Optimization of Dosage Regimen of Meropenem in Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation: A Prospective Cohort Study

Soyoung Kang
Yonsei University
Seungwon Yang
Yonsei University
Jongsung Hahn
Yonsei University
June Young Jang
Yonsei University
Kyoung Lok Min
Yonsei University
Jin Wi
Gachon University Gil Medical Center
Min Jung Chang (mjchang@yonsei.ac.kr)
Yonsei University https://orcid.org/0000-0002-8408-5907

Research

Keywords: Meropenem, extracorporeal membrane oxygenation, ECMO, dosage optimization, population pharmacokinetics

Posted Date: April 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-416701/v1

Abstract

Background

Patients receiving venoarterial extracorporeal membrane oxygenation (VA ECMO) therapy often require antibiotics to prevent and treat infections. Our objective was to determine an optimal dosage regimen of meropenem in patients receiving VA ECMO by developing a population pharmacokinetic model.

Methods

This was a prospective cohort study. Blood samples were collected during ECMO (ECMO-ON) and after ECMO (ECMO-OFF). The population pharmacokinetic model was developed using nonlinear mixed-effects modelling. A Monte Carlo simulation was used (n=10,000) to assess the probability of target attainment.

Results

Thirteen adult patients on ECMO receiving meropenem were included. Meropenem pharmacokinetics was best fitted by a two-compartment model. Covariate analysis indicated that continuous renal replacement therapy (CRRT) was negatively correlated with clearance (CL). The final pharmacokinetic model was: CL (L/h) = 3.79×0.44^{CRRT}; where use of CRRT = 1, no CRRT = 0, central volume of distribution (L) = 2.4, peripheral volume of distribution (L) = 8.56, and intercompartmental clearance (L/h) = 21.3. According to the simulation results, 1–2 g q8h intravenous administration over 20 min was sufficient in patients without CRRT for both susceptible (minimum inhibitory concentration (MIC) = 2 mg/L) and resistant (MIC = 8 mg/L) pathogens, regardless of ECMO use (40% *f*T>MIC target). However, if more aggressive treatment is needed (100% *f*T>MIC target), dose increment or extended infusion is recommended.

Conclusions

We established a population pharmacokinetic model for meropenem in patients receiving VA ECMO and suggested an optimal dosage regimen. These results should improve treatment success and survival in VA ECMO patients.

Clinicaltrials.gov registration # NCT02581280

Background

Venoarterial extracorporeal membrane oxygenation (VA ECMO) provides mechanical circulatory support for patients with cardiopulmonary failure.[1] There have been exponential increases in ECMO use and survival rates since 2009.[2–4] However, infection is still a common complication during ECMO because it requires use of percutaneously inserted devices with large-diameter catheters, and critically ill patients themselves are generally vulnerable to infection.[4, 5] Consequently, broad-spectrum antibiotics such as meropenem are needed to prevent and treat infections in patients receiving ECMO support.[4, 6]

It is well known that VA ECMO affects the pharmacokinetics (PK) of several drugs,[7–9] altering their volume of distribution (Vd) and clearance (CL) because of inherent physiological changes associated with ECMO and critical illness.[10–14] Non-pulsatile blood flow from VA ECMO reduces glomerular filtration rate and consequently reduces the CL of drugs.[15] Patients with profound cardiogenic shock during VA ECMO commonly need more aggressive volume support for haemodynamic stabilization,[16] which widely alters the effect of ECMO treatment on PK parameters. In addition, PK changes in patients receiving ECMO are dependent on the physicochemical properties of the drugs.[7] Therefore, exact predictions of PK changes in VA ECMO are difficult.[17]

Meropenem, which is the carbapenem antibiotic agent, has broad-spectrum activity against common pathogens identified during ECMO, such as *Staphylococcus aureus*, including methicillin-resistant strains, *Klebsiella* spp., *Pseudomonas* spp., and *Acinetobacter* spp.[18] The most common complications of infection during ECMO are sepsis and ventilator-associated pneumonia (VAP).[19] Since ECMO patients can be exposed to multiple sources of infection by various pathogens, it is essential to use a wide range of antibiotics, including meropenem.

The optimal PK/pharmacodynamics (PD) index to assess the bactericidal activity of meropenem is the percentage of the time in which the free drug concentration is above the MIC of a pathogen during the antibiotic dosing interval (*f*T > MIC).[20–23] An *f*T > MIC of 40% is frequently used for maximum bactericidal effect, as reported by a recent *in silico* study,[23, 24] but this is still controversial.

Several clinical studies recommend therapeutic drug monitoring to ensure 100% *f*T > MIC for beta-lactams in critically ill patients.[25–27] Other reports have suggested that PK targets maintain plasma beta-lactam concentrations of more than 4 times the MIC (*f*T > 4×MIC) for optimal treatment of severe infections.[28, 29]

Meropenem is an important antibiotic agent that can successfully treat infections during ECMO therapy, but the factors affecting PK changes and optimal dosage regimen for meropenem in patients during ECMO are still inconclusive. There have been recent investigations using population PK analysis that have dosage recommendations for meropenem in patients receiving ECMO.[30, 31] However, PK changes are expected to differ depending on the type of ECMO, and these previous studies evaluated data from a mixed patient population treated with VA and venovenous (VV) ECMO. Moreover, they did not directly compare patients receiving ECMO with patients who were weaned off of ECMO.

Thus, the present study aimed to describe the PK profiles of meropenem by comparing patients receiving VA ECMO with patients after ECMO treatment. In addition, optimal dosage regimens were determined according to individual characteristics by simulating various dosing scenarios in patients on both VA ECMO and continuous renal replacement therapy (CRRT).

Methods

Ethics and study design

This prospective cohort study was conducted from May 2016 to January 2019 in the cardiac intensive care unit of Severance Hospital in Seoul, South Korea. The study was approved by the Severance Hospital Institutional Review Board (approval number: 4-2014-0919) and conducted in accordance with the principles of the Declaration of Helsinki and national and institutional standards and was registered at Clinicaltrials.gov (NCT02581280). Written informed consent was obtained from the unconscious participants' legally acceptable representatives.

Patients and treatments

Adult patients (≥ 18 years) receiving VA ECMO and concomitantly receiving meropenem were included in this study. Patients who were allergic to carbapenem, pregnant, or taking any medication that may have altered plasma meropenem concentrations were excluded. Patients with normal kidney function received 1 g meropenem q8h as an intravenous injection over 20 min as per protocol. Patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m^2, as calculated by the Modification of Diet in Renal Disease (MDRD) study equation or patients on CRRT received 1 g meropenem q12h.

ECMO and CRRT system

The ECMO system consisted of a centrifugal blood pump with a controller (Capiox® SP-101, Terumo Inc., Tokyo, Japan), a conduit tube (Capiox® EBS with X coating, Terumo Inc.), and an air-oxygen mixer (Sechrist® Industries, Inc., Anaheim, CA, USA). It was connected percutaneously between the femoral vein and peripheral cannulation of the femoral artery. If needed, continuous venovenous haemodiafiltration (CVVHDF) (Prismaflex®; Gambro Inc., Meyzieu, France) with a Prismaflex® ST100 filter was utilized for CRRT. The ECMO and CRRT settings were recorded.

Data collection

Data associated with demographics, renal and hepatic functions, blood chemistry, vital signs, blood cell counts, and details of ECMO and CRRT were collected. As allowed by the clinical situation, blood samples were collected during ECMO (ECMO-ON group) through the existing radial arterial line at the following times: pre-dose (0 min); 0.5, 1, 3, and 6 h after meropenem administration; and immediately before the next dose according to administration frequency (8 h or 12 h). If the patients were administered meropenem after them weaning off of ECMO (ECMO-OFF group), blood samples were collected at the aforementioned times. The actual sampling time was recorded. The blood samples were collected in EDTA-coated tubes and immediately centrifuged (1,500 ×g at 4°C for 10 min). The plasma samples were stored at -80°C until analysis.

Meropenem assay

Meropenem concentrations were measured using liquid chromatography-mass spectrometry (LC-MS, Ultimate 3000 RS-Q-Exactive Orbitrap Plus; Thermo Fisher Scientific, Waltham, MA, USA) in the Yonsei Center for Research Facilities. The plasma samples were deproteinized using acetonitrile with sulfamethoxine as an internal standard. The mixture was vortexed for 10 sec and then

centrifuged (10 min at 10,000 **g**), and the supernatant was filtered using a 0.45-μm syringe filter. 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 40°C and a flow rate of 0.4 mL/min. The mobile phase was comprised of solvent A (0.1% formic acid in water) and solvent B (100% acetonitrile) with the following elution gradient maintained at 90% A for 4 min, reduced to 5% A over 10 min, maintained at 5% A for 1 min, increased to 90% A over 0.5 min, and maintained at 90% A for 1.5 min. The lower limit of quantification was 0.1 mg/L. The inter- and intra-assay coefficients of variation were < 15%.

PK model development

The population PK model was conducted based on non-linear mixed-effects modelling using NONMEM (version 7.4.1; ICON Development Solutions, Dublin, Ireland) and Pirana (version 2.9.7; Certara, Princeton, NJ, USA). The Xpose4 package (version 4.6.1; https://github.com/UUPharmacometrics/xpose4/releases) in R (version 3.5.3; http://www.r-project.org) was used to visualize and evaluate the models.

The plasma concentration-time profiles for meropenem were fitted to one-, two-, or three-compartment models using the first-order conditional estimation method with the interaction estimation option. Interindividual variability (IIV) of PK parameters was evaluated using an exponential variance model assumed a log-normal distribution. Residual unexplained variability (RUV) was tested using an additive, exponential, and combined random error model. The model was selected based on a minimum objective function value (OFV), validity of the estimated relative standard error (RSE), shrinkage of PK parameters, and visual inspection of the goodness-of-fit plot. The likelihood ratio test was performed in the NONMEM program to assess statistical significance between the nested models. A decrease in the OFV of at least 3.84 was judged statistically significant for an added parameter (P value < 0.05, $\chi 2$ distribution, degree of freedom = 1). For visual inspection, the goodness-of-fit plot was expressed as the observed concentrations vs. population predictions (PRED) or individual predictions (IPRED), and conditional weighted residuals (CWRES) vs. PRED.

Covariate screening

To evaluate the influence of covariates on the meropenem PK parameters, the following potential covariates were tested: demographic variables (sex, age, weight, and height), ECMO-associated variables (during ECMO or weaned off of ECMO and ECMO flow rate [LPM, litres per minute]), CRRT-associated variables (use of CRRT, blood flow rate, CRRT 6 h prior to urine output, dialysate flow rate), complete blood count (absolute white blood cells, red blood cells, haemoglobin, and platelets), renal function (serum creatinine [SCr], blood urea nitrogen [BUN], creatinine clearance (CrCL) estimated via the Cockcroft-Gault equation, and eGFR estimated via the MDRD equation), liver function (alanine transaminase, aspartate aminotransferase, and total bilirubin), biomarkers of inflammation (C-reactive protein and procalcitonin), blood pressure, tympanic body temperature, and social variables (smoking status and alcohol consumption). In addition, to reflect the inherent correlation with patient status and improvement in critical illness between the ECMO-ON and ECMO-OFF groups, we tested time since ECMO initiation and ECMO termination as individual covariate. Most data were tested as time-varying covariates, except fixed variables, such as sex, age, and smoking status, which were considered time-independent.

Covariates were evaluated using linear, exponential, power, and proportional models based on the stepwise covariate modelling (SCM) process. If needed, the continuous covariates were centred on their median values. For forward selection, a P value < 0.05 (OFV reduction of > 3.84) and for backward elimination, a P < 0.01 (OFV increase of > 6.64) were considered to measure significance. The final covariate model selection was based on biological or clinical plausibility, RSE, shrinkage of PK parameters, a condition number of < 1,000, and visual improvement in the goodness-of-fit plot.

Model validation

To evaluate the precision and robustness of the final PK model, an automated sampling importance resampling (SIR) algorithm (sampling = 5,000, resampling = 1,000, five iterations) and a prediction-corrected visual predictive check (pcVPC) were carried out using the Perl Speaks NONMEM toolkit version 4.9.0.[32, 33] The medians with 95% confidence intervals for the replicates from the SIR algorithm were compared with the estimated PK parameters from the final model. Furthermore, the simulated pcVPC results with the 5th percentile, median, and 95th percentile curves were visually assessed.

Simulations

Monte Carlo simulations were performed using the estimated PK parameters to assess the effect of the screened covariates on the predicted meropenem concentrations (n = 10,000). Intravenous intermittent infusion (II) over 20 min and intravenous extended

infusion (EI) over 3 h and 6 h were simulated by the following dosage regimens: 1 g q12h, 2 g q12h, 0.5 g q8h, 1 g q8h, and 2 g q8h over a 24-h period since the first meropenem administration. In addition, intravenous continuous infusion (CI) over 8 h (q8h) of 0.5, 1, and 2 g were simulated. The % *f*T > MIC was determined for each simulated subject by linear interpolation. The PTA was calculated by counting subjects achieving more than 40% *f*T > MIC and 100% *f*T > MIC; the dosage scenario that achieved PTA above 90% was considered to be efficient. The MIC, the clinical breakpoint for meropenem, that was used was 2 mg/L for susceptible strains and 8 mg/L for resistant strains according to EUCAST (ver. 10.0, valid from 2020-01-01).

Results

Patients and treatments

Thirteen patients were included in our study, and eleven of them received VA ECMO because of acute myocardial infarction (MI). Five patients received CRRT concomitantly among the six patients in the ECMO-ON group; two patients received CRRT among the nine patients in the ECMO-OFF group. Two patients were sampled repeatedly based on their ECMO status. The median values of age, weight, SCr, and APACHE II score were 55 years, 65.8 kg, 1.2 mg/dL, and 30, respectively, at the initiation of ECMO. The median value of eGFR was 70.4 mL/min/1.73 m^2, and the eGFR of all patients not receiving CRRT was above 30 mL/min/1.73 m^2 (Table 1).

Table 1
Demographic information and baseline characteristics of all enrolled patients

ECMO	Patient no.*	Age (yr)	Sex	Wt (kg)	Ht (m)	Diagnosis	SCr (mg/dL)	CRRT	eGFR (mL/min/1.73 m^2)	APACHE II score	Length of hospital stay (days)
On	1	48	M	74.6	1.73	Acute MI	na#	yes	na#	34	15
	2	54	M	74.6	1.70	Acute MI,	na#	yes	na#	32	27
	3	53	M	82.9	1.68	Acute MI	na#	yes	na#	44	40
	4	55	F	69.9	1.64	Acute MI	na#	yes	na#	30	200
	5	74	M	93.3	1.70	Acute MI	na#	yes	na#	36	21
	6	57	M	53.1	1.68	Acute MI	1.06	no	76.5	29	36
Off	4*	55	F	67.4	1.64		1.2	no	49.6	30	200
	6*	57	M	53.1	1.68		0.88	no	94.9	29	36
	7	53	F	48.2	1.46	Acute MI	na#	yes	na#	37	75
	8	75	M	53.9	1.60	Acute MI	na#	yes	na#	40	75
	9	48	M	61.1	1.72	Acute MI	1.3	no	64.3	22	21
	10	57	F	60.0	1.62	VF arrest	0.5	no	127.3	30	29
	11	59	M	77.5	1.68	Acute MI, VF arrest	2.0	no	36.5	28	37
	12	51	M	63.0	1.62	VF arrest	0.7	no	120.4	26	36
	13	66	M	67.4	1.68§	Acute MI	1.3	no	60.3	14	23
		55 (53–58)		67.4 (57–74.6)	1.68 (1.63–1.70)		1.2 (0.7–1.56)		70.4 (57.6–101.3)	30 (28.5–35)	36 (25–57.5)

* The same number represents the same patient according to the ECMO status.

§ The mean value was used because data were missing.

Not listed because it is CRRT-dependent.

ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; M, male; F, female; Wt, weight; Ht, height; SCr, serum creatinine; eGFR, estimated glomerular filtration rate according to Modification of Diet in Renal Disease Study equation; VF, ventricular fibrillation; MI, myocardial infarction; yr, year

Table 2
Parameter estimates of the base model and final model

Parameter	Base model	Final model	
	Population estimate (RSE)	Population estimate (RSE)	SIR median (2.5th–97.5th percentile)
Fixed effects (θ)			
CL (L/h)	2.65 (32%)	3.79 (26%)	3.77 (2.69–5.37)
Central volume of distribution, V1 (L)	2.53 (21%)	2.4 (38%)	2.76 (0.59–4.84)
Peripheral volume of distribution, V2 (L)	9.61 (38%)	8.56 (22%)	8.36 (5.59–12.93)
Intercompartmental clearance, Q (L/h)	20.8 (9%)	21.3 (17%)	19.94 (9.37–33.41)
θ_{CRRT} on CL	-	0.44 (30%)	0.45 (0.29–0.62)
Random effects (% CV)			
Interindividual variability (ω^2)			
CL	69.4 (36%)	47.1 (49%)	49.2 (32.2–74.2)
V2	61 (103%)	44 (154%)	51.1 (7.7–108)
Residual unexplained variability (σ^2)	49.7 (18%)	47.3 (21%)	49.0 (40.9–60.2)

RSE, relative standard error; CV, coefficient of variation; SIR, sampling importance resampling

Population PK analysis

The time profile of meropenem plasma concentrations was best fitted by a two-compartment model with IIV on CL and peripheral volume of distribution (V2). The RUV was best explained by an exponential error model. After stepwise selection, use of CRRT for CL was included in the final PK model; the CL of the patients receiving CRRT was lower than that of the patients not receiving CRRT (ΔOFV = 16.8, condition number = 164.5). As covariates, the use of ECMO and the time since ECMO initiation and ECMO termination were not selected by the SCM process because they were not shown to be statistically significant and did not improve the goodness-of-fit of the model. The CrCL and eGFR were not selected for the same reason. The final PK model is described as follows.

$$CL\ (L/h) = 3.79 \times 0.44^{CRRT};\ \text{where the use of CRRT} = 1,\ \text{no use of CRRT} = 0 \quad (1)$$

$$V1\ (L) = 2.4 \quad (2)$$

$$V2\ (L) = 8.56 \quad (3)$$

$$Q\ (L/h) = 21.3 \quad (4)$$

where V1 is the central volume of distribution and Q is the intercompartmental clearance.

The values of CL from Eq. (1) were 3.79 L/h and 1.67 L/h in patients with CRRT and without CRRT, respectively. The parameter estimates and SIR results with 95% confidence intervals are presented in Table 3. All ETA shrinkage values were < 40% in the final model. All parameters had acceptable RSE values, except for the IIV of V2. The goodness-of-fit plots are shown in Additional file 1. Both population and individual predictions were distributed uniformly across the line of equality. The plots of CWRES vs. PRED did not show any trends. The pcVPC plot showed that approximately 10% of the observed data was positioned 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).

Table 3
Recommended dose regimen for meropenem

Target	Normal therapy (40% *f*T > MIC)		More aggressive therapy (100% *f*T > MIC)	
	For susceptible pathogens (MIC = 2 mg/L)	For resistant pathogens (MIC = 8 mg/L)	For susceptible pathogens (MIC = 2 mg/L)	For resistant pathogens (MIC = 8 mg/L)
without CRRT	**1–2 g q8h II** 0.5 g q8h EIs or CI	**1–2 g q8h II** 0.5 g q8h EIs or CI	1–2 g q8h EIs or CI	2 g q8h EI over 6 h or CI
with CRRT	**1 g q12h II** **0.5 g q8h II** 0.5 g q8h EIs or CI	**1 g q12h II** **0.5 g q8h II** 0.5 g q8h EIs or CI	**1 g q12h II** **0.5 g q8h II** 0.5 g q8h EIs or CI	1 g q8h EIs 0.5–1 g q8h CI
The bold doses indicate the standard dosage regimens in the manuscript.				
II, intravenous intermittent infusion over 20 min; EIs, intravenous extended infusions over 3 h and 6 h; EI, intravenous extended infusion; CI, intravenous continuous infusion; CRRT, continuous renal replacement therapy				

Simulations

The final PK model was used for the Monte Carlo simulation (n = 10,000), and the simulated PTA vs. MIC profiles for various dosage scenarios are shown in Additional file 2. Almost all dosage scenarios were sufficient to achieve a PTA above 90% at 40% *f*T > MIC regardless of the administration frequency, route (II, EI, or CI), pathogen susceptibility, and use of CRRT. Target PTAs could be more readily achieved with EI or CI than with II; when comparing EI over 3 h with EI over 6 h, there was little noticeable difference in achieving target PTAs. However, when more aggressive treatment was needed (i.e., PTA above 90% at 100% *f*T > MIC), achieving the target PTA was difficult in the simulated scenarios using II.

The recommended dosage regimens are shown in Table 3. Whether on ECMO or not, the standard doses of meropenem in patients with normal kidney function (1–2 g q8h II) and those in patients receiving CRRT (1 g q12h II or 0.5 g q8h II) were sufficient to cover both susceptible (MIC = 2 mg/L) and resistant (MIC = 8 mg/L) pathogens. Moreover, lower doses (0.5 g q8h for patients with normal kidney function and 0.5 g q8h for patients during CRRT) can also be recommended via EI or CI. If more aggressive treatment is needed, EI or CI is generally recommended. In patients not receiving CRRT, 2 g q8h EI over 6 h or CI is recommended against resistant pathogens. When the patients receiving CRRT require aggressive treatment against resistant pathogens, the minimum recommended dose is 1 g q8h EI or 0.5–1 g q8h CI.

Discussion

This prospective cohort study was designed to develop a population PK model for meropenem in patients receiving VA ECMO, and to explore the appropriate dosage regimen of meropenem by analysing the probability of target attainment using Monte Carlo simulations. In our final PK model, a two-compartment model best fit the time course of plasma meropenem concentrations. This study revealed that the use of ECMO did not have a significant impact on the PK of meropenem. Meanwhile, meropenem CL was 0.44 times lower in patients with CRRT than in patients without CRRT (kidney function > 30 mL/min/1.73 m^2); however, the contributing factors related to CRRT did not help improve the final PK model. As the result of PTA assessment, the standard dose of meropenem was deemed sufficient to cover both susceptible and resistant pathogens in patients receiving CRRT (1 g q12h II or 0.5 g q8h II) or in patients with preserved renal function (1–2 g q8h II) regardless of ECMO. However, if aggressive treatment was needed, EI over 3–6 h or CI instead of II, or incremental dosing was appropriate. These results can help provide a clinically appropriate dosage regimen for meropenem in patients receiving both VA ECMO and CRRT.

In our study, CL decreased in patients receiving CRRT regardless of VA ECMO treatment. Meropenem is reported to be excreted mainly by the kidneys, and renal function indices such as eGFR estimated by the MDRD Study equation and CrCL estimated via the Cockcroft-Gault equation were also found to have a positive relationship with meropenem CL.[30, 31] We assessed the relationship between renal function and meropenem CL in the univariate analysis among non-CRRT patients. However, renal function indices were

excluded as covariates because they did not improve robustness of the PK model, which differed from CRRT added to CL as a covariate. This result may be explained by the small number of patients enrolled in the present study and the fact that almost all included patients without CRRT had eGFR > 30 mL/min/1.73 m^2. In our final PK model, eGFR was not selected as a covariate; however, this does not indicate that dose adjustments according to estimated renal function are not required.

No covariates, including the use of VA ECMO, affected the Vd of meropenem in our PK model. Patients undergoing VA ECMO generally need vigorous volume support, including resuscitation fluid and transfusion, owing to the initial circuit priming volume and their haemodynamic instability.[34] This could lead to increased circulating volume, but meropenem is relatively hydrophilic; it has low protein binding affinity[35] and its sequestration on the ECMO surface may not be high. Because of these properties, VA ECMO may have little effect on the Vd of meropenem despite the larger circulating volume. Other investigators have also reported similar results, in that the use of ECMO did not influence the Vd of meropenem.[30, 31]

Moreover, our findings showed that VA ECMO did not significantly alter the PK of meropenem, consistent with the results of previous PK studies in patients receiving meropenem during both VA and VV ECMO.[30, 31, 36] A recent review suggested that the PK change in ECMO patients was more reflective of critical illness than the ECMO device.[17] Therefore, the PK changes observed for meropenem might be affected not by ECMO use but by critical illness, which includes renal and hepatic hypoperfusion, hypoxia, and systemic inflammation; thus, therapeutic drug monitoring is recommended.[7, 17]

In our study, the current standard dosage recommendation was still effective, but EI or CI provided better PTA, and either infusion is recommended when aggressive treatment is needed. The clinical benefits of prolonged administration of beta-lactams, which display time-dependent activity, have previously been shown.[37–40] One issue in the prolonged administration of meropenem is time-and temperature-dependent degradation.[41–43] However, data from several studies have suggested that > 90% meropenem remains *in vitro* after 5–6 h at room temperature,[41, 43] and recent evidence suggests that meropenem degradation during CI is insignificant at the end of a 12-h dosing interval at room temperature.[44] Therefore, we suggest that EI over 3 h or 6 h would be better than CI if the PK/PD target were to be attained, since meropenem stability during infusion would not be a concern.

To the best of our knowledge, this study is the first to investigate the PK changes in meropenem by comparing patients during VA ECMO with those weaned off of VA ECMO and to suggest the optimal dosage of meropenem according to various scenarios between ECMO and CVVHDF as CRRT. However, this study was limited by the relatively small sample size, and therefore, the data may not have provided robust PK parameter estimates. We attempted to use the ECMO-OFF group as a control to directly compare the effects on ECMO and reduce IIV between the control and intervention groups. However, only two patients could be included in both the ECMO-ON and ECMO-OFF groups because meropenem is not a first-line antibiotic according to our hospital protocol. Finally, our PK model was restricted to patients receiving VA ECMO and CVVHDF as CRRT, which is merely one mode of ECMO and CRRT. Therefore, the applicability of our results to all modes of ECMO is limited.

Conclusion

In conclusion, we established a population PK model for meropenem in patients receiving ECMO. Moreover, we suggest optimized dosage regimens to provide adequate bactericidal activity. The standard dosage regimen (1–2 g q8h II) was sufficient to treat both susceptible and resistant pathogens. If more aggressive therapy is needed, a dose increment or EI over 3–6 h is recommended. These findings will contribute to the successful treatment of infections with meropenem in patients receiving VA ECMO by providing proper dosage regimens.

Declarations

Ethics approval and consent to participate

The study was approved by the Severance Hospital Institutional Review Board (approval number: 4-2014-0919) and was registered at Clinicaltrials.gov (NCT02581280). Written informed consent was obtained from the unconscious participants' legally acceptable representatives.

Consent for publication

Written informed consent was obtained from the participants' legal representatives for publication of their individual details in this manuscript. The consent form is held by the authors' institution and is available for review by the Editor.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy concerns and institutional policy but are available from the corresponding author on reasonable request.

Competing interests

We have no conflict of interest to declare.

Funding

This work was supported by a grant (No. 2021R1F1A1070549) from the National Research Foundation (NRF) of Korea, funded by the Korean government (Ministry of Science, ICT & Future Planning).

Authors' contributions

SK, JW, and MJC designed the study, performed the population PK analysis, interpreted the results of the analysis, and draft the manuscript. JW and MJC supervised the design, conducted the study, and revised the manuscript. SK, SY, JH, JYJ, and KLM collected the blood sample and patient data. SY assisted technical PK modelling and reviewed the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to acknowledge all of the staff of the cardiac intensive care unit of Severance Hospital for their practical support and patient care. They played a crucial role in the successful completion of this study.

References

1. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engström AE, Lagrand WK, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med. Springer Berlin Heidelberg; 2016;42:pp. 1922–34.
2. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA United States. 2009;302:1888–95.
3. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet (London, England). England; 2009;374:1351–63.
4. Thiagarajan RR, Barbaro RP, Rycus PT, McMullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal Life Support Organization Registry International Report 2016. ASAIO J. 2017;63:60–7.
5. Loforte A, Marinelli G, Musumeci F, Folesani G, Pilato E, Martin Suarez S, et al. Extracorporeal membrane oxygenation support in refractory cardiogenic shock: treatment strategies and analysis of risk factors. Artif Organs [Internet]. 2014;38:E129-41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24841637.
6. Sherwin J, Heath T, Watt K. Pharmacokinetics and Dosing of Anti-infective Drugs in Patients on Extracorporeal Membrane Oxygenation: A Review of the Current Literature. Clin Ther [Internet]. Elsevier; 2016;38:1976–94. Available from: http://dx.doi.org/10.1016/j.clinthera.2016.07.169.
7. Cheng V, Abdul-Aziz M-HH, Roberts JA, Shekar K. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. J Thorac Dis [Internet]. 2018 [cited 2019 Dec 2];10:S629–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29732181.
8. Hahn J, Choi JH, Chang MJ. Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients. J Clin Pharm Ther [Internet]. 2017;42:661–71. Available from: http://doi.wiley.com/10.1111/jcpt.12636.

9. Cheng V, Abdul-Aziz MH, Roberts JA, Shekar K. Overcoming barriers to optimal drug dosing during ECMO in critically ill adult patients. Expert Opin Drug Metab Toxicol [Internet]. Taylor & Francis; 2019;15:103–12. Available from: https://doi.org/10.1080/17425255.2019.1563596.
10. Ha MA, Sieg AC. Evaluation of Altered Drug Pharmacokinetics in Critically Ill Adults Receiving Extracorporeal Membrane Oxygenation. Pharmacother J Hum Pharmacol Drug Ther [Internet]. 2017;37:221–35. Available from: http://doi.wiley.com/10.1002/phar.1882.
11. Shekar K, Roberts JA, Mcdonald CI, Ghassabian S, Anstey C, Wallis SC, et al. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care [Internet]. 2015;19:164. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25888449.
12. Seghaye MC, Grabitz RG, Duchateau J, Busse S, Dabritz S, Koch D, et al. Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations. J Thorac Cardiovasc Surg United States. 1996;112:687–97.
13. Shekar K, Roberts JA, Mcdonald CI, Fisquet S, Barnett AG, Mullany DV, et al. Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care [Internet]. BioMed Central Ltd; 2012;16:R194. Available from: http://ccforum.com/content/16/5/R194.
14. Butler J, Pathi VL, Paton RD, Logan RW, MacArthur KJ, Jamieson MP, et al. Acute-phase responses to cardiopulmonary bypass in children weighing less than 10 kilograms. Ann Thorac Surg Netherlands. 1996;62:538–42.
15. Mousavi S, Levcovich B, Mojtahedzadeh M. A systematic review on pharmacokinetic changes in critically ill patients: role of extracorporeal membrane oxygenation. Daru [Internet]. 2011;19:312–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22615675%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3304397.
16. Thiele H, Ohman EM, De Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: An update 2019. Eur Heart J. 2019;40:2671–83.
17. Abdul-Aziz MH, Roberts JA. Antibiotic dosing during extracorporeal membrane oxygenation: does the system matter? Curr Opin Anaesthesiol [Internet]. 2020;33:71–82. Available from: http://insights.ovid.com/crossref?an=00001503-202002000-00011.
18. Darville T. Imipenem and meropenem. Semin Pediatr Infect Dis [Internet]. 1999;10:38–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1045187099800089.
19. Koerner MM, Harper MD, Gordon CK, Horstmanshof D, Long JW, Sasevich MJ, et al. Adult cardiac veno-arterial extracorporeal life support (VA-ECMO): prevention and management of acute complications. Ann Cardiothorac Surg [Internet]. 2019 [cited 2020 Aug 31];8:66–75. Available from: ://dx.doi.org/10.21037/acs.2018.12.09.
20. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis [Internet]. 1995;22:89–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7587056.
21. Nielsen EI, Cars O, Friberg LE. Pharmacokinetic/Pharmacodynamic (PK/PD) Indices of Antibiotics Predicted by a Semimechanistic PKPD Model: a Step toward Model-Based Dose Optimization. Antimicrob Agents Chemother [Internet]. 2011;55:4619–30. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.00182-11.
22. Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin Ther [Internet]. Elsevier; 2016;38:1930–47. Available from: http://dx.doi.org/10.1016/j.clinthera.2016.06.015.
23. Kristoffersson AN, David-Pierson P, Parrott NJ, Kuhlmann O, Lave T, Friberg LE, et al. Simulation-based evaluation of PK/PD indices for meropenem across patient groups and experimental designs. Pharm Res. 2016;33:1115–25.
24. Drusano GL. Prevention of Resistance: A Goal for Dose Selection for Antimicrobial Agents. Clin Infect Dis [Internet]. 2003;36:S42–50. Available from: http://academic.oup.com/cid/article/36/Supplement_1/S42/303192/Prevention-of-Resistance-A-Goal-for-Dose-Selection.
25. Li C, Du X, Kuti JL, Nicolau DP. Clinical Pharmacodynamics of Meropenem in Patients with Lower Respiratory Tract Infections. Antimicrob Agents Chemother [Internet]. 2007;51:1725–30. Available from: https://aac.asm.org/content/51/5/1725.
26. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: Defining antibiotic levels in intensive care unit patients: Are current ß-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis [Internet]. 2014;58:1072–83. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciu027.

27. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother [Internet]. 2015;70:3178–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26188037.
28. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, et al. Therapeutic drug monitoring of β-lactams in critically ill patients: Proof of concept. Int J Antimicrob Agents [Internet]. Elsevier B.V.; 2010 [cited 2020 Sep 1];36:332–9. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2010.06.008.
29. Mouton JW, Vinks AA. Continuous infusion of beta-lactams. Curr Opin Crit Care [Internet]. 2007;13:598–606. Available from: http://journals.lww.com/00075198-200710000-00023.
30. Hanberg P, Öbrink-Hansen K, Thorsted A, Bue M, Tøttrup M, Friberg LE, et al. Population pharmacokinetics of meropenem in plasma and subcutis from patients on extracorporeal membrane oxygenation treatment. Antimicrob Agents Chemother [Internet]. 2018;62:1–13. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.02390-17.
31. Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, et al. The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Crit Care [Internet]. 2014;18:565. Available from: http://ccforum.biomedcentral.com/articles/10.1186/s13054-014-0565-2.
32. Dosne A-G, Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. J Pharmacokinet Pharmacodyn [Internet]. 2017;44:509–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28887735.
33. Post TM, Freijer JI, Ploeger BA, Danhof M. Extensions to the Visual Predictive Check to facilitate model performance evaluation. J Pharmacokinet Pharmacodyn [Internet]. 2008;35:185–202. Available from: http://link.springer.com/10.1007/s10928-007-9081-1.
34. Shekar K, Fraser JF, Smith MT, Roberts JA. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care [Internet]. Elsevier Inc.; 2012;27:741.e9-741.e18. Available from: http://dx.doi.org/10.1016/j.jcrc.2012.02.013.
35. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res [Internet]. 2018;46:D1074–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29126136.
36. Donadello K, Antonucci E, Cristallini S, Roberts JA, Beumier M, Scolletta S, et al. β-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: A case–control study. Int J Antimicrob Agents [Internet]. Elsevier B.V.; 2015;45:278–82. Available from: http://dx.doi.org/10.1016/j.ijantimicag.2014.11.005.
37. Mohd Hafiz A-A, Staatz CE, Kirkpatrick CMJ, Lipman J, Roberts JA. Continuous infusion vs. bolus dosing: implications for beta-lactam antibiotics. Minerva Anestesiol [Internet]. 2012;78:94–104. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21730935.
38. Bauer KA, West JE, O'Brien JM, Goff DA. Extended-Infusion Cefepime Reduces Mortality in Patients with Pseudomonas aeruginosa Infections. Antimicrob Agents Chemother [Internet]. 2013;57:2907–12. Available from: http://aac.asm.org/lookup/doi/10.1128/AAC.02365-12.
39. Kuti JL, Nightingale CH, Knauft RF, Nicolau DP. Pharmacokinetic properties and stability of continuous-infusion meropenem in adults with cystic fibrosis. Clin Ther. 2004;26:493–501.
40. Roberts JA, Kirkpatrick CMJJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: Intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother [Internet]. J Antimicrob Chemother; 2009 [cited 2020 Aug 28];64:142–50. Available from: https://academic.oup.com/jac/article/64/1/142/754903.
41. Berthoin K, Le Duff CS, Marchand-Brynaert J, Carryn S, Tulkens PM. Stability of meropenem and doripenem solutions for administration by continuous infusion. J Antimicrob Chemother [Internet]. 2010;65:1073–5. Available from: https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/dkq044.
42. Patel PR, Cook SE. Stability of meropenem in intravenous solutions. Am J Heal Pharm [Internet]. American Society of Health-Systems Pharmacy; 1997 [cited 2020 Aug 28];54:412–21. Available from: https://academic.oup.com/ajhp/article/54/4/412/5155238.
43. Viaene E, Chanteux H, Servais H, Mingeot-Leclercq M-P, Tulkens PM. Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother [Internet]. American Society for Microbiology Journals; 2002 [cited 2020 Aug 28];46:2327–32. Available from: http://aac.asm.org/.

44. Venugopalan V, Manigaba K, Borgert SJ, Cope J, Peloquin CA, Klinker KP. Training a Drug to Do New Tricks: Insights on Stability of Meropenem Administered as a Continuous Infusion. Microbiol Insights [Internet]. 2018;11:117863611880454. Available from: http://journals.sagepub.com/doi/10.1177/1178636118804549.

Figures

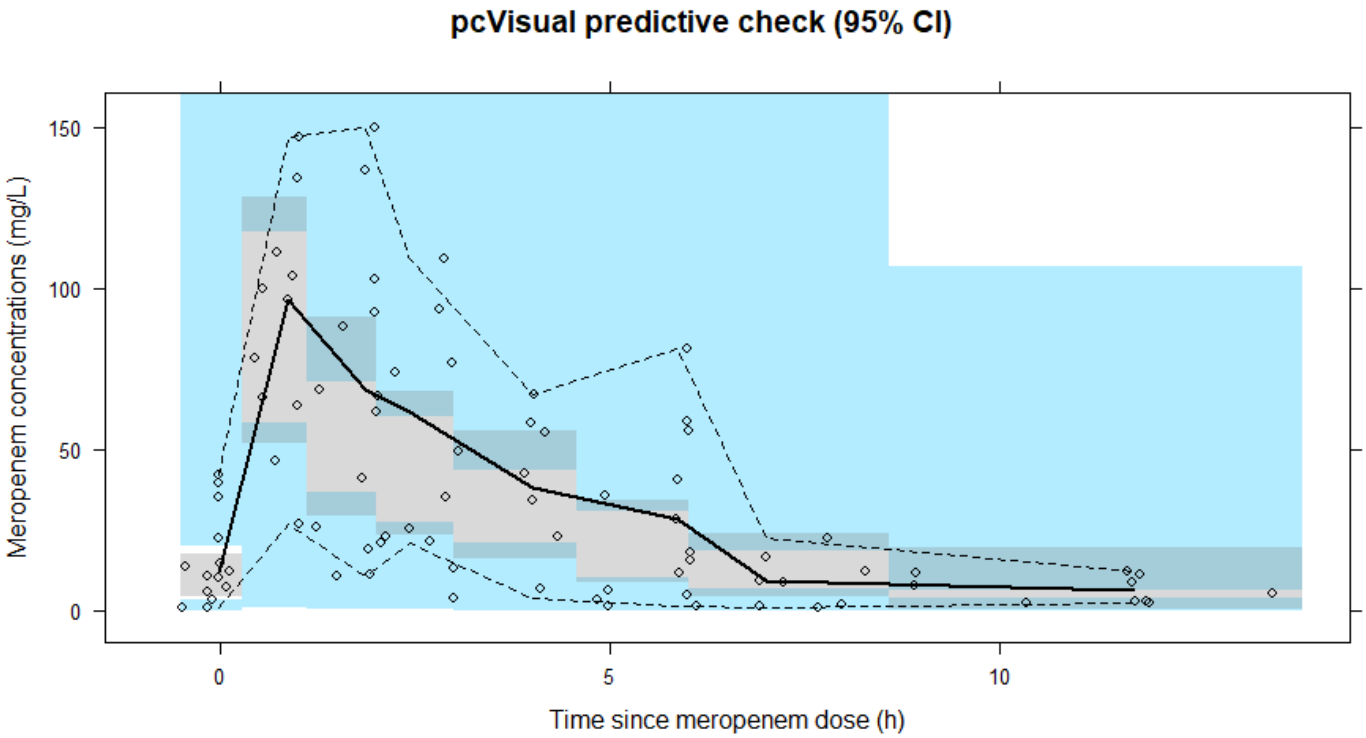

Figure 1

Prediction-corrected visual predictive check plot The prediction-corrected visual predictive check plot shows that the 5th to 95th percentiles of the predicted data overlap most of the observed data based on time since meropenem dose. Open diamonds, plasma meropenem 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 percentile, and 95th percentile constructed from 5,000 simulated data sets of individuals from the original data set.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- Additionalfile2.docx