Population Pharmacokinetics of Doripenem in Critically Ill Patients with Sepsis in a Malaysian Intensive Care Unit

Mohd H. Abdul-Aziz,^{a,b} Azrin N. Abd Rahman,^{b,c} Mohd-Basri Mat-Nor,^d Helmi Sulaiman,^e Steven C. Wallis,^a Jeffrey Lipman,^{a,f} Jason A. Roberts,^{a,f} Christine E. Staatz^{c,g}

Burns, Trauma, and Critical Care Research Centre, The University of Queensland, Brisbane, Australia^a; School of Pharmacy, International Islamic University of Malaysia, Kuantan, Pahang, Malaysia^b; School of Pharmacy, The University of Queensland, Brisbane, Australia^c; Department of Anesthesiology and Intensive Care, School of Medicine, International Islamic University of Malaysia, Kuantan, Pahang, Malaysia^d; Infectious Diseases Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia^e; Royal Brisbane and Women's Hospital, Brisbane, Australia^f; Australian Centre of Pharmacometrics, Brisbane, Australia^g

Doripenem has been recently introduced in Malaysia and is used for severe infections in the intensive care unit. However, limited data currently exist to guide optimal dosing in this scenario. We aimed to describe the population pharmacokinetics of doripenem in Malaysian critically ill patients with sepsis and use Monte Carlo dosing simulations to develop clinically relevant dosing guidelines for these patients. In this pharmacokinetic study, 12 critically ill adult patients with sepsis receiving 500 mg of doripenem every 8 h as a 1-hour infusion were enrolled. Serial blood samples were collected on 2 different days, and population pharmacokinetic analysis was performed using a nonlinear mixed-effects modeling approach. A two-compartment linear model with between-subject and between-occasion variability on clearance was adequate in describing the data. The typical volume of distribution and clearance of doripenem in this cohort were 0.47 liters/kg and 0.14 liters/kg/h, respectively. Doripenem clearance was significantly influenced by patients' creatinine clearance (CL_{CR}), such that a 30-ml/min increase in the estimated CL_{CR} would increase doripenem CL by 52%. Monte Carlo dosing simulations suggested that, for pathogens with a MIC of 8 mg/liter, a dose of 1,000 mg every 8 h as a 4-h infusion is optimal for patients with a CL_{CR} of 30 to 100 ml/min, while a dose of 2,000 mg every 8 h as a 4-h infusion is best for patients manifesting a CL_{CR} of >100 ml/min. Findings from this study suggest that, for doripenem usage in Malaysian critically ill patients, an alternative dosing approach may be meritorious, particularly when multidrug resistance pathogens are involved.

Doripenem, a member of the carbapenem class of antibiotics, demonstrates broad antibiotic activity, including against the troublesome multidrug-resistant (MDR) pathogens (1). The pharmacokinetic (PK) profile of doripenem closely resembles that of other carbapenems. Similarly, this antibiotic demonstrates time-dependent activity, where the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with its efficacy is the duration of time (T) that free plasma drug concentrations remain above the MIC of the offending pathogen ($fT_{>MIC}$) (2). Doripenem has been approved for complicated intraabdominal and urinary tract infections in the United States and is also indicated for nosocomial pneumonia in Europe and the Asia-Pacific region. In Malaysia, doripenem is commonly reserved for the management of complicated infections deemed to be caused by *Pseudomonas aeruginosa* and, to some extent, *Acinetobacter baumannii*. As per local antibiotic guidelines, patients receiving doripenem in a Malaysian intensive care unit (ICU) typically receive a standard dose of 500 mg every 8 h as a 1-h intravenous (IV) infusion. However, the appropriateness of this dosing regimen is disputable, as it is based on PK/PD data derived from earlier studies which mostly recruited heterogeneous cohorts of healthy volunteers and non-critically ill Caucasian patients (3–6). Importantly, results of subsequent PK/PD studies suggest that current recommendations may be grossly flawed in critically ill patients and that optimal dosing requirements may significantly differ from that initially proposed (7–9).

Antibiotic dosing in critically ill patients is rarely a straightforward process (10). Extreme alterations in antibiotic PK, particularly increases in volume of distribution (V) and profound increases or decreases in renal drug clearance (CL), are common

occurrences in the ICU and may severely influence drug exposure (11, 12). To further complicate matters, pathogens that are usually isolated in the ICU differ from those in the general wards, as they are commonly less susceptible to the current antibiotic armamentarium (13, 14). Additionally, local microbiology and antibiotic resistance patterns may greatly vary across different geographical regions, affecting antibiotic dosing requirements (15). In this context, it is imperative to consider regional antibiotic susceptibility data whereby, in the Asia-Pacific region, the MIC required to inhibit the growth of 90% of organisms (MIC_{90}) for doripenem against *P. aeruginosa* was reported as 8 mg/liter (15, 16). However, a typical dose of 500 mg every 8 h as a 1-h infusion is reported to be effective only against pathogens with an MIC of ≤ 2 mg/liter; its application, therefore, is likely to fail in such a scenario (4, 6).

Current population PK models which describe doripenem disposition have mostly been developed in heterogeneous Caucasian patient groups (3, 4, 6–8, 17, 18). However, it is likely that the PK of doripenem may vary across different races; therefore, the exist-

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Address correspondence to Mohd H. Abdul-Aziz, mohd.abdulaziz1@uqconnect.edu.au.

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ing PK models may not accurately characterize the PK differences in Malaysian critically ill patients (19). Interethnic differences, such as relatively smaller body size and lower body fat distribution among Malaysian critically ill patients as opposed to their Caucasian counterparts, may influence doripenem exposure. Consequently, dosing requirements may also differ between these two patient populations.

In this study, we aimed to describe the population PK of doripenem in Malaysian critically ill patients with sepsis and also to investigate sources of PK variability. With this resulting model, we then sought to develop clinically relevant dosing guidelines specifically for these patients.

MATERIALS AND METHODS

Setting. This prospective, open-label PK study was undertaken in a general ICU of a tertiary hospital in Pahang, Malaysia, between November 2012 and October 2013. The study was registered and approved by the Medical Research Ethics Committee Malaysia (NMRR-12-649-13058). Written informed consent to participate in the study was obtained from each participant or their legally authorized representatives.

Study population. Patients were eligible for recruitment if they were adult (≥ 18 years old) ICU patients and were prescribed doripenem for the treatment of sepsis (defined as presumed or confirmed infection with systemic inflammatory response syndrome manifesting in the previous 48 h). Patients were excluded if they required any form of extracorporeal renal support, were pregnant or lactating mothers, or were known or presumed to be allergic to doripenem or any of the carbapenem antibiotics.

Doripenem administration and ancillary treatments. Doripenem (Doribax; Janssen-Cilag, Raritan, NJ) was administered over 1 h using a volumetric infusion pump controller at a dose of 500 mg in 100 ml of 0.9% sodium chloride as part of the patients' prescribed courses of therapy. All subsequent patient management, including the addition of other antibiotics and drugs, was at the discretion of the treating clinician and was not affected by study procedures.

Study protocol. Pharmacokinetic sampling was performed during one 8-h dosing interval on day 1 (i.e., representing a scenario when patients were presumed to be at their worst clinically) and day 3 (i.e., representing a scenario when patients were presumed to be more clinically stable) of doripenem treatment. Blood samples (3 ml) were drawn from a central line and were collected into lithium-heparinized tubes at the following times on day 1 (occasion 1) and day 3 (occasion 2) of therapy: immediately before the first doripenem dose was administered, then at 0.5, 0.75, 1, 1.5, 2, 4, and 8 h after the start of the infusion.

Blood samples were immediately refrigerated at 4°C and, within 1 h, centrifuged at 3,000 rpm for 10 min to separate plasma. Plasma samples were frozen at -80°C within 24 h of collection. The frozen plasma samples were shipped on dry ice by a commercial courier company and were then assayed at the Burns, Trauma, and Critical Care Research Centre (BTCCRC), The University of Queensland, Australia.

Apart from blood collection, various demographic, anthropometric, and clinical data were also collected prospectively. The severity of illness indices, which included the acute physiology and chronic health evaluation (APACHE) II score on admission (20) and the sequential organ failure assessment (SOFA) scores on each occasion of sampling (21), were recorded. Creatinine clearance (CL_{CR}) was estimated on each occasion of sampling using the Cockcroft-Gault formula (22).

Doripenem assay. Doripenem concentrations in plasma samples were measured, after protein precipitation, by a validated high-performance liquid chromatography method with ultraviolet detection on a Shimadzu Prominence (Shimadzu Corporation, Kyoto, Japan) instrument. Cefotaxime was used as the internal standard. Samples were assayed in batches alongside calibration standards and quality-control replicates at high, medium, and low concentrations. All bioanalysis techniques were conducted

in accordance with the U.S. Food and Drug Administration's guidance for industry on bioanalysis (23). The assay limit for doripenem in plasma was 0.2 mg/liter, with precision and accuracy determined at 5.7% and 4.4%, respectively. Linearity of the assay was demonstrated in the range of 0.2 to 100 mg/liter. Interassay precision and accuracy, determined at three different concentrations over three separate days, were all within 7%. Observed concentrations of doripenem were corrected for protein binding by reducing the concentrations by 10% (24).

Population pharmacokinetic analysis: software. Plasma concentration-time data for doripenem were analyzed using nonlinear mixed-effect modeling approach in NONMEM version 7.3 (Icon Development Solutions, Ellicott City, MD, USA) with an Intel Fortran compiler and Perl-Speaks-NONMEM (PsN) version 4.0 (25). Throughout the model building process, typical population PK parameter estimates, between-subject variability (BSV), between-occasion variability (BOV), and residual unexplained variability (RUV) were estimated using the first-order conditional estimation with the interaction method. Data exploration and visualization, as well as model diagnostics, were performed using PsN version 4.0 (26), Pirana version 2.7.1 (27), and Xpose version 4.0 (<http://xpose.sourceforge.net>) in R (<http://www.r-project.org>) (28).

Structural and stochastic model development. Plasma concentration-time data for doripenem were fitted to one-, two- and three-compartment disposition models with first-order elimination using the ADVAN subroutines from the NONMEM library. BSV and BOV were evaluated using an exponential variability model. BSV was evaluated on all PK parameter estimates; when significant, it was then included in the next model-building step. Covariance between values of BSV was estimated using a variance-covariance matrix. Additive, proportional, and combined residual random error models were tested to describe RUV.

Competing models were assessed on the basis of minimum objective function value (OFV), goodness-of-fit diagnostics, and their physiological plausibility. A reduction in the OFV of >3.84 for one degree of freedom was considered a statistically significant improvement ($P < 0.05$) for a nested model. Observed versus population-predicted concentration (PRED) or individual-predicted concentration (IPRED) plots, individual weighted residual versus IPRED plots, and conditional-weighted residual (CWRES) versus time-after-dose plots were used to evaluate the graphical goodness-of-fit of various models.

Covariate screening and model development. Potential covariates that were clinically plausible were screened for their influence on the PK of doripenem. Factors tested included patient total body weight, estimated CL_{CR} , and SOFA score on the day of investigation. Covariate effects were identified via visual (scatter plots) and also numerical (stepwise, generalized additive models by Xpose version 4.0) methods. Allometric scaling was applied *a priori* and fixed to theory-based values of 3/4 for clearances and 1 for volumes of distribution, all standardized to a body weight of 70 kg (29). The covariate-parameter models that were evaluated were linear, piecewise-linear, exponential, power, and sigmoidal models. During the covariate model-building process, stepwise forward inclusion and backward elimination approaches were employed. Reductions in the OFV of >3.84 ($P < 0.05$) and of >10.83 ($P < 0.01$) were required for a covariate to be considered significant in the forward inclusion and backward elimination steps, respectively.

Model evaluation and prediction. A nonparametric bootstrap method ($n = 5,000$) was used to assess the final model accuracy and stability. From the bootstrap empirical posterior distribution, 95% confidence interval (CI) for the bootstrap replicates was obtained and compared with parameter estimates from the final model. A visual predictive check (VPC) was also performed by simulating 5,000 patients to evaluate the predictive performance of the final model. Visual checks were performed by overlaying the observed data points with the 95% confidence intervals of the simulated 5th, 50th, and 95th percentile curves.

Dosing simulations. Different doripenem dosing regimens in subjects with various degrees of renal function were examined using Monte Carlo simulation in NONMEM. Final PK model parameter estimates

TABLE 1 Clinical and demographic details of the enrolled patients

Patient	Sex ^a	Age (yr)	BMI (kg/m ²) ^b	APACHE II ^c	SOFA ^d	Admission diagnosis	CL _{CR} (ml/min) ^e	Causative pathogen	Clinical outcome
1	M	68	23.4	22	10	Intraabdominal sepsis	30	Nil identified	Survived
2	M	39	21.8	17	7	VAP ^f	77	<i>A. baumannii</i>	Died
3	F	19	16.7	11	3	VAP	161	<i>A. baumannii</i>	Survived
4	M	74	29.7	18	5	Intraabdominal sepsis	65	<i>A. baumannii</i>	Died
5	M	61	29.7	12	6	VAP	119	Nil identified	Survived
6	M	49	23.2	19	6	VAP	116	Nil identified	Survived
7	M	31	22.6	16	7	Intraabdominal sepsis	92	Nil identified	Survived
8	M	44	20.8	21	5	VAP	126	<i>A. baumannii</i>	Died
9	M	54	24.2	39	7	VAP	36	Nil identified	Survived
10	M	58	24.7	20	5	VAP	44	<i>A. baumannii</i>	Survived
11	M	57	19.3	15	4	VAP	99	<i>P. aeruginosa</i>	Survived
12	F	31	22.2	23	5	Intraabdominal sepsis	66	Nil identified	Survived
All patients									
Median		52	22.9	19	6		85		
IQR ^g		33–60	21.1–24.6	15–22	5–7		49–118		

^a M, male; F, female.^b BMI, body mass index.^c APACHE II, acute physiology and chronic health evaluation II; APACHE II score on admission.^d SOFA, sequential organ failure assessment; SOFA score on admission.^e CL_{CR}, estimated Cockcroft-Gault creatinine clearance; estimated CL_{CR} on admission.^f VAP, ventilator-associated pneumonia.^g IQR, interquartile range.

were used to generate concentration-time profiles based on 1,000 simulations. Both 1- and 4-h infusions of 250 mg, 500 mg, 1,000 mg, and 2,000 mg of doripenem every 8 h were examined in subjects with a CL_{CR} of 30 ml/min, 50 ml/min, 70 ml/min, 100 ml/min, and 150 ml/min. The probability of target attainment (PTA) for a dosing regimen was calculated as the percentage of patients achieving an $fT_{>MIC}$ of 40% for a given MIC. These probabilities were then plotted against a range of MICs, and optimal dosing was denoted by achieving at least 90% PTA.

RESULTS

Demographic and clinical data. A total of 140 plasma samples across two sampling occasions were collected from 12 critically ill patients. Demographic and clinical characteristics of the recruited patients are presented in Table 1. More than 65% of the cohort was male and ≥ 45 years of age. Median APACHE II and SOFA scores on admission were 19 and 6, respectively. Median SOFA scores were similar on both sampling occasions. More than half of the patients had an estimated CL_{CR} of ≥ 80 ml/min on ICU admission. The median CL_{CR} on occasion 1 (88.0 ml/min) was higher than on occasion 2 (72.0 ml/min). The majority (66.7%) received doripenem for ventilator-associated pneumonia, and the most prevalent causative pathogen identified was *A. baumannii*. All patients required invasive mechanical ventilation and vasopressor support. Three patients died during their ICU stays, and the deaths were more likely to be related to patients' preexisting comorbidities and progressive worsening of their clinical conditions. All three patients had a pre-ICU hospital stay of ≥ 2 months prior to study inclusion.

Pharmacokinetic model-building. The time course of doripenem in plasma was adequately described by a two-compartment linear model with combined residual error. BSV on CL ($\Delta OFV = -97.1$), central volume of distribution (V_1 ; $\Delta OFV = -46.6$), and peripheral volume of distribution (V_2 ; $\Delta OFV = -8.04$) significantly improved the model fit. Introduction of BOV on CL ($\Delta OFV = -26.9$) resulted in further model improvement.

During covariate testing inclusion of an influence of CL_{CR}

(normalized to the population mean value of 82.5 ml/min) on CL improved the model fit (decreasing the OFV by 32.3 points and reducing BSV on CL from 56.7% to 10.4%). The influence of CL_{CR} on CL of doripenem was best described in an exponential relationship as shown in equation 1:

$$CL = \theta_{CLpop} \times e^{\theta_{CLCR} \times (CL_{CR} - 82.5)} \quad (1)$$

where CL is the estimated doripenem clearance in a given individual (in liters/h/70 kg), θ_{CLpop} is the typical value of doripenem clearance in the population, θ_{CLCR} describes the influence of creatinine clearance on doripenem clearance, and CL_{CR} is the patient's estimated creatinine clearance (in ml/min). Typical PK parameter estimates from the base and final model are summarized in Table 2.

Basic goodness-of-fit plots, including the CWRES versus time-after-dose plot, demonstrated that the final model adequately described the data with little model mis-specification (Fig. 1). PRED and IPRED values were in good agreement with observed doripenem concentrations. CWRES values were generally homogeneously distributed over the sampling period. In a VPC plot associated with the final model, the predicted median curve demonstrated a good fit to the observed data, albeit with a slight overprediction of concentrations during the elimination phase (Fig. 2). Results from the nonparametric bootstrap further corroborated the robustness of the final model, demonstrating narrow 95% confidence intervals with bootstrap median values close to typical population PK parameter estimates of the final model (Table 2).

Dosing simulations. The PTAs for 40% $fT_{>MIC}$ of various doripenem dosing regimens, with various MIC and CL_{CR} values, are presented in Fig. 3. In patients with a CL_{CR} of 70 ml/min, a standard doripenem dose of 500 mg every 8 h as a 1-h infusion demonstrated optimal rates of PTA ($>90\%$) against pathogens with an MIC of ≤ 2 mg/liter. In other scenarios, alternative dosing strategies showed better rates of target attainment; 1,000-mg and

TABLE 2 Typical population parameter estimates for the base and final covariate models and the 5,000 bootstrap runs

Parameter	Base model	Final model ^a	Bootstrap (<i>n</i> = 5,000)			
			Mean	Median	95% CI ^b	
					2.5%	97.5%
OFV ^c	381.03	348.76				
Fixed effects ^d						
CL (liters/h/70 kg)	11.5	10.1	9.9	9.9	8.9	10.9
V ₁ (liters/70 kg)	15.5	15.5	16.1	15.8	10.5	22.0
V ₂ (liters/70 kg)	17.9	17.7	18.6	18.1	12.2	26.6
Q (liters/h/70 kg)	36.6	36.3	36.1	36.8	28.4	41.5
θ _{CLCR} ^e		0.014	0.014	0.014	0.012	0.017
BSV ^f						
CL (%)	56.7	10.4	14.8	14.3	4.8	21.5
V ₁ (%)	62.0	59.7	59.3	57.2	22.8	87.0
V ₂ (%)	73.3	73.8	68.4	64.7	40.0	94.0
BOV ^g						
CL (%)	33.9	22.2	16.2	8.7	4.11	28.3
Random error						
Proportional (% CV)	8.3	9.0	10.0	9.1	3.7	18.8
Additive (SD ^h) (mg/liter)	1.31	1.25	0.97	1.17	0.17	1.64

^a Final model:

$$CL = \theta_{CLpop} \times e^{\theta_{CLCR}} \times (CL_{CR} - 82.5) \times \left(\frac{WT}{70}\right)^{0.75}$$

$$V_1 = \theta_{V1pop} \times \left(\frac{WT}{70}\right)$$

$$V_2 = \theta_{V2pop} \times \left(\frac{WT}{70}\right)$$

$$Q = \theta_{Qpop} \times \left(\frac{WT}{70}\right)^{0.75}$$

^b CI, confidence interval.^c OFV, objective function value.^d CV, coefficient of variation; CL, clearance; V₁, volume of distribution of central compartment; V₂, volume of distribution of peripheral compartment; Q, intercompartmental clearance.^e θ_{CLCR}, effect of estimated Cockcroft-Gault creatinine clearance on doripenem clearance.^f BSV, between-subject variability.^g BOV, between-occasion variability.^h SD, standard deviation.

2,000-mg doses every 8 h as a 4-h infusion demonstrated optimal rates of PTA against pathogens with MICs of ≤8 and ≤16 mg/liter, respectively. Increasing CL_{CR} values were associated with lower rates of PTA for the same MIC. With increasing MIC values, the likelihood of obtaining optimal PTA diminished, while increasing the dose and prolonging the duration of infusion resulted in higher rates of PTA.

DISCUSSION

Despite profound PK and physiological differences from the noncritically ill population, critically ill patients are typically given conventional dosing regimens (30), potentially leading to suboptimal antibiotic exposure and, subsequently, therapeutic failures. Failure of emerging antibiotics in several recent clinical trials recruiting critically ill patients underscores the deficiencies associated with the licensed one-dose-fits-all dose in this unique population (31, 32). Furthermore, the ramifications of this simplistic dosing approach may be more severe in some geographical regions, particularly among the Southeast Asian countries, where

local microbiology and antibiotic resistance patterns significantly vary from those of the Western countries. In our current study, we were able to demonstrate how bacterial susceptibility and physiological changes associated with critical illness substantially influence optimal doripenem exposure and, importantly, how these alterations may be circumvented via alternative dosing strategies.

In our cohort of critically ill patients, the PK of doripenem was best described using a two-compartment model with zero-order input and first-order elimination. Such a disposition model is in agreement with other currently available literature in critically ill patients with conserved renal function (7, 9, 18, 33). Typical V (V₁ + V₂) of doripenem in our cohort was 0.47 liters/kg (range, 0.14 to 1.7 liters/kg), which is generally consistent with other reports in critically ill patients with conserved renal function (0.30 to 0.54 liters/kg) (7, 9, 18, 33). This estimate is considerably larger than that previously described in healthy volunteers (0.22 to 0.24 liters/kg) (34, 35) and noncritically ill patients (0.18 to 0.24 liters/kg) (17, 36–38). This was anticipated, as the V of hydrophilic antibiotics, such as aminoglycosides (39, 40)

FIG 1 Goodness-of-fit plots associated with the final population pharmacokinetic model for doripenem. The solid black line represents the line of identity, and the dashed gray line represents the smooth fitting for observations. Clinical observations are represented by black solid circles.

and beta-lactams (12), is often reported to be 2-fold greater in critically ill patients. This could be attributed to extreme fluid extravasation into the interstitium, a phenomenon commonly associated with increasing sickness severity (41). Furthermore, medical interventions, including aggressive fluid resuscitation (42) and mechanical ventilation (43), both of which were provided to all of our patients during their earlier course of therapy, have been associated with increased V .

The typical CL of doripenem in this cohort was 0.14 liters/kg/h (range, 0.06 to 0.45 liters/kg/h), which is generally consistent with that reported in critically ill patients with conserved renal function (0.12 to 0.25 liters/kg/h) (7, 9, 18, 33). However, this estimate is notably lower than that previously described in healthy volunteers (0.22 to 0.25 liters/kg/h) (34, 35) and noncritically ill patients (0.16 to 0.25 liters/kg/h) (8, 36–38). The differences were expected, as the noncritically ill population would presumably have better end-organ function than our patient cohort. Consistent with previous data (4, 33, 36, 38), estimated Cockcroft-Gault CL_{CR} , a surrogate measure for renal function in our analysis, albeit less accurate than the measured CL_{CR} , was a key predictor of doripenem CL. This relationship is highly predictable, since doripenem is extensively cleared via renal elimination; approximately 75%, and in some reports up to 90%, of doripenem is cleared via the renal route (35). Based on equation 1, a 30-ml/min increase in the estimated CL_{CR} would increase doripenem CL by 52%.

Our model was also significantly improved with the incorpora-

tion of BOV on CL, denoting a certain degree of variability in doripenem CL between the first and second sampling occasions. Based on equation 1, doripenem CL on day 1 (0.16 liters/kg/h) was approximately 30% higher than on day 2 (0.12 liters/kg/h). Essentially, this means that dosing requirements in this population may be dynamic and, as such, that regular dosing reviews and modifications may also be needed throughout antibiotic treatment. Given that variability in antibiotic exposures is being increasingly reported in critically ill patients, beta-lactam therapeutic drug monitoring is highly warranted in this population, and the approach would appear to be meritorious not only to prevent underdosing, which may increase the likelihood of antibiotic resistance, but also to minimize the risk of adverse effects during therapy.

Augmented renal clearance (ARC) (44) is highly prevalent in most ICU settings (17.9% to 41.1%) (45, 46), including Malaysian critically ill populations (47), and has been linked with subtherapeutic concentrations of beta-lactams and poor clinical outcomes (11, 48, 49). In patients with an elevated CL_{CR} (≥ 130 ml/min), a conventional one-dose-fits-all approach to doripenem dosing appears to be grossly flawed. Our Monte Carlo simulations highlighted that, while a standard dose of 500 mg every 8 h as a 1-h infusion in a patient with a CL_{CR} of 70 ml/min would have 98.7% probability of target attainment against pathogens with an MIC of 2 mg/liter, a patient with ARC manifesting a CL_{CR} of 150 ml/min would only have 9.9% probability of target attainment. The repercussions of neglecting the phenomenon when dosing antibiotics in critically ill patients can be highlighted by the premature

FIG 2 Visual predictive check plot associated with the final population pharmacokinetic model for doripenem. The solid black circles represent the observed data, the solid gray line represents the 50th percentile of the observed data, the solid black line represents the 50th percentile of the simulated data, the dashed gray lines represent the 5th and 95th percentiles of the observed data, the dashed black lines represent the 5th and 95th percentiles of the simulated data, and the shaded areas represent the 95% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated plasma concentrations.

termination of a phase III, prospective, multicenter, randomized, double-blind clinical trial comparing a fixed 7-day course of doripenem (1,000 mg every 8 h as a 4-h infusion) with a 10-day course of imipenem-cilastatin (1,000 mg every 8 h as a 1-h infusion) in critically ill adult patients with ventilator-associated pneumonia (31). The trial was terminated when interim analyses revealed greater clinical failure and mortality rates in the doripenem treatment arm. Crucially, further analysis in the modified intention-to-treat group also showed that patients receiving doripenem with high CL_{CR} (>150 ml/min) had clinical cure rates 27% worse than the comparator group (95% CI, 1.4% to 55.4%). Essentially, patients at high risk of ARC, such as young trauma patients without significant organ dysfunction (44), need to be identified early so that appropriate dose modifications can be implemented immediately.

In Malaysia, particularly in our ICU, doripenem monotherapy is reserved for the management of complicated infections deemed to be caused by *P. aeruginosa* and, to some extent, *A. baumannii*. In two large antibiotic susceptibility prevalence studies conducted in the Asia-Pacific region (15, 16), the MIC_{90} for doripenem against *P. aeruginosa* was 8 mg/liter. Our data suggest that, for such an MIC , a dose of 1,000 mg every 8 h as a 4-h infusion is optimal for patients with a CL_{CR} of 30 to 100 ml/min and that a dose of 2,000 mg every 8 h as a 4-h infusion is best for patients manifesting a $CL_{CR} >100$ ml/min. Such recommendations are consistent with several large pharmacodynamic simulation studies conducted in the Asia-Pacific region (50, 51) as well as in other parts of the world (3, 52). This study

provides additional PK/PD data to support an alternative doripenem dosing approach in critically ill patients, particularly when pathogens with high $MICs$ are involved. However, future clinical studies, preferably in the form of a multinational randomized controlled trial, are required to ascertain the clinical efficacy and safety of the suggested doripenem dosing regimen in this patient group. For *A. baumannii*, which is commonly MDR, empirical combination antibiotic therapy is currently preferred instead of doripenem monotherapy in our ICU. Furthermore, the MIC_{90} for doripenem against *A. baumannii* in the Asia-Pacific region was reported as ≥ 32 mg/liter (15, 16). For such an MIC , even with a dose of 2,000 mg every 8 h as a 4-h infusion, optimal exposure was only achieved for patients with reduced CL_{CR} in our cohort (e.g., <70 ml/min).

This study has several limitations. A relatively small number of critically ill patients ($n = 12$) with a narrow body weight range were included; thus, our model may not fully characterize the PK of doripenem in all Malaysian ICU patients. A number of patients with conserved renal function were recruited to examine altered dosing approaches in this cohort. Dosing recommendations derived from our Monte Carlo simulations should not be extrapolated to other patient populations, such as the obese or those on extracorporeal renal support. We also acknowledge limitations with the Cockcroft-Gault formula in estimating renal function in this cohort, with measured CL_{CR} more appropriate in the ICU setting. Neither free (unbound) doripenem concentrations nor drug concentration at the sites of infections (e.g., epithelial lining fluid concentrations) were measured in this study. The total

FIG 3 The probability of target attainment for various simulated doripenem dosing regimens to achieve 40% $fT_{>MIC}$ in patients with a creatinine clearance of 30 ml/min (top left), 50 ml/min (top right), 70 ml/min (middle left), 100 ml/min (middle right), and 150 ml/min (bottom). The dashed black lines denote optimal doripenem dosing, which was signified by achieving at least 90% probability of target attainment.

doripenem concentration was measured and applied in the analysis with correction for protein binding. We believe that this approach is highly acceptable for drugs with low protein-binding properties, such as doripenem (approximately 10% protein bound) (53).

Conclusions. Critically ill patients frequently manifest extreme physiological changes, which may alter antibiotic pharmacokinetics and subsequently reduce effective drug exposure. Importantly, findings from this study further show that the licensed one-dose-fits-all dosing strategy for doripenem is likely to be flawed in the critically ill population. An alternative dosing approach, such as the empirical use of a prolonged 4-h infusion, may be considered to account for pharmacokinetic and illness-severity differences in this unique patient population, particularly when MDR Gram-negative organisms are involved.

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