plasma concentration of antibiotics because of PK changes as a result of ECMO therapy creates concern for an increased risk of infection-related mortality (5). Thus, a deep understanding of the PK changes in patients receiving ECMO is essential to provide optimal dosing and to perform therapeutic drug monitoring (16).

However, fewer PK studies have investigated cefpirome compared with other antibiotics; moreover, no previous study has investigated the PK changes of cefpirome in patients receiving ECMO (17–20). Further, few studies have suggested the appropriate dosage of antibiotics for patients receiving ECMO, and there is a need for effective and safe antibiotics suitable for use during ECMO. To recommend the pertinent dosage for cefpirome in patients during ECMO, we aimed to evaluate the population PKs and pharmacodynamic profiles of cefpirome.

RESULTS

Subjects. The demographic characteristics of the patients are shown in Table 1. The 15 eligible patients had a median age of 63 years (interquartile range [IQR], 51.5 to 70.5 years), median duration of ECMO support of 166.1 h (IQR, 124.2 to 254.0 h), and median serum creatinine concentration (SCr) of 1.58 mg/dl during ECMO and 1.83 mg/dl after ECMO. Five patients received continuous renal replacement therapy (CRRT) treatment during ECMO. The median acute physiology and chronic health

TABLE 2 Parameter estimates and SIR results

Parameter	Base model population estimate (RSE, %)	Final model	
		Population estimate (RSE, %)	SIR median (2.5th−97.5th percentile)
Fixed effect (θ)			
Clearance, CL (liters/h)	3.6 (15)	5.71 (12)	5.77 (4.47−7.29)
Central volume of distribution, V1 (liters)	10.3 (21)	2.74 (30)	2.91 (1.54−5.26)
Peripheral volume of distribution, V2 (liters)	19.5 (22)	16.7 (14)	16.6 (13.0−22.5)
Intercompartmental clearance, Q (liters/h)	9.62 (19)	9.43 (23)	9.68 (7.18−12.5)
θSCr/1.6 on CL		0.487 (7)	0.489 (0.42−0.57)
θECMO on CL		1.41 (10)	1.40 (1.26−1.57)
θECMO on V1		4.22 (48)	3.90 (1.94−8.27)
Random effect (% CV)			
Interindividual variability (ω)			
Clearance	58.8 (34)	35.1 (47)	36.3 (25.3−53.5)
Central volume of distribution	26.5 (89)	37.4 (37)	38.7 (17.9−57.8)
Peripheral volume of distribution	92.6 (73)	47.5 (38)	48.3 (35.4−62.8)
Proportional residual variability (σ)	25.7 (19)	21.7 (20)	21.9 (19.2−25.1)

evaluation II score was 32 (IQR, 29 to 36). The ECMO-ON plasma samples were collected from 14 patients during ECMO, whereas ECMO-OFF samples were collected from 8 patients after ECMO. In total, 152 plasma samples were collected, and none of the samples were below the limit of quantitation.

Population PK analysis. The plasma concentration-time profiles were drawn in Fig. S2 in the supplemental material. The observed plasma concentration-time profiles of cefpirome were best explained by the two-compartment model (Advan 3). The interindividual variability (IIV) included CL, central volume of distribution (V1), and peripheral volume of distribution (V2). The residual variability was best described by a proportional residual error model. Individual parameters such as half-life, C_{max}, and time to C_{max} were represented in Table S1 in the supplemental material. For forward step, SCr among the covariates relating renal functions was selected because the change of objective function value (ΔOFV) was the largest (−32.898) compared to that for creatinine clearance (CrCL) by Cockcroft-Gault and estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) equation (−5.85 and −14.24, respectively). In addition, relative standard error (RSE) for parameters was more reasonable for SCr than CrCL and eGFR. Finally, the SCr for CL and the use of ECMO for CL and V1 were found to influence PK parameter changes (ΔOFV = −64.71, condition number = 315). The final PK model was as follows: $CL = 5.71 \times 0.487^{(SCr\ in\ mg/dl/1.6)} \times 1.41^{ECMO}$ liters/h, where ECMO-ON = 1 and ECMO-OFF = 0; $V1 = 2.74 \times 4.22^{ECMO}$ liters, where ECMO-ON = 1 and ECMO-OFF = 0; V2 = 16.7 liters; and intercompartmental clearance (Q) = 9.43 liters/h. When SCr is 1.6 mg/dl, population CL on ECMO-ON is 3.92 liters/h and that on ECMO-OFF is 2.78 liters/h.

The goodness-of-fit plots for the final model are presented in Fig. S1 in the supplemental material. Both population predictions (PRED) and individual predictions (IPRED) were distributed uniformly across the line of equality. Additionally, the plots of conditional weighted residuals (CWRES) versus PRED and versus time after the first cefpirome dose were relatively evenly distributed around zero and did not show any trends. We checked the interindividual variability (ETA) correlation plot for the final PK model, but it has not shown any trends (see Fig. S3 in the supplemental material).

Model validation. The PK parameter estimates for cefpirome from the base and final PK models and the sampling importance resampling (SIR) results are summarized in Table 2. All parameter estimates were distributed within the 95% confidence intervals (CIs) and were similar to the median value from SIR results with acceptable RSEs, which indicated that the precision of the model was good. All ETA shrinkage values were <30% in the final model. The prediction-corrected visual predictive check (pcVPC) plot showed that approximately 10% of the observed data were positioned

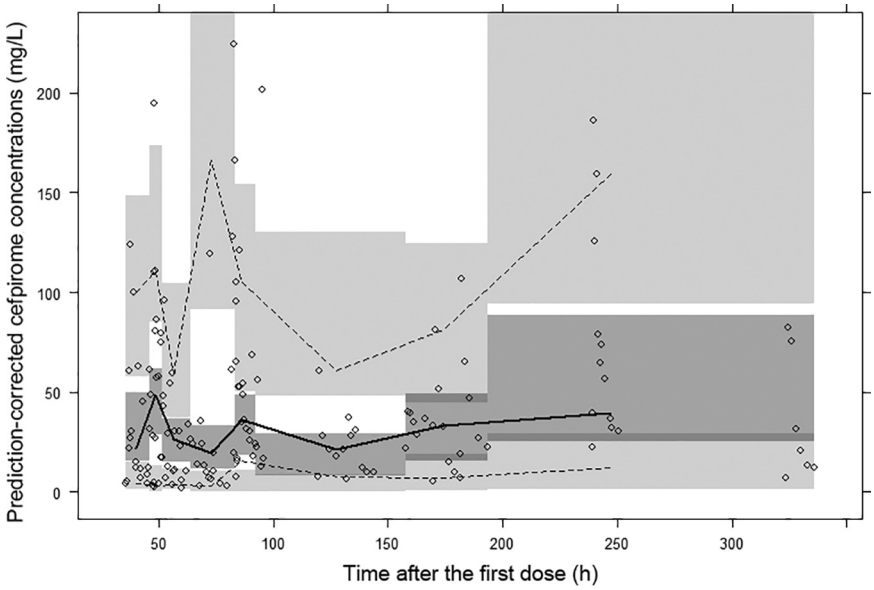

FIG 1 The prediction-corrected visual predictive check plot showed that the 5th to 95th percentiles of the predicted data overlapped most of the observed data. Open circles, observed cefpirome concentrations; solid line, median; lower and upper dashed lines, 5th and 95th percentiles of the observed data, respectively; shaded areas, 95% confidence intervals for simulated predicted median, 5th, and 95th percentile constructed from 5,000 simulated data sets of individuals from the original data set.

outside of the 5th to 95th percentiles of the predicted data, which suggested that the predictive performance of the final model was adequate (Fig. 1).

Simulations. The simulated probability of target attainment (PTA) versus MIC profiles for the different intravenous bolus (i.v.-bolus) and extended infusion dosage regimens with ECMO-ON and ECMO-OFF at each SCr are shown in Fig. 2 and Table S2 in the supplemental material. The calculated PTA in ECMO-ON tended to be slightly lower than that in ECMO-OFF for the same SCr. Additionally, patients with a lower SCr, representative of better kidney function, obtained lower PTA than those with higher SCr during the same ECMO condition.

The assessed cumulative fraction of response (CFR) and recommended dose according to SCr and administration practice (i.v.-bolus versus extended infusion) in patients during ECMO are shown in Fig. 3. All CFR results are shown in Table S3 in the supplemental material. CFR was higher following extended infusion delivery than in the i.v.-bolus and lower in ECMO-ON than in ECMO-OFF in the same dosing scenario. The CFRs were higher than 95% for *Streptococcus pneumoniae*, *Enterobacter* spp., *Escherichia coli*, and *Klebsiella* spp. for all doses of cefpirome, regardless of the presence of ECMO. The dosage regimens of 2 g every 8 h (q8h) for i.v.-bolus and 2 g every 12 h (q12h) for extended infusion were recommended for *Pseudomonas aeruginosa* treatment in patients during ECMO with SCr values of up to 0.9 mg/dl. It was difficult to achieve target CFR for *Acinetobacter* spp. at a low SCr.

DISCUSSION

We explored the population PK model for cefpirome during ECMO and performed a pharmacodynamic analysis using Monte Carlo simulations under dosing regimens for various pathogens. The most important clinically relevant finding was that CL and V1 were increased in the presence of ECMO at the same SCr. Additionally, SCr was negatively correlated with CL. PTA and CFR were slightly decreased by lower SCr and during ECMO. None of the parameters related to ECMO, such as liters per minute (LPM) and revolutions per minute (RPM), helped in understanding factors influencing the final PK model. The optimal dosage of cefpirome in patients with normal kidney function receiving ECMO was recommended to be 2 g cefpirome q8h (6 g/day) for i.v.-bolus or

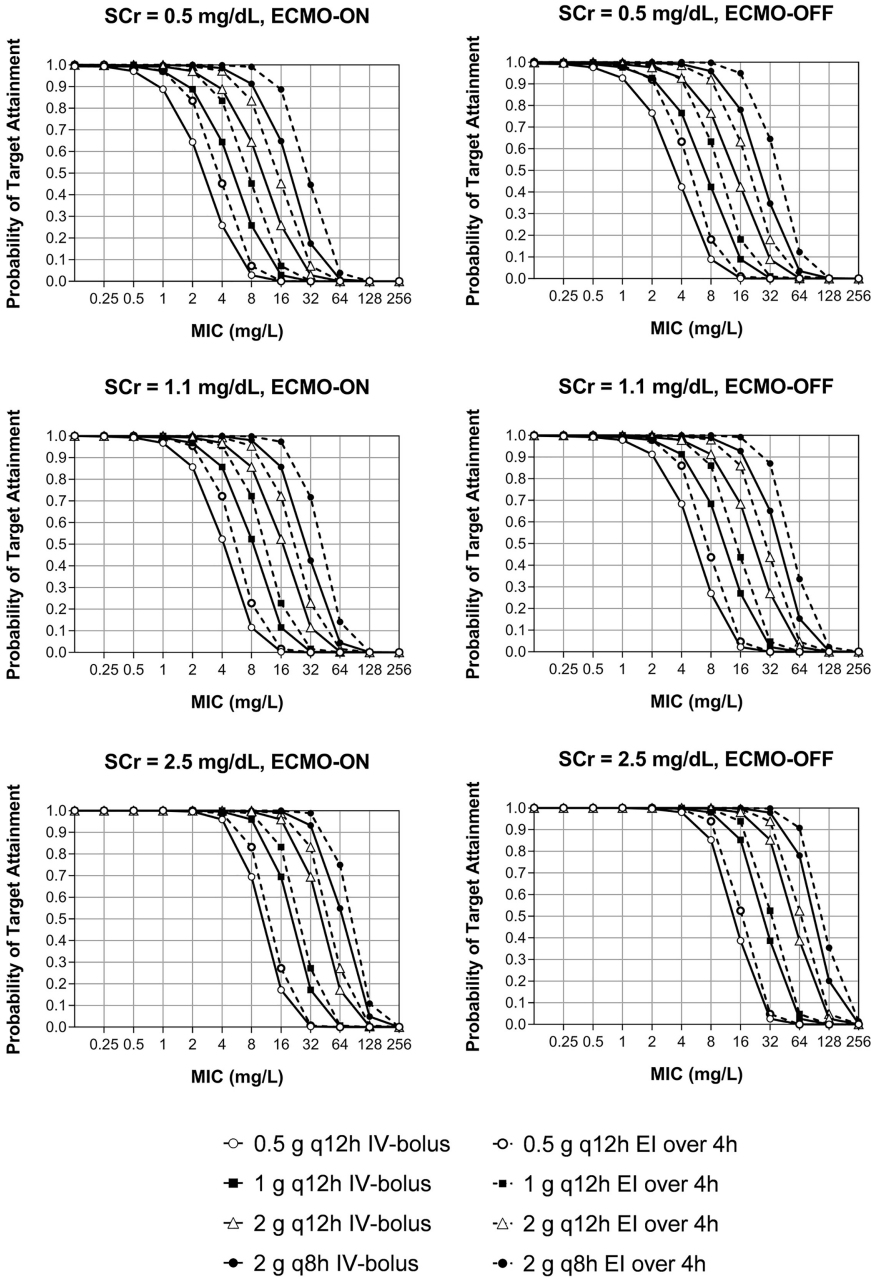

FIG 2 Probability of target attainment for 5,000 simulated subjects administered cefpirome. Simulated probability of target attainment (PTA) according to cefpirome dosing, serum creatinine concentration (SCr), and the presence of ECMO. i.v.-bolus, intravenous bolus injection; EI over 4h, extended infusion over 4 h; ECMO-ON, patients during ECMO; ECMO-OFF, patients after ECMO termination. The target for the analysis was for free plasma concentrations to be above the MIC for at least 65% of the dosing interval.

2 g q12h (4 g/day) for extended infusion over 4 h; moreover, dose reduction based on SCr was recommended (Fig. 3). To the best of our knowledge, this study is the first to suggest the appropriate dosage of cefpirome for critically ill patients receiving veno-arterial ECMO (VA-ECMO).

In our study, the CL was 3.92 liters/h for the ECMO-ON group when SCr is 1.6 mg/dl, which was lower than the values reported by previous studies in critically ill patients (7.54 liters/h) (17). The reduction in cefpirome CL in our study can be explained by the renal impairment caused by hemodynamic instability (21). VA-ECMO-related factors, such as systemic inflammation due to the exposure of blood to artificial surfaces,

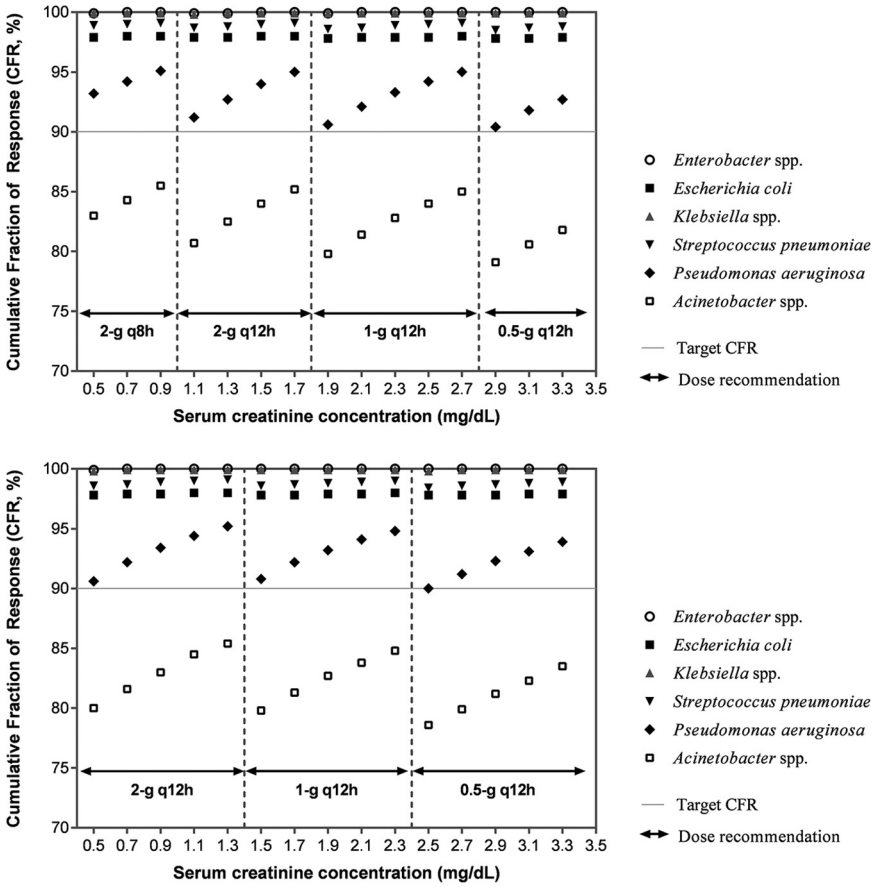

FIG 3 Cumulative fraction of response after administration of the recommended dosage of cefpirome based on serum creatinine concentration range in patients during extracorporeal membrane oxygenation. Simulated cumulative fraction of response (CFR) according to the recommended dose for intravenous bolus injection (top) or extended infusion over 4 h (bottom) based on *Pseudomonas aeruginosa*.

hemolysis, or hemoglobinuria, may also contribute to renal dysfunction (22, 23). This trend was also found in PK studies of cefepime in pediatric patients receiving ECMO (24, 25).

Prior studied asserted that the ECMO system can exacerbate drug PK changes in patients receiving ECMO compared with those of critically ill patients not receiving ECMO (16, 26). One interesting finding was the increase in V1 in patients receiving ECMO. Patients with cardiogenic shock who receive ECMO are critically ill and in a systemic inflammatory state; profound shock causes deterioration that leads to a vasodilatory state (27–29). Moreover, the extra circulating volume from ECMO circuits, rigorous fluid resuscitation, and frequent transfusion induces an increased circulatory volume in patients receiving ECMO (30). Thus, V1 might be increased in patients with ECMO. Although cefpirome is a hydrophilic and low protein binding substance (12), an increase in V1 following cefpirome sequestration in the ECMO circuits could not be excluded (31, 32).

Another finding was that cefpirome CL was higher in the ECMO-ON group. This relationship may partly be explained by circuit loss of cefpirome. Significant losses are known to occur for some drugs in ECMO circuits owing to oxidation and photodegradation (33, 34). The manufacturer's information states that reconstituted cefpirome solutions are stable for up to 6 h under indoor light at room temperature; subsequently, they should be stored at 2°C to 8°C and protected from light (35). In practice, the cefpirome solution in the blood was exposed to light and heating lamps for more than 12 h in the ECMO device, which may have caused drug degradation. Moreover, cefpirome was reported to have a low molecular weight and be structurally stable (35,

36); therefore, physiological changes by ECMO, such as interactions between retrograde flow returned from VA-ECMO and native flow from the aorta, are not expected to affect the CL of cefpirome (22).

In our final model, as the SCr increased, cefpirome CL decreased. Cefpirome is predominantly (80% to 90%) eliminated by the kidney (12); thus, a negative correlation between cefpirome CL and SCr is reasonable. An excellent relationship between creatinine clearance (CrCL) and systemic cefpirome CL has been reported (19). Further, CrCL, measured from an 8 h urine collection, was screened as a covariate for CL (17). The use of CRRT and SCr was screened simultaneously through univariate analysis; however, the use of CRRT was dropped out through stepwise covariate modeling because it did not improve the robustness of the PK model after SCr was first added to CL as covariate. Although SCr is not reflected in CRRT intensity directly, CRRT could contribute fairly to the decrease in SCr (37). In addition, a previous study reported that a certain fraction of the cefpirome is filtered through CRRT (38). So, it is not surprising that CRRT is not included in our final cefpirome PK model.

To assess the ability of cefpirome to kill bacteria in patients receiving ECMO, the CFRs for *S. pneumoniae*, *Enterobacter* spp., *E. coli*, *Klebsiella* spp., *P. aeruginosa*, and *Acinetobacter* spp., which are frequently identified pathogens in culture during ECMO, were calculated using the MIC distribution from EUCAST (39). Our findings were different from those of a previous study, in which i.v.-bolus or continuous infusions of cefpirome failed to achieve bactericidal targets for *P. aeruginosa* or *Acinetobacter* spp. in patients with sepsis (17). The dosing simulations confirmed that the current treatment, 2 g q12h for i.v.-bolus, was considered sufficient to treat infections caused by *S. pneumoniae*, *Enterobacter* spp., *E. coli*, or *Klebsiella* spp.; moreover, a lower dosage, i.e., 0.5 g q12h for i.v.-bolus, was sufficient regardless of ECMO. For *P. aeruginosa*, the optimal dose was 2 g q8h for i.v.-bolus or 2 g q12h for extended infusion in ECMO patients with normal SCr. For patients with relatively high SCr, dose reduction to 0.5 to 1 g q12h is recommended. To treat *Acinetobacter* spp., 2 g q8h or 2 g q12h is recommended in clinical settings; however, there are some SCr ranges for which no appropriate dose exists.

The cefpirome dose required to meet the CFR target tended to be lower for extended infusion than for i.v.-bolus. Prior studies have noted the clinical benefits of prolonged infusions of beta-lactams because they have time-dependent activity (40). Although maximum efficacy and minimal toxicity are expected from a continuous cefpirome infusion, the degradation after reconstitution should not be overlooked. Cefpirome degradation follows pseudo-first-order kinetics and is stable for up to 6 h at room temperature in aqueous solution (17, 35). Therefore, we suggested a 4 h infusion, and our findings supported the notion that patients simulated for the same dosing for extended infusion over 4 h were more likely to meet the bactericidal targets than those for i.v.-bolus in every scenario.

Simulation-based pharmacokinetic/pharmacodynamic (PK/PD) analysis using PK/PD indices provides optimal drug therapy through a quantitative description of drug effects, so this is used frequently in therapeutic areas nowadays (41). Many studies have been conducted to identify the PK/PD indices that best predict the effect of antibiotics. Beta-lactam activity has been considered as almost dependent on the percent of time for free plasma concentrations to be above the MIC (% fT$>$MIC) (42–44). Recently, predictive breakpoints of cephalosporin against *Pseudomonas aeruginosa* were reported greater than 53% *f*T$>$MIC (45), and we used the magnitude of 65% *f*T$>$MIC for cefpirome to cover enough for several pathogens according to previous studies (17, 42).

This study has some limitations. The number of patients enrolled was small. To evaluate covariates in population PK modeling, a minimum of 50 patients has been suggested (46). However, considering the patient characteristics receiving ECMO, 15 patients were not few, and Shekar et al. also evaluated that a minimum of 12 patients receiving ECMO would be enough for population PK analysis (47). In addition, the evaluations proved the robustness of our final model and provided sufficient evidence

that our study demonstrated the optimal dosage regimen of cefpirome in patients receiving ECMO. To reduce variability among subjects and enhance accurate model prediction, our PK model was restricted in patients receiving VA-ECMO, which is merely one mode of ECMO. So, the generalizability of these results to all ECMO mode is limited. Thirdly, the ECMO-OFF group was included in the PK model analysis, and our result might be inherently correlated with patient status and improvement; however, all subjects in the ECMO-OFF group were still critically ill patients who needed intensive care until sampling. A recent review demonstrated that PK changes in patients receiving ECMO reflect more critical illness than ECMO therapy itself (16).

In conclusion, we established a population PK model for cefpirome during ECMO. Moreover, the optimal dosage regimen was obtained to provide adequate bactericidal activity during ECMO. Future studies on a larger number of patients receiving ECMO will support the effective use of cefpirome.

MATERIALS AND METHODS

Study design and ethics. This prospective cohort study was conducted from January 2018 to January 2019 in the cardiac intensive care unit of Severance Hospital, a tertiary academic hospital in Seoul, South Korea. The study was approved by the Severance Hospital Institutional Review Board (approval number 4-2014-0919) and registered at Clinicaltrials.gov under identifier NCT02581280. Written informed consent was acquired from the unconscious participants' legally acceptable representatives. This study followed strengthening the reporting of observational studies in epidemiology (STROBE) recommendations.

Subjects. Eligible patients were 19 years of age or older, receiving venoarterial ECMO (VA-ECMO) and concomitantly receiving cefpirome as per the hospital protocol for infection prophylaxis. The study excluded patients who were allergic to beta-lactams, pregnant, or taking any medication that may have altered plasma cefpirome concentrations.

Extracorporeal membrane oxygenation system. The ECMO system comprised a centrifugal blood pump with a controller (Capiox SP-101; Terumo Inc., Tokyo, Japan), a conduit tube (Capiox EBS with X coating; Terumo Inc., Tokyo, Japan), and an air-oxygen mixer (Sechrist Industries, CA, USA). The settings of ECMO were recorded.

Study procedures. Cefpirome was administered at the start of ECMO to prevent infection. According to hospital protocol, patients with normal kidney function received 2 g cefpirome every 12 h (q12h) as an intravenous bolus injection. Patients with an estimated glomerular filtration rate of less than 50 ml/min/1.73 m^2, as calculated by the MDRD equation, received a 50% dose reduction. If needed, continuous venovenous hemodiafiltration (Prismaflex; Gambro Inc., Meyzieu, France) with a Prismaflex ST100 filter was applied as continuous renal replacement therapy (CRRT).

The study was initiated at least 24 h after ECMO was started. Blood samples were collected through the existing radial arterial line at predose and at least one random point during each of the following time periods after cefpirome administration: 0.5 to 1, 2 to 3, 4 to 6, 8 to 10, and 12 h (ECMO-ON). The actual sampling time was recorded. If the patients were successfully weaned off ECMO and continued cefpirome, blood samples were collected after ECMO termination as control (ECMO-OFF). Blood samples were collected in EDTA-coated tubes and then immediately centrifuged (1,500 $\times$ *g* at 4°C for 10 min). The obtained plasma was refrigerated at −80°C until analysis.

To analyze the cefpirome plasma concentrations, liquid chromatography-mass spectrometry (LC-MS) (Ultimate 3000 RS-LTQ Orbitrap XL; Thermo Fisher Scientific, MA, USA) was used. The plasma samples (250 μl) were denatured using 250 μl 5% thiobarbituric acid with doxofylline as an internal standard. The mixture was centrifuged (10 min at 10,000 $\times$ *g*). LC-MS was performed on an Acquity UPLC BEH C_{18} column (1.7 μm, 2.1 mm by 100 mm; Waters, MA, USA) with a column temperature of 50°C and a flow rate of 0.4 ml/min. Solvent A (0.1% formic acid in water) and solvent B (0.1% formic acid in methanol) comprised the mobile phase. The mobile phase composition was as follows: 100% A for 1 min, gradient elution to 100% B at 16 min, 100% B until 20 min, and finally a gradient elution to 100% A at 22 min. The assay was validated within the range of 1.0 to 64.0 mg/liter; the lower limit of quantification was 1.0 mg/liter. The inter- and intra-assay coefficients of variation were below 15%.

Base model development. Base model development was conducted using the first-order conditional estimation method with interaction algorithm in NONMEM version 7.4.1 (ICON Development, MD, USA) and Pirana version 2.9.7 (Certara, NJ, USA). Xpose4 package version 4.6.1 (http://xpose.sourceforge.net/) (48) in R version 3.5.3 (http://www.r-project.org) was used to visualize and evaluate the models. The plasma cefpirome concentrations were fitted to one-, two-, or three-compartment models. An exponential variance model for the interindividual variability (η) of PK parameters was evaluated; η was assumed to have a log-normal distribution with a mean of zero and a variance of ω^2. Proportional, additive, and combined residual error models in linear DV were tested for residual variability (ε), which assumed a log-normal distribution with a mean of zero and a variance of σ^2.

The model was selected based on a minimum objective function value (OFV), the validity of the estimated relative standard error (RSE), and visual inspection of the goodness-of-fit plot. An OFV reduction of >3.84 (χ^2 distribution, degrees of freedom = 1, $P < 0.05$) was considered statistically significant. For visual inspection, the basic goodness-of-fit plot was expressed as the observed concentrations versus individual predictions (IPRED) or population predictions (PRED) and conditional weighted

residuals (CWRES) versus PRED or time since the first cefpirome dose. In addition, the ETA correlation plot, individual plots, and QQ plots were visually inspected.

Covariate model development. To evaluate the influence of covariates on the cefpirome PK parameters, the following potential covariates were tested: demographic variables (sex, age, weight, and height), ECMO-associated variables (during ECMO or weaned off ECMO, ECMO flow rate [LPM, liters per minute], and ECMO pump speed [RPM, revolutions per minute], time from ECMO start [h]), use of CRRT, complete blood count (absolute white blood cells, red blood cells, hemoglobin, and platelets), renal function (serum creatinine [SCr], blood urea nitrogen [BUN], CrCL estimated via Cockcroft-Gault equation, and eGFR via the MDRD equation), liver function (alanine transaminase, aspartate aminotransferase, and total bilirubin), biomarkers of inflammation (C-reactive protein and procalcitonin), blood pressure, body temperature, and social variables (smoking and alcohol). All data were recorded during sampling and tested as time-varying covariates.

Covariates were evaluated using linear, exponential, power, and proportional models; influential covariates were selected in a stepwise manner. If needed, the continuous covariates were centered by their median values. For forward selection, a P value of <0.05 was applied (OFV reduction of >3.84); for backward elimination, a P value of <0.001 was used (OFV increase of >10.83). When the correlation was shown between covariates in stepwise modeling, we did not select them simultaneously. The final covariate model selection was based on biological or clinical plausibility, RSE of PK parameters, a condition number of $<1,000$, and visual improvement in the goodness-of-fit plot (49).

Model validation. To evaluate the precision and robustness of the base model and final covariate model, the sampling importance resampling (SIR) method (sampling = 5,000, resampling = 1,000, 5 iterations) and a prediction-corrected visual predictive check (pcVPC) (n = 5,000) were conducted using the Perl-Speaks-NONMEM toolkit version 4.9.0 (50, 51). The median with 95% confidence intervals (CI) for the SIR results was compared with the estimated PK parameters from the final model. Additionally, the simulated VPC results with the 5th, median, and 95th percentile curves were visually assessed.

Simulations. To assess the probability of target attainment (PTA) at 72 h after the start of cefpirome, Monte Carlo simulations were performed on the basis of the estimated PK parameters using NONMEM. Intravenous bolus injection (i.v.-bolus) and extended infusion over 4 h dosage regimens of 0.5 g q12h, 1 g q12h, 2 g q12h, and 2 g every 8 h (q8h) were simulated. To assess the effect of serum creatinine concentration (SCr), which was selected as covariates in the final PK model, and the use of ECMO on the predicted cefpirome concentrations, SCr of 0.5 to 3.3 mg/dl (in increments of 0.2 mg/dl) were simulated for the ECMO-ON and ECMO-OFF groups. Each simulated concentration-time profile was generated for 1,000 subjects per dosage regimen. From these data, when a protein binding constant of 10% was applied (12), the % $fT>$MIC was determined for each simulated subject by linear interpolation. The PTA was calculated by counting subjects who achieved at least 65% $fT>$MIC for optimal bacteria killing in terms of efficacy (17, 42); a PTA of $\geq$0.9 was considered robust (17, 42).

MIC distribution. The MIC distribution for cefpirome, which was 0.008 to 256 mg/liter in this study, was derived from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (https://mic.eucast.org/Eucast2/SearchController) for 103 strains of *Acinetobacter* spp., 39 strains of *Enterobacter* spp., 5,728 strains of *Escherichia coli*, 794 strains of *Klebsiella* spp., 704 strains of *Pseudomonas aeruginosa*, and 767 strains of *Streptococcus pneumoniae*. The PTA for each regimen and the MIC distribution were used to calculate the cumulative fraction of response (CFR). A CFR of over 90% was targeted (52).

Data availability. The data sets generated and/or analyzed during the current study are not publicly available owing to privacy concerns and institutional policies but are available from the corresponding author upon request.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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S.K., J.W., and M.J.C. designed the study, performed the population PK analysis, interpreted the results of the analysis, and drafted the manuscript. J.W. and M.J.C. supervised the design of the study, conducted the study, and revised the manuscript. S.K., J.Y.J., D.K., J.Y.L., and K.L.M. collected the blood samples and patient data. J.H., K.L.M., and S.Y. assisted in technical PK modeling. S.K. conducted the drug concentration assays and validation. All authors read and approved the final manuscript.

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