J Antimicrob Chemother 2015; **70**: 207–216
doi:10.1093/jac/dku354 Advance Access publication 12 September 2014

Journal of Antimicrobial Chemotherapy

Modelled target attainment after meropenem infusion in patients with severe nosocomial pneumonia: the PROMESSE study

Frédéric Frippiat[1]*†, Flora Tshinanu Musuamba[2]†, Laurence Seidel[3], Adelin Albert[3], Raphaël Denooz[4], Corinne Charlier[4], Françoise Van Bambeke[5], Pierre Wallemacq[6], Julie Descy[7], Bernard Lambermont[8], Nathalie Layios[8], Pierre Damas[8] and Michel Moutschen[1]

[1]Department of Infectious Diseases and General Internal Medicine, University Hospital of Liège, Liège, Belgium; [2]School of Pharmacy, University College, London, UK; [3]Department of Biostatistics, University Hospital of Liège, Liège, Belgium; [4]Department of Toxicology, University Hospital of Liège, Liège, Belgium; [5]Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium; [6]Louvain Centre for Toxicology and Applied Pharmacology, Université catholique de Louvain, Brussels, Belgium; [7]Department of Microbiology, University Hospital of Liège, Liège, Belgium; [8]Intensive Care Unit, University Hospital of Liège, Liège, Belgium

*Corresponding author. Tel: +0032(0)43667172; Fax: +0032(0)43668583; E-mail: f.frippiat@chu.ulg.ac.be
†These two authors have contributed equally to the work.

Received 23 April 2014; returned 28 June 2014; revised 6 August 2014; accepted 9 August 2014

Objectives: The objective of this study was to propose an optimal treatment regimen of meropenem in critically ill patients with severe nosocomial pneumonia.

Patients and methods: Among 55 patients in intensive care treated with 1 g of meropenem every 8 h for severe nosocomial pneumonia, 30 were assigned to intermittent infusion (II; over 0.5 h) and 25 to extended infusion (EI; over 3 h) groups. Based on plasma and epithelial lining fluid (ELF) concentrations determined at steady-state, pharmacokinetic modelling and Monte Carlo simulations were undertaken to assess the probability of attaining drug concentrations above the MIC for 40%–100% of the time between doses (%T > 1-fold and 4-fold MIC), for 1 or 2 g administered by either method.

Results: Penetration ratio, measured by the ELF/plasma ratio of AUCs, was statistically higher in the EI group than in the II group (mean ± SEM: 0.29 ± 0.030 versus 0.20 ± 0.033, $P = 0.047$). Considering a maximum susceptibility breakpoint of 2 mg/L, all dosages and modes of infusions achieved 40%–100% T > 1-fold MIC in plasma, but none did so in ELF, and only the 2 g dose over EI achieved 40%–100% T > 4-fold MIC in plasma.

Conclusions: The optimum regimen to treat severe nosocomial pneumonia was 2 g of meropenem infused over 3 h every 8 h. This regimen achieved the highest pharmacodynamic targets both in plasma and in ELF.

Keywords: epithelial lining fluid concentrations, Monte Carlo simulations, critically ill patients

Introduction

Severe nosocomial pneumonia in patients in ICUs is caused by a wide range of bacteria and is associated with high rates of morbidity and mortality, as well as high costs.[1,2] In this setting, prompt use of β-lactams remains the cornerstone of antibiotic therapy, and among these drugs, meropenem is often chosen because it is well tolerated and has a wide spectrum of activity.

Meropenem is a time-dependent antibiotic: maintaining unbound drug concentrations in plasma above the MIC for pathogens for at least 40% of the time between doses (≥40% T > MIC) is usually required for optimal bactericidal activity.[3,4] In serious bacterial infections this goal could be extended to 100% of the dosing interval,[5–7] so that extended infusion (EI, i.e. dose delivered over several hours) or even continuous infusion (i.e. dose delivered over 24 h) has been proposed in place of the usual intermittent infusion (II, i.e. over a few minutes) to improve pharmacokinetic (PK) and pharmacodynamic (PD) properties.[5–13]

Furthermore, drug concentration at the site of infection seems to influence efficacy.[3,4] Dosage of antibiotics in the epithelial lining fluid (ELF) is advocated as the best marker of drug exposure at the site of infection in patients with pneumonia, particularly for extracellular respiratory tract pathogens, although this method has some limitations.[14–17]

Because PK data can be difficult to obtain, especially at the site of infection, population PK modelling and Monte Carlo simulations

have been developed to predict PK/PD profiles of several antibiotics for a large number of subjects, including ICU patients.[12,13,18]

Aims

The aim of the PROMESSE (PROtocol MEropenem Steady State Evaluation) study, performed in critically ill patients with severe nosocomial pneumonia, was to determine whether EI (over 3 h) of 1 g of meropenem every 8 h offered PK/PD advantages in plasma and ELF in comparison with II (over 0.5 h), in order to predict an optimal treatment regimen in this setting. After collecting drug concentrations in plasma and ELF, we used a population model to describe the PK variability of meropenem concentrations and we performed Monte Carlo simulations to assess the probability of target attainment (PTA) for the two different modes of infusion for a range of PK/PD breakpoints and MICs for extracellular Gram-negative pathogens that are likely to be encountered in ICUs.

Patients and methods

Study design and participants

This was a single-centre, open-label, prospective comparative study that was conducted in five ICUs, with a total of 42 medical and surgical beds, at the Centre Hospitalier Universitaire du Sart Tilman, Liège, Belgium between January and September 2012. The study was approved by the local ethics committee, and informed consent was obtained from close relatives of the patients because all patients were ventilated at the time of inclusion.

Eligible patients had to meet the following inclusion criteria: age >18 years; diagnosis of late-onset (>5 days after admission) ventilator-associated pneumonia or hospital-acquired pneumonia requiring mechanical ventilation; and glomerular filtration rate (GFR) ≥30 mL/min (calculated according to the four-variable Modification of Diet in Renal Disease formula[19] or by measurement of creatinine clearance based on 24 h urine) or acute kidney injury with indication for continuous venovenous haemofiltration (CVVH). The following exclusion criteria were used: pregnancy; life expectancy <3 days; allergy to β-lactams; GFR <30 mL/min and no required CVVH; previous use of meropenem within 15 days; and colonization with pathogens known to be resistant to meropenem.

The definition of pneumonia required clinical criteria and/or a simplified clinical pulmonary infection score ≥6 points.[20,21] Clinical criteria were: new or progressive radiological pulmonary infiltrate plus two or more of temperature >38 or <35.5°C, leucocyte count >12 000 or <4000 cells/mm^3 or purulent respiratory secretions.[20]

Data collection

In addition to GFR estimation, various demographic and clinical data were collected, including age, sex, weight, duration of hospital stay and/or ICU stay before onset of pneumonia, and the presence of severe sepsis, septic shock, concomitant bacteraemia, liver cirrhosis and surgical drain. Simplified acute physiology score (SAPS) III and SOFA score were calculated at the onset of pneumonia. Crude 30 day mortality and in-hospital mortality were also collected.

Treatment and sampling

Assignment of patients to treatment groups was initially performed in a sequential manner, followed by a third phase of recruitment to ensure that the exact numbers of patients defined in the protocol were reached in each group. Patients from this phase were arbitrarily assigned treatment by a named operator. Meropenem (Meronem®, AstraZeneca Pharmaceuticals, Belgium) was administered as either II (infusion over 0.5 h) in 30 patients (II group) or EI (infusion over 3 h) in 25 patients (EI group), at a dose of 1 g every 8 h, which is usually recommended in nosocomial pneumonia.[1] The drug was dissolved in 50 mL of 0.9% saline solution and injected into a central venous catheter via a volumetric pump with an infusion dead space of <2 mL.[22]

All plasma and ELF samples were obtained at steady-state, i.e. after at least three doses. The times of the start of infusion, end of infusion and sampling were recorded by intensive care nurses. Samples were excluded from the analysis if they were not collected within 15 min either side of the expected time of sampling. Blood samples (2 mL) were collected from indwelling arterial catheters before and 0.5, 1, 3, 4 and 6 h after the start of meropenem infusion. Simultaneously, ELF samples (one per patient) were collected by a standardized mini-bronchoalveolar lavage (mini-BAL) procedure with 2×20 mL of sterile 0.9% normal saline solution, using a non-bronchoscopic BAL catheter (Bal-Cath® system, Kimberly Clark, Zaventem, Belgium), with all of the samples being collected by the same operator.[15] Patients were assigned to subgroups of five patients per time-point to cover the whole PK profile in ELF (i.e. six within the II group and five within the EI group as only II patients underwent mini-BAL at 0.5 h). Blood and ELF samples were immediately centrifuged at 3000 rpm for 10 min; the supernatant was immediately separated and kept at −80°C until analysis. After sampling, a switch to an alternative regimen was systematically considered with the infectious diseases physician to promote de-escalation based on the clinical, radiological, biological and microbiological results.

Analytical methods

Concentrations of meropenem in plasma and ELF were measured with a simple and rapid UPLC method with ultraviolet detection.[23] Briefly, 50 μL of plasma (or 2 mL of ELF) was spiked with cefamandole, which was used as an internal standard, and cleaned up by solid-phase column extraction prior to UPLC analysis. The extracted samples were analysed using an Acquity UPLC BEH C18 column (100×2.1 mm i.d., 1.7 μm, Waters, MA, USA) with a mobile phase consisting of a methanol and ammonium formate buffer mixture in gradient mode. Ultraviolet detection was set at 300 nm, and the total run time was 13 min. The method developed was linear over the concentration range of 1.0–180.0 mg/L in plasma and 0.01–2.0 mg/L in ELF. Between- and within-run accuracy and precision were all within 15%.[23] The unbound (free) fraction of meropenem was not measured, but we believed that this was not necessary as the drug has a low protein binding of 2%–8%.[4,12]

The concentrations of urea in the plasma and ELF were determined with the Urea Nitrogen/1900 kit (Roche Professional Diagnostics, Mannheim, Germany). Urea was hydrolysed in the presence of urease in ammonia and carbon dioxide. Then ammonia was combined with 2-oxoglutarate and NADH in the presence of the enzyme glutamate dehydrogenase. This reaction produced L-glutamate and NAD+. The urea concentration was directly proportional to the rate of decrease in the NADH concentration, which was determined by absorption spectroscopy at 340 nm. Limits of quantification were 0.06 and 0.01 g/L in the plasma and ELF, respectively. The concentration of meropenem in ELF was thereafter determined using urea as an endogenous marker, according to the following formula:[15]

$$MER_{ELF} = \frac{MER_{BAL} \times urea_{PLA}}{urea_{BAL}}$$

where MER_{ELF} is the concentration of meropenem in ELF, MER_{BAL} is the concentration of meropenem in the mini-BAL fluid, $urea_{PLA}$ is the concentration of urea in plasma (collected concomitantly with bronchoscopy) and $urea_{BAL}$ is the concentration of urea in the mini-BAL fluid.

PK analysis

Non-compartmental analysis was performed for descriptive purposes, to explore preliminary data and to generate an objective basis to enable

comparison of our findings with previously published results on penetration ratios in ELF.[24–26] The AUCs in the plasma and ELF were computed using the linear trapezoidal rule. Individual AUCs were calculated for each patient's plasma sample (the value considered at the end of the dosing interval was the same as that measured at time 0 because no samples were drawn at that point and steady-state was deemed to have been reached) and were compared by classical Student's *t*-test. Since each patient underwent one mini-BAL and there were five patients per timepoint, only one AUC in ELF could be calculated in each group (EI and II) based on the mean values at each timepoint. The AUC in plasma was also calculated in each group as done for ELF, i.e. based on the same five patients at each timepoint. This allowed calculation of the penetration ratio, measured by the ELF/plasma AUC ratio. To compare the penetration ratio in the II and EI groups, the bootstrap method was used to derive SEMs of the estimates.

A population PK model was developed to enable Monte Carlo simulations to be performed for the subsequent PK/PD analysis. A non-linear mixed-effects modelling approach was performed with NONMEM, version 7.2 (double precision, Icon Development Solutions, Ellicott City, MD, USA) and PsN-toolkit version 3 (a programming library for non-linear mixed-effects modelling).[27,28] Briefly, the first-order conditional estimation approach with interaction between parameters was used throughout the entire modelling process, and one-, two- and three-compartment structural models were tested. PK parameters were estimated with NONMEM in terms of intercompartmental clearance (*Q*, L/h), clearance from the central compartment (L/h) and volumes

Table 1. Demographic, clinical and microbiological data of the 55 patients

	All ($n=55$)	II group ($n=30$)	EI group ($n=25$)	*P*
Demographic and clinical data				
male	35 (63.6)	17 (56.7)	18 (72.0)	0.24
age (years)	63.4±15.1	61.5±17.9	65.7±10.9	0.31
weight (kg)	78.4±18.4	82.3±19.9	73.7±15.4	0.084
hospital stay before onset of pneumonia (days)	17.3±18.1	15.9±18.5	18.9 17.9	0.54
ICU stay before onset of pneumonia (days)	8.4±10.7	9.6±12.8	7.0±7.4	0.37
clinical criteria of pneumonia	46 (83.6)	27 (90.0)	19 (76.0)	0.16
simplified CPIS ≥6	52 (94.5)	30 (100.0)	22 (88.0)	0.088[d]
SAPS III[a]	74.8±13.5	73.4±13.7	76.5±13.3	0.40
SOFA score[a]	7.7±4.1	7.7±4.1	7.6±4.0	0.98
severe sepsis	39 (70.9)	19 (63.3)	20 (80.0)	0.18
septic shock	12 (21.8)	5 (16.7)	7 (28.0)	0.31
concomitant bacteraemia	12 (21.8)	3 (10.0)	9 (36.0)	**0.02**
liver cirrhosis	6 (10.9)	3 (10.0)	3 (12.0)	0.81
CL_{CR} (MDRD)				
>60 mL/min	31 (56.4)	17 (56.7)	14 (56.0)	0.73
30–59 mL/min	13 (23.6)	8 (26.7)	5 (20.0)	
CVVH	11 (20.0)	5 (16.7)	6 (24.0)	
CVVH with residual renal function	2 (3.6)	1 (3.3)	1 (4.0)	0.91
CL_{CR} (using the urine of 24 h)				
not performed	13 (23.6)	7 (23.3)	6 (24.0)	0.34
>120 mL/min	17 (30.9)	12 (40)	5 (20.0)	
119–60 mL/min	11 (20.0)	4 (13.3)	7 (28.0)	
<60 mL/min	14 (25.5)	7 (23.3)	7 (28.0)	
presence of surgical drains	18 (32.7)	10 (33.3)	8 (32.0)	0.92
30 day mortality	21 (38.2)	12 (40.0)	9 (36.0)	0.76
in-hospital mortality	30 (54.5)	17 (56.7)	13 (52.0)	0.73
antibiotic de-escalation	35 (63.6)	17 (56.7)	18 (72.0)	0.24
number of doses before sampling	6.5±4.1	6.8±4.2	6.2±4.0	0.59
Microbiological data; susceptibility testing: S/I/R (%)[b]				
P. aeruginosa	8 (87.5/0/12.5)	5	3	0.43
A. baumannii	1 (0/0/100)	1	0	0.31
Enterobacteriaceae [ESBL]	29 (100/0/0) [6]	13 [3]	16 [3]	0.25
total of Gram-negative bacteria	38[c]	19	19	0.99

CPIS, clinical pulmonary infectious score; MDRD, Modification of Diet in Renal Disease formula.
The values are presented as *n* (%) or the mean±SD.
[a]Calculated at the onset of pneumonia.
[b]Based on EUCAST breakpoints (S≤2; R>8 mg/L): S, susceptible; I, intermediate; and R, resistant.
[c]Thirty-eight Gram-negative bacteria isolated in 35 patients (two Enterobacteriaceae isolated simultaneously in three subjects).
[d]Fisher's exact test.

of distribution (L) of the different compartments, using conventional equations. An additional compartment was added each time to model the ELF concentrations.

The interindividual variability in the PK parameters was estimated with the use of an exponential model, and all parameters were initially tested. Additive, proportional and mixed error models were tested for residual error. A full model approach was implemented for covariate model building with age, sex, weight, presence of severe sepsis, septic shock, concomitant bacteraemia, liver cirrhosis, surgical drain, SAPS III, SOFA score and creatinine clearance (GFR) tested as covariates on volumes of distribution and/or clearance parameters. Allometric and multiplicative functions were used for continuous and categorical variables, respectively. The model stability and accuracy were evaluated by bootstrapping, normalized prediction distribution errors and visual predictive check.[29]

PD analysis and Monte Carlo simulations

On the basis of the population PK model, simulations were created with NONMEM®, and concentrations of meropenem in plasma and ELF were generated for 5000 virtual subjects for each of four scenarios: 1 or 2 g administered by II and 1 or 2 g administered by EI every 8 h. Subsequently, the % T>MIC values in plasma and ELF were calculated for each virtual subject. The 90% PTA was obtained by counting the subjects who achieved 40%, 54% and 100% T>1-fold and 4-fold MICs, ranging from 0.0625 to 64.0 mg/L. Bactericidal activity of meropenem is usually 40% T>1-fold MIC,[3,4] but some authors consider that the maximal bactericidal effect of β-lactams (including meropenem) occurs when concentrations exceed the MIC by up to 5-fold for up to 100% of the dosing interval, particularly in critically ill patients and/or for pathogens with high MICs.[4–6] For this reason we assessed PD targets at 40%, 54% and 100% T>1-fold or 4-fold MIC. We selected 54% T>MIC because it is the PD clinical breakpoint threshold chosen by EUCAST for meropenem,[30] based on the findings of Li *et al.*[31] We used the breakpoints defined by EUCAST for *Pseudomonas* spp., *Acinetobacter* spp. and Enterobacteriaceae (susceptibility, intermediate and resistance thresholds of ≤2, 4–8 and >8 mg/L, respectively).[30]

Statistical analysis

Data were summarized as mean and SD for quantitative variables while frequency tables were used for the categorical findings. Mean values were compared by one-way analysis of variance and the χ^2 test was used to compare proportions. For comparing the penetration ratio in the two study groups, a *Z*-test was used based on the SEMs derived from the bootstrap method. Results were considered significant at the 5% critical level ($P<0.05$). Data analysis was carried out using the SAS (version 9.3 for Windows) and S-PLUS (version 8.1) statistical packages.

Results

Patient enrolment, exclusions and adverse events

Among 63 patients enrolled, five patients in the II group were excluded during treatment ($urea_{BAL}$ undetectable in three subjects, massive desquamation and unexpected high concentration of meropenem in the mini-BAL fluid in one and inversion of plasma samples in one), as were three in the EI group ($urea_{BAL}$ undetectable in two subjects and moderate haemorrhage and unexpected high concentration of meropenem in the mini-BAL fluid in one). Therefore, eight patients were included in the third enrolment phase to complete each treatment group. Meropenem and mini-BAL were well tolerated without any significant adverse events.

Patients' demographic, clinical, PK and microbiological data

The patients' demographic, clinical and microbiological characteristics are described in Table 1. No significant differences were observed in the evaluated parameters, except for a trend towards higher weight and lower concomitant bacteraemia in the II patients. The eight patients included in the third enrolment phase had the same demographic and diseases profile as other patients. Increased risk of death at 30 days was associated with bacteraemia (OR 7.75, 95% CI: 1.79–33.6; $P=0.006$), severe sepsis (OR 6.65, 95% CI: 1.33–33.2; $P=0.021$) and high SAPS III (OR 1.06, 95% CI: 1.02–1.10; $P=0.0036$) in the univariate analysis and with bacteraemia (OR 16.6, 95% CI: 2.04–136; $P=0.0086$), high SAPS III (OR 1.07, 95% CI: 1.02–1.13; $P=0.0085$) and the II group (OR 4.90, 95% CI: 0.92–26.3; $P=0.063$) in the multivariate analysis.

Sampling was performed after a median of six doses of meropenem (range 3–22), with no statistically significant difference between the two groups. Eleven patients received CVVH, and 30.9% had augmented renal clearance (>120 mL/min) with GFR calculated using 24 h urine ($n=42$). Forty-six pathogens were isolated from 41 patients (23 from 21 patients in the II group; 23 from 20 patients in the EI group; two different pathogens were isolated in five subjects), no pathogens were cultured from the remaining nine (30%) II patients and five (20%) EI patients and this was not statistically significant. Six of the pathogens were Gram-positive (three methicillin-susceptible and two methicillin-resistant *Staphylococcus aureus*; one *Streptococcus pneumoniae*) and were excluded. Among the Gram-negative bacteria, *Haemophilus influenzae* was identified twice (one patient in each group), and this bacterium was not tested against meropenem; therefore, 38 bacteria were considered as invasive for microbiological analysis (29 Enterobacteriaceae, 8 *Pseudomonas aeruginosa* and 1 *Acinetobacter baumannii*). The distribution of MICs for *P. aeruginosa* was as follows: ≤ 0.25 mg/L, four strains; 0.5 mg/L, two strains; 1 mg/L, one strain; >8 mg/L, one strain.

The results of the AUC in plasma, AUC in ELF and penetration ratio are presented in Table 2. The mean values of AUC_{0-24} of meropenem concentrations in plasma were similar in the two groups (422 ± 48.3 and 502 ± 67.0 mg·h/L in the II group and the EI group, respectively; $P=0.26$), but concentrations in ELF

Table 2. Comparison of AUC in plasma and ELF

Parameter	II group	EI group	*P*
All patients[a] ($n=30$, II group; $n=25$, EI group)			
AUC_{0-24} in plasma (mg·h/L)	422 ± 48.3	502 ± 67.0	0.26
Patients at each timepoint ($n=5$)[b]			
AUC_{0-24} in plasma (mg·h/L)	396 ± 37.7	515 ± 68.4	0.082
AUC_{0-24} in ELF (mg·h/L)	80.3 ± 11.8	150 ± 24.2	0.010
ELF/plasma penetration ratio	0.20 ± 0.033	0.29 ± 0.030	0.047

The values are presented as the mean ± SEM. SEM values were derived by the bootstrap method.
[a]AUC in plasma calculated for each patient in each group.
[b]Calculated using ELF and plasma data of the five patients who underwent mini-BAL at each timepoint.

were significantly lower in the II group than in the EI group (80.3 ± 11.8 versus 150.0 ± 24.2 mg·h/L; $P = 0.010$). Consequently, the AUC penetration ratio was higher in the EI group than in the II group (0.29 ± 0.030 versus 0.20 ± 0.033) and this was statistically significant ($P = 0.047$).

Subjects with creatinine clearance >120 mL/min had a significantly lower AUC in plasma than subjects with creatinine clearance <120 mL/min in both groups: mean ± SEM 226 ± 16.8 versus 561 ± 77.7 mg·h/L in the II group ($P < 0.0001$) and 201 ± 25.4 versus 467 ± 60.4 mg·h/L in the EI group ($P < 0.0001$), respectively. It was not possible to compare the AUC in ELF between the two groups due to the small number of patients (e.g. EI group and creatinine clearance >120 mL/min, $n = 5$). A high PK interindividual variability was observed in the plasma and ELF concentrations in both groups, as observed in Figure 1.

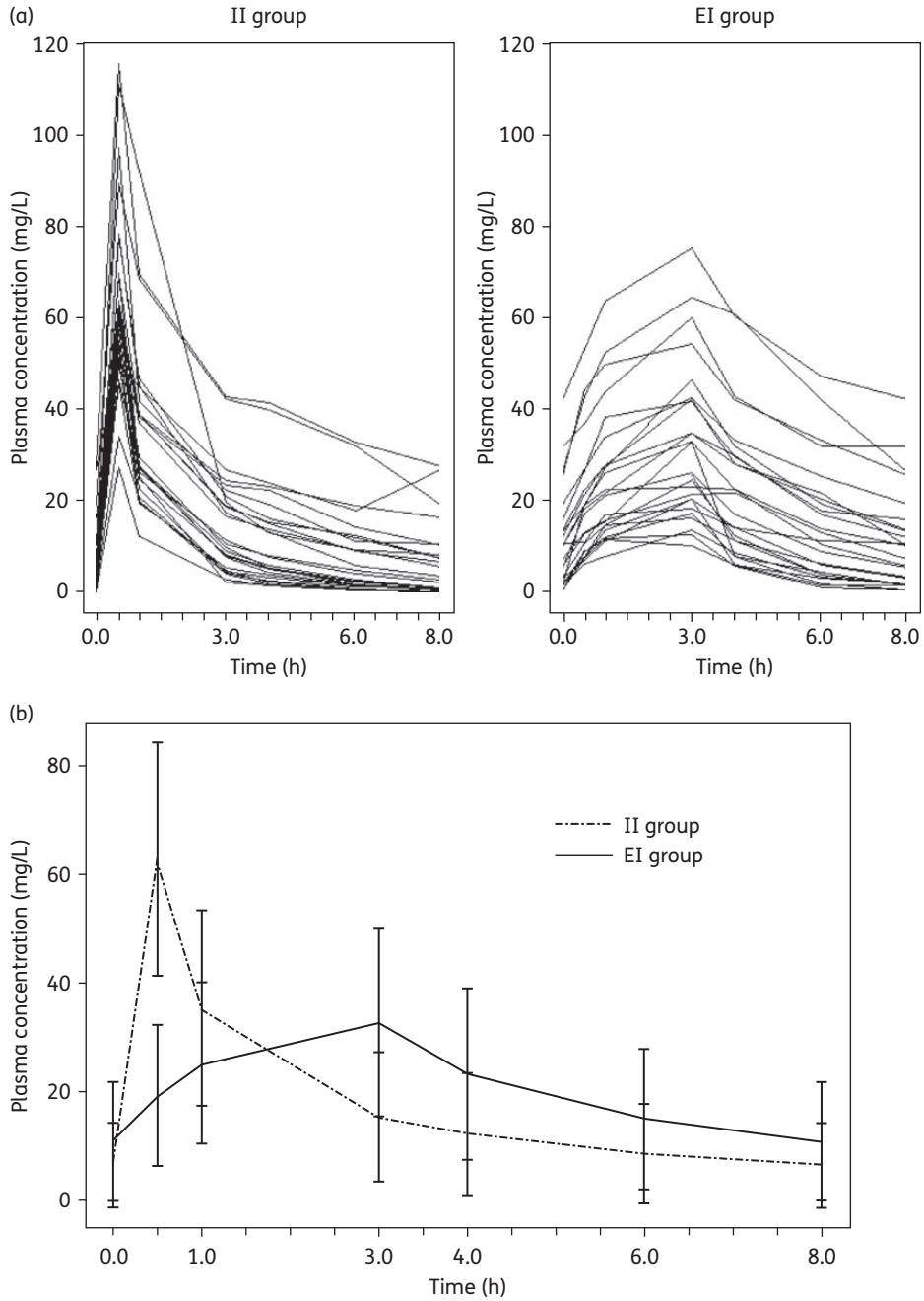


Figure 1. Observed steady-state concentrations of 1 g of meropenem every 8 h in plasma and ELF. II group, 0.5 h infusion rate; $n = 30$. EI group, 3 h infusion rate; $n = 25$. 0.0 = pre-dose sampling. (a) Interindividual variability observed in plasma (six samples per patient) in both II and EI groups. (b) Mean plasma concentration–time curves (±SD) observed in both II and EI groups. (c) Interindividual variability observed in ELF (one sample per patient, five patients per timepoint, except at 0.5 h where only II patients underwent mini-BAL) in both II and EI groups.

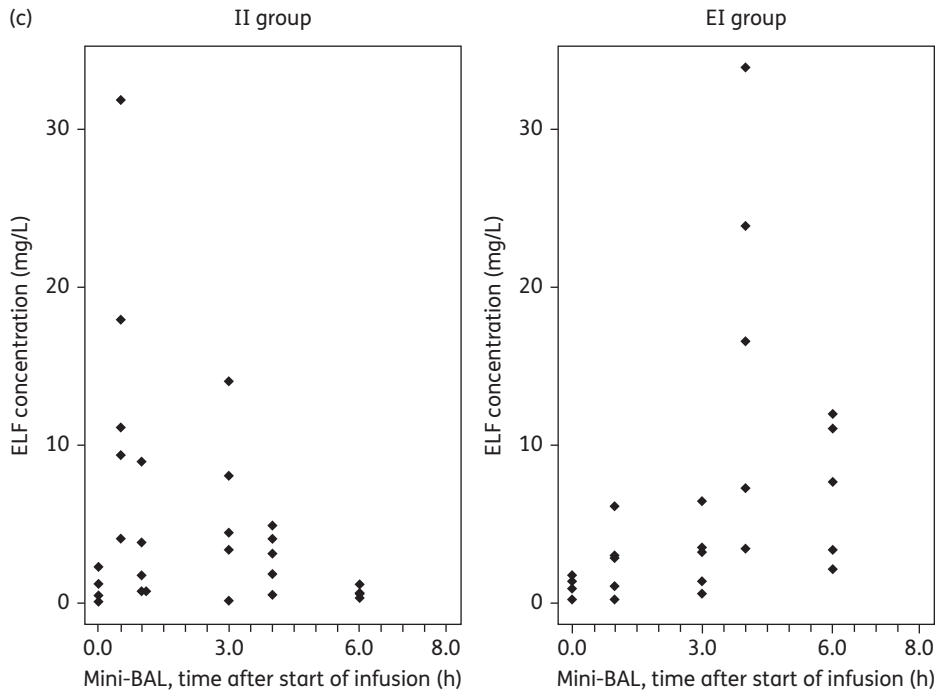


Figure 1. *Continued*

Model building

PK modelling was performed with the data from 375 (99.2%) of the expected 378 plasma samples and 55 ELF samples. A two-compartment model provided an adequate fit to the plasma data. An additional compartment was added to describe ELF concentrations. PK parameters were described in terms of systemic clearance, volume of the central compartment (V_c), volume of the peripheral compartment (V_p), volume of the ELF compartment (V_E) and intercompartmental clearance (Q). Interindividual variability components were necessary to describe the clearance and the volume of distribution terms. A mixed model was retained for residual errors with proportional and additive components. Body weight was retained as a significant covariate on volumes of the central compartment whereas creatinine clearance was a significant covariate on total clearance. Estimated shrinkage was found to be <20% for all random effects parameters. Model parameters including bootstrap results are presented in Table 3. Goodness-of-fit plots show that the model adequately fitted plasma and ELF concentrations, as displayed in Figure 2 and Figure S1 (available as Supplementary data at *JAC* Online). Good overlap between the observed and predicted plasma and mini-BAL concentrations indicates that the model predicts outcomes well and is suitable for use in Monte Carlo simulations. The developed model was used to simulate concentrations in plasma and ELF that could serve as a basis from which to compute % T>MIC as a PK/PD parameter of interest.

Table 3. Population PK model characteristics

Parameter	Final model estimate	Bootstrap CI
TVCL (L/h)	10.2	8.3–10.9
TVQ_E (L/h)	66.5	7.3–9.9
TVQ_P (L/h)	6.9	5.32–8.55
TVV_c (L)	5.2	4.3–5.1
TVV_p (L)	12.1	2.6–40.1
TVV_E (L)	11.3	10.1–12.6
ΘWT on V_c	0.6	0.41–0.79
ΘGFR on CL	0.73	0.38–0.86
σprop	0.2	0.1–0.2
σadd	0.8	0.7–0.9

TVCL, typical value for renal clearance; TVQ_E, typical value for the intercompartmental clearance between the central and ELF compartments; TVQ_P, typical value for the intercompartmental clearance between the central and peripheral compartments; TVV_c, typical value for the volume of the central compartment; TVV_p, typical value for the volume of the peripheral compartment; TVV_E, typical value for the volume of the ELF compartment; ΘWT on V_c, allometric effect of the total body weight on the volume of the central compartment; ΘGFR on CL, allometric effect of GFR on renal clearance; σprop, proportional error; σadd, additive error.

Monte Carlo simulations and PD analysis

The proportion of simulated subjects in which PTA would be achieved was ≥90% of patients for several PK/PD targets (40%, 54% or 100% T>MIC) against a range of MICs in plasma and ELF for the different meropenem doses (1 versus 2 g) and methods of infusion [II (0.5 h) versus EI (3 h)] and is displayed in Figure 3. The corresponding PK/PD breakpoints are summarized in Table 4. Universally, two parameters were observed: first, the PK/PD breakpoints were one dilution higher with EI than with II

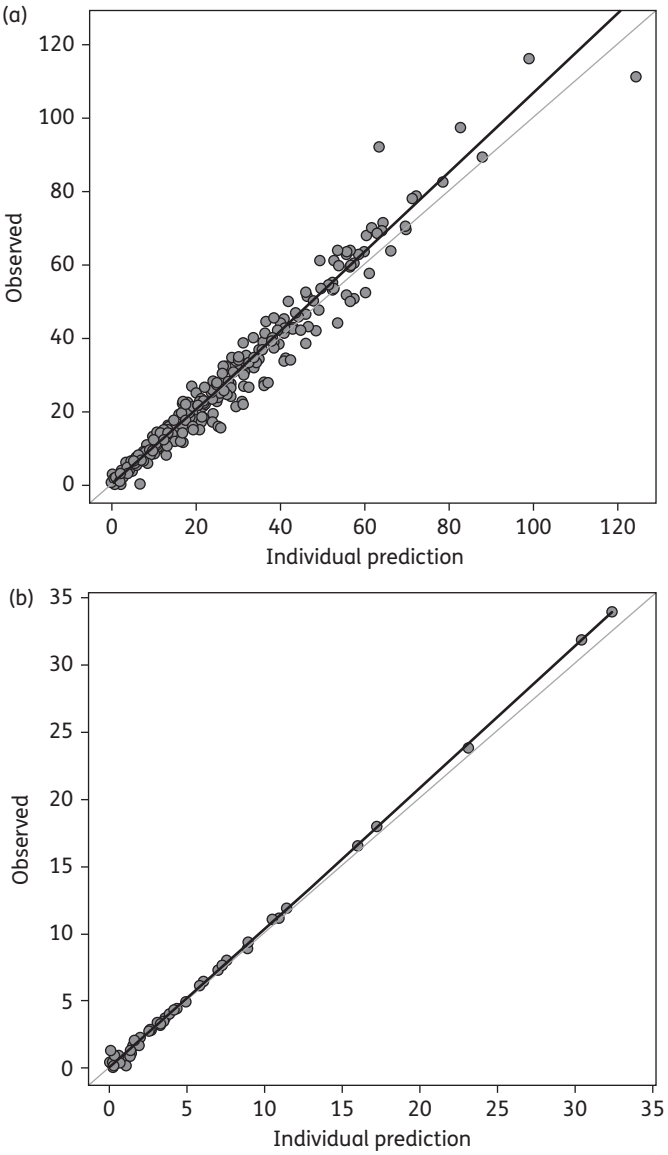


Figure 2. Fit of the model to the observed data for (a) the plasma concentration (mg/L) and (b) the ELF concentration (mg/L) for meropenem in ICU patients with severe nosocomial pneumonia.

for a defined dose (e.g. for 1 g and a PD target of 40% T>MIC, the PK/PD breakpoints were 4 and 0.5 mg/L with EI and 2 and 0.25 mg/L with II in plasma and ELF, respectively); and second, similar results were obtained for 2 g given over 0.5 h and for 1 g given over 3 h every 8 h, both in plasma and ELF. A notable exception to these two parameters was present when considering 100% T>1-fold or 4-fold MIC as a target, where there was no difference between the two modes of administration (except for 2 g in plasma where the PK/PD breakpoint remained one dilution higher with EI than with II). Of note, no difference was observed between the PD targets of 40% or 54% T>MIC in any scenario. The lowest PK/PD breakpoint in ELF was 0.06 mg/L (for 1 g over 0.5 h with a therapeutic target of 40%–100% T>4-fold MIC) and the highest was 1.0 mg/L (for 2 g over 3 h and a therapeutic target of 40%–54% T>1-fold MIC).

Thus, considering the EUCAST susceptibility breakpoint of 2 mg/L, all dosages and both modes of infusion reached the targets from 40% to 100% T>1-fold MIC in plasma, but not in ELF. Only the 2 g dose over 3 h achieved a 4-fold MIC (i.e. 8 mg/L) in plasma from 40% until 100% of the dosing interval.

Discussion

This study, performed with meropenem in patients with severe nosocomial pneumonia, showed a significant higher AUC penetration ratio with EI than with II and better PK/PD parameters both in plasma and in ELF with 2 g infused over 3 h every 8 h.

Contrary to what was done in most of previously published studies on the topic,[15,16,24–26] the penetration of meropenem in ELF was only described using the ratio between the AUC in ELF and the AUC in plasma, rather than comparing concentrations simultaneously obtained in plasma and ELF at individual timepoints. This was done since the equilibrium between the compartments does not occur instantaneously, and the concentration–time profiles of antibiotics in plasma and ELF can increase and decrease at different paces from each other (known as system hysteresis): penetration ratios may therefore vary in magnitude with the chosen sampling times.[16,32]

To date, three studies have been conducted to assess PK/PD characteristics for meropenem in ELF,[24–26] but only one was conducted in critically ill patients with ventilator-associated pneumonia and using AUC penetration ratios.[26] The ELF-to-plasma penetration ratios of 1 g of meropenem infused over 0.5 h ranged, depending on the sampling time considered, from 0.32 to 0.53 in healthy volunteers after multiple doses,[25] and from 0.19 to 1.04 in patients without acute pneumonia undergoing diagnostic bronchoscopy after a single dose.[24] These results were higher than ours (range from 0.11 to 0.32 in the II group and from 0.12 to 0.49 in the EI group, data not shown). By contrast, a study performed in patients with ventilator-associated pneumonia who received ertapenem at steady-state showed penetration ratios ranging from 0.28 to 0.46,[15] and another study of healthy volunteers who received single-dose biapenem showed a mean penetration ratio of 0.20 for both 0.5 and 3 h infusions.[33]

On the basis of the ratios of the AUC, Lodise *et al.*[26] found mean and median penetration ratios of 0.82 and 0.26, respectively, in patients with ventilator-associated pneumonia when they performed a 9999-subject Monte Carlo simulation for single-dose 2 g meropenem given over 3 h. In that study, substantial variability in the penetration ratio was shown with 10th and 90th percentiles being 3.7% and 178.0%, respectively, without clear physiological explanation. Finally, using a microdialysis-based approach, Tomaselli *et al.*[34] found a lung interstitial fluid-to-serum AUC ratio of 0.41±0.21 in seven patients with pneumonia and metapneumonic pleural empyema treated by decortications. In summary, our findings confirm those from previous studies,[15,24–26,33,34] objectifying a relatively low ELF/plasma penetration ratio of 0.2–0.3 for carbapenems in comparison with other β-lactams.[16,26,35]

The PK characteristics of meropenem in plasma described in the present study are similar to those from previous studies performed in critically ill ICU patients with or without pneumonia.[10–12,36–39] The total volume of distribution was large (28.6 L) due to the high proportion of patients with severe

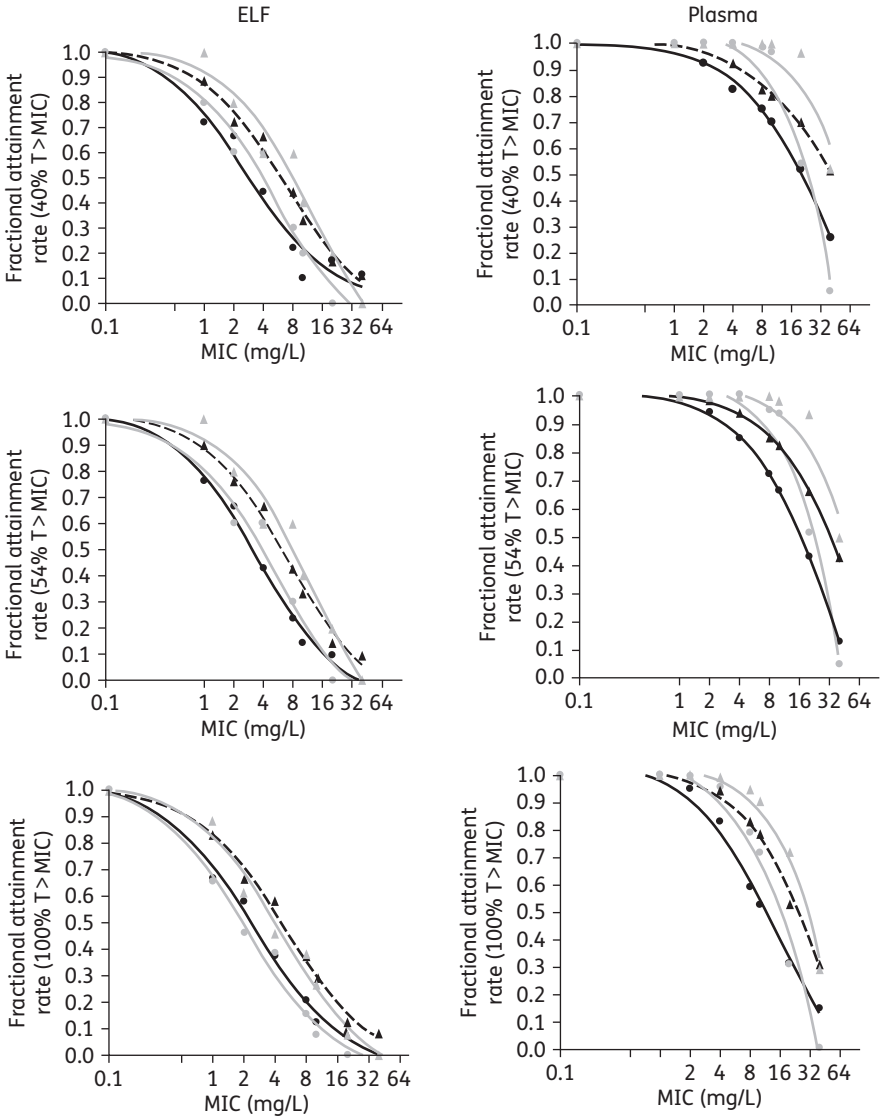


Figure 3. Target attainment rates in ELF (left) and plasma (right) after different dosing regimens: continuous black line with black circles: 1 g, 0.5 h infusion; continuous light grey line with light grey circles: 1 g, 3 h infusion; broken black line with black triangles, 2 g, 0.5 h infusion; and continuous grey line with grey triangles, 2 g, 3 h infusion.

illness (severe sepsis, septic shock and bacteraemia present in 71%, 22% and 22%, respectively), and drug clearance was low (10.2 L/h) due to globally decreased renal function (creatinine clearance 30–59 mL/min in 23.6% and CVVH required in 20% of patients).[12] Analysis of urine samples collected after 24 h revealed accelerated renal clearance (>120 mL/min) in 31% of patients. This variability in renal function is possibly the most important factor that could account for the high interindividual variability in concentrations in plasma and ELF between the two groups.[5,12,26]

The PK/PD parameter that correlates with efficacy of β-lactams is the proportion of the dosing interval during which the concentration of unbound (free) drug in plasma remains above the MIC of a specific pathogen (% T>MIC). For meropenem the threshold value is widely considered to be 40% T>1-fold MIC,[3,4] but recent clinical data found that values of 54%–76% T>MIC are also predictive of clinical and microbiological responses in patients with infections of the lower respiratory tract.[31,36] Some authors consider that the maximal bactericidal effect of β-lactams (including meropenem) occurs when concentrations exceed the MIC by up to 5-fold for up to 100% of the dosing interval, particularly in critically ill patients and/or for pathogens with high MICs.[5–7] For this reason we assessed PD targets at 40%, 54% and 100% T>1-fold or 4-fold MIC. We selected 54% T>MIC because it is the PD clinical breakpoint threshold chosen by EUCAST for meropenem,[30] based on the findings of Li *et al.*[31] Our results showed no difference between PD targets of 40% or 54% in any scenario. Similar results were obtained in plasma and ELF using 2 g over 0.5 h and 1 g over 3 h, except for a PD target of 100% T>MIC, where no advantage of EI over II was observed in the ELF.

Considering EUCAST breakpoints,[30] our data suggest that susceptible pathogens (MICs of up to 2 mg/L) could be successfully treated with 1 g of meropenem infused over 0.5 h every 8 h if

Table 4. PK/PD breakpoints in plasma and ELF for specific PD targets according to different dosages and modes of infusion

	PK/PD targets (mg/L) for PTA of ≥90%							
	mode of infusion and dose							
	II (0.5 h)				EI (3 h)			
	1 g		2 g		1 g		2 g	
PD target in the specified compartment	plasma	ELF	plasma	ELF	plasma	ELF	plasma	ELF
40% T>1× MIC	2	0.25	4	0.5	4	0.5	8	1
40% T>4× MIC	0.5	0.0625	1	0.125	1	0.125	2	0.25
54% T>1× MIC	2	0.25	4	0.5	4	0.5	8	1
54% T>4× MIC	0.5	0.0625	1	0.125	1	0.125	2	0.25
100% T>1× MIC	2	0.25	4	0.5	2	0.25	8	0.5
100% T>4× MIC	0.5	0.0625	1	0.125	0.5	0.0625	2	0.125

the 40–100% T>1-fold MICs are taken to be the relevant PK/PD targets in plasma. However, 2 g infused over 3 h every 8 h would be required to reach the same PK/PD target (i.e. in plasma) for pathogens that have intermediate susceptibility (MICs of 8 mg/L) or for susceptible pathogens when PK/PD targets of 40%, 54% and 100% T>4-fold MIC are required. Notably, 1 g infused over 0.5 h every 8 h is usually recommended for patients with nosocomial pneumonia, but not 2 g infused over 3 h every 8 h.[1] In contrast, for ELF, our study shows that EUCAST susceptibility breakpoints are not reached since PK/PD breakpoints range from 0.06 to 1.0 mg/L, depending on the dose, duration of infusion and PK/PD target selected. Reaching sufficient concentrations at the infected site seems a logical prerequisite for efficacy,[16,17,35] but no clinical study has yet documented the possible correlations between ELF and plasma concentrations and clinical or microbiological outcomes.[5,16,17] Consequently, caution must be applied in presuming that the magnitudes of the PD parameters in ELF are the same as those proposed for plasma.[16]

The limitations associated with this evaluation include first its single-centre and non-randomized design. Second, we were not able to analyse the impact of the type of infusion's modality on the mortality, since only crude mortality was collected, microbiological evolution was lacking (such as bacterial load reduction or occurrence of failure and/or resistance during meropenem treatment) and de-escalation was performed in 63.6% of cases after 3.0±1.3 days. Third, our data were collected from a 1 g dosing regimen and simulations were performed for 1 and 2 g dosing regimens, using a model developed with a data-driven approach. This latter assumed linear PK of meropenem, such as observed in plasma over a dose range of 250–2000 mg.[40] However, a study performed in healthy volunteers showed that plasma concentrations increased proportionally with doses of meropenem, while concentrations in ELF tended to decrease as meropenem doses increased, without clear explanation.[25] Fourth, whilst renal function and body weights of the study subjects were heterogeneous, owing to inclusion of patients requiring CVVH and those with accelerated renal function, the PK/PD analysis was performed globally. Finally, as many patients in our study were severely ill, the results might not be applicable to all ICU populations. This range of patients, however, reflects real life in the ICU.

In conclusion, with regard to penetration ratios of the AUC and PD targets observed both in plasma and in ELF, better results were obtained with EI than with II. Meropenem should be used empirically at the dosage of 2 g infused over 3 h every 8 h to treat severe nosocomial pneumonia occurring in the ICU until identification of a specific aetiological pathogen. These conclusions should be confirmed and validated in a larger prospective study investigating the correlation between PK/PD parameters in ELF and plasma and clinical and microbiological outcomes to assess if the magnitudes of exposure required in ELF are similar to those observed in plasma.

Acknowledgements

We thank all of the patients, relatives and clinical staff involved in this study, as well as Francesca Lipari for her technical assistance.

Funding

The study was supported by a research grant from the Centre Hospitalier Universitaire de Liège, Belgium (Fonds d'Investissement de Recherche Scientifique, FIRS, no. 4733).

Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Niederman MS, Craven DE, Bonten MJ *et al*. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388–416.

2 Bartlett JG, Barie PS, Niederman MS *et al*. Workshop on clinical trials of antibacterial agents for hospital-acquired pneumonia and ventilator-associated pneumonia. *Clin Infect Dis* 2010; **51** Suppl 1: 1–3.

3 Craig WA. Pharmacokinetic/pharmacodynamics parameters: rational for antibacterial dosing of mices and men. *Clin Infect Dis* 1998; **26**: 1–12.

4 Nicolau DP. Pharmacokinetic and pharmacodynamics properties of meropenem. *Clin Infect Dis* 2008; **47** Suppl 1: 32–40.

5 Gonçalves-Pereira J, Póvoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams. *Crit Care* 2011; **15**: R206.

6 Chytra I, Stepan M, Benes J *et al*. Clinical and microbiological efficacy of continuous versus intermittent application of meropenem in critically ill patients: a randomized open-label controlled trial. *Crit Care* 2012; **28**: R113.

7 Roberts JA, Ulldemolins M, Roberts MS *et al*. Therapeutic drug-monitoring of β-lactams in critically ill patients: proof of concept. *Int J Antimicrob Agents* 2010; **36**: 332–9.

8 Dulhunty JM, Roberts JA, Davis JS *et al*. Continuous infusion of β-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. *Clin Infect Dis* 2013; **56**: 236–44.

9 Falagas ME, Tansarli GS, Ikawa K *et al*. Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. *Clin Infect Dis* 2013; **56**: 272–82.

10 Jaruratanasirikul S, Sriwiriyajan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection. *Antimicrob Agents Chemother* 2005; **49**: 1337–9.

11 Thalhammer F, Traunmüller F, El Menyawi I *et al*. Continuous infusion versus intermittent administration of meropenem in critically ill patients. *J Antimicrob Chemother* 1999; **43**: 523–7.

12 Roberts JA, Kirkpatrick CM, Roberts MS *et al*. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *J Antimicrob Chemother* 2009; **64**: 142–50.

13 Nicasio AM, Eagye KJ, Nicolau DP *et al*. Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia. *J Crit Care* 2010; **25**: 69–77.

14 Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: methodological considerations. *Antimicrob Agents Chemother* 1992; **36**: 1171–5.

15 Boselli E, Breilh D, Saux MC *et al*. Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia. *Intensive Care Med* 2006; **32**: 2059–62.

16 Rodvold KA, George JM, Yoo L. Penetration of anti-infective agents into pulmonary epithelial lining fluid. *Clin Pharmacokinetic* 2011; **50**: 637–64.

17 Kiem S, Schentag JJ. Interpretation of antibiotic concentration ratios measured in epithelial lining fluid. *Antimicrob Agents Chemother* 2008; **52**: 24–36.

18 Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. *J Antimicrob Chemother* 2011; **66**: 227–31.

19 Levey AS, Coresh J, Balk E *et al*. National Kidney Foundation: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137–47.

20 Ferrer M, Liapikou A, Valencia M *et al*. Validation of the American Thoracic Society-Infectious Diseases Society of America guidelines for hospital-acquired pneumonia in the intensive care unit. *Clin Infect Dis* 2010; **50**: 945–52.

21 Luna CM, Blanzaco D, Niederman MS *et al*. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med* 2003; **31**: 676–82.

22 Claus B, Buyle F, Robays H *et al*. Importance of infusion volume and pump characteristics in extended administration of β-lactam antibiotics. *Antimicrob Agents Chemother* 2010; **54**: 4950.

23 Denooz R, Charlier C. Simultaneous determination of five β-lactam antibiotics (cefepim, ceftazidim, cefuroxim, meropenem and piperacillin) in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; **864**: 161–7.

24 Allegranzi B, Cazzadori A, Di Perri G *et al*. Concentration of single-dose meropenem (1 g iv) in bronchoalveolar lavage and epithelial lining fluid. *J Antimicrob Chemother* 2000; **46**: 319–22.

25 Conte JE, Golden JA, Kelley MG *et al*. Intrapulmonary pharmacokinetics and pharmacodynamics of meropenem. *Int J Antimicrob Agents* 2005; **26**: 449–56.

26 Lodise TP, Sorgel F, Melnick D *et al*. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother* 2011; **55**: 1606–10.

27 Lindbom L, Pihlgren P, Jonsson EN. PsN-toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Meth Programs Biomed* 2005; **79**: 241–57.

28 The R project for statistical computing. http://www.r-project.org/ (17 july 2014, date last accessed).

29 Ette EI, Ludden TM. Population pharmacokinetic modeling: The importance of informative graphics. *Pharm Res* 1995; **12**: 1845–55.

30 *Clinical Breakpoints-Bacteria*. http://www.eucast.org/clinical_breakpoints/.

31 Li C, Du X, Kuti JL *et al*. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob Agents Chemother* 2007; **51**: 1725–30.

32 Mouton JW, Theuretzbacher U, Craig WA *et al*. Tissue concentrations: do we ever learn ?. *J Antimicrob Chemother* 2008; **61**: 235–7.

33 Kikuchi E, Kikuchi J, Nasuhara Y *et al*. Comparison of the pharmacodynamics of biapenem in bronchial epithelial lining fluid in healthy volunteers given half-hour and three-hour intravenous infusions. *Antimicrob Agents Chemother* 2009; **53**: 2799–803.

34 Tomaselli F, Maier A, Matzi V *et al*. Penetration of meropenem into pneumonic human lung tissue as measured by in vivo microdialysis. *Antimicrob Agents Chemother* 2004; **48**: 2228–32.

35 Ambrose P, Bhavnani SM, Ellis-Grosse EJ *et al*. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! *Clin Infect Dis* 2010; **51** Suppl 1: 103–10.

36 Zhou QT, He B, Zhang C, Zhai SD *et al*. Pharmacokinetics and pharmacodynamics of meropenem in elderly Chinese with lower respiratory tract infections. *Drugs Aging* 2011; **28**: 903–12.

37 Jaruratanasirikul S, Limapichat T, Jullangkoon M *et al*. Pharmacodynamics of meropenem in critically ill patients with febrile neutropenia and bacteraemia. *Int J Antimicrob Agents* 2011; **38**: 231–6.

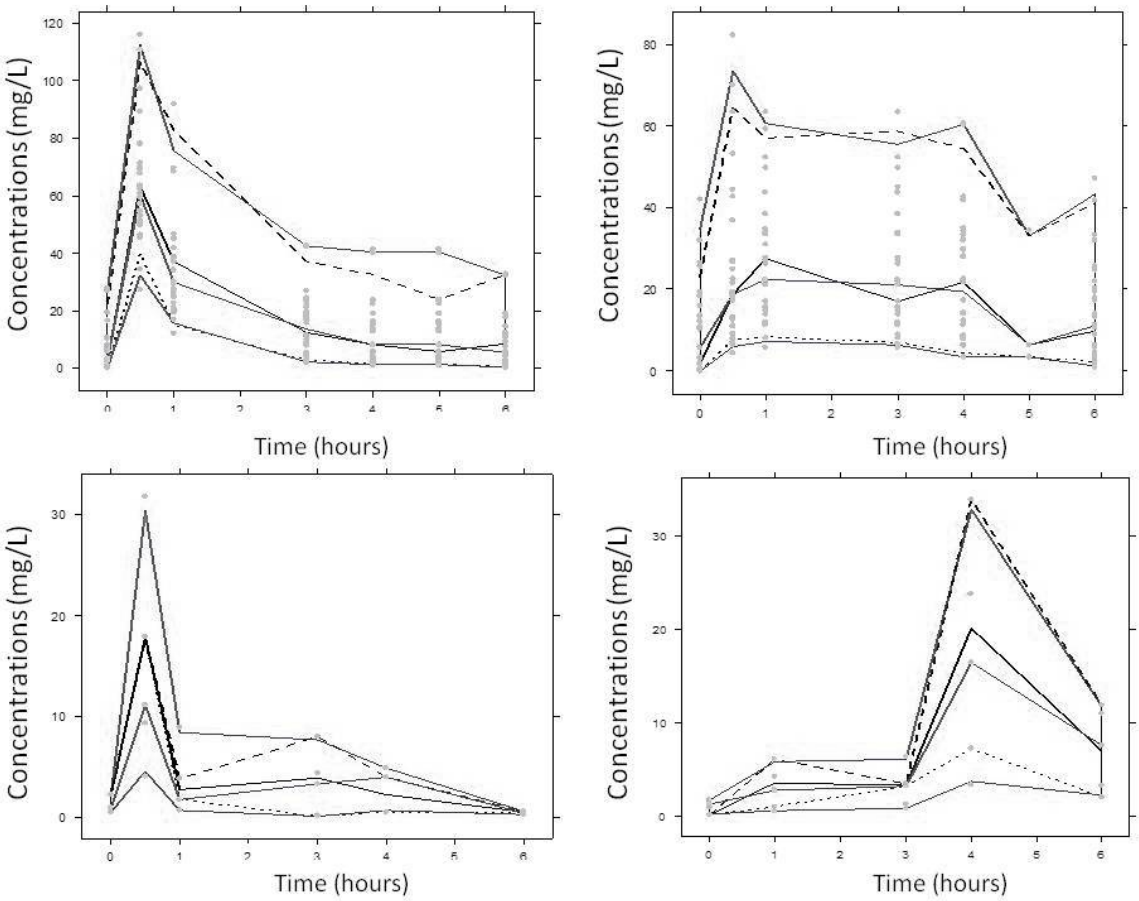
38 Kitzes-Cohen R, Farin D, Piva G *et al*. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. *Int J Antimicrob Agents* 2002; **19**: 105–10.

39 Binder L, Schwörer H, Hoppe S *et al*. Pharmacokinetics of meropenem in critically ill patients with severe infections. *The Drug Monit* 2013; **35**: 67–70.

40 Drusano GL, Hutchison M. The pharmacokinetics of meropenem. *Scand J Infect Dis* 1995; **96**: 11–6.

Supplementary data

Figure S1. Visual predictive check plots.



Left panel: intermittent infusion group, right panel: extended infusion group. Upper panels: plasma data, lower panels, epithelial lining fluid data. Grey circles: observed concentrations. Grey lines: 95% prediction intervals of the observed concentrations (2.5, 50 and 97.5 percentiles on the observed concentrations). Black lines: simulated 95% prediction intervals of the simulated concentrations in 200 simulated patients, dotted lines: 2.5% percentiles, continuous line: median, dash line: 97.5% percentiles.