Pharmacokinetic/Pharmacodynamic Analysis for Doripenem Regimens in Intensive Care Unit Patients

Ryota Tanaka,*a Yuhki Sato,a Koji Goto,b Norihisa Yasuda,b Yoshifumi Ohchi,b Yosuke Suzuki,a Tamio Ueno,a Kentaro Ito,a Tetsuya Kaneko,a Shusaku Kurogi,a Ko Nonoshita,a and Hiroki Itoh,a

*aDepartment of Clinical Pharmacy, Oita University Hospital; Yufu, Oita 879–5593, Japan; bDepartment of Anesthesiology and Intensive Care, Faculty of Medicine, Oita University; Yufu, Oita 879–5593, Japan; and cClinical Laboratory Center of Oita University Hospital; Yufu, Oita 879–5593, Japan.

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Doripenem (DRPM) is a broad-spectrum antibacterial agent often used as empirical therapy for critically ill patients, although there is a lack of studies validating the recommended dosage regimen for patients admitted to intensive care unit (ICU), based on pharmacokinetic (PK)/pharmacodynamic (PD) index. In this study, we estimated the free time above minimum inhibitory concentration (%T>MIC) of DRPM using population PK analysis of 12 patients in ICU, and evaluated the validity of the dosage regimen stratified by creatinine clearance. Using a 2-compartment population PK model reported previously, the mean total clearance or distribution volume of DRPM estimated by Bayesian estimation was significantly lower or higher than that of based on population PK model. The estimated %T>MIC (%) of the recommended standard (normal renal function: 0.5 g every 8 h, moderate: 0.25 g every 8 h, severe renal impairment: 0.25 g every 12 h) and higher doses (normal: 1.0 g every 8 h, moderate: 0.5 g every 8 h, severe: 0.25 g every 8 h) against MICs of 0.5, 1 and 2 µg/mL exceeded 40% in all patients. When stratified by creatinine clearance, the PK/PD breakpoints estimated by Monte Carlo simulation in three grades of renal function tended to be higher than the previously reported PK/PD breakpoints for patients with urinary tract infection, an infection of lesser severity than ICU patients. These results suggest that the dosage regimen stratified by renal function derived from Japanese package insert may be sufficient to achieve effective treatment in ICU patients.

Key words doripenem; pharmacokinetic/pharmacodynamic analysis; intensive care unit; breakpoint

Doripenem (DRPM) is a newer carbapenem antimicrobial agent with potent and broad spectrum activities against Gram-positive, Gram-negative and anaerobic bacteria, and is more potent against Pseudomonas aeruginosa than other carbapenems.1–3) Doses of 0.5–3.0 g daily in two or three divided doses administered by 0.5 or 1 h infusion are used commonly to treat infectious diseases such as pneumonia, complicated urinary tract infection and intra-abdominal infections. In order to provide optimal antimicrobial therapy, selecting an effective and well-tolerated dosage regimen based on pharmacokinetic (PK)/pharmacodynamic (PD) index is important. For DRPM and other β-lactams with time-dependent antimicrobial activity, an effective dosage regimen requires that the blood concentrations exceed the minimum inhibitory concentration (MIC) of the infecting bacteria for at least 40% of the dosing interval.4) Therefore, the appropriate dosage regimen based on time above MIC (%T>MIC) is of great importance when using DRPM.

Critically ill patients in the intensive care unit (ICU) are often affected by infections, and are given antimicrobial agents with a broad spectrum.5) In particular, since severe sepsis and septic shock are major causes of morbidity and mortality in the ICU, early use of carbapenems including DRPM as an empirical therapy is recommended by international guidelines for the management of severe sepsis and septic shock.5) Since inadequate antibiotic therapy is a critical determinant of mortality in patients admitted to ICU with overwhelming infection, the choice of not only an antibiotic with appropriate spectrum guided by local bacterial epidemiological data, but also proper dosing regimen governed by PK/PD index is extremely important for successful treatment of these patients.6)

Previous investigations suggest that the pathophysiology of critical illness may cause significant PK changes of various drugs.8) Critically ill patients in the ICU are often complicated by multiple organ dysfunction syndromes that may include renal and/or hepatic dysfunction.9) This will result in decreased drug clearance, prolonged half-life, and potential toxicity from elevated blood concentrations and/or accumulation of metabolites. On the other hand, patients with sepsis may have significantly increased cardiac output and renal perfusion leading to elevated creatinine clearance (Ccr), which results in very high drug clearance and low blood concentration in the case of renally excreted drugs.10) Therefore, the importance of individualized approaches to dosing of drugs, especially renally excreted drugs, in critical ill patients has been highlighted. Doripenem is excreted renally,11) and is frequently used for critically ill patients in ICU. However, there is a lack of studies validating the dosage regimen based on PK/PD index of DRPM for these patients.

The overall aim of this study was to evaluate the validity of the recommended dosage regimens of DRPM based on renal function for patients admitted to ICU. First, the plasma concentrations of DRPM after infusion were determined using HPLC. Second, the PK parameters were analyzed by Bayesian estimation using a population PK model reported previously. Finally, the PK/PD breakpoint estimated by Monte Carlo simulation using the above parameters was compared to the PK/PD breakpoint for patients with urinary tract infection and prostatitis, an infection of lesser severity than ICU patients reported by Ikawa et al.12)
PATIENTS AND METHODS

Subjects Twelve patients admitted to the ICU at Oita University Hospital, who were given DRPM between July 2013 and May 2015 were studied. Patients who were on continuous hemodi- lution were excluded. Written informed consent was obtained from either the patients or their legally authorized representatives. The protocol for this study was approved by the Oita University Faculty of Medicine Ethics Committee (Judgement reference number: 613) before the study was started.

Procedures and Sample Collection DRPM (Finibax®; Shionogi Co., Ltd., Osaka, Japan) was infused intravenously at a dose of 0.5 g (n=11; Ccr≥30) or 0.25 g (n=1; Ccr<30) every 8 h. Each dose was reconstituted in 20 mL of normal saline and given as an intravenous drip over 1 h. Blood samples were collected from an indwelling arterial line into heparinized tubes. Blood sampling was conducted before DRPM treatment and at 1 (just prior to the end of infusion), 2, 4, 6 and 8 h after initiating infusion. Blood samples were centrifuged at 1900×g at 4°C for 5 min, and plasma samples were frozen immediately and stored at −40°C until assay.

DRPM Assay Total DRPM concentration in plasma was measured according to the HPLC method described by Ikeda et al.13 with modification. Briefly, 50 µL of 100 µg/mL meropenem in extra pure water (internal standard) and 400 µL of extra pure water were added to 20 µL of plasma in a polyethylene centrifuge tube. After vortexing, the mixture was applied to a solid phase extraction (SPE) column (Oasis HLB 30 mg/mL, 30 µm particle size; Waters, MA, U.S.A.) conditioned with 1 mL of methanol and equilibrated with 1 mL of extra pure water. The SPE column was washed with 1 mL of extra pure water, and eluted with 1 mL of methanol. After evaporating to dryness under N2 gas stream at 40°C, the organic extract was reconstituted with 150 µL of mobile phase. Then, 50 µL of the resulting solution was injected into the chromatographic system. The HPLC system (Waters 2695) was used with a Shiseido Capcell Pak C18 MGII column (5 µm, 250 mm×4.6 mm; Shiseido Co., Tokyo, Japan) and ultraviolet absorbance detection (Waters 2489 UV/Vis) at a wavelength of 295 nm. The mobile phase was a mixture of 50 mM sodium phosphate buffer (pH 3.2) and acetonitrile (93.5:6.5, v/v). The flow rate of the mobile phase was set at 1 mL/min, and the column and sample cooler temperatures were 40 and 10°C, respectively. Peaks were recorded and integrated using Empower3® (Waters). The separation of DRPM and internal standard was satisfactory, and was free of interfering peaks from the plasma matrix. The limit of quantification for this assay was 0.5 µg/mL, and the method was linear from 0.5 µg/mL to 100 µg/mL (r²=0.999). Assay reproducibility was assessed by coefficients of variation (CVs). The intra-day CVs for samples containing 1.5, 15 and 75 µg/mL were 3.3, 1.9 and 3.4%, respectively, while the corresponding inter-day CVs were 12.3, 6.8 and 4.0%. Since previous study reported plasma protein binding rate of DRPM in humans is 8.1%,14 the free plasma concentration of DRPM was calculated by multiplying total plasma concentration by 0.919.

PK Analysis Nandy et al.15 developed a population PK model of DRPM based on a 2-compartment infusion model from data of phase 1, 2 and 3 studies conducted in both healthy volunteers and critically ill patients. We used this model to estimate the PK parameters of DRPM for each subject. This model was parameterized in terms of total clearance (CL), central volume of distribution (V₁), distribution clearance between the central and peripheral compartments (Q) and peripheral volume of distribution (V₂), as shown in the following covariate model:

\[
\begin{align*}
CL (L/h) &= 13.6 \times (Ccr/98)^{0.659} \\
V_1 (L) &= 11.6 \times (WT/73)^{0.596} \\
Q (L/h) &= 4.74 \times (WT/73)^{1.06} \\
V_2 (L) &= 6.04 \times (Ccr/98)^{0.417} \times (WT/73)^{0.840} \times (AGE/40)^{0.307} (4)
\end{align*}
\]

where Ccr, WT and AGE are creatinine clearance (mL/min), body weight (kg) and age (years), respectively, of each subject. Creatinine clearance was calculated by the Cockcroft–Gault equation.16 The Bayesian estimate was employed to estimate individual PK parameters from plasma concentrations of each subject based on the population PK parameters, using least squares algorithms [MULTI (BAYES)].17 The plasma concentration profiles were simulated based on the population PK parameters or Bayesian-estimated PK parameters.

PK/PD Target Attainment The free %T>MIC (fT>MIC (%)) was defined as the percentage of time for which DRPM free plasma concentration remains above the MIC for a dosing period. The fT>MIC (%) against MICs 0.5, 1, 2, 4, 8 and 16 µg/mL were estimated from the simulated plasma concentration profiles after Bayesian estimation of DRPM for each subject. The subjects were stratified by Ccr into three grades of renal function, as described in the Japanese package insert: normal renal function (Ccr≥60), moderate (60>Ccr≤30) and severe renal impairment (30>Ccr) (Partial modification).18 Simulation was performed for each renal function group, assuming that DRPM was infused at a standard dosage regimen (normal: 0.5 g every 8 h, moderate: 0.25 g every 8 h, severe: 0.25 g every 12 h) or a higher dosage regimen (normal: 1.0 g every 8 h, moderate: 0.5 g every 8 h, severe: 0.25 g every 8 h) (Table 1).

Monte Carlo Simulation From the PK parameters obtained in this study, a 10000-subject Monte Carlo simulation was conducted to calculate estimates of fT>MIC (%) for each dosing regimen of DRPM against MICs 0.5, 1, 2, 4, 8, 16 and 32 µg/mL. The probability of target attainment (PTA) for a dosing regimen was calculated as the percentage of patients achieving fT>MIC (%) of 40% for a given MIC.19 These probabilities were then plotted against the range of MICs. The PK/PD breakpoint was defined as the highest MIC at which 90% PTA. For each DRPM dosage regimen, the PK/PD break-
point obtained from patients with critical illness in this study was compared to the PK/PD breakpoint reported by Ikawa et al.\(^{23}\) for patients with urinary tract infection and prostatitis, an infection of lesser severity than ICU patients.

**Statistical Analysis** Statistical analyses were performed using Predictive Analysis Software (PASW) Statistics version 21 (SPSS Inc., Chicago, IL, U.S.A.). Data are expressed as mean±standard deviation (S.D.). Differences between PK parameters based on previous PPK model and after Bayesian estimation were analyzed by a paired t-test or a Wilcoxon signed rank test. A \(p<0.05\) was considered statistically significant.

**RESULTS**

The demographic and clinical parameters of the patients (\(n=12\)) in this study are shown in Table 2. Eleven patients were males. The mean age at the time of enrollment was 63.8 years (range 15–86 years). The mean WT was 62.1 kg (50.0–71.6 kg), and mean Ccr was 76.0 mL/min (20.7–155.6 mL/min). Ccr varied widely among patients (S.D.=37.4), and one patient had a low Ccr of 20.7. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 15.8±5.2 (8–24).

The PK parameters averaged from individual data of 12 subjects based on previous population PK model or after Bayesian estimation by five observed concentrations are shown in Table 3. The \(CL\), \(V_1\), \(V_2\) and \(Q\) based on population PK model were 10.8 L/h, 10.6 L, 5.2 L and 4.0 L/h, respectively. On the other hands, the \(CL\), \(V_1\), \(V_2\) and \(Q\) after Bayesian estimation were 9.0 L/h, 14.1 L, 10.6 L and 5.8 L/h, respectively. The \(CL\) after Bayesian estimation was significantly lower than that based on population PK model. The \(V_1\), \(V_2\) and \(Q\) were significantly higher than these based on population PK model. In addition, the mean individual plasma concentration profiles after Bayesian estimation of DRPM was tend to be higher than than that of simulated using population PK parameters (Fig. 1).

The \(fT>MIC\) (%) for standard and higher regimens of DRPM against MICs 0.5–16 µg/mL for three grades of renal function were calculated based on Bayesian-estimated individual PK parameters (Table 4). The estimated \(fT>MIC\) (%) against MICs 0.5, 1 and 2 µg/mL exceeded 40% in all patients. The percentage of achieving \(fT>MIC\) (%) higher than 40% against MICs 4, 8 and 16 µg/mL in patients with normal renal function were 75% (6/8), 0% (0/8) and 0% (0/8), respectively, for standard regimen; and 100% (8/8), 75% (6/8) and 0% (0/8) for higher regimen. The corresponding achievement rates in patients with moderate renal impairment were 67% (2/3), 0% (0/3) and 0% (0/3) for standard regimen; and 100% (3/3), 67% (2/3) and 0% (0/3) for higher regimen. The only patient with severe renal failure attained \(fT>MIC\) (%) higher than 40% against MICs up to 4 µg/mL for only higher regimen.

In patients with Ccr>60 mL/min, the PK/PD breakpoints obtained by Monte Carlo simulation for standard and higher DRPM regimens in the present study were 2 and 4 µg/mL, respectively (Fig. 2). These values were higher than the PK/PD breakpoints (1, 2 µg/mL) reported previously for patients with urinary tract infection and prostatitis\(^{22}\) (Table 5). In patients with 60>Ccr≥30 and 30>Ccr, the mean PK/PD breakpoints

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**Table 2. Demographic and Clinical Characteristic of Patients in Intensive Care Unit Treated with Doripenem (DRPM) in This Study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12</td>
</tr>
<tr>
<td>No. of males/females</td>
<td>11/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.8±18.3 (15–86)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>62.1±6.4 (50.0–71.6)</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>76.0±37.4 (20.7–155.6)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>15.8±5.2 (8–24)</td>
</tr>
</tbody>
</table>

**Table 3. Pharmacokinetic (PK) Parameters Averaged from Individual Data of 12 Subjects Based on Population PK (PPK) Model or after Bayesian Estimation**

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Based on PPK model</th>
<th>Bayesian-estimated</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CL) (L/h)</td>
<td>Mean±S.D. 10.8±3.6</td>
<td>Mean±S.D. 9.0±3.1</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>Range 4.7–17.6</td>
<td>Range 4.9–15.1</td>
<td></td>
</tr>
<tr>
<td>(V_1) (L)</td>
<td>Mean±S.D. 10.6±0.6</td>
<td>Mean±S.D. 14.1±2.7</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Range 9.6–11.5</td>
<td>Range 10.9–21.1</td>
<td></td>
</tr>
<tr>
<td>(V_2) (L)</td>
<td>Mean±S.D. 5.2±1.0</td>
<td>Mean±S.D. 10.6±6.6</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>Range 3.4–6.9</td>
<td>Range 2.0–21.3</td>
<td></td>
</tr>
<tr>
<td>(Q) (L/h)</td>
<td>Mean±S.D. 4.0±0.4</td>
<td>Mean±S.D. 5.8±1.82</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Range 3.4–4.6</td>
<td>Range 2.2–8.2</td>
<td></td>
</tr>
</tbody>
</table>

PK, pharmacokinetic; \(CL\), total clearance; \(V_1\), central volume of distribution; \(V_2\), peripheral volume of distribution; \(Q\), distribution clearance between the central and peripheral compartments.
for standard and higher regimens were 1–2 and 2 µg/mL, respectively, which tended to be higher than the PK/PD break-points (1, 2 µg/mL) reported in previous study.\(^{12}\)

**DISCUSSION**

In this study, to estimate the \(fT > \text{MIC} (%)\) for each subject, individual PK parameters were analyzed by Bayesian estimation using a previously reported population PK model, which is a 2-compartment model with zero-order input and first-order elimination developed by Nandy et al.\(^{15}\) The model was constructed utilizing nonlinear mixed effects models based on pooled data from studies conducted in the United States, including not only phase I studies with healthy volunteers, but also phase II and III studies with severely ill patients. Thus, the model is critically useful as a predictive tool for estimating individual PK parameters of various populations.

Nalda-Molina et al.\(^{19}\) used the model to estimate the empirical Bayesian estimates of PK parameters of DRPM in neurological patients with no active neurological disease or central nervous system infection. Patients who require intensive care have extremely variable pathophysiological conditions such as systemic inflammatory response syndrome, multiple organ failure and acute kidney injury. In the present study, the underlying disease, pathogen and infectious focus varied widely among patients. Furthermore, as DRPM was administered as empirical therapy for conditions without clearly identified pathogens, a few patients were likely to have no infection. Taken the above factors into consideration, we selected the model reported by Nandy et al.\(^{15}\) as the population PK model to implement Bayesian estimate in our study. In addition, in order to make predicted concentration profile more concrete, Bayesian estimate was implemented using five observed concentration.

In the ICU, carbapenems, especially DRPM, are one of the most important and commonly prescribed antibiotics as empirical therapy for patients with critical infections.\(^{5,6}\) To avoid inappropriate antimicrobial therapy that could lead to extended therapy, poor prognosis and high mortality rate,

![Fig. 2. Probability of Target Attainment (PTA) for Dosage Regimens of Doripenem (DRPM) Stratified by Renal Function at a Standard Dosage Regimen (Normal: 0.5 g Every 8 h (●), Moderate: 0.25 g Every 8 h (■), Severe: 0.25 g Every 12 h (▲)) or a Higher Dosage Regimen (Normal: 1.0 g Every 8 h (○), Moderate: 0.5 g Every 8 h (□), Severe: 0.25 g Every 8 h (△)) Achieving 40%\(T > \text{MIC}\)](image)

Table 4. The Percentage of Free Time above Minimum Inhibitory Concentration (\(fT > \text{MIC} (%)\)) against MICs 0.5, 1, 2, 4, 8 and 16 µg/mL for Standard and High Dosage Regimens for Each Subject after Bayesian Estimation

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No.</th>
<th>Creatinine clearance (mL/min)</th>
<th>Dosage regimen</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Ccr&gt;60</td>
<td>1</td>
<td>155.6</td>
<td>0.5×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>129.7</td>
<td>1×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>109.2</td>
<td>0.5×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>97.0</td>
<td>1×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>64.7</td>
<td>0.5×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>62.5</td>
<td>1×3</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>62.3</td>
<td>0.5×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>62.2</td>
<td>1×3</td>
<td>100</td>
</tr>
<tr>
<td>60≥Ccr&gt;30</td>
<td>9</td>
<td>55.9</td>
<td>0.25×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>54.4</td>
<td>0.5×3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>50.3</td>
<td>0.25×3</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>20.7</td>
<td>0.25×2</td>
<td>100</td>
</tr>
<tr>
<td>30≥Ccr</td>
<td></td>
<td></td>
<td>0.25×3</td>
<td>100</td>
</tr>
</tbody>
</table>
DRPM requires at least fT>MIC (%) of 40% during the dosing interval, because fT>MIC (%) has been reported to be an important PK/PD parameter associated with antibacterial activity, indicating time-dependent antibacterial activity. In the present study, the estimated fT>MIC (%) for the standard dose of DRPM against MICs up to 2 µg/mL exceeded 40% in all patients (Table 4). Thus, the standard dosage regimen in this study may be sufficient to achieve effective treatment for patients admitted to ICU. However, in vitro activities [MIC for 90% of the organisms (MIC90)] of DRPM against common bacteria responsible for ventilator-associated pneumonia, catheter-related bloodstream infection and urinary tract infection, which often develop in ICU, are 0.06 µg/mL for methicillin-susceptible Staphylococcus aureus, coagulase-negative staphylococci, Escherichia coli and Citrobacter spp.; 0.12 µg/mL for Klebsiella spp. and Enterobacter spp.; 0.25 µg/mL for Proteus mirabilis and Serratia spp.; 4 µg/mL for Acinetobacter spp.; and 8 µg/mL for Enterococcus faecalis and Pseudomonas aeruginosa, according to the latest global surveillance. In the case of infections by Acinetobacter, E. faecalis, P. aeruginosa and other bacteria with MIC ≥8 µg/mL, even the recommended higher dosage regimen may be insufficient to ensure success in empirical therapy. Previous PK/PD modeling of DRPM in healthy volunteers and patients with renal dysfunction found that 1-h infusion of 0.5 g of DRPM every 8 h achieved good coverage for bacteria with MICs up to 1 µg/mL, while 4-h infusion of 1 g every 8 h achieved good coverage for pathogens with MICs of 8 µg/mL. Hence, other methods of administration such as prolonged infusion time and/or escalated doses may also be required for ICU patients in order to cover resistant bacteria.

The current study in critically ill patients under intensive care indicated that the PK/PD breakpoints for standard and higher DRPM regimens tended to be about two fold higher than the PK/PD breakpoints obtained in a previous study (Table 5). Additionally, the mean total clearance or distribution volume of DRPM estimated by Bayesian estimation was significantly lower or higher than that of based on population PK model (Table 3). The results are not consistent with previous report that DRPM clearance and volume of distribution in critically ill patients are larger than that in non-critically ill patients. Patients with sepsis may develop significantly increased cardiac output and renal perfusion leading to elevated Ccr. However, only a few subjects in our study who were diagnosed with sepsis had very high level of Ccr (Tables 2, 4). On the other hand, the diagnosis of acute kidney injury in clinical practice, which comprises approximately 30% of all patients admitted to ICU, is judged by an increase in serum creatinine or a reduction in urine output. However, serum creatinine does not accurately reflect the glomerular filtration rate (GFR) during acute kidney injury. In addition, Martin et al. demonstrated that Ccr calculated by the Cockcroft–Gault formula inaccurately estimated renal function in ICU patients, and was 17 mL/min higher than measured Ccr. Thus, overestimation of renal function from using Ccr calculated by Cockcroft–Gault formula would lead to unnecessary dose increase in some patients. This situation may contribute to the elevated PK/PD breakpoint of DRPM in ICU patients in this study, because the dosage of DRPM recommended in the Japanese package insert is stratified according to Ccr calculated by Cockcroft–Gault formula. Several studies demonstrated the superiority of serum cystatin C over creatinine in detecting minor GFR reduction. In addition, estimated GFR or Ccr calculated using cystatin C predicts vancomycin trough levels better than Ccr calculated by Cockcroft–Gault formula. In fact, the mean estimated GFR (69.1±33.1 mL/min) or Ccr (46.6±24.6 mL/min) calculated using cystatin C levels before DRPM administration tended to be lower than the mean Ccr calculated by Cockcroft–Gault formula (76.0±37.4 mL/min). Thus, the dosage regimen of DRPM, a renally excreted drug, for ICU patients may need to be also established by stratifying renal function based on GFR or Ccr estimated using cystatin C.

The present study had two limitations. At first, the population of this study included a few patients who were likely to have no infection. Abdul-Aziz et al. performed population pharmacokinetics analysis of DRPM using a nonlinear mixed-effects modeling in 12 critically ill patients with sepsis in a Malaysian ICU. They showed the typical total clearance and distribution volume of DRPM were 0.14 L/kg/h and 0.47 L/kg, respectively, which are almost the same parameters (Total clearance: 0.14 L/kg/h, distribution volume: 0.40 L/kg) as the patients of our report. However, previous Monte Carlo simulation revealed that the PK/PD breakpoints for standard or higher DRPM regimen in every group with Ccr of 70, 50 and 30 mL/min were 2 or 4 µg/mL, respectively, which is slightly higher than that in present study. Thus, the variation in PK/PD breakpoints may be caused by a subtle difference in population. Secondly, the population PK model established by Nandy et al. was developed in non-Japanese subjects, which may contribute to the difference between the PK/PD breakpoint observed in this study and the PK/PD breakpoint reported previously. However, the population mean parameters estimated using a previously reported population PK model for Japanese subjects were comparable to those estimated by the population PK model reported by Nandy et al. Hence, the difference in ethnicity in the development of two population PK models established by Nandy et al. or Ikawa et al. would be expected.
may have little influence on our results.12,15)

In conclusion, the current PK/PD study found that the PK/PD breakpoint of DRPM for ICU patients tended to be higher compared to non-ICU patients, suggesting that the dosage regimens described in the Japanese package insert may be sufficient to achieve effective treatment in ICU patients.

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**Conflict of Interest**  The authors declare no conflict of interest.

**REFERENCES**


