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Pharmacokinetics of meropenem in critically ill patients receiving continuous venovenous haemofiltration: A randomised controlled trial of continuous infusion versus intermittent bolus administration

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ABSTRACT

The objective of this study was to describe the pharmacokinetics of meropenem, administered by continuous infusion (CI) or intermittent bolus (IB), in critically ill patients receiving continuous venovenous haemofiltration (CVVH) and to evaluate the frequency of pharmacokinetic/pharmacodynamic target attainment with each dosing strategy. This was a prospective, randomised controlled trial in critically ill patients receiving CVVH and administered meropenem by CI or IB. Serial meropenem concentrations in plasma and ultrafiltrate were measured after administration of a standard total daily dose (4 g/day on Day 1, followed by 3 g/day thereafter) on two occasions during antibiotic therapy. Meropenem pharmacokinetic parameters were calculated using a non-compartmental approach. Sixteen critically ill patients receiving CVVH concurrently treated with meropenem were randomised to CI ($n = 8$) or IB dosing ($n = 8$). IB administration resulted in higher maximum concentrations (C_{max}) [64.7 (58.9–80.3) and 64.8 (48.5–81.8) mg/L, respectively] on both sampling occasions compared with CI ($P < 0.01$ and $P = 0.04$, respectively). CI resulted a higher meropenem steady-state concentration (C_{ss}) on occasion 1 [26.0 (24.5–41.6) mg/L] compared with the minimum concentration (C_{min}) observed for IB patients [17.0 (15.7–19.8) mg/L; $P < 0.01$]. CVVH contributed to ca. 50% of meropenem total clearance in these patients. The administered meropenem doses resulted in plasma drug concentrations that were >4× the targeted susceptibility breakpoint (2 mg/L) for 100% of the dosing interval, for both groups, on both occasions. CI could be an alternative to IB for meropenem administration in critically ill patients receiving CVVH.

1. Introduction

Effective antibiotic dosing is considered one of the key interventions to reduce mortality in critically ill patients with severe sepsis or septic shock [1]. Administration by continuous infusion (CI) is one of the approaches advocated to improve β-lactam drug exposure in critical illness [2–8], particularly in an era of emerging bacterial resistance and limited availability of new antibiotics. Multiple studies have evaluated this method of β-lactam administration in various critically ill subgroups, demonstrating that CI achieves the required drug concentrations more consistently than conventional intermittent bolus (IB) dosing [6–10].

Existing literature on β-lactam CI generally excludes critically ill patients treated with renal replacement therapy (RRT), a group for which additional data are urgently required as substantial amounts of drug may be cleared by this extracorporeal technique [11]. Indeed, previous data have shown that standard carbapenem dosing regimens were insufficient for critically ill patients receiving RRT [12]. As such, CI may offer a more effective dosing option, increasing the likelihood of achieving therapeutic concentrations in this patient group.

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The objectives of this study were therefore to describe the pharmacokinetics of meropenem administered by CI or IB to critically ill patients receiving continuous venovenous haemofiltration (CVVH). We also aimed to describe the frequency of pharmacokinetic/pharmacodynamic (PK/PD) target attainment of meropenem with each method of administration.

2. Patients and methods

This was a prospective, randomised controlled pharmacokinetic study performed in a 12-bed intensive care unit (ICU) of a major tertiary hospital in Malaysia (Kuantan, Pahang, Malaysia). The study was approved by the local ethics committee, and consent to participate was obtained from the patient's legally authorised representative.

2.1. Patient selection and data collection

All adult patients (age ≥18 years) admitted to the ICU with severe sepsis or septic shock and receiving CVVH for oliguric or anuric renal impairment were eligible for enrolment. Meropenem was prescribed at the discretion of the treating physician. Patients were randomised to receive the same dose of meropenem, administered by either CI or IB, using random allocations selected from sequentially numbered opaque sealed envelopes.

2.2. Meropenem administration

All patients received meropenem (DBL™ Meropenem for Injection; Hospira Healthcare, Chennai, India). Patients in the CI group ($n = 8$) were administered a loading dose of 1 g of meropenem in 20 mL of 0.9% sodium chloride over 30 min via a central line, followed immediately by CI over 24 h (125 mg/h). Owing to stability issues, meropenem was prepared every 8 h by diluting 1 g of meropenem in 100 mL of 0.9% sodium chloride. Patients in the IB group ($n = 8$) received 2 g of meropenem as a 30-min infusion via a central line for the first dose, followed by 1 g every 8 h thereafter. In both groups, meropenem was administered using a volumetric infusion pump controller, and all patients received a total dose of meropenem of 4 g/day on Day 1 and 3 g/day thereafter.

2.3. Continuous renal replacement therapy

CVVH was performed in all patients using an Aquarius™ system (Edwards Lifesciences, Saint-Prex, Switzerland). Polysulfone®-type haemofilters with a surface area of 1.2 m^2 (Aquamax12™; Baxter Healthcare, Zurich, Switzerland) were used. In all patients, CVVH was started at least 4 h prior to the sampling period. Vascular access was obtained via the internal jugular or femoral vein using a 14-French double-lumen catheter. The ultrafiltrate rate was set at 2000 mL/h [median effluent flow rate, 30.09 mL/kg/h; interquartile range (IQR), 25.00–33.33 mL/kg/h], combining pre- and post-dilution fluid replacement at a 1:1 ratio. The targeted blood flow rate was 200 mL/min. Net fluid removal was between 50 mL/h and 100 mL/h depending on the clinical circumstance. Lactate-containing (PrismaSol®; Gambro, Sondalo, Italy) or lactate-free (Duosol™; B. Braun, Glandorf, Germany) solutions were used as the replacement solution, and the circuit was anticoagulated with heparin (100 U/mL) at the discretion of the attending physician.

2.4. Sample collection

Pharmacokinetic sampling occurred during one 8-h or 24-h dosing interval between Days 1–3 of treatment (occasion 1), and during an 8-h dosing interval between Days 4–6 of treatment (occasion 2). For each sample, 3 mL of blood was collected in a lithium heparin tube, pre-filter, at 0, 15, 30, 45, 60, 120, 240, 480 and 1440 min (CI only) and post-filter at 30, 120 and 480 min on occasion 1. For occasion 2, 3 mL of blood was collected in a lithium heparin tube, pre-filter or at arterial line, at 0, 15, 30, 45, 60, 120, 240, 480 and post-filter at 480 min. Ultrafiltrate samples were collected and measured at 120, 240, 360 and 480 min, and 3 mL aliquots were kept for analysis. All samples were immediately centrifuged at 3000 rpm for 10 min and plasma was separated and frozen at −80 °C.

2.5. Meropenem assay

Meropenem concentrations in plasma and ultrafiltrate were determined by validated assay methods on a Shimadzu Prominence (Shimadzu Corp., Kyoto, Japan) high-pressure liquid chromatography (HPLC) system at the Burns, Trauma and Critical Care Research Centre of The University of Queensland (Brisbane, Australia). The assay was conducted alongside a standard curve and quality control replicates at high, medium and low concentrations. The limit of quantification for meropenem was 0.2 mg/L and linearity was validated from 0.2 mg/L to 100 mg/L (plasma) and from 1 mg/L to 200 mg/L (ultrafiltrate). All results were within 5% for all matrices at all levels, and the assay was validated and conducted according to criteria specified by the US Food and Drug Administration (FDA) guidance on bioanalysis [13].

2.6. Pharmacokinetic analysis

Pharmacokinetic parameter values were estimated using non-compartmental methods. The area under the concentration–time curve from 0 to 8 h in plasma ($AUC_{0-8\ plasma}$) or ultrafiltrate ($AUC_{0-8\ ultrafiltrate}$) was calculated using the linear trapezoidal rule. Total body clearance (CL_{total}) was calculated as dose/$AUC_{0-8\ plasma}$. The maximum concentration for the dosing period (C_{max}) and the minimum concentration for the dosing period (C_{min}) were the observed values. The apparent terminal elimination rate constant (k_e) was determined from log-linear least-squares regression analysis of concentrations from 2 to 8 h (bolus dosing). The apparent volume of distribution during the terminal phase (V_d) was calculated as CL_{total}/k_e, and the half-life ($t_{1/2}$) was calculated as $\ln(2)/k_e$ (bolus dosing). The extraction ratio (ER) across the filter was calculated as the ratio of the meropenem post-filter blood sample concentration to the pre-filter blood sample concentration. The sieving coefficient (S_c) was calculated as the ratio of the concentration of meropenem in the ultrafiltrate to the concentration in the pre-filter blood. Clearance by CVVH (CL_{CVVH}) was calculated using the equation $CL_{CVVH} = A_{CVVH}/AUC_{0-8\ ultrafiltrate}$ (where A_{CVVH} is the total amount of meropenem recovered in the ultrafiltrate in one dosing interval). Clearance not mediated by CVVH ($CL_{non\text{-}CVVH}$) was calculated using the equation $CL_{non\text{-}CVVH} = CL_{total} - CL_{CVVH}$.

2.7. Pharmacodynamic analysis

A susceptibility breakpoint of 2 mg/L for meropenem against common pathogens, based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2013 database [14] was used to determine the frequency of PK/PD target attainment. Based on previous publications [15,16], for IB administration a plasma drug concentration ≥4× the minimum inhibitory concentration (MIC) for more than 40% of the dosing interval (40% $T_{>4\times MIC}$) was considered as a suitable PK/PD target, whereas for CI administration a plasma concentration 5× the MIC breakpoint over the entire dosing interval (100% $T_{>5\times MIC}$) was required.

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Table 1
Demographic and clinical data of patients[a]

Characteristic	Continuous infusion ($n = 8$)	Intermittent bolus ($n = 8$)	P value[b]
Sex (male/female) (n)	7/1	4/4	0.28
Age (years)	47.5 (32.0–63.3)	44.5 (29.0–60.8)	0.90
Height (cm)	166.0 (161.5–170.8)	151.0 (150.0–158.3)	0.006*
Weight (kg)	80.0 (68.5–80.0)	60.0 (50.0–63.8)	0.003*
APACHE II score	30.0 (26.5–32.5)	32.5 (29.8–37.8)	0.13
SOFA score (upon ICU admission)	15.5 (13.3–18.5)	14.5 (14.0–17.8)	0.90
SOFA score (upon study inclusion)	16.0 (13.0–16.8)	17.5 (14.8–18.8)	0.11

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit.
[a] Data are presented as median (interquartile range) unless otherwise stated.
[b] All P values were calculated using Mann–Whitney test, except for sex that used the Fisher's exact test.
* Indicates statistically significant ($P < 0.05$).

2.8. Statistical analysis

Data were analysed using Microsoft Excel (Microsoft Corp., Redmond, WA) and GraphPad Prism® v.6.0 (GraphPad Software Inc., San Diego, CA). Continuous data are presented as the median (IQR). A Fisher's exact test was used to compare categorical data, and a Mann–Whitney test for continuous data. A Wilcoxon signed-rank test was used for paired data. A P value of <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics

In total, 16 patients were enrolled, with 8 randomised to CI and 8 to IB. Study participants' demographics, illness severity and anthropometric data are presented in Table 1. There were no significant differences between the groups in terms of age, sex, severity of illness and organ dysfunction, although those receiving CI has greater weight and height (see Table 1). Seven patients in the CI group and six in the IB group were still in the ICU on the second occasion of sampling. However, of these, only three patients in the CI group and five in the IB group were receiving ongoing CVVH.

3.2. Meropenem concentrations

The observed plasma concentration–time profiles for meropenem on occasion 1 of sampling (Days 1–3 of treatment) and occasion 2 (Days 4–6 of treatment) in patients receiving CI and IB are shown in Fig. 1. IB administration resulted in a significantly higher C_{max} on both occasions. Conversely, CI resulted in a significantly higher steady-state concentration (C_{ss}) compared with the C_{min} observed in IB patients on occasion 1 only (Table 2).

Table 3 summarises the pharmacokinetic parameters for patients receiving CVVH on two sampling occasions. Overall, the parameter estimates were numerically higher on occasion 1 for both CI and IB, except for CL_{total}, ER and $CL_{non\text{-}CVVH}$, as well as S_c in patients who received IB. However, all differences were statistically insignificant ($P > 0.05$) when comparing paired data. The median (IQR) meropenem V_d and $t_{1/2}$ in patients who received IB administration were 0.43 (0.40–0.50) L/kg and 4.4 (4.1–5.1) h, respectively, however these data were unable to be calculated in patients who received CI.

3.3. Pharmacokinetic/pharmacodynamic target attainment

Overall, the meropenem dosing regimen used in this study resulted in plasma concentrations that were >4× the targeted susceptibility breakpoint (2 mg/L) for 100% of the dosing interval in patients receiving IB administration on both occasions of sampling. In the CI group, the plasma concentrations were all >10× the susceptibility breakpoint throughout the entire dosing interval on both occasions of sampling.

4. Discussion

This prospective study of meropenem pharmacokinetics in critically ill patients receiving CVVH has demonstrated that CI produces

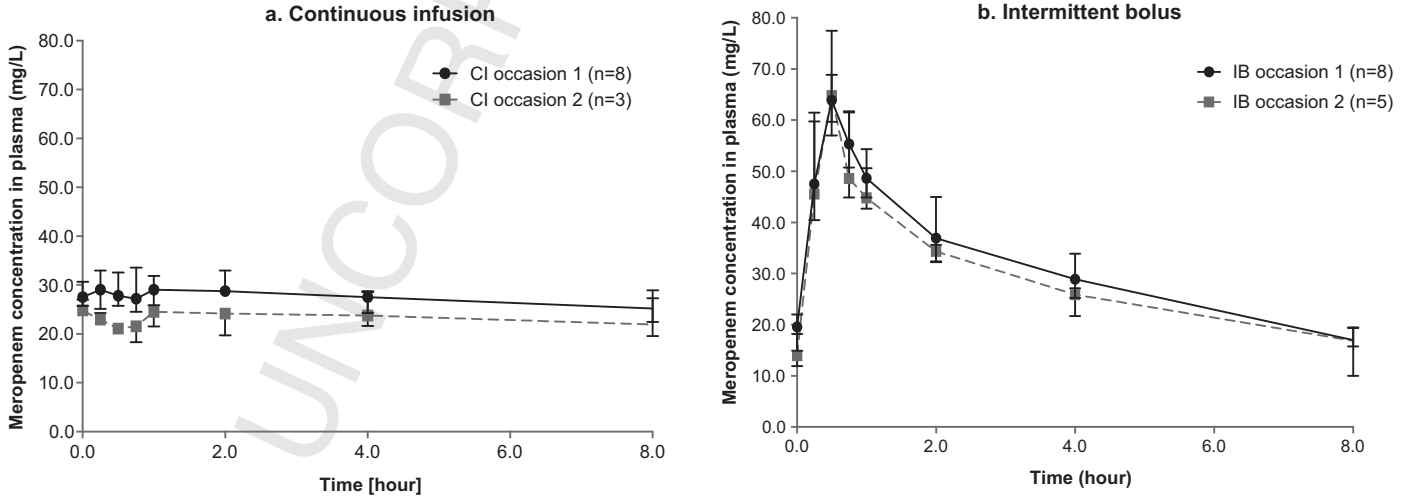

Fig. 1. Concentration–time profiles of meropenem in plasma (median and interquartile range) at an 8-h dosing interval during occasion 1 (Days 1–3, cumulative meropenem doses received = 3–4 g) and occasion 2 (Days 4–6, cumulative meropenem doses received = 9–10 g) by (a) continuous infusion and (b) intermittent bolus administration.

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Table 2
Meropenem pharmacokinetic parameters between continuous infusion (CI) and intermittent bolus (IB) dosing.

Parameter	Occasion 1 (Days 1–3)[a]		*P* value[b]	Occasion 2 (Days 4–6)[a]		*P* value[b]
	CI ($n=8$)	IB ($n=8$)		CI ($n=3$)	IB ($n=5$)	
C_{max} (mg/L)	34.51 (28.97–47.10)	64.66 (58.89–80.33)	0.0006*	24.80 (22.69–33.36)	64.80 (48.45–81.80)	0.04*
C_{min} or C_{ss} (mg/L)	25.96 (24.51–41.64)	16.99 (15.67–19.83)	0.003*	21.91 (17.18–32.64)	16.86 (9.73–19.72)	0.14
$AUC_{0-8\ plasma}$ (mg h/L)	215.28 (195.95–250.35)	250.82 (215.48–294.79)	0.27	186.30 (144.71–241.03)	234.79 (174.53–288.36)	0.36
CL_{total} (mL/kg/min)	0.96 (0.86–1.01)	1.13 (0.88–1.60)	0.19	1.12 (0.86–1.69)	1.29 (1.07–1.49)	0.86
S_c	1.02 (0.93–1.14)	1.10 (1.04–1.31)	0.15	0.92 (0.81–1.07)	1.21 (1.02–1.40)	0.14
ER	0.89 (0.85–1.01)	0.95 (0.86–1.02)	0.70	0.93 (0.86–0.96)	0.97 (0.88–1.09)	0.45
$AUC_{0-8\ ultrafiltrate}$ (mg h/L)	188.44 (182.93–208.80)	226.70 (192.08–342.25)	0.16	147.60 (122.64–218.28)	179.29 (167.39–288.55)	0.25
A_{CVVH} (mg)	442.44 (410.92–481.34)	482.00 (422.06–540.08)	0.49	346.71 (335.51–482.43)	429.98 (378.85–576.02)	0.25
CL_{CVVH} (mL/kg/min)	0.49 (0.43–0.58)	0.58 (0.52–0.67)	0.06	0.49 (0.46–0.67)	0.66 (0.56–0.67)	0.50
$CL_{non\text{-}CVVH}$ (mL/kg/min)	0.45 (0.38–0.56)	0.55 (0.32–1.03)	0.56	0.63 (0.40–1.02)	0.63 (0.40–0.92)	0.85

C_{max}, maximum concentration; C_{min}, minimum concentration; C_{ss}, concentration at steady state; $AUC_{0-8\ plasma}$, area under the concentration–time curve from 0 to 8 h in plasma; CL_{total}, total clearance; S_c, sieving coefficient; ER, extraction ratio; $AUC_{0-8\ ultrafiltrate}$, area under the concentration–time curve from 0 to 8 h in ultrafiltrate; A_{CVVH}, total amount of meropenem recovered in ultrafiltrate in one dosing interval; CL_{CVVH}, clearance by continuous venovenous haemofiltration; $CL_{non\text{-}CVVH}$, clearance not mediated by continuous venovenous haemofiltration.

[a] Data are presented as the median (interquartile range).
[b] *P* values were calculated using the Mann–Whitney test.
* Indicates statistically significant ($P<0.05$).

a significantly higher C_{ss} compared with the C_{min} observed with IB administration when samples were drawn between Days 1–3 of therapy. The dosing regimen chosen for this study is the same as that recommended by the product information for use in patients with 'normal' renal function. For both methods of administration, this dose resulted in meropenem plasma concentrations that easily met the chosen PK/PD targets and were in fact greater than 4× MIC for the entire dosing interval when considering a susceptibility breakpoint of 2 mg/L. These results demonstrate that lower doses overall of meropenem could be used with the RRT settings [median (IQR) effluent flow rate, 30.09 (25.00–33.33) mL/kg/h] used in this study.

In patients who continued to receive CVVH on Days 4–6, meropenem concentrations tended to be lower than those observed earlier during treatment (Days 1–3). These changes were not statistically significant, although the fact many patients were not eligible for sampling on occasion 2 (due to discontinuation of RRT) limits this analysis. Temporal variability in pharmacokinetic parameters can also be related to a number of patient factors, including recovering native renal function. Unfortunately, quantifying such changes remains problematic, as ongoing RRT will confound the interpretation both of plasma biochemistry and of mathematical estimates of renal function. However, $CL_{non\text{-}CVVH}$ improved during occasion 2 sampling both in the CI and IB groups, which might indicate recovering of intrinsic renal function or upregulation of non-renal elimination pathways. For treatment of pathogens with higher MICs, this could represent an advantage for CI in terms of more consistent achievement of therapeutic concentrations, although this observation appears to be more dependent on dose rather than infusion duration.

The observed median meropenem CL_{total} was similar to that reported in previous studies [17–21]. Of note, CVVH accounted for ca. 50% of meropenem CL_{total}, either administered by CI or IB, which is also in agreement with previous work [22,23]. In comparison with data derived from studies using similar continuous renal replacement therapy (CRRT) intensity [21,24,25], we found that the impact of extracorporeal clearance was slightly higher in this study. This could be explained by differing patient factors, including the presence of residual native renal function, as described in previous reports [24,26]. This is highly likely given that in this study cohort, all patients were oligo-anuric, such that significant intrinsic renal clearance would be very unlikely.

Despite reported physiological differences in Asian patients compared with Western patients [27], the observed median V_d in patients who received IB dosing was comparable with previous findings in critically ill patients receiving variable CRRT settings (0.30–0.50 L/kg) [12,17–19,21,22,28,29].

The dosing regimen used in this study easily achieved the selected PK/PD targets for meropenem administered by either CI or IB. The result suggests that in critically ill patients receiving

Table 3
Meropenem pharmacokinetics in patients continuing to receive continuous venovenous haemofiltration on both occasions.

Parameter	Continuous infusion ($n=3$)[a]		*P* value[b]	Intermittent bolus ($n=5$)[a]		*P* value[b]
	Occasion 1	Occasion 2		Occasion 1	Occasion 2	
C_{max} (mg/L)	37.34 (28.87–37.40)	24.80 (22.69–33.36)	0.25	64.97 (61.42–86.92)	64.80 (48.45–81.80)	0.31
C_{min} or C_{ss} (mg/L)	27.75 (26.41–32.39)	21.91 (17.18–32.64)	0.50	19.12 (16.78–24.42)	16.86 (9.73–19.72)	0.13
$AUC_{0-8\ plasma}$ (mg h/L)	231.38 (211.11–256.67)	186.30 (144.71–241.03)	0.25	282.35 (250.82–351.09)	234.79 (174.53–288.36)	0.13
CL_{total} (mL/kg/min)	0.98 (0.87–1.01)	1.12 (0.86–1.69)	0.50	0.98 (0.84–1.14)	1.29 (1.07–1.49)	0.13
S_c	0.94 (0.92–1.05)	0.92 (0.81–1.07)	0.75	1.08 (0.95–1.27)	1.21 (1.02–1.40)	0.31
ER	0.88 (0.84–0.88)	0.93 (0.86–0.96)	0.50	0.95 (0.78–1.06)	0.97 (0.88–1.09)	0.81
$AUC_{0-8\ ultrafiltrate}$ (mg h/L)	199.00 (183.62–212.07)	147.60 (122.64–218.28)	0.50	247.00 (194.45–373.27)	179.29 (167.39–288.55)	0.06
A_{CVVH} (mg)	465.63 (448.47–486.57)	346.71 (335.51–482.43)	0.50	522.55 (482.01–666.66)	429.98 (378.85–576.02)	0.13
CL_{CVVH} (mL/kg/min)	0.51 (0.46–0.60)	0.49 (0.46–0.67)	0.75	0.65 (0.50–0.68)	0.66 (0.56–0.67)	0.63
$CL_{non\text{-}CVVH}$ (mL/kg/min)	0.42 (0.38–0.50)	0.63 (0.40–1.02)	0.50	0.34 (0.22–0.56)	0.63 (0.40–0.92)	0.19

C_{max}, maximum concentration; C_{min}, minimum concentration; C_{ss}, concentration at steady state; $AUC_{0-8\ plasma}$, area under the concentration–time curve from 0 to 8 h in plasma; CL_{total}, total clearance; S_c, sieving coefficient; ER, extraction ratio; $AUC_{0-8\ ultrafiltrate}$, area under the concentration–time curve from 0 to 8 h in ultrafiltrate; A_{CVVH}, total amount of meropenem recovered in ultrafiltrate in one dosing interval; CL_{CVVH}, clearance by continuous venovenous haemofiltration; $CL_{non\text{-}CVVH}$, clearance not mediated by continuous venovenous haemofiltration.

[a] Data are presented as the median (interquartile range).
[b] *P* values were calculated using the Wilcoxon signed-rank test, which compares paired data from patients sampled on both occasions.

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CVVH, choice of dose rather than mode of administration may be the more important consideration for clinicians. Earlier studies of meropenem in CRRT demonstrated that lower meropenem doses (e.g. 1–2 g/day) rarely enabled concentrations to be maintained above higher MICs (e.g. >2 mg/L) [18,19,23,24,29], supporting the need for more aggressive meropenem dosing in this population [12]. Interestingly, despite higher meropenem dosing (e.g. 3 g/day) in patients receiving higher intensity CRRT, this was still suboptimal for the desired therapeutic target [22].

Importantly, the current study has highlighted that unselected application of meropenem CI in the ICU is unlikely to deliver additional benefits in some patient groups, such as those receiving CVVH. However, given the varying effects of different CRRT settings on meropenem clearance [22,30], dose individualisation based on individual patient circumstances should still be considered the best approach for optimal dosing.

We wish to acknowledge the following limitations. First, this was a single-centre study from a patient population different to that encountered in other regions. Despite this, we believe these data provide useful insights into this area of practice. Second, local ICU management may be different to that used in other institutions and therefore any recommendation from this work may not be directly transferable to other ICU populations. Third, the EUCAST database was used to evaluate achievement of the PK/PD index during meropenem treatment and this may underestimate the scenario in a clinical data set. However, in the absence of these data locally, these susceptibility breakpoints are a useful guide for antibiotic dosing. Finally, we did not specifically measure intrinsic renal function, and therefore other than by examining $CL_{non\text{-}CVVH}$, we cannot reliably quantify changes in intrinsic renal function over time.

5. Conclusion

CI administration resulted in more rapid and sustained meropenem concentrations compared with IB. The dosing regimen used in this study was associated with achievement of the desired meropenem PK/PD target both for CI and IB, suggesting that a lower dose could be considered in this CRRT setting if susceptible pathogens are present. If more resistant pathogens are being targeted then CI is likely to result in more consistent achievement of PK/PD targets.

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Competing interests

None declared.

Ethical approval

The lead site was Ministry of Health Malaysia, with ethical approval granted by the Medical Research Ethics Committee [NMRR-12-573-12765, December 2012].

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