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Maximally effective dosing regimens of meropenem in patients with septic shock

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Objectives: To use a population pharmacokinetic approach to define maximally effective meropenem dosing recommendations for treatment of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* infections in a large cohort of patients with septic shock.

Methods: Adult patients with septic shock and conserved renal function, treated with meropenem, were eligible for inclusion. Seven blood samples were collected during a single dosing interval and meropenem concentrations were measured by a validated HPLC-MS/MS method. Monte Carlo simulations were employed to define optimum dosing regimens for treatment of empirical or targeted therapy of *A. baumannii* and *P. aeruginosa*. EudraCT-no. 2014-002555-26 and NCT02240277.

Results: Fifty patients were included, 26 male and 24 female, with a median age of 64 years with an all-cause 90 day mortality of 34%. A two-compartment linear model including creatinine clearance (CL_{CR}) as a covariate best described meropenem pharmacokinetics. For empirical treatment of *A. baumannii*, 2000 mg/6 h was required by intermittent (30 min) or prolonged (3 h) infusion, whereas 6000 mg/day was required with continuous infusion. For *P. aeruginosa*, 2000 mg/8 h or 1000 mg/6 h was required for both empirical and targeted treatment. In patients with a CL_{CR} of $\leq$100 mL/min, successful concentration targets could be reached with intermittent dosing of 1000 mg/8 h.

Conclusions: In patients with septic shock and possible augmented renal clearance, doses should be increased and/or administration should be performed by prolonged or continuous infusion to increase the likelihood of achieving therapeutic drug concentrations. In patients with normal renal function, however, standard dosing seems to be sufficient.

Introduction

Early and appropriate antibiotic therapy appears to be the most effective way to improve patient outcomes in sepsis, an approach that is reinforced in the newly updated Surviving Sepsis Guidelines.[1–3] However, the most appropriate dose and administration strategy for the chosen antibiotic is generally not well defined.[4] Sepsis may induce changes in renal function, as well as increased capillary leakage with subsequent tissue oedema leading to an increase in capillary-to-cell diffusion distances.[5] Aggressive fluid resuscitation in patients with sepsis will lead to significant changes in the volume of distribution of certain antibiotics that may result in low trough serum and tissue concentrations.[6,7] In contrast, as sepsis-induced acute kidney injury develops, there is a risk that patients will attain high and potentially toxic antibiotic concentrations if doses are not properly adjusted.[8] Thus, there is a risk both of under-treatment and of achieving potentially toxic antibiotic concentrations due to the highly variable pharmacokinetics of antibiotics in patients with sepsis.

Meropenem is a broad-spectrum carbapenem antibiotic, widely used as empirical or targeted therapy in critically ill patients.[9] Like other β-lactams, meropenem displays a time-dependent bactericidal activity, data for which suggest that the unbound (free) concentration should exceed the MIC by >40% of the dosing interval (40% $fT_{>MIC}$) for optimal efficacy.[10–12] However, achievement of these target exposures is not consistent in critical illness. Therefore, to increase the likelihood of reaching those therapeutic exposures, dosing approaches that deviate from the Product Information may be required. It has been suggested that dosing regimens guided by population pharmacokinetic models from a large sample of critically ill patients would help assist clinicians in daily practice. However, most pharmacokinetic models developed in critically ill patients, including those for meropenem, are based on only a small number of patients and are unlikely to explain all the pharmacokinetic variability in this patient population,[4,13–19] and none have focused exclusively on patients with septic shock. Previous analyses attempting to define sample sizes that can provide adequate statistical power for population pharmacokinetic analysis have suggested that the inclusion of approximately 50 patients is desirable.[20]

The objectives of this study were to use population pharmacokinetics to define maximally effective meropenem dosing regimens for treatment of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in patients with septic shock.

Methods

Setting

This was a single-centre observational pharmacokinetic study conducted at a tertiary mixed ICU with 23 beds and approximately 1200 admissions per year. The study was approved by the scientific ethics committee of Copenhagen, Denmark (approval no. H-3-2014-074), the Danish Data Protection Agency (approval no. 30-1252) and the Danish Health and Medicines Authority (registration no. 2014062429). By Danish legislation the study was considered a pharmaceutical trial and was therefore registered with the European Clinical Trials Database (EudraCT-no. 2014-002555-26) and Clinical Trials (NCT02240277) and monitored according to Good Clinical Practice (GCP) by the GCP unit of the University of Copenhagen (project no. 2014-699).

Written informed consent was obtained from the patients' legal substitute decision-makers and from the patients.

Study population

Adult patients (≥18 years) with septic shock who were treated, either empirically or by targeted therapy, with meropenem, as sole agent or in combination with other antimicrobials, were eligible for inclusion. The study investigators had no influence on the therapeutic strategy or dosing. The trial was performed before the sepsis-3 criteria[21] were published, and thus the previous definition was used.[22] Septic shock was defined as sepsis with persistent hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg) despite adequate fluid resuscitation or the requirement for vasopressor support. Patients with a serum creatinine concentration <170 μM were eligible. The exclusion criteria were as follows: (i) patients with serum creatinine concentration ≥170 μM; (ii) use of renal replacement therapy; (iii) pregnancy; or (iv) a history of allergy to meropenem.

Study protocol

Seven blood samples, for each enrolled subject, were drawn during a single dosing interval: pre-dose, 30 min, 45 min, 1 h, 2 h, 4 h and 8 h after administration. Meropenem was administered as an injection over no more than 10 min on all occasions. Dosage was per discretion of the treating doctor. Urine was collected over the 8 h period and analysed for creatinine and urea concentrations. Additional clinical and demographic data of the patient were collected from the department's clinical information system.

Sample handling and storage

Blood samples were immediately stored at 4 °C and centrifuged at 2000 **g** for 10 min within 4 h of sampling. Plasma samples were pipetted to cryovials and stored at −80 °C until analysis of meropenem concentration.

Meropenem assay

Plasma concentrations of meropenem were measured from 0.2 to 100 mg/L by validated HPLC-MS/MS performed on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer. Plasma sample (10 μL) was spiked with internal standard ([d6]-meropenem). Acetonitrile was added to precipitate any proteins. An aliquot of the solution was injected into the HPLC-MS/MS system. Hydrophilic interaction liquid chromatography (HILIC) was validated for the measurement of meropenem. Mobile phase A was 0.1% formic acid in water (v/v) and mobile phase B was 100% acetonitrile with 0.1% formic acid (v/v). The stationary phase was a SeQuant zic-HILIC 2.1×20 mm (5.0 μm) analytical guard column with a SeQuant ZIC-HILIC, 2.1×50 mm, 5.0 μm, 200 Å column. Separations were effected with a gradient flow of 75% mobile phase B at 0.3 mL/min, producing a back-pressure of approximately 350 psi. Meropenem was monitored by positive-mode electrospray at multiple reaction monitoring (MRM) of 383.50 → 68.15 (measurement) and 383.50 → 141.10. The labelled internal standard [d6]-meropenem was monitored in positive mode at 390.15 → 147.00 (measurement) and 390.15 → 67.90. The assay method was validated using FDA criteria for bioanalysis. Precision was within 5.5% and accuracy was within 9.0%. The method was linear from 0.2 to 100 mg/L, with a limit of quantification of 0.2 mg/L and a limit of detection of 0.02 mg/L.

Population pharmacokinetic modelling

One- and two-compartment models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the freely available Pmetrics® software package for R (Los Angeles, CA, USA).[23,24] Elimination from the central compartment and intercompartmental distribution into the peripheral compartment (two-compartment model) were modelled as first-order processes. Discrimination between different models used comparison of the −2 log likelihood (−2LL). A P value of <0.05 was considered statistically significant.

Population pharmacokinetic covariate screening

Age, gender, body weight, BMI, measured creatinine clearance (CL_{CR}), calculated CL_{CR} using the Cockcroft–Gault equation, SOFA score, APACHE II score and simplified acute physiology score (SAPS) II were evaluated as clinically relevant and physiologically plausible covariates. Covariate selection was performed using a stepwise linear regression from R on all covariates and Bayesian posterior parameters. Potential covariates were separately entered into the model and statistically tested by use of the −2LL values. If inclusion of the covariate resulted in a statistically significant improvement in the −2LL values ($P < 0.05$) and/or improved the goodness-of-fit plots, then the covariate was retained in the final model.

Model diagnostics

Goodness of fit was assessed by linear regression, with an observed–predicted (both population- and individual-predicted concentrations) plot, coefficients of determination and −2LL values. Predictive performance was

based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models. The internal validity of the population pharmacokinetic model was assessed by the bootstrap resampling method ($n = 1000$) and normalized prediction distribution errors (NPDEs).[25] Using the visual predictive check method, parameters obtained from the bootstrap method were plotted with the observed concentrations. NPDE plots were checked for normal distribution characteristics and trends in the data errors.

Probability of target attainment (PTA)

Monte Carlo simulations ($n = 1000$) were employed using Pmetrics® to determine the PTA of achieving a pharmacokinetic/pharmacodynamic target of $fT_{>MIC} = 40\%$ during a 30 min intermittent infusion and a pharmacokinetic/pharmacodynamic target of $fT_{>MIC} = 100\%$ for prolonged (3 h) and continuous infusions for various MICs (0.125–32 mg/L). A fixed 2% unbound fraction of meropenem was used for the simulations according to previously published data.[26] Intravenous intermittent doses and prolonged infusion of 500, 1000 and 2000 mg, at 6, 8 and 12 h intervals, and continuous infusion in the range of 1000–8000 mg/24 h (after the administration of associated loading dose to the corresponding intermittent dosing regimen) were simulated. Four different levels of renal function (CL_{CR} of 30, 50, 100 and 200 mL/min) were also included in the simulation process. *A priori* a dosing regimen was considered successful if the PTA was ≥95%.

Fractional target attainment (FTA) calculation

The MIC distributions for *A. baumannii* and *P. aeruginosa* from the EUCAST database (available at www.eucast.org; accessed 10 January 2017) were used to determine FTA. These two species were chosen as they are known to be difficult to treat and therefore serve as good examples for the FTA simulation. The FTA identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) of meropenem against an MIC distribution. For targeted therapy, MICs of ≤2 mg/L (the cut-off value for susceptibility according to EUCAST) were used and for empirical therapy, an MIC range of 0.016–512 mg/L (i.e. MICs for both susceptible and resistant isolates) was used. *A priori* a dosing regimen was considered successful if the FTA was ≥90%.

Results

We included 51 patients with septic shock, 27 males and 24 females, with a median age of 64 years. One patient (male) withdrew consent, leaving 50 patients in the final analysis. The demographics and clinical data are presented in Table 1. The predominant origin of sepsis was soft tissue (the study site is a national referral centre for necrotizing fasciitis), followed by pulmonary focus. The patients had a median APACHE II score of 26 and a SOFA score of 9 (at day of inclusion), and all-cause mortality at 90 days was 34%. Meropenem dosing was 1000 mg/8 h in 41 patients, 2000 mg/8 h in 8 patients and 1000 mg/12 h in 1 patient. The main individual sites of infection, microbiological findings and the patients' responses to treatment are presented in Table S1 (available as Supplementary data at *JAC* Online).

Pharmacokinetic model

A two-compartment linear model best described the time-course of the total plasma meropenem concentrations (Figure 1) with zero-order input of drug into the central compartment. The only covariate that improved the fit of the model was CL_{CR}. After including this covariate, the −2LL values decreased ($P < 0.05$) and the overall goodness-of-fit improved. Thus, CL_{CR} was retained in the final model. The final covariate model was described as follows:

$$\text{meropenem clearance} = \text{TVCL} \times [2 + (CL_{CR} \times 0.083)]$$

Table 1. Demographics and clinical data for patients included in the study

Characteristics	Patient values
Age (years), median (range)	64 (24–89)
Sex (male/female), *n*/*n*	26/24
BMI (kg/m^2), median (range)	26 (17–55)
Serum creatinine (μM), median (range)	99 (39–220)
8 h CL_{CR} (mL/min), median (range)	67 (7–204)
Serum albumin (g/L), median (range)	19 (11–34)
Fluid balance in ICU (mL), median (range)	+1243 (−4349 to +16380)
Fluid balance in the last 24 h (mL), median (range)	+974 (−3352 to +5040)
Days of treatment before sampling, median (range)	1.3 (0.5–10)
Origin of sepsis, *n* (%)	
lung	13 (26)
abdomen	9 (18)
urinary tract	0
soft tissue	19 (38)
other	9 (18)
APACHE II score at admission, median (range)	26 (10–41)
SAPS II, median (range)	50 (22–87)
SOFA score (at day of inclusion), median (range)	9 (5–14)
Survival at 90 days, %	66

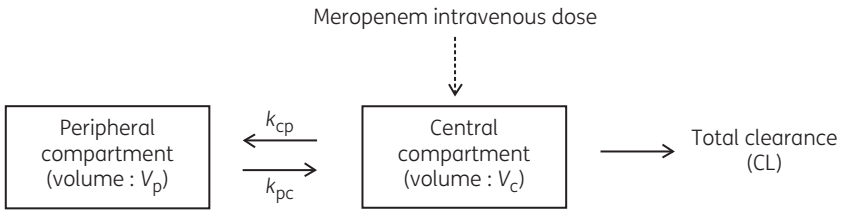

Figure 1. Structural pharmacokinetic model for meropenem in patients with septic shock. CL, clearance; V_c, volume of the central compartment; k_{cp}, rate constant for drug distribution from the central to peripheral compartment; k_{pc}, rate constant for drug distribution from the peripheral to central compartment.

Table 2. Parameter estimates for meropenem from the final covariate two-compartment population pharmacokinetic model

Parameter	Mean	SD	Coefficient of variation	Variance	Median
CL (L/h)	7.34	3.07	40.578	1.22	6.82
V_c (L)	16.155	6.107	37.802	37.292	16.916
k_{cp} (h^{-1})	1.579	1.501	95.001	2.252	0.735
k_{pc} (h^{-1})	2.683	5.364	199.905	28.774	1.283

CL, total meropenem clearance; V_c, central volume of distribution; k_{cp}, rate constant for drug distribution from the central to peripheral compartment; k_{pc}, rate constant for drug distribution from the peripheral to central compartment.

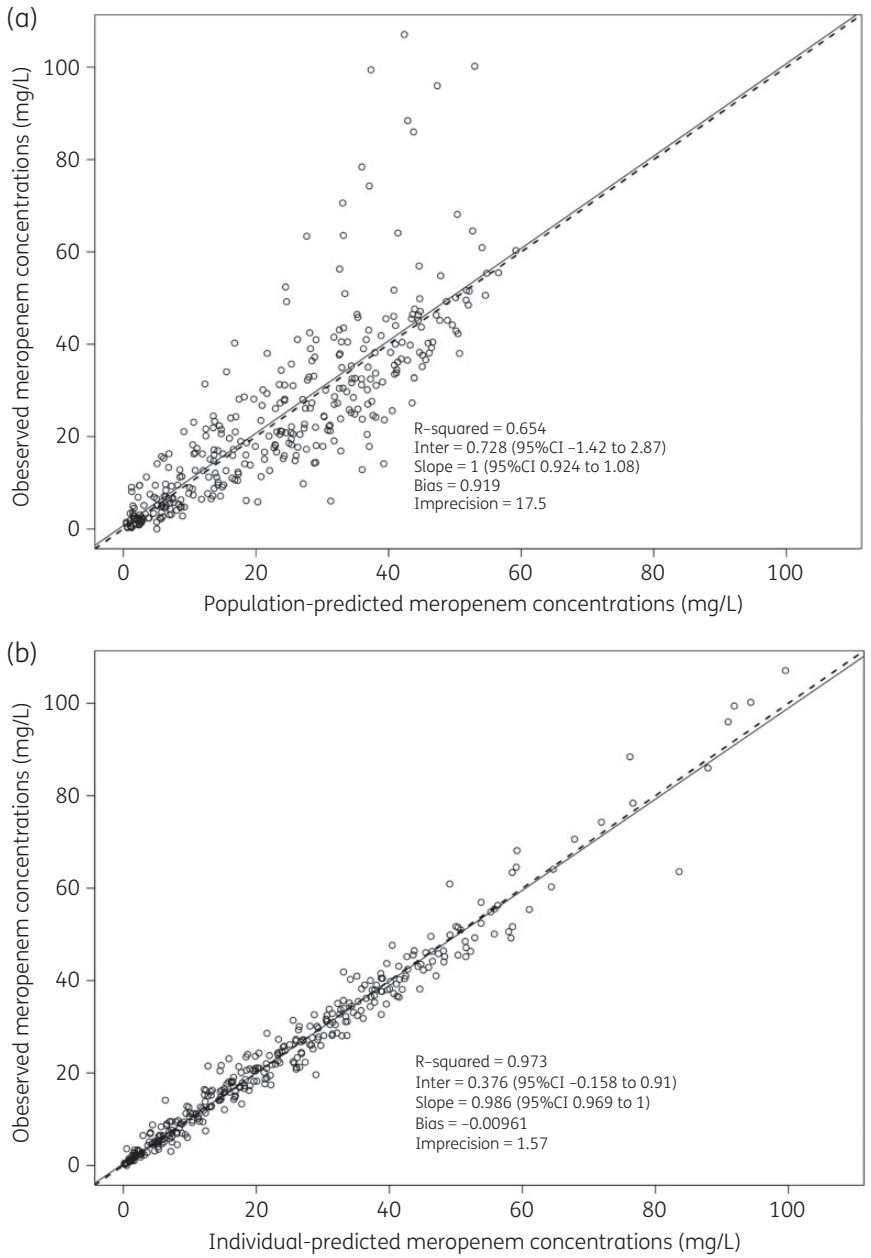

Figure 2. Diagnostic plots for the final covariate two-compartment model. Observed versus (a) population-predicted total meropenem concentrations and (b) individual-predicted total meropenem concentrations.

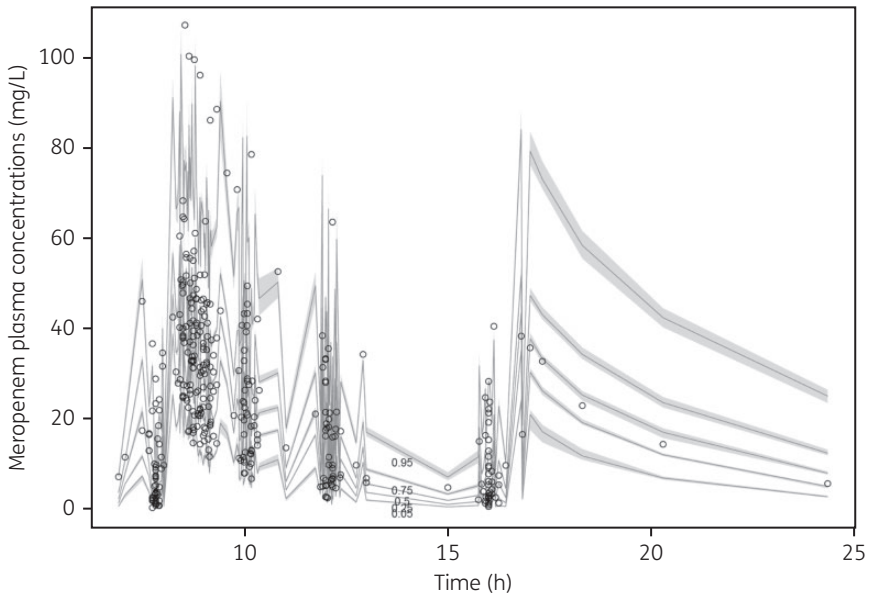

Figure 3. Visual predictive check of total meropenem plasma concentrations. The median and 5th–95th percentiles of simulated data, with their respective 95% CIs, are shown. Individual points represent observed data.

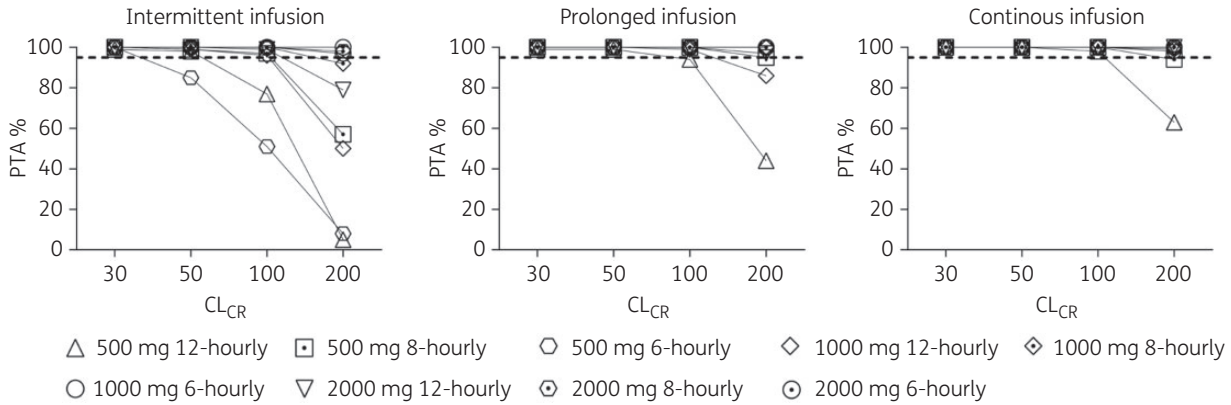

Figure 4. Monte Carlo simulation for meropenem PTA (drug concentrations $fT_{>MIC} = 40\%$ for intermittent dosing and $fT_{>MIC} = 100\%$ for prolonged and continuous infusion of the dosage interval to achieve bactericidal activity) at different CL_{CR}, dosage regimens and methods of administration for a meropenem target MIC of 2 mg/L (EUCAST breakpoint for susceptibility). The broken horizontal line indicates meropenem PTA of 95% above which the PTA was considered successful.

where TVCL is the typical value of meropenem clearance and CL_{CR} is in mL/min.

The mean (SD) population pharmacokinetic parameter estimates from the final covariate two-compartment model are shown in Table 2. The diagnostic plots to confirm the goodness of fit of the model were considered acceptable and are shown in Figure 2 and Figure 3. The final covariate model was then used for dosing simulations.

Dosing simulations

PTA

The results of the Monte Carlo simulation showed that, for all concentrations and intervals, a prolonged or continuous infusion increased the likelihood of attaining the target PTA (Figure 4, Figure S1 and Table S2). For intermittent dosing, 2000 mg/8 h (6000 mg) or 1000 mg/6 h (4000 mg) was required to have a 100% likelihood of achieving the target exposure $fT_{>MIC} = 40\%$ for all CL_{CR}. For prolonged infusion, the lowest breakpoints for reaching $fT_{>MIC} = 100\%$ for all levels of CL_{CR} were 1000 mg/8 h (3000 mg) or 500 mg/6 h (2000 mg), and for continuous infusion, the lowest dose was 2000 mg.

FTA

As for PTA, the likelihood for reaching FTA $\geq$90% increased with a prolonged or continuous infusion and reduction in CL_{CR}. To reach FTA $\geq$90% in empirical therapy of *A. baumannii*, in all categories of renal function, a daily dose of 8000 mg of meropenem was

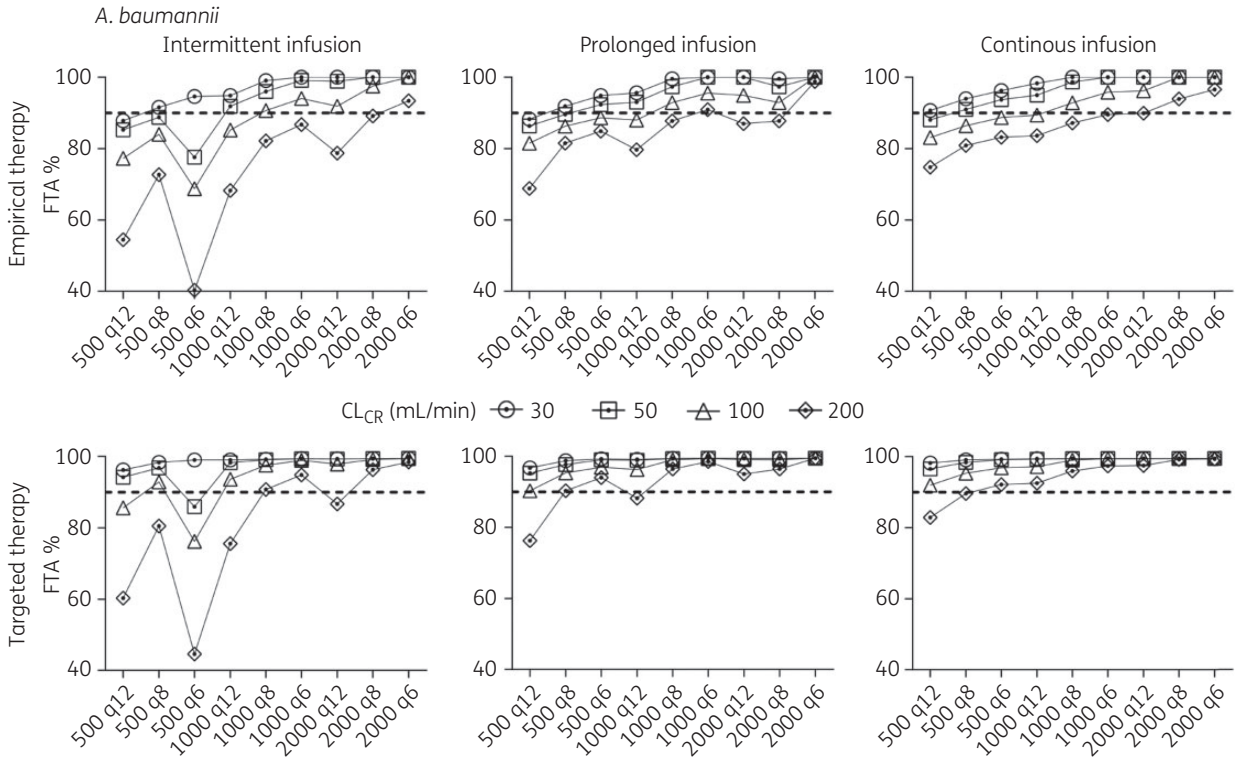

Figure 5. FTA for *A. baumannii* at different CL_{CR}, dosage regimens and methods of administration. The EUCAST MIC distribution of 0.016–512 mg/L was used for empirical treatment and ≤2 mg/L for targeted treatment and considered successful if the FTA was ≥90%. q6, four times daily dosing; q8, three times daily dosing; q12, two times daily dosing.

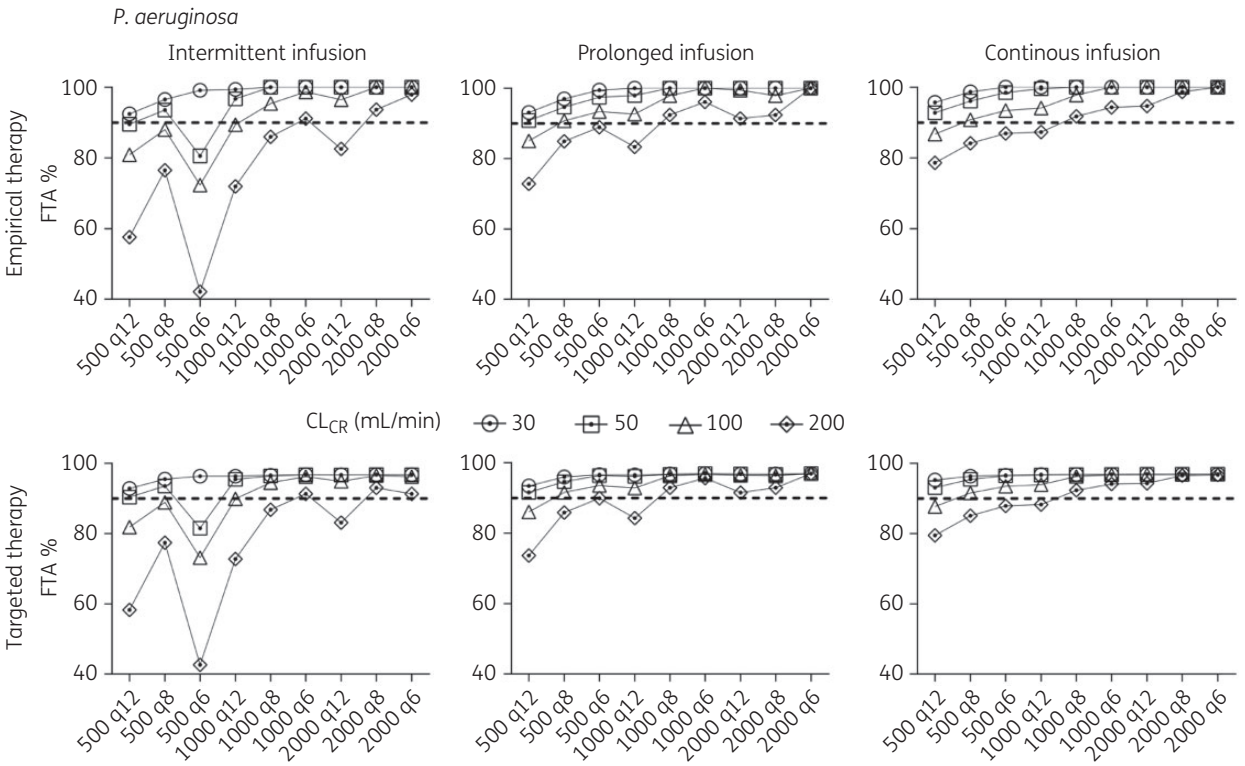

Figure 6. FTA for *P. aeruginosa* at different CL_{CR}, dosage regimens and methods of administration. The EUCAST MIC distribution of 0.016–512 mg/L was used for empirical treatment and ≤2 mg/L for targeted treatment and considered successful if the FTA was ≥90%. q6, four times daily dosing; q8, three times daily dosing; q12, two times daily dosing.

required for intermittent boluses and prolonged infusion, which could be reduced to a daily dose of 6000 mg for continuous infusion. As expected, lower doses were required for targeted therapy where a dose of 6000 mg daily was required for intermittent dosing and 3000 mg daily was sufficient for prolonged infusion, which could be reduced to 2000 mg daily for continuous infusion (Figure 5 and Table S3). For *P. aeruginosa*, a daily dose of either 2000 mg/8 h (6000 mg) or 1000 mg/6 h (4000 mg) was required for target attainment of ≥90% with intermittent dosing. However, 4000 mg, at 12 h intervals, only reached an FTA of approximately 83%. A 3000 mg daily dose was sufficient for prolonged or continuous infusion. These doses were the same for empirical as well as targeted treatment (Figure 6 and Table S3).

Discussion

In this prospective population pharmacokinetic study of meropenem, based on a large sample size, we developed a population pharmacokinetic model for patients with septic shock and a serum creatinine <170 μM. Despite advances in treatment of sepsis, these patients still have a high mortality and therefore are likely to benefit most from early and appropriate antibiotic dosing; they are also at high risk of under-dosing due to altered pharmacokinetics.[7,27] These patients therefore pose a great challenge for clinicians aiming to provide maximally effective therapy.[7]

The influence of mode of administration was emphasized by the PTA and FTA analyses. To achieve a PTA >90%, the difference in the dose needed was 2–4 times higher for intermittent dosing compared with prolonged or continuous infusion. The goal for intermittent dosing was set to achieve $fT_{>MIC} = 40\%$, whereas it was $fT_{>MIC} = 100\%$ for prolonged or continuous infusion, which even further suggests the pharmacodynamic benefits of the more extended dosing regimens. For FTA, the difference in daily dose needed was approximately 1.5-fold between intermittent dosing versus prolonged or continuous infusion in both *A. baumannii* and *P. aeruginosa*. In the present study, we chose to focus the treatment model on two challenging pathogens that pervade critical care units (*A. baumannii* and *P. aeruginosa*) as these can stand as a reference for treatments of other, less difficult to treat, organisms. The FTA results also emphasized the importance of more frequent administration if intermittent dosing is used since a daily dose administered every 12 h had a much lower likelihood of achieving the targeted time above MIC compared with the same dose administered at a more frequent interval. It should be noted that all simulations of continuous infusion included a loading dose over 30 min with the same dose that was to be infused.

Regarding the FTA of *A. baumannii* and *P. aeruginosa*, a standard dose of 1000 mg/8 h as an intermittent 30 min infusion achieved plasma pharmacokinetic/pharmacodynamic targets to adequately cover both targeted and empirical therapy except for the highest CL_{CR} group. This indicates that even in settings or patient categories where these bacteria are common enough to warrant empirical coverage, there seems to be no need to increase the dose beyond standard dosing if the patient has normal or slightly impaired renal function (≤100 mL/min). Similar conclusions have been reached in other recent studies in critically ill patients where meropenem pharmacokinetics/pharmacodynamics have been studied.[15,28]

CL_{CR} was the only covariate that manifested a significant effect on meropenem pharmacokinetics. This is in line with several other studies of both meropenem and other β-lactam antibiotics.[11,28] A recent study on meropenem pharmacokinetics/pharmacodynamics in obese, critically ill patients demonstrated that CL_{CR} had a much higher influence on target attainment compared with BMI or any other weight descriptor.[28] This was also shown in our model on PTA where the group with the highest CL_{CR} of 200 mL/min was at high risk of not achieving the target of $fT_{>MIC} = 40\%$. This group of patients with augmented renal clearance would thus be the group to benefit the most from a prolonged or continuous infusion where the likelihood of target attainment is much higher. Alternatively, a more active approach in this type of patients with dynamic physiological changes is to measure the actual concentrations and apply a therapeutic drug monitoring (TDM) programme as this would likely even further increase the precision of targeted antibiotic plasma concentrations. With the high doses needed in this patient population a TDM programme would potentially also reduce the risk of achieving supratherapeutic plasma levels, which otherwise could increase the potential adverse events and toxicity that are associated with high concentrations of β-lactam antibiotics.

With 50 patients included in this study, it is to our knowledge the largest pharmacokinetic study of meropenem in critically ill patients to date. This sample size has previously been described as a requirement for reliably estimating the standard deviation of a universal population and has made it possible to perform a robust analysis, where the conclusions drawn from the data will have high external validity.[20]

Our study also has some limitations. We cannot make any conclusion regarding dosing in patients with severe acute kidney injury or patients receiving renal replacement therapy as these patients were not included. Also, we have measured and modelled the pharmacokinetic data from plasma concentrations and we do not have any information regarding the meropenem concentration at the site of infection. Even though there is an association between plasma and tissue concentration, a direct linearity is not likely due to the difference in penetration into various tissues.[29] Also, this study was not powered for evaluation of clinical outcome and thus we cannot draw any conclusions with regards to meropenem exposure and outcome.

Conclusions

In conclusion, meropenem pharmacokinetics are mostly influenced by renal clearance and less so by distribution volume. In patients with septic shock and a possible augmented renal clearance, doses may need to be increased and/or administration performed with prolonged or continuous infusion to increase the likelihood of achieving the target plasma concentrations. In patients with normal to slightly decreased renal function, however, standard dosing seems to be sufficient.

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Transparency declarations

None to declare.

Supplementary data

Tables S1–S3 and Figure S1 are available as Supplementary data at *JAC* Online.

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