Population Pharmacokinetics of Meropenem in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

Arantxazu Isla,¹ Alicia Rodríguez-Gascón,¹ Iñaki F. Trocóniz,² Lorea Bueno,² María Ángeles Solinís,¹ Javier Maynar,³ José Ángel Sánchez-Izquierdo⁴ and José Luis Pedraz¹

1 Laboratory of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of the Basque Country, Vitoria-Gasteiz, Spain

2 Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra, Pamplona, Spain

3 Intensive Care Unit, Santiago Apóstol Hospital, Vitoria-Gasteiz, Spain

4 Intensive Care Unit, Doce de Octubre Hospital, Madrid, Spain

Abstract

Background and objective: Meropenem is a carbapenem antibacterial frequently prescribed for the treatment of severe infections in critically ill patients, including those receiving continuous renal replacement therapy (CRRT). The objective of this study was to develop a population pharmacokinetic model of meropenem in critically ill patients undergoing CRRT.

Patients and methods: A prospective, open-label study was conducted in 20 patients undergoing CRRT. Blood and dialysate-ultrafiltrate samples were obtained after administration of 500 mg, 1000 mg or 2000 mg of meropenem every 6 or 8 hours by intravenous infusion. The data were analysed under the population approach using NONMEM version V software. Age, bodyweight, dialysate plus ultrafiltrate flow, creatinine clearance (CLCR), the unbound drug fraction in plasma, the type of membrane, CRRT and the patient type (whether septic or severely polytraumatized) were the covariates studied.

Results: The pharmacokinetics of meropenem in plasma were best described by a two-compartment model. CLCR was found to have a significant correlation with the apparent total clearance (CL) of the drug during the development of the covariate model. However, the influence of CLCR on CL differed between septic and polytraumatized patients ($CL = 6.63 + 0.064 \times CLCR$ for septic patients and $CL = 6.63 + 0.72 \times CLCR$ for polytraumatized patients). The volume of distribution of the central compartment (V_1) was also dependent on the patient type, with values of 15.7 L for septic patients and 69.5 L for polytraumatized patients. The population clearance was 15 L/h, and the population apparent volume of distribution of the peripheral compartment was 19.8 L. From the base to the final model, the interindividual variabilities in CL and the V_1 were significantly reduced. When computer simulations were carried out and efficacy indexes were calculated, it was shown that polytraumatized patients and septic patients with conserved renal function may not achieve adequate efficacy indexes to deal with specific infections. Continuous infusion of meropenem is recommended for critically septic patients and polytraumatized patients when pathogens with a minimum inhibitory concentration (MIC) of ≥ 4 mg/L are isolated. Infections caused by pathogens with an MIC of ≥ 8 mg/L should not be treated with meropenem in polytraumatized patients without or with moderate renal failure because excessive doses of meropenem would be necessary.

Conclusion: A population pharmacokinetic model of meropenem in intensive care patients undergoing CRRT was developed and validated. CLCR and the patient type (whether septic or polytraumatized) were identified as significant covariates. The population pharmacokinetic model developed in the present study has been employed to recommend continuous infusion protocols in patients treated with CRRT.

Background

Meropenem is a carbapenem antibacterial with a wide spectrum of activity, including Gram-positive, Gram-negative and anaerobic microorganisms. It has shown clinical and bacteriological efficacy in the treatment of a wide range of serious infections in adults and children, and is prescribed for the treatment of infections in critically ill patients in intensive care due to its high degree of activity, its tolerability and its low incidence of toxicity.^[1]

Meropenem has linear pharmacokinetic properties over the dose range of 0.25–2 g, with an elimination half-life of approximately 1 hour in healthy volunteers.^[1,2] Meropenem is eliminated by both metabolism and excretion. In healthy volunteers, 19–27% of a 1 g dose is excreted as a microbiologically inactive open β -lactam metabolite,^[3] and up to 83% of the dose has been recovered unaltered in the urine.^[4]

Meropenem is commonly administered to critically ill patients. The structural and pharmacokinetic characteristics of meropenem (i.e. water solubility, relatively small molecular weight [383.5 D] and low protein binding) allow for efficient removal of this drug by continuous renal replacement therapy (CRRT). Hydrophilic antimicrobials such as carbapenems are at higher risk of daily pharmacokinetic variations in critically ill patients.^[5] Consequently, they should be more closely monitored, and their dosages should be streamlined according to the underlying diseases in order to prevent under- or overexposure,^[5] to avoid treatment failure and to improve survival. The pharmacokinetics of meropenem in critically ill patients undergoing CRRT have been published previously,^[6–16] but a population pharmacokinetic analysis has never been performed. Population pharmacokinetics seek to (i) identify the measurable pathophysiological factors that cause changes in the dose-concentration relationship; (ii) quantify the extent of those changes; and (iii) estimate the magnitude of the unexplained variability in the patient population.^[17]

Considering the high pharmacokinetic variability in critically ill patients and the lack of population pharmacokinetic information on meropenem in such patients, the purpose of this study was to develop a population pharmacokinetic model of meropenem in critically ill patients undergoing CRRT with the objectives of quantifying the degree of interindividual variability (IIV) in the model parameters and identifying the patient characteristics responsible for IIV.

Methods

Study Design and Setting

A prospective, open-label study was conducted in intensive care unit patients undergoing CRRT. Twenty patients (15 males and five females) meeting the following criteria were eligible for inclusion in the study: (i) age >18 years; (ii) treatment with CRRT

for >1 day for ≥ 20 h/day; and (iii) isolated or expected causative pathogen susceptible to meropenem. The guardians of all patients provided written informed consent. Complete medical histories were obtained for all patients, and complete physical examinations and laboratory reviews of serum chemistry and haematology profiles were performed and reviewed before collection of samples for pharmacokinetic analysis. The study was conducted in accordance with good clinical practice and was approved by the medical ethical committees of the Santiago Apóstol Hospital (Vitoria-Gasteiz, Spain) and Doce de Octubre Hospital (Madrid, Spain).

Renal Replacement Therapy

All patients were undergoing CRRT, which has been defined as any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for, or aimed at being applied for, 24 hours/day.^[18] In our study, patients were specifically treated with continuous venovenous haemofiltration (CVVH, $n = 10$) or continuous venovenous haemodiafiltration (CVVHDF, $n = 10$).

Vascular access was obtained with 13.5 FG dual lumen catheters (Niagara, Bard Canada, Inc., Mississauga, Ontario, Canada). Haemodiafiltration machines (PRISMA, Hospal, Lyon, France; or MULTIFILTRATE, Fresenius Medical Care, Bad Homburg, Germany) were used with polyacrylonitrile AN69 HF 0.9 m² membranes (PRISMA M100, Hospal) in 16 patients or polysulfone membranes (Ultraflux AV600S, 1.4 m² Fresenius polysulfone®, Fresenius Medical Care) in four patients. The blood flow was maintained between 100 mL/min and 220 mL/min. In the CVVHDF procedures, the dialysate flow rate was 500 mL/h or 1000 mL/h into the dialysate compartment of the filter in a blood flow countercurrent direction. The ultrafiltrate obtained was replaced as clinically indicated at rates ranging from 800 mL/h to 2500 mL/h. Replacement fluids were delivered prefilter.

Drug Administration, Sampling Procedure and Analytical Methods

Blood and dialysate-ultrafiltrate samples were obtained over one or more dosing intervals at steady state after administration of 500 mg, 1000 mg or 2000 mg of meropenem every 6 or 8 hours by intravenous infusion. Blood samples (4 mL, using lithium heparin as an anticoagulant) were obtained from a prefilter device immediately before dosing, at the end of the infusion, at 20, 30 and 45 minutes, and at 1, 3 and 6 hours after the beginning of the infusion. Another sample was collected 8 hours after the beginning of the infusion in patients to whom meropenem was administered every 8 hours. Trough and peak samples were obtained on the following day or days in some patients. Simultaneously, dialysate-ultrafiltrate samples (3 mL) were taken directly from the dialysate-

ultrafiltrate device. Blood specimens were centrifuged within 1 hour for 10 minutes at $1500 \times g$ at 4°C . Plasma and dialysate-ultrafiltrate samples were immediately frozen at -20°C . The samples were then stored at -80°C within 1 week and analysed within 1 month.

Determination of meropenem concentrations in plasma and dialysate-ultrafiltrate fluid was performed by validated^[19,20] high-performance liquid chromatography with a Waters apparatus (Waters Corp., Milford, MA, USA) coupled to a spectrophotometric detector.^[16] The method used for plasma samples consisted of protein precipitation with acetonitrile, followed by washing with dichloromethane. The dialysate-ultrafiltrate samples did not require any preparation. Separation was performed on a $\mu\text{Bondapak C18}$ ($30\text{ cm} \times 3.9\text{ mm} \times 10\text{ }\mu\text{m}$; Waters Corp.) with ultraviolet detection (296 nm). The mobile phase contained acetate buffer/acetonitrile (95 : 5, v/v) and was delivered at 2 mL/min. The assay was linear over the concentration ranges of 0.25–100 $\mu\text{g/mL}$ for the plasma samples and 0.1–100 $\mu\text{g/mL}$ for the dialysate-ultrafiltrate samples. The intra- and inter-day coefficients of variation (CV) ranged from 0.67% to 9.64% for the plasma samples and from 0.31% to 10.64% for the dialysate-ultrafiltrate samples at the three concentrations tested (0.75 $\mu\text{g/mL}$, 10 $\mu\text{g/mL}$ and 75 $\mu\text{g/mL}$ for the plasma and 0.3 $\mu\text{g/mL}$, 5 $\mu\text{g/mL}$ and 75 $\mu\text{g/mL}$ for the dialysate-ultrafiltrate). The bias at these concentrations ranged from 2.02% to 14.44% for the plasma samples and from 0.11% to 9.85% for the dialysate-ultrafiltrate fluid. The lower limit of quantification was considered the lowest level included in the calibration curve (0.25 $\mu\text{g/mL}$ in plasma and 0.10 $\mu\text{g/mL}$ in dialysate-ultrafiltrate), where the measures of the intra-day CV and bias were 11.69% and 10.10% for the plasma samples and 0.98% and 9.11% for the dialysate-ultrafiltrate samples. No interfering peaks were detected with the assay.

Population Pharmacokinetic Data Analysis

All data, including the concentrations of meropenem in plasma (C_p) and in dialysate-ultrafiltrate (C_u) from all of the patients participating in the study, were fitted simultaneously under the population approach using the first-order conditional estimation (FOCE) method with INTERACTION implemented in NONMEM version V software.^[21]

IIV was modelled exponentially, and the residual variability for the two types of measurements (the plasma and dialysate-ultrafiltrate concentrations) was initially described with a combined error model; however, if during the model selection process one of the components (the additive or the proportional) of the residual error model was negligible, it was deleted from the model.

Selection between models was based on the precision of parameter estimates, goodness-of-fit plots, and the minimum value of the objective function [$-2 \times \log(\text{likelihood})$; -2LL] provided by NONMEM. A difference of 3.84 and 6.63 points in -2LL between

two nested models differing in one parameter is significant at the 5% and 1% levels, respectively. Since some of the models that were compared were not nested, -2LL was not used directly for comparative purposes, and the value of the Akaike Information Criteria (AIC),^[22] computed as equation 1:

$$\text{AIC} = -2\text{LL} + 2 \times \text{Np} \quad (\text{Eq. 1})$$

where Np is the number of the parameters in the model, was used instead. The model with the lowest value of the AIC, given that the precision of the model parameters and the data description were adequate, was selected.

Population model parameters were expressed as the corresponding estimate together with the %CV computed as the ratio between the standard error provided by NONMEM and the estimate of the parameter multiplied by 100. The magnitude of IIV was also expressed as the %CV.

The model development process was performed in three steps. First, a base population model without incorporating covariates and capable of describing the data appropriately was selected. Disposition of the total drug in plasma was modelled using compartmental models parameterized in terms of the apparent volumes of distribution and total plasma and distribution clearances. The concentrations of meropenem in dialysate-ultrafiltrate were modelled as the product between the C_p and the sieving coefficient (S_c), a parameter to also be estimated and defined as the fraction of the drug eliminated across the membrane during CRRT. The significance of the off-diagonal elements of the Ω variance-covariance matrix was also evaluated at this stage.

The covariate model was built in the second step. Age, bodyweight (BW), dialysate plus ultrafiltrate flow (FLOW), creatinine clearance (CLCR) and the unbound drug fraction in plasma (f_u) were the continuous covariates evaluated for significance. The type of membrane (MEMB; = 1 for AN69 or = 2 for polysulfone), CRRT (= 1 for CVVHDF or = 2 for CVVH) and patient type (1 for septic or 2 for polytraumatized) were the categorical covariates studied. Table I lists the covariate information of the patients included in the current study. The relationships between covariates and individual pharmacokinetic parameter estimates were first explored graphically. Each covariate was added individually to the base model, and those covariates that showed a significant impact were then incorporated (starting with the covariate that led to the largest drop in -2LL) one at a time until the full covariate model was obtained. If an added covariate did not cause a significant decrease in -2LL , it was removed. This forward inclusion approach was followed by its reverse (backward elimination), whereby a covariate found not to be significant was dropped in favour of the simpler model. This procedure continued until no more covariates could be eliminated. During the forward inclusion and

Table I. Summary of patient characteristics^a

Covariate	All patients (n = 20)	Septic patients (n = 13)	Polytraumatized patients (n = 7)
Age (y)	56.2 (20.5) [21–83]	68.5 (12.3)	33.4 (9.8)
Bodyweight (kg)	73.1 (6.9) [59–85]	71.6 (7.2)	75.7 (6.1)
Gender (%)			
female	25.0	30.8	14.3
male	75.0	69.2	85.7
CL _{CR} (mL/min) ^b	37.4 (42.3) [0–118]	22.0 (32.4)	66.1 (45.8)
Total protein concentration in plasma (g/dL)	4.7 (0.9) [3.1–6.0]	4.6 (0.9)	5.0 (0.7)
Albumin concentration in plasma (g/dL)	2.0 (0.5) [0.9–2.9]	2.0 (0.7)	1.9 (0.1)
Total bilirubin concentration in plasma (g/dL)	0.9 (0.4) [0.3–1.7]	0.9 (0.4)	0.7 (0.3)
FLOW (mL/h)	1910.0 (616.4) [1000–2800]	2284.6 (299.6)	1214.3 (393.4)
f _u	0.79 (0.08) [0.63–0.98]	0.79 (0.09)	0.79 (0.07)
SOFA score	13.1 (4.0) [8–21]	11.9 (2.8)	15.1 (5.2)
APACHE II score	19.4 (6.8) [7–31]	17.5 (6.2)	22.9 (6.9)
CRRT (%)			
CVVH	50.0	38.5	71.4
CVVHDF	50.0	61.5	28.6

a Values are expressed as mean (SD) [range] unless specified otherwise.

b Determined as $CL_{CR} = (Ucr \cdot Vu) / (Pcr \cdot t)$, where Ucr and Pcr are the creatinine concentrations in urine and plasma, respectively, Vu is the urine volume collected in 24 hours and t is the urinary collection time (1440 min).^[23]

APACHE II = Acute Physiology and Chronic Health Evaluation II; **CL_{CR}** = creatinine clearance; **CRRT** = continuous renal replacement therapy; **CVVH** = continuous venovenous haemofiltration; **CVVHDF** = continuous venovenous haemodiafiltration; **FLOW** = dialysate plus ultrafiltrate flow; **f_u** = unbound fraction of the drug in plasma; **SOFA** = sequential organ failure assessment.

backward exclusion approaches, the levels of significance used were 5% and 1%, respectively.

The selected population model was evaluated in the third step using the visual predictive check^[24] and parametric bootstrap.

Visual Predictive Check

Simulations of the meropenem plasma concentration-time profiles were performed from 1000 simulated individuals receiving a 500-mg or 2000-mg intravenous infusion for 20 minutes every 6 hours using the final model and its model parameter estimates, including IIV. For each dose group, the concentration-time profiles corresponding to the 5th, 50th and 95th quantiles were represented together with the corresponding observations.

Parametric Bootstrap

One thousand datasets with the same characteristics as the original dataset were simulated on the basis of the selected model, and the model parameters were then re-estimated. Bias and precision were calculated by computing the median performance error (MPE) and the median of the absolute performance error (MAPE), respectively. For each simulation providing a successful minimization run, the performance error (PE) was calculated as equation 2:

$$PE = \frac{P_{sim} - P}{P} \times 100 \quad (\text{Eq. 2})$$

where P_{sim} and P represent the parameter model estimate from a simulated dataset and the original dataset, respectively. The absolute performance error (APE) was defined as the absolute value of the PE.

Results

Meropenem was well tolerated in all patients; no adverse reactions attributable to meropenem treatment were reported, including tubulointerstitial nephritis.

The pharmacokinetic profiles were best described with a two-compartment model. The data supported the inclusion of IIV in total plasma clearance (CL), the apparent volume of distribution of the central compartment (V_1) and the S_c . The off-diagonal elements of the Ω variance-covariance matrix resulted in a non-significant effect ($p > 0.05$). The additive and proportional elements of the combined error models were needed for both the C_p and the C_u ; however, the estimates of the residual variance differed between the two types of observations.

Among the examined covariates, age, BW, MEMB and CRRT did not show significant covariate effects ($p > 0.05$) on any of the

pharmacokinetic parameters. During the forward covariate inclusion approach, CL_{CR}, FLOW, and the patient type were found to be significant for CL ($p < 0.05$). CL was described as the sum of the renal clearance (affected by CL_{CR} and the patient type), non-renal clearance (not affected by any of the explored covariates) and extracorporeal clearance (calculated as the product between FLOW and the S_c). In the case of the V_1 , the f_u and the patient type were the covariates exerting a significant effect ($p < 0.05$). The following equations describe CL and the V_1 in the full model, incorporating all of the covariates selected during the forward inclusion approach (equation 3):

$$\begin{aligned} CL &= \theta_{CL} + \theta_{CLCR(\text{septic})} \times CL_{CR} + S_c \times FLOW \\ CL &= \theta_{CL} + \theta_{CLCR(\text{polytraumatized})} \times CL_{CR} + S_c \times FLOW \\ V_1 &= \theta_{V(\text{septic})} \times f_u \\ V_1 &= \theta_{V(\text{polytraumatized})} \times f_u \end{aligned} \quad (\text{Eq. 3})$$

Deletion from the full model of the f_u and FLOW covariates did not elicit a significant increase in $-2LL$ ($p > 0.01$). The parameter estimates of the final selected model, which incorporates the significant covariates CL_{CR} and the patient type, are presented in table II, where it can be observed that all parameters were estimated with adequate precision.

Inclusion of the selected covariates in the model decreased the degree of IIV, with respect to the basic model, from 150% to 38% in CL and from 85% to 45% in the V_1 . The IIV associated with the S_c was 18%. The additive and proportional residual errors corresponding to the C_p were 0.22 mg/L and 21%, respectively, and those corresponding to the C_u were 0.15 mg/L and 25%, respectively.

The mean population estimate of CL was a linear function of CL_{CR} in both groups of patients, with an intercept of 6.63 L/h and slopes of 0.063 and 0.72 for septic and polytraumatized patients, respectively. The V_1 was also dependent on the patient type, with values of 15.7 L for septic patients and 69.5 L for polytraumatized patients. The population CL was 15 L/h, and the population apparent volume of distribution of the peripheral compartment was 19.8 L.

The goodness-of-fit plots presented in figure 1, together with the results of the visual predictive check shown in figure 2, confirmed graphically that the selected model was supported by data. The MPE and MAPE values obtained from 966 successful minimization runs were below 10% and 30% for most of the model parameters, with the exception of the IIV of CL (MPE = -17%) and $\theta_{CLCR(\text{septic})}$ and the IIV of the S_c (MAPE = 46% and 41%, respectively).

Figure 3 explores the impact of the two selected covariates, CL_{CR} and the patient type, on the plasma concentration-time

profiles of meropenem administered as an intravenous infusion of 500 mg or 2000 mg. It is clear that both covariates are likely to have a clinical impact.

Discussion

The objective of this analysis was to develop a population pharmacokinetic model of meropenem in critically ill patients undergoing CRRT by using plasma and dialysate-ultrafiltrate concentration data from 20 patients. Several previous studies have reported on the pharmacokinetics of meropenem in critically ill patients undergoing CRRT by using traditional pharmacokinetic analysis.^[6-16] In contrast, by using population pharmacokinetic methods, this study extends the analysis to address potentially important covariates in order to estimate their influence on pharmacokinetic parameters and the magnitude of the variability that could not be assessed in the other studies. A bibliographical search in MEDLINE and using the WINSPIRS computer system failed to identify other studies of population pharmacokinetics of meropenem in patients undergoing CRRT.

A two-compartment model was preferred to a one-compartment model, as it provided a much better fit when base models without incorporation of covariates were evaluated in the first step of the model building. The precision of the parameter estimates in

Table II. Population pharmacokinetic model parameter estimates of meropenem after intravenous administration

Parameter or covariate model	Estimate (%CV)	IIV (%CV)
$CL = \theta_{CL} + \theta_{CLCR} \times CL_{CR}$		38 (2)
θ_{CL}	6.63 (13)	
$\theta_{CLCR(\text{septic})}$	0.064 (41)	
$\theta_{CLCR(\text{polytraumatized})}$	0.72 (21)	
V_1 (L)		
$V_{1(\text{septic})}$	15.7 (10)	45 (35)
$V_{1(\text{polytraumatized})}$	69.5 (18)	
CL_D (L/h)	15 (14)	NE
V_2 (L)	19.8 (11)	NE
S_c	0.72 (6.3)	18 (47)
Additive error (mg/L)		NA
C_p	0.22 (20)	
C_u	0.15 (85)	
Proportional error (%)		NA
C_p	21 (11)	
C_u	25 (22)	

CL = total plasma clearance; **CL_{CR}** = creatinine clearance; **CL_D** = distribution clearance; **C_p** = concentrations of meropenem in plasma; **C_u** = concentrations of meropenem in dialysate-ultrafiltrate; **IIV** = interindividual variability; **NA** = not applicable; **NE** = not estimated; **S_c** = sieving coefficient; **V₁** = apparent volume of distribution of the central compartment; **V₂** = apparent volume of distribution of the peripheral compartment.

Fig. 1. Goodness-of-fit plots obtained from the final population pharmacokinetic model selected for meropenem. (a), (b) and (c) correspond to the total plasma concentrations; (d), (e) and (f) correspond to the dialysate-ultrafiltrate concentrations. **DV** = observed values; **IPRED** = individual model predictions; **PRED** = typical population predictions; **WRES** = weighted residuals provided by NONMEM.

the selected structural model suggested that the model parameters were estimated with reasonable precision. The goodness of fit was confirmed by the plots of population and individual model predictions versus observations and weighted residuals versus time for both the plasma data and the dialysate-ultrafiltrate data. When possible, the comparison between the pharmacokinetic parameters obtained by the population analysis method and the traditional approach can serve as an indicator of the accuracy of the population pharmacokinetic models. In this study, the pharmacokinetic parameters were consistent with the values calculated by the traditional approach previously published.^[16]

Population pharmacokinetics are a very useful instrument to provide quantitative inspection of the influence of several pathophysiological and clinical covariates on the pharmacokinetic profile of drugs. In our study, CLCR was found to have a significant correlation with CL during the development of the covariate model, which is in accordance with the established finding that up to 83% of the administered dose of meropenem is recovered in the

urine.^[4] However, the influence of CLCR differed between septic and polytraumatized patients. In this way, renal clearance of meropenem varied extensively from septic patients to severely polytraumatized patients. The V_1 also differed between these two types of patients.

Other studied covariates such as age, BW, FLOW, f_u , MEMB and CRRT were not included in the final model. However, there should probably be another covariate, not included in the protocol, that would have allowed us to specify and determine why meropenem showed different pharmacokinetics in septic and polytraumatized patients. In fact, polytraumatized patients received large quantities of intravenous fluid during an extended treatment period, which could have resulted in an expanded extracellular compartment, as occurs with other drugs.^[25-30] However, the volumes of fluid administered in both groups of patients, among other possible parameters, were not included in the data collection sheet when the study was designed. According to all of this, we must emphasize the importance of the patient's clinical status in

Fig. 2. Results of the model exploration exercise where total plasma concentration-time profiles of meropenem were obtained from 1000 simulated individuals receiving a 20-min infusion of (a) 500 mg or (b) 2000 mg.

Fig. 3. Typical population simulated plasma concentration-time profiles of meropenem administered as an intravenous 20-min infusion of (a) 500 mg or (b) 2000 mg to patients as a function of creatinine clearance (CLCR). The values of CLCR chosen for the simulation exercise correspond to the minimum, first, second and third percentiles and the maximum values seen in the studied populations.

characterizing the pharmacokinetic profile of the drug in critically ill patients.

The potential clinical significance of the statistically-based selected covariates was studied by computer simulations. Figure 3 shows the effects of CLCR on the typical population pharmacokinetic profiles of meropenem for each type of patient and under the same dosing schedule used in the current study. First, it appears clear that sepsis and polytrauma have an important effect on the pharmacokinetic characteristics of meropenem. Then, CLCR has a much greater impact on plasma disposition of meropenem in septic patients than in polytraumatized patients.

These pharmacokinetic results emphasize that meropenem CL is higher in polytraumatized patients and in those with better renal function. However, pharmacodynamic considerations should also be taken into account. For β -lactam antibacterial agents, the pharmacokinetic/pharmacodynamic predictor of clinical efficacy is the time during which the serum drug concentration is above the minimum inhibitory concentration (T>MIC) of the infecting pathogen. In critically ill patients, a T>MIC of 100% should be obtained. The US National Committee for Clinical Laboratory Standards^[31] has established breakpoints for susceptible, intermediate susceptible and resistant strains of Enterobacteriaceae, *Pseudomonas* and *Staphylococcus* of ≤ 4 mg/L, 8 mg/L and ≥ 16 mg/L, respectively. The breakpoint for susceptible *Haemophi-*

lus and *viridans* group streptococci is ≤ 0.5 mg/L, and the value for susceptible *Streptococcus pneumoniae* and *Neisseria meningitidis* is ≤ 0.25 mg/L. Our results (figure 3) show that polytraumatized patients may not achieve adequate efficacy indexes to deal with specific infections, especially Enterobacteriaceae, *Pseudomonas* and *Staphylococcus*, even after receiving high doses of meropenem. Septic patients with conserved renal function will probably not achieve plasma drug concentrations above the MIC of some pathogens during the entire dosing interval. In these cases, administration of meropenem as a continuous infusion would be recommendable for optimization of antimicrobial therapy when an isolated or expected causative pathogen has an MIC of ≥ 4 mg/L. Continuous infusion of other β -lactams, such as ceftazidime,^[32] has also been recommend in critically ill patients with severe acute renal failure undergoing CRRT. Table III summarizes the recommended continuous infusion protocol of meropenem for critically septic patients and polytraumatized patients when pathogens with MIC values of 4 mg/L, 8 mg/L and 16 mg/L are isolated. This protocol is based on the population pharmacokinetic model developed in the present study. Infections caused by pathogens with an MIC of ≥ 8 mg/L should not be treated with meropenem in polytraumatized patients without or with moderate renal failure because excessive doses of meropenem would be necessary.

Table III. Continuous intravenous infusion rates of meropenem in septic and polytraumatized patients with different degree of renal function that allow achievement of plasma drug concentrations above 4 mg/L, 8 mg/L and 16 mg/L

Patient type	MIC (mg/L)	Infusion rate [mg/h (mg/day)]					
		CLCR (mL/min)					
		0	10	25	50	75	100
Septic	4	27 (637)	29 (698)	33 (790)	39 (944)	46 (1097)	52 (1251)
	8	53 (1273)	58 (1396)	66 (1580)	79 (1887)	91 (2195)	104 (2502)
	16	106 (2546)	116 (2792)	132 (3160)	157 (3775)	183 (4389)	209 (5004)
Polytraumatized	4	27 (637)	55 (1328)	99 (2365)	171 (4093)	243 (5821)	315 (7549)
	8	53 (1273)	111 (2655)	197 (4729)	341 (8185)	485 (11 641)	629 (15 097)
	16	106 (2546)	221 (5311)	394 (9458)	682 (16 370)	970 (23 282)	1258 (30 194)

CLCR = creatinine clearance; MIC = minimum inhibitory concentration.

Conclusion

A population pharmacokinetic model of meropenem in intensive care patients on CRRT was developed and validated. The two-compartment model gave a better description of the data than the one-compartment model and was retained as the base model.

CLCR and the patient type (whether the patient was septic or polytraumatized) were identified as significant covariates that accounted for part of the variability in the pharmacokinetic behaviour of this drug in these patients. The population pharmacokinetic model developed in this study has been helpful for establishing dosage regimens of meropenem administered by continuous infusion to patients undergoing CRRT, taking into account that the objective will be to guarantee drug concentrations above the MIC of the causative pathogen because meropenem is a time-dependent activity agent.

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Correspondence: Dr José Luis Pedraz, Laboratorio de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Paseo de la Universidad nº 7, 01006 Vitoria-Gasteiz, Spain.
E-mail: joseluis.pedraz@ehu.es