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NONMEM population pharmacokinetic and Monte Carlo dosing simulation of ertapenem in patients with sepsis

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An alteration of pharmacokinetics (PK) due to pathophysiological changes in patients with critical illnesses have the impact on the drug levels in plasma, consequently affecting the achievement of pharmacodynamics (PD) targets of antibiotics. The objectives of this study were (i) to determine the population PK, and (ii) to assess the probability of target attainment (PTA) of ertapenem in patients with critical conditions. The study examined the population PK of ertapenem using NONMEM and performed the assessment of the PTAs of achieving 40 and 80% of the time that the free drug level exceeds over the MIC ($fT_{>MIC}$). The central and peripheral volumes of distribution were 49 (with the %CV of 67.10) and 91.90 (with the %CV of 78.90) L, respectively, and total clearance of ertapenem was 15.40 (with the %CV of 46.80) L/h. Our PD analysis for achieving a target of 40% $fT_{>MIC}$ in patients with normal renal function, the dosing of 1 g once daily can cover a MIC of 0.5 mg/L and for a higher minimum inhibitory concentration (MIC) of 1 mg/L, the dosing should be increased to 2 g once daily. Moreover, the achievements of PTAs in patients with lower GFRs were greater than those of PTAs in patients with higher GFRs. In conclusion, higher than maximum recommended dosing of ertapenem may be required for achieving the PD targets in septic patients with critical illnesses; however, in renal impaired patients the required dosage regimens may be lower than recommended dosing.

Key words: Pharmacokinetics, pharmacodynamics, ertapenem, sepsis, Monte Carlo simulation.

INTRODUCTION

The worldwide spread of antibiotic-resistant bacteria remain a crucial public health concern resulting in increased mortality and morbidity rates and health care costs in patients with critical illnesses (Manyahi et al.,

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2020; Santoro et al., 2020; Serra-Burriel et al., 2020). The 2019 antibiotic resistance threats study by Centers for the Disease Control and Prevention of the United States reported that more than 2.8 million patients were infected with antibiotic-resistant pathogens causing more than 35,000 deaths in this year (CDC, 2019). Extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* has been increasingly found over the last 2 decades in both community and hospital settings and spreading rapidly throughout the world (Doi et al., 2017). ESBLs have been found to be the enzymes responsible for enabling the mechanism of drug resistance of these microorganisms, resulting in resistance to several β-lactam antimicrobial agents such as penicillins, cephalosporins and aztreonam, but not to carbapenems. Therefore, carbapenems are becoming the appropriate antibiotics therapy for these microorganisms (Pitout and Laupland, 2008; Brolund, 2014; Rodríguez-Baño et al., 2018; Gutiérrez-Gutiérrez and Rodríguez-Baño, 2019).

Ertapenem, a carbapenem antibiotic, has a good activity against ESBL-producing *Enterobacteriaceae*, but poor activity against *Pseudomonas aeruginosa* and *Acinetobacter*. This agent can be used via once a day dosing due to its high protein binding, resulting in long elimination half-life. Ertapenem has been licensed in the United States and Europe for several indications. The standard dosage regimen of 1000 mg intravenous of ertapenem has low side effects (Curran et al., 2003; Zhanel et al., 2005; Burkhardt et al., 2007; Doi, 2020). Ertapenem is the time-dependent antibiotic, and the percentage of time that the free drug level exceeds over the MIC (%$fT_{>MIC}$) is the pharmacodynamics (PD) index that best predicts the killing effect of drug (Bader et al., 2019). However, an alteration of PK due to pathophysiological changes in patients with critical illness has the impact on the plasma concentrations of antibiotics (Bergen et al., 2017; Chai et al., 2020). The objectives of this study were (i) to determine the population PK, and (ii) to assess the probability of target attainment (PTA) of ertapenem in patients with critical illnesses.

MATERIALS AND METHODS

Subjects

This prospective, PK study of ertapenem was undertaken on eleven patients who were admitted to Songklanagarind Hospital during March to December 2019. The inclusion criteria were: (i) patients with sepsis (Singer et al., 2016), and (ii) age >18 years. The exclusion criteria were: (i) pregnancy, (ii) septic shock, (ii) hypersensitivity to β-lactams, and (iv) chronic renal impairment. The severity of illness were assessed by APACHE II and SOFA scores. The study protocol was reviewed and approved by the Ethics Committee of Faculty of Medicine, Prince of Songkla University (Ethical approval: REC 58-372-14-1; Clinical Trials: NCT03859362) and written informed consent was obtained from each participant.

Drugs and chemicals

Ertapenem (Invanz®) was donated from MSD, Ltd, Bangkok, Thailand. Ertapenem and imipenem standard powder were purchased from Sigma-Aldrich (Saint Louis, MO, USA) and U.S. Pharmacopeia (Rockville, MD, USA), respectively.

Study design

All participants received treatment with a 0.5 h infusion, 1 g once daily of ertapenem for 10 days. Ertapenem PK studies were carried out on the 3rd dose of drug administration, and a Monte Carlo simulation (MCS) was performed to assess the efficacy of ertapenem.

Blood sampling

Blood (~5 ml) was drawn via heparinized intravascular catheter at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after the start of the 3rd dose of ertapenem administration. All samples were centrifuged for 10 min at 4°C within 5 min and stored in freezer (-80°C).

Ertapenem assays

The free ertapenem levels were assayed by High Performance Liquid Chromatography (HPLC) with UV detection, at 305 nm (Gordien et al., 2006). The samples were transferred into an ultrafilter and centrifuged at 14,000×g for 10 min at 4°C to separate the unbound drug. A 100 µl aliquot was added with an internal standard (imipenem 25 mg/L in 40 mM phosphate buffer pH 4.0) at a ratio of 1:1. The mixture was vortexed for 30 sec and then 80 µl was injected onto the column. The mobile phase was 10 mM phosphate buffer, pH adjusted to 6.5 with orthophosphoric acid (phase A) and acetonitrile (phase B). A gradient elution program was applied at a flow rate of 1 ml/min as follows: 0-2 min, 94 and 6% for phases A and B, respectively; 2-7 min, 82 and 18%, phases A and B, respectively, and then returned to 94 and 6%, respectively, at 7-10 min. The lower limit of quantitation was 0.25 mg/L. The intra-assay precision values were 1.24, 2.49 and 3.27% for concentrations of 1, 50 and 100 mg/L, respectively. The interassay precision values were 1.24, 2.84 and 3.74% for concentrations of 1, 50 and 100 mg/L, respectively. The accuracy values were 103.26, 97.70 and 95.32% and the recovery values were 102.75, 111.83 and 102.57% for concentrations of 1, 50 and 100 mg/L, respectively.

Population pharmacokinetic analysis

The population PK was analysed using NONMEM® 7.4.3 (Icon Development Solution, Ellicott City, MD, USA) with the aid of Perl-Speaks-NONMEM version 4.9.0 (Uppsala University, Uppsala, Sweden). Pirana program (Certara, Princeton, NJ, USA) was used to capture and display the model development. R program version 3.6.0 along with R Studio version 1.4.1106 were used for data post-processing and visualization. The different structural models, including one-, two- and three disposition compartment models with linear elimination, were investigated to find the best fit for ertapenem concentration-time profiles. The PK parameters were

estimated using a first-order conditional estimation with interaction between eta and epsilon (FOCE-I) method. The inclusion of an interindividual variability (IIV) on PK parameters was implemented using an exponential error model, and covariances between IIV terms were estimated if they showed any significant correlations. An additive, proportional, or combined additive plus proportional error models were considered for residual variability. The shrinkage for each parameter was also assessed, and values of less than 25% were considered acceptable.

After establishing the appropriate structural model, the effects of age, gender, actual body weight, ideal body weight, body mass index, mechanical ventilation, serum albumin, APACHE II score, SOFA score, creatinine clearance calculated by the Cockcroft-Gault equation ($CL_{CR\ (CG)}$) and Jelliffe equation ($CL_{CR(JEL)}$), and glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (GFR_{EPI}) and Modification of Diet in Renal Disease study equation (GFR_{MDRD}) were investigated as potential covariates affecting ertapenem PK parameters. These covariates were incorporated into the structural model using a stepwise covariate modeling algorithm. A covariate was kept in the model if it improved the model fit, as assessed by a reduction in objective function value (OFV) of at least 3.84 units ($P < 0.05$) and an increase of at least 6.64 units ($P < 0.01$) for forward addition and backward deletion procedure, respectively. The model selection was based on the minimum OFV, Akaike Information Criterion (AIC), parameter accuracy, goodness-of-fit plots and various diagnostic plots. A non-parametric bootstrap analysis (n = 2,000) was conducted to ascertain the final model's robustness and to generate confidence intervals of all parameter estimates. In addition, the predictive ability of the final model was also evaluated by a prediction-corrected visual predictive check (n = 2,000).

Pharmacodynamics assessment

Crystal Ball program (version 11.2, Oracle Corporation, Denver, CO, USA) was used for Monte Carlo simulations (MCS) analysis to determine the PTAs of several dosing regimens and duration of infusions of ertapenem. The PK parameters, IIV (including covariance terms), and the uncertainty of each parameter were used for simulating drug levels. As GFR was found to influence ertapenem clearance, the simulated subjects were divided into three different renal function groups (GFR 0-29.99, 30-59.99, 60-120 ml/min). Thereafter, 10,000 virtual subjects were simulated for each dosing regimen and $\%fT_{>MICs}$ (40% and 80% $fT_{>MIC}$) were used as the PK/PD targets for ertapenem.

RESULTS

The important characteristics of patients are summarized in Table 1. The average unbound plasma concentration-time profiles are displayed in Figure 1. Concentrations below the LLOQ value, which represented only 1.7% of the dataset, were imputed with LLOQ/2 value. A total of 119 free plasma concentrations were used for population PK analysis. A two-compartment model with first-order elimination best described the ertapenem concentration-time profiles. A combined additive plus proportional error model were selected to characterize the residual variability. An IIV was assigned to all parameters. However, the IIV of intercompartment clearance (Q) was very low, therefore it was not estimated and was fixed to zero. There were moderate to high correlations between several of the random effects, and therefore covariance terms between the IIV on total clearance (CL), central volume of distribution (V_C) and peripheral volume of distribution (V_P) were estimated, resulting in an 11.3-unit decrease in the Akaike Information Criterion (AIC) compared with the initiating model. After covariate testing, GFR_{EPI} was the only significant covariate describing the clearance of ertapenem. The inclusion of GFR_{EPI} for CL significantly improved the model fit (ΔOFV = -15.2) and reduced the IIV of CL from 68.0% to 46.8%. Of note, GFR_{MDRD}, $CL_{CR\ (CG)}$ and $CL_{CR(JEL)}$ also improved the model fit, but the OFV reduction was less than GFR_{EPI}. There was no significant covariate that explained V_C and V_P. The final population PK parameters of ertapenem are shown in Tables 2, 3 and Supplementary Table 1. All final parameters were estimated with acceptable precision, and the percentages of eta and epsilon shrinkage were low (<10%). The parameters estimated from the final model were similar to the median value and all were within the 95% confidence interval obtained from the bootstrap analysis, indicating the robustness of the final model. The goodness-of-fit plots for the final model showed no apparent bias in model predictions (Figure 2). The pcVPC (Figure 3) also confirmed the good predictive performance of the model, as the observed 5th, 50th, and 95th percentiles were within the 80% confidence intervals for the simulated 5th, 50th, and 95th percentiles at every time point. The PTAs of ertapenem in patients with various ranges of GFR on the 1st and 3rd dose of drug administration are shown in Supplementary Table 2 and Table 4. The PTAs of ertapenem in patients with GFR 60-120 ml/min are shown in Figure 4.

DISCUSSION

A change in pathophysiological condition in patient with sepsis can occur which can also result in PK changes for antibiotics (Taccone et al., 2011; Bergen et al., 2017; Chai et al., 2020). The shifting of fluid used for resuscitation of sepsis from blood vessels into the extravascular space can lead to a greater total volume of distribution (V) compared to those from healthy subjects (Taccone et al., 2011; Varghese et al., 2011). Moreover, end-organ dysfunction, particularly renal impairment due to sepsis, can occur, resulting in decreased renal clearance of antibiotics (Bergen et al., 2017; Chai et al., 2020). Therefore, changes of V and CL of antibiotics for management of sepsis result in unpredictable plasma concentrations and, consequently, unacceptable outcomes. A previous study with burn patients examining PK changes of ertapenem (Dailly et al., 2013) found that the mean values of V were higher than that from normal subjects (Wiskirchen et al., 2013). In our study, the V of

Table 1. Characteristics of the 11 study patients with sepsis[a].

Patient no.	Gender	Age (year)	BMI (kg/m^2)	Serum CR (mg/dL)	GFR_{EPI} (mL/min)	APACHE II score	SOFA score	Fluid balance (L)	Comorbidities	Treatment outcome
1	M	75	18.07	1.00	73.30	16	1	4.17	Crohn's disease, CVA, UGIB, HAP	Bacterial eradication
2	M	60	20.76	2.21	31.22	18	3	2.24	DLP, HT, CVA, DVT, CAP, UGIB	Bacterial eradication
3	M	81	22.58	0.88	80.56	18	2	7.15	SSS, HT, DLP, Parkinson's disease, BPH, MI	Bacterial eradication
4	F	86	22.94	0.66	79.99	20	6	2.73	UGIB, PH, CVA	Bacterial eradication
5	F	66	33.30	0.44	105.19	21	3	0.02	CVA, Cirrhosis, DM, HT, CAP	Bacterial eradication
6	M	64	21.10	0.59	106.99	16	3	3.16	CVA, HT	Bacterial eradication
7	F	85	24.89	1.16	42.90	12	0	1.02	UTI, HT, bilateral renal calculi, complete heart block	Bacterial eradication
8	F	57	29.43	0.37	118.62	12	0	4.25	MI, UTI, DM, CVA	Bacterial eradication
9	M	77	25.35	1.46	45.74	14	1	1.01	HT, DM, DLP, Gout, COPD, UTI	Bacterial eradication
10	M	56	23.88	0.90	95.14	8	2	1.16	CHF, HT, CVA, AF, SIADH	Bacterial eradication
11	M	28	17.10	0.87	117.45	14	2	2.59	DVT, thyroid carcinoma	Bacterial eradication

[a] M, male; F, female; yr, years; BMI, body mass index; CR, creatinine; GFR_{EPI}, estimated glomerular filtration rate using the chronic kidney disease epidemiology collaboration equation; APACHE, acute physiology and chronic health evaluation; SOFA, sepsis-related organic failure assessment; Fluid balance, fluid intake minus fluid output for 48 hours during the administration of ertapenem; CVA, cerebrovascular disease; UGIB, upper gastrointestinal bleeding; HAP, hospital-acquired pneumonia; DLP, dyslipidemia; HT, hypertension; DVT, deep vein thrombosis; CAP, community-acquired pneumonia; SSS, sick sinus syndrome; BPH, benign prostatic hypertrophy; MI, myocardial infarction; PH, pulmonary hypertension; DM, diabetes mellitus; UTI, urinary tract infection; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; AF, atrial fibrillation; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

ertapenem was also found to be higher than that from normal subjects (Wiskirchen et al., 2013). This finding may be explained by noting that our patients had severe illness. In our study, a two-compartment model was the best model for describing the ertapenem concentration-time profiles, which was in accordance with other studies (Zhou et al., 2014; Goutelle et al., 2018). In addition, the binding of a drug to the plasma protein plays a crucial role in antimicrobial activity due to the binding effect on the PK and PD of an antibiotic. The unbound drug is the only fraction of an antibiotic that can penetrate into the infection sites in interstitial tissues or body fluids and correlates with the efficacy of the agent. Changes in plasma protein binding can alter PK parameters, consequently affecting the achievement of PD targets of antibiotics (Zeitlinger et al., 2011; Heuberger et al., 2013; Shah et al., 2015; Onufrak et al., 2016). An *in vivo* microdialysis study found that the free fraction of ertapenem in extravascular space were much lesser than the total drug levels in plasma (Burkhardt et al., 2006). Another study in obese patients found that the average free fraction of ertapenem in interstitial tissues were variable and approximately 50.7 and 75.4%, respectively, of the free drug exposure in plasma (Wittau et al., 2017). Moreover, this drug has been found to have near-linear PK and high protein binding with a range from 92 to 95% (Majumdar et al., 2002; Curran et al., 2003; Zhanel et al., 2005; Burkhardt et al., 2007; Zusman et al., 2015).

Recent studies have reported that the clinical

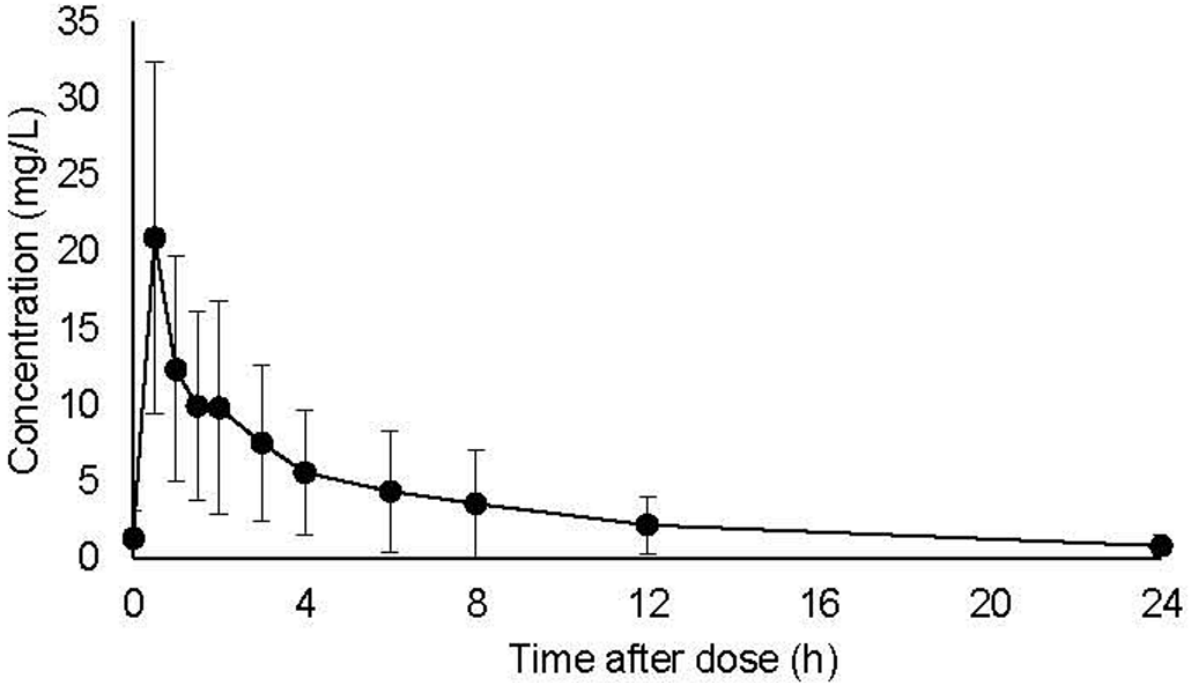

Figure 1. The plots between concentrations (mean ± standard deviation) and time of 1 g every 24 h of ertapenem in 11 patients.

Table 2. Population PK parameters of ertapenem in the 11 study patients with sepsis calculated from the final model[a].

Population PK parameter	Estimate	Interindividual variability (%CV)
CL (L/h)	15.4	46.8
V_C (L)	49.0	67.1
V_P (L)	91.9	78.9
Q (L/h)	29.6	-

[a]CL, total clearance; V_c, central volume of distribution; V_P, peripheral volume of distribution; Q, intercompartment clearance; %CV, percentage of coefficient of variation.

breakpoint of ertapenem against *Enterobacteriaceae* was 0.5 mg/L (CLSI, 2020; EUCAST, 2020). The standard dosing of 1 g once daily of ertapenem has been prescribed for coverage of ESBL-producing *Enterobacteriaceae* in several disease situations. A previous study in morbidly obese patients on this dosing found that the free fraction of ertapenem achieved the PTA of 40% $T_{>MIC}$ for MICs of ≥0.5 mg/L in plasma (Wittau et al., 2017). Previous studies in animal found that for antimicrobial killing effect of β-lactams, the target of 100% $T_{>MIC}$ was unnecessary (Vogelman et al., 1988; Craig, 1995) and bactericidal killing activities of carbapenems were found at the target of 40% $T_{>MIC}$ (Drusano, 2003). Moreover, several clinical studies showed that an extended infusion of β-lactam antibiotics for the treatment of patients with severe infections had lower mortality (Lodise et al., 2007; Shabaan et al., 2017; Vardakas et al., 2018; Yu et al., 2018) and higher rates of clinical improvement (Abdul-Aziz et al., 2016; Shabaan et al., 2017; Yu et al., 2018) and microbiologic eradication (Shabaan et al., 2017) than short-term infusion. Our MCS analysis found that the achievement of the PTAs by the extended infusion of ertapenem were higher compared to the short infusion, findings which were similar to previous studies with other β-lactam antibiotics (Masich et al., 2018; Thabit et al., 2019). Therefore, we believe that a prolonged infusion time of drug administration for this drug should be a good strategy to augment the probability of achieving PK/PD targets and therapeutic outcomes. Our PD analysis for achieving a target of 40%

Table 3. Population PK parameters of ertapenem from the base and final models[a].

Parameter	Base model (MOFV=180.017)		Final model[b] (MOFV = 145.534)		
	Estimate	%RSE	Estimate	%RSE	95% CI of Bootstrap estimate
Fixed-effect parameter					
CL (L/h)	14.7	18.5	15.4	12.7	12.4-19.0
θ_1			0.62	39.7	0.15-1.16
V_C (L)	49.4	20.6	49.0	20.1	32.0-62.9
V_P (L)	84.2	21.4	91.9	22.9	52.2-134.2
Q (L/h)	30.2	17.1	29.6	17.9	19.1-40.1
Interindividual variability (IIV)					
IIV on CL (%CV)	68.0	34.8	46.8	24.9	22.0-55.5
IIV on V_C (%CV)	66.7	32.8	67.1	30.2	41.5-83.2
IIV on V_P (%CV)	80.6	48.9	78.9	40.9	45.1-107.0
IIV on Q (%CV)	NE	-	NE	-	-
Covariance between CL and V_C			0.29	26.9	0.05-0.41
Covariance between CL and V_P			0.31	27.0	0.07-0.44
Covariance between V_C and V_P			0.43	36.2	0.09-0.75
Residual variability					
Proportional (%CV)	19.3	17.1	19.7	17.8	16.0-22.5
Additive (mg/L)	0.15	46.3	0.14	42.7	0.07-0.21

[a]CL, total clearance; θ_1, exponent for GFR_{EPI} as covariate for CL; V_C, central volume of distribution; V_P, peripheral volume of distribution; Q, intercompartment clearance; %CV, percentage of coefficient of variation; MOFV, minimum objective function value; NE, not estimated; %RSE, percentage of relative standard error; CI, confidence interval; GFR_{EPI}, glomerular filtration rate calculated by Chronic Kidney Disease Epidemiology Collaboration. [b]The final PK model parameter: $CL\ (L/h) = 15.4 \times (GFR_{EPI}/82)^{\theta_1}$.

$fT_{>MIC}$ in patients with normal renal function, the dosing of 1 g once daily can cover a MIC of 0.5 mg/L and for a higher MIC of 1 mg/L, the dosing should be increased to 2 g once daily. In immunodeficiency host, the PD targets for achieving the optimal therapeutic outcomes of β-lactams should be nearly 100% $fT_{>MIC}$. A previous study in this patient population found that the achievement of the optimal clinical response of meropenem was occurred when the $\%T_{>MIC}$ were >75% (Ariano et al., 2005). The dosing of 1 g once daily achieved the PTAs for only a MIC of 0.25 mg/L. An increase in ertapenem dosage up to 2 g every 24 h for the treatment of tuberculosis was safe with few adverse effects (Zuur et al., 2018). In addition, we found that the achievements of PTAs in patients with lower GFRs were greater than those of PTAs in patients with higher GFRs. Therefore, the use of ertapenem for treatment of severe infections associated with renal end organ dysfunction requires lower dosage regimens than in patients without end organ dysfunction.

The current study had a notable strength, in that the measured drug concentrations in this study were the free form of ertapenem which is the fraction of drug that correlates to the efficacy of antimicrobial activity. However, the study also had

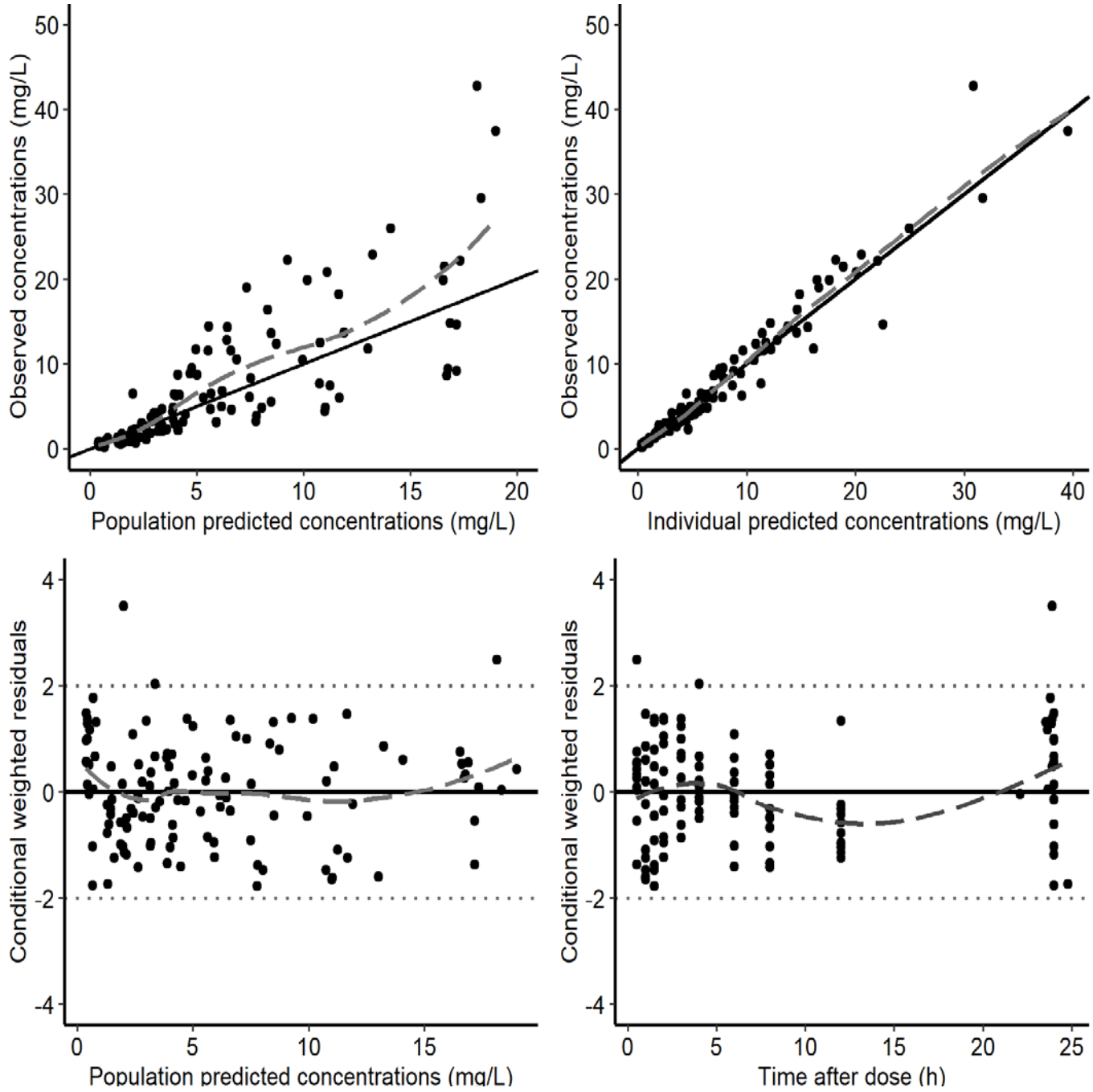

Figure 2. The basic goodness-of-fit plots of the final ertapenem pharmacokinetic model. Solid lines represent the lines of identity, and the dashed lines is the locally weighted scatterplot smoothing lines to indicate trends.

a few notable limitations. First, our study was conducted with the small number of patients. Second, the low-body-weight patients may affect the values of PK, therefore, the results of the study should be extrapolated with caution for using in the general population.

In conclusion, an increased *V* of ertapenem was observed in this study on the pathophysiological changes in septic patients with multiple comorbidities, therefore higher than maximum recommended dosage regimens may be required in this patient group. However, patients with renal end organ dysfunction may require lower-than-recommended dosing. A prospective well-designed study

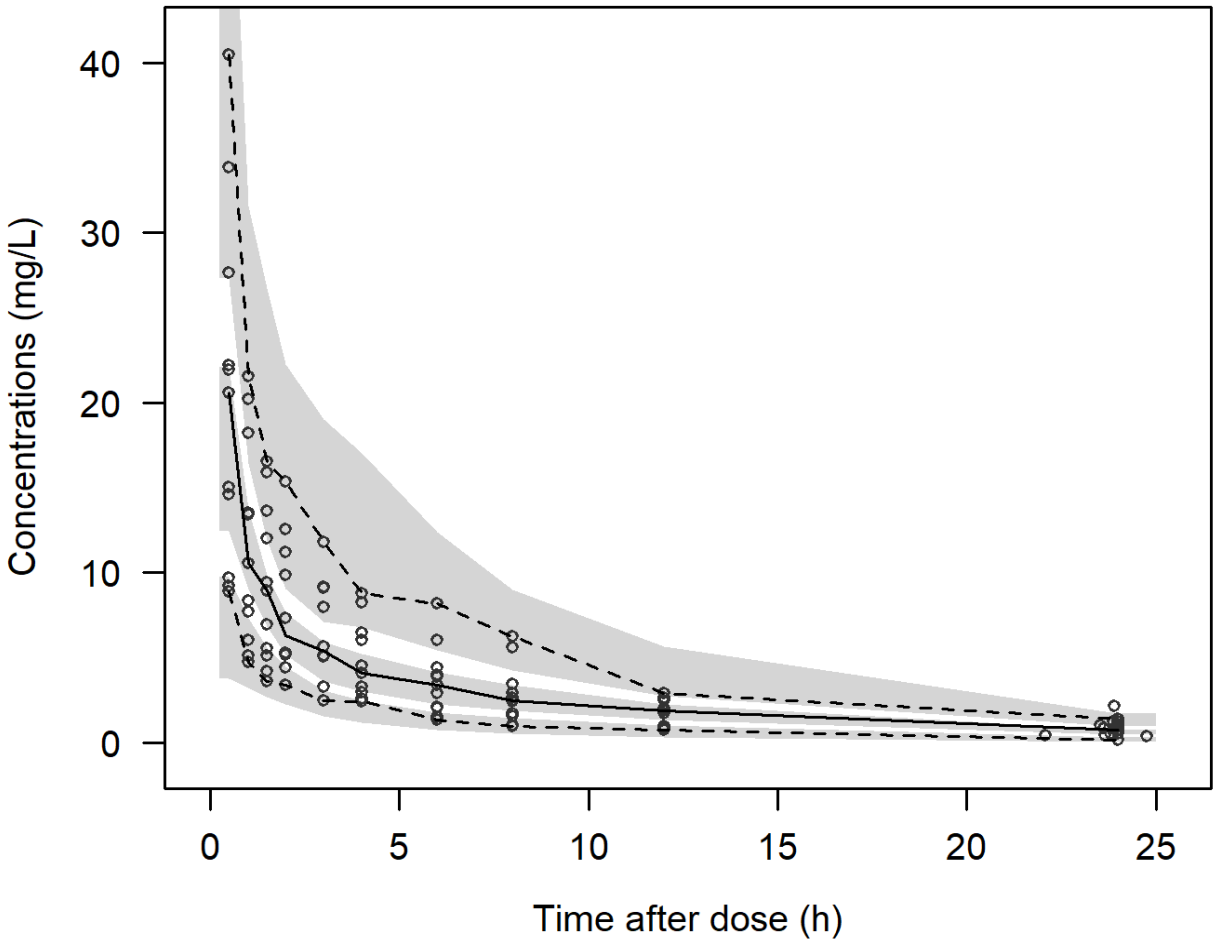

Figure 3. Prediction-corrected visual predictive check (pcVPC) of the final population pharmacokinetic model. Open circles indicate observed concentrations. The solid lines represents the 50th percentiles of the observations, and the dashed lines represent the 5th and 95th percentiles of the observations. The shaded areas are the 80% confidence intervals around the 5th, 50^{th,} and 95th percentiles of the simulated data.

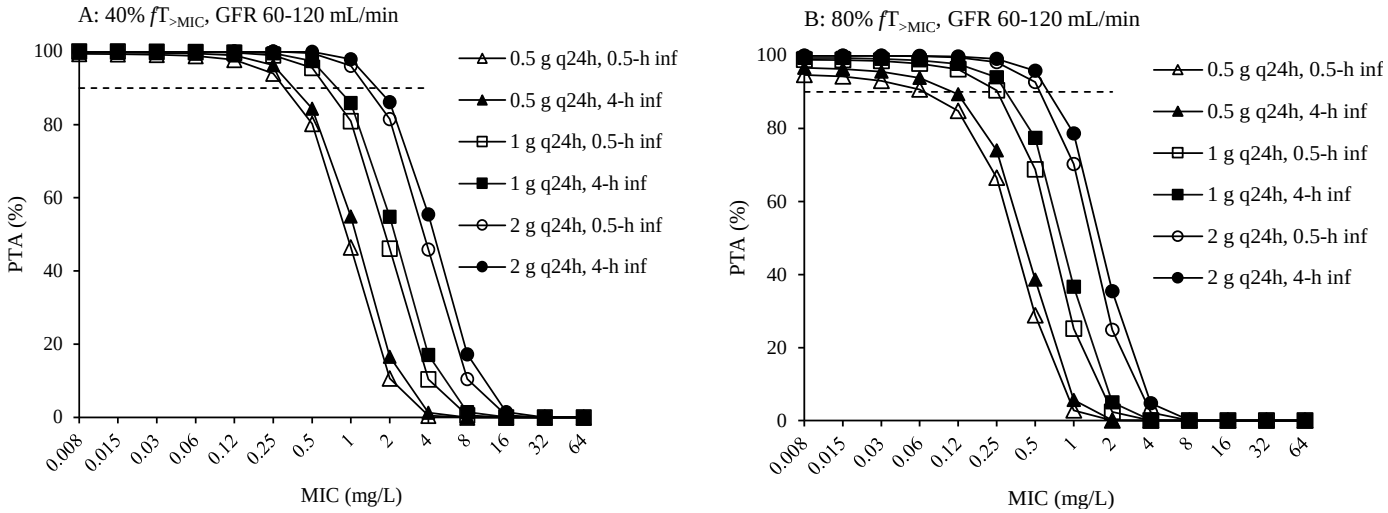

Figure 4. Probability of target attainment (PTA) of ertapenem in 11 patients with sepsis.

Table 4. Probability of target attainment (PTA) for ertapenem regimens achieving 40% $fT_{>MIC}$ and 80% $fT_{>MIC}$ at various glomerular filtration rate levels (GFR) in the 11 study patients with sepsis on the 3rd dose of drug administration.

Dosage regimen	Duration of infusion (h)	MIC (mg/L)	Probability of attaining the following %$fT_{>MIC}$					
			GFR 0-29.99		GFR 30-59.99		GFR 60-120	
			40%	80%	40%	80%	40%	80%
0.5 g q24 h	0.5	0.25	99.73	98.18	98.71	92.38	93.94	66.52
		0.5	98.37	92.85	93.65	73.26	80.17	28.84
		1	90.46	73.48	73.15	31.32	46.47	2.78
		2	66.44	39.98	34.82	4.6	10.61	0.04
	4	0.25	99.74	98.19	99.09	93.58	96.2	74.02
		0.5	98.49	93	94.9	78.36	84.35	38.6
		1	90.84	74.66	76.62	38.54	54.92	5.63
		2	67.69	41.92	39.33	6.72	16.62	0.12
1 g q24 h	0.5	0.25	99.99	99.75	99.9	99.76	98.93	90.38
		0.5	99.84	98.51	99.31	98.55	95.48	68.75
		1	98.22	92.38	93.84	90.79	80.94	25.15
		2	89.57	71.95	73	65.02	46.14	2.35
		4	64.5	38.39	34.18	23.25	10.37	0.01
	4	0.25	100	99.84	99.93	99.01	99.46	93.96
		0.5	99.95	99.14	99.46	95.64	97.38	77.36
		1	98.99	94.14	95.3	78	85.9	36.62
		2	91.56	75.25	75.74	36.81	54.79	4.98
		4	67.86	41.67	38.79	6.81	17.11	0.13
2 g q24 h	0.5	0.5	100	99.88	99.97	99.29	99.46	92.72
		1	99.89	98.96	99.36	94.87	96.06	70.21
		2	98.4	92.46	93.53	73.07	81.49	24.83
		4	89.34	72.1	72.15	29.95	45.88	2.21
		8	30.83	12.27	6.53	0.19	10.48	0
	4	0.5	100	99.91	100	99.44	99.9	95.82
		1	99.97	99.05	99.65	96.04	97.84	78.66
		2	98.86	93.95	95.41	79.18	86.17	35.43
		4	90.99	75.33	76.59	38.2	55.46	4.79
		8	67.92	41.26	8.67	0.45	17.22	0.11

in septic patients is needed to investigate these findings.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Supplementary Table 1. Population pharmacokinetic parameters and relative standard errors obtained from the FOCE-I and SAEM estimation methods[a].

Parameter	FOCE-I method (MOFV=180.017)		SAEM method (MOFV=179.543)	
	Estimated	%RSE	Estimated	%RSE
Fixed-effect parameter				
CL (L/h)	14.7	18.5	14.4	21.6
V_C (L)	49.4	20.6	47.3	23
V_P (L)	84.2	21.4	82.9	29.4
Q (L/h)	30.2	17.1	30.1	13.4
Interindividual variability (IIV)				
ω^2_{CL}	0.462	34.8	0.508	16.9
ω^2_{VC}	0.445	32.8	0.515	24.7
ω^2_{VP}	0.651	48.9	0.776	31.8
ω^2_{Q}	NE	-	NE	-
Residual variability				
σ^2_{Prop}	0.0371	17.1	0.0364	18.2
σ^2_{Add}	0.0231	46.3	0.0244	57.8

[a]FOCE-I, first-order conditional estimation with eta-epsilon interaction estimation method; SAEM, Stochastic Approximation Expectation Maximization estimation method; %RSE, percentage of relative standard error; CL, total clearance; V_C, central volume of distribution; V_P, peripheral volume of distribution; Q, intercompartment clearance; ω^2_{CL}, interindividual variability of CL; ω^2_{VC}, interindividual variability of V_C; ω^2_{VP}, interindividual variability of V_P; ω^2_{Q}, interindividual variability of Q; NE, not estimated; σ^2_{Prop}, proportional residual variability; σ^2_{Add}, additive residual variability.

Supplementary Table 2. Probability of target attainment (PTA) for ertapenem regimens achieving 40% $fT_{>MIC}$ and 80% $fT_{>MIC}$ at various glomerular filtration rate levels (GFR) in the 11 study patients with sepsis on the 1st dose of drug administration.

Dosage regimen	Duration of infusion (h)	MIC (mg/L)	Probability of attaining the following %$fT_{>MIC}$					
			GFR 0-29.99		GFR 30-59.99		GFR 60-120	
			40%	80%	40%	80%	40%	80%
0.5 g q24 h	0.5	0.25	99.39	97.2	97.43	89.61	91.24	63.84
		0.5	96.13	89.58	89.66	68.13	75.22	26.69
		1	82.62	67.46	65.8	26.5	41.03	2.44
		2	52.81	33.64	29.53	3.66	8.7	0.04
	4	0.25	99.51	97.49	98.24	91.12	93.98	71.31
		0.5	96.97	90.55	90.91	72.34	80.8	34.92
		1	83.37	69.04	68.63	32.25	49.17	4.24
		2	53.46	34.66	33.04	5.09	13.82	0.09
1 g q24 h	0.5	0.25	99.97	99.55	99.71	98.12	98.51	88.84
		0.5	99.58	97.89	98.38	91.65	93.78	65.75
		1	96.68	89.97	89.11	67.17	76.73	22.64
		2	82.07	66.67	64.58	24.41	39.9	1.68
		4	51.68	33.53	27.51	3.37	8.63	0.05
	4	0.25	99.99	99.58	99.85	98.38	99.23	92.29
		0.5	99.79	98.39	99.09	93.4	95.9	74.6
		1	97.68	91.36	91.59	73.37	81.56	32.37
		2	84.54	69.92	68.55	31.59	49.76	3.99
		4	54.21	35.67	32.41	4.92	14.44	0.07

Supplementary Table 2. Cont'd

2 g q24 h	0.5	0.5	100	99.68	99.89	98.57	99.08	91.63
		1	99.75	98.23	98.47	92.57	94.02	65.39
		2	96.6	89.64	89.83	67.9	75.89	21.65
		4	81.89	66.48	65.25	24.93	40.37	1.66
	4	0.5	99.98	99.86	99.97	98.88	99.54	94.03
		1	99.88	98.45	99.34	93.61	95.96	74.86
		2	97.7	91.09	91.89	73.29	80.77	30.54
		4	83.69	68.53	68.7	31.55	48.98	3.43