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Pharmacokinetics of Doripenem in Healthy Koreans and Monte Carlo Simulations to Explore Optimal Dosage Regimens in Patients With Normal and Enhanced Renal Function

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Background: Dose adjustment is often required in patients with normal or enhanced renal function. The aim of this study is to investigate the pharmacokinetic (PK) properties of doripenem and explore optimal dosing regimens in patients with normal or enhanced renal function according to various minimum inhibitory concentrations (MICs).

Methods: The authors conducted a clinical trial and analyzed PK samples in 11 healthy Korean subjects applying noncompartmental analysis and a population approach. The population PK parameter estimates were used in Monte Carlo simulations to explore optimal dosing regimens for a probability of target attainment of 90% at 40% fT_{MIC} (free drug concentrations above MIC).

Results: The time course of doripenem concentrations was well described by a 2-compartment model. The population typical values of clearance and steady-state volume were 22.9 L/h and 19.1 L, respectively, and were consistent with our noncompartmental analysis results. When the MIC was greater than 1 mcg/mL, at least increasing the dose or prolonging the infusion time was essential in patients with normal or enhanced renal function.

Conclusions: These results suggest that dosage adjustment such as increasing the dose or lengthening the infusion time should be considered in patients with normal or enhanced renal function.

Key Words: doripenem, pharmacokinetics, Monte Carlo simulation, optimal dosage regimen

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INTRODUCTION

Doripenem is a broad-spectrum antibiotic that has similar efficacy to other carbapenems and some potential advantages. The in vitro activity of doripenem is similar to that of imipenem against Gram-positive bacteria and to that of meropenem against Gram-negative bacteria. One large difference of doripenem compared with meropenem and imipenem is its outstanding activity against *Pseudomonas aeruginosa*.[1–5] In a meta-analysis that included 4 phase III clinical trials to investigate the safety and efficacy of doripenem in patients with complicated intraabdominal infections and nosocomial pneumonia/ventilator-associate pneumonia due to *P. aeruginosa*, the clinical success rates favored doripenem over the comparators.[6] Another meta-analysis, which included 6 clinical trials, suggested that the safety and efficacy of doripenem were not significantly different from the comparators for treating bacterial infections.[7] Another advantage of doripenem is its physicochemical stability. It is stable for 12–24 hours at room temperature (25°C) and 8–16 hours at 30–40°C; it can be stably infused over 4 hours as well as 1 hour.[8–11] Furthermore, doripenem has a lower seizure-inducing potential than other carbapenems in nonclinical and clinical settings.[12,13]

Despite these many advantages, safety and efficacy concerns were recently raised from a clinical trial, particularly regarding the treatment of ventilator-associated pneumonia (VAP).[14] In that study, the 28-day all-cause mortality rate was higher for patients with *P. aeruginosa* VAP in the doripenem group (35.3%; n = 6/17) than for those in the imipenem/cilastatin group (0%; n = 0/10) in the microbiological

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intention-to-treat population, who had one or more Gram-negative pathogens identified. The clinical cure rate was also lower for patients in the doripenem group (45.6%) than for patients in the imipenem/cilastatin group (56.8%) in the microbiological intention-to-treat group. Considering this study, the US FDA–approved label changes for doripenem describing increased mortality for patients with VAP and removing bacterial VAP as an indication for doripenem[15]; the European Medicines Agency (EMA) also withdrew the marketing authorization for doripenem in 2014.[16] Moreover, a recent pharmacokinetic (PK) and pharmacodynamic (PD) study revealed that the approved dosage regimens of doripenem can be inadequate for patients with normal or mildly impaired renal function. In the case of patients with a creatinine clearance rate (CL_{CR}) of 50–90 mL/min, a dosing regimen of 500 mg every 8 hours by 1-hour intravenous (i.v.) infusion was suboptimal and did not reach a probability of target attainment (PTA) above 90% when the minimum inhibitory concentration (MIC) was ≥2 mcg/mL. In this situation, the PTA was defined as the probability of patients with an fT_{MIC} (the percentage of a dosing interval in which the free drug concentration exceeds the MIC) of ≥40% for a certain MIC. In the case of patients with a creatinine clearance (CL_{CR}) of 90–130 mL/min, the same regimen could not produce a PTA above 90% when the MIC was ≥1 mcg/mL. Moreover, patients with an augmented renal clearance (CL_{CR} > 130 mL/min) in intensive care units should be treated with 4-hour infusions to reach a PTA above 90%.[17]

Although doripenem is widely used in South Korea for the treatment of community-acquired pneumonia, nosocomial pneumonia, chronic bronchitis, infected bronchiectasis, secondary infection of chronic respiratory diseases, complex abdominal infections, and complicated infections of the urinary tract including kidney infections, studies using a dense sampling design for PK profiling have not been performed in healthy Koreans or Korean patients with normal renal function.

In this study, we aimed to investigate the PK properties of doripenem in healthy Koreans and to explore optimal dosage regimens for patients with normal and enhanced renal function by applying population PK analysis and Monte Carlo simulations.

MATERIALS AND METHODS

Subjects

Eligible subjects were healthy adult male and female volunteers between the ages of 19 and 55 years old and within 20% of their ideal body weight, with no acute or chronic disease.

The key exclusion criteria included a history of pulmonary, cardiovascular, endogenous, renal, gastrointestinal, psychologic, neurologic, or hematologic diseases; clinically significant findings on routine laboratory tests (eg, serology, hematology, serum chemistry, and urinalysis) or 12-lead ECG analysis; a history of hypersensitivity to β-lactam antibiotics; and the use of drugs that potentially interact with doripenem within 14 days before the study. This study protocol was reviewed and approved by the institutional review board of the Pusan National University Hospital (IRB No. 1611-003-059) and was performed in accordance with the Declaration of Helsinki and Korean Good Clinical Practice. A written informed consent form was signed by each healthy volunteer before study enrollment.

Study Design

A single 250 mg dose of doripenem diluted in 100 mL of normal saline was i.v. infused over the course of 1 hour. Venous blood samples of 8 mL each were collected into heparin Vacutainer tubes (367880; BD, Franklin Lakes, NJ) at 0 (predose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after starting infusion. In total, 12 sampling times per subject were used to obtain PK parameters for both noncompartmental analysis (NCA) and population analysis, considering an infusion time of 1 hour, terminal elimination half-life of 0.95–1.2 hours in healthy subjects,[18–20] and dosing interval of 8 hours for patients with a CL_{CR} above 50 mL/min.

Drug Assay

Doripenem plasma concentrations were determined using a validated ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC-MS/MS) assay. In brief, 0.3 mL aliquots were vortexed with 1000 mcL of methanol containing an internal standard (ampicillin 200 ng/mL) for 5 minutes and then centrifuged (5424R; Eppendorf, Hamburg, Germany) at 13,000*g* for 10 minutes. The 1000 mcL supernatants were transferred to 10 mL glass tubes and then concentrated by SpeedVac concentrator (SPD2010; Thermo Fisher Scientific, Waltham, MA). The supernatant was injected into the UHPLC using a mobile phase consisting of a mixture of −0.01 mol/L ammonium formate containing 0.1% formic acid and methanol in a ratio of 95:5 at a flow rate of 0.3 mL/min (Agilent 1290 Infinity; Agilent Technologies, Santa Clara, CA). Mass spectrometry was conducted using atmospheric pressure chemical ionization to produce ions from liquid samples (API 4000 triple quadruple mass spectrometer; AB Sciex, Concord, ON, Canada). The lower limit of quantification was 0.01 mcg/mL. The assay was linear over a range of 0.01–50 mcg/mL (R^2 = 1.000). The sample concentrations for quality controls were 0.02, 0.2, 2, and 20 mcg/mL. Five replicates for each concentration were tested for 3 days. The intrabatch precision (coefficient of variation (CV) of a set of results from the arithmetic mean of the set) and accuracy (closeness of the agreement between the result of a measurement and the true value) for quality control samples were 0.72%–3.5% and 91.3%–109%, respectively. The interbatch precision and accuracy were 2.1%–5.7% and 94.1%–104%, respectively.

Noncompartmental PK Analysis

An NCA was performed to evaluate the plasma concentration–time profiles of doripenem using Phoenix WinNonlin (version 6.3; Certara, Princeton, NJ). The following PK parameters were evaluated: maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), last quantifiable concentration (C_{last}), time for C_{last} (T_{last}), area under the plasma concentration–time curve from zero until T_{last} (AUC_{last}), plasma concentration–time curve from zero to

infinity (AUC_{inf}), area under the concentration–time curve extrapolated from T_{last} to infinity as a percentage of AUC_{inf} (AUC_{extra}), and area under the moment curve from time of dosing to T_{last} ($AUMC_{last}$). C_{max}, $T_{max,}$ C_{last}, and T_{last} were determined from the observed data. AUC_{last} was calculated by applying the linear trapezoidal rule. AUC_{inf} was calculated as $AUC_{last} + C_{last}/\lambda_z$, where λ_z is the terminal elimination rate constant determined by log-linear regression analysis of the measured plasma concentrations in the terminal elimination phase. AUC_{extra} was calculated as $(AUC_{inf} - AUC_{last})/AUC_{inf}$, total body clearance ($CL_{NCA}$) as dose/$AUC_{inf}$, $t_{1/2\lambda z}$ as/ln (2)/λ_z, and AUMC extrapolated to infinity ($AUMC_{inf}$) as $AUMC_{last} + (T_{last} \times C_{last})/\lambda_z + C_{last}/\lambda_z$. The volume of the distribution ($V_{ss,\ NCA}$) was estimated as $MRT_{inf} \times CL_{NCA}$, where MRT_{inf} is the mean residence time extrapolated to infinity, which was calculated as $AUMC_{inf}/AUC_{inf}$.

Population PK Analysis

Population PK analysis was implemented using NONMEM (version 7.3; ICON, Dublin, Ireland). First-order conditional estimation with interaction method was used for the population PK analysis, as it accounts for the interaction between interindividual variability (IIV) and residual unexplained variability. One- and two-compartment models with first-order kinetics were tested using ADVAN1 and ADVAN3 from the PK model library in NONMEM. The IIVs for PK parameters were assumed to have log-normal distribution as an exponential error model, defined as $\theta_i = \theta \times \exp(\eta_i)$, where θ is the typical value of the PK parameter, θ_i is an individual parameter, and η_i is the IIV, following normal distribution with a mean of 0 and a variance of ω^2. An additive error model, a proportional error model, and a combined additive and proportional error model were tested for residual unexplained variability. NONMEM objective function values (OFVs), diagnostic goodness-of-fit plots, and relative SEs for parameter estimates were evaluated to select the better models. In a log-likelihood ratio test, a decrease of greater than 3.84 with 1 degree of freedom in the OFV (ΔOFV) between 2 nested models or a decrease of 5.99 with 2 degrees of freedom was considered a significant model improvement.

Stepwise forward selection and backward elimination were performed to explore significant covariates for PK parameters. A significant covariate should have clinical relevance as well as a correlation with empirical Bayes estimates of the PK parameter. The statistical significance criteria were $P < 0.05$ (ΔOFV < -3.84 with 1 degree of freedom) for inclusion and $P < 0.01$ (ΔOFV > 5.99 with 1 degree of freedom) for exclusion. The tested covariates for total clearance (CL) were age, sex, CL_{CR} (determined by the Cockcroft–Gault equation), and serum creatinine level (SCR), whereas the tested covariates for intercompartment clearance (Q), central volume of distribution (V_c), and peripheral volume of distribution (V_p) were age and sex.

The final PK model was evaluated using Perl-speaks-NONMEM software (version 4.4.8 [https://uupharmacometrics.github.io/PsN/]). A visual predictive check was performed by comparing the observed plasma concentrations with 90% prediction intervals from 1000 simulated data sets using the final PK parameters and significant covariates.

PD Target Attainment

To explore the steady-state concentration–time profiles of doripenem for the current dosing regimen and the need for dose adjustment in patients with normal or enhanced renal function, a 10,000-subject Monte Carlo simulation using NONMEM was conducted using the final PK parameter estimates, including typical values, for between-subject variability and within-subject variability. The structural PK parameters and body weights were assumed to follow log-normal distributions. The percentage of protein-unbound drug (f) was fixed at 91.9% because the proportion of doripenem bound to protein is approximately 8.1%.[15] The PTAs in 216 conditions, including all combinations of 3 doses (500, 750, and 1000 mg), 4 infusion times (1, 2, 3, and 4 hours), 2 dosing intervals (8 and 12 hours), and 9 MICs (0.125, 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mcg/mL), were evaluated using the simulated subjects. The PTA should be over 90% for a regimen to be considered optimal.

The steady-state concentrations after multiple infusions were used to calculate fT_{MIC}. The times above MIC before and after steady-state maximum concentrations ($C_{ss,max}$) for the 2-compartment model were calculated separately and summed. The peak concentration at the end of the infusion ($C_{ss,max}$) was calculated using the following equation:

$$C_{ss,max} = C_1 + C_2,$$

where

$$C_1 = R \times \frac{A}{\alpha} \times \frac{\left(1 - e^{-\alpha \times Tinf}\right)}{\left(1 - e^{-\alpha \times Tint}\right)},$$

$$C_2 = R \times \frac{B}{\beta} \times \frac{\left(1 - e^{-\beta \times Tinf}\right)}{\left(1 - e^{-\beta \times Tint}\right)},$$

$$R = \text{Dose} \times \text{unbound fraction} / T_{inf},$$

$$\alpha = \left\{ K10 + K21 + K12 + \sqrt{(K10 + K21 + K12)^2 - 4 \times K10 \times K21} \right\} \Big/ 2,$$

$$\beta = \left\{ K10 + K21 + K12 - \sqrt{(K10 + K21 + K12)^2 - 4 \times K10 \times K21} \right\} \Big/ 2,$$

$$A = (\alpha - K21)/(V_c \times (\alpha - \beta)),$$

$$B = (K21 - \beta)/(V_c \times (\alpha - \beta)),$$

$$K10 = CL/V_c,$$

$$K12 = Q/V_c,$$

$$K21 = Q/V_p,$$

where T_{inf} is the infusion time, T_{int} is the dosing interval, V_c and V_p are the central and peripheral volumes of distribution, respectively; CL is the total clearance; and Q is the intercompartmental clearance.

The trough concentration ($C_{ss,min}$) before the next dosing was calculated using:

$$C_{ss,min} = C_1 \times e^{-\alpha \times (Tint - Tinf)} + C_2 \times e^{-\beta \times (Tint - Tinf)}.$$

The equation for concentration changes over time (C_{ss}) after $C_{ss,min}$, except after a new dosing, becomes:

$$C_{ss} = C_1 \times e^{-\alpha \times (Tint - Tinf)} \times e^{-\alpha \times Time} + C_2 \times e^{-\beta \times (Tint - Tinf)} \times e^{-\beta \times Time}.$$

Then, the concentration ($C_{ss,inf}$) changes over time, including a new dosing, were calculated by:

$$C_{ss,inf} = C_1 \times e^{-\alpha \times (Tint - Tinf)} \times e^{-\alpha \times Time} + C_2 \times e^{-\beta \times (Tint - Tinf)} \times e^{-\beta \times Time} + R \times \left\{ \frac{A}{\alpha} \times \left(1 - e^{-\alpha \times Time}\right) + \frac{B}{\beta} \times \left(1 - e^{-\beta \times Time}\right) \right\}. \quad (1)$$

The equation for the concentration after $C_{ss,max}$ then became:

$$C_{ss} = C_1 \times e^{-\alpha \times Time} + C_2 \times e^{-\beta \times Time}. \quad (2)$$

The total time (in minute) above the MIC was summed by using the simulated individual PK parameters by the application of Equations 1 and 2 and the duration.

RESULTS

Subjects

Fifteen healthy volunteers were screened, and 12 subjects (6 males/6 females) were enrolled in the study. One male subject did not appear and was excluded from this study. Twelve plasma samples per subject were used for the PK analysis. The demographic characteristics of the 11 healthy subjects are described in Table 1 and **Supplementary Table 1** (**Supplemental Digital Content 1,** http://links.lww.com/TDM/A250).

TABLE 1. Characteristics of Healthy Subjects

Demographic Factor	Mean	CV%	Median	Range
Age (yr)	25	9.84	24	22–30
HT (cm)	166	5.70	166	152–178
WT (kg)	60.9	16.6	57.0	50–80
BMI (kg/m^2)	22.0	9.59	21.6	19–26
SCR (mg/dL)	0.74	22.5	0.71	0.56–0.95
CL_{CR} (mL/min)	122	9.47	123	101–139

BMI, body mass index; CL_{CR}, creatinine clearance determined by the Cockcroft–Gault equation; HT, height; SCR, serum creatinine level; WT, weight.

NCA

The NCA PK parameters are presented in Table 2 and **Supplementary Table 2** (**Supplemental Digital Content 1,** http://links.lww.com/TDM/A250). The mean (CV%) for C_{max} and AUC_{inf} were 9.7 mg/L (23.9%) and 12.0 h·mg/L (27.7%), respectively. The mean (CV%) for $t_{1/2\lambda z}$ calculated by log-linear regression on the terminal elimination phase was 1.01 hours (34.1%). The mean (CV%) for CL_{NCA} and $V_{ss,NCA}$ were 22.7 L/h (33.7%) and 20.1 L (33.3%), respectively. A single molecule of doripenem remained in the body for 0.892 hours (17.5%).

Population PK Analysis

The time course of doripenem concentration was well described by a 2-compartment model (ΔOFV = −59.605

TABLE 2. Noncompartmental PK Parameters of Doripenem in Healthy Subjects

Parameter	Mean	CV%	Median	Range
C_{max} (mg/L)	9.72	23.9	10.2	7.03–13.81
T_{max} (h)	1	0.00	1	1–1
$t_{1/2\lambda z}$ (h)	1.01	34.1	0.910	0.654–1.86
C_{last} (mg/L)	49.0	66.5	36.5	12.0–111
T_{last} (h)	7	14.3	6	6–8
AUC_{last} (h·mg/L)	12.0	27.7	13.7	6.68–16.2
AUC_{INF} (h·mg/L)	12.0	27.7	13.8	6.07–16.3
AUC_{extra} (%)	0.609	71.3	0.467	0.149–1.65
CL_{NCA} (L/h)	22.7	33.7	18.1	15.3–37.3
$V_{ss,NCA}$ (L)	20.1	33.3	19.0	11.5–29.6
$AUMC_{last}$ (h·h·mg/L)	16.2	31.7	15.3	8.44–24.9
$AUMC_{INF}$ (h·h·mg/L)	16.8	31.6	15.7	8.62–25.7
MRT_{INF} (h)	0.892	17.5	0.875	0.635–1.17

AUC_{extra}, area under the concentration–time curve extrapolated from T_{last} to infinity as a percentage of AUC_{inf}; AUC_{inf}, area under the plasma concentration–time curve from zero to infinity; AUC_{last}, area under the plasma concentration–time curve from zero to the T_{last}; $AUMC_{inf}$, AUMC extrapolated to infinity; $AUMC_{last}$, area under the moment curve from dosing time to T_{last}; C_{last}, last quantifiable concentration; CL_{NCA}, clearance for NCA; C_{max}, maximum observed plasma concentration; MRT_{inf}, mean residence time extrapolated to infinity; $t_{1/2\lambda z}$, $\ln(2)/\lambda_z$ (λ_z, terminal elimination rate constant determined by log-linear regression analysis of the measured plasma concentrations in the terminal elimination phase); T_{last}, time for C_{last}; T_{max}, time to reach C_{max}; $V_{ss,NCA}$, steady-state volume.

compared with the 1-compartment model). The basic PK parameters were CL, V_c, Q, and V_p. Exponents of 0.75 and 1 for allometric scaling of weight on clearance terms and volume terms, respectively, were fixed based on fractal geometry theory, as the population size was insufficient to estimate the values.[21,22] The expression for the allometric scaling was:

$$\theta = \theta_{TV} \times \left(\frac{WT}{WT_{MED}}\right)^{k},$$

where θ is the parameter value for a subject with a body weight of WT kg, θ_{TV} is the typical parameter value for a subject with a median body weight (WT_{MED}) of 57 kg, and k is the allometric exponent. All tested covariates did not significantly improve the PK model and were not selected for the final PK model.

Figure 1 shows the time course of individual-observed concentrations, individual-predicted concentration, and population-predicted concentration. Most C_{max} values were slightly underpredicted, whereas those of subjects 3 and 9 were considerably biased. These results were also observed in the goodness-of-fit plots (Fig. 2), but the trends in the distribution of residuals in (A), (B), (C), and (D) were negligible, and a strong correlation between observed and individual-predicted concentrations is shown in Figure 2D. The individual PK parameters of the final PK model are provided in Table 3. The CL, V_c, Q, and V_p were determined using maximum a posteriori Bayesian estimation, whereas the other parameters were calculated from the 4 estimates (Table 3 and see **Supplementary Table 3**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A250). The mean (CV%) for CL, V_c, Q, and V_p was 23.7 L/h (27.6%), 17.5 L (27.1%), 1.92 L/h (12.3%), and 3.34 L (16.6%), respectively. The mean (CV%) for the half-life of K10 ($t_{1/2}$), α ($t_{1/2\alpha}$), and β ($t_{1/2\beta}$) was 0.518 hours (15.7%), 0.453 hours (14.0%), and 1.37 hours (7.1%), respectively. The mean (CV %) for V_{ss}, which is the algebraic sum of the V_c and V_P, was 20.8 L (22.4%) (see **Supplementary Table 3**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A250). The population typical values (relative SE) for CL, V_c, Q, and V_p were 22.0 L/h (10.2%), 16.0 L (13.0%), 1.83 L/h (22.3%), and 3.13 L (14.7%), respectively (Table 3). The CV for the IIV (relative SE) for CL and V_c was 31.6% (19.2%) and 35.3% (22.1%), respectively. The final PK model supported the correlation between CL and V_c (correlation coefficient of 0.871; ΔOFV = −10.059). Residual variability was best explained by a proportional error model defined as $Y_{ij} = Y_{ij,PRED} + Y_{ij,PRED} \times \varepsilon_{ij}$, where Y_{ij} is the jth

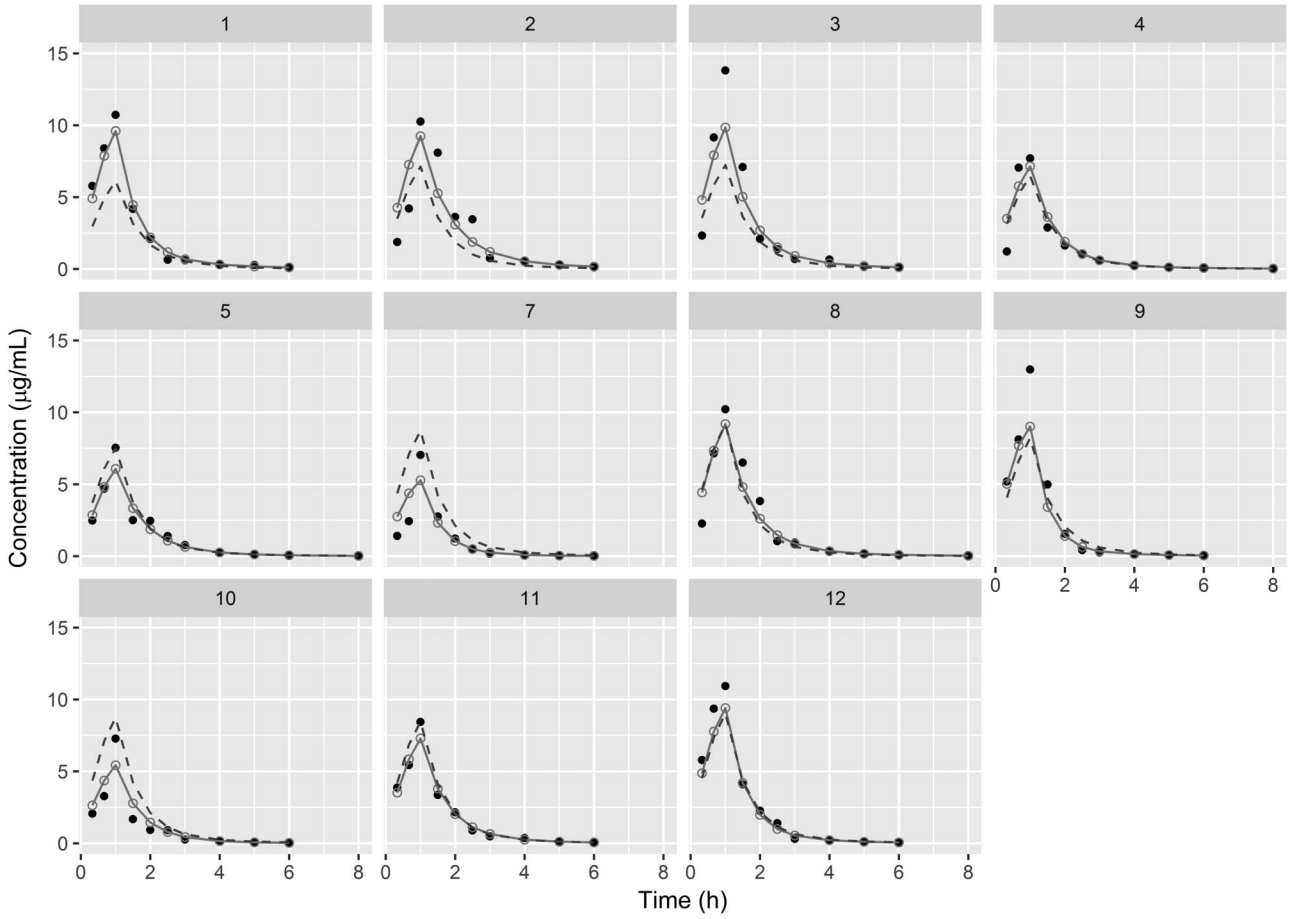

FIGURE 1. Individual plots: closed circle, observed concentrations; open circle and solid line, individual-predicted concentrations; and dashed line, population-predicted concentrations.

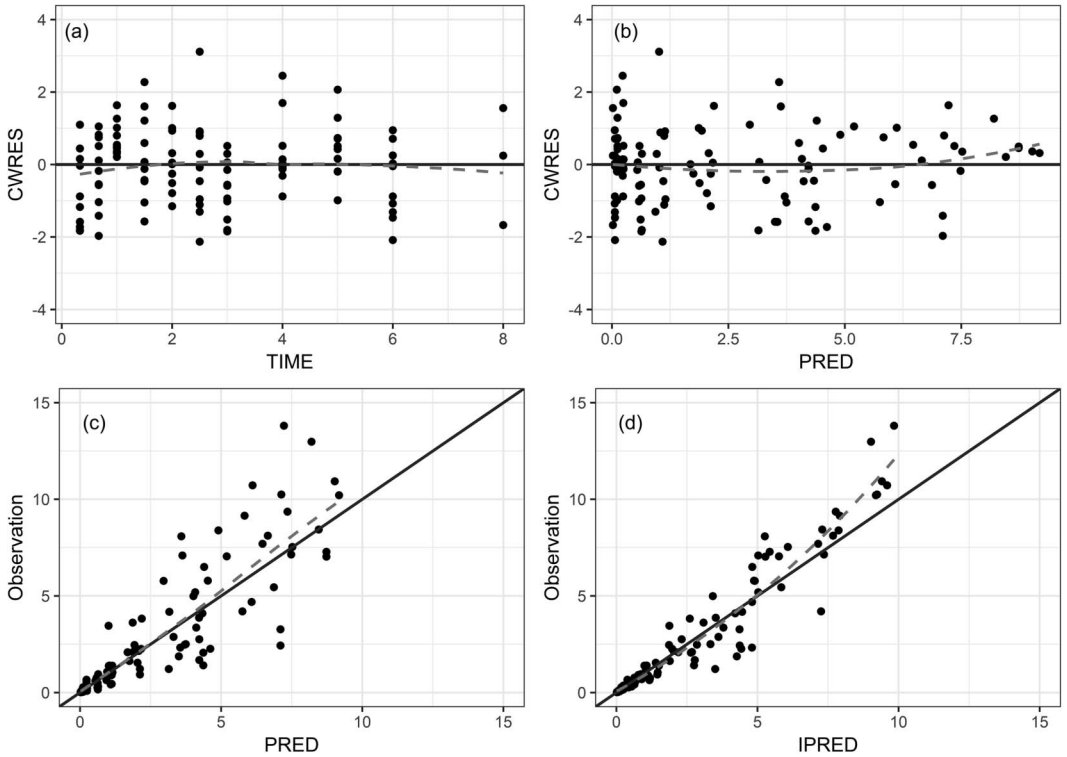

FIGURE 2. Goodness-of-fit plots: (A) conditional weighted residuals versus time, (B) conditional weighted residuals versus population model–predicted concentration, (C) observed concentration versus population-predicted concentration, and (D) observed concentration versus individual-predicted concentration. The gray lines are smooth curves. CWRES, conditional weighted residuals; IPRED, individual-predicted concentration; PRED, population-predicted concentration.

concentration in individual i, $Y_{ij,PRED}$ is the jth predicted concentration in individual i, and ε_{ij} is the unexplained residual variability for jth concentration in individual i, which is normally distributed with mean 0 and variance ω^2 (Table 3).

Most of the observed data were within the 90% prediction interval in the visual predictive check, indicating the adequacy of the PK model (Fig. 3).

TABLE 3. Population PK Parameter Estimates of the Final PK Model of Doripenem in Healthy Subjects

Parameter	Estimates	RSE (%)	Bootstrap Median (95% CI)
Structural model			
CL (L/h)	22.0	10.2	21.8 (17.8–27.2)
V_C (L)	16.0	13.0	15.8 (12.0–20.3)
Q (L/h)	1.83	22.3	1.81 (1.03–2.83)
V_P (L)	3.13	14.7	3.16 (2.15–4.11)
IIV			
ω_{CL} (%)	31.6	19.2	29.6 (13.8–40.6)
ω_V (%)	35.3	22.1	33.0 (11.6–48.3)
$\omega_{CL\text{-}V\ correlation}$	0.871	21.9	
Residual unexplained variability			
$\sigma_{Proportional}$	0.301	7.63	0.296 (0.252–0.341)

Final PK model: $CL = \Theta_{TVCL} \times (WT/57)^{0.75}$; $V_C = \Theta_{TVVc} \times (WT/57)$; $Q = \Theta_{TVQ} \times (WT/57)^{0.75}$; $V_P = \Theta_{TVVp} \times (WT/57)$.

95% CI, 95% confidence intervals (CIs) estimated with 1000 simulation data sets using the final population PK model; CL, total body clearance; Q, intercompartmental clearance; RSE, relative SE; V_C, central volume of distribution; V_P, peripheral volume of distribution.

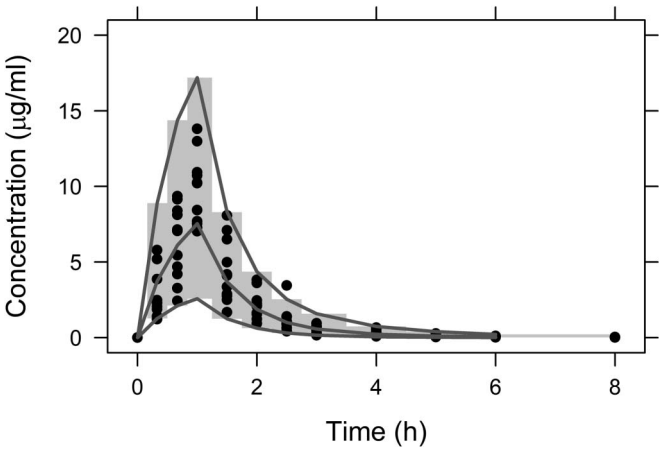

FIGURE 3. Visual predictive check by simulated concentrations of 1000 virtual data sets: closed circle, observed concentrations; shaded areas, 90% prediction intervals (5th–95th percentile) for simulated concentrations. The solid lines are the fifth, 50th, and 95th percentiles for simulated concentrations.

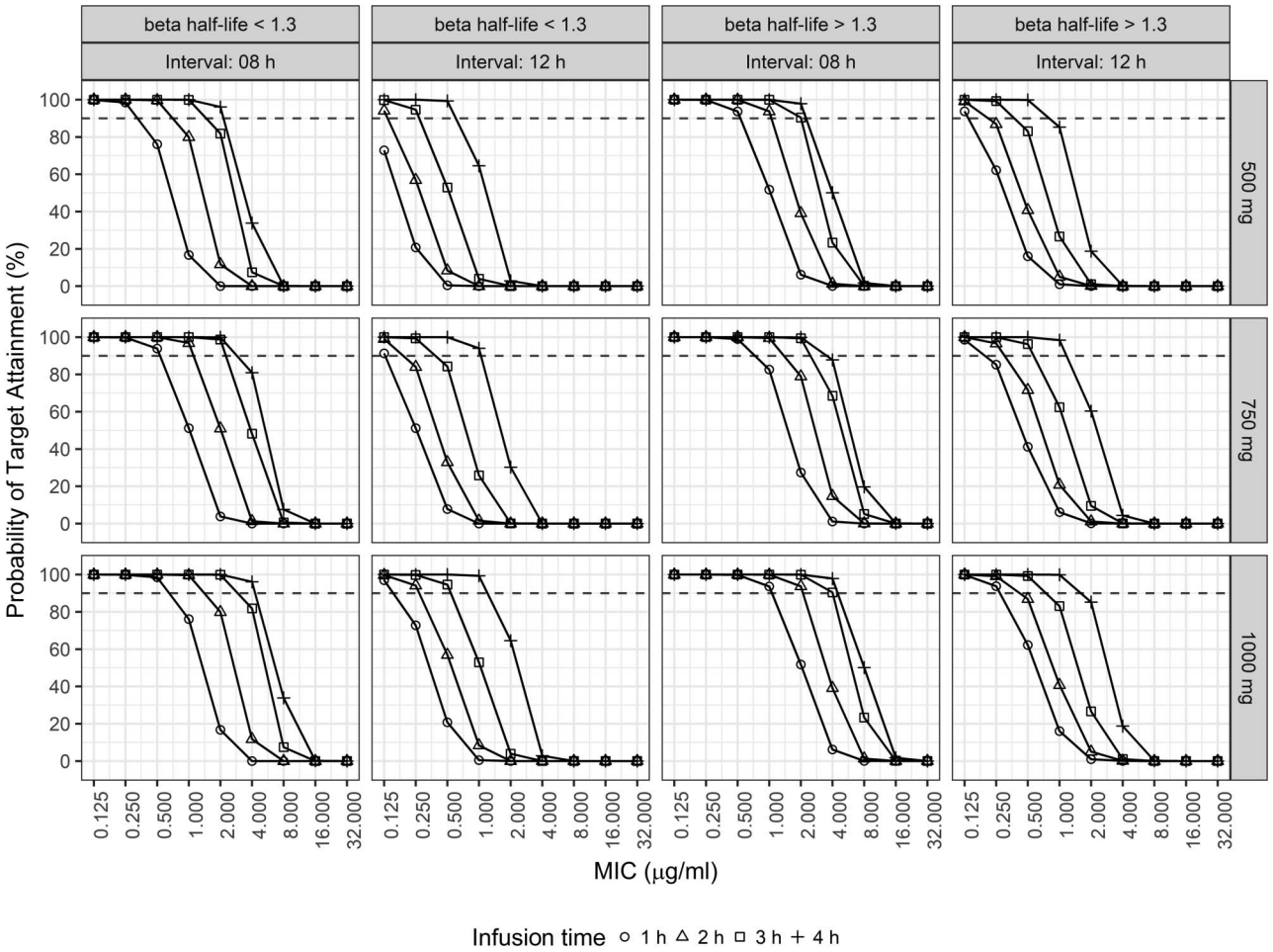

FIGURE 4. Probabilities of target attainment (fT_{MIC} above 40%) with various dosing regimens (dosing intervals of 8 or 12 hours; infusion time of 1, 2, 3, or 4 hours; and dose of 500, 750, or 1000 mg) for simulated patients with various MICs and first quartile value of 1.3 hours for beta half-life.

PD Target Attainment

Figure 4 shows the PTA of the 10,000 virtual patients in 216 simulation conditions, including various dosing regimens and MICs. To evaluate the PTA according to the doripenem elimination rate, 10,000 virtual patients were divided into 2 groups based on the first quartile value (1.3 hours) of half-life for the elimination-dominant phase (β-$t_{1/2}$) rather than CL_{CR} because CL_{CR} was not included as a significant covariate for clearance of doripenem. In the case of patients with a β-$t_{1/2}$ >1.3 hours, the current dosing regimen of 500 mg by 1-hour i.v. infusion every 8 hours was optimum when the MIC for a CL_{CR} of >50 mL/min was 0.5 mcg/mL or less, whereas it was not sufficient for the patients with a $t_{1/2}$ of less than 1.3 hours when the MIC was 0.5 mcg/mL. When the MIC was 1

TABLE 4. Values for Clearance (CL) and Steady-State Volume of Distribution (V_{ss}) in the Previous Population PK analysis in Patients

			Typical Value		Conversion Value	
Author, Year	**Ethnicity**	**Population**	**CL (L/h)**	**V_{ss} (L)**	**CL (L/h)**	**V_{ss} (L)**
Harada et al, 2013[31]	Japanese	Elderly	10.1	22.3	28.5	22.3
Matsuo et al, 2015[28]	Japanese	Renal impairment	13.8	15.4	15.1	15.4
Abdul-Aziz et al, 2016[27]	Malaysian	ICU	10.1	33.2	15.3	27.2
Chung et al, 2016[29]	Unknown	Obese	12.5	29.5	12.7	1.27
Lee et al, 2017[17]	Korean	Critically ill	6.52	16.7	10.5	16.0

Typical value, typical population parameter estimates; conversion value, conversion values derived by substituting median covariate values of our study to each formula of the previous studies.

ICU, intensive care unit.

mcg/mL, a 1-hour dosing regimen of 500 mg every 8 hours was suboptimal, whereas a 2-hour infusion was appropriate for patients with a β-$t_{1/2}$ >1.3 hours, and a 3-hour infusion was appropriate for patients with a β-$t_{1/2}$ <1.3 hours. A 4-hour dosing regimen of 500 mg every 8 hours or a 3-hour dosing regimen of 750 mg every 8 hours was appropriate when the MIC was 2 mcg/mL or less in both groups. When the MIC was 4 mcg/mL, a 4-hour dosing regimen of 1000 mg every 8 hours was required.

Safety

No subjects experienced adverse events after doripenem administration.

DISCUSSION

Doripenem has been unavailable to ventilator patients with pneumonia in the United States and to all patients in the European Union since 2014 because it was shown to be less efficacious and safe than imipenem/cilastatin.[14] These results seem to have originated from the use of doripenem without PK/PD evaluation. Various PK/PD studies have shown that dosage regimen adjustments are necessary not only for patients with renal impairment but also for patients with normal or augmented renal clearance.[17,23–29] We expected that PD predictions based on an adequate understanding of doripenem PK will enhance efficacy without increasing side effects, and we conducted the first clinical study to investigate doripenem PK in healthy Korean volunteers. In this study, we explored the efficacy in various situations, including various dosage regimens and MICs, by applying Monte Carlo simulations with the final PK parameters.

To evaluate the PK properties of doripenem, we analyzed plasma concentrations, applying both the NCA method and population approach. The clearance and steady-state volume of distribution obtained from both analyses were not significantly different, whereas the half-lives were significantly different. Because CL_{NCA} and $t_{1/2\lambda z}$ were not normally distributed based on Kolmogorov–Smirnov tests (P = 0.025 and 0.048, respectively), the clearance and half-lives were compared using the Wilcoxon signed-rank test. The steady-state volume of distribution was normally distributed in both analyses and compared using paired t tests. The P values of the 2 paired-sample comparisons for clearance and steady-state volume of distribution were 0.109 and 0.339, respectively. The P value of the Wilcoxon signed-rank test between $t_{1/2\lambda z}$ and $t_{1/2\beta}$ was 0.014. When performing the NCA, the number of points used in calculating λ_z was 3–7, implying that samples in the distribution-dominant phase might be included in the elimination-dominant phase because of measurement error or inappropriate sampling times to estimate an apparent terminal half-life or elimination phase half-life of the 2-compartment model.

Comparing our NCA results with those of previous studies based on 250 mg, the mean C_{max} for doripenem of 9.72 mg/L is generally consistent with the other results (10.0–11.5 mg/L) in healthy subjects, whereas the mean AU-C_{inf} of 12.0 h·mg/L is considerably smaller (15.8–18.2 h·mg/L).[19,30,31] The mean CL_{NCA} of 22.7 L/h is larger than the previously observed values of 16.0 L/h[30] and 14.6 L/h,[19] and the mean $V_{ss,NCA}$ of 20.1 L is in the previously observed range of 16.8–24.8 L.[19,30] The mean CL_{NCA} was greater than the mean CL_{CR} of 122 mL/min (7.32 L/h) in these subjects. In previous NCA studies, the renal clearance of doripenem, composed of glomerular filtration and tubular secretion, was 12.5 L/h[30] and 10.3 L/h in healthy subjects.[19] Our population analysis gave results that were consistent with our NCA parameters. The typical population Bayesian estimates for clearance (CL) and V_{ss} (V_c + V_p) in our study were 22.0 L/h and 19.1 L, respectively, whereas they were 14.5 L/h and 15.3 L, respectively, in a previous study conducted with 24 healthy subjects.[18] Our typical value for CL was considerably larger than the typical values in the previous population PK analysis, which included patients in various conditions (Table 4). The conversion values derived by substituting the median covariate values from our study in the formulas of the previous studies also showed large differences. Extrapolation of a study was not reliable because of the large differences in body weights between the patient population and our healthy subjects.[29] As it was in the NCA, the typical CL in our study was higher than the median CL_{CR} of 123 mL/min (7.38 L/h). The probable cause of the increased clearance for doripenem was enhanced active tubular secretion or metabolism by dipeptidase 1 (DPEP1), located in the human renal cortex. In a study of 24 healthy subjects, the mean plasma clearance was 15.9 L/h and the mean renal clearance was 10.3 L/h.[15] Assuming a CL_{CR} of 7.38 L/h, the renal clearance of 2.92 L/h, excluding CL_{CR}, and the nonrenal clearance of 5.6 L/h were not negligible. Considering a tubular secretion proportion of 10%–20% for creatinine in healthy humans,[32] the tubular secretion might have been 3.38–3.94 L/h in this study. In a ^{14}C-labeled doripenem PK study, the urinary recovery of total radioactive substances was 95.3% of the administered dose, and the amount of primary metabolite was 18.5% (92.9 mg) of the administered 500 mg,[30] meaning that a substantial amount of doripenem was eliminated by metabolism. In this study, the total clearance was 16 L/h and the nonrenal clearance was 3.5 L/h, indicating that clearance by active tubular secretion was higher than 5.12 L/h, assuming a CL_{CR} of 7.38 L/h. However, the mechanism of tubular secretion for doripenem has not been investigated thus far. We did not measure concentrations of doripenem metabolites and could not confirm nonrenal clearance. DPEP1 plays a significant role in doripenem metabolism and hydrolyzes various dipeptides and β-lactam antibiotics as a zinc-metalloenzyme in the kidney.[33,34] There have been many studies on DPEP1 expression, which is negatively or positively associated with several cancers, including breast lobular carcinoma,[35] Wilms' tumor,[36] pancreatic ductal adenocarcinoma,[37] and colorectal cancer.[38,39] However, there seems to be no research on DPEP1 overexpression and its impact on kidney function, and we could not find previous mechanistic studies for enhanced tubular secretion or metabolism of carbapenem.

To explore the optimal dosage regimen for patients with normal and enhanced renal function, we conducted Monte Carlo simulations using the final PK parameter estimates in our healthy Korean subjects. Because creatinine clearance was not selected in this study as a significant influential

covariate for doripenem clearance, we arbitrarily used the half-life of the elimination-dominant phase ($t_{1/2\beta}$) as a criterion for renal function. The simulated 10,000 virtual subjects were divided into 2500 subjects with enhanced renal function and 7500 subjects with normal renal function, based on the first quartile value of 1.3 hours for $t_{1/2\beta}$ (Fig. 4). We intended to examine the significance of dosage adjustment according to renal function, although we could evaluate the PTA without this criterion. However, if possible, using half-life rather than clearance could be more intuitive and helpful for dosage regimen adjustment because the elimination rate of the drug is determined by the combination of both clearance and volume of distribution. The present results show the necessity of dosage adjustment or therapeutic drug monitoring in patients with enhanced renal function when they are infected by pathogens with doripenem MIC of 0.5 mcg/mL. In all patients with normal or enhanced renal function who are infected by pathogens with a doripenem MIC over 0.5 mcg/mL, increased dose and/or prolonged infusion are essential. According to our results, if a patient with enhanced renal function is infected by *P. aeruginosa* with a Clinical and Laboratory Standard Institute breakpoint of 2 mcg/mL,[40] a dosage regimen of doripenem 750 mg with 3-hour infusion is optimal. To treat a patient infected by *Acinetobacter* spp. with a susceptibility breakpoint of 1 mcg/mL according to the European Committee on Antimicrobial Susceptibility Testing,[41] a dosage regimen of doripenem 500 mg with 3-hour infusion is optimal.

Our study has several limitations. First, the number of subjects was too small to find covariate effects on PK parameters during the population PK analysis, although it was sufficient to find PK properties in the NCA. Second, an effect of creatinine clearance on doripenem clearance was not revealed. Therefore, we used the half-life of the elimination-dominant phase as a criterion to divide the virtual patients into 2 groups of normal and enhanced renal function. These divisions seemed to be appropriate to evaluate and support the need for dosage adjustment in normal or enhanced renal function. Third, the final PK model should be reinforced by clinical data, as it does not have any useful covariate. Fourth, patients with or without augmented renal clearance were not included in this study. Therefore, the simulation results from extrapolating the data of this population should be interpreted with caution. Finally, we did not verify clinical outcomes based on the population modeling and simulation. Despite these drawbacks, our study is valuable because, to the best of our knowledge, it is the first such clinical study for doripenem and establishes the first 2-compartment model in healthy Korean subjects.

CONCLUSIONS

Our study assesses the PK properties of doripenem in healthy Korean subjects by applying NCA and a population approach. The concentration–time profile of doripenem is best explained by a 2-compartment model. This model will be useful to establish a future robust and refined PK model with expanded data. Our results suggest that dosage adjustment, such as increasing the dose or lengthening the infusion time, should be considered in patients with normal or enhanced renal function, when patients are infected by pathogens with doripenem MIC above 1 mcg/mL. Furthermore, therapeutic drug monitoring will be helpful to improve clinical outcomes in patients with normal or enhanced renal function as well as in patients with impaired renal function.

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