Population Pharmacokinetics and Dose Optimization of Cefpirome during Extracorporeal Membrane Oxygenation

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A Dissertation

Submitted to the Department of

Pharmaceutical Medicine and Regulatory Science

and the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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June 2020

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June 2020

ACKNOWLEDGEMENTS

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기쁨과 행복을 나눠준 한아에게 고맙습니다.

제가 어떤 어려운 길을 택해도 쿨하게 응원해주는 엄마, 아빠, 언니, 동생에게 무한대로 감사합니다. 누구보다도 내 편에서 정신적으로 의지가 되어주는 남편 덕분에 무사히 학위를 마쳤습니다. 나의 사랑하는 가족들 모두에게 감사드립니다.

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List of Abbreviations

CFR	Cumulative Fraction of Response
CI	Confidence Intervals
CL	Clearance
Cmax	Maximum Concentration
Cmin	Minimum Concentration
CrCL	Creatinine Clearance
CRRT	Continuous Renal Replacement Therapy
CWRES	Conditional Weighted Residuals
ECMO	Extracorporeal Membrane Oxygenation
eGFR	Estimated Glomerular Filtration Rate
EUCAST	European Committee on Antimicrobial Susceptibility Testing
*f*T>MIC	The Percentage of Time Period that the Free Drug Concentration above the MIC of A Pathogen During Dosing Interval
IIV	Interindividual Variability
IPRED	Individual Predictions
IV-bolus	Intravenous Bolus Injection
MDRD	Modification of Diet in Renal Disease Study
MIC	Minimum Inhibitory Concentration
NONMEM	Nonlinear Mixed Effects Modelling
OFV	Objective Function Value
PD	Pharmacodynamic
PK/PD	Pharmacokinetic and Pharmacodynamic
PK	Pharmacokinetic
PRED	Population Predictions
PTA	Probability of Target Attainment
Q	Intercompartmental Clearance
q12h	Every 12 h
q8h	Every 8 h
QQ	Quantile-Quantile

RSE	Relative Standard Error
SCr	Serum Creatinine level
SIR	Sampling Importance Resampling
V1	Central Volume of Distribution
V2	Peripheral Volume of Distribution
VA	Veno-arterial
Vd	Volume of Distribution
VPC	Visual Predictive Check
VV	Veno-venous

ABSTRACT

Population pharmacokinetics and dose optimization of cefpirome during extracorporeal membrane oxygenation

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Background

Extracorporeal membrane oxygenation (ECMO) is a mechanical circulatory support for patients with profound cardiogenic shock. 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, broad-spectrum antibiotics such as cefpirome (4^{th} generation cephalosporin) are required for prophylaxis and the treatment of infection during ECMO. ECMO-associated pharmacokinetic (PK) changes in beta-lactams vary, and it is known to require therapeutic drug monitoring is needed to guide antibiotic dosing during ECMO. However, no previous study has investigated the PK changes of cefpirome in patients receiving ECMO.

Purpose

To develop a populationPK model for cefpirome and recommend the optimal dosage regimen based on patient characteristics and minimum inhibitory concentration (MIC) distribution in patients receiving ECMO.

Methods

This prospective study included cardiogenic shock patients treated with cefpirome during ECMO. Blood samples were collected at pre-dose (0 min) and 0.5–1 h, 2–3 h, 4–6 h, 8–10 h, and 12 h after cefpirome administration during ECMO (ECMO-ON) and after ECMO discontinuation (ECMO-OFF). The plasma concentrations of cefpirome were analyzed using a validated liquid chromatography–mass spectrometry. The population PK model development was conducted using the first-order conditional estimation method with interaction algorithm in Nonlinear Mixed Effects Modelling (NONMEM), and stepwise covariate modeling based on likelihood ratio test. In addition, the validity of the estimated relative standard error of PK parameters, and visual inspection of the goodness-of-fit plot, ETA correlation plot, individual plots, and Quantile-Quantile (QQ) plots were used in population PK model development. To validate the precision and robustness of the PK model, automated sampling importance resampling method (sampling = 5,000, resampling = 1,000, and 5 iterations) and a visual predictive check (n = 5,000) were performed. Monte Carlo simulation was used to assess the probability of target attainment (PTA)

and cumulative fraction of response (CFR) based on the MIC distribution according to European Committee on Antimicrobial Susceptibility Testing.

Results

The fifteen eligible patients had a median age of 63 years (Interquartile range 51.5–70.5 years), and median 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 simultaneously. The ECMO-ON plasma samples were collected from 14 patients during ECMO, whereas ECMO-OFF samples were collected from 8 patients. In total, 152 plasma samples were collected. The observed plasma concentration-time profiles of cefpirome were best described by a two-compartment model (ADVAN 3). Covariate analysis indicated that serum creatinine concentration level (SCr) was negatively correlated with clearance (CL), and the presence of ECMO increased CL and the central volume of distribution (V1). In addition, time after ECMO termination on ECMO-OFF group were found to influence CL changes. The final PK model was as follows: on ECMO-ON group, CL (L/h) = $8.75 \times 0.456^{(\text{SCr (mg/dL)}/1.6)}$, V1 (L) = 10.2, peripheral volume of distribution (V2) (L) = 17.1, intercompartment clearance (Q) (L/h) = 10.4; on ECMO-OFF group, CL (L/h) = $3.87 \times 0.456^{(\text{SCr (mg/dL)}/1.6)} \times (1 + 0.0123 \times \text{Time after ECMO termination (h)})$, V1(L) = 3.43, V2 (L) = 17.1, Q (L/h) = 10.4. 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 to meet the target CFR (90%). However, the PTA in 100 h after ECMO-OFF was lower than those in 48 h after ECMO-OFF; it has been shown that cefpirome dose requirements increase over time after ECMO termination. The calculated PTA and CFR via extended infusion administration was higher than those via intravenous bolus injection (IV-bolus) in patients with same SCr and ECMO status. 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.

Conclusions

This is the first study on a population pharmacokinetic model and pharmacodynamic analysis for cefpirome in patients receiving ECMO, and appropriate cefpirome dosage regimens were recommended. The results of this study suggest that SCr and the status of ECMO is important to make a decision of optimal dose for cefpirome. Dose optimization of cefpirome may improve treatment success and survival in patients receiving ECMO.

KEYWORDS: cefpirome, cephalosporin, extracorporeal membrane oxygenation, population pharmacokinetics, pharmacodynamics, dose optimization

1. INTRODUCTION

1.1. Introduction of ECMO

Extracorporeal membrane oxygenation (ECMO), also called extracorporeal life support, is a mechanical bypass to provide gas exchange and hemodynamic support for patients with profound cardiogenic shock (Ouweneel et al., 2016; Shekar et al., 2014). After Gibbon developed the heart-lung machine in 1953, Bartlett set up the modern ECMO system to treat the first neonatal ECMO survivor (Bartlett et al., 1974). Since 2009, when a multicenter randomized controlled trial, CESAR (the conventional ventilatory support versus ECMO for severe adult respiratory failure), and an observational study, ANZ-ECMO (Australia and New Zealand ECMO), were published, the number of ECMO runs and survival rates in adults increased with an exponential (Davies et al., 2009; Peek et al., 2009; Thiagarajan et al., 2017).

There are two modes of ECMO commonly used in adults, veno-venous (VV) ECMO and veno-arterial (VA) ECMO (Figure 1) (Shekar, Fraser, et al., 2012). VV ECMO is used in patients with isolated refractory respiratory failure to support only gas exchange. Drainage cannula are placed the inferior vena cava via femoral jugular veins. The oxygenated blood from the ECMO circuit merged into remnant blood not passing through the circuit, and then blood is pumped by the left heart and run into systemic circulation. In other words, heart function as well as pulmonary vascular resistance need to be adequate to ensure systemic oxygen delivery (Fraser et al.,

2012). Common indications for VV ECMO are severe bacterial or viral pneumonia, acute respiratory distress syndrome, aspiration syndromes, primary graft failure after lung transplantation. Additionally, VV ECMO can be applied when airway obstruction, smoke inhalation, pulmonary hemorrhage or massive hemoptysis, and so on (Fraser et al., 2012).

VA ECMO is transitional support system to the treatment of cardiogenic shock refractory to conventional medical management, and to gain time for transplantation of heart or implantation of left ventricular assist devices (Hamdi & Palmer, 2017; Loforte et al., 2014). The deoxygenated blood is drained from the right atrium or major vein especially femoral; oxygenation and carbon dioxide removal proceed via the oxygenator of the ECMO system, and then oxygenated blood is returned to the peripheral cannulations via femoral, or carotid arteries (Hamdi & Palmer, 2017; Makdisi & Wang, 2015). Common indications for VA ECMO are cardiogenic shock, inability to wean from cardiopulmonary bypass after cardiac surgery, primary graft failure after heart or heart-lung transplantation, sepsis with profound cardiac depression, and myocarditis, and so on (Fraser et al., 2012).

Complications according to ECMO system are associated with significant increase in morbidity and mortality; it could be related to the underlying pathology of patients or ECMO condition itself such as surgical insertion, circuit tubing and anticoagulation (Makdisi & Wang, 2015). 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, the most frequently observed complication is infection (Thiagarajan et al., 2017). So, broad-spectrum antibiotics are required for prophylaxis and the treatment of infection during ECMO (Austin et al., 2017; Vogel et al., 2011).

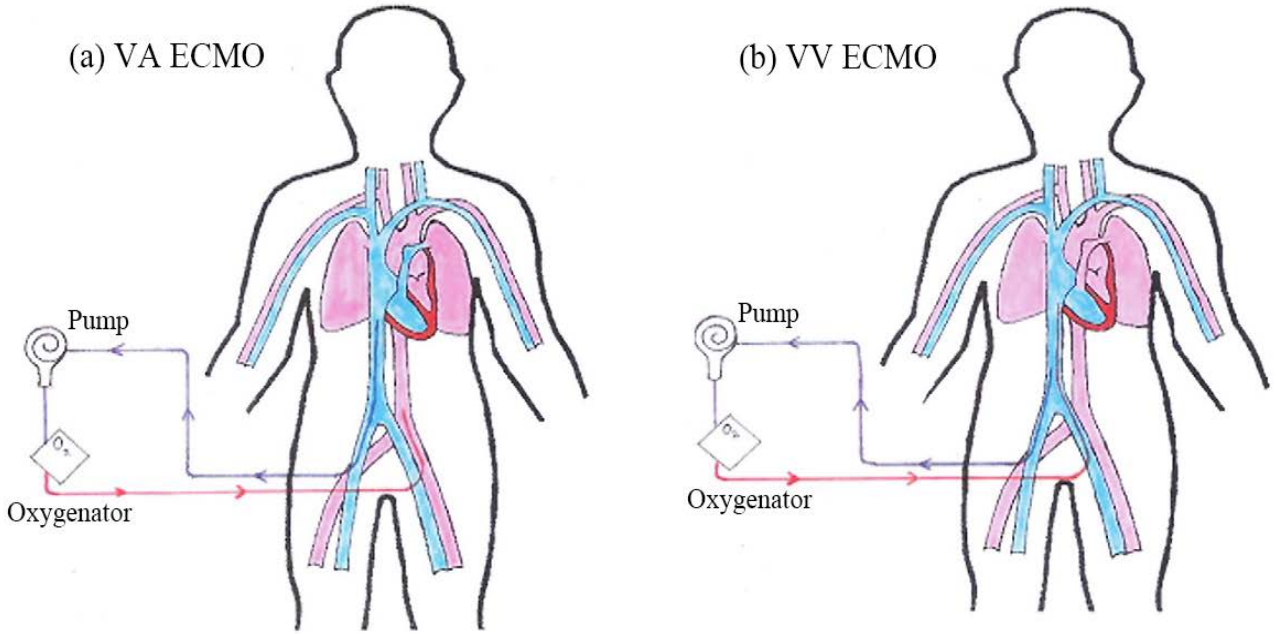


Figure 1. The scheme of two modes of ECMO

(a) Veno-arterial (VA) ECMO, (b) Veno-venous (VV) ECMO; Deoxygenated blood from venous system represents blue, and oxygenated blood represents red. (Shekar, Fraser, et al., 2012)

1.2. The changes of drug pharmacokinetics during ECMO

Several studies have suggested changes in drug pharmacokinetics (PKs) during ECMO, and the summary was shown in Table 1 (Cheng et al., 2018, 2019; Hahn et al., 2019; Wi et al., 2017; Wishart et al., 2006, 2018; Yang et al., 2017) (*Micromedex Solution. Truven Health Analytics, Inc. Ann Arbor, MI. Available at:* http://www.micromedexsolutions.com. *Accessed February 14, 2020*). Typically, owing to drug sequestration in ECMO circuits, volume of distribution (Vd) is increased (Ha & Sieg, 2017; Shekar, Roberts, Mcdonald, et al., 2012). Drug properties such as molecular size, lipophilicity, plasma protein binding ratio, and degree of ionization have an effect on drug sequestration in ECMO circuits (Shekar et al., 2015; Shekar, Fraser, et al., 2012). Furthermore, Vd is also increased because of hemodilution and the inherent physiological changes associated with ECMO and critical illness (Hahn et al., 2017). In addition, the ECMO circuit triggers an inflammatory response to cause capillary leak and edema, which contribute the increase of Vd (Butler et al., 1996; Seghaye et al., 1996).

Whereas clearance (CL) is generally decreased owing to renal and hepatic hypoperfusion and hypoxia (Ha & Sieg, 2017; Shekar, Fraser, et al., 2012). Nonpulsatile blood flow associated with VA ECMO results in activation of renin-angiotensin system, reduction of urine production, and decreased glomerular filtration rate in consequence (Many et al., 1967; Mousavi et al., 2011). In addition, inflammation caused by ECMO apt to reduce the expression of drug-metabolizing

enzymes such as cytochrome P450 (Rivory et al., 2002; Sherwin et al., 2016). In other words, the PK changes of a drug in the ECMO device are dependent on the physiochemical properties of the drug, the states of disease; therefore, exact prediction is difficult (Cheng et al., 2018).

Beta-lactam antibiotics are relatively hydrophilic with varying protein binding ratios; therefore, ECMO-associated PK changes in beta-lactams also vary (Cheng et al., 2018; Donadello et al., 2015; Udy et al., 2018; Veiga & Paiva, 2018). The risk of subtherapeutic plasma concentration of antibiotics by PK changes according to ECMO therapy could lead therapeutic failure, and an increased risk of infection-related mortality is concerned (Sherwin et al., 2016; Vogel et al., 2011). Thus, a deep understanding of the PK changes in patients receiving ECMO is essential to provide optimal dosing and to perform therapeutic drug monitoring (Abdul-Aziz & Roberts, 2020). Third- and fourth-generation cephalosporins, as broad-spectrum antibiotics, are usually recommended for patients receiving ECMO (Glater-Welt et al., 2016; Schutze & Heulitt, 1995; Vogel et al., 2011). However, fewer PK studies have investigated cefpirome compared with other antibiotics (Joukhadar et al., 2002; Lipman et al., 2001; Roos et al., 2007; Sauermann et al., 2005); moreover, no previous study has investigated the PK changes of cefpirome in patients receiving ECMO. 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.

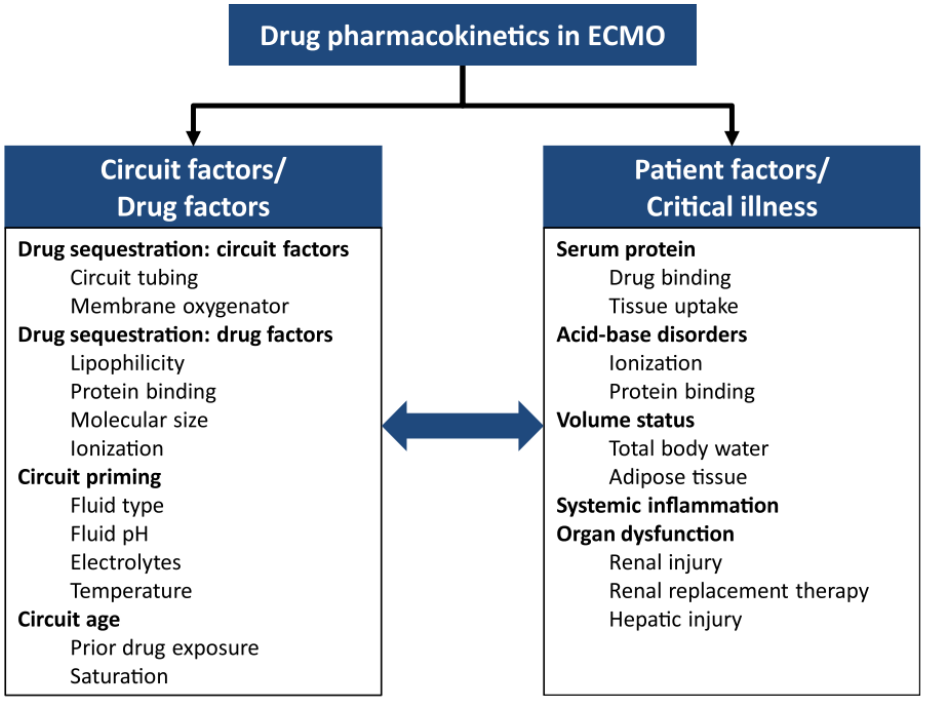


Figure 2. Factors influencing drug PK in patients during ECMO

(Ha & Sieg, 2017)

Table 1. Summary of drug physicochemical properties and PK changes during ECMO

Drugs	Physicochemical property	Protein binding	PK changes	Dosing recommendation
Midazolam	Lipophilic (logP = 3.9)	97%	Significant circuit drug sequestration	Higher loading dose with higher daily doses
Dexmedetomidine	Lipophilic (logP = 2.8)	94%		
Fentanyl	Lipophilic (logP = 4.1)	80–86%		Considering alternative agents; only use for short-term
Propofol	Lipophilic (logP = 3.8)	97–99%		Insufficient data but likely to require higher doses over time
Remifentanil	Moderate lipophilic (logP = 1.4)	70%	Higher Vd, Increased CL	Higher dose needed according to sex and ECMO pump speed
Sufentanil	Lipophilic (logP = 3.24)	91–93%	Higher Vd, Decreased CL	The body temperature and total plasma protein level is crucial during ECMO
Morphine	Hydrophilic (logP = 0.9)	20–35%	Minimal to moderate circuit drug sequestration	Higher loading dose with higher daily doses
Beta-lactams	Relatively hydrophilic	Variable	Minimal to moderate circuit drug sequestration, Enlarged Vd	Critically ill dosing strategy and TDM if available
Aminoglycosides	Hydrophilic	Relatively low	Minimal sequestration, Higher Vd, Decreased CL	Insufficient data and TDM if available

Vancomycin	Hydrophilic (logP = -3.1)	18–55%	Minimal sequestration, Higher Vd	Critically ill dosing strategy and TDM if available
Teicoplanin	Hydrophilic	88–91%	Lower Vd, Decreased Q	Higher doses needed during ECMO and CRRT
Fluoroquinolones	Relatively hydrophilic	Low to moderate	Minimal sequestration	Critically ill dosing strategy
Caspofungin	Low lipophilicity (logP = 1)	97%	Minimal to moderate sequestration	Insufficient data
Voriconazole	Low lipophilicity (logP = 1)	58%	Moderate sequestration	Higher initial loading and daily doses, TDM if available

Vd, volume of distribution; CL, clearance; Q, intercompartmental clearance; TDM, therapeutic drug monitoring; logP, octanol-water partition coefficient

1.3. Introduction and PK of cefpirome

Cefpirome is a semi-synthetic fourth generation cephalosporin with a broad-spectrum activity, first developed in the 1980s. Cefpirome is highly active against *Enterobacter,* methicillin-susceptible *Staphylococcus aureus, Klebsiella* spp. and *Citrobacter* spp. (Machka & Braveny, 1983; Wiseman & Lamb, 1997); it is less active against *Pseudomonas aeruginosa* than ceftazidime (*Cefpirome. Micromedex, Accessed February 14, 2020*). Cefpirome is used to treat hospitalized patients with moderate to severe infections (Visalli et al., 1998; Wiseman & Lamb, 1997). Cefpirome demonstrate improved penetration through the outer membrane of bacterial cell wall, because it binds to penicillin-binding proteins and have poor affinity for beta-lactamase (Wiseman & Lamb, 1997).

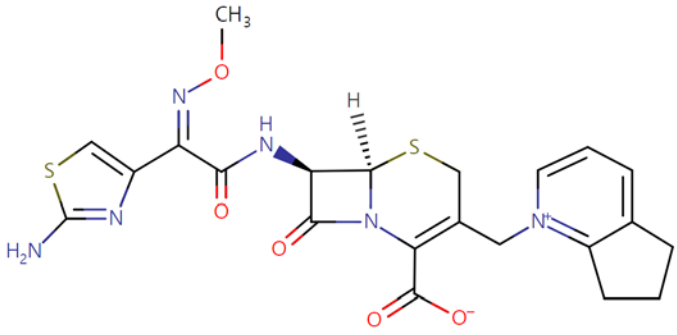


Figure 3. Molecular structure of cefpirome

The recommended dose for the treatment of hospitalized patients with severe infection or febrile neutropenia is 2 g every 12 hours given by intravenous bolus

injection (IV-bolus) over 3–5 minutes or by infusion 20–30 minutes (Wiseman & Lamb, 1997). Because the elimination of cefpirome is predominantly via renally, 25–50% reduced dose is recommended in renal impairment patients (*Cefpirome. Micromedex, Accessed February 14, 2020*).

Cefpirome has a low molecular weight (512 g/mol), and is highly hydrophilic compound (Banyai et al., 2000). The Vd for cefpirome at steady state was between 15.3 and 21.3 L in healthy volunteers, and approximately 10 % of cefpirome was bound to plasma protein. Biological half-life of elimination phase was 2 h (Malerczyk et al., 1987). The drug about 80 % of an administered dose was recovered unchanged via the urine, and CL for cefpirome was ranged from 6.6 to 10.6 L/h in healthy volunteers. In consequence, half-life of elimination phase was increased in patients with moderate to severe renal failure. The mean elimination half-life was from 1.7 to 2.3 h (Wiseman & Lamb, 1997). Table 2 shows the previous studies on PK of cefpirome in patients with severe sepsis or who needed antibiotics. However, as far as we know, there was no PK study and dose optimization in patients receiving ECMO.

Table 2. Previous studies on pharmacokinetic of cefpirome

Patient demographics	Best-fitted compartmental model	PK parameters	Covariates	References
N = 10, age 41.2 ± 19 years, severe sepsis	Two-compartmental model	Vd = 24 L (range 14 – 43), CL = 7.8 L/h (range 4.5 – 13.2), half-life = 2.5 h (range 1.8 – 6.7)	· No covariate searching	(Lipman et al., 2001)
Patients: N = 12, age 67.2 ± 8.1 years, severe sepsis or septic shock; Healthy volunteers: N = 6, age-matched	Two-compartmental model	Patients: Vd = 25.9 ± 7.1 L, CL = 4.5 ± 0.66 L/h, half-life = 3.33 ± 0.52 h, Cmax = 164 ± 14 mg/L; Healthy volunteers: Vd = 14.6 ± 1.3 L, CL = 4.68 ± 0.48 L/h, half-life = 2.57 ± 0.48 h, Cmax = 210 ± 19 mg/L	· No covariate searching	(Joukhadar et al., 2002)
Patients: N=11, age 66 ± 8 years, Severe sepsis; Healthy volunteers: N=7, age 26 ± 5 years	Non-compartmental model	Patients: Vd = 21.9 ± 4.5 L, CL = 4.8 ± 1.56 L/h, half-life = 3.05 ± 0.9 h; Healthy volunteers: Vd = 15.8 ± 5.6 L, CL = 6.3 ± 1.86 L/h, half-life = 1.58 ± 0.5 h	· No covariate searching · Dosing intervals of not more than 8 h should be preferred in septic patients	(Sauermann et al., 2005)

N=12, age 18 to 70 years (median 41), ICU patients	Three-compartmental model	V1 = 9.04 L, V2 = 4.59 L, V3 = 8.63 L, CL = 7.54 L/h, Q2 = 1.39 L/h, Q3 = 26.2 L/h	・ Weight on V1 and CrCL measured by 8-h urine collection on CL	(Roos et al., 2007)
N=6, age 60-75 years, CVVH-dependent patients with sepsis and multiple organ dysfunction syndrome	Two-compartmental model	Vd = 23.5 ± 4.6 L, CL = 1.92 ± 0.4 L/h, CVVH clearance = 0.42 ± 0.3 L/h, half-life = 8.8 ± 2.3 h	・ No covariate searching ・ The close relationship of serum and ultrafiltrate drug concentrations	(Van Der Werf et al., 1999)
N=8, age 62.6 ± 7.9 years, anuric patients with acute kidney failure treated by CVVH	One-compartmental model	Vd = 118 ±36 L, CL = 35.3 ± 9.87 L/h, hemofiltration clearance = 2.6 ± 0.5 L/h, half-life = 2.36 ± 0.59 h	・ No covariate searching ・ 2 g q8h may be insufficient during CVVH against *P. aeruginosa*	(Banyai et al., 2000)
Patients: N = 9, age 31 (19-53 years), trauma patients with systemic inflammatory response syndrome; Healthy volunteers: N = 9, Age 30 (27-49 years)	Non-compartmental model	Patients: Vd = 20.3 L (70 kg) (range 14 – 38.5), CL = 7.6 L/h (range 4.3 – 14.9), half-life = 2.2 h (range 1.5 – 2.8); Healthy volunteers: Vd = 18.2 L (70 kg) (range 14.7 – 25.9), CL = 6.1 L/h (range 5.1 – 8.8), half-life = 2.1 h (range 1.8 – 2.3)	・ No covariate searching	(Jacolot et al., 1999)

Vd, volume of distribution; V1, central volume of distribution; V2 and V3, peripheral volume of distribution; CL, clearance, Q2 and Q3, intercompartmental clearance; CVVH, continuous venovenous hemofiltration; CrCL, creatinine clearance, Cmax, maximum plasma concentration of cefpirome; ICU, intensive care unit

1.4. The PK/PD indices to optimize cefpirome dose regimen

Simulation-based pharmacokinetic and 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 (Peck & Cross, 2007). Many studies have been conducted to identify the PK/PD indices that best predict the effect of antibiotics, such as the ratio of the maximal free drug concentration to the minimum inhibitory concentration (MIC) (*f*Cmax/MIC), the ratio of the area under the free drug concentration-time curve to the MIC (*f*AUC/MIC), and the percentage of time period that the free drug concentration above the MIC of a pathogen during dosing interval (*f*T>MIC) (Mouton et al., 2005). Beta-lactam activity has been considered as almost dependent on *f*T>MIC (Craig, 1995; Nielsen et al., 2011; Onufrak et al., 2016; Udy et al., 2018). The percentile of *f*T>MIC to acquire the appropriate bactericidal effect is 60–70% for cephalosporins (Udy et al., 2018). Moreover, a study had reported that *f*T>MIC is more predictive for beta-lactams with short half-life (MacVane et al., 2014); the mean half-life of cefpirome was reported as 1.7–2.3 h (Wiseman & Lamb, 1997). Recently, predictive breakpoints of cephalosporin against *Pseudomonas aeruginosa* was reported greater than 53% *f*T>MIC (MacVane et al., 2014), so the magnitude of 65% *f*T>MIC for cefpirome was used to cover enough to several pathogens in previous studies (Craig, 1995; Roos et al., 2007).

The probability of target attainment (PTA) was used to calculate the probability

that at least a specific value of a pharmacodynamic (PD) index *in silico* predictions (Bradley et al., 2003; Nielsen et al., 2011). And the cumulative fraction of response (CFR) was defined as the expected population PTA for a specific drug dose and a specific population of pathogens (Mouton et al., 2005).

1.5. The aim of the study

The specific objective of this study was to recommend the pertinent dosage for cefpirome in patients during ECMO. To achieve this purpose, the population PK of cefpirome was explored and PD profiles which is the ability of bacterial killing for cefpirome was assessed in patients receiving VA ECMO.

2. Methods

2.1. Study design and subjects

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 was registered in Clinicaltrials.gov (NCT02581280). Written informed consent was acquired from the unconscious participants' legally acceptable representatives. This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE).

The eligible patients were 19 years of age or older, receiving 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.

2.2. ECMO 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® Ind., CA, USA). The ECMO circuit was connected in parallel to the heart and lungs from femoral venous to femoral arterial cannulation with a 17-Fr arterial and 21-Fr venous cannula (BioMedicus Medtronic Inc., MN, USA). The settings of ECMO were recorded.

2.3. Cefpirome dose and sample collection

Cefpirome was administered at the start of ECMO to prevent infection. According to the 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 Modification of Diet in Renal Disease Study (MDRD) equation, received a 50% dose reduction. If needed, continuous veno-venous hemodiafiltration (Prismaflex; Gambro Inc., Meyzieu, France) with Prismaflex ST 100 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 pre-dose and at least one random point during each of the following time periods after cefpirome administration: 0.5–1, 2–3, 4–6, 8–10, and 12 h (ECMO-ON) (Figure 4). The actual sampling time was recorded. If the patients were successfully weaned off ECMO and continued cefpirome, blood samples were collected after ECMO termination (ECMO-OFF). Blood samples were collected in EDTA-coated tubes and then immediately centrifuged (1,500 ×*g* at 4°C for 10 min). The obtained plasma was refrigerated at -80°C until analysis.

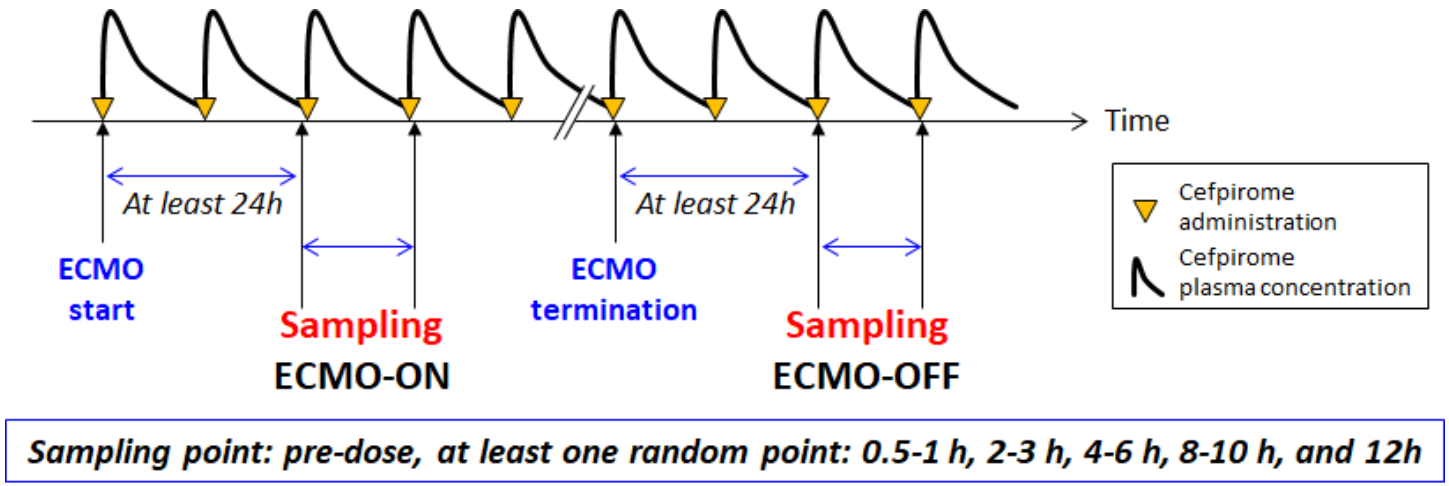


Figure 4. The scheme of sample collection

2.4. Cefpirome plasma concentration 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 ×*g*). LC–MS was performed on an Acquity UPLC BEH C18 column (1.7 μm, 2.1 mm × 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: 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 1.0–64.0 mg/L; the lower limit of quantification was 1.0 mg/L. The inter- and intra-assay coefficients of variation were below 15%.

2.5. Population PK analysis

2.5.1. 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/) 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 (IIV, 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) of PK parameters. An OFV reduction of >3.84 (χ^2 distribution, degrees of freedom = 1, $p < 0.05$) was considered statistically significant. For visual inspection, the 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 after the first cefpirome dose. In addition, the ETA correlation plot, individual plots, and QQ plots were visually inspected.

2.5.2. 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), ECMO pump speed (RPM, revolutions per minute), time after ECMO start, and time after ECMO termination), use of CRRT, complete blood count (absolute white blood cells, red blood cells, hemoglobin, and platelets), renal function (serum creatinine level (SCr), blood urea nitrogen, creatinine clearance (CrCL) estimated via Cockcroft-Gault equation, and estimated glomerular filtration rate (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, and visual improvement in the goodness-of-fit plot (Bonate et al., 2012).

2.6. Model validation

To evaluate the precision and robustness of the base model and final covariate model, automated sampling importance resampling (SIR) method (sampling = 5,000, resampling = 1,000, and 5 iterations) and a visual predictive check (VPC) (n = 5,000) were conducted using the Perl Speaks NONMEM toolkit version 4.9.0 (Dosne et al., 2017; Keizer et al., 2013). 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 5th, median, and 95th percentile curves were visually assessed.

2.7. Dosing simulations

2.7.1. Monte Carlo simulation

To assess the PTA at 72 h after the start of cefpirome, Monte Carlo simulations were performed on the basis of the estimated PK parameters using NONMEM. R version 3.5.3 (http://www.r-project.org) was used to draw simulation datasets up. IV-bolus and extended infusion over 1 h, 2 h, and 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 SCr, which was selected as covariates in the final PK model, and the use of ECMO on the predicted cefpirome concentrations, SCr of 0.5–3.3 mg/dL (in increments of 0.2 mg/dL) were simulated for the ECMO-ON and ECMO-OFF groups. Especially, the ECMO-OFF group were simulated from 48 h and 100 h after ECMO termination. The total number of simulated scenarios were 720 (Table 3). Each simulated concentration-time profile was generated for 1,000 subjects per dosage regimen.

Table 3. Simulated scenario

Simulated cefpirome regimen		
Amount	Frequency	Administration
0.5 g 1 g 2 g	q12h	Intravenous bolus Extended infusion over 1h Extended infusion over 2h Extended infusion over 4h
2 g	q8h	
Simulated values for covariates		
Serum creatinine level	ECMO	Time after ECMO termination
0.5–3.3 mg/dL (increments of 0.2 mg/dL)	ON	-
	OFF	48 h 100 h

2.7.2. Calculation of PTA and CFR

From simulated data, when a protein binding constant of 10% (Wiseman & Lamb, 1997) was applied, the % *f*T > MIC was determined for each simulated subject by linear interpolation using R version 3.5.3. The PTA was calculated by counting subjects who achieved at least 65% *f*T>MIC for optimal bacteria killing in terms of efficacy (Craig, 1995; Roos et al., 2007); a PTA of ≥0.9 was considered to be effective (Craig, 1995; Roos et al., 2007).

The MIC distribution for cefpirome, which was 0.008–256 mg/L in this study, was derived from the European Committee on Antimicrobial Susceptibility Testing (EUCAST; https://mic.eucast.org/Eucast2/SearchController; accessed September 2019) 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* (Table 4). The PTA for each regimen and the MIC distribution were used to calculate the CFR as below equation (Mouton et al., 2005).

$$\sum_{i=1}^{n} PTAi \times Fi$$

The subscript *i* upto n indicates the MIC range from lowest to highest value of a population pathogens. PTA*i* means the PTAs of each MIC category; and F*i* is the fraction of the population of pathogens at MIC = *i*. A CFR of over 90% was targeted (DeRyke et al., 2007).

Table 4. MIC distribution from EUCAST

MIC (mg/L)	Pathogens (number of strains)					
	Acinetobacter spp	*Enterobacter* spp	*Escherichia coli*	*Klebsiella* spp	*Pseudomonas aeruginosa*	*Streptococcus pneumoniae*
0.008	0	0	1	5	0	2
0.016	0	0	234	66	0	155
0.032	0	5	1503	324	0	62
0.064	0	4	2359	251	0	216
0.125	0	14	1023	69	0	259
0.25	0	4	268	32	1	15
0.5	7	5	88	22	9	24
1	19	5	47	17	135	2
2	16	1	46	4	262	4
4	33	1	20	2	154	7
8	4	0	9	1	77	9
16	11	0	14	0	38	6
32	1	0	16	0	16	2
64	12	0	9	0	6	0
128	0	0	86	1	6	4
256	0	0	5	0	0	0
Total	103	39	5728	794	704	767

3. Results

3.1. Demographic information and characteristics of enrolled patients

The demographic characteristics of the enrolled patients are shown in Table 5. The 15 eligible patients had a median age of 63 years (Interquartile range 51.5–70.5 years), and median SCr of 1.58 mg/dL during ECMO and 1.83 mg/dL after ECMO. Five patients received CRRT treatment during ECMO simultaneously. The median Acute Physiology and Chronic Health Evaluation II score was 32 (IQR 29–36) at the initiation of ECMO support.

The characteristics of the variables associated with ECMO are summarized in Table 6. The median duration of ECMO support was 6.92 days (Interquartile range 5.17–10.58 days). The indication for ECMO therapy for twelve patients was acute myocardial infarction. Other 3 patients were needed ECMO for treatment of arrhythmogenic right ventricular dysplasia, pulmonary thromboembolism, and myocarditis. The median and maximal sampling time from ECMO initiation on ECMO-ON group was 49.9 h and 111.9 h, respectively; and those from ECMO termination on ECMO-OFF group was 44.2 h and 90.4 h, respectively.

The ECMO-ON plasma samples were collected from 14 patients during ECMO, whereas ECMO-OFF samples were collected from 8 patients. In total, 152 plasma samples were collected, and none of samples below the limit of quantitation.

Table 5. Demographic information and baseline characteristics of all enrolled patients

Patient no.	Sex	Age (yr)	Weight (kg)*		SCr level* (mean, mg/dL)		Use of CRRT*		APACHE II score	Length of hospital stay (days)
			ECMO -ON	ECMO -OFF	ECMO -ON	ECMO -OFF	ECMO -ON	ECMO -OFF		
1	Male	34	92.9	84.9	2.46	2.31	yes	yes	32	102
2	Male	69	72	69.4	2.55	2.3	no	yes	30	54
3	Female	52	49.2	48.4	3.41	1.56	no	yes	37	74
4	Male	72	69.6	-	2.06	-	no	-	36	44
5	Male	63	81.7	-	3.11	-	yes	-	46	7
6	Male	82	61.8	58.8	1.65	1.24	yes	yes	32	92
7	Male	75	98.3	-	0.44	-	yes	-	36	20
8	Female	27	60.5	-	0.40	-	no	-	36	53
9	Male	76	-	54.3	-	2.11	-	yes	40	74
10	Male	52	76.3	72.5	1.37	2.26	yes	no	31	12
11	Female	62	60.5	58.3	0.61	0.85	no	no	32	24
12	Male	67	75	65.7	1.55	1.56	no	no	24	26
13	Male	51	71	-	1.14	-	no	-	26	35
14	Male	66	65.5	-	1.61	-	no	-	14	22
15	Male	42	60	-	0.95	-	no	-	28	31
Median	-	63	70.3	62.3	1.58	1.84	-	-	32	35
IQR	-	51.5 – 70.5	60.8 – 76.0	57.3 – 70.2	0.99 – 2.36	1.48 – 2.27	-	-	29 – 36	23 – 64

* The data was collected during sampling; -, no data because of no sampling

SCr, serum creatinine concentration; CRRT, continuous renal replacement therapy; APACHE II, acute physiology and chronic health evaluation II

Table 6. The values associated with ECMO of all enrolled patients

Patient no.	Indication of ECMO	Duration of ECMO (days)	ECMO-ON			ECMO-OFF
			RPM* (mean ± SD)	LPM* (mean ± SD)	Time from ECMO start# (h)	Time from ECMO termination# (h)
1	ARVD	8.73	2506	5.22 ± 0.08	96.6	43.1
2	AMI	6.35	2761 ± 60.9	3.56 ± 0.37	51.1	90.4
3	AMI	7.16	2244	3	111.9	39.9
4	AMI	15.07	2764	3.44 ± 0.10	42.2	-
5	AMI	6.92	2841	4.37 ± 0.35	51.5	-
6	AMI	3.59	2300 ± 5.3	1.86 ± 0.21	36.7	24.5
7	AMI	17.56	2115 ± 375.5	2.24 ± 0.65	41.3	-
8	Myocarditis	30.01	2444	3.97 ± 0.08	48.6	-
9	AMI	1.44	-	-	-	45.2
10	AMI	3.74	2004 ± 163.6	3.14 ± 0.35	38.9	45.2
11	AMI	4.74	2363 ± 142	2.26 ± 0.17	63.9	72
12	PTE	11.89	2505 ± 0.38	4.62 ± 0.12	133	39.6
13	AMI	9.28	3814 ± 168	3.41 ± 0.24	43	-
14	AMI	5.61	2543 ± 396	2.8 ± 0.49	40.3	-
15	AMI	6.83	2099 ± 65.0	2.51 ± 0.11	92.6	-
Median		6.92	2444	3.25	49.9	44.2
IQR		5.17 – 10.58	2244 – 2764	2.69 – 3.99	41.5 – 85.4	39.8 – 51.9

* The data was collected during sampling

Sampling start point

-, no data because of no sampling

RPM, revolutions per minute; LPM, liters per minute; ARVD, arrhythmogenic right ventricular dysplasia; AMI, acute myocardial infarction; PTE, pulmonary thromboembolism; ECMO, extracorporeal membrane oxygenation

3.2. Population PK model development

3.2.1. Exploratory data analysis for PK model development

Figure 5 shows the plasma concentration-time course after the cefpirome dose from 15 patients on ECMO-ON group and 8 patients on ECMO-OFF group.

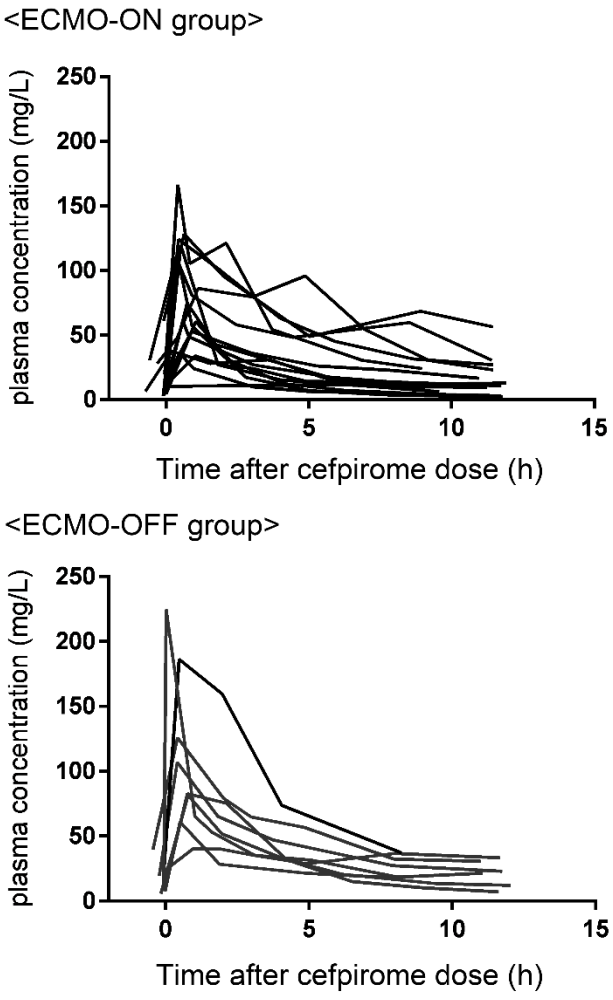


Figure 5. Plasma concentration-time course of cefpirome

3.2.2. Base model

The observed plasma concentration-time profiles of cefpirome were best explained by the two-compartment model (ADVAN 3). The PK parameter estimates estimated by base model was represented in Table 7. The IIV included CL, central volume of distribution (V1), and peripheral volume of distribution (V2). The residual variability was bet described by a proportional residual error model. IIV on intercompartmental clearance (Q) was fixed as zero. Allometric scaling of weight did not improve significantly the model fit. The base model had an OFV of 852.04. No correlation was seen between ETAs. Figure 6 shows the basic goodness-of-fit plots of base model. Both PRED and IPRED were distributed uniformly across the line of equality. Additionally, the plots of CWRES versus PRED and versus time after the first cefpirome dose were relatively evenly distributed around zero and did not show any trends. ETA correlation plots did not show any trends.

Table 7. Cefpirome PK parameter estimates estimated by a two-compartment base model

Parameter	Population estimate (RSE)
Fixed effects (θ)	
CL (L/h)	3.6 (15%)
V1 (L)	10.3 (21%)
V2 (L)	19.5 (22%)
Q (L/h)	9.62 (19%)
Random effects (% CV*)	
Interindividual variability (ω)	
CL	58.8 (34%)
V1	26.5 (89%)
V2	92.6 (73%)
Proportional residual variability (σ)	25.7 (19%)

CL, clearance; V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; RSE, relative standard error; CV, coefficient of variation

* Calculated according to SQRT (omega)*100

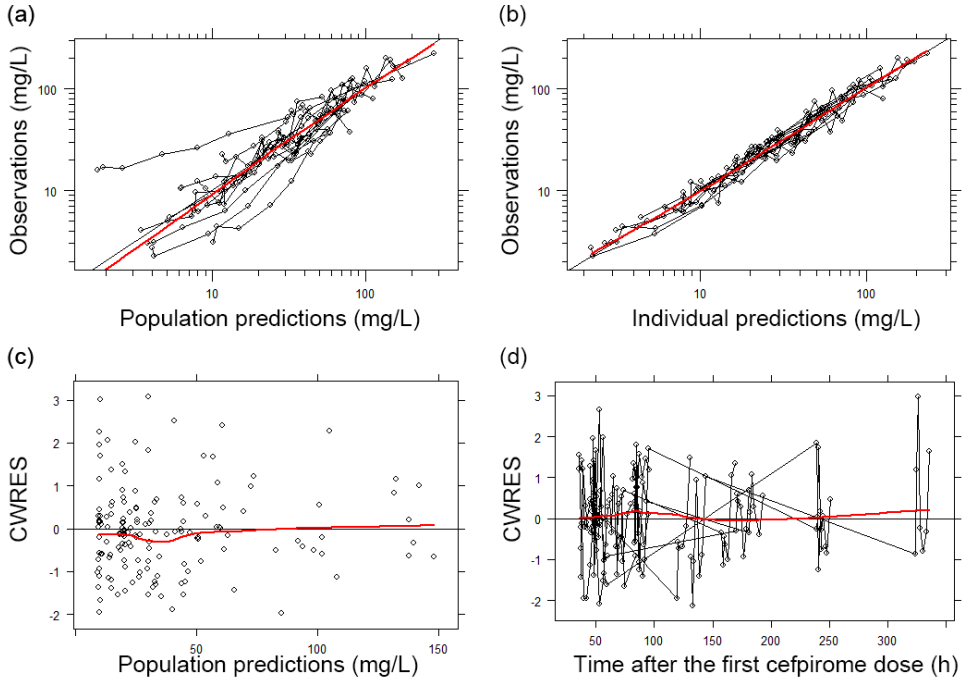


Figure 6. The basic goodness-of-fit plots of the base model

Log of observed cefpirome concentrations versus (a) population predicted concentrations (PRED) and (b) individual predicted concentrations (IPRED); conditional weighted residuals (CWRES) versus (c) population predicted concentrations (PRED) and (d) time after the first cefpirome administration.

3.2.3. Covariate model

All candidates for covariate was tested in stepwise covariate selection. For forward step, SCr among the covariates relating renal functions was selected because ΔOFV was the largest (-31.946), compared to those for CrCL by Cockcroft-Gault and eGFR by MDRD equation (-5.85 and -14.24, respectively). In addition, RSE for parameters was more reasonable for SCr than CrCL and eGFR. The use of ECMO was selected for CL and V1. None of the parameters related to ECMO such as LPM and RPM helped to understand factors influencing to the final PK model. We tested time after ECMO termination as another covariate on both CL and V1, and this covariate did not affect V1, only associated with CL. Finally, the SCr for CL, the use of ECMO for CL and V1, and time after ECMO termination on ECMO-OFF group for CL were found to influence PK parameter changes (OFV = 771.189, ΔOFV based on base model = –80.853). Table 8 represents the change of OFV values when the covariates included in the final model are added one by one starting from the base model.

Table 8. The change of OFV values

Model*		OFV	ΔOFV
Base model		852.042	
1	Base model + SCr on CL	820.096	-31.946
2	1st model + ECMO on CL	801.528	-18.568
3	2nd model + ECMO on V1	791.382	-10.146
4	3rd model + Time after ECMO termination on CL	771.189	-20.193

*Order added as a covariate

The final PK model was as follows:

on ECMO-ON group,

CL (L/h) = $8.75 \times 0.456^{(SCr\,(mg/dL)/1.6)}$,

V1 (L) = 10.2,

V2 (L) = 17.1,

Q (L/h) = 10.4;

on ECMO-OFF group,

CL (L/h) = $3.87 \times 0.456^{(SCr\,(mg/dL)/1.6)} \times (1 + 0.0123 \times$ Time after ECMO termination (h)),

V1(L) = 3.43,

V2 (L) = 17.1,

Q (L/h) = 10.4.

When SCr is 1.6 mg/dL, population CL on ECMO-ON is 3.99 L/h, and those on 48 h and 100 h after ECMO termination is 2.81 L/h and 3.94 L/h, respectively. Individual parameters such as half-life, maximum concentration (Cmax), and time to Cmax were represented in Table 9. The median half-lives of ECMO-ON and ECMO-OFF were 5.59 and 6.05, respectively.

Table 9. Individual parameters based on final PK model

Patient no.	ECMO-ON				ECMO-OFF			
	Half-life (h)[a]	Cmax (mg/L)[b]	Time to Cmax (h) [c]	Cefpirome dosing	Half-life (h) [a+]	Cmax (mg/L) [b]	Time to Cmax (h) [c]	Cefpirome dosing
1	4.02	166.42	0.42	2 g q12h	3.92	186.20	0.46	2 g q12h
2	7.38	194.91	0.38	2 g q12h	6.66	125.66	0.42	2 g q12h
3	15.02	128.20	0.63	1 g q12h	7.25	106.87	0.40	1 g q12h
4	5.12	123.96	0.43	2 g q12h	-	-	-	-
5	12.99	110.23	0.35	1 g q12h	-	-	-	-
6	8.11	61.10	0.58	1 g q12h	9.45	60.91	0.50	1 g q12h
7	7.29	52.83	0.88	2 g q12h	-	-	-	-
8	3.24	110.79	0.40	2 g q12h	-	-	-	-
9	-	-	-	-	5.43	224.63	0.02	1 g q12h
10	8.91	33.94	1.03	1 g q12h	15.06	40.13	0.95	1 g q12h
11	3.45	74.74	0.73	2 g q12h	3.38	81.28	0.78	2 g q12h
12	4.54	37.51	0.20	1 g q12h	3.85	82.64	0.75	1 g q12h
13	3.43	60.48	0.93	2 g q12h	-	-	-	-
14	6.06	119.17	0.05	1 g q12h	-	-	-	-
15	4.94	35.88	0.47	1 g q12h	-	-	-	-
Median	5.59	92.49	0.45	-	6.05	94.76	0.48	-
IQR	4.15-7.93	54.7-122.8	0.4-0.7	-	3.9-7.8	76.2-140.8	0.4-0.76	-

[a]Calculated according to ln(2)/{0.5 × [(k12 + k21 + k) - SQRT((k12 + k21 + k)^2 - 4 × k21 × k)]}, where k12 = Q/V1; k21 = Q/V2; k = CL/V1

[+]Data based on time to Cmax

[b]Cmax is the plasma concentration which was sampled immediately after administration.

[c]Time to Cmax is the actual time at Cmax sampling.

3.2.4. Model diagnostics

Figure 7 shows the basic goodness-of-fit plots for the final PK model. Both PRED and IPRED were distributed uniformly across the line of equality. Additionally, the plots of CWRES versus PRED and versus time after the first cefpirome dose were relatively evenly distributed around zero and did not show any trends. Figure 8 shows ETA correlation plots, and any trends was not shown. The individual plots of individual predictions and observations versus time after the first cefpirome dose were shown in Figure 9.

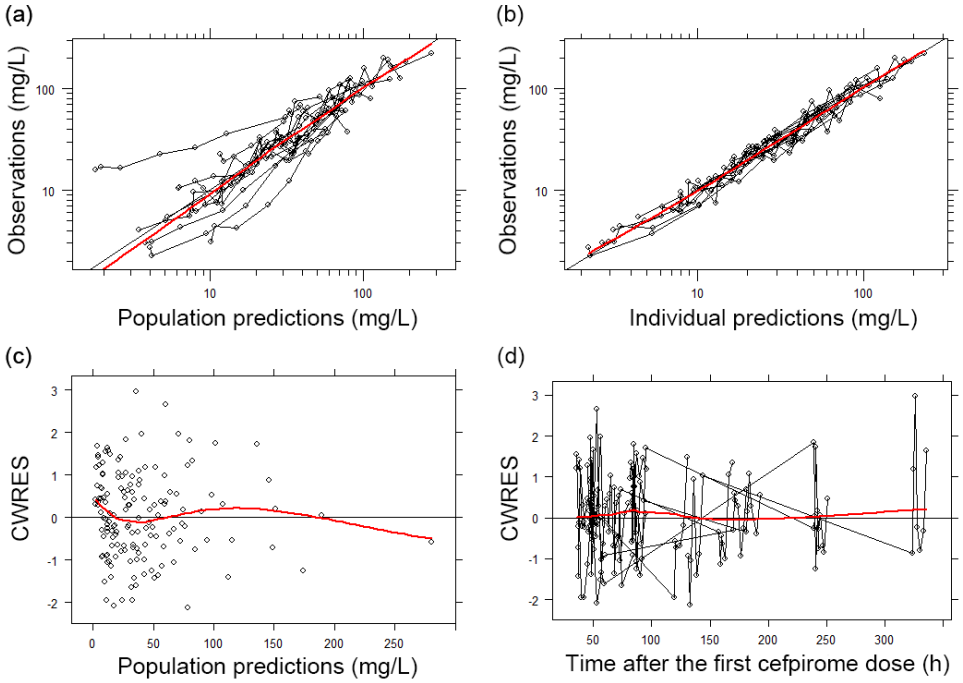


Figure 7. Goodness-of-fit plot of the final population PK model for cefpirome

Log of observed cefpirome concentrations versus (a) population predicted concentrations (PRED) and (b) individual predicted concentrations (IPRED); conditional weighted residuals (CWRES) versus (c) population predicted concentrations (PRED) and (d) time after the first cefpirome administration
Red solid line, smooth trend line

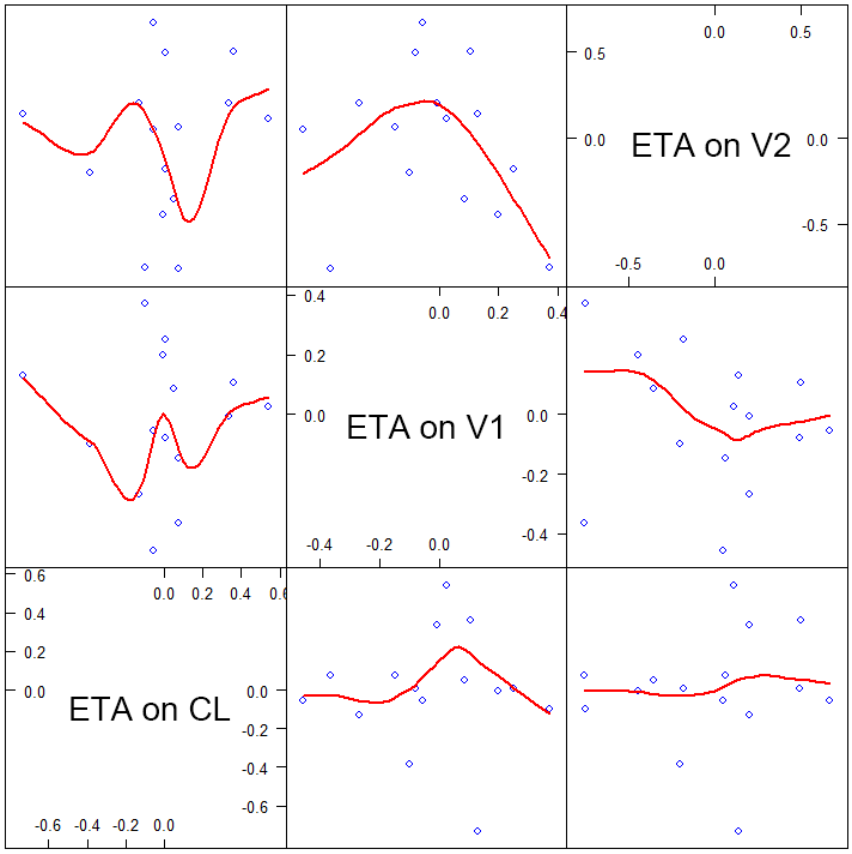


Figure 8. Scatterplot matrix of ETAs on final PK model

Open circles, each ETA on the parameter; Solid line, smooth trend line

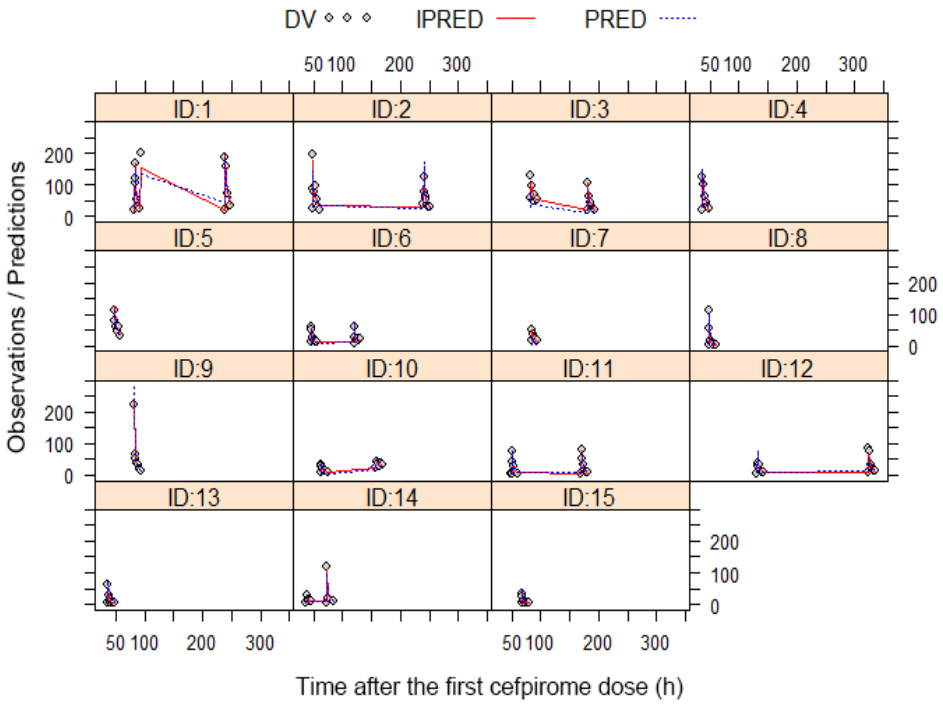


Figure 9. Individual plots of individual prediction, population predictions and observations versus time

DV, Circles, observed concentration of cefpirome; IPRED, solid line, individual prediction of cefpirome; PRED, dashed line, population prediction of cefpirome

3.3. Model validation

The PK parameter estimates for cefpirome from the final PK models and the SIR results are summarized in Table 10. All parameter estimates were distributed within the 95% 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 <34% in final PK model.

The VPC plot showed that approximately 10% of the observed data were positioned outside the 5^{th} to 95^{th} percentiles of the predicted data, which suggested that the predictive performance of the final model was adequate (Figure 10).

Table 10. Parameter estimates in final PK model and SIR result

Parameter	Final model	
	Population estimate (RSE)	**SIR median (2.5th–97.5th percentile)**
Fixed effects (θ)		
CL (L/h)	3.87 (8%)	3.83 (4.47–7.29)
V1 (L)	3.43 (27%)	3.54 (1.54–5.26)
V2 (L)	17.1 (14%)	16.9 (13.0–22.5)
Q (L/h)	10.4 (15%)	10.3 (7.18–12.5)
θSCr/1.6 on CL	0.456 (10%)	0.455 (0.42–0.57)
θECMO on CL	2.26 (16%)	2.30 (1.26–1.57)
θTime.ECMOoff on CL	0.0123 (24%)	0.0123 (0.0069–0.0187)
θECMO on V1	2.98 (41%)	2.88 (1.65–5.22)
Random effects (% CV*)		
Interindividual variability (ω)		
CL	30.2 (56%)	31.0 (20.7–47.6)
V1	33.9 (90%)	34.2 (7.8–56.0)
V2	47.3 (41%)	49.4 (31.4–72.4)
Proportional residual variability (σ)	20.9 (14%)	21.2 (18.6–24.5)

CL, clearance; V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; Time.ECMOoff, Time since ECMO termination; RSE, relative standard error; CV, coefficient of variation
* Calculated according to SQRT(omega)*100

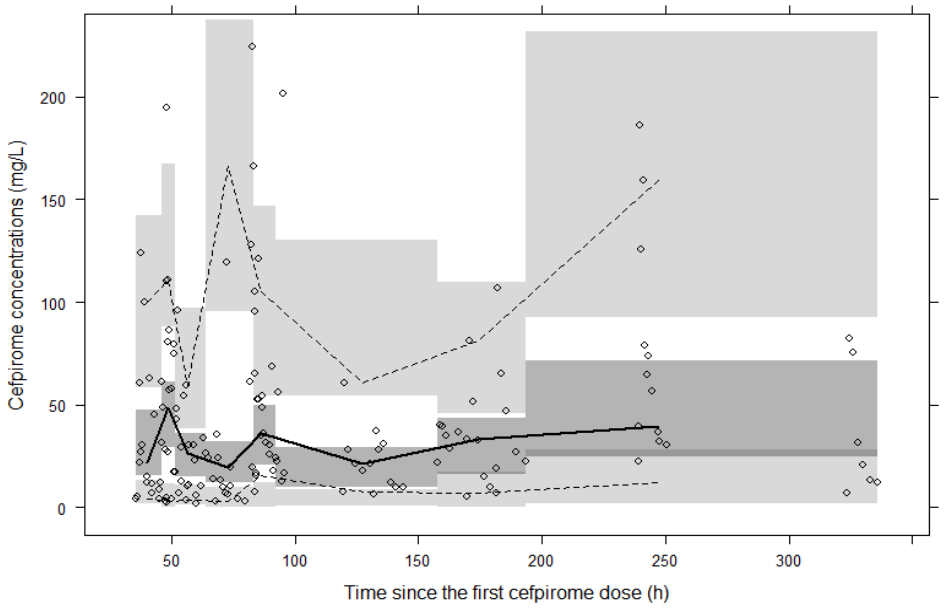


Figure 10. The visual predictive check plot showed that the 5th to 95th percentiles of the predicted data overlapped most of the observed data

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 datasets of individuals from the original dataset

3.4. Dose simulations and optimization

3.4.1. Dose simulations

To investigate the effect of various scenarios on PK profiles and establish optimal dosage regimen for cefpirome, Monte Carlo simulation was conducted using final PK model. Figure 11 and 12 show the mean of Monte Carlo simulated cefpirome concentration for the conventional recommended dosage regimen, i.e. 2 g q12h for each administration methods when SCr was 1.5 mg/dL. Figure 13 represents the mean of simulated cefpirome concentration stratified by the ECMO status as same as with aforementioned condition in log scale. The mean of simulated cefpirome concentration over time since the first cefpirome administration according to administration practices was shown in Figure 14.

The simulation results show that as infusion time increased, simulated Cmax were decreased and minimum concentration (Cmin) were increased. The simulated Cmax was lowest in patients receiving ECMO, and the highest in patients 48 h after ECMO termination at same administration method. In patients 100 h after ECMO termination, simulated Cmax and Cmin tended to be lower than in patients 48 h after ECMO termination. The simulated Cmax was highest in IV-bolus and lowest in extended infusion over 4 h, and the simulated Cmin was highest at extended infusion over 4 h. Time to Cmax was highest immediately after the end of injection or infusion in all administration method.

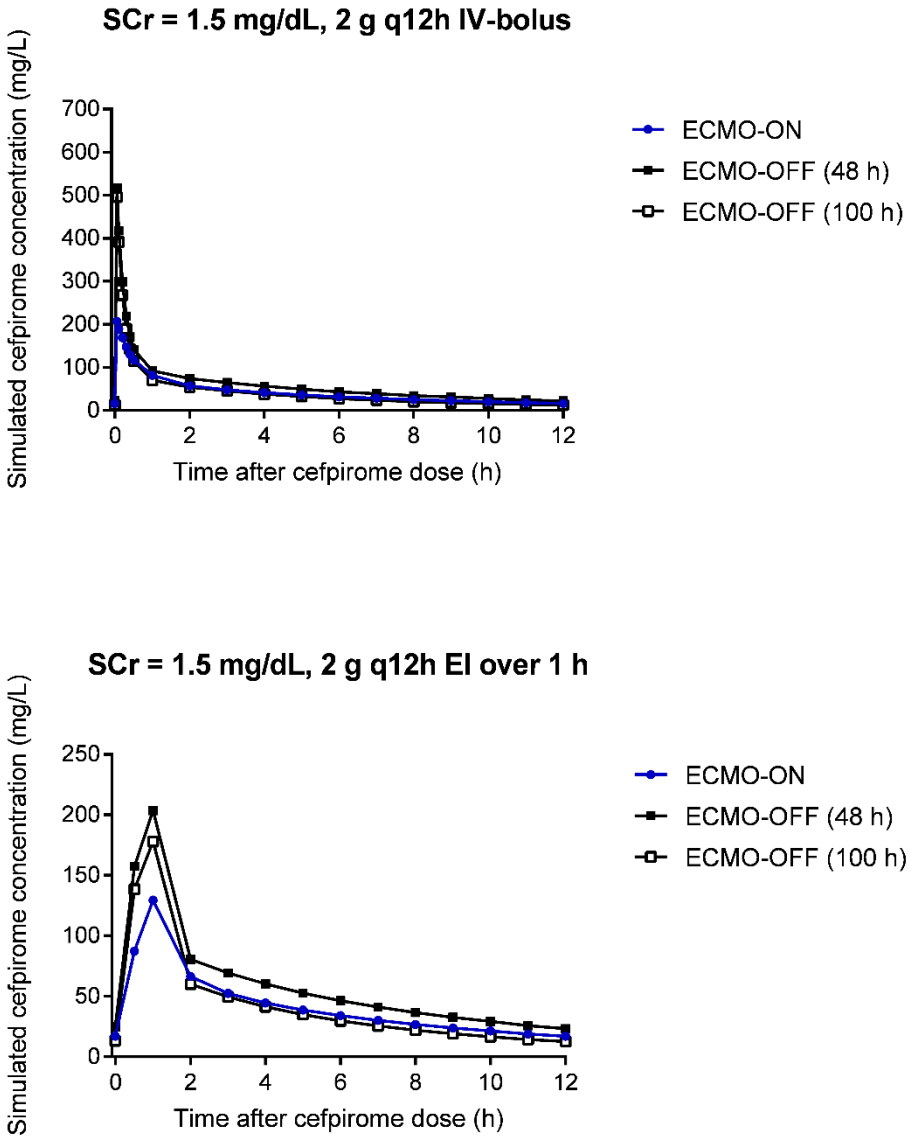


Figure 11. Simulated mean cefpirome concentrations for 2 g q12h IV-bolus and extended infusion over 1 h when SCr is 1.5 mg/dL

Patients were stratified for ECMO status and time after ECMO termination. 2 g q12h IV-bolus (Top); 2 g q12h extended infusion over 1 h (Bottom).

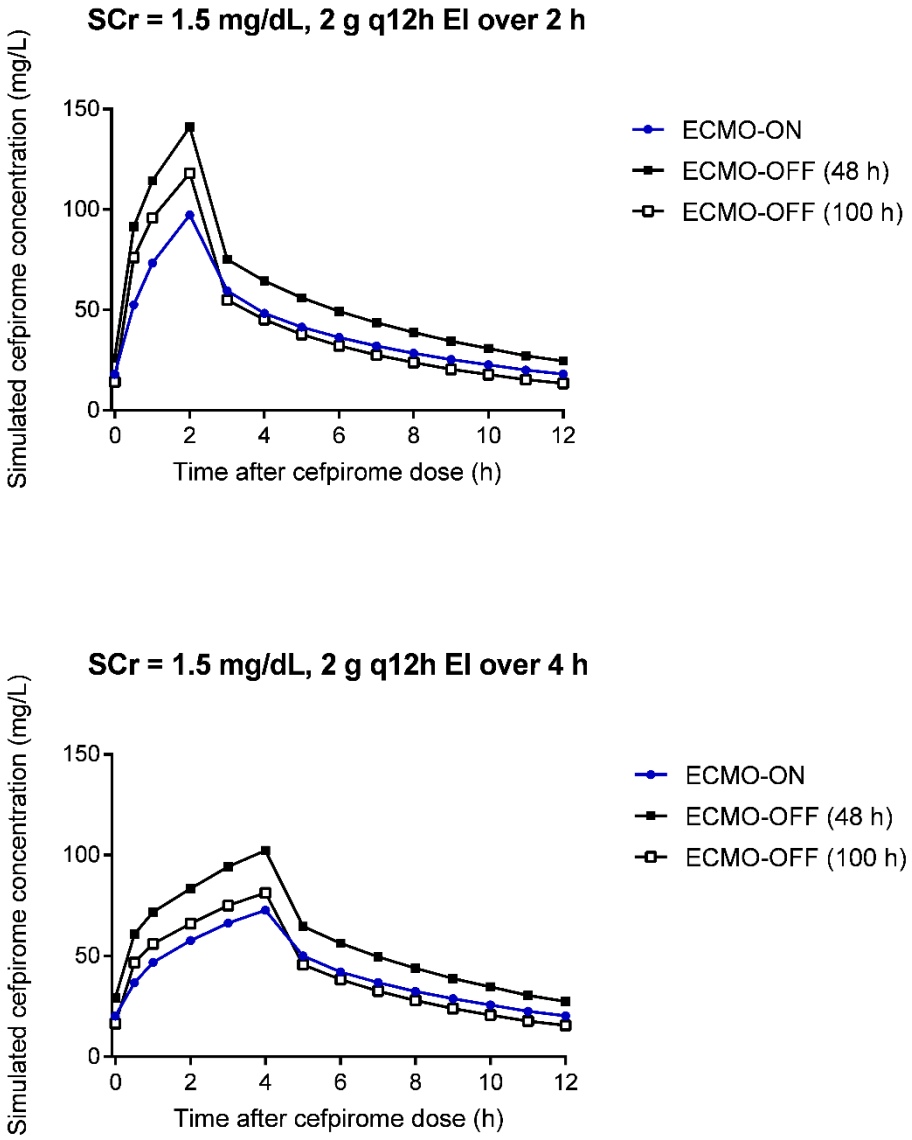


Figure 12. Simulated mean cefpirome concentrations for 2 g q12h extended infusion over 2 h and over 4 h when SCr is 1.5 mg/dL

Patients were stratified for ECMO status and time after ECMO termination. 2 g q12h extended infusion over 2 h (Top); 2 g q12h extended infusion over 4 h (Bottom).

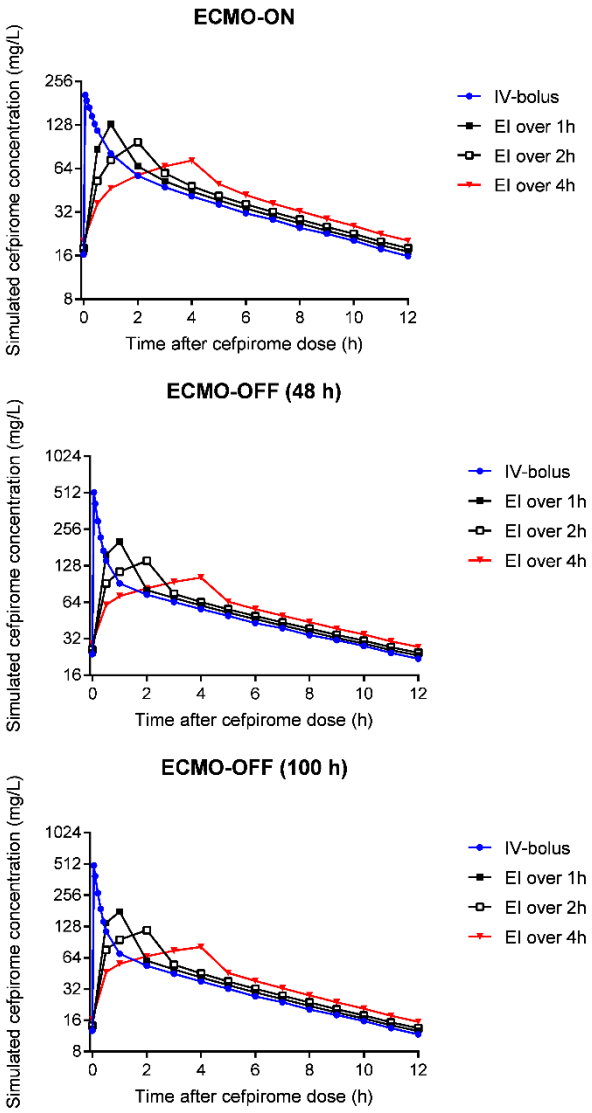


Figure 13. Log of simulated mean cefpirome concentrations for 2 g q12h when SCr is 1.5 mg/dL

Patients were stratified for administration method (IV-bolus, extended infusion over 1 h, extended infusion over 2 h, and extended infusion over 4 h). In patients receiving ECMO (Top); In patients 48 h after ECMO termination (Middle); In patients 100 h after ECMO termination (Bottom).

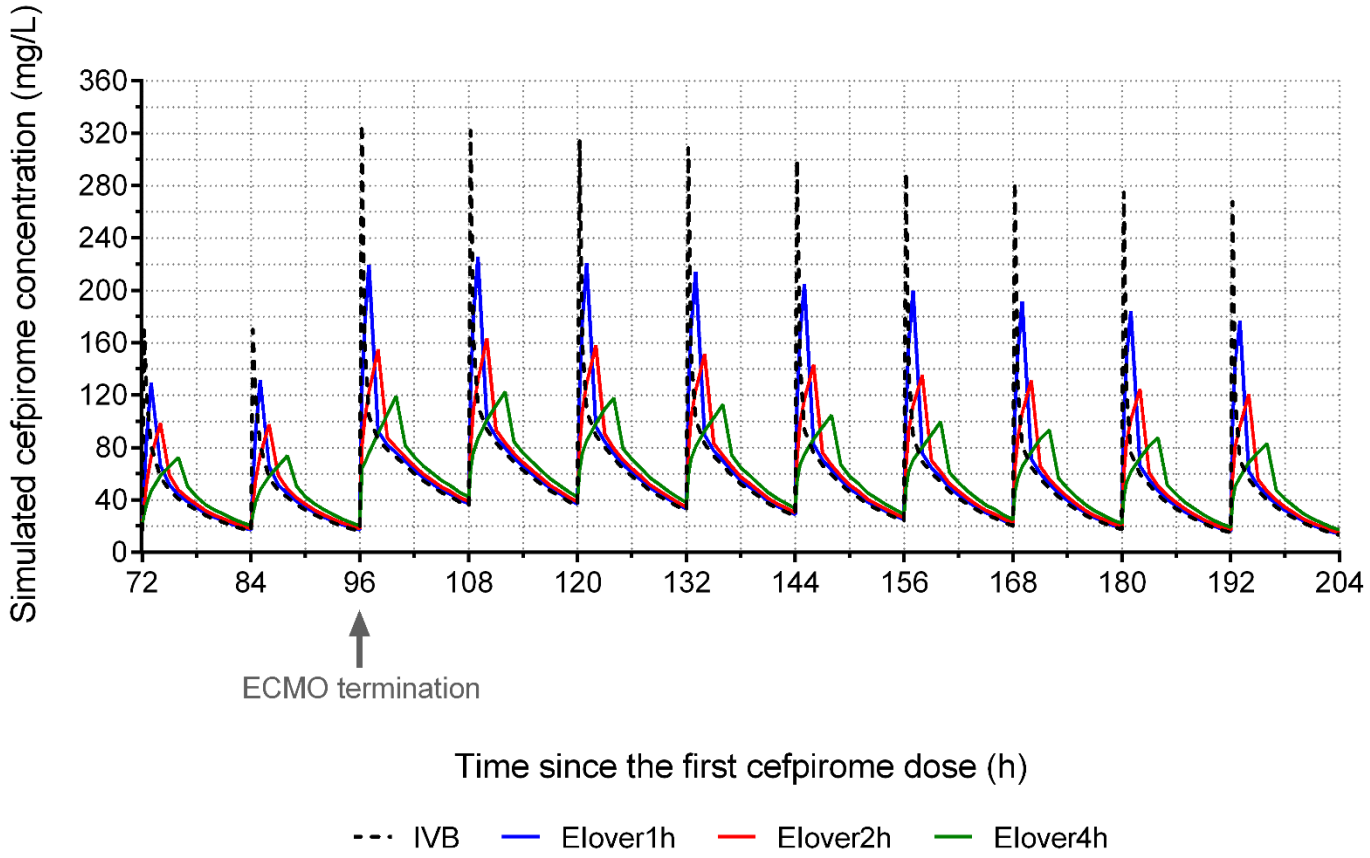


Figure 14. Simulated mean cefpirome concentrations over time since the first dose for 2 g q12h according to administration practice when SCr is 1.5 mg/dL

3.4.2. Dose optimization

The simulated PTA vs. MIC profiles for the different IV-bolus and extended infusion over 1 h, 2 h, and 4 h were shown in Figure 15–19. The figures were drawn at serum creatinine levels of 0.5, 1.1, 1.9, 2.5, and 3.1 mg/dL in patients receiving ECMO (ECMO-ON), in patients after 48 h of ECMO termination (48 h after ECMO-OFF), and in patients after 100 h of ECMO termination (100 h after ECMO-OFF).

The calculated PTA and CFR via extended infusion administration was higher than those via IV-bolus in patients with same SCr and ECMO status. The PTA in ECMO-ON tended to be slightly lower than those in 48 h after ECMO-OFF. However, the PTA in 100 h after ECMO-OFF tended to be slightly decreased than those in 48 h after ECMO-OFF, and those occasionally in ECMO-ON. This tendency was seen more in patients with lower SCr levels who have normal kidney function. Additionally, patients with a lower SCr, representative of better kidney function, obtained lower PTA than those with higher SCr during the same ECMO condition. Higher SCr levels tended to be decrease the difference of PTA achievement between IV-bolus and extended infusion for the same cefpirome dose; in other words, the lower SCr level, which representative of better kidney function, was shown to be increase the difference of PTA achievement between IV-bolus and extended infusion for the same cefpirome dose.

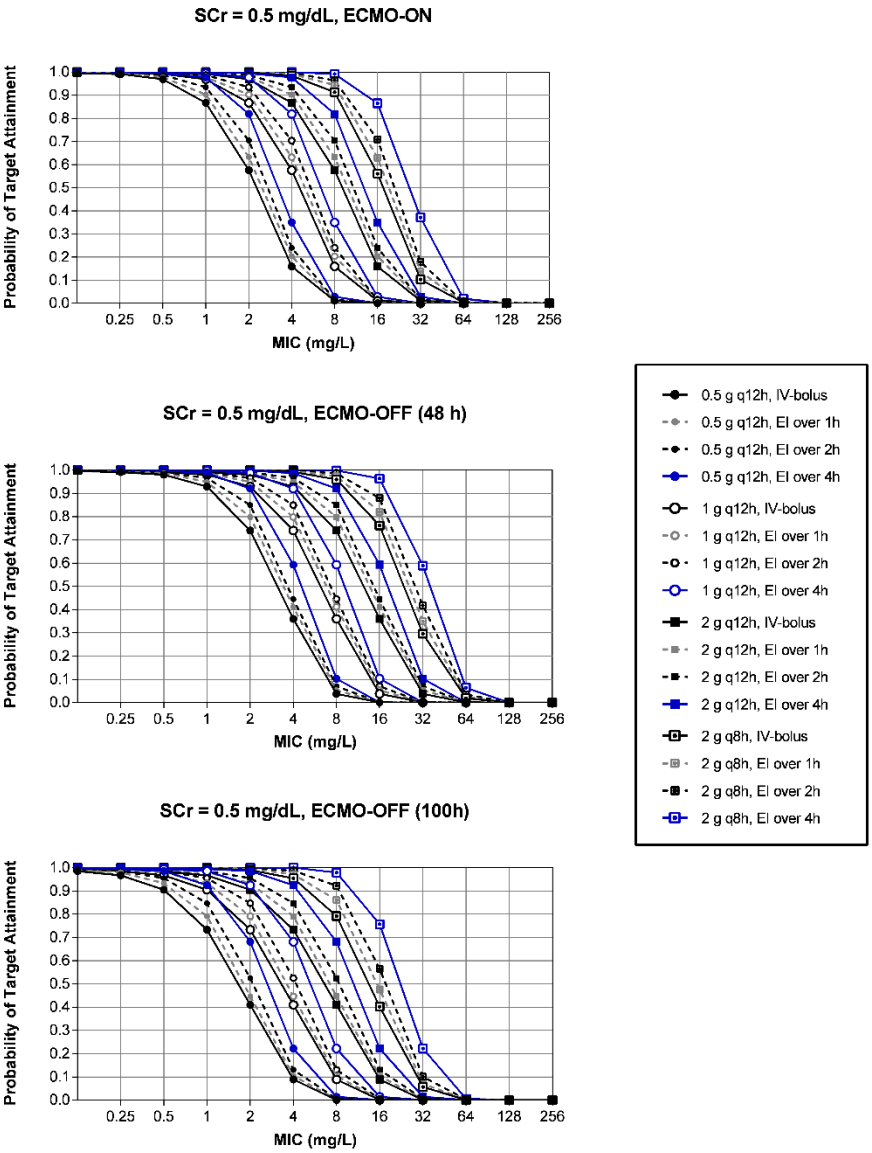


Figure 15. The simulated probability of target attainment in patients with serum creatinine levels of 0.5 mg/dL

Patients were stratified for dosage regimens. The simulated PTA in patients receiving ECMO (Top); those in patients after 48 h of ECMO termination (Middle); those in patients after 100 h (Bottom).

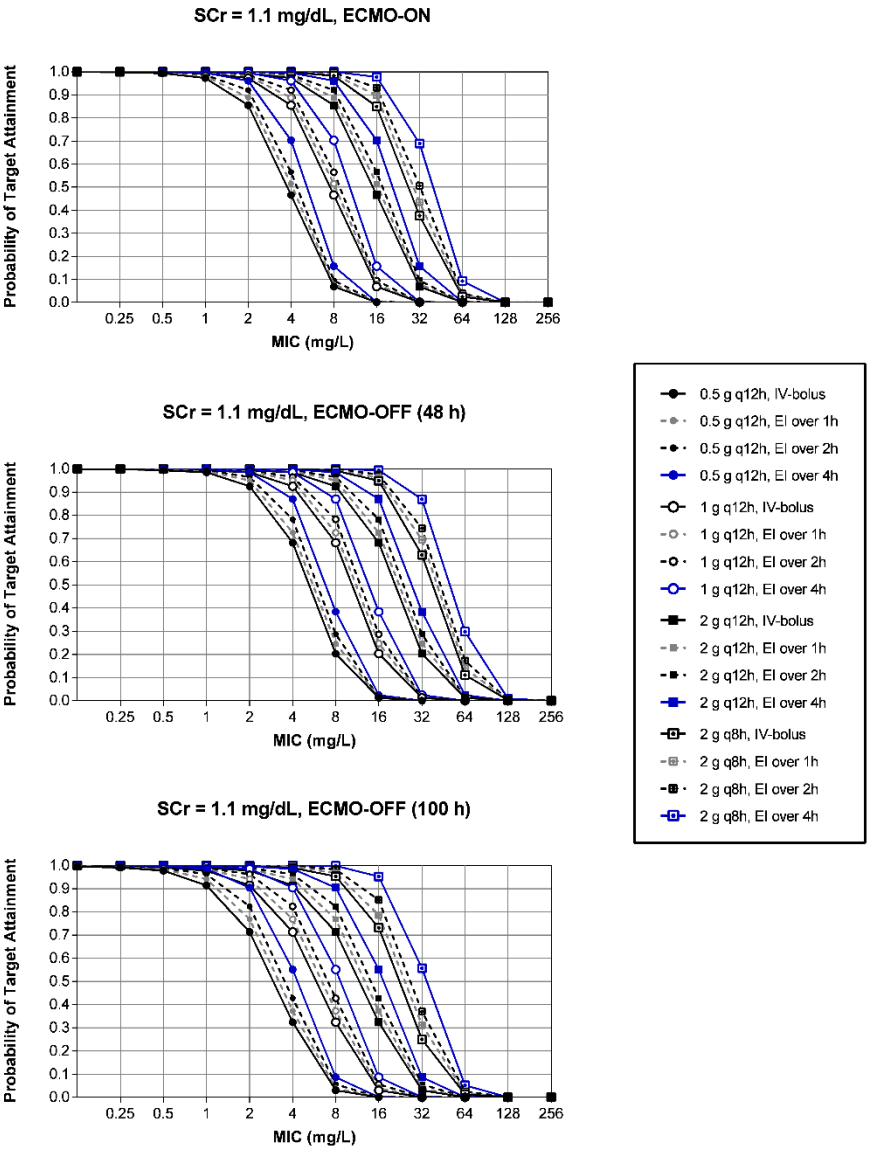


Figure 16. The simulated probability of target attainment in patients with serum creatinine levels of 1.1 mg/dL

Patients were stratified for dosage regimens. The simulated PTA in patients receiving ECMO (Top); those in patients after 48 h of ECMO termination (Middle); those in patients after 100 h (Bottom).

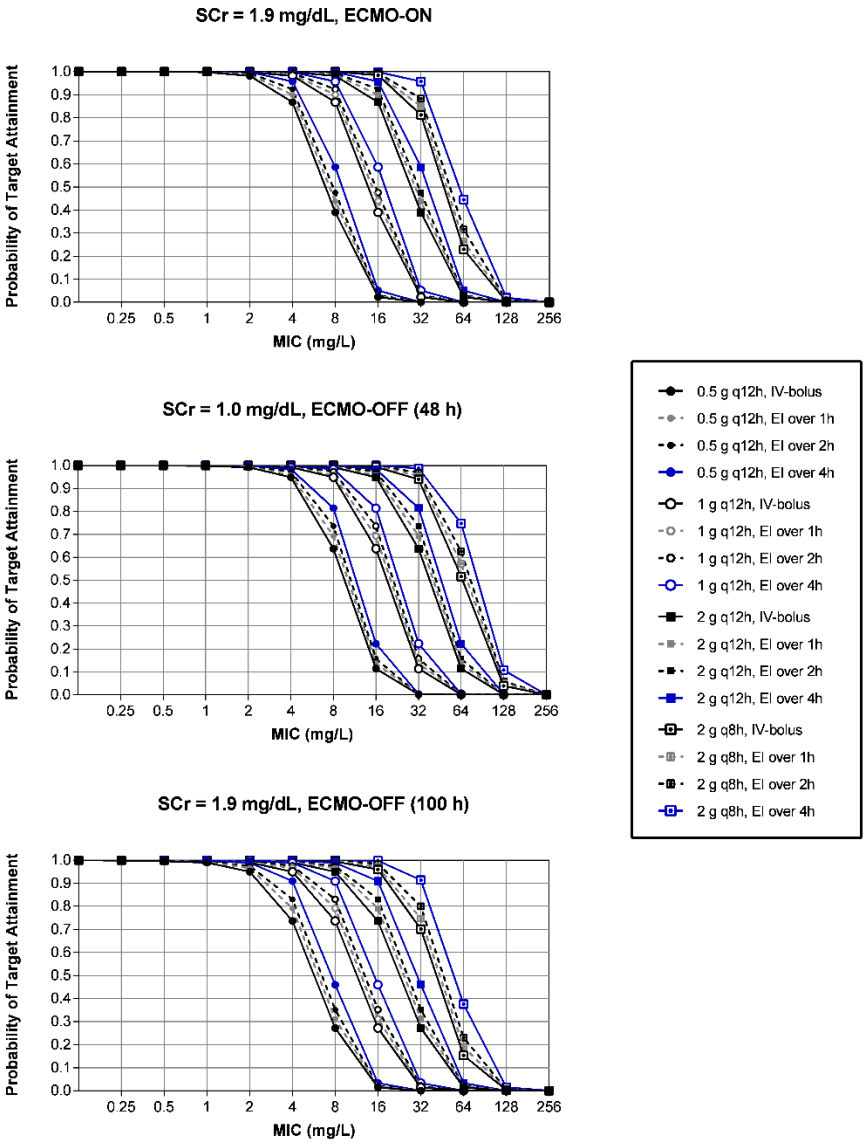


Figure 17. The simulated probability of target attainment in patients with serum creatinine levels of 1.9 mg/dL

Patients were stratified for dosage regimens. The simulated PTA in patients receiving ECMO (Top); those in patients after 48 h of ECMO termination (Middle); those in patients after 100 h (Bottom).

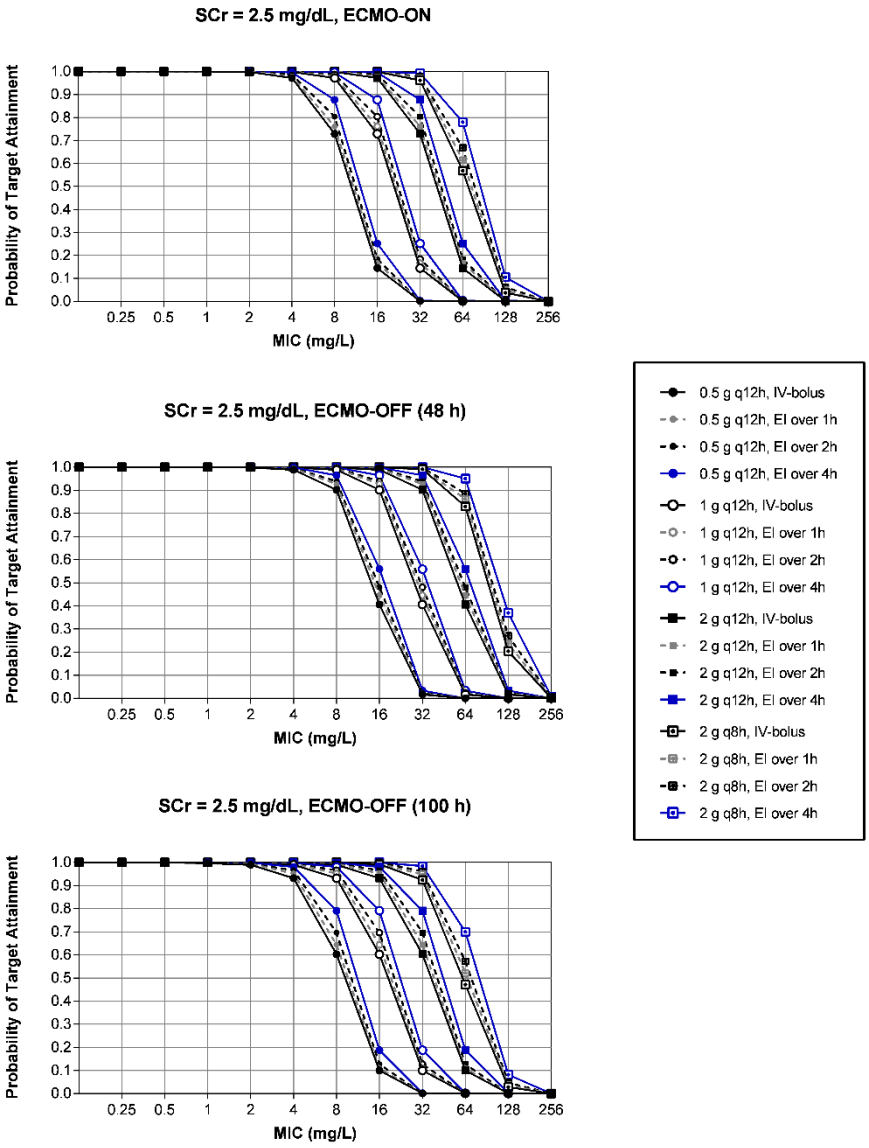


Figure 18. The simulated probability of target attainment in patients with serum creatinine levels of 2.5 mg/dL

Patients were stratified for dosage regimens. The simulated PTA in patients receiving ECMO (Top); those in patients after 48 h of ECMO termination (Middle); those in patients after 100 h (Bottom).

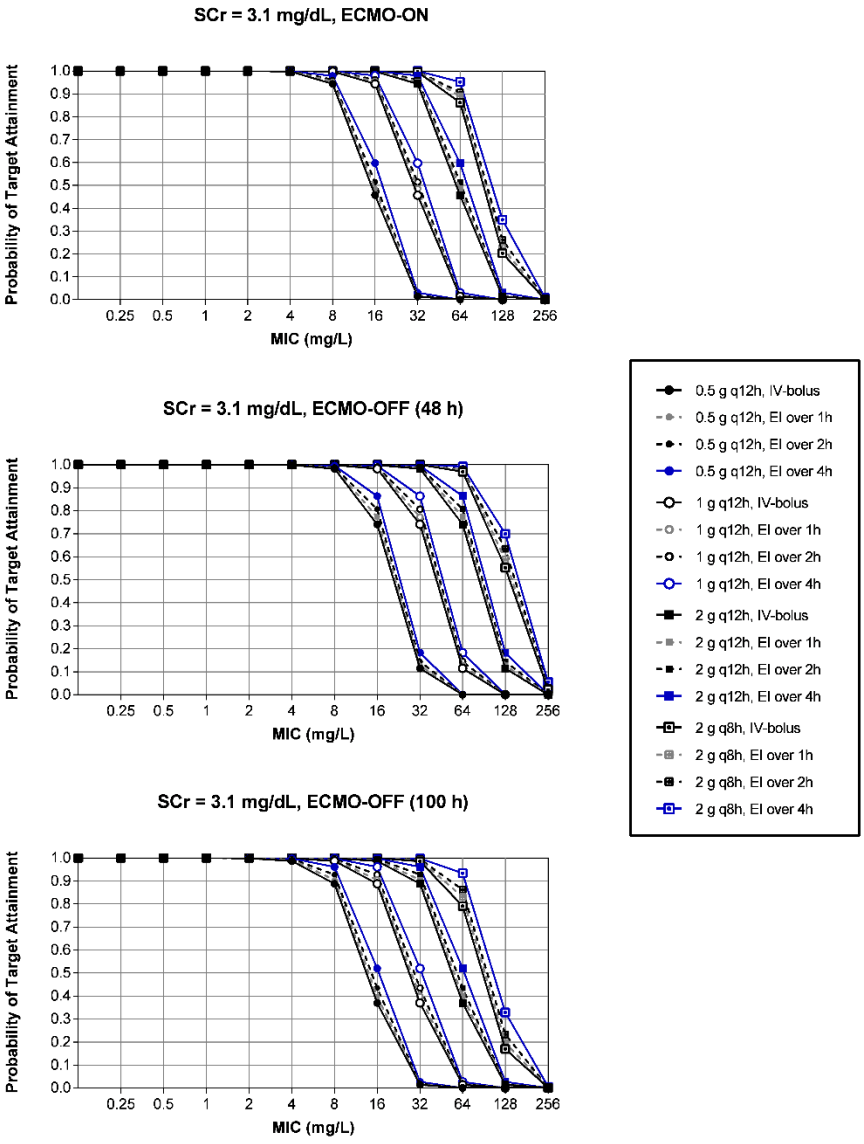


Figure 19. The simulated probability of target attainment in patients with serum creatinine levels of 3.1 mg/dL

Patients were stratified for dosage regimens. The simulated PTA in patients receiving ECMO (Top); those in patients after 48 h of ECMO termination (Middle); those in patients after 100 h (Bottom).

CFR was higher following extended infusion delivery than in the IV-bolus, and the longer infusion was achieved higher CFR. However, since the CFR was achieved fairly higher in the extended infusion over 4 h than in those over 1 h and 2 h on the basis of *Pseudomonas aeruginosa*, the optimal dose was determined based on IV-bolus and extended infusion over 4 h in consideration of both clinical convenience and benefit (Table 11–13). CFR was achieved lower in patients receiving ECMO than in patients 48 h after ECMO termination in the same dosing scenario. But the CFR in patients 100 h after ECMO termination was diminished again fairly than those in patients 48 h after ECMO termination.

The recommended doses according to SCr and administration practice (IV-bolus versus extended infusion) were represented in Figure 20 and 21 based on *P.aeruginosa*, because *P.aeruginosa* is less susceptible against cefpirome among all target pathogens except *Acinetobacter* spp. The dosage regimens of 2 g q8h for IV-bolus and 2 g q12h for extended infusion over 4 h were recommended for *P. aeruginosa* treatment in patients during ECMO with SCr values of up to 0.9 mg/dL in consideration of clinical convenience. The CFRs were higher than 95% for *S. pneumoniae*, *Enterobacter* spp., *E. coli*, and *Klebsiella* spp. for all doses of cefpirome, regardless of the presence of ECMO. It was difficult to achieve target CFR for *Acinetobacter* spp. at a low SCr.

Table 11. Dose regimens to meet target CFR based on *Pseudomonas aeruginosa* according to administration practice in patients receiving ECMO

	IV-bolus				Extended infusion over 1 h				Extended infusion over 2 h				Extended infusion over 4 h			
SCr (mg/dL)	**0.5 g q12h**	**1 g q12h**	**2 g q12h**	**2 g q8h**	**0.5 g q12h**	**1 g q12h**	**2 g q12h**	**2 g q8h**	**0.5 g q12h**	**1 g q12h**	**2 g q12h**	**2 g q8h**	**0.5 g q12h**	**1 g q12h**	**2 g q12h**	**2 g q8h**
0.5	43.0	66.7	82.6	92.5	46.8	69.9	84.7	93.5	51.0	73.2	86.7	94.4	58.6	78.8	89.9	96.1
0.7	50.0	72.1	85.9	93.8	53.9	75.1	87.6	94.6	57.4	77.7	89.2	95.3	64.3	82.1	91.7	96.7
0.9	57.2	77.3	88.9	94.9	60.1	79.3	90.0	95.6	62.9	81.1	91.0	96.1	69.3	85.0	93.2	97.2
1.1	62.8	80.9	90.9	95.9	65.4	82.5	91.7	96.4	68.0	84.1	92.7	96.8	73.4	87.2	94.3	97.5
1.3	68.0	84.0	92.6	96.6	70.6	85.5	93.3	96.9	72.7	86.8	94.0	97.2	77.2	89.2	95.2	97.9
1.5	72.9	86.8	94.0	97.2	75.1	88.0	94.6	97.4	76.8	89.0	95.1	97.6	80.6	91.0	96.1	98.2
1.7	77.2	89.1	95.2	97.6	78.7	90.0	95.6	97.8	80.1	90.7	95.9	98.0	83.3	92.4	96.7	98.4
1.9	80.5	90.9	96.0	98.0	82.0	91.7	96.4	98.1	83.2	92.3	96.7	98.3	85.4	93.4	97.2	98.6
2.1	83.5	92.5	96.7	98.3	84.5	93.0	96.9	98.4	85.5	93.4	97.2	98.5	87.3	94.3	97.6	98.8
2.3	86.0	93.7	97.3	98.5	86.7	94.0	97.4	98.6	87.4	94.4	97.6	98.7	89.0	95.2	97.9	98.9
2.5	87.8	94.5	97.6	98.7	88.4	94.9	97.8	98.8	89.2	95.2	97.9	98.9	90.6	95.9	98.2	99.0
2.7	89.7	95.5	98.0	98.9	90.2	95.7	98.1	98.9	90.8	96.0	98.3	99.0	91.8	96.5	98.5	99.2
2.9	91.3	96.2	98.4	99.0	91.7	96.4	98.4	99.1	92.0	96.6	98.5	99.2	92.8	96.9	98.6	99.3
3.1	92.5	96.7	98.6	99.2	92.8	96.9	98.6	99.2	93.0	97.0	98.7	99.3	93.7	97.3	98.8	99.4
3.3	93.4	97.2	98.7	99.3	93.7	97.3	98.8	99.4	93.9	97.4	98.8	99.4	94.4	97.6	98.9	99.5
*Ratio to meet target CFR	**63.3%**				**68.3%**				**68.3%**				**73.3%**			

IV-bolus, intravenous bolus injection; SCr, serum creatinine

Colored compartments where SCr and dose regimen intersect indicate that they meet the target CFR under that condition.

*Calculated according to (colored compartment) / (all compartment, 60) * 100

Table 12. Dose regimens to meet target CFR based on *Pseudomonas aeruginosa* according to administration practice in patients 48 h after ECMO termination

SCr (mg/dL)	IV-bolus				Extended infusion over 1 h				Extended infusion over 2 h				Extended infusion over 4 h			
	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h
0.5	57.0	76.6	88.2	95.0	60.9	79.3	89.8	95.7	63.7	81.3	90.9	96.4	70.0	85.2	93.2	97.3
0.7	63.0	80.6	90.5	95.9	66.1	82.6	91.6	96.5	68.7	84.3	92.6	97.0	74.9	87.9	94.6	97.7
0.9	68.4	83.9	92.3	96.7	71.1	85.5	93.2	97.1	73.6	87.1	94.0	97.4	78.3	89.8	95.5	98.0
1.1	73.3	86.8	93.8	97.3	75.8	88.2	94.5	97.5	77.8	89.4	95.2	97.8	81.6	91.5	96.3	98.3
1.3	77.7	89.2	95.1	97.7	79.6	90.3	95.6	98.0	81.0	91.1	96.0	98.1	84.2	92.8	96.9	98.5
1.5	81.0	91.0	96.0	98.1	82.7	91.9	96.4	98.3	83.8	92.6	96.7	98.4	86.4	93.9	97.4	98.7
1.7	83.9	92.5	96.7	98.4	85.3	93.3	97.1	98.5	86.2	93.8	97.3	98.7	88.3	94.8	97.8	98.9
1.9	86.4	93.8	97.3	98.6	87.5	94.4	97.6	98.8	88.3	94.8	97.7	98.8	89.9	95.6	98.1	99.0
2.1	88.6	94.9	97.8	98.8	89.3	95.3	97.9	98.9	90.1	95.6	98.1	99.0	91.6	96.4	98.4	99.2
2.3	90.3	95.7	98.1	99.0	91.1	96.1	98.3	99.1	91.7	96.4	98.4	99.1	92.6	96.8	98.6	99.3
2.5	92.0	96.5	98.5	99.2	92.4	96.7	98.5	99.2	92.8	96.9	98.6	99.3	93.6	97.2	98.8	99.4
2.7	93.1	97.0	98.7	99.3	93.4	97.2	98.7	99.4	93.7	97.3	98.8	99.4	94.4	97.6	98.9	99.6
2.9	94.0	97.4	98.8	99.5	94.3	97.5	98.9	99.5	94.6	97.7	99.0	99.6	95.2	97.9	99.1	99.7
3.1	94.8	97.8	99.0	99.6	95.2	97.9	99.1	99.6	95.4	98.0	99.1	99.7	95.8	98.2	99.2	99.8
3.3	95.6	98.1	99.2	99.7	95.8	98.2	99.2	99.7	96.0	98.3	99.3	99.8	96.3	98.4	99.3	99.8
*Ratio to meet target CFR	**75.0%**				**76.7%**				**80.0%**				**81.7%**			

IV-bolus, intravenous bolus injection; SCr, serum creatinine

Colored compartments where SCr and dose regimen intersect indicate that they meet the target CFR under that condition.

*Calculated according to (colored compartment) / (all compartment, 60) * 100

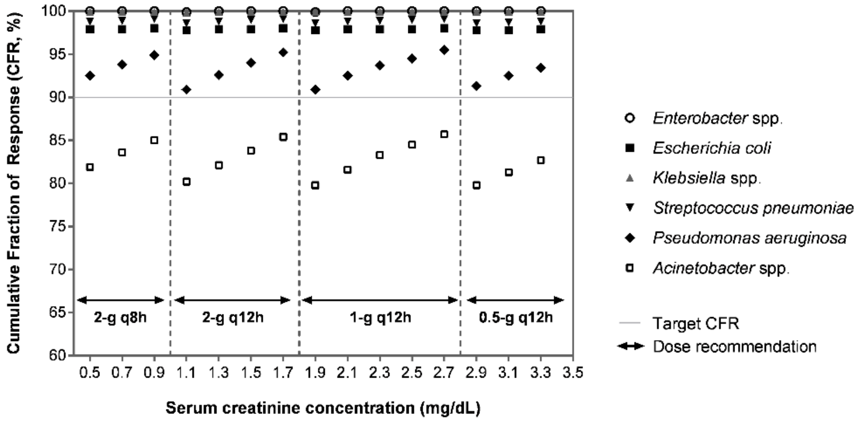
Table 13. Dose regimens to meet target CFR based on *Pseudomonas aeruginosa* according to administration practice in patients 100 h after ECMO termination

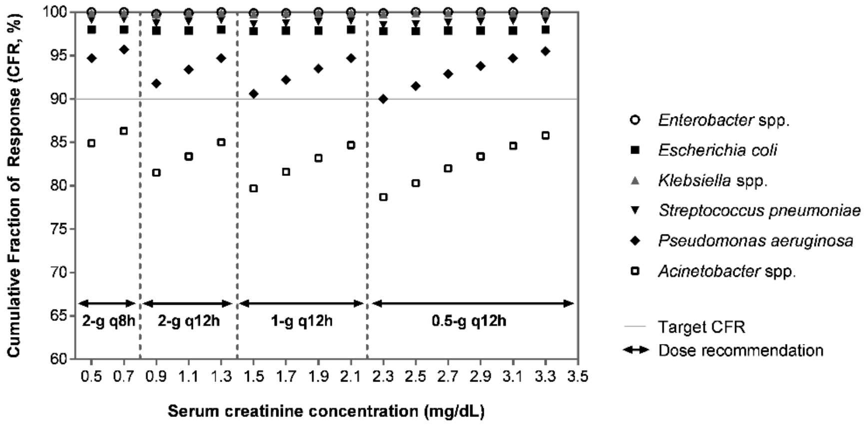
SCr (mg/dL)	IV-bolus				Extended infusion over 1 h				Extended infusion over 2 h				Extended infusion over 4 h			
	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h	0.5 g q12h	1 g q12h	2 g q12h	2 g q8h
0.5	33.6	57.3	75.7	89.6	36.9	61.0	78.6	91.4	41.9	65.8	81.9	92.9	51.3	73.6	87.0	95.1
0.7	40.6	63.8	80.2	91.6	44.6	67.5	82.8	93.0	48.6	70.8	85.0	94.1	57.9	78.0	89.4	95.9
0.9	47.3	69.3	83.8	93.3	51.2	72.5	85.9	94.3	55.3	75.8	87.9	95.1	63.4	81.3	91.1	96.7
1.1	54.2	74.5	87.0	94.5	58.2	77.5	88.8	95.3	61.7	80.0	90.2	96.0	68.2	84.2	92.7	97.1
1.3	60.7	79.0	89.6	95.5	63.6	81.0	90.8	96.2	66.7	83.1	92.0	96.7	72.8	86.8	94.0	97.5
1.5	66.2	82.6	91.6	96.4	68.8	84.2	92.5	96.9	71.5	85.8	93.4	97.2	77.0	89.1	95.1	97.9
1.7	71.0	85.5	93.1	97.1	73.7	87.1	94.0	97.4	76.2	88.5	94.8	97.7	80.3	90.8	95.9	98.1
1.9	76.0	88.3	94.6	97.5	78.0	89.5	95.2	97.8	79.8	90.4	95.7	98.0	83.3	92.3	96.7	98.4
2.1	79.8	90.4	95.7	97.9	81.3	91.2	96.1	98.2	82.7	92.0	96.5	98.3	85.5	93.5	97.2	98.7
2.3	82.7	91.9	96.4	98.3	84.0	92.6	96.7	98.4	85.4	93.3	97.1	98.6	87.5	94.4	97.6	98.8
2.5	85.5	93.4	97.1	98.5	86.5	93.9	97.3	98.6	87.6	94.5	97.6	98.8	89.2	95.2	97.9	98.9
2.7	87.8	94.5	97.6	98.7	88.6	94.9	97.8	98.8	89.3	95.3	97.9	98.9	91.1	96.1	98.3	99.1
2.9	89.6	95.4	98.0	98.9	90.4	95.8	98.1	99.0	91.0	96.1	98.3	99.1	92.2	96.6	98.5	99.3
3.1	91.3	96.2	98.3	99.1	91.9	96.5	98.5	99.2	92.4	96.7	98.5	99.2	93.2	97.1	98.7	99.4
3.3	92.6	96.8	98.6	99.3	93.0	97.0	98.7	99.3	93.3	97.1	98.7	99.4	94.1	97.4	98.9	99.5
*Ratio to meet target CFR	**55%**				**60.0%**				**63.3%**				**68.3%**			

IV-bolus, intravenous bolus injection; SCr, serum creatinine

Colored compartments where SCr and dose regimen intersect indicate that they meet the target CFR under that condition.

*Calculated according to (colored compartment) / (all compartment, 60) * 100


Cumulative Fraction of Response (CFR, %)
100
95
90
85
80
75
70
65
60
2-g q8h
2-g q12h
1-g q12h
0.5-g q12h
0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1 2.3 2.5 2.7 2.9 3.1 3.3 3.5
Serum creatinine concentration (mg/dL)
Enterobacter spp.
Escherichia coli
Klebsiella spp.
Streptococcus pneumoniae
Pseudomonas aeruginosa
Acinetobacter spp.
Target CFR
Dose recommendation


Cumulative Fraction of Response (CFR, %)
100
95
90
85
80
75
70
65
60
2-g q8h
2-g q12h
1-g q12h
0.5-g q12h
0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1 2.3 2.5 2.7 2.9 3.1 3.3 3.5
Serum creatinine concentration (mg/dL)
Enterobacter spp.
Escherichia coli
Klebsiella spp.
Streptococcus pneumoniae
Pseudomonas aeruginosa
Acinetobacter spp.
Target CFR
Dose recommendation

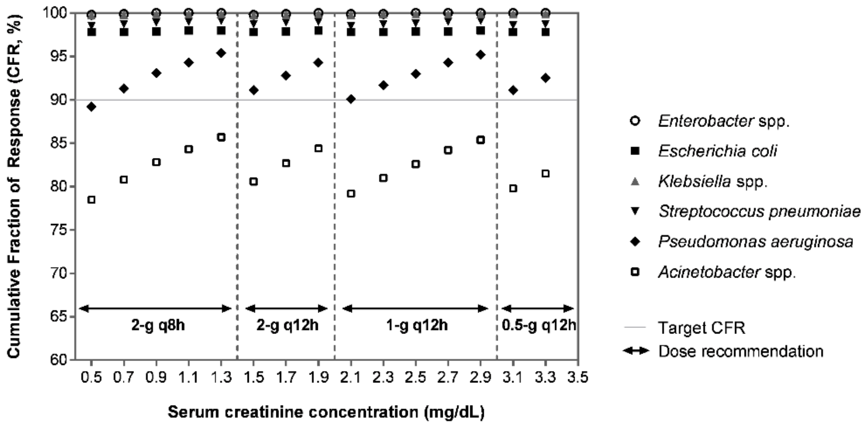
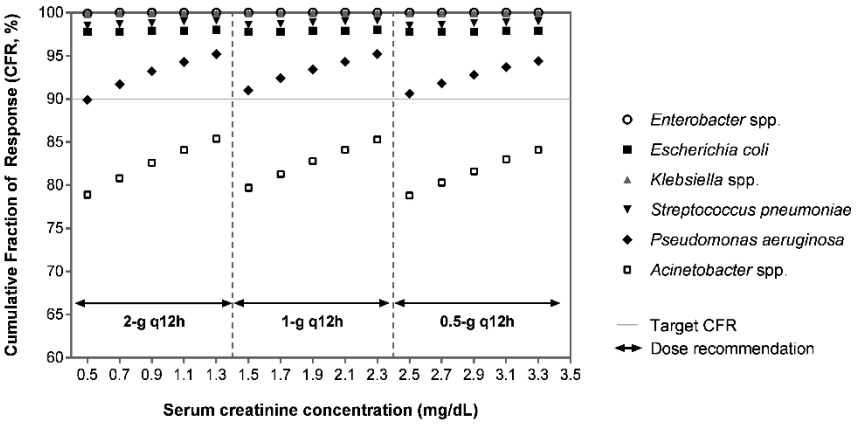
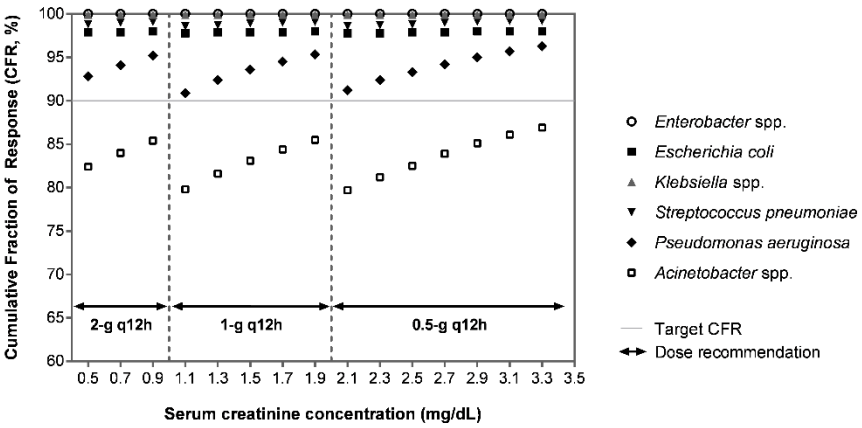

Cumulative Fraction of Response (CFR, %)
100
95
90
85
80
75
70
65
60
2-g q8h
2-g q12h
1-g q12h
0.5-g q12h
0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9 2.1 2.3 2.5 2.7 2.9 3.1 3.3 3.5
Serum creatinine concentration (mg/dL)
Enterobacter spp.
Escherichia coli
Klebsiella spp.
Streptococcus pneumoniae
Pseudomonas aeruginosa
Acinetobacter spp.
Target CFR
Dose recommendation

Figure 20. Cumulative fraction of response after intravenous bolus injection of the recommended dosage of cefpirome based on serum creatinine concentration range

Simulated Cumulative fraction of response (CFR) according to the recommended dose for intravenous bolus injection (IV-bolus) based on *Pseudomonas aeruginosa* in patients receiving ECMO (Top), in patients 48 h after ECMO termination (Middle), and in patients 100 h after ECMO termination (Bottom).





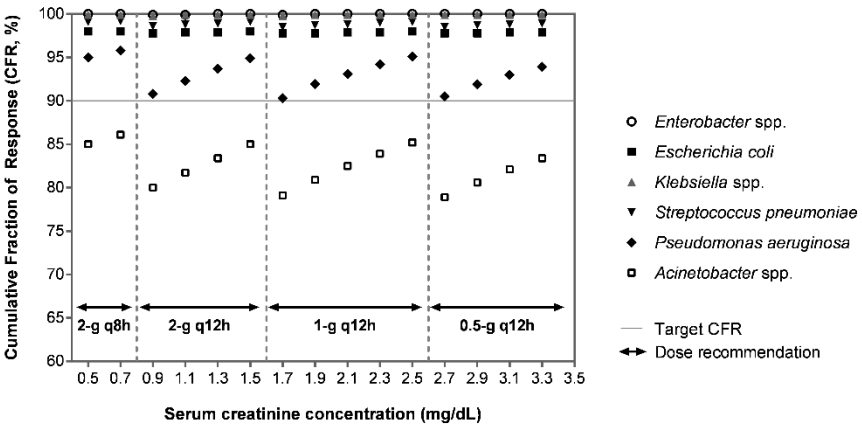


Figure 21. Cumulative fraction of response after extended infusion over 4 h of the recommended dosage of cefpirome based on serum creatinine concentration range

Simulated Cumulative fraction of response (CFR) according to the recommended dose for extended infusion over 4 h based on *Pseudomonas aeruginosa* in patients receiving ECMO (Top), in patients 48 h after ECMO termination (Middle), and in patients 100 h after ECMO termination (Bottom).

4. Discussion

4.1. Findings of the research

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, and CL increased over time since ECMO termination.at the same SCr. Additionally, SCr was negatively correlated with CL. None of the parameters related to ECMO such as LPM and RPM helped to understand factors influencing to the final PK model. The calculated PTA and CFR, when cefpirome was administered by extended infusion, were higher than those by IV-bolus in patients with same SCr and ECMO status. PTA was slightly decreased by lower SCr and during ECMO, and the higher dose needed to meet target CFR. In addition, PTA in 100 h after ECMO termination tended to be slightly decreased than those in 48 h after ECMO termination, and those occasionally in ECMO-ON, especially in low SCr range. 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 IV-bolus or 2 g q12h (4 g/day) for extended infusion over 4 h; moreover, dose reduction based on SCr was recommended. To the best of our knowledge, this study is the first to suggest the appropriate dosage of cefpirome for critically ill patients receiving VA ECMO.

4.2. PK parameter changes for cefpirome in ECMO patients

In our study, the CL was 3.99 L/h on 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 L/h) (Roos et al., 2007). The reduction in cefpirome CL in our study can be explained by the renal impairment caused by hemodynamic instability (Vincent & De Backer, 2013). VA ECMO-related factors, such as systemic inflammation due to the exposure of blood to artificial surfaces, hemolysis, or hemoglobinuria, may also contribute to renal dysfunction (Askenazi et al., 2012; Murphy et al., 2015). This trend was also found in PK studies of cefepime in pediatric patients receiving ECMO (Shoji et al., 2016; Zuppa et al., 2019).

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 (Kohsaka et al., 2005; Lim, 2016; Tsai et al., 2015). Moreover, the extra circulating volume from ECMO circuits, rigorous fluid resuscitation, and frequent transfusion induces an increased circulatory volume in patients receiving ECMO (Steinhorn et al., 1989). Thus, V1 might be increased in patients with ECMO. Although cefpirome is a hydrophilic and low protein binding substance (Wiseman & Lamb, 1997), an increase in V1 following cefpirome sequestration in the ECMO circuits could not be excluded (Shekar, Roberts, Mcdonald, et al., 2012; Wildschut et al., 2010).

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 (Lemaitre et al., 2015; Leven et al., 2017). 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–8°C and protected from light (Sugioka et al., 1990). 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 (Sugioka et al., 1990; Zalewski et al., 2014); 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 (Murphy et al., 2015).

The ECMO-OFF as a covariate may inherently correlate with patient status and improvement, so we tested time since ECMO termination as another covariate. As time elapsed since ECMO termination, population CL for cefpirome also increased; when SCr is 1.6 mg/dL, population CL on 48 h and 100 h after ECMO termination is 2.81 L/h and 3.94 L/h, respectively. These results are likely to be related to recovery of the kidney function gradually after ECMO termination; CL was decreased for a while just after ECMO termination, then CL was increased over time and reached as the level similar to when ECMO is connected at 100 h since ECMO

termination. Renal failure is usually occurred in adult patients receiving VA ECMO at frequency of 12.3% (Thiagarajan et al., 2017), because nonpulsatile blood flow related to VA ECMO is associated with a decreased glomerular filtration rate (Many et al., 1967; Mousavi et al., 2011). Moreover, a study in pediatric patients receiving ECMO reported that renal recovery occurred in 96% before discharge (Paden et al., 2011).

In our final model, as the SCr increased, cefpirome CL decreased. Cefpirome is predominantly (80%–90%) eliminated by the kidney (Wiseman & Lamb, 1997); thus, a negative correlation between cefpirome CL and SCr is reasonable. An excellent relationship between CrCL and systemic cefpirome CL has been reported (Sauermann et al., 2005). Further, CrCL, measured from an 8-h urine collection, was screened as a covariate for CL (Roos et al., 2007). The use of CRRT and SCr were 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 CRRT intensity directly, CRRT could contribute fairly to the decreased in SCr (Troyanov et al., 2003). In addition, previous study reported that a considerable fraction of the cefpirome is removed through CRRT. So, it is not surprising the CRRT does not included in our final cefpirome PK model (Van Der Werf et al., 1999).

4.3. Dose optimization and their rationales

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 (Abrams et al., 2019), were calculated using the MIC distribution from EUCAST. Our findings were different from those of a previous study, in which IV-bolus or continuous infusions of cefpirome failed to achieve bactericidal targets for *P. aeruginosa* or *Acinetobacter* spp. in patients with sepsis (Roos et al., 2007). The dosing simulations confirmed that the current treatment, 2 g q12h for IV-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 IV-bolus was sufficient, regardless of ECMO. For *P. aeruginosa*, the optimal dose was 2 g q8h for IV-bolus or 2 g q12h for extended infusion over 4 h in ECMO patients with normal SCr. For patients with relatively high SCr, dose reduction to 0.5–1 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 over 4 h than for IV-bolus; the CFR achievements of the extended infusion over 1–2 h were slightly higher than IV-bolus, but those were fairly lower than extended infusion over 4 h. Prior studies have noted the clinical benefits of

prolonged infusions of beta-lactams because they have time-dependent activity (Bauer et al., 2013). 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 (Roos et al., 2007; Sugioka et al., 1990). 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 IV-bolus in every scenario.

4.4. Study limitations

This study has some limitations. The number of patients enrolled was small. To evaluate covariates in population PK modelling, a minimum 50 patients has been suggested (Ribbing & Niclas Jonsson, 2004). 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 (Shekar, Roberts, Welch, et al., 2012). 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 of 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; but all in ECMO-OFF group were still critically ill patients who is needed intensive care until sampling. A recent review demonstrated that PK changes in patients receiving ECMO reflect more critical illness than ECMO therapy itself (Abdul-Aziz & Roberts, 2020). In addition, time after ECMO termination, representing the improvement of patients' status, was included in final PK model.

5. Conclusion

This is the first study to evaluate the population PK and PD analysis and to suggest the appropriate dosage of cefpirome in critically ill patients receiving VA ECMO, to the best of our knowledge. 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.

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APPENDICES

Appendix A

The part of this thesis was already published at Antimicrobial Agents and Chemotherapy (Kang et al. 2020). Copyright of articles was permitted from journals.

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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,

Citation Kang S, Jang JY, Hahn J, Kim D, Lee JY, Min KL, Yang S, Wi J, Chang MJ. 2020. Dose optimization of cefpirome based on population pharmacokinetics and target attainment during extracorporeal membrane oxygenation. Antimicrob Agents Chemother 64:e00249-20. https://doi.org/10.1128/AAC.00249-20.

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Received 6 February 2020
Returned for modification 16 February 2020
Accepted 26 February 2020
Accepted manuscript posted online 2 March 2020
Published 21 April 2020

Appendix B

CONTROL STREAM FOR A FINAL MODEL

```
$SUBROUTINE ADVAN3 TRANS4
$PK
;--- FIXED EFFECT DEFINITION ----
TVCL = THETA(1)*THETA(5)**(SCR/1.6)*THETA(6)**ECMO
            *(1+(1-ECMO)*THETA(8)*ETIM_OFF)
TVV1 = THETA(2)*THETA(7)**ECMO
TVQ = THETA(3)
TVV2 = THETA(4)

;--- RANDOM EFFECT DEFINITION ---
CL = TVCL*EXP(ETA(1))
V1 = TVV1*EXP(ETA(2))
Q = TVQ*EXP(ETA(3))
V2 = TVV2*EXP(ETA(4))

S1=V1
K=CL/V1
K12=Q/V1
K21=Q/V2

$ERROR
W=F
Y=F+F*EPS(1)
IPRED=F ;INDIVIDUAL PREDICTION
IRES=DV-IPRED ;INDIVIDUAL RESIDUAL
IWRES=IRES/W ;INDIVIDUAL WEIGHTED RESIDUAL

$THETA
```

```
(0, 3.87) ;CL
(0, 3.43) ;V1
(0, 10.4) ;Q
(0, 17.1) ;V2
(0, 0.456) ; SCr on CL
(0, 2.26) ; ECMO on CL
(0, 2.98) ; ECMO on V1
(0, 0.0123); ECMO_OFFtime on CL

$OMEGA
0.0911 ; CL
0.115 ; V1
0 FIX ; Q
0.224 ; V2

$SIGMA 0.0435

$ESTIMATION SIG=3 MAXEVAL=9999 METHOD=1 INTER NOABORT
$COVARIANCE PRINT=E

$TABLE ID TIME DV IPRED PRED CWRES IWRES PRINT ONEHEADER
    FILE=SDTAB211
$TABLE ID CL V1 Q V2 ETA(1) ETA(2) ETA(3) ETA(4) K K12 K21 FILE=PATAB211
    NOPRINT ONEHEADER NOAPPEND
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    TMP SCR BUN WBC RBC HGB PLT CRP PROC CRCL EGFR AST FILE=COTAB211
    NOPRINT ONEHEADER NOAPPEND
$TABLE ID SEX ECMO CRRT SMO ACH FILE=CATAB211 NOPRINT ONEHEADER
    NOAPPEND
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ABSTRACT (Korean)

체외막산소화장치 적용 중
세피롬의 집단 약동학 및 용량/용법 최적화 연구

연세대학교 일반대학원
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강소영

연구 배경

체외막산소화장치(extracorporeal membrane oxygenation, ECMO)는 기존의 약물 치료에 반응이 없는 심장성 쇼크 환자에서 일시적으로 순환기 기능을 보조하여 자가 회복에 필요한 시간을 확보하기 위한 기계장치이다. 중환자는 일반적으로 감염에 취약한 상태이며, 대구경 카테터를 사용하여 경피적으로 삽입하는 ECMO 장치는 매우 침습적이므로 세피롬(4세대 세팔로스포린계열 항생제)과 같은 광범위 항생제의 투여는 ECMO 적용 중 감염의 예방 및 치료에 필수적이다. 세팔로스포린과 같은 베타-락탐계 항생제의 ECMO 관련 약동학적

변화는 다양하고 예측이 어려워 치료적 약물농도감시(therapeutic drug monitoring, TDM)가 필요한 것으로 알려져 있다. 그러나 ECMO를 적용한 환자에서 세피롬의 약동학적 변화를 조사하고, 적정 투여 용량 및 용법을 제시한 연구는 아직까지 없었다.

연구 목적

ECMO 적용 중 세피롬의 집단 약동학 모델을 개발하고, 환자의 특성 및 병원체의 최소억제농도(minimum inhibitory concentration, MIC) 분포를 기반으로 최적의 용량/용법을 제시하여, ECMO 적용 중 세피롬의 치료 효과를 극대화하고자 한다.

연구 방법

본 전향적 연구는 심장성 쇼크로 인하여 ECMO를 연결하고 세피롬을 투여받은 중환자를 대상으로 하였다. 혈액 샘플은 ECMO를 적용한 도중(ECMO 적용 그룹)과 ECMO를 중단한 이후(ECMO 중단 그룹)에 각각 채취하였으며, 세피롬 투여 직전(0 분) 1회 및 투여 후 0.5–1시간, 2–3시간, 4–6시간, 8–10시간 중 각각 1회와 12시간에 1회 수집하였다. 세피롬의 혈장 농도는 검증된 액체 크로마토그래피–질량분석법을 사용하여 분석하였다. 집단 약동학 모델은 비선형 혼합효과 모델링(nonlinear Mixed Effects Modelling, NONMEM)을 이용하여 상호작용을 고려한 일차 조건부 추정(first-order conditional estimation method with interaction, FOCE+I) 방법으로 추정하였다. 유의한 영향을 미치는 공변량을 도출하기 위하여 우도비 검정(likelihood ratio test)에 기반한 단계적 공변량 선택법(stepwise covariate modeling)을 적용하였다. 또한 추정한 모델의 상대표준오차(relative standard error)의 타당성과

적합도 그래프(goodness-of-fit plot), ETA 상관관계 그래프, 환자별 그래프, 정규성 검토 그래프(QQ plot)의 시각적 검사를 기반으로 최적의 집단 약동학 모델을 개발하고자 하였다. 모델의 정확성과 견고함을 증명하기 위하여 자동화된 sampling importance resampling (SIR) 방법(sampling = 5,000, resampling = 1,000, and 5 iteration)과 visual predictive checks (pc-VPCs) (n=5,000)를 수행하였다. 몬테카를로 시뮬레이션(Monte Carlo simulation)을 이용하여 목표도달확률(probability of target attainment, PTA)을 계산하고, European Committee on Antimicrobial Susceptibility Testing (EUCAST)에 따른 MIC 분포에 기초하여 cumulative fraction of response (CFR)을 평가하였다.

연구 결과

총 15명의 환자가 이 연구에 포함되었다. 환자 연령의 중위값은 63세(사분범위 51.5–70.5세)였다. 혈중 크레아티닌(serum creatinine, SCr) 농도는 ECMO 적용 중에 중간값 1.58 mg/dL 이었고, ECMO 중단 후에 중간값 1.83 mg/dL였다. 5명의 환자는 ECMO와 지속적 신대체요법(continuous renal replacement therapy, CRRT)을 동시에 받았다. ECMO 적용 그룹의 혈장 샘플은 ECMO를 적용하고 있는 14명의 환자로부터 수집되었고, ECMO 중단 그룹의 혈장 샘플은 ECMO를 성공적으로 중단한 8명의 환자로부터 수집되었다. 총 152개의 혈장 샘플이 수집되었다.

관찰된 세피롬의 혈장 농도–시간 프로필은 2구획 모델에 의해 가장 잘 설명되었다. 공변량 분석 결과, 혈중 크레아티닌 농도가 증가하면 약물 청소율(clearance)은 감소하는 음의 상관관계를 보였으며, 에크모 적용 중에는 청소율 및 중심 분포용적(central volume of distribution, V1)이 증가하는 양상을 보였다. 또한 ECMO 중단 직후에 세피롬의 청소율이

감소하였다가 시간이 지날수록 다시 증가하는 변화가 관찰되었다. 최종 약동학 모델은 다음과 같다: ECMO 적용 그룹에서, CL (L/h) = 8.75 × $0.456^{(\text{혈중 크레아티닌 농도(mg/dL)}/1.6)}$, V1 (L) = 10.2, 말초 분포용적(peripheral volume of distribution, V2) (L) = 17.1, 컴파트먼트 간 청소율(intercompartment clearance, Q) (L/h) = 10.4; ECMO 중단 그룹에서, CL (L/h) = 3.87 × $0.456^{(\text{혈중 크레아티닌 농도(mg/dL)}/1.6)}$ × (1 + 0.0123 × ECMO 중단 후 시간(h)), V1(L) = 3.43, V2 (L) = 17.1, Q (L/h) = 10.4.

시뮬레이션 결과, ECMO 적용 중에 혈중 크레아티닌 농도가 낮은 환자는 ECMO 중단 후 혈중 크레아티닌 농도가 높은 환자보다 목표도달확률이 낮았다. 따라서 목표 CFR 기준(90%)을 충족시키기 위해 보다 고용량의 세피롬 투여량이 요구되었다. 한편 ECMO 중단 후 100시간이 지난 시점의 목표도달확률은 ECMO 중단 후 48시간이 지난 시점의 목표도달확률보다 낮았고, ECMO 중단 후 시간이 지날수록 세피롬 투여 요구량이 증가하는 것으로 나타났다. 동일한 혈중 크레아티닌 농도와 동일한 ECMO 상태를 갖는 환자에서 같은 용량의 세피롬을 투여시간을 연장시킨 확장정맥투여(extended infusion)방법으로 투여했을 때, 일시 정맥투여(intravenous bolus injection, IV-bolus) 방법에 비하여 목표도달확률 및 CFR이 높았다. 즉, 일시 정맥투여에 비해 확장정맥투여 방법으로 투여 시, 같은 정도의 CFR을 달성하기 위한 약물 투여 요구량이 더 낮았다. 정상적인 신기능을 가지면서 ECMO를 적용한 환자에서는 일시 정맥투여의 경우 8시간 마다 2 g, 4시간의 확장정맥투여의 경우 12시간 마다 2 g의 세피롬 투여가 권장된다.

연구 결론

이 연구는 ECMO를 적용한 환자에서 세피롬에 대한 집단 약동학 모델을

수립하고 약력학적 분석을 통해 적정 용량용법을 권장한 최초의 연구이다. 이 연구의 결과는 혈중 크레아티닌 농도와 ECMO 적용 상태(ECMO 적용 여부 및 ECMO 중단 후 시간)가 세피롬의 적정 용량/용법을 결정하는 데 중요하다는 점을 시사하고 있다. 이 연구 결과를 통해 ECMO 환자의 치료 성공과 생존율을 향상시킬 것으로 기대된다.

핵심 단어: 세피롬, 세팔로스포린, 체외막산소화장치, 집단약동학, 약력학, 용량용법 최적화