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Doripenem dosing regimens in Asian critically ill patients with continuous renal replacement therapy

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1. Introduction

Antibiotic dosing in critically ill patients with continuous renal replacement therapy (CRRT) is still challenging. Pharmacokinetic changes in critically ill patients such as increased volume of distribution and decreased protein binding affinity affect hydrophilic drug dosing regimens [1]. Consequently, we might prescribe inadequate doses of antimicrobial agents in patients with CRRT [1] which can affect the morbidity and mortality associated with sepsis [2]. Requirement of loading dose and higher maintenance doses for this group of patients has been suggested to achieve pharmacokinetic and pharmacodynamic targets [3].

Continuous renal replacement therapy has been utilizing to effectively remove fluid and waste products in this group of patients due to hemodynamic instability [4]. Doripenem is a water-soluble carbapenem antibiotic and commonly used for Gram negative infection in intensive care unit (ICU) [5]. It can be removed by CRRT due to small molecular weight (438.52 Da) and low volume of distribution (16.8 L) [6].

The recommended dosing regimens from clinical resources are mostly from the pharmacokinetic studies in Western patients and there were a few studies conducted in Asian population [7-12]. No suggested doripenem dosing regimens for CRRT patients based on Asian pharmacokinetic parameters exists. This study aimed to define the optimal doripenem dosing regimens using pharmacokinetic parameters from Asian population and body weights of Asian critically ill patients and to evaluate the probability of target attainment (PTA) of recommended dosing regimens from available clinical resources.

2. Method

2.1. Mathematical pharmacokinetic models

Mathematical pharmacokinetic models with first order elimination of acute kidney disease patients receiving CRRT were developed to predict doripenem disposition in 48 h of the initial therapy [13-15]. Previously published doripenem pharmacokinetic parameters in Asian population such as volume of distribution, non-renal clearance and effluent rates [7,8] and related variability from critically ill patients receiving CRRT were selected and gathered to create models of virtual patients with three modalities. The commonly used modalities consisted of continuous venovenous hemofiltration (CVVH) with pre-hemofilter dilution techniques, which replacement fluid is added in blood before going through hemofilter, respectively, and continuous venovenous hemodialysis (CVVHD) [16]. We added population-specific correlation (r^2) between patient's body weight, non-renal clearance and volume of distribution into the models to create population-specific virtual patients. Lower limit of body weight was set at >40 kg assuming that the virtual patients are adult. In addition, body weights used in the models

Abbreviations: AKI, Acute kidney injury; CL, Clearance; CL_{HD}, Transmembrane clearance; CL_{HF}, Transmembrane clearance; CL_{NR}, Non-renal clearance; CLSI, Clinical Laboratory Standards Institute; CRRT, Continuous renal replacement therapy; CVVH, Continuous venovenous hemofiltration; CVVHD, Continuous venovenous hemodialysis; $fT_{>4MIC}$, The cumulative percentage of a 48 h period with 4 times MIC; g, gram; h, Hour; ISN, International Society of Nephrology; k, Elimination rate constant; KDIGO, Kidney Disease: Improving Global Outcomes; kg, Kilogram; L, Liter; LD, Loading dose; MCS, Monte Carlo simulations; mg, Milligram; MIC, Minimum inhibitory concentration; mL, Milliliter; N, Number; PTA, Probability of target attainment; q, every; Qb, Blood flow rate; Qd, Dialysate flow rate; Qplasma, Plasma flow rate; Qreplacement, Replacement fluid flow rate; Quf, Ultrafiltrate flow rate; *r2*, Population-specific correlation; SA, Saturation coefficient; SC, Sieving coefficient; SD, Standard deviation; EA-AKI, Southeast Asia entitled The Epidemiology and Prognostic Factors for Mortality in Intensive Care Unit Patients with Acute Kidney Injury in Southeast Asia; Vd, Volume of distribution.

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of virtual patients were obtained from an international database of the International Society of Nephrology (ISN) funded prospective multicenter observational ongoing study of AKI epidemiology in Southeast Asia entitled The Epidemiology and Prognostic Factors for Mortality in Intensive Care Unit Patients with Acute Kidney Injury in Southeast Asia [SEA-AKI] [17]. It enrolled 6644 critically ill patients from Thailand, Laos and the Philippines. The body weight from this study was used as a representative of Asian body weights of critically ill patients.

Transmembrane drug clearance was calculated as multiplying effluent flow rate, dialysate (Qd) and/or ultrafiltrate (Quf) flow rate, by extraction coefficient that are sieving coefficient (SC) for hemofiltration and saturation coefficient (SA) for hemodialysis [16]. Blood flow rate (Q_{blood}) for all settings was prescribed as 200 mL/min. The equations used in the models were defined as follows [16]:

$$CL_{HD}\ (L/h) = SA * Qd$$

$$CL_{HF}(post)\ (L/h) = SC * Quf$$

$$CL_{HF}(pre)\ (L/h) = SC * Quf * [Qplasma/(Qplasma + Qreplacement)]$$

$$k = (CL_{NR} + CL_{HD})/Vd$$

$$k = (CL_{NR} + CL_{HF})/Vd$$

where CL_{HF} is transmembrane clearance in hemofiltration; Qplasma is plasma flow rate (Qplasma = Qblood*(1-hematocrit)); hematocrit is 30%; Qreplacement is replacement fluid flow rate (Qreplacement = Quf); CL_{HD} is transmembrane clearance in hemodialysis; Qd is dialysate flow rate; CL_{NR} is non-renal clearance.

Effluent rates were prescribed as Kidney Disease: Improving Global Outcomes (KDIGO) recommendation of 20–25 mL/kg/h [4]. Moreover, higher effluent rate of 35 mL/kg/h was included in the models to reflect an average common effluent rate when high volume CRRT is commenced [18].

Doripenem dosing regimens from available drug dosing recommendations [19] were evaluated in the models. These recommendations vary from 250 mg every 24 h to 1000 mg every 8 h based on renal function.

2.2. Monte Carlo simulation and probability of target attainment

Following a previously published method [13-15], Monte Carlo simulation (Crystal Ball Classroom edition, Oracle) generates drug concentration-time profiles of a group of 5000 virtual patients for each dose to evaluate the probability of target attainment (PTA). PTA was predicted using pharmacodynamic target of the amount of time in which free doripenem concentration that exceeds the 4 times minimum inhibitory concentration (MIC) of *Pseudomonas aeruginosa* [20,21]. In this study, at least 40% of dosing interval (40% $fT_{>4MIC}$) [22] and MIC breakpoint [23] of 2 for *Pseudomonas aeruginosa* were applied in the models for the first 48 h of initial doripenem therapy. The optimal doses were defined as achieving the PTA target at least 90% of 5000 virtual patients with the lowest daily dose to emphasize doripenem efficacy and minimize toxicity. Different doripenem dosing regimens including recommendations for critically ill patients of intermittent were evaluated to define the optimal doses.

3. Results

Gathered pharmacokinetic parameters from available doripenem pharmacokinetic studies in Asian patients receiving continuous renal replacement therapy were presented in Table 1. Range limits and patient's body weight which were included in the simulations were also shown in Table 1

PTAs of selected dosing regimens of doripenem using the pharmacodynamic target as 4 times MIC of 40% $fT_{>4MIC}$ were defined in Table 2. The optimal dosing regimens of doripenem for Asian patients receiving CRRT based on pharmacodynamic target was 500 mg every 8 h. These regimens were also recommended for different 3 effluent rates of KDIGO suggested effluent rates of 20–25 mL/kg/h and high volume CRRT of 35 mL/kg/h for Asian critically ill patients with aforementioned pharmacodynamic targets (Table 3).

4. Discussion

This is the first study to use Asian pharmacokinetic parameters such as volume of distribution and non-renal clearance with Monte Carlo simulation technique to define optimal doripenem dosing regimens for Asian critically ill patients receiving CRRT. As aforementioned in Method section, body weights used in the models were extracted from SEA-AKI study to be a representative of Asian sized critically ill patients [17]. Different effluent rates of 20, 25, and 35 mL/kg/h applied in the CRRT models were recommended from KDIGO and the international survey study to reflect real life practice [4,18]. All necessary parameters were incorporated into pharmacokinetic models to predict doripenem disposition in critically ill patients receiving CRRT for 48 h. Additionally, correlations between used pharmacokinetic parameters were applied in the models to create population-specific virtual patients.

Pharmacokinetic changes play major roles in antimicrobial dosing. Volume of distribution of hydrophilic antimicrobials tends to increase according to fluid accumulation, and hypoalbuminemia [1,3]. Volume of distribution of doripenem in critically ill patients reported in previously published studies and used in this simulation was 27.38 ± 12.81 L [7,8]. It was larger than the average value in healthy subjects of 16.8 L. The change in doripenem volume of distribution contributed to sub-therapeutic concentrations and the need of higher dose to achieve pharmacodynamic targets. Moreover, Vossen and colleagues [10] conducted a pharmacokinetic study in Austria and revealed that non-renal clearance in critically ill patients receiving CRRT was approximately 98 mL/min compared with 2 pharmacokinetic studies from the critically ill Asian population of approximately 45 mL/min [7,8]. The non-renal clearance in Vossen's study population was approximately twice as high when compared with the non-renal clearance found in an Asian population. As aforementioned, recommended doripenem dosing regimens for patients receiving CRRT should be derived from pharmacokinetic studies in a similar group of patients in terms of severity and race.

Achieving maximum bactericidal effect of carbapenems requires at least 40% of time interval between two doses [22]. Jones and colleagues performed the in vitro study of doripenem activity and their results revealed that bactericidal effect was observed at 4 times MIC for *Pseudomonas aeruginosa* [21]. In addition, previous clinical and pharmacokinetic-pharmacodynamic studies utilizied aggressive pharmacodynamics target of 4 times MIC breakpoint to evaluate antimicrobial efficacy and clinical outcomes [24,25], we decided to apply the pharmacodynamics target of 40%$fT_{>4MIC}$ in the models to evaluate recommended dosing regimens and define optimal doripenem dosing regimens for patients receiving CRRT.

Optimal doripenem dosing regimens for treating *Pseudomonas aeruginosa* infection in critically ill patients receiving 2 CRRT modalities and 3 different effluent flow rates regarding KDIGO recommended effluent rates and most common rates applied in ICU settings was 500 mg every 8 h.

Hidaka et al. conducted a pharmacokinetic study in 6 Japanese patients undergoing CRRT and reported that the optimal doripenem dosing regimen in patients receiving continuous hemodiafiltration was 250 mg every 12 h [7]. The effluent flow rate prescribed in this study was only 800 ml/h which contributed less extracorporeal clearance compared with other studies that used approximately 1000–2000 mL/h or KDIGO recommended effluent rate of

Table 1
Demographic and pharmacokinetics simulation parameters of doripenem.

Pharmacokinetics parameter	Ranges [limits]
Weight (kg)	60.72 ± 14.5 [40-∞] [14]
Volume of distribution (L)	27.38 ± 12.81 [10.88–62.90] [7,8]
Non-renal clearance (mL/min)	44.62 ± 13.39 [30.2–66.30] [7,8]
Free fraction	0.92 ± 0.18 [0–1] [6]
Sieving coefficient (SC)	0.49 ± 0.27 [0.089–1] [7,9,10]
Saturation coefficient (SA)	0.58 ± 0.31 [0.064–1] [7,9-12]

20–25 mL/kg/h. Undoubtedly, the recommendations from Ohchi and colleagues [26] that performed a pharmacokinetic study in Japanese critically ill patients receiving continuous hemodiafiltration with total effluent flow rate of 2400 mL/h were 1–1.5 g of doripenem daily. It showed that effluent flow rate is a major contribution of drug dosing consideration. However, both Hidaka's and Ohchi's studies [7,26] were basic pharmacokinetic studies using small numbers of patients and calculations based on only pharmacokinetic parameters to suggest doripenem dosing regimens. Our recommendations of 500 mg every 8 h were from simulations in a group of 5000 virtual patients for each dosing regimen with combination of pharmacokinetic and pharmacodynamic targets to define optimal dosing regimens.

Compared with dosing recommendations from Vossen and colleagues' study [10], a regimen of loading doses of 1.5–2 g followed by 1 g every 8 h was suggested to attain the pharmacodynamic target of doripenem concentrations exceeded 4 times MIC for entire dosing interval (100% $fT_{>4MIC}$). While our study used less aggressive target than Vossen's (40% $fT_{>4MIC}$), some in vitro and clinical trials suggested at least 40% of dosing interval of pharmacodynamic target is generally acceptable [22,24,25]. Moreover, patients' body weights and non-renal clearances in Vossen's study was considerably higher than ours (92.4 + 24.8 vs 60.72 ± 14.5 kg, and approximately 98 vs 45 mL/min, respectively) while other pharmacokinetic parameters were slightly different [10]. As reasons mentioned above, it could be explained why our suggested doripenem dosing regimen in aggressive pharmacodynamics target of 500 mg every 8 h was lower than recommendations from Vossen's study. Asian critically ill patients with lower body weight and non-renal clearance would need lower doses than Caucasian population.

Table 2
PTAs of recommended doripenem dosing regimens for Gram negative infections in 2 CRRT modalities with different effluent rates and aggressive pharmacodynamic target ($fT_{>4MIC}$).

Effluent rate	Dosing regimens	Probability of Target Attainment (40%$fT_{>4MIC}$)	
		CVVH	CVVHD
20 mL/kg/h	250 mg Q24h	0%	0%
	250 mg Q12h	2%	1%
	250 mg Q8h	49%	38%
	500 mg Q24h	2%	1%
	500 mg Q12h	88%	85%
	500 mg Q8h	100%	100%
	1000 mg Q 8 h	100%	100%
25 mL/kg/h	250 mg Q24h	0%	0%
	250 mg Q12h	2%	<1%
	250 mg Q8h	42%	33%
	500 mg Q24h	1%	<1%
	500 mg Q12h	86%	80%
	500 mg Q8 h	100%	100%
	1000 mg Q8h	100%	100%
35 mL/kg/h	250 mg Q24h	0%	0%
	250 mg Q12h	<1%	<1%
	250 mg Q8h	32%	23%
	500 mg Q24h	<1%	<1%
	500 mg Q12h	79%	68%
	500 mg Q8h	100%	98%
	1000 mg Q8h	100%	100%

CVVH; continuous venovenous hemofiltration, CVVHD; continuous venovenous hemodialysis.

Table 3
Recommendations of doripenem dosing regimens for treating Gram-negative infections (MIC of 2) in critically ill patients receiving CRRT.

Effluent rates	CVVH	CVVHD
20–25 mL/kg/h	500 mg every 8 h	500 mg every 8 h
35 mL/kg/h	500 mg every 8 h	500 mg every 8 h

CVVH; continuous venovenous hemofiltration, CVVHD; continuous venovenous hemodialysis.

Recent pharmacokinetic trial conducted in Australian critically ill patients receiving continuous venovenous haemodiafiltration from Roberts and colleagues revealed that a doripenem dosing regimen of 500 mg every 8 h was required to attain the pharmacodynamic target of 40% dosing interval of doripemen exceeded MIC value of ≤4 mg/L [11]. The median body weights in this study was 77 kg (67–96 kg) that was higher than average body weight used in models of our study. The total effluent flow rates and non-renal clearance in Roberts's study was similar to our parameters used in the models [11]. However, Roberts' study applied less aggressive pharmacodynamic target using 1 time MIC compared with 4 times MIC in our simulations. The optimal dosing regimen in our study with aggressive pharmacodynamics target was aligned with Roberts's suggestion. Body weights, effluent flow rates and selected pharmacodynamic targets mainly contributed to total doripenem clearance and dosing regimens.

Some drugs can be removed by membrane interaction known as adsorption phenomenon. Clinical impact of this effect is not fully investigated, CRRT hemofilter types, however, do not significantly affect extracorporeal drug clearance and selection of drug dosing regimen according to early saturation of adsorption [16].

Based on our simulation with MCS that generates virtual adult critically ill patients related using pharmacokinetic parameters from previously published studies and ICU patient's body weights, the doripenem dosing recommendation should be applied for only patients who match our assumption such as anuric patients, same effluent flow rates. Additionally, our study applied the MIC breakpoint of 2 mg/L from the Clinical Laboratory Standards Institute in the models [23]. Dosing adaptation regarding different MIC values form each setting would be suggested. Infection caused by a pathogen with low MIC value requires smaller dosing regimen to overcome the pharmacodymanic target. Using the optimal doripenem dosing regimen form our results cannot be used in settings that a resistant *P. aeruginosa* is a major concern. Clinical validation of those results is warrant.

5. Conclusion

A doripenem dosing regimen of 500 mg every 8 h was recommended for *P. aeruginosa* infection in Asian critically ill patients receiving continuous renal replacement therapy with both KDIGO recommended effluent rates and high volume CRRT. Some literature based dosing regimens for patients receiving CRRT could not attain the pharmacodynamic target. Different body size and effluent rate were important factors to appropriately dose antimicrobial agents in patients receiving CRRT. Validation of the recommendations is absolutely needed.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WC contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the manuscript. PP, TC, AB and CP analyzed and interpreted the data regarding simulations and probability of target attainment. NS involved in data collection and drafting and revising the manuscript. SP interpreted the data regarding simulations and probability of target attainment and also involved in drafting and revising the manuscript.

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