Pharmacokinetics of Imipenem in Critically Ill Patients with Life-threatening Severe Infections During Support with Extracorporeal Membrane Oxygenation

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Abstract

Background Extracorporeal membrane oxygenation (ECMO) has become increasingly used for lifesaving respiratory and/or cardiac failure support in critically ill patients, including those with life-threatening severe infections. This cardiopulmonary bypass device has been shown to enhance the profound pathophysiological changes in this patient population, resulting in an alteration of the pharmacokinetics of antimicrobial agents.

Objective The aim of this study was to determine the effect of ECMO on the pharmacokinetics of imipenem in critically ill patients supported by this cardiopulmonary bypass device.

Methods The study was conducted in critically ill patients with respiratory and/or cardiac failure and severe infections who were supported by ECMO. All patients received a 1-h infusion of 0.5 g of imipenem every 6 h and imipenem pharmacokinetics studies were carried out on the fourth dose of drug administration.

Results Ten patients were enrolled in this study. The pharmacokinetics parameters of imipenem were found to be highly variable. The volume of distribution, total clearance, elimination half-life and the area under the concentration–time curve between 0 and 6 h were 33.38 ± 13.89 L, 9.99 ± 10.47 L/h, 12.01 ± 29.63 h and 88.93 ± 54.07 mg•h/L, respectively.

Conclusions Pathophysiological changes in critically ill patients with severe infections during support with ECMO had a greater impact on altered pharmacokinetic patterns of imipenem than those that occur in critically ill patients without ECMO support. Therefore, the largest licensed dose, 1 g every 6 h, of imipenem, may be required to maintain adequate drug concentrations to achieve the pharmacokinetic/pharmacodynamic targets for effective antimicrobial therapy in this patient population.

Key Points

Pathophysiological changes in critically ill patients with severe infections during support with ECMO had a greater impact on altered pharmacokinetic patterns of imipenem than those that occur in critically ill patients without ECMO support.

The largest licensed dosage of imipenem may be required to maintain adequate drug concentrations in this patient population.

1 Introduction

Extracorporeal membrane oxygenation (ECMO), a cardiopulmonary bypass device, has been increasingly used in critical conditions for severely ill patients in intensive care units (ICU). ECMO is a temporal lifesaving system that can provide partial or complete support for patients with respiratory and/or cardiac failure for whom conventional treatments have been unsuccessful [1, 2]. One of the big challenges for physicians who take care of these patients is that ECMO has been shown to enhance the profound pathophysiological changes in these critical patients, leading to alterations in the pharmacokinetics of many therapeutic drugs, including increased volume of distribution (V_d) and decreased total clearance (CL) of various important antimicrobial agents for the treatment of severe infections [1–4]. However, studies on the impact of ECMO on the pharmacokinetics of antimicrobial agents have usually been done in pediatric populations, resulting in difficulties

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extrapolating the data for use in adult populations due to significant differences in absorption, distribution, metabolism and excretion of therapeutic drugs between these two populations [1–3].

Imipenem, a hydrophilic β -lactam antibiotic, has a relatively low V_d at steady state and has been found to be < 10 to 20% bound to proteins. This agent has been found to be eliminated by renal clearance, primarily via glomerular filtration and tubular secretion, with an elimination half-life of approximately 1 h [5, 6]. Imipenem, a broad spectrum carbapenem, is commonly prescribed for treatment of nosocomial infections involving highly resistant pathogens [5, 6]. In common with other β -lactams, this drug exhibits primarily time-dependent antimicrobial activity, and the pharmacodynamic index that best correlates with antimicrobial activity is the exposure time during which the free drug concentration remains above the minimal inhibitory concentration (MIC) ($fT_{>MIC}$) of the pathogen [7, 8]. However, to date, there have been limited pharmacokinetic studies of antimicrobial agents, especially imipenem, in these critical conditions [1, 9]. Therefore, the aim of this study was to determine the effect of ECMO on the pharmacokinetics of imipenem in critically ill adult patients supported by this cardiopulmonary bypass device.

2 Patients and Methods

2.1 Study Population and Design

The study was conducted in critically ill patients with respiratory and/or cardiac failure and severe infections admitted into the ICU of Songklanagarind Hospital, the largest tertiary care center in southern Thailand, between December 2015 and February 2019. Included patients were aged ≥ 18 years with cardiopulmonary failure and were supported by ECMO receiving a 1-h infusion of 0.5 g imipenem/cilastatin diluted in 100 mL of normal saline solution, delivered via infusion pump at a constant flow rate, every 6 h for the treatment of severe infections for 14 days. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital, and written informed consent was obtained from each subject's legally acceptable representative before enrollment.

2.2 Drugs and Chemicals

Imipenem/cilastatin (Tienam[®]) was purchased from MSD, Thailand. Imipenem standard powder was purchased from the U.S. Pharmacopeia (Rockville, MD, USA) as pure powder. All the solvents were of high-performance liquid chromatography (HPLC) grade.

2.3 Blood Sampling

The imipenem pharmacokinetic studies were carried out during administration of the fourth dose of imipenem (18–24 h after the start of the regimen) in the ICU with the air conditioning at an average temperature of 25 °C. Blood samples (~3 mL) were obtained from a heparinized intravascular catheter (on the side of the body opposite that used for administration of the study drug) by direct venipuncture at the following times: before (time zero) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 h after the fourth dose of each regimen. The blood samples were added to a heparinized tube and centrifuged at 1000 g for 10 min not later than 15 min after collection. An equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v) was added to each plasma sample [10, 11], which was then vortexed and stored at –80 °C until analysis within 1 week.

2.4 Imipenem Assay

This assay was used for measuring imipenem concentrations only, not for cilastatin concentrations. The concentrations of imipenem were determined by reverse-phase HPLC. The samples were prepared by the method of Garcia-Capdevila et al. [10]. Briefly, 250 μ L of the stabilizing solution was added to 250 μ L of the sample. The mixture was then subjected to ultrafiltration, using an Ultrafree[®]-MC Centrifugal Filter Unit, for 10 min at 6000 g. An aliquot of the sample (50 μ L) was injected onto a Nova-Pak C18 column (Waters Associates) using an automated injection (Waters e2695 Plus autosampler; Waters associates, Milford, MA, USA). The mobile phase used 0.2 M borate buffer, pH 7.2, at a flow rate of 1 mL/min. The column effluent was monitored by a photodiode array detector (Waters 2996; Waters associates, Milford, MA, USA) at 300 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The validation tests were found to be within acceptable limits as per the 2013 US Food and Drug Administration Guidance on Bioanalytical Method Validation [12]. The lower limit of quantitation (LLOQ) of imipenem was 0.25 mg/L. This assay was found to be selective as no interference was found with biological matrix on six individual blank plasma. The method was found to be linear in the concentration range of 0.25–100 mg/L by following the regression equation $y = 13558X + 2303.3$ with correlation coefficients (r^2) of 0.9997. The intra-assay reproducibility values characterized by coefficients of variation (CVs) were 0.19%, 0.71% and 0.11% for samples containing 0.75, 20 and 75 mg/L, respectively. For intra-assay, the relative biases were 0.44%, 1.57%, and 0.36% for samples

containing 0.75, 20, and 75 mg/L, respectively. The inter-assay reproducibility precision values, calculated by CVs, were 0.39%, 1.63% and 0.23% for samples containing 0.75, 20 and 0.75 mg/L, respectively. For inter-assay, the relative biases were 0.38%, 2.47%, and 0.33% for samples containing 0.75, 20, and 75 mg/L, respectively. A short-term stability study showed that at room temperature for sample containing 0.75 and 75 mg/L, the concentrations of imipenem losses were < 1% for at least 1 h. A long-term stability study showed that at -80°C for sample containing 0.75 and 75 mg/L, the concentrations of imipenem losses were < 5% for at least 14 days. All plasma samples were tested within 7 days of collection and analyzed within 1 h after thawing process. The recovery values were $98.67 \pm 0.57\%$, $94.71 \pm 2.00\%$ and $102.70 \pm 1.15\%$ for sample containing 0.75, 20, and 75 mg/L, respectively. Carry-over testing was performed, but no-carry over was found.

2.5 Pharmacokinetics and Statistical Analysis

Pharmacokinetics analysis was conducted using two-compartmental pharmacokinetic analysis. The maximum plasma concentrations ($C_{\max}$), minimum plasma concentrations ($C_{\min}$), area under the concentration–time curve between 0 and 6 h (AUC_{0-6}), distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), V_d , CLs, the rate at which the drug leaves the system from the central compartment (k_{10}), intercompartment transfer rate constant from compartment X1 to X2 (k_{12}) and intercompartment transfer rate constant from compartment X2 to X1 (k_{21}) were determined using Win-Nonlin Version 1.1 (Scientific Consulting Inc., NC, USA). The results were expressed as mean $\pm$ standard deviation. The relationships between the pharmacokinetic parameters and clinical covariates, including sex, age, body-weight, body mass index, serum albumin, creatinine clearance (CL_{Cr}), acute physiology and chronic health evaluation II (APACHE II) score, sepsis-related organic failure assessment (SOFA) score, fluid balance, concomitant medications and flow rate of ECMO circuit were analyzed. The mean pharmacokinetic parameters of imipenem of all patients were compared to values obtained from critically ill patients without ECMO from our 3 previous studies in 18 critically ill patients [13–15] and to values obtained from our previous study in 8 healthy volunteers [16] at the same dosage regimen, using the t test. For the critically ill patients without ECMO group, the two-compartmental pharmacokinetic analysis was conducted using the data from our 3 previous studies in 13 critically ill patients with VAP [13, 14] and 5 serious bacteremia in immunocompromised patients with febrile neutropenia [15]. The p values of < 0.05 were considered to be significant.

3 Results

The demographic data of all patients are shown in Table 1 and the demographic data of the critically ill patients without ECMO (the control group) are shown in Table 2. The ECMO characteristics of all patients are shown in Table 3. The mean imipenem pharmacokinetic parameters are shown in Table 4. The individual plasma concentration–time profiles of imipenem of all patients are shown in Fig. 1. The plasma concentration values of imipenem of all patients characterized by CVs were 76.42%, 50.32%, 66.15%, 67.60%, 61.36%, 46.68%, 48.71%, 58.86%, 71.46% and 71.62% at the following times: before (time zero) and 0.25, 0.5, 0.75, 1, 2, 3, 4, 5 and 6 h after the fourth dose of each regimen, respectively. The V_d , CL, $t_{1/2\beta}$ and AUC_{0-6} were 33.38 ± 13.89 L, 9.99 ± 10.47 L/h, 12.01 ± 29.63 h and 88.93 ± 54.07 mg•h/L, respectively. The CL_{Cr} as estimated by the Cockcroft and Gault equation and APACHE II scores were significant covariates describing the CL and k_{10} of imipenem, whereas SOFA score was significant covariate explaining $t_{1/2\beta}$, k_{10} , and $C_{\min}$, of imipenem. There were no significant covariates that explained the V_d of imipenem. Among the ten enrolled patients, the plasma concentrations at 2.4 h after the fourth dose of imipenem of all patients were ≥ 2 mg/L and nine patients were ≥ 4 mg/L, while, the trough concentrations of imipenem in eight patients were ≥ 2 mg/L and four patients were ≥ 4 mg/L.

4 Discussion

Alteration of pathophysiological conditions in critically ill patients with life-threatening severe infections causes pharmacokinetic changes, including V_d and CL for antibiotics. An extravasation of a large volume of fluid resuscitation into extravascular spaces, associated with endothelial damage and subsequently enhanced capillary permeability, results in a larger V_d than the values obtained from healthy volunteers. In addition, the initial hyperdynamic state of severe infection is associated with a high cardiac output and increased renal blood flow, resulting in enhancement of renal clearance of antimicrobial agents. On the other hand, however, decreased renal clearance with end-organ dysfunction may occur with severe infections and septic shock in late-state disease [17–19]. In critically ill patients with severe sepsis being supported by ECMO, the enhancement of pharmacokinetic changes of antimicrobial agents can occur as a result of the patient's altered pathophysiological condition by this life-support modality and the extent of drug loss due to direct extraction by the circuit which depends primarily on the physicochemical properties of the antibiotics and the circuit component materials [1–3, 20]. However, most

Table 1 Demographic data of 10 critically ill patients with severe infections during support with extracorporeal membrane oxygenation

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _{Cr} (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
1	M	60	67	25.22	128.35	1.9	Squa. cell CA of lung, ARDS, septic shock, malaria, post pneumonec- tomy	VAP	<i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>	27	11	Norepinephrine, colistin, ceftazidime, dornicum, fentanyl, furosemide, omeprazole
2	M	45	54	18.04	42.41	1.9	RHD, severe MR, severe TR, CHF, AF cardio- genic shock, septic shock, cardiac arrest, CBD stone, hyper- thyroidism	CRBSI	Suspected GNB	28	17	Adrenaline, dopamine, norepinephrine, vancomycin, atropine, cordarone, fentanyl, omeprazole, hydrocortisone, methimazole
3	F	54	65	27.14	71.18	1.8	STEMI, cardiogenic shock, car- diac arrest, DM, HT, DVT	Ruptured appendicitis	GNB	38	13	Adrenaline, dopamine, norepinephrine, actrapid, aspirin, clopidogrel, cordarone, dornicum, enalapril, fentanyl, furosemide, glipizide, insulatard, isosorbide dinitrate

Table 1 (continued)

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _{Cr} (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
4	F	43	55	28.06	32.13	3.0	Aortic dissection type A, AR, cardiac tamponade, HT	Suspected nosocomial infection	Suspected GNB	43	15	Adrenaline, dopamine, norepinephrine, vancomycin, actrapid, atropine, cefazolin, cordarone, fentanyl, furosemide, hydrocortisone
5	M	67	78	28.65	17.46	2.3	IHD, CHF, cardiogenic shock, pneumothorax, DM, HT, DLP, CKD	VAP	GNB	35	17	Dopamine, norepinephrine, actrapid, aspirin, cordarone, clonidogrel, fentanyl, furosemide
6	M	53	60	23.44	22.24	2.4	Brugada syndrome with respiratory failure, CHF, cardiogenic shock, septic shock, ARDS	VAP	<i>A. baumannii</i>	33	20	Adrenaline, dopamine, noradrenaline, vancomycin, aspirin, clonidogrel, midazolam
7	F	40	55	22.03	43.87	1.7	Severe CAP, septic shock, ARDS, acute pyelonephritis	VAP	GNB	42	18	Adrenaline, noradrenaline, doxycycline, oseltamivir, azithromycin, actrapid, adenocor, cordarone, furosemide, hydrocortisone

Table 1 (continued)

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _{Cr} (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
8	F	37	73	28.52	150.45	2.5	SVC obstruction, Horner's syndrome, desmoid type fibromatosis, DM, severe tracheal stenosis, septic shock	Aspiration pneumonia	GNB	19	13	Noradrenaline, piperacillin/tazobactam, dexamethasone, metformin
9	M	18	55	19.03	144.75	3.0	Severe neck and thoracic abdominal injury, pneumothorax, cardiac arrest, post pneumonectomy	VAP	<i>P. aeruginosa</i> , <i>A. baumannii</i>	26	12	Norepinephrine, ciprofloxacin, colistin, fosfomycin, fentanyl, furosemide
10	M	55	70	24.22	110.19	2.2	Severe CAP with respiratory failure, PE, ARDS, DVT	VAP	GNB	25	10	Norepinephrine, ceftriaxone, oseltamivir, azithromycin, atracurid, fentanyl, morphine
Mean ± SD		–	47.20 ± 13.85	63.20 ± 8.66	24.43 ± 3.83	76.30 ± 52.28	2.27 ± 0.47	–	–	31.60 ± 7.89	14.60 ± 3.31	–

AF atrial fibrillation, *APACHE* acute physiology and chronic health evaluation, *AR* aortic regurgitation, *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *BW* body weight, *CAP* community-acquired pneumonia, *CBD* common bile duct, *CHF* congestive heart failure, *CKD* chronic kidney disease, *CL_{Cr}* creatinine clearance, *CRBSI* catheter-related bloodstream infection, *DLP* dyslipidemia, *DM* diabetes mellitus, *DVT* deep vein thrombosis, *F* female, *GNB* Gram-negative bacilli, *HT* hypertension, *IHD* ischemic heart disease, *M* male, *MR* mitral regurgitation, *PE* pulmonary embolism, *RHD* rheumatic heart disease, *SD* standard deviation, *SOFA* sepsis-related organ failure assessment, *Squa. cell CA* squamous cell carcinoma, *STEMI* ST-segment elevation myocardial infarction, *SVC* superior vena cava, *TR* tricuspid regurgitation, *VAP* ventilator-associated pneumonia

Table 2 Demographic data of 18 critically ill patients without extracorporeal membrane oxygenation

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _G (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
1	M	60	63	N/A	92.11	3.4	Multiple GSW at neck, chest and abdomen with laceration of liver and small intestine, complete spinal cord injury	VAP	<i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i>	27	6	Vancomycin, cefoperazone/sulbactam, ciprofloxacin, ceftriaxone, ceftazidime, amikacin, actrapid
2	M	77	55	21.45	102.21	2.8	Lymphoma, HT, SIADH	VAP	<i>P. aeruginosa</i>	27	N/A	Piperacillin/tazobactam, ceftriaxone, vancomycin
3	M	86	60	24.97	N/A	N/A	N/A	VAP	GNB	N/A	N/A	N/A
4	M	72	75	N/A	133.65	2.9	COPD, old CVA with recent hemorrhagic stroke, HT	VAP	<i>K. pneumoniae</i>	25	4	Piperacillin/tazobactam, aminophylline
5	M	64	78	N/A	82.63	N/A	Severe MS with MVR, mild TR, embolic stroke, AF	VAP	GNB	26	6	Ranitidine, phenytoin, warfarin
6	F	33	51	22.44	96.65	3.7	Coma, MS with MVR	VAP	<i>P. aeruginosa</i>	16	6	Ceftriaxone, amikacin, furosemide, aspirin, warfarin
7	M	62	68	N/A	124.86	2.4	CA lung	VAP	<i>K. pneumoniae</i>	13	2	Clindamycin, ceftriaxone, ampicillin, morphine
8	M	58	82	31.44	91.00	1.8	Gouty arthritis, COPD, HT, DVT	VAP	<i>P. aeruginosa</i>	16	5	Metoclopramide, omeprazole, warfarin

Table 2 (continued)

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _G (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
9	M	58	69	24.19	61.97	N/A	Ischemic heart disease, HT	VAP	GNB	12	3	Vancomycin, furosemide, nifedipine, aspirin
10	F	39	63	23.42	159.83	2.1	Ruptured cerebral aneurysm	VAP	<i>Moraxella catarrhalis</i>	29	7	Piperacillin/tazobactam, fentanyl, phenytoin
11	M	62	33	12.27	132.41	1.8	Bronchiectasis	VAP	<i>P. aeruginosa</i>	17	4	Ceftazidime, omeprazole, fentanyl, diazepam
12	F	61	62	25.81	94.79	2.2	Multiple traumatic bone fracture with septic shock	VAP	<i>P. aeruginosa</i>	21	N/A	Cefazolin, ceftazidime, furosemide, morphine, omeprazole, warfarin
13	F	44	43	15.79	157.20	N/A	Esophagegocutaneous fistula	VAP	<i>K. pneumoniae</i> , <i>Stenotrophomonas maltophilia</i>	14	N/A	Vancomycin, gentamicin, furosemide, nifedipine, fentanyl, aminophylline, aspirin
14	M	68	87	33.15	113.77	2.9	PTCL with neutropenia	Bacteremia	<i>Escherichia coli</i>	25	4	Filgrastim, doxorubicin, cyclophosphamide, vincristine, prednisolone
15	F	19	48	22.93	186.09	4.3	AML with neutropenia	Bacteremia	<i>K. pneumoniae</i>	20	5	Cytarabine, idarubicin, filgrastim
16	F	18	74	30.33	241.57	4.3	AML with neutropenia	Bacteremia	<i>E. coli</i>	22	4	Vancomycin, filgrastim, cytarabine
17	M	39	64	23.58	95.81	3.6	ALL with neutropenia	Bacteremia	<i>P. aeruginosa</i>	14	4	Co-trimoxazole, dexamethasone, cytarabine, vincristine

Table 2 (continued)

Patient no.	Sex	Age (year)	BW (kg)	BMI (kg/m ²)	CL _G (mL/min)	Serum albumin (g/dL)	Comorbidities	Source of infection	Pathogens	APACHE II score	SOFA score	Concomitant medications
18	F	59	51	23.78	51.58	4.2	MM with neutropenia	Bacteremia	<i>E. coli</i>	19	4	Co-trimoxazole, dexamethasone, cyclophosphamide, doxorubicin, vincristine, mesna, filgrastim
Mean ± SD	–	54.39 ± 18.71	62.56 ± 14.08	24.00 ± 5.56	118.71 ± 47.20	3.03 ± 0.90	–	–	–	20.18 ± 5.57	4.57 ± 1.34	–

AF atrial fibrillation, ALL acute lymphoblastic leukemia, AML acute myeloid leukemia, APACHE acute physiology and chronic health evaluation, BMI body mass index, BW body weight, CA cancer, CL_{cr} creatinine clearance, COPD chronic obstructive pulmonary disease, CVA cerebrovascular accident, F female, DVT deep vein thrombosis, GNB Gram-negative bacilli, GSW gunshot wound, HT hypertension, M male, MM multiple myeloma, MS mitral stenosis, MVR mitral valve replacements, N/A not available, PTCL peripheral T-cell lymphoma, RHD rheumatic heart disease, SD standard deviation, S/ADH syndrome of inappropriate secretion of antidiuretic hormone, SOFA sepsis-related organ failure assessment, TR tricuspid regurgitation, VAP ventilator-associated pneumonia

of the previous studies supporting these findings in critical settings with ECMO support, were conducted in neonatal populations [1, 2]. Several pharmacokinetic studies in adult populations have reported that V_d and CL were unchanged when compared to values obtained from critically ill patients without ECMO [1, 21, 22]. Ex vivo studies have demonstrated that highly lipophilic and protein-bound antibiotics are prone to increased sequestration when subjected to an ECMO circuit. However, imipenem has been found to be a hydrophilic and low protein-binding antimicrobial agent [20]. Therefore, the degree of extraction of imipenem by the circuit may not be markedly high when compared to the highly lipophilic and high protein-bound antimicrobial agents. In addition, imipenem in concentrated solutions has been found to have the greatest instability among the β -lactam antibiotics. A previous study showed that imipenem remained 90% stable for 3 h and 30 min at 25 °C and was degraded by up to 25% within 24 h, at that temperature [23]. Therefore, the stability of imipenem is an important consideration if this agent is being considered for the treatment of severe sepsis in patients being supported by ECMO. Our study found that the plasma concentrations of imipenem characterized by CVs were high (range, 46.68% to 76.42%), resulting in highly variable pharmacokinetic parameters of imipenem. This finding may be due to other variabilities in hypoalbuminemia, renal function, positive fluid balance and the use of inotropic drugs from differing severe comorbidities across the patient population. The mean values of V_d and $t_{1/2\beta}$ were 0.54 ± 0.25 L/kg and 12.01 ± 29.63 h, which were > 3-fold greater than the value obtained from healthy volunteers, but the mean values of CL were not statistically significantly different [16].

A previous case report of trough concentrations of 1 g every 6 h of imipenem in two lung transplant recipients supported with ECMO found the concentrations to be highly variable, 11.3 and 2.7 mg/L, both of which were higher than the MICs of the two isolated microorganisms [9]. The current study was conducted to determine the effect of ECMO on the pharmacokinetics of imipenem in very critically ill patients with life-threatening severe Gram-negative bacilli infections, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. The altered pharmacokinetics of imipenem in the current study were different from previous pharmacokinetic studies in critically ill patients without ECMO support [13–15]. In the current study, the V_d of imipenem was greater and the CL of imipenem was lower than the values obtained from patients without ECMO support [13–15]. A possible explanation for the pharmacokinetic changes in this study would be that all recruited patients had a critical illness complicated by a life-threatening severe infection and half of them had septic shock, resulting in a positive fluid balance in all patients from receiving large volumes of fluid for management of shock and maintaining

Table 3 Characteristics of extracorporeal membrane oxygenation (ECMO) in 10 critically ill patients with severe infections during support with extracorporeal membrane oxygenation

Patient no.	Type	Duration (d)	Indication	Flow rate (L/min)	Fluid balance (L)	Outcome
1	VV	22.00	Respiratory failure	3.5	2.84	Death
2	VA	6.25	Cardiac failure	4.70	9.07	Death
3	VA	7.04	Cardiac failure	3.40	1.66	Clinical improvement
4	VA	1.71	Cardiac failure	1.50	2.90	Death
5	VA	3.46	Respiratory and cardiac failure	2.70	3.75	Death
6	VA	10.58	Respiratory and cardiac failure	3.50	5.30	Death
7	VA	2.00	Respiratory and cardiac failure	3.50	11.51	Death
8	VV	5.04	Respiratory failure	1.80	5.73	Death
9	VV	6.92	Respiratory failure	2.90	5.43	Clinical improvement
10	VV	12.54	Respiratory failure	2.40	4.75	Clinical improvement
Mean $\pm$ SD	–	7.75 $\pm$ 6.08	–	2.99 $\pm$ 0.94	5.29 $\pm$ 3.00	–

d day(s), *h* hour(s), fluid balance fluid intake minus fluid output for 48 h during administration of imipenem, *SD* standard deviation, *VA* venoarterial ECMO, *VV* venovenous ECMO

Table 4 Pharmacokinetic parameters (mean $\pm$ SD) of imipenem in 10 critically ill patients with severe infections during support with extracorporeal membrane oxygenation (ECMO) compared with 18 critically ill patients without ECMO and 8 healthy volunteers

Pharmacokinetic parameter	Patients with ECMO	Patients without ECMO ^b	Healthy volunteers ^c
$C_{\max}$ (mg/L)	24.37 $\pm$ 14.45	15.86 $\pm$ 5.77	48.43 $\pm$ 5.89 ^a
$C_{\min}$ (mg/L)	4.78 $\pm$ 3.78	0.69 $\pm$ 0.79 ^a	0.62 $\pm$ 0.31 ^a
AUC ₀₋₆ (mg·h/L)	88.93 $\pm$ 54.07	28.17 $\pm$ 13.92 ^a	–
$t_{1/2\alpha}$ (h)	0.92 $\pm$ 2.47	0.28 $\pm$ 0.31	–
$t_{1/2\beta}$ (h)	12.01 $\pm$ 29.63	7.37 $\pm$ 24.31	1.32 $\pm$ 0.27 ^a
V_d : total (L)	33.38 $\pm$ 13.89	21.32 $\pm$ 15.01 ^a	9.41 $\pm$ 1.44 ^a
V_d : per body weight (L/kg)	0.54 $\pm$ 0.25	0.39 $\pm$ 0.45	0.16 $\pm$ 0.02 ^a
CL: total (L/h)	9.99 $\pm$ 10.47	21.49 $\pm$ 9.57 ^a	7.95 $\pm$ 1.04
CL: per body weight (L/h·kg)	0.15 $\pm$ 0.14	0.39 $\pm$ 0.30 ^a	0.14 $\pm$ 0.02
k_{10} (h ⁻¹)	1.90 $\pm$ 2.15	1.36 $\pm$ 1.08	0.56 $\pm$ 0.18
k_{12} (h ⁻¹)	7.16 $\pm$ 6.39	4.47 $\pm$ 6.27	–
k_{21} (h ⁻¹)	1.40 $\pm$ 0.98	2.71 $\pm$ 2.23	–

AUC₀₋₆ the area under the concentration–time curve between 0 and 6 h, $C_{\max}$ maximum plasma concentration, $C_{\min}$ minimum plasma concentration, k_{10} , the rate at which the drug leaves the system from the central compartment, k_{12} intercompartment transfer rate constant from compartment X_1 to X_2 , k_{21} intercompartment transfer rate constant from compartment X_2 to X_1 , $t_{1/2\alpha}$ distribution half-life, $t_{1/2\beta}$ elimination half-life, VAP ventilator-associated pneumonia, V_d volume of distribution at steady state

^a $p < 0.05$ versus patients during support with ECMO

^bData from our 3 previous studies in 13 critically ill patients with VAP [13, 14] and 5 serious bacteremia in immunocompromised patients with febrile neutropenia [15]

^cData from our previous study in 8 healthy volunteers [16]

the ECMO circuit flows. All recruited patients had APACHE II scores of ≥ 19 and SOFA scores of ≥ 10 and one-half of them were experiencing renal dysfunction, as defined by CL_{cr} values of ≤ 60 mL/min. Moreover, all enrolled patients had hypoalbuminemia due to decreased protein synthesis in the liver and were receiving several concomitant medications, particularly inotropic agents for the treatment of shock. Studies in animal infection models have found that bactericidal effects of carbapenems against *Escherichia coli*

and *P. aeruginosa* in a murine thigh infection model were observed when plasma drug concentrations were above the MIC for 40% of the dosing interval [24]. However, for life-threatening severe infections in immunocompromised hosts, the $fT_{>MIC}$ target required for sufficient bactericidal effects are increased to almost 100% [25–27]. By referral to the European Committee on Antimicrobial Susceptibility Testing MIC distributions, the epidemiological cut-offs for *P. aeruginosa* and *A. baumannii* were 4 and 1 mg/L,

Fig. 1 The individual plasma concentration–time profiles of imipenem in 10 critically ill patients with severe infections during support with extracorporeal membrane oxygenation. The broken lines represent the MICs of 2 and 4 mg/L. *MIC* minimal inhibitory concentration, $T_{>MIC}$ time during which the drug concentration remains above the MIC

respectively. By referral to the Clinical and Laboratory Standards Institute, the MIC breakpoints for *P. aeruginosa* and *Acinetobacter* spp. were 4 and 2 mg/L, respectively. In the current study, we found that the plasma concentrations of imipenem 40% $T_{>MIC}$ for MICs of 2 and 4 mg/L and 100% $T_{>MIC}$ for a MIC of 2 mg/L could be achieved in most patients, whereas only some patients could achieve 100% $T_{>MIC}$ for a MIC of 4 mg/L. Therefore, high dosage recommendation of imipenem should be required for coverage of highly resistant microorganisms in life-threatening severe infections during support with ECMO.

The current study had a few limitations that must be considered. First, the number of enrolled patients was small and not case–control matched with critically ill patients without ECMO support. Therefore, further large, well-designed clinical trials to determine the effect if any of ECMO on the pharmacokinetic parameters of imipenem in this patient population are required. Second, the population pharmacokinetics of imipenem were not analyzed and a Monte Carlo simulation was not performed to determine the effects of different dosing approaches.

5 Conclusion

Pathophysiological changes in critically ill patients with severe infections during support with ECMO had a greater impact on altered pharmacokinetic patterns of imipenem than those that occur in critically ill patients without ECMO

support. Therefore, the largest licensed dose, 1 g every 6 h, of imipenem, may be required to maintain adequate drug concentrations to achieve the pharmacokinetic/pharmacodynamic targets for effective antimicrobial therapy in this patient population.

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Compliance with Ethical Standards

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Conflicts of interest Sutep Jaruratanasirikul, Veerapong Vattanavanit, Maseetoh Samaeng, Monchana Nawakitrangsan and Somchai Sriwiriyanjan have no conflicts of interest that are relevant to the content of this paper.

Ethical approval All procedures performed in studies involving human participants were in accordance with the study protocol, the Ministerial Ordinance on GCP for Drugs, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol (code EC-56-065-14-1-1) was approved by the IRB at Songklanagarind Hospital on 17 December 2012.

Informed consent Informed consent was obtained from each subject's legally acceptable representative before enrollment.

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