

Pharmacokinetics of short versus extended infusion meropenem dosing in critically ill patients: a pilot study

Katherine M Langan, Jovan Jacob, Jian Li, Roger L Nation, Rinaldo Bellomo, Benjamin Howden and Paul DR Johnson

Meropenem is often used in critically unwell patients because of its broad spectrum of antibacterial activity and stability against deactivation by most beta-lactamases.^{1,2} Its efficacy is related to the cumulative percentage of a 24-hour period that the drug concentration exceeds the minimum inhibitory concentration (MIC) of the organism under steady-state pharmacokinetic (PK) conditions ($\%T_{MIC}$).³ For meropenem, the required $\%T_{MIC}$ for bactericidal activity is 40%–50% of the dosing interval. Meropenem is principally renally excreted and antibiotic clearance is correlated with creatinine clearance (CrCl).^{1,2} In studies of healthy volunteers, it has an elimination half-life of about 1 hour.² However, critically ill patients have altered physiology and all these parameters may be altered.^{4–10}

The recommended dosing schedule for meropenem is 500–1000 mg, 8–12 hourly, by short (5–30-minute) intermittent infusions.¹ This has the potential to expose the patient to unnecessarily high peaks and low troughs. Thus, continuous infusion has been advocated because it may provide a higher $\%T_{MIC}$ than intermittent infusions, especially at higher MICs.^{11,12} However, there are practical limitations with this approach. There are also some doubts about the stability of meropenem in solution after 6 hours, especially at higher temperatures.^{13–15} A regimen involving intermittent 3-hour infusions might avoid concerns about drug stability and is logistically preferable to a continuous infusion.

There is some evidence from Monte Carlo dosing simulations that 500 mg infused over 3 hours may achieve at least a similar $\%T_{MIC}$ to 1000 mg infused over 30 minutes,^{16–22} although much of the data in this area are derived from healthy volunteers, who have lower variability in PK parameters such as clearance compared with critically ill patients. Patients with critical illness may have significantly reduced or elevated clearance,^{8,9,23} thus, attainment of PK–pharmacodynamic (PK–PD) targets, such as $\%T_{MIC}$, may differ.^{23,24} The aim of our study was to compare the plasma-concentration–time profile and the $\%T_{MIC}$ achieved with intermittent infusion of meropenem 1000 mg administered by standard 30-minute infusion, with meropenem 500 mg administered as an extended 3-hour infusion, in critically ill patients.

ABSTRACT

Objective: To test whether a prolonged 3-hour infusion of meropenem 500 mg achieves an equivalent proportion of time above the minimal inhibitory concentration (MIC) ($\%T_{MIC}$) to that of meropenem 1000 mg given over 30 minutes.

Design, setting and participants: A randomised cross-over study in 10 critically ill patients.

Method: We administered meropenem as a 1000 mg, 30-minute infusion or as a 500 mg, 3-hour infusion. We determined serial plasma concentrations for each dosing episode and performed comparisons of $\%T_{MIC}$ at different MICs.

Outcome measures: The percentage of time that meropenem was above its MIC.

Results: For low MICs (≤ 2 mg/L), both regimens attained a $\%T_{MIC} > 40\%$ in all patients. For an MIC of 4 mg/L, this target was attained in all but one patient, but with an MIC of 8 mg/L, three patients in each group had a $\%T_{MIC} < 40\%$. There was no difference in target attainment between the two regimens for MICs up to 8 mg/L. There was marked variability in the pharmacokinetic and hence the pharmacokinetic–pharmacodynamic parameters between individuals. Several patients had elevated creatinine clearances and, with both regimens, their target attainment was poor.

Conclusions: Meropenem at 1000 mg over 30 minutes achieved a similar $\%T_{MIC}$ to meropenem at 500 mg given over 3 hours. Meropenem pharmacokinetics were highly variable from individual to individual.

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Materials and methods

Patients

We performed a prospective, randomised cross-over study of adult patients prescribed meropenem by intensivists in a 24-bed general intensive care unit in a tertiary hospital in Melbourne, Australia. Patients considered for inclusion in this study were those needing a predicted duration of meropenem therapy ≥ 3 days. Potential participants were

excluded if they had a history of type I hypersensitivity reaction to meropenem or other beta-lactams, they had suspected or proven bacterial meningitis, or consent was unable to be obtained from the participant or their next of kin. Demographic information about the patient such as age, sex, weight, height, comorbidities and Acute Physiology and Chronic Health Evaluation (APACHE) II score was collected. The patient's serum creatinine concentration and information about the requirement for haemofiltration were collected at baseline and on a daily basis during the study.

Study design

This prospective study had an open, randomised two-way cross-over design. Ethics approval was obtained from the Austin Health Human Research Ethics Committee (protocol 2008/03406). Consent to participate was obtained from the patient or from their legally authorised representative. Patients were initially treated with meropenem, at a dose and frequency determined by their treating clinician, for at least 48 hours before being enrolled in the study. This was due to clinician concerns about treating unstable, critically unwell patients with a lower dose (500 mg) of meropenem. Once patients started participating in the study, they received either meropenem 1000 mg as a standard infusion over 30 minutes, or meropenem 500 mg as an extended infusion over 3 hours. Each investigational regimen was given for 48 hours and the patients were then crossed over to the alternative treatment arm for another 48 hours. The order in which the participants received the regimens was selected using a web-based, computerised, random number generator. The dosage interval was every 8 hours for patients with normal renal function (defined as an estimated CrCl > 50 mL/minute using the Cockcroft–Gault equation).³ For patients with a CrCl ≤ 50 mL/minute or receiving continuous venovenous haemofiltration, the dosing interval was increased to every 12 hours.^{25,26} This reflected standard practice in this ICU. The dosage interval for a given patient was the same for both arms of the study. Further therapy after completion of the study was at the discretion of the ICU clinician.

Drug administration and sampling

All patients received meropenem (Merrem, AstraZeneca) which was reconstituted in 50 mL of either 5% dextrose or compound sodium lactate solution and administered through a separate lumen of a central venous catheter, at a constant flow rate over the desired infusion duration via a volumetric infusion pump (Alaris Gemini PC-1 or PC-2 pump, CareFusion). All blood samples were collected at steady state, immediately before the third dose of each regimen, and during this dosing interval. For the 30-minute

infusion regimen, blood samples were obtained halfway through the infusion (at 15 minutes), at the end of the infusion, and then at 2, 4, 6 and 8 hours. For the 3-hour infusion regimen, blood samples were obtained halfway through the infusion (at 1.5 hours), at the end of the infusion, and at 4, 6 and 8 hours. For patients with a 12-hour dosing interval, an additional sample was obtained at 12 hours. Blood samples (5 mL each in lithium–heparin tubes) were obtained from arterial catheters and immediately centrifuged at 1250 g for 10 minutes; the plasma samples were then frozen at –70°C. The samples were assayed within 2 months of collection.

Analytical methods

All samples from both treatment arms for each patient were analysed concurrently. Meropenem concentrations in plasma were determined by high-performance liquid chromatography (HPLC) using a modification of a method reported by Ikeda et al.²⁷ To an aliquot of plasma (100 µL), an equal volume of 3-(N-morpholino)propanesulfonic acid buffer and 400 µL of methanol was added. Following brief vortex mixing and centrifugation, a 50 µL aliquot of the clear supernatant liquid was injected onto the HPLC column (PhenoSphere-Next [Phenomex] 5µ C18 250×4.60 mm, preceded by a guard column) maintained at 25°C. A gradient elution mobile phase (5% methanol in 0.1% trifluoroacetic acid [TFA] to 80% methanol in 0.1% TFA over 4 minutes, returning to the initial composition over 0.5 minutes) flowing at 0.7 mL/minute was used. The column eluent was monitored for UV absorbance at 311 nm. Calibration curve samples (0.5–64 mg/L) and independently prepared quality control (QC) samples (1.5, 15 and 60 mg/L) were analysed with each batch of patient samples. Based on analysis of QC samples, measured concentrations were within 7.5% of nominal concentrations (accuracy) and the coefficients of variation were less than 3.3% (reproducibility) across the calibration range. The lower limit of quantification was 0.5 mg/L. Patient samples with concentrations above 60 mg/L were reanalysed after appropriate dilution. Due to the low plasma protein binding of meropenem,²⁸ differentiation was not made between total and unbound concentrations.

Pharmacokinetic and pharmacodynamic analysis

Individual plasma-concentration–time curves were plotted for each regimen for each patient. The elimination half-life ($t_{1/2}$), area under the plasma concentration versus time curve across the dosage interval (τ , 8 or 12 hours, depending on CrCl, as noted above) at steady state ($AUC_{0-\tau}$), total clearance (CL) and volume of distribution (V) were determined by non-compartmental analysis using WinNonlin version 5 (Pharsight). The $AUC_{0-\tau}$ was calculated by the linear trape-

Table 1. Summary of steady-state pharmacokinetic parameters of meropenem after a 1000 mg 30-minute infusion, or a 500 mg 3-hour extended infusion, in 10 critically ill patients

Parameter	CrCl (mL/min)	C _{max} (mg/L)	C _{min} (mg/L)	t _{1/2} (hours)	AUC _{0-τ} (mgh/L)	CL (L/h)	V (L)
Median 1000 mg 3-hour infusion (IQR)	77.3 (47.3–108)	54.2 (40.8–72.2)	4.9 (1–7.9)	2.66 (1.4–3.7)	207.7 (65.8–276.9)	4.8 (3.6–15.2) [0.09 (0.04–0.17)]*	18.9 (15.3–25.4) [0.23 (0.19–0.38)]†
Median 500 mg 30-minute infusion (IQR)	75.8 (65–90)	21 (10.3–28.5)	3.12 (1.1–6.2)	2.63 (1.5–4.1)	118.4 (40.8–149.2)	4.2 (3.4–12.3) [0.08 (0.05–0.16)]*	20.4 (17.9–25.7) [0.28 (0.24–0.33)]†
<i>P</i>	0.76	0.0025**	0.43	0.76	0.07	0.94 [0.76]*	0.76 [0.88]†

CrCl = creatinine clearance rate. C_{max} = maximal measured plasma concentration. C_{min} = plasma concentration at the end of the dosing interval. t_{1/2} = elimination half-life under the plasma concentration versus time curve across the dosage interval (τ, 8 or 12 hours depending on CrCl). AUC_{0-τ} = area under the moment curve during the dosing interval (τ, 8 or 12 hours depending on CrCl). CL = total clearance. V = volume of distribution. IQR = interquartile range. * Normalised for actual bodyweight (L/h/kg). † Normalised for actual bodyweight (L/kg). ***P* < 0.05 (statistically significant difference).

zoidal rule; the CL was calculated as dose/AUC_{0-τ}; the t_{1/2} was calculated as 0.693 divided by the elimination rate constant (k_{el}) which was determined by log-linear least-squares regression analysis of the drug concentrations in the terminal, log-linear phase; and V was calculated as CL/k_{el}. The peak plasma concentration (C_{max}) was defined as the maximal measured plasma concentration and the trough plasma concentration (C_{min}) was defined as the plasma concentration at the end of the dosing interval.

The %T_{MIC} was determined by visual interpolation of the time–concentration curve for MICs of 2, 4, 8, 16 and 32 mg/L. For patients in whom an organism was isolated, MIC was performed by meropenem Etest or agar dilution sensitivity (ADS) testing. The %T_{MIC} for the specific isolate was then calculated from the relevant time–concentration curves. Etests were performed as described in the product information (Etest antimicrobial susceptibility testing for in vitro diagnostic use, AB Biodisk). Several well isolated colonies from a 24–48-hour pure culture were homogenised in saline to obtain a turbidity equivalent to 0.5 McFarland standard. This solution was inoculated onto a Müller–Hinton agar plate, using a rota-plater. A meropenem Etest strip was then applied to the agar plate and the MIC was read at 48 hours. The read point was where the inhibition ellipse intersected the strip. The determination of the meropenem MIC by the ADS method was performed according to Clinical Laboratory and Standards Institute performance standards²⁹ by inoculating 10⁴ colony-forming units onto Müller–Hinton agar containing meropenem in a concentration of 0.5, 1, 2 and 4 mg/L. After 16–18 hours, these plates were read for growth and the MIC was determined to be the lowest concentration at which no growth occurred.

Statistical analyses

Statistical analysis was performed using Stata/IC, version 11.0 (StataCorp) and Prism, version 5 (GraphPad). All results

are expressed as medians and interquartile ranges (IQRs) unless otherwise specified. Comparisons were made between groups using a Wilcoxon signed-rank test or the Kruskal–Wallis test. *P* values of <0.05 were considered statistically significant.

Results

Patient demographics

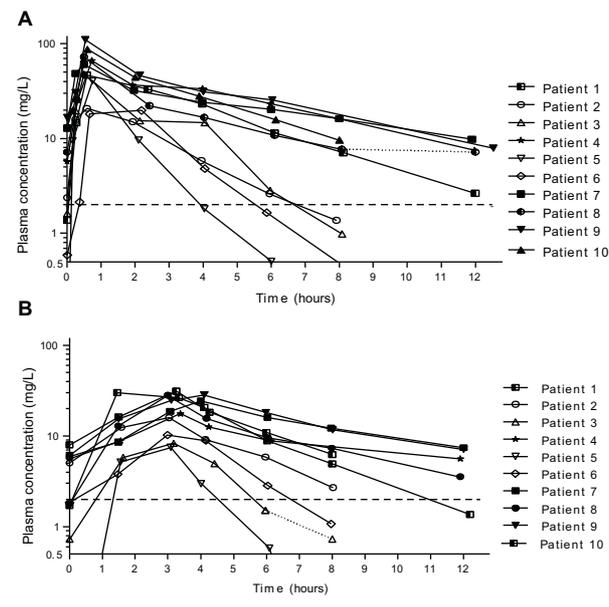
Ten patients with a range of admission diagnoses completed the study protocol (see Appendix Supplementary Table 1 online at cicm.org.au/journal.php). Their median age was 67 years (range, 20–75 years) and 60% were men. The actual bodyweight range of patients was 50–113 kg (median, 76 kg). As a result of the wide variation in bodyweight, the weight-normalised meropenem dose varied considerably: between 8.9 mg/kg/dose and 20 mg/kg/dose for the meropenem 1000 mg dose, and between 4.4 mg/kg/dose and 10 mg/kg/dose for the meropenem 500 mg dose. The median APACHE score was 23 (range, 11–40), with five patients having an APACHE score ≥ 25, indicating severe critical illness. The 30-day mortality was 10% (one of 10 patients).

Five patients had meropenem administered 12-hourly as they had renal impairment. Four of these patients were treated with continuous haemofiltration during the study (Patients 4, 7, 8 and 9), although Patient 8 only received haemofiltration during the 3-hour infusion (see Appendix Supplementary Table 1). Patient 1 had renal impairment but did not have any renal replacement therapy. There were no significant differences in the median serum creatinine (*P* = 0.73) or calculated CrCl (*P* = 0.76) at the beginning of each infusion regimen (Table 1).

Pharmacokinetics

Each patient had six to eight plasma concentrations obtained to construct 20 PK profiles. The steady-state

Figure 1. Meropenem infusion, steady-state, plasma concentration–time profiles of 10 critically ill patients; 1000 mg infused over 30 minutes (A), and 500 mg infused over 3 hours (B)



Closed symbols = haemofiltered patients. Half-closed symbols = renal impairment (creatinine clearance ≤ 50 mL/min) but not haemofiltered. Open symbols = normal renal function (creatinine clearance > 50 mL/min). Dashed line = plasma concentration 2 mg/L (the Clinical Laboratory Standards Institute breakpoint for *Pseudomonas aeruginosa*); lower limit of quantification was 0.5 mg/L.

plasma-concentration–time profiles for each patient are shown in Figure 1. On two occasions, the next dose was inadvertently given before blood was drawn, therefore the trough plasma concentration from the previous dose was substituted for these concentrations for PK analysis. This decision was confirmed to be appropriate by using the elimination rate constant to calculate the expected values.

Table 1 is a summary of the PK data (data for individual patients are available in Appendix Supplementary Table 2 online at cicm.org.au/journal.php). The C_{\min} was not significantly different between the two regimens (meropenem 1000 mg dose C_{\min} , 4.9 mg/L [IQR, 1–7.9 mg/L]; meropenem 500 mg dose C_{\min} , 3.1 mg/L [IQR, 1.1–6.2 mg/L]; $P=0.47$). There was considerable variation observed among individuals.

The half-lives, clearance rates and volumes of distribution were not significantly different between the groups ($P=0.76$, 0.94 and 0.76, respectively). As would be expected with the higher dosage, there was a trend towards a greater AUC_{0-7} with the 1000 mg, 30-minute infusion (median, 207.7 mg·h/L [IQR, 65.8–276.9 mg·h/L]) compared with the 500 mg, 3-hour infusion (median, 118.4 mg·h/L [IQR, 40.8–149.2 mg·h/L]) ($P=0.07$). The median clearance of meropenem in our study was 4.8 L/h (IQR, 3.6–15.2 L/h)

for the 1000 mg, 30-minute infusion regimen, and 4.2 L/h (IQR, 3.4–12.3 L/hour) for the 500 mg, 3-hour infusion regimen. See Table 1 for weight-adjusted clearance rates.

For both regimens, there was reduced clearance in patients who had haemofiltration compared with those who did not. The median clearance rate for the 1000 mg, 30-minute infusion group of patients undergoing haemofiltration was 3.2 L/hour (IQR, 2.6–3.6 L/hour), and for those not undergoing haemofiltration was 8.9 L/hour (IQR, 4.7–15.8 L/hour) ($P=0.033$). In the the 500 mg, 3-hour infusion group, the patients undergoing haemofiltration had a median clearance rate of 3.65 L/hour (IQR, 3.24–4.24 L/hour), and the patients not undergoing haemofiltration had a median clearance rate of 9.67 L/hour (IQR, 3.88–15.76 L/hour) ($P=0.017$).

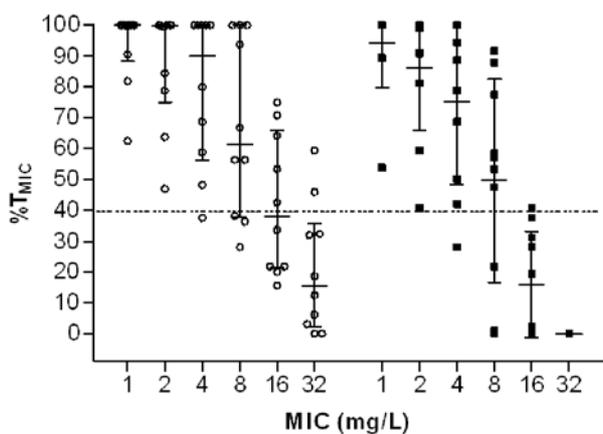
The volume of distribution did not differ with haemofiltration status. Patients who had an increased CrCl (> 100 mL/minute) had significantly greater meropenem clearance than the other patients, in both regimens. For the 1000 mg, 30-minute infusion group, the median clearance was 15.8 L/hour (IQR, 8.9–15.8 L/hour) for patients with increased CrCl, compared with a median clearance of 3.9 L/hour (IQR, 3.3–4.9 L/hour) ($P=0.02$) for patients with $CrCl \leq 100$ mL/minute. There were similar findings for the 500 mg, 3-hour infusion group; for patients with increased CrCl, the median clearance was 15.8 L/hour (IQR, 7.1–21.9 L/hour), and for the other patients, the median clearance was 3.9 L/hour (IQR, 3.4–4.5 L/hour) ($P=0.03$).

Target attainment

Figure 2 is a summary of % T_{MIC} with each infusion type at various specified MICs. There was no significant difference in the % T_{MIC} between the two different regimens if the MIC was 2 mg/L ($P=0.73$), 4 mg/L ($P=0.40$) or 8 mg/L ($P=0.13$). For MICs greater than this, neither regimen obtained a % T_{MIC} greater than 40%. It should be noted that with the 500 mg, 3-hour infusion, Patient 5 never achieved a plasma concentration > 8 mg/L and Patient 3 only reached this concentration for a very short period (see Figure 1). In these two patients, a suboptimal % T_{MIC} with the 1000 mg, 30-minute infusion also occurred. They were both young, previously healthy men; Patient 3 was 33 years old with varicella pneumonitis and Patient 5 was 20 years old with multitrauma. Their calculated CrCl rates were much greater than 100 mL/minute. Patient 6 also had suboptimal plasma concentrations with both regimens and a calculated CrCl > 100 mL/minute. She was a 70-year-old patient with diabetes who had been admitted with multitrauma. An additional two patients (Patients 4 and 7) took 1 hour or more to achieve a plasma concentration of 8 mg/L or greater with the 500 mg, 3-hour infusion. They were both undergoing haemofiltration.

With the 1000 mg, 30-minute infusion, the % T_{MIC} was significantly less for patients who had a calculated CrCl

Figure 2. Comparison of target attainment ($\%T_{MIC}$) for specified MIC values of meropenem 1000 mg, 30-minute infusion with meropenem 500 mg, 3-hour infusion, in 10 critically ill patients



MIC = minimum inhibitory concentration. $\%T_{MIC}$ = cumulative percentage of a 24-hour period that drug concentration exceeds MIC of the organism under steady-state pharmacokinetic conditions. Open circles = meropenem 1000 mg, 30-minute infusion. Closed squares = meropenem 500 mg, 3-hour infusion. Unbroken vertical lines with horizontal error bars = median $\%T_{MIC}$ with interquartile ranges. Dotted

>100 mL/minute at MICs of 2, 4 and 8, compared with patients with a calculated CrCl \leq 100 mL/minute. For example, at an MIC of 4 mg/L, the median $\%T_{MIC}$ was 47.7% (IQR, 43.0%–55.0%) for those with an elevated calculated CrCl, but was 100% (IQR, 81.4%–100%) for all other patients. There were similar findings with the 500 mg, 3-hour infusion group. At an MIC of 4 mg/L, the median $\%T_{MIC}$ was 30.5% (IQR, 23.3%–58.6%) for patients with an elevated calculated CrCl, but was 94.5% (IQR, 80.0%–100%) for all other patients. There were no significant differences with either regimen if those with a CrCl of 50 mL/minute were compared with those with a CrCl \geq 50 mL/minute.

With the 1000 mg, 30-minute infusion group, the $\%T_{MIC}$ was greater for MICs of 4, 8 and 16 mg/L if the patient was undergoing haemofiltration compared with those who were not. However, with the 500 mg, 3-hour infusion group, there were no statistically significant differences in the $\%T_{MIC}$ for patients undergoing haemofiltration compared with those who were not.

There were four clinical isolates of gram-negative bacteria; one *Proteus mirabilis* and three *Pseudomonas aeruginosa* isolates (see Appendix Supplementary Table 1). Most had MICs <4 mg/L with the exception of *P. aeruginosa* isolated in sputum from Patient 6. Its MIC was 3 mg/L and a $\%T_{MIC}$ >40% was attained with both regimens; 55.6% with the 1000 mg, 30-minute infusion group and 62.5% with the 500 mg, 3-hour infusion group. All patients achieved microbiological cure.

Discussion

Extended infusions of carbapenems have been advocated to achieve a better PK profile and hence better bacterial killing, especially for organisms with a higher MIC.^{30,31} This form of administration may also be one way to achieve similar efficacy with less medicine and therefore less cost. Much of this information (with a few notable exceptions^{26,32,33}) has been obtained from Monte Carlo simulation based on PK data from healthy volunteers.^{20,22} Our study comprised a general cohort of critically ill patients with variability in renal function; some patients required haemofiltration and others had increased CrCl. Overall, the median clearance was less than in previous studies in healthy volunteers³⁴ and similar to other reported studies in critically ill patients,^{8,23} with a wide coefficient of variation (71.1% and 82.5%, respectively, for the 1000 mg and the 500 mg regimens). For patients who did not undergo haemofiltration, the high clearances were similar to a previous report of a cohort of septic patients without renal dysfunction.⁹ Those who received haemofiltration had lower clearances and longer half-lives, similar to other critically ill patients receiving high volume haemofiltration.³⁵ Interestingly, the volume of distribution in these critically ill patients was more similar to healthy volunteers^{1,20,34} than that reported from patients with sepsis but without renal dysfunction.^{6,26,36} This may relate to extracellular fluid differences between these groups and once again highlights the diversity in PKs in the critically ill.

In our study, intermittent administration of a 500 mg, 3-hour infusion, compared with a 1000 mg, 30-minute infusion, achieved a similar $\%T_{MIC}$ for all but the higher MICs (16 mg/L and above). This was mainly due patients receiving the 500 mg, 3-hour infusion failing to reach these higher plasma concentrations. With this extended infusion, four of the 10 patients did not achieve a plasma concentration above 16 mg/L and none ever had a plasma concentration above 32 mg/L. There were also several patients who failed to achieve an adequate (>40%) $\%T_{MIC}$ for an MIC of 8 mg/L with both infusion regimens.

Eguchi and colleagues found in their Monte Carlo simulation that the best target attainment was achieved by an initial, short 30-minute infusion of 500 mg, followed by an extended infusion of 4–6 hours.³⁷ Thus, an initial bolus infusion may have overcome this problem and achieved better target attainment. Patients with increased CrCl, and hence meropenem clearance, had significantly poorer target attainments with either regimen for MICs in the intermediate susceptibility range for *P. aeruginosa*. It is important to note that the MIC of three of the four clinical isolates in this study were all low and sensitive, according to the Clinical and Laboratory Standards Institute 2012 performance standards for antimicrobial susceptibility testing interpretative breakpoint criteria. Additionally, one of the isolates of *P. aeruginosa* had an MIC in the

intermediate range. For all these clinical isolates, either administration method would have resulted in adequate target attainment. Therefore, the lower dose, more economical regimen would be the best option.³¹ However, in many ICU settings, where organisms with higher MICs are more routinely encountered (particularly for *P. aeruginosa*³⁸), neither of these dosing regimens would have been adequate, especially if the desired target plasma concentration is two- to fourfold the MIC of the organism for more than 40% of the dosing interval.¹¹ The meropenem regimen should therefore be tailored to the known or anticipated MIC for an individual.

Another problem which became apparent in our study was the dosage regimen for patients receiving haemofiltration. The recommended meropenem dosages ranged in the literature from 500–1000 mg, 12-hourly^{25,39} to the standard dosage of 1000 mg, 8-hourly,^{16,40} with much variability reported for the clearance and half-life of meropenem in this group. At our ICU, the dose interval for meropenem was routinely increased from every 8 hours to every 12 hours for patients with renal impairment, including those receiving haemofiltration. Patients who were not receiving haemofiltration had a longer meropenem half-life than those who were receiving haemofiltration but would have achieved a greater % T_{MIC} with a standard (8-hourly) dosing interval.

Our study has some limitations. It was performed in a single institution with a small number of patients. Given the intensive nature of the blood sampling for determination of plasma meropenem concentrations in this study, it is unlikely that larger scale studies will be able to be easily performed, and this is one of the reasons why Monte Carlo simulation is commonly used in this area. Our study was heterogeneous in terms of patients recruited, their renal function and their requirements for haemofiltration, and in terms of patients with increased CrCl. The dosing schedule was also varied according to renal status, but the cross-over design will have mitigated some of these issues. CrCl was estimated from serum creatinine concentration and use of the Cockcroft–Gault equation, rather than from urinary and ultrafiltration measurement of creatinine. As serum creatinine may not have been at steady state in these patients, this calculation may have underestimated or overestimated their actual clearance. However, these patients had all been inpatients in the ICU for at least 48 hours at the time of the study and were relatively clinically stable. Due to the nature of our study, no conclusions can be drawn about clinical outcome. Serum measurements were performed at steady state, which also limits the extrapolation of results to the early phase of sepsis, during which PK parameters may be different.⁴⁰

One of the strengths of our study is its broad inclusion criteria. Patients in this study represented real-world ICU patients. As shown in Figure 1, there was marked interindividual variation in the time to achieve plasma concentrations of

meropenem likely to be inhibitory, and in the % T_{MIC} . This variation is obscured to some extent by only considering summary statistics such as the median. Patients likely to have a less optimal % T_{MIC} can be predicted to some extent (eg, young patients and patients with high calculated CrCl), but our data underline the need to consider appropriate dosing in not only these individuals but also in older patients and those receiving haemofiltration. Appropriate dosing of antibiotics in ICU patients, especially those with renal failure and receiving renal replacement therapy, is an evolving area. This study adds to the impetus to obtain rapid, accurate, plasma drug concentrations in critical care, for all antibiotics, not just a select few such as vancomycin and gentamicin.

Conclusions

Our study shows that, overall, an extended 3-hour infusion with meropenem 500 mg achieves a similar PK–PD profile to that of 1000 mg infused over 30-minutes, but neither regimen is likely to be effective in all patients with life-threatening infections caused by pathogens with MICs above 2 mg/L. Patients with increased CrCl are especially at risk of poor target attainment. Patient variation suggests the need for individualised dosing, guided by estimated CrCl and perhaps even the use of real-time drug concentration monitoring, for patients with serious infections with gram-negative organisms with high MICs.

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Competing interests

None declared.

Author details

Katherine M Langan, Infectious Diseases Registrar^{1,2}

Jovan Jacob, Analytical Chemist³

Jian Li, Professor and NHMRC Senior Research Fellow³

Roger L Nation, Professor of Drug Disposition and Dynamics³

Rinaldo Bellomo, Director of Research^{2,4}

Benjamin Howden, Microbiologist^{1,2}

Paul D R Johnson, Deputy Director^{1,2}

1 Department of Infectious Diseases, Austin Health, Melbourne, VIC, Australia.

2 Department of Medicine, University of Melbourne, Melbourne, VIC, Australia.

3 Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia.

4 Department of Intensive Care Medicine, Austin Health, Melbourne, VIC, Australia.

Correspondence: rinaldo.bellomo@austin.org.au

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Appendix. This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Supplementary table 1. Demographic data of ten critically ill patients receiving sequential meropenem 1000 mg, 30 min infusion and 500 mg, 3 hour infusion^a

Patient number	Age (yr)	Sex	Actual Body weight (kg)	Intensive Care Admission Diagnosis	Co-morbidities	APACHE II score	Renal Impairment, CVVHF ^a	Site of isolate, Organism isolated, Meropenem MIC (mg/L)
1	75	Male	60	Urosepsis	Parkinson's disease	18	Renal impairment but no CVVHF	Blood culture <i>Proteus mirabilis</i> MIC 0.32 mg/L
2	50	Male	88	Typhilitis post bone marrow transplant	Multiple myeloma	30	No	-
3	33	Male	98	Varicella pneumonitis	-	21	No	-
4	67	Male	113	Cardiac surgery, Bilateral forefoot amputation for ischemia	Type 2 diabetes mellitus ESRF CCF PVD Gout	25	Yes; CVVHF	Arterial line tip <i>P. aeruginosa</i> MIC 0.64 mg/L
5	20	Male	75	Multitrauma with spinal cord injury	Asthma	11	No	-
6	70	Female	77	Multitrauma with spinal cord injury	Type 2 diabetes mellitus Hypertension Asthma	17	No	Sputum <i>P. aeruginosa</i> MIC 3.0 mg/L
7	73	Male	100	Sepsis; <i>Staphylococcus aureus</i> bacteraemia	Type 2 DM Hypertension Hypercholesterolaemia TKR; OA Hemicolectomy; dysplasia	33	Yes; CVVHF	Blood culture <i>Staphylococcus aureus</i> MIC 0.47 mg/L
8	68	Female	50	Bleeding duodenal ulcer post femoral fracture	Hypertension Hypercholesterolaemia Osteoporosis	15	Yes; CVVHF but only during 3-h infusion	-
9	67	Female	75	Acute Hepatitis A with fulminant liver failure	Hypertension Hypercholesterolaemia TIAs	40	Yes; CVVHF	Wound <i>P. aeruginosa</i> MIC < 0.5 mg/L
10	65	Female	66	Septic shock; aetiology unknown	Ulcerative colitis Hypertension Hypercholesterolemia Asthma/COPD Recurrent DVT	26	No	-

^aAbbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II score; CVVHF, Continuous Venous Venous Hemofiltration; CABG, Coronary Artery Bypass Grafting; DM, Diabetes mellitus; ESRF, End Stage Renal Failure; CCF, Congestive Cardiac Failure; PVD: Peripheral Vascular Disease; TKR, Total Knee Replacement; OA, Osteoarthritis; TIAs, Transient Ischaemic Accidents; COPD, Chronic Obstructive Pulmonary Disease; DVT, Deep Vein Thrombosis.

Supplementary table 2. Pharmacokinetic parameters of meropenem in ten intensive care patients after a 1000 mg, 30 min infusion and a 500 mg, 3 hour extended infusion^a

	1000 mg infused over 30 min									500 mg infused over 3 hours								
Patient Number	CrCl (mL/min)	BFR (L/h)	UFR (L/h)	C _{max} (mg/L)	C _{min} (mg/L)	t _{1/2} (h)	AUC _{0-τ} (mg·h/L)	CL (L/h)	V (L)	CrCl (mL/min)	BFR (L/h)	UFR (L/h)	C _{max} (mg/L)	C _{min} (mg/L)	t _{1/2} (h)	AUC _{0-τ} (mg·h/L)	CL (L/h)	V (L)
1#	47.3	-	-	46.4	2.7	2.69	202.4	4.9	19.2	48.1	-	-	29.9	1.36	2.1	149.2	3.4	10.0
2	108.0	-	-	20.7	1.4	1.80	65.8	15.2	39.5	81.9	-	-	15.9	2.70	2.0	70.6	7.1	20.9
3	138.3	-	-	48.0	1.00	1.39	112.6	8.9	17.8	157.3	-	-	8.3	0.73	1.3	31.7	15.8	30.0
4*	65.6	1.2	2.0	66.5	7.5	3.90	301.6	3.3	18.6	75.6	1.2	2.0	17.6	5.61	5.7	110.2	4.5	37.4
5	171.4	-	-	40.8	< 0.5	0.64	63.3	15.8	14.6	180	-	-	7.5	< 0.5	0.1	22.9	21.9	3.9
6	107.6	-	-	19.8	0.5	1.30	63.5	15.8	29.5	90	-	-	10.3	1.1	1.5	40.8	12.3	25.6
7*	40.2	1.2	2.5	60.4	9.8	4.86	276.9	3.6	25.3	45.2	1.2	2.5	24.3	7.4	5.7	160.0	3.1	25.7
8*	44.0	-	-	72.2	7.2	3.74	213.1	4.7	25.4	65	1.2	2	28.0	3.5	3.2	126.6	4.0	18.5
9*	89.0	1.2	2.0	109.7	7.9	3.67	389.3	2.6	15.3	71	1.2	2.0	28.5	7.1	4.1	149.2	3.4	19.7
10	62.0	-	-	87.4	9.6	2.43	258.9	3.9	13.6	76	-	-	31.2	6.2	3.2	128.8	3.9	17.9

^aAbbreviations: CrCL, creatinine clearance; CVVHF, continuous venovenous hemofiltration; BFR, blood flow rate; UFR, ultrafiltrate rate; C_{max}, maximal measured plasma concentration; C_{min}, plasma concentration at the end of the dosing interval; t_{1/2}, elimination half-life under the plasma concentration versus time curve across the dosage interval (τ, 8 or 12 h depending on creatinine clearance as noted above); AUC_{0-τ}, area under the moment curve during the dosing interval (τ, 8 or 12 h depending on creatinine clearance as noted above); CL, total clearance; V, volume of distribution. * CVVHF and dosing interval 12 hours. # Renal impairment and dosing interval 12 hours.