Journal of Antimicrobial Chemotherapy (2009) **64**, 142–150
doi:10.1093/jac/dkp139
Advance Access publication 27 April 2009

JAC

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

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Received 27 November 2008; returned 26 January 2009; revised 19 March 2009; accepted 21 March 2009

***Objectives*: To compare the plasma and subcutaneous tissue concentration–time profiles of meropenem administered by intermittent bolus dosing or continuous infusion to critically ill patients with sepsis and without renal dysfunction, and to use population pharmacokinetic modelling and Monte Carlo simulations to assess the cumulative fraction of response (CFR) against Gram-negative pathogens likely to be encountered in critical care units.**

***Patients and methods*: We randomized 10 patients with sepsis to receive meropenem by intermittent bolus administration (*n*=5; 1 g 8 hourly) or an equal dose administered by continuous infusion (*n*=5). Serial subcutaneous tissue concentrations were determined using microdialysis and compared with plasma data for first-dose and steady-state pharmacokinetics. Population pharmacokinetic modelling of plasma data and Monte Carlo simulations were then undertaken with NONMEM®.**

***Results*: It was found that continuous infusion maintains higher median trough concentrations, in both plasma (intermittent bolus 0 versus infusion 7 mg/L) and subcutaneous tissue (0 versus 4 mg/L). All simulated intermittent bolus, extended and continuous infusion dosing achieved 100% of pharmacodynamic targets against most Gram-negative pathogens. Superior obtainment of pharmacodynamic targets was achieved using administration by extended or continuous infusion against less susceptible *Pseudomonas aeruginosa* and *Acinetobacter* species.**

***Conclusions*: This is the first study to compare the relative concentration–time data of bolus and continuous administration of meropenem at the subcutaneous tissue and plasma levels. We found that the administration of meropenem by continuous infusion maintains higher concentrations in subcutaneous tissue and plasma than by intermittent bolus dosing. Administration by extended or continuous infusion will achieve superior CFR against less-susceptible organisms in patients without renal dysfunction.**

Keywords: β-lactams, pharmacokinetics, pharmacodynamics, continuous infusion, microdialysis, tissue distribution

Introduction

Meropenem is a carbapenem antibiotic frequently prescribed for the treatment of hospital-acquired infections. For critically ill patients with sepsis or septic shock, early and appropriate antibiotic therapy is recognized as the most important intervention available to clinicians.[1–3] Depending on local susceptibility patterns, meropenem is a suitable choice for this indication because

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of its very broad spectrum of activity against Gram-negative and -positive organisms.

Meropenem is a time-dependent antibiotic, whose antibacterial activity is related to the time for which the free concentration is maintained above the MIC during a dosing interval ($fT_{>MIC}$).[4] The $fT_{>MIC}$ required for optimal bactericidal activity for carbapenems has been reported to be 40% using *in vitro* and *in vivo* animal models.[5] Cephalosporins are reported to require 50%–70% $fT_{>MIC}$ and penicillin 50%–60% $fT_{>MIC}$ for maximal bactericidal activity.[5]

A significant challenge for critical care physicians is achieving appropriate target site concentrations in critically ill patients with sepsis. Physiological changes associated with the disease process can increase drug volume of distribution (V) and drug clearance leading to low plasma concentrations.[3] Data from critically ill patients with sepsis and septic shock show that this altered physiology can reduce tissue concentrations of antibiotics.[6,7] Given that tissues are the source of many infections,[8] altered dosing that seeks to increase the opportunity for therapeutic concentrations should be considered.

For time-dependent antibiotics, continuous infusion has been shown to optimize the attainment of pharmacodynamic targets in plasma.[9] However, limited data comparing the tissue pharmacokinetics of intermittent bolus and continuous dosing of β-lactam antibiotics exist.[7,10] A population pharmacokinetic analysis that provides pharmacokinetic–pharmacodynamic data on different dosing regimens is required to guide dosing in this difficult patient population.

Aims

The aims of this study were: (i) to compare the observed plasma and subcutaneous tissue concentration–time profiles of meropenem administered by intermittent bolus dosing or continuous infusion to critically ill patients with sepsis and without renal dysfunction; (ii) to describe the pharmacokinetic variability of meropenem in this cohort using a population pharmacokinetic model; and (iii) to assess the plasma pharmacokinetic–pharmacodynamic profile of various meropenem dosing regimens and to assess the expected probability of target attainment (PTA) by MIC and cumulative fraction of response (CFR) against Gram-negative pathogens likely to be encountered in critical care units.

Patients and methods

This study was performed in an 18 bed tertiary referral critical care unit. Ethical approval was obtained from the local hospital (protocol 2005/072) and university ethics committees (protocol 2005000619). The study was conducted following the guidelines of the Declaration of Helsinki. Consent to participate was obtained from the patient's legally authorized representative. Inclusion criteria were known or suspected sepsis[11] of a critically ill patient and normal renal function (defined as plasma creatinine concentration <120 μmol/L). Clinical indications for meropenem included nosocomial pneumonia, soft tissue infection, intra-abdominal sepsis and empirical therapy for sepsis without proven source. In accordance with usual practice, all patients had an indwelling arterial cannula. Patients were randomized using random numbers concealed in opaque sealed envelopes to receive the same dose of meropenem by intermittent bolus or continuous administration.

Drug administration and dosage

All patients received meropenem (Merrem IV®; Astra Zeneca, Sydney, Australia). The patients in the continuous treatment group ($n=5$) received a loading dose of 500 mg (in 10 mL of water-for-injection infused by central line over 3 min) followed immediately by a continuous infusion of 3000 mg of meropenem over 24 h [given as three 1000 mg infusions over 8 h in 250 mL of 0.9% sodium chloride—meropenem is stable for at least 8 h at 22°C (data on file)]. The patients in the intermittent bolus group ($n=5$) were given a 1500 mg meropenem first dose (in 10 mL of water-for-injection infused by central line over 5 min) and then 1000 mg (in 10 mL of water-for-injection infused by central line over 3 min) every 8 h. The dose for both groups on day 1 was 3500 mg and 3000 mg/day thereafter.

In both the groups, meropenem was administered through a separate lumen of a central venous catheter using a volumetric infusion pump controller (Gemini PC2 iMed; Alaris Medical Systems, San Diego, CA, USA).

Blood sampling

Five millilitres of blood was collected using the indwelling arterial catheter for each blood sample to determine plasma meropenem concentrations. On day 1, samples were collected at ~0, 3, 5, 7, 10 15, 20, 30, 45, 60, 90, 150, 240, 360 and 480 min. On days 2–5 (steady state), blood samples were taken in line with an intermittent bolus dose or change of continuous infusion bag at 0, 5, 30, 60, 120, 180, 240, 360 and 480 min. Specimens were centrifuged at 3000 rpm for 10 min and then frozen at −20°C for subsequent analysis. All samples were assayed individually within 7 days of collection.

In vivo microdialysis

Microdialysis was the technique chosen to measure the free (or unbound) antibiotic concentration in subcutaneous tissue. Given that the free antibiotic concentration determines antibacterial effect,[12] this information is particularly useful. This technique is used by many critical care physicians who are interested in drug concentrations in epithelial lining fluid, ascites, cerebrospinal fluid and blood in case of remote infection. The principles and details of microdialysis have been described previously.[13] Briefly, microdialysis is based on the sampling of analytes from the extracellular space by diffusion across a semi-permeable membrane. *In vivo*, this process is accomplished by constantly perfusing the microdialysis probe with a physiological solution at a low flow rate. Once the probe is implanted in the tissue, analytes diffuse across the membrane from the extracellular fluid into the perfusate and may be sampled and analysed. In this study, a microdialysis probe (CMA 60; Microdialysis AB, Stockholm, Sweden) with a molecular weight cut-off of 20 kDa, an outer diameter of 0.6 mm and a membrane length of 30 mm was aseptically placed in the subcutaneous tissue of the upper arm of each patient. The probe was perfused with cefalotin (2 μg/L; internal standard) in 0.9% sodium chloride at a flow rate of 1.6 μL/min.[14] After commencement of meropenem, microdialysis samples were collected at ~30 min intervals on day 1 and days 2–5 of the antibiotic treatment. Plasma samples and microdialysis samples were collected during the same dosing periods. Samples were stored at −20°C for analysis within 7 days of collection. The recovery of meropenem in the microdialysate solution was interpolated from the loss of internal standard (cefalotin) across the

microdialysis membrane into the subcutaneous tissue:[15]

$$\text{Percentage meropenem recovery} = 100 \times (C_{in} - \text{mean}\, C_{out}/C_{in})$$

where C_{in} is the 2 mg/L cefalotin (perfusate) and C_{out} the measured cefalotin concentration in microdialysate.

Drug assay

Plasma meropenem concentrations were measured using HPLC with UV detection (Waters HPLC system with 510 pump, 717 autosampler and 486 Tunable Absorbance Detector set at 218 nm λ) using an isocratic mobile phase of 12% methanol/10 mM aqueous sodium dihydrogen phosphate (PBS), pH 6.5 and a 5 μm Gemini C18 column. The internal standard for the HPLC assay was ertapenem. HPLC assays had inter- and intra-day reproducibility of 5.6% and 0.6%, respectively. The limit of quantification for meropenem was 1.0 mg/L and the coefficient of correlation for the assay was 1.000.

Microdialysate meropenem and cefalotin (internal standard) concentrations were concurrently measured using liquid chromatography–tandem mass spectrometry (LC–MS/MS) using a gradient system with buffer A (99.9% water/0.1% formic acid) and buffer B (94.9% acetonitrile/5% water/0.1% formic acid). The flow rate was 0.3 mL/min and the injection volume was 50 μL, which was drawn from a solution consisting of 5 μL sample and 70 μL internal standard. Buffer A ran at 100% from 0 to 5 min, then decreased the rate from 100% to 20% from 5 to 12 min (with buffer B increasing from 0% to 80%), then increased again from 20% to 100% from 12 to 13 min (with buffer B decreasing from 80% to 0%) to complete the assay. The internal standard for the LC–MS/MS assay was penicillin G. LC–MS/MS assays had inter- and intra-day reproducibility of 5.6% and 3.9% for meropenem and 6.1% and 3.3% for cefalotin, respectively. The limit of quantification for meropenem was 0.032 mg/L and that for cefalotin was 0.125 mg/L. The coefficient of correlation for assay linearity was 0.997 for meropenem and 0.999 for cefalotin.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 (Chicago, IL, USA). Mann–Whitney *U*-test or Fisher's exact test was used to compare the demographic and clinical characteristics between the intermittent bolus and continuous treatment groups. P values <0.05 were considered significant.

Pharmacokinetic and pharmacodynamic analyses

The concentration versus time data for meropenem in plasma were analysed by a non-linear mixed-effects modelling approach[16] using NONMEM, Version 6.1 (GloboMax LLC, Hanover, MD, USA) with double precision with the COMPAQ VISUAL FORTRAN compiler. The NONMEM runs were executed using Wings for NONMEM (WFN 6.1.3). Data were analysed using the first-order conditional estimation (FOCE) method with INTERACTION.

For the population pharmacokinetic analysis, the plasma meropenem concentrations were fitted to one-, two- or three-compartment models using subroutines from the NONMEM library.[16] The concentration–time profile can be described as

$$y_{ij} = f_{ij}(\theta_i, x_{ij}) \cdot e^{\varepsilon 1 ij} + \varepsilon_{2ij} \quad (1)$$

where y_{ij} is the jth observed concentration at timepoints x_{ij} for the ith subject. Also, θ_i represents the fixed-effects parameter of the structural model to be estimated and f_{ij} is the function for the prediction of the jth response for the ith subject. Finally, ϵ_{ij} denotes the jth measurement error for the ith subject. In other words, ϵ_{ij} is the difference of the observed concentration from the predicted concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance σ^2.

Between-subject variability (BSV) and between-occasion variability (BOV)

BSV was modelled using an exponential variability model:

$$\theta_i = \theta \cdot e^{\eta_i} \quad (2)$$

where θ_i is the value of the parameter for the ith subject, θ is the typical value of the parameter in the population and finally η_i is a random vector, with normal distribution, zero mean and variance–covariance matrix of BSV Ω to be estimated.

BOV is the variability of a parameter within a subject during treatment and includes between-occasion variability and within-occasion variability. BOV was assumed to be log-normally distributed and modelled over the two pharmacokinetic study occasions:

$$\theta_{i,k} = \theta \cdot e^{\eta_i + \eta_{i,k}} \quad (3)$$

where $\theta_{i,k}$ is the value of the parameter for the ith subject on the kth occasion.

Model diagnostics

Statistical comparison of nested models was based on a χ^2 test of the difference in the objective function. A decrease in the objective function of 3.84 units ($P<0.05$) was considered significant.

Goodness-of-fit was evaluated by visual inspection of diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual versus time and residual versus predicted concentrations.

Bootstrap

A non-parametric bootstrap method[17] ($n=1000$) was used to study the uncertainty of all pharmacokinetic parameter estimates. From the bootstrap empirical posterior distribution, we have been able to obtain the 95% confidence interval (2.5–97.5 percentile) for the parameters, as described previously.[18]

Covariate screening

The covariates analysed were age, weight, body mass index, lean body weight, sepsis organ failure assessment score, plasma creatinine, creatinine clearance measured by 8 h urine collection and creatinine clearance estimated via Cockroft–Gault equation (using total body weight) normalized to 6 L/h. The individual covariates were centred by the median or standard values of occasion 1 and occasion 2. Individual empirical Bayesian (*post hoc*) parameters were plotted against covariate values to assess relationships. If a trend between covariates and pharmacokinetic parameter was observed, then it was considered for inclusion in the population model. Possible covariates were added in a stepwise fashion into the model. Covariates were

kept in the model if there was improvement in the fit over the base model, i.e. decrease in objective function and decrease in the BSV of the parameter.

Visual predictive checks

Using the final covariate model, a visual predictive check was performed by simulating 2000 subjects to assess the predictive performance of the model. The visual predictive checks were generated using a Perl Script (version 1e).[19] The visual checks and representative percentiles [10th, 25th, 50th (median), 75th and 90th percentiles] were visually assessed using Prism® 2005 (Version 4.03).

Dosing simulations

Dosing simulations of plasma data were performed, as the relationship of subcutaneous tissue concentrations to clinical and bacteriological effect is yet to be defined. Three intermittent bolus administration, three extended infusion and three continuous infusion dosing regimens were simulated using Monte Carlo simulations. The three intermittent bolus dose regimens (infusion over 3 min) evaluated were 500 mg every 8 h, 1000 mg every 8 h and 2000 mg every 8 h. The three extended infusion regimens (infusion over 4 h) were 500 mg every 8 h, 1000 mg every 8 h and 2000 mg every 8 h. The three continuous infusion regimens evaluated were 1500, 3000 and 6000 mg of meropenem every 24 h including a loading dose of 500 mg. Each Monte Carlo simulation generated free concentration–time profiles for 1000 subjects per dosing regimen using the parameters from the final covariate model. A value of 2% protein binding was used in all simulations.[20] From these data the $fT_{>MIC}$ was calculated for each simulated subject using linear interpolation. The PTA was obtained by counting the subjects who achieved 40% $fT_{>MIC}$. The predictive efficacy of the model was tested by simulating the meropenem concentrations and thereafter the PTAs for a 50-year-old 70 kg person with plasma creatinine concentrations of 50, 100, 200 and 300 μmol/L.

CFR

MIC_{90} data of Gram-negative pathogens from the 2004–05 Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) database previously reported by Rhomberg *et al.*[21,22] were used to determine the CFR. The MYSTIC programme is a global, multicentre surveillance study containing data for nosocomial pathogens from around the world. The CFR identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against the MIC breakpoints of likely pathogens. The CFR was calculated according to the Gram-negative organism susceptibility data provided by the 2004–05 US MYSTIC database[21,22] using 40% $fT_{>MIC}$. This target was chosen as it represents the maximum bactericidal activity in *in vitro* and animal studies.[5] The PTA for achieving 40% $fT_{>MIC}$ was calculated for the stated Gram-negative organisms for each simulated patient at MIC values from 0.06 to 16 mg/L. The dosing regimens were considered successful if the CFR was 100%.

Results

Patient demographics

Ten patients were enrolled with five patients randomized to intermittent bolus and five patients to continuous dosing. All patients were ventilated and fulfilled the criteria for sepsis,[11] with three

Table 1. Demographic, clinical and pharmacokinetic data

	Intermittent bolus infusion	Continuous infusion	*P* value
Number of subjects (males/females)	3/2	4/1	0.20[a]
Age (years)	55.0 (48.0–61.0)	57.0 (54.0–63.0)	0.60[b]
Total body weight (kg)	80 (75–85)	75 (75–85)	0.83[b]
Height (cm)	170 (170–180)	175 (173–183)	0.40[b]
Day 1 SOFA score	3 (3–4)	5 (2–8)	0.52[b]
Day 2 SOFA score	3 (2–3)	3 (2–4)	1.00[b]
Plasma creatinine concentration (μmol/L)	73 (55–101)	82 (58–112)	0.47[b]
Creatinine clearance (mL/min)	106 (98–127)	93 (69–161)	0.60[b]
Outcome (no. of survivors/no. of non-survivors)	5/0	3/2	0.06[a]
Plasma C_{max} (mg/L)	93 (74–119)	48 (46–64)	0.05[b]
Subcutaneous tissue C_{max} (mg/L)	31 (4–83)	11 (6–13)	0.47[b]
Day 1 plasma C_{min} (mg/L)	0 (0–2)	7 (5–16)	0.02[b]
Day 2 plasma C_{min} (mg/L)	0 (0–0)	8 (5–12)	0.01[b]
Day 1 subcutaneous tissue C_{min} (mg/L)	0 (0–0)	4 (3–8)	0.02[b]
Day 2 subcutaneous tissue C_{min} (mg/L)	0 (0–0)	4 (4–4)	0.03[b]
Day 1 plasma AUC_{0-8} (mg·h/L)	97.2	99.0	0.92[b]
Day 2 plasma AUC_{0-8} (mg·h/L)	69.1	67.55	1.00[b]
Day 1 subcutaneous tissue AUC_{40-48} (mg·h/L)	71.5	8.8	0.47[b]
Day 2 subcutaneous tissue AUC_{40-48} (mg·h/L)	30.3	38.8	0.29[b]

SOFA, sepsis organ failure assessment; C_{max}, observed peak concentration; C_{min}, observed trough concentration (describes steady-state concentration, C_{ss}, for continuous infusion). Creatinine clearance calculated using the Cockroft–Gault equation.[32] Not normally distributed data are expressed as median (interquartile range).

[a]Data are not normally distributed (Fisher's exact test).

[b]Data are not normally distributed (Mann–Whitney *U*-test).

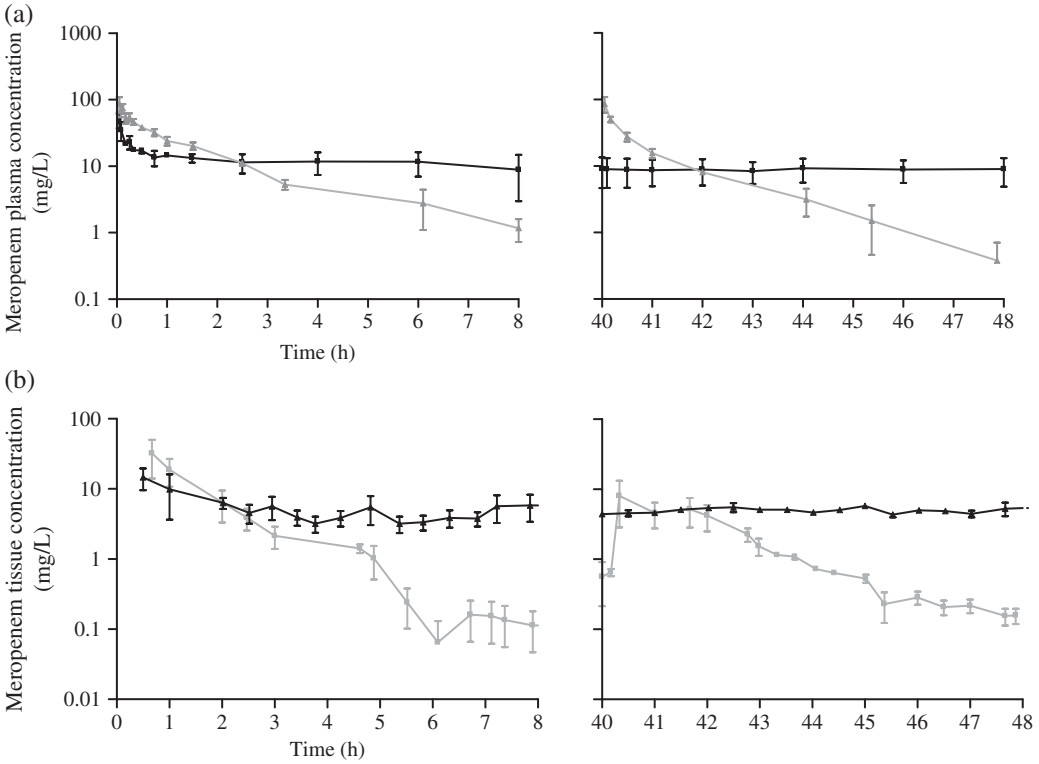

Figure 1. Observed (median ± interquartile range) concentrations for meropenem administered to critically ill patients with sepsis by intermittent bolus dosing (grey lines and symbols) and continuous infusion (black lines and symbols) for (a) plasma and (b) subcutaneous tissue. The sampling on days 2–5 has been described as occasion 2 from 40 to 48 h.

Table 2. Bootstrap parameter final estimates of the final base model

Parameter	Average	95% Confidence interval	
Fixed effects			
clearance (CL), L/h	13.6	12.2	14.9
central volume of distribution (V1), L	7.9	5.8	10.8
peripheral volume of distribution (V2), L	14.8	12.5	17.7
inter-compartmental clearance (Q), L/h	56.3	38.1	78.1
Random effects			
between-subject variability (Ω_{BSV}), CV%			
BSVCL	15.3	0.0	25.3
BSVV1	44.7	0.0	62.1
BSVQ	22.3	0.0	63.8
BSVV2	8.4	0.0	23.2
between-occasion variability (Ω_{BOV}), CV%			
BOVCL	11.8	0.0	16.3
BOVV1	27.7	0.0	43.7
BOVQ	11.8	0.0	69.1
BOVV2	28.8	13.2	40.4
Random error			
residual unexplained variability			
CV, CV%	15.2	9.4	21.9
SD, mg/L	0.43	0.28	0.66

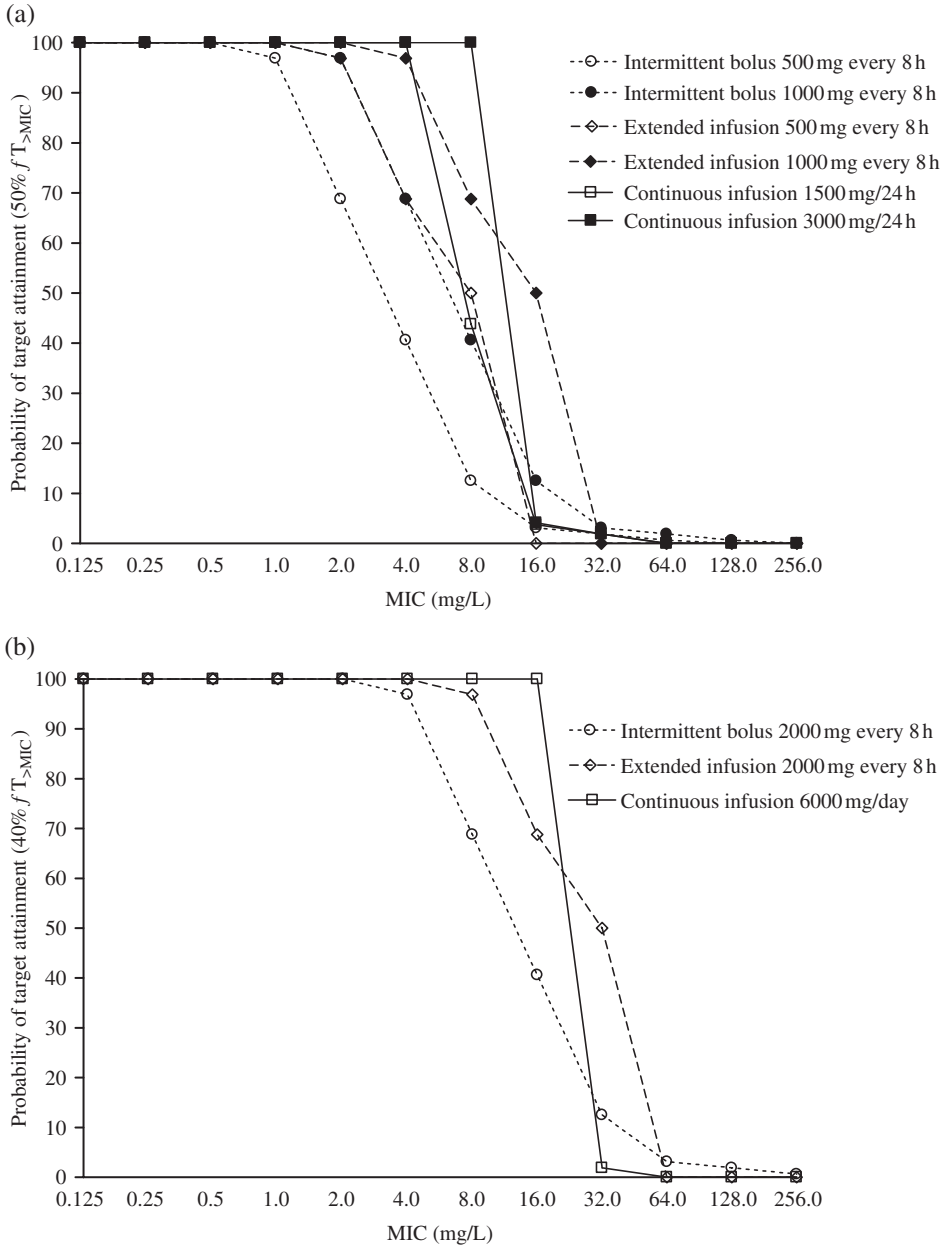

Figure 2. PTA for meropenem administered by intermittent bolus (infused over 3 min), extended infusion (infused over 4 h) or continuous infusion as (a) 1500–3000 mg per 24 h period and (b) 6000 mg per 24 h period. All patients given continuous infusion doses initially received a 500 mg loading dose. The chosen target for analysis was 40% $fT_{>MIC}$ for plasma concentrations. Inf, infusion.

patients also receiving vasopressor therapy (noradrenaline dose >0.1 μg/kg/min in one patient and <1 μg/kg/min in two patients). Patients were evenly matched with regard to demographic data and level of sickness severity, were generally younger than a normal sepsis cohort and did not have any observed form of renal dysfunction (Table 1).

Drug concentrations

The observed concentration–time profiles of meropenem administered by intermittent bolus or continuous dosing are depicted in Figure 1(a) (plasma) and Figure 1(b) (subcutaneous tissue). In total, 222 plasma and 274 microdialysis samples were taken. The comparative area under the concentration–time curve (AUC), peak concentrations (C_{max}) and trough concentrations (C_{min}; intermittent bolus dosing group) or steady-state concentration (C_{ss}; continuous infusion group), in a dosing period, are described in Table 1.

Model building

Pharmacokinetic modelling was performed using the data from the 222 plasma concentration samples. The objective function for the one-compartment model was 1176.301, two-compartment model was 1055.963 and three-compartment model was 1052.809 (non-significant improvement from two-compartment model; statistically significant change required is

3.84). The best base model, based on the model building criteria, consisted of a two-compartmental linear model and a combined residual unknown variability. Other linear models could not be supported as they did not result in an improvement in objective function value or BSV. No variance–covariance matrix could be supported between any of the parameters. No difference in drug clearance could be supported between the intermittent bolus and continuous infusion groups. The model supported between-occasion variability on clearance, central *V* (V1), peripheral *V* (V2) and inter-compartmental clearance (*Q*). Total *V* was calculated as the sum of V1 and V2. The final objective function for this model was 733.264. The values of the parameters for the final base model are given in Table 2. Table 2 also presents the 95% confidence interval for the parameters computed from all bootstrap runs.

The only covariate that described meropenem clearance was renal function described using the Cockroft–Gault equation normalized to 6 L/h (fCG). The addition of this parameter reduced the objective function by 13.805. The final model was represented by:

$$\mathrm{TVCL} = \theta_1 \cdot \mathrm{fCG} \quad (4)$$

where TVCL is the typical value of clearance.

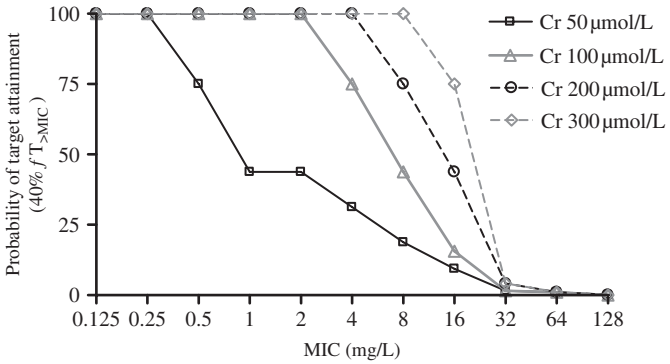

Figure 3. PTA for meropenem administered by intermittent bolus (infused over 5 min), in a 50-year-old 70 kg male with plasma creatinine concentrations of 50, 100, 200 and 300 μmol/L. Cr, plasma creatinine concentration.

Goodness-of-fit plots for the final model were evaluated and showed no apparent visual or statistical bias for the prediction as shown in Figure S1 (Supplementary data available at *JAC* Online http://jac.oxfordjournals.org). A visual predictive check with the final covariate model for occasion 1 and occasion 2 also confirmed the goodness-of-fit of the model to the observed data as shown in Figure S2 (Supplementary data available at *JAC* Online http://jac.oxfordjournals.org). These plots show that the final pharmacokinetic model describes the measured meropenem concentrations adequately on both occasions. All subsequent meropenem Monte Carlo dosing simulations were then based on this model.

Dosing simulations

PTA versus MIC profiles for dosing simulations for different intermittent bolus, extended and continuous infusions are depicted in Figure 2 for meropenem dosing of 1500–3000 mg/day (a) and 6000 mg/day (b). Administration by extended or continuous infusion appeared to achieve superior pharmacodynamic targets compared with intermittent bolus dosing ($fT_{>MIC}$ 40%) against higher MICs (4–16 mg/L).

Figure 3 describes the PTAs for a simulated patient with different levels of renal dysfunction. It is evident from the results that with improving renal function, the ability to achieve pharmacodynamic targets diminishes.

CFR

The assessment of CFR for various dosing simulations that achieved >40% $fT_{>MIC}$ for the first dose is described in Table 3. These data suggest that against Gram-negative pathogens obtained from the 2004–05 US MYSTIC database, all intermittent bolus, extended and continuous infusion dosing regimens achieve high pharmacodynamic targets (100% success) against *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Serratia marcescens* and *Citrobacter* species. This result is due to the presence of high susceptibility of most nosocomial pathogens treated with meropenem. Against the less susceptible *Pseudomonas aeruginosa* and *Acinetobacter* species, the achievement of pharmacodynamic targets was significantly reduced with intermittent bolus administration. Administration

Table 3. CFR (%) for meropenem on day 1 of treatment for Gram-negative pathogens for various intermittent bolus, extended and continuous dosing strategies of meropenem in critically ill patients with sepsis

		Intermittent bolus dosing			Extended infusion			Continuous infusion		
Organism	MIC_{90} (mg/L)	500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	1500 mg/day	3000 mg/day	6000 mg/day
E. coli	0.06	100	100	100	100	100	100	100	100	100
K. pneumoniae	0.06	100	100	100	100	100	100	100	100	100
Enterobacter sp.	0.12	100	100	100	100	100	100	100	100	100
S. marcescens	0.12	100	100	100	100	100	100	100	100	100
Citrobacter sp.	0.12	100	100	100	100	100	100	100	100	100
P. aeruginosa	8	12.5	40.6	68.8	50	68.8	96.9	43.8	100	100
Acinetobacter sp.	16	3.1	12.5	40.6	0	50	68.8	3.8	4.1	100

MIC_{90}, minimum inhibitory concentration for 90% of tested strains. The target chosen was 40% $fT_{>MIC}$. Susceptibility data obtained from the 2004–05 MYSTIC surveillance programme in the USA.[21,22]

of high doses by extended or continuous infusion was required to achieve 40% $fT_{>MIC}$ against these pathogens.

Discussion

The data presented in this study provide support for contemporary intermittent bolus dosing regimens for meropenem against most Gram-negative pathogens that remain highly susceptible. This would appear to be especially important in younger, critically ill patients without renal dysfunction. Against the less susceptible *P. aeruginosa* (MIC_{90} 8 mg/L) and *Acinetobacter* species (MIC_{90} 16 mg/L), better pharmacodynamic targets are likely to be achieved by administering 3 or 6 g of meropenem by extended or continuous infusion than by intermittent boluses of the same daily dose. At present, the manufacturer's product information recommends a dosing regimen for patients with no renal dysfunction of 500–1000 mg 8 hourly by bolus infusion over 5 min.[20] It follows, therefore, that over ensuing years, as susceptibility of organisms to meropenem decreases, use of extended or continuous infusions will become advantageous for maximizing the likelihood of bacteriological efficacy because of superior attainment of pharmacodynamic targets at higher MICs.

From an antibiotic distribution viewpoint, only one previous paper could be found that describes the relative β-lactam antibiotic plasma and subcutaneous tissue concentration profiles when administered by both intermittent bolus dosing and continuous infusion.[7] The present data from this study show that the continuous infusion maintains statistically significantly higher C_{ss} concentrations than intermittent bolus dosing C_{min}. This was also observed in the plasma data.

The 40% $fT_{>MIC}$ pharmacodynamic target for carbapenem antibiotics has been determined in *in vitro*, *ex vivo* and animal *in vivo* studies.[5] A recent paper by Li *et al.*[23] has suggested that an $fT_{>MIC}$ of 54% is optimal in patients with lower respiratory tract infections. This study raises the possibility that the pharmacodynamic targets obtained from *in vitro* and *in vivo* studies may not translate precisely across to targets required for the treatment of human bacterial infections. It also provides further support for administration of meropenem by extended or continuous infusion. A similar finding for an $fT_{>MIC}$ target longer than that described in *in vitro*, *ex vivo* and animal i*n vivo* studies has recently been described by McKinnon *et al.*[24] for the cephalosporin antibiotics cefepime and ceftazidime (pharmacodynamic target 60%–70%). In this retrospective analysis of studies in critically ill patients, the authors demonstrated clinical and bacteriological benefits for maintaining 100% T>MIC.[24]

In the present cohort of critically ill patients with sepsis, we identified different values of *V* and clearance compared with previous studies for meropenem in healthy volunteers,[25] but similar values to previous studies in critically ill patients.[26–28]

Meropenem *V* was significantly larger in the present patient group with a calculated median total *V* of 22.7 L compared with other studies in healthy volunteers (mean 12.4 L).[25] Our results are similar to those from other pharmacokinetic studies in critically ill patients.[26–28] The concept of increased *V* in sepsis is likely to be related to the level of sickness severity[29] and has been described previously for other antibiotics.[30]

Drug clearance was larger in this cohort of critically ill patients with sepsis (13.6 L/h) compared with other studies in critically ill patients (7.7–9.4,[28] 9.3[26] and 11.5[27]). It is important to note that this was a generally young cohort of patients and none of the patients had any measured renal dysfunction. Interestingly, a previous study in healthy volunteers (12.4 L/h)[25] described similar meropenem clearance despite other studies typically describing higher clearances in critically ill patients compared with healthy volunteers.[7,31] The increased clearance that we observed in our cohort compared with the other studies in critically ill patients is likely to be due to the good renal function of this young patient cohort (mean creatinine clearance 100 mL/min). This observed value exceeds that observed in the studies by Thalhammer *et al.*[28] (creatinine clearance 84 mL/min), Kitzes-Cohen *et al.*[26] (creatinine clearance 78 mL/min) and Novelli *et al.*[27] (creatinine clearance 61 mL/min).

The small cohort of 10 patients could be considered a limitation of this study given the variability of different levels of patient sickness severity that can affect patient pharmacokinetics. The small cohort may have also prevented other covariates from being shown to be significant and predictive of the variability of pharmacokinetic parameters. A larger cohort could not be enrolled due to the difficulty of consenting for first-dose pharmacokinetics in a patient population where immediate dosing is essential for optimal clinical outcomes. Despite this, statistically significant differences in trough meropenem concentrations were observed between each group, indicating that the cohort size was sufficient for this end. Other limitations are that the patients enrolled did not have renal failure, which limits the generalizability of results to patients with 'normal' renal function, and that the potential value of using pharmacokinetic/pharmacodynamic parameters as guides for establishing optimal dosing regimens using tissues concentrations has not been validated.

Conclusions

Contemporary literature evaluating treatment of sepsis recommends further research into optimizing antibiotic dosing to further reduce morbidity and mortality. This study provides new information on subcutaneous tissue concentrations of meropenem administered by intermittent bolus and continuous dosing and has used Monte Carlo dosing simulations from plasma data to show that administration by extended or continuous infusion may provide advantages over intermittent bolus dosing for less-susceptible organisms. However, the current high susceptibility of many organisms to meropenem ensures a high likelihood of success against most pathogens regardless of the method of dosing selected. For treatment of less-susceptible *P. aeruginosa* and *Acinetobacter* species, administration by extended or continuous dosing may be clinically advantageous due to superior achievement of target exposures, particularly in critically ill patients with sepsis and without renal dysfunction.

Acknowledgements

We would like to thank Melissa Rutt for assaying serum samples by HPLC.

Funding

We would like to acknowledge funding of our research centre by the National Health and Medical Research Council of Australia

(Project Grant 519702), the Australia and New Zealand College of Anaesthetists (ANZCA 06/037), the Society of Hospital Pharmacists of Australia, the Queensland State Government Smart State Initiative and the Royal Brisbane and Women's Hospital Research Foundation. J. A. R. is funded by a scholarship from the National Health and Medical Research Council of Australia (Public Health Postgraduate Scholarship 409931).

Transparency declarations

None to declare.

Supplementary data

Figures S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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