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Short Communication

Population pharmacokinetics and simulations of imipenem in critically ill patients undergoing continuous renal replacement therapy

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ABSTRACT

Various dose regimens of imipenem have been prescribed in critically ill patients undergoing continuous renal replacement therapy (CRRT) but there are limited information on its pharmacokinetics (PK) and treatment efficacy. The aim of this study was to describe the population PK of imipenem in patients receiving CRRT, and utilize this model to inform optimal dosing regimens using pharmacokinetics/pharmacodynamics (PK/PD) target as a surrogate marker for treatment efficacy. Population PK modelling was undertaken in 20 patients receiving CRRT to characterize variabilities and identify influential covariates. Monte Carlo simulations were performed to evaluate differences in probability of target attainment (PTA) between empirically used dosing regimens (0.5 g q6h, 1 g q8h, and 1 g q6h), and to explore the impact of CRRT intensity and identified covariates on target attainment. Imipenem concentration data were adequately described using a one-compartment model. Residual diuresis and burn injury were identified modifiers for imipenem endogenous clearance. The simulations showed that the impact of CRRT intensity on target attainment is clinically irrelevant, whereas urine output and burn injury influence PTA for pathogens with an MIC $\geq$ 4 mg/L. At an MIC $\leq$ 2 mg/L, satisfactory PTAs (>80%) were achieved for all three investigated dose regimens regardless of urine output, burn injury, and CRRT intensity. Our results indicate that from a safety perspective, 0.5 g q6h imipenem is optimal in these patients for pathogens with an MIC $\leq$ 2 mg/L, and 1 g q6h is recommended for non-burn patients with anuria against MIC 4–16 mg/L.

1. Introduction

Imipenem is a leading antibiotic of the carbapenem family with a broad antibacterial spectrum against Gram-positive, Gram-negative and anaerobic bacteria [1]. This drug is frequently used in the treatment of critically ill patients with severe infections because of its wide spectrum of antimicrobial activity. Imipenem is a β-lactam and exhibits time-dependent bactericidal activity; the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with its clinical efficacy is free plasma concentration above the minimum inhibitory concentration of the pathogens ($fT>MIC$) with a target of fractional time at least 40% [2].

Imipenem is a hydrophilic molecule with a plasma half-life of 1 h and low plasma protein binding (around 20%) [3]. When administered alone, imipenem is rapidly metabolized to an inactive metabolite in the brush-border of the kidney by the enzyme dehydropeptidase (DHP-1) [4]. Therefore, it is commonly co-administered in a 1:1 ratio with a DHP-1 inhibitor, cilastatin. The combination of imipenem with cilastatin leads to renal excretion of about 70% of unchanged imipenem and effectively reduces the renal toxicity of the drug [3,4].

Continuous renal replacement therapy (CRRT) is routine for clinical management of critically ill patients with renal failure or some non-renal indications, such as severe sepsis to achieve extracorporeal blood purification [5]. The commonly used modalities of CRRT include continuous venovenous haemofiltration (CVVH), continuous venovenous haemodialysis (CVVHD), and continuous venovenous haemodiafiltration (CVVHDF) [6]. Early and aggressive antibiotic therapy is very important in the treatment of critically ill patients with serious infections. However, appropriate antibiotic dosing in critically ill patients, particularly patients receiving CRRT, is a challenging task. The rapidly changing physiology (e.g. organ dysfunction) in critically ill patients might lead to markedly altered

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antibiotic PK and PD [7]. The influence of the type and intensity of CRRT on elimination of drugs further complicates the design of antibiotic dosing regimens.

Antibiotic dosing is best optimized using population PK/PD analysis with Monte Carlo simulation. This approach comprises pooling existing antibiotic data and integrating prior information for dose regimen optimization. Several published studies have evaluated the PK of imipenem in a small number (8 to 12) of critically ill patients undergoing CRRT in diverse CRRT settings [8-13]. Unfortunately, the population PK of imipenem in critically ill patients receiving CRRT has not been demonstrated. Furthermore, a broad dose range of 0.5 to 1 g imipenem q6h to q12h was empirically prescribed in these patients and efficacy was rarely evaluated.

Therefore, the aims of this study were as follows: 1) to determine the population PK parameters and the degree of inter-individual variability (IIV) of imipenem in critically ill patients undergoing CRRT; 2) to identify the influential patient characteristics responsible for the IIV of imipenem; 3) to perform Monte Carlo simulations for investigating the influences of different dosing regimens, intensity of CRRT, and identified covariates on the probability of target attainment (PTA) by MIC.

2. Methods

2.1. Study data

An extensive literature search was conducted using PubMed and Google Scholar to find published imipenem PK data in critically ill patients undergoing CRRT treated with imipenem-cilastatin (up to August 2018). A total of six studies published in 1992 to 2016 were identified [8-13]. Two of these were imipenem PK studies with specific dosing information, sampling schemes and individual concentration-time data included in the analysis [12,13]. In the first study, Wen et al. [12] conducted a PK comparison study of imipenem in plasma and effluent samples in 10 critically ill patients receiving CVVHDF (one patient with CVVH) over 1 h infusion of imipenem-cilastatin 0.5 g q6h (8 patients) or 1 g q8h (2 patients). In the second study, Boucher et al. [13] evaluated the endogenous and extracorporeal clearance of imipenem and cilastatin in 10 burn intensive care unit (ICU) patients undergoing CVVH given imipenem-cilastatin 1 g q6h (9 patients) or 0.75 g q6h (1 patient) over 1 h infusion. Demographics, clinical characteristics and CRRT settings from these two studies are documented in Table 1. Plasma concentration data were digitized using WebPlotDigitizer (version 4.1) and a total of 134 concentration data were obtained. Free imipenem plasma concentrations were determined in the Wen et al. study; total concentrations were reported in the Boucher et al. study. For the total concentrations, a value of 20% plasma protein binding was applied for further population PK analysis.

2.2. Population pharmacokinetic modelling

Non-linear mixed-effects modelling was carried out in NONMEM® (version 7.3, Icon Development Solutions, Ellicott City, MD, USA) using the algorithm of FOCEI for parameter estimation. The modeling was assisted by PSN (version 4.60, Uppsala University, Uppsala, Sweden), and Pirana software (version 2.9.6) was used as the interface. The diagnostic plots were generated using R® 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

The IIV of PK parameters was modeled as log normal, and an exponential error model was applied for residual variance using a log-transform-both-sides approach. Total body clearance (CL_{total}) was modeled as a sum of endogenous clearance (CL_{body}) and extracorporeal clearance (CL_{CRRT}) by CRRT. Individual extracorporeal clearances by CVVH were reported in the Boucher et al. study. The CL_{CRRT} from the Wen et al. study under CVVHDF was calculated as: saturation coefficient (S_d) × (dialysis + ultrafiltrate rate) [7]. CL_{CRRT} values are shown in Table 1.

Model development and selection were guided by the following metrics and graphics: objective function value (OFV), condition number, relative standard error of the parameter estimates, and goodness-of-fit plots. A decrease in OFV of 3.84 ($P < 0.05$) for one degree of freedom was considered statistically significant. Age, body weight, urine output, APACHE II score, and percentage of burned total body surface area (%TBSA) were the continuous covariates evaluated. Sex, patient type (non-burn patients and burn patients), and degree of diuresis (anuria, oliguria, and preserved urine output) were the categorical covariates tested. Anuria, oliguria, and preserved urine output were defined by the classification of urine output of < 100 mL/24 h, 100 to 500 mL/24 h, and >500 mL/24 h, respectively. The covariate effects were first explored graphically on empirical Bayes estimates of PK parameters. The potential covariates identified in the graphic analysis step were then tested by stepwise forward selection ($P < 0.05$ as inclusion criteria).

Final model validation was evaluated by the prediction-corrected visual predictive check (pcVPC) (1000 simulations), the normalized prediction distribution errors (NPDE), and parameter uncertainty check using sampling importance resampling (SIR) procedure.

2.3. Monte Carlo simulations

Monte Carlo simulations were carried out using the final population PK model to investigate the influence of dosage regimens, intensities of CRRT, and identified covariates (i.e. burn injury and degree of diuresis) on the PTA at steady-state in patients with 70 kg body weight. Briefly, three categories of diuresis (anuria, oliguria, and preserved urine output) for both non-burn patients and burn patients were simulated at three empirical dosage regimens (0.5 g q6h, 1 g q6h, and 1 g q8h) under three different intensities of CRRT (20, 37, and 74 mL/h/kg). 20 mL/h/kg is the standard intensity of CRRT commonly used, and 37 and 74 mL/h/kg were the median and highest intensities of CRRT used in the studied patients, respectively. For each scenario, 10 000 virtual patients were simulated for generating free imipenem concentration-time profiles. The percentage of patients with at least 40% of the $fT>MIC$ against MIC distributions (0.5–16 mg/L) for pathogens commonly treated with imipenem were determined. A PTA of >80% was considered acceptable, and >90% desirable.

3. Results

3.1. Population pharmacokinetics

Imipenem PK concentrations were adequately described by one-compartment model with linear elimination. The data supported the estimation of IIV on CL_{body} and apparent volume of distribution (V_d). Among the examined covariates, patient type and degree of diuresis were found to be significant for CL_{body} ($P < 0.05$). Inclusion of burn injury effect on CL_{body} reduced the variability of CL_{body} from 57.2% to 44.1%. Introduction of diuresis effect on CL_{body} further decreased the variability to 36.6%. Burn patients were found to have a 81.7% higher CL_{body} than non-burn patients. Patients with oliguria or preserved urine output displayed 43.4% or 65.9% higher CL_{body} than anuric patients, respectively. The final imipenem population PK model is displayed with equations 1–4:

$$CL_{total} = CL_{CRRT} + CL_{body} \quad (1)$$

Table 1
Demographics and characteristics of the study patients receiving continuous renal replacement therapy (CRRT).

Study	Patient ID	Sex	Age (years)	Body weight (kg)	Urine output (mL/24h)	APACHE II score	Blood flow (mL/min)	TYPE of CRRT	CRRT intensity (mL/h/kg)[c]	Saturation coefficient	CRRT clearance (L/h)	Dosing regimen	TBSA%[a]	Isolated pathogen (imipenem MIC in μg/mL)	Outcome
Wen, et al. 2016	1	Male	33	80	1940	15	150	CVVHDF	30	1[d]	2.38	0.5g q6h	–	*Enterobacter aerogenes* (1)	Died
	2	Male	59	80	2125	17	150	CVVHDF	35	1[d]	2.80	0.5g q6h	–	*Klebsiella pneumoniae* (1)	Survived
	3	Male	69	70	1220	13	150	CVVH	36	1[d]	2.52	0.5g q6h	–	–	Survived
	4	Female	74	45	260	20	150	CVVHDF	51	1[d]	2.31	0.5g q6h	–	*Acinetobacter baumannii* (1)	Died
	5	Male	47	90	40	16	150	CVVHDF	27	1[d]	2.45	1g q8h	–	*Escherichia coli* (1)	Survived
	6	Male	32	70	55	20	150	CVVHDF	35	1[d]	2.44	1g q8h	–	–	Died
	7	Male	87	70	65	23	150	CVVHDF	35	1[d]	2.42	0.5g q6h	–	*Escherichia coli* (16)	Died
	8	Male	50	70	0	26	150	CVVHDF	34	1[d]	2.40	0.5g q6h	–	–	Died
	9	Female	76	75	500	26	150	CVVHDF	29	1[d]	2.18	0.5g q6h	–	*Pseudomonas aeruginosa* (1)	Survived
	10	Male	78	60	30	15	150	CVVHDF	42	1[d]	2.50	0.5g q8h	–	*Acinetobacter baumannii* (16)	Died
Boucher, et al. 2016	11	Male	21	105	882	3	300	CVVH	38	1.17	4.67	1g q6h	18	*Pseudomonas aeruginosa* (≤ 1)	Survived
	12	Male	28	63	618	14	300	CVVH	50	1.12	3.53	1g q6h	33	*Pseudomonas aeruginosa* (≤ 1)	Survived
	13	Male	55	61	730	7	350	CVVH	57	1.19	4.14	1g q6h	10	*Pseudomonas aeruginosa* (2)	Survived
	14	Male	56	60	0	8	300	CVVH	74	1.05	4.66	1g q6h	22	*Pseudomonas aeruginosa* (1)	Died
	15	Male	45	179	13	19	400	CVVH	36	0.84	5.41	1g q6h	6	*Pseudomonas aeruginosa* (2)	Survived
	16	Male	72	108	233	18	300	CVVH	58	0.92	5.76	1g q6h	10	*Pseudomonas aeruginosa* (2)	Survived
	17	Male	65	76	257	20	260	CVVH	59	0.89	3.99	1g q6h	15	*Pseudomonas aeruginosa* (2)	Died
	18	Female	55	74	1040	10	320	CVVH	43	1.06	3.37	1g q6h	20	*Acinetobacter baumannii* (–)	Survived
	19	Female	67	60	92	22	350	CVVH	70	0.94	3.95	1g q6h	0.25	*Pseudomonas aeruginosa* (2)	Died
	20	Male	36	108	0	18	300	CVVH	32	0.96	3.32	0.75g q6h	95	*Acinetobacter baumannii* (–)	Survived
	Median	–	55.5	72	245	17.5	205	–	37	–	3.36	–	–	–	–
	IQR[b]	–	42.8-69.8	62.5-82.5	37.5-768	13.8-20	150-300	–	34.5-52.8	–	2.44-4.03	–	–	–	–

[a] TBSA%, percentage of burned total body surface area.
[b] IQR, interquartile range.
[c] CRRT intensity: (ultrafiltration rate + dialysis rate)/weight.
[d] The saturation coefficients of Wen et al. were not available and were assumed to be 1. CVVHDF - continuous venovenous haemodiafiltration; CVVH - continuous venovenous haemofiltration

Table 2
Parameter estimates of the final population pharmacokinetic model and the results of the sampling importance resampling (SIR) approach

Parameter	Final pharmacokinetic model	SIR results	
	Estimate (RSE%) [Shrinkage%]	Median	95% CI
Fixed effects			
$\theta_{CL_{body}}$ (L/h)	6.11 (14.2)	6.00	4.42–7.46
θ_{BURN} (Burn injury)	0.817 (41.6)	0.856	0.327–1.458
θ_{DIUR} (Oliguria)	0.434 (40.6)	0.471	0.043–0.861
θ_{DIUR} (Preserved diuresis)	0.659 (59.2)	0.697	0.082–1.436
V_d (L)	34.2 (11.6)	34.770	27.17–42.96
Inter-individual variability (IIV)			
CL_{body} (CV%)	36.6 (42.4) [4.5]	39.6	28.2–54.7
V_d (CV%)	47.2 (20.4) [6.0]	48.7	37.1–59.3
Residual variability			
Proportional error* (%)	26.3 (37.1) [13.7]	27.1	22.9–32.3

RSE, relative standard error; CI, confidence interval; V_d, apparent volume of distribution; $\theta_{CL_{body}}$, typical value of endogenous clearance in non-burn patients with anuria; θ_{BURN}, factor for the influence of burn injury on CL_{body}; θ_{DIUR} (Oliguria), factor for the influence of oliguria on CL_{body}; θ_{DIUR} (Preserved diuresis), factor for the influence of preserved diuresis on CL_{body}.
CV (%) is calculated according to: CV (%) $= \sqrt{\exp(\omega^2) - 1} \times 100\%$. ω^2: the variance estimate in the log-domain.
* An additive error model in the log-transformed domain was used to characterize the residual unexplained variability, which approximates to a proportional error in the normal domain.

$$CL_{CRRT} = S_d \times CRRT_{intensity}\ (mL/h/kg) \times \text{Body weight}\ (kg)/1000 \quad (2)$$

$$CL_{body} = \theta_{CL_{body}} \cdot (1+\theta_{BURN}) \cdot (1+\theta_{DIUR}) \cdot e^{\eta_{CL_{body}}} \quad (3)$$

$$\theta_{BURN} = 0; \text{non} - \text{burn patients}$$

$$\theta_{BURN} = 0.817; \text{burn patients}$$

$$\theta_{DIUR} = 0; \text{patients with anuria}$$

$$\theta_{DIUR} = 0.434; \text{patients with oliguria}$$

$$\theta_{DIUR} = 0.659; \text{patients with preserved diuresis}$$

$$V_d = \theta_{V_d} \cdot e^{\eta_{V_d}} \quad (4)$$

where $CRRT_{intensity}$ is CRRT intensity, which is the sum of ultrafiltration rate and dialysis rate, divided by body weight. θ is population estimate, and η is IIV.

PK parameters of the final model are summarized in Table 2. The model showed very small levels of η-shrinkage for CL_{body} (4.5%) and V_d (6.0%), and the reliability and robustness of the parameter estimates were confirmed by SIR results. The goodness-of-fit plots shown in Fig. 1 demonstrated that the model adequately described the observations. The pcVPC plot and NPDE histogram provided as Supplementary data (Figs. S1 and S2) indicated good predictive performance of the model.

3.2. Simulations and target attainment

PTA versus MIC profiles for non-burn patients and burn patients with various degree of diuresis at three different dosing regimens under CRRT intensity of 37 and 20 mL/h/kg are presented in Figs. 2–3. PTA profiles under CRRT intensity of 74 mL/h/kg are shown in Figures S3 as Supplementary data. The simulations showed that satisfactory PTAs (>80%) were achieved for MICs up to 2 mg/L for the three dosage regimens, regardless of urine output, burns, and CRRT intensity. For MIC at 4 mg/L, 1 g q6h regimen achieved greater than 80% PTAs in all simulated scenarios. Instead, 0.5 g q6h and 1 g q8h regimens lead to significantly decreased PTAs for burn patients with oliguria or preserved urine output. For MIC at 8 mg/L, non-burn patients with anuria given 0.5 g q6h under CRRT intensity of 20 and 37 mL/h/kg, non-burn patients (whatever urine output) and burn patients with anuria given 1 g q6h (regardless of CRRT intensity), non-burn patients with anuria or oliguria given 1 g q8h under CRRT intensity of 20 and 37 mL/h/kg, and non-burn patients with anuria given 1 g q8h under CRRT intensity of 74 mL/h/kg reached >80% PTA. For MIC at 16 mg/L, only non-burn patients with anuria given 1 g q6h under CRRT intensity of 20 and 37 mL/h/kg produced the desired PTA.

4. Discussion

In the present study, we reported the PK of imipenem in 20 non-burn and burn critically ill patients receiving CRRT using a population approach. To our knowledge, this is the first population PK study of imipenem in critically ill patients receiving CRRT. In previous studies [8-10,14], the PK of imipenem in patients had been described using one-compartment, two-compartment, and three-compartment models. The above models were evaluated during our method development, and the one-compartment model was found to be optimal with our dataset.

In previous imipenem PK studies of critically ill patients with anuria under CRRT (CVVH and CVVHDF), mean imipenem endogenous clearance of 6.5–9.7 L/h and central volume of distribution of 24.3–35.3 L were reported [8-10]. We found a very similar volume of distribution (34.2 L) in our studied patients. For non-burn patients with anuria, the estimated endogenous clearance was 6.11 L/h, which is comparable to previous reports. Interestingly, we found that residual diuresis and burn injury were modifiers of imipenem endogenous clearance. The level of diuresis is believed to be strongly associated with the residual renal function, which contributes to imipenem clearance by urine excretion. The influence of diuretic effects on clearance was also demonstrated for meropenem, another carbapenem antibiotic, in critically ill patients undergoing CRRT [15]. Our analysis showed that burn patients had increased endogenous clearance compared with non-burn patients. The elevated imipenem clearance in burn patients aligns with earlier work for other carbapenems, such as meropenem and doripenem, in patients receiving CRRT [16-18]. During the hypermetabolic phase (48 h after burns) for patients with burn injury, an increased cardiac output with a subsequent increase in

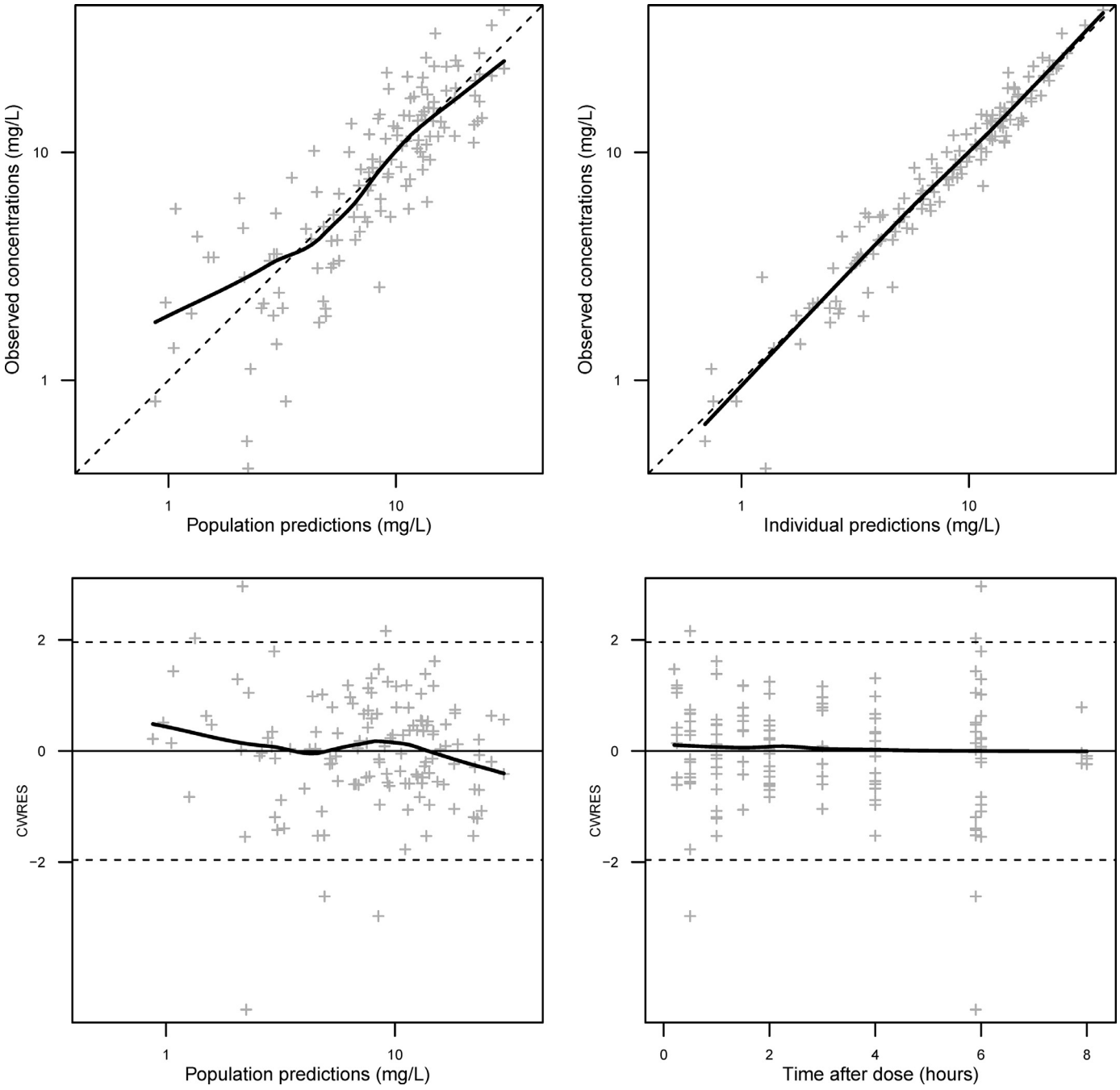

Fig. 1. Goodness-of-fit plots of the final imipenem population pharmacokinetics model. Top left panel: observed concentrations vs. population predictions of imipenem in plasma. Top right panel: observed concentrations vs. individual predictions of imipenem in plasma. Bottom left panel: conditional weighted residuals (CWRES) vs. population predicted imipenem concentrations. Bottom right panel: CWRES vs. time.

renal blood flow and glomerular filtration rate was reported [19]. As a consequence, elevated drug plasma clearance occurred in burn patients compared with non-burn patients.

Our simulation results demonstrated that currently used imipenem dosing regimens (0.5 g q6h, 1 g q6h, and 1 g q8h) achieved favorable target attainment in patients against susceptible pathogens with an MIC of $\leq$ 2 mg/L, regardless of the residual renal function, burn injury and CRRT intensity. These pathogens include the most common Gram-negative aerobic microorganisms found in the ICU, such as strains of *Klebsiella, Escherichia coli*, and *Enterobacter*. Among these three dose regimens, 0.5 g q6h showed the lowest excessive plasma peak concentrations and thus would reduce the risk of imipenem-induced side effects, such as seizures. From a safety perspective, 0.5 g q6h would be the optimal dose for CRRT patients against pathogens with an identified MIC $\leq$ 2 mg/L. However, for pathogens with MIC $\geq$ 4 mg/L, which are commonly less susceptible to imipenem, particularly *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, 0.5 g q6h is likely to be subtherapeutic in most patients. In this case, a dose of 1 g q6h could achieve satisfactory target attainments for infections in burn patients with an MIC of 4 mg/L, non-burn patients with an MIC of 4–8 mg/L, and non-burn anuric patients with an MIC of $\leq$ 16 mg/L.

For the modifiers of imipenem total clearance, CRRT intensity showed a rather limited impact on PTA, thus it does not influence decisions on dosing regimen. This can be explained by the fact that the contribution of CRRT to total clearance is relatively small, rep-

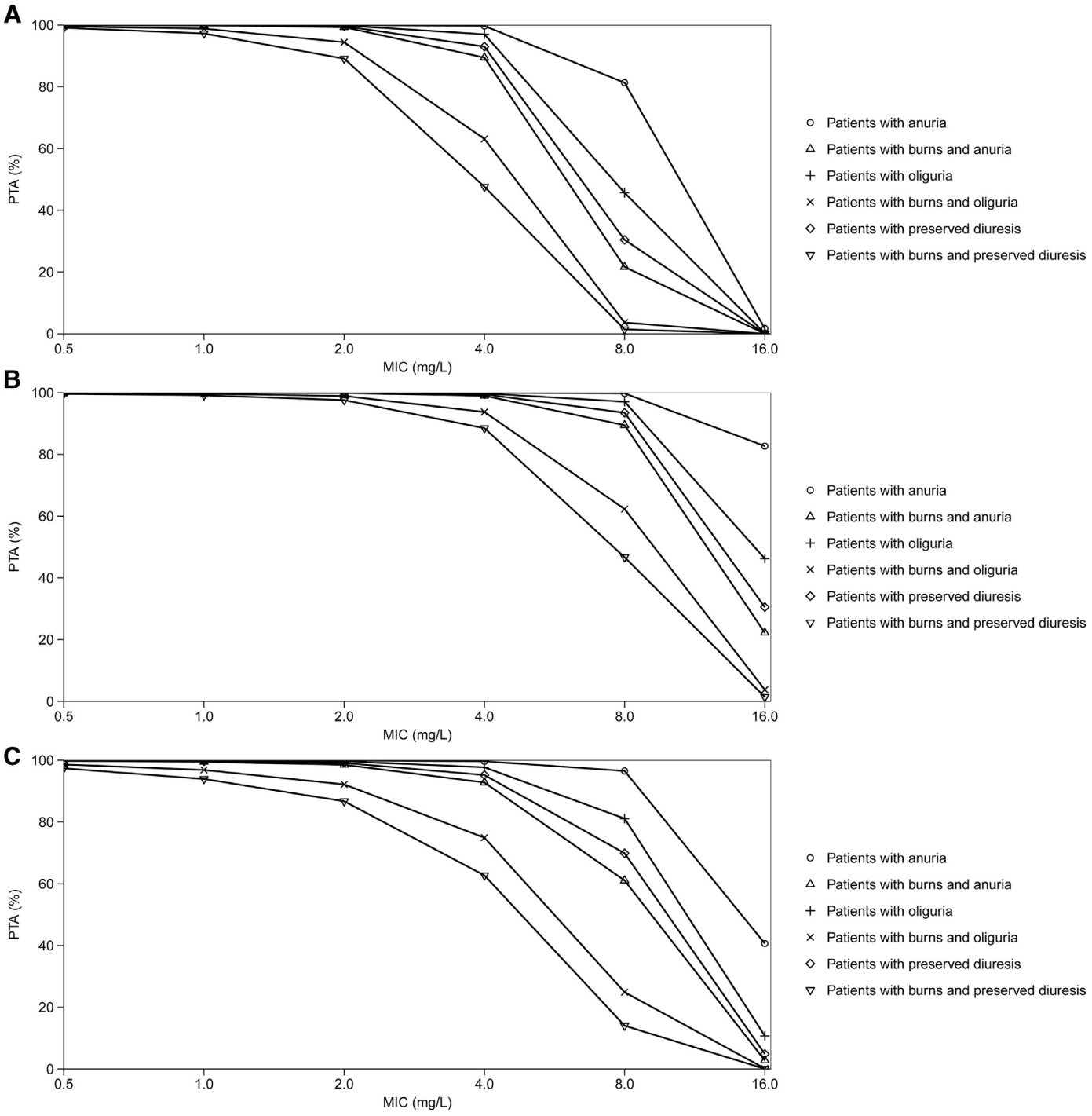

Fig. 2. The probability of target attainment (PTA) vs. minimum inhibitory concentration (MIC) for non-burn patients and burn patients (body weight 70 kg) with different levels of diuresis given doses of 0.5 g q6h (top panel, A), 1 g q6h (middle panel, B), and 1 g q8h (bottom panel, C) at steady state under continuous renal replacement therapy (CRRT) intensity of 37 mL/h/kg. The PKPD target was $fT>MIC$ exceeded 40%. A base 2 logarithmic scale was used for the x-axis.

resenting only 10% to 40% of CL_{total} as shown in our studied patients. Residual diuresis and burn injury were associated with clinically irrelevant changes in the PTA for pathogens with an MIC of $\leq$ 2 mg/L. However, diuretic and burn effects would significantly decrease the PTA for pathogens with an MIC of $\geq$ 4 mg/L and thus are important considerations for dose adjustments.

The present study has some limitations. First, the backward elimination approach was not carried out during our covariate screening. The generalizability of our identified covariates needs to be confirmed in larger clinical studies. Second, a typical body weight of 70 kg was employed during our simulations to calculate the effluent flow rate (i.e. CRRT intensity $\times$ body weight). The body weight effect on PTA was not explored as the impact of CRRT intensity and body weight on PTA was considered to be interchangeable for non-obese patients. Third, our simulation study was carried out using a target of 40% $fT>MIC$. Some studies indicate that an aggressive target of 100% $fT>MIC$ or even 100% $fT>4\times MIC$ for carbapenems might be required in critically ill patients for better clinical outcomes [20]. However, these aggressive PK/PD targets have been shown to be difficult to reach with currently

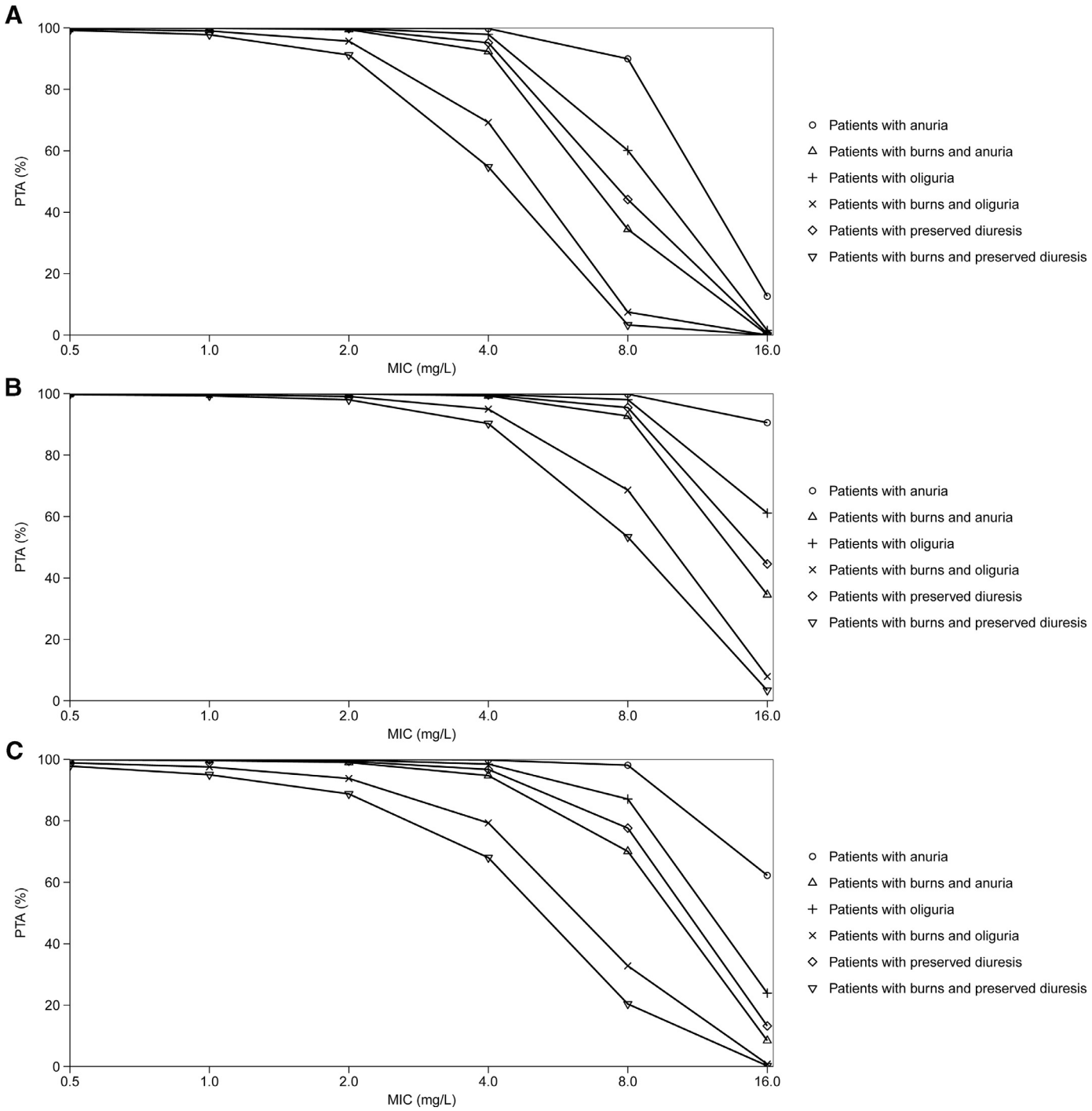

Fig. 3. The probability of target attainment (PTA) vs. minimum inhibitory concentration (MIC) for non-burn patients and burn patients (body weight 70 kg) with different levels of diuresis given doses of 0.5 g q6h (top panel, A), 1 g q6h (middle panel, B), and 1 g q8h (bottom panel, C) at steady state under continuous renal replacement therapy (CRRT) intensity of 20 mL/h/kg. The PKPD target was $fT>MIC$ exceeded 40%. A base 2 logarithmic scale was used for the x-axis.

used empirical dose regimens of imipenem and it is debatable which target is more suitable [20].

5. Conclusions

In conclusion, a population PK model of imipenem in critically ill patients receiving CRRT was presented in this study. Residual diuresis and burn injury were identified as significant modifiers for imipenem endogenous clearance in these patients. CRRT intensity leads to small changes in total clearance and thus has a very limited impact on target attainment, and dose adjustments based on intensity seem to be unnecessary. Our study demonstrated that 0.5 g q6h is desirable for CRRT patients with an MIC $\leq$ 2 mg/L (regardless of urine output and burn injury), and 1 g q6h is preferred for non-burn CRRT patients with anuria with an MIC of 4–16 mg/L.

Declarations

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Competing interests

None

Ethical approval

Not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2018.10.006.

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