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

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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.¹² 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.³⁴ 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.¹³ 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

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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 formula19 or by measurement of creatinine clearance based on 24 h urinalysis) 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 <4 000 cells/mm³ 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 simple and rapid UPLC method with ultraviolet detection.23 Briefly, 50 μL of plasma (or 2 mL of ELF) was spiked with ceftaroline, 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 120 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%.5,12

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 ammonium 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 mg/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 penetra-
tion 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 dos-
ing 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 time-
point, 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 simu-
lations 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

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

CPIS, clinical pulmonary infectious score; MDRD, Modification of Diet in Renal Disease formula.
The values are presented as n (%) or the mean ± SD.
aCalculated at the onset of pneumonia.
bBased on EUCAST breakpoints (S ≤ 2; R > 8 mg/L): S, susceptible; I, intermediate; and R, resistant.
cThirty-eight Gram-negative bacteria isolated in 35 patients (two Enterobacteriaceae isolated simultaneously in three subjects).
dFisher’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.5-6 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 PK clinical breakpoint threshold chosen by EUCAST for meropenem,20 based on the findings of Li et al.21 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 χ² 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 dosers 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 AUC₀₋₂₄ of meropenem concentrations in plasma were similar in the two groups (42.2 ± 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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>II group</th>
<th>EI group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₂₄ in plasma (mg·h/L)</td>
<td>42.2 ± 48.3</td>
<td>502 ± 67.0</td>
<td>0.26</td>
</tr>
<tr>
<td>AUC₀₋₂₄ in ELF (mg·h/L)</td>
<td>80.3 ± 11.8</td>
<td>150 ± 24.2</td>
<td>0.010</td>
</tr>
<tr>
<td>ELF/plasma penetration ratio</td>
<td>0.20 ± 0.033</td>
<td>0.29 ± 0.030</td>
<td>0.047</td>
</tr>
</tbody>
</table>

The values are presented as the mean ± SEM. SEM values were derived by the bootstrap method.

*AUC in plasma calculated for each patient in each group.

*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 
\( (80.3 \pm 11.8 \text{ versus } 150.0 \pm 24.2 \text{ mg h/L; } P=0.010) \). Consequently, 
the AUC penetration ratio was higher in the EI group than in the
II group (0.29 \( \pm \) 0.030 versus 0.20 \( \pm \) 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 \( \pm \) SEM 226 \( \pm \) 16.8
versus 561 \( \pm \) 77.7 mg.h/L in the II group (\( P<0.0001 \)) and
201 \( \pm \) 25.4 versus 467 \( \pm \) 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 (\( \pm \) 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.
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.

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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Final model estimate</th>
<th>Bootstrap CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVCL (L/h)</td>
<td>10.2</td>
<td>8.3–10.9</td>
</tr>
<tr>
<td>TVQ_E (L/h)</td>
<td>66.5</td>
<td>7.3–9.9</td>
</tr>
<tr>
<td>TVQ_P (L/h)</td>
<td>6.9</td>
<td>5.32–8.55</td>
</tr>
<tr>
<td>TVV_c (L)</td>
<td>5.2</td>
<td>4.3–5.1</td>
</tr>
<tr>
<td>TVV_p (L)</td>
<td>12.1</td>
<td>2.6–40.1</td>
</tr>
<tr>
<td>TVV_E (L)</td>
<td>11.3</td>
<td>10.1–12.6</td>
</tr>
<tr>
<td>θ WT on V_c</td>
<td>0.6</td>
<td>0.41–0.79</td>
</tr>
<tr>
<td>θ GFR on CL</td>
<td>0.73</td>
<td>0.38–0.86</td>
</tr>
<tr>
<td>s prop</td>
<td>0.2</td>
<td>0.1–0.2</td>
</tr>
<tr>
<td>s add</td>
<td>0.8</td>
<td>0.7–0.9</td>
</tr>
</tbody>
</table>

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; θ WT on V_c, allometric effect of the total body weight on the volume of the central compartment; θ GFR on CL, allometric effect of GFR on renal clearance; s prop, proportional error; s add, additive error.
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>MIC. 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 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, 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, but only one was conducted in critically ill patients with ventilator-associated pneumonia and using AUC penetration ratios. 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, and from 0.19 to 1.04 in patients without acute pneumonia undergoing diagnostic bronchoscopy after a single dose. 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, 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.

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, 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. The total volume of distribution was large (28.6 L) due to the high proportion of patients with severe...
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). 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.

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 (% T > MIC). For meropenem the threshold value is widely considered to be 40% T > MIC, 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. 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. 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, based on the findings of Li et al. 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, 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...

![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.](http://jac.oxfordjournals.org/)

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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. 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, but no clinical study has yet documented the possible correlations between ELF and plasma concentrations and clinical or microbiological outcomes. Consequently, caution must be applied in presuming that the magnitudes of the PD parameters in ELF are the same as those proposed for plasma.

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. 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. 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
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Transparency declarations
None to declare.

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

References

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

<table>
<thead>
<tr>
<th>PD target in the specified compartment</th>
<th>mode of infusion and dose</th>
<th>II (0.5 h)</th>
<th>EI (3 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 g</td>
<td>2 g</td>
</tr>
<tr>
<td>Plasmap ELF</td>
<td></td>
<td>plasma</td>
<td>ELF</td>
</tr>
<tr>
<td>40% T &gt; 1x MIC</td>
<td></td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>40% T &gt; 4x MIC</td>
<td></td>
<td>0.5</td>
<td>0.0625</td>
</tr>
<tr>
<td>54% T &gt; 1x MIC</td>
<td></td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>54% T &gt; 4x MIC</td>
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<td>0.5</td>
<td>0.0625</td>
</tr>
<tr>
<td>100% T &gt; 1x MIC</td>
<td></td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>100% T &gt; 4x MIC</td>
<td></td>
<td>0.5</td>
<td>0.0625</td>
</tr>
</tbody>
</table>

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


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.