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Meropenem dosing optimization on day 1 and steady state in critically ill patients without significant renal impairment

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This study aimed to characterize meropenem pharmacokinetics and optimise dosing for the initial and steady state in critically ill patients. Adult patients receiving meropenem were recruited, with sampling performed on days 1 (Occasion 1) and 3 (Occasion 2) of therapy. A composite target of free drug concentrations above the minimum inhibitory concentration for the entire dosing interval (100%fT > MIC) and a concentration below the toxicity threshold of 45 mg/L was used. Thirty-seven patients, with a median age of 52 years, and a median estimated creatinine clearance (CLcr) and CKD Epidemiology Collaboration (CKD-EPI) estimated glomerular filtration rate (eGFR) of 68.6 mL/min and 78.2 mL/min/1.73 m^2, respectively, were recruited. Twenty-four patients reached the composite target on Occasion 1, and 21 on Occasion 2. No significant factors influenced target attainment on Occasion 1, but plasma albumin, CLcr, recent surgery, and infusion methods significantly influenced it on Occasion 2. A two-compartment model with first-order elimination best characterized meropenem's plasma pharmacokinetics, with CKD-EPI eGFR and recent surgery significantly affecting clearance. Continuous infusion achieved the highest probability of target attainment in dosing simulations for isolates with MIC of 2–8 mg/L. Our study demonstrates that renal function, recent surgical interventions, and infusion methods should be considered in optimizing meropenem dosing in critically ill patients.

Keywords Beta-lactam antibiotics, Continuous infusion, Pharmacokinetics, Pharmacodynamics, Meropenem, Sepsis

Meropenem, a broad-spectrum antibiotic, is frequently used in the intensive care unit (ICU). Its effectiveness against a wide array of bacteria, such as *Pseudomonas aeruginosa*, ampC β-lactamase-producing, and extended-spectrum β-lactamase (ESBL)-producing *Enterobacterales*, makes it an ideal choice as an empiric and targeted antibiotic in ICU. It has been identified as the most effective agent among commonly used beta-lactam antibiotics for nosocomial infections in the Optimizing Pharmacodynamic Attainment using the MYSTIC Antibiogram (OPTAMA) program[1].

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Nevertheless, treatment success hinges not only on the antibiotic spectrum of activity, but also on achieving early therapeutic concentrations through timely initiation of dose-optimized antibiotics. Achieving this in ICU patients can be challenging because meropenem has been reported to exhibit variable plasma concentrations in this population[2–4]. Mechanical and pharmacological interventions, as well as physiological changes, can increase its volume of distribution and alter its clearance, potentially leading to either subtherapeutic or supratherapeutic concentrations[5]. Numerous studies have reported this problem, with a significant proportion of ICU patients failing to achieve the pharmacokinetic/pharmacodynamic (PK/PD) target for maximal meropenem activity for treating severe infections[2,3,6].

Based on earlier pre-clinical infection models, meropenem exhibits optimal antibacterial activity when free drug concentrations remain above the MIC for at least 40% of the dosing interval (40% $fT_{>MIC}$)[7]. However, more aggressive PK/PD targets have been recommended for critically ill patients with severe infections, ranging from 100% $fT>_{MIC}$ to 100% $fT>_{4\ X\ MIC}$[8–11]. Prolonged infusions have been shown to achieve these targets more effectively than intermittent infusions[12]. Furthermore, a recent randomized controlled trial and associated meta-analysis have described reduced mortality with prolonged infusions over intermittent infusions[13,14]. It is likely that early and sustained achievement of effective concentrations will increase the likelihood of positive clinical outcomes in critically ill patients, however little pharmacokinetic data over the course of treatment is available to inform dosing.

This study aimed to optimize initial and steady-state dosing of meropenem in critically ill patients. The objectives included identifying key factors that contribute to target attainment, describing the population pharmacokinetics of meropenem in this patient group, and determining the most effective dosing regimens.

Results

Patient demographics and baseline characteristics

In this study, thirty-seven critically ill patients were recruited, and the majority were from SASMEC (n = 17), followed by HUSM (n = 15) and UMMC (n = 5). The median age of participants was 52 (interquartile range, IQR 40–62), with male predominance (20, 54.1%). Median weight and body mass index (BMI) were 63 (IQR 60–70) kg and 24 (IQR 21–26) kg/m^2, respectively. The median baseline creatinine was 97 (IQR 60–118) µmol/L. Median CLcr and CKD-EPI eGFR were 68.6 (IQR 41.4–99.6) mL/min and 78.2 (IQR 48.7–112.9) mL/min/1.73 m^2, respectively. The most common infection was pneumonia (25, 67.6%) with bacteremia present in 12 (32.4%) patients. Most patients received 1 g meropenem every 8 h via extended (n = 15) or continuous (n = 17) infusion. Table 1 presents the patients' demographics, baseline characteristics, and meropenem dosing regimens.

A total of 337 plasma samples across two sampling occasions were collected from 37 critically ill patients. Twenty-six patients were sampled across two occasions. Total meropenem concentrations ranged between 1.26 to 76.60 mg/L on Occasion 1 and between 0.21 mg/L to 52.16 mg/L on Occasion 2. Marked variability (CV of $\geq$ 42%) in concentrations was observed across sampling time points and sampling occasions (Fig. 1).

PK/PD target attainment

Twenty-nine patients were included in the PK/PD target attainment analysis on Occasion 1, and 26 were included on Occasion 2. Overall, 26 patients (90%) achieved 100% $fT_{>MIC}$ on Occasion 1, and 21 patients (81%) achieved 100% $fT_{>MIC}$ on Occasion 2. For patients who were assessable on both Occasions 1 and 2 (n = 17), 14 (82%) patients achieved 100% $fT_{>MIC}$. Two patients (7%) demonstrated toxic meropenem concentrations on Occasion 1, and no patients demonstrated toxic meropenem concentrations on Occasion 2. Overall, 24 (83%) patients achieved the pre-defined therapeutic concentration range on Occasion 1, and 21 patients (81%) on Occasion 2.

On Occasion 1, there were no differences in patient characteristics and treatment-related variables between those who achieved the composite PK/PD target and those who did not (Tables 2 and 3). However, on Occasion 2, plasma albumin concentrations, estimated creatinine clearance (CLcr) calculated by Cockcroft-Gault equation, recent surgery within the previous 24 h, and meropenem dosing and infusion methods influenced the target attainment.

Pharmacokinetic model building

A two-compartment model with first-order elimination best described the time course of meropenem in plasma. The model was parameterized as clearance (CL in L/hr), volume of distribution of central compartment (V1 in L), volume of distribution of peripheral compartment (V2 in L), and intercompartmental clearance (Q in L/h). All parameters were log-transformed. Between-subject variability (BSV) was estimated for CL, V1, and Q, and between-occasion variability (BOV) was estimated for CL. A combined error model described residual unexplained variability.

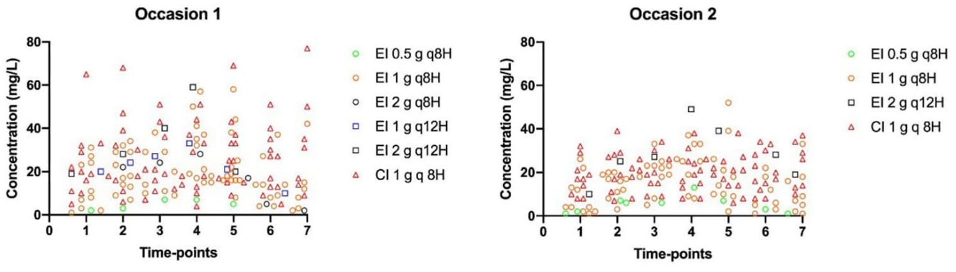
During covariate testing, the inclusion of CKD-EPI eGFR effect (normalized to the population median value of 97 mL/min) on meropenem CL improved the model fit (decreasing the OFV by 28.86 points and reducing BSV on CL from 56 to 35%). The addition of previous surgery in the last 24 h on meropenem CL resulted in further model improvement (decreasing the OFV by 12.39 points and reducing BSV on CL from 35 to 27%). The relationships were best described as shown in the equations below:

$$CL = CLpopx\left(\frac{eGFR}{97}\right)^{0.58}$$

where CL is the estimated meropenem clearance in a given individual (in L/hr), CL_{pop} is the typical value of meropenem clearance in the population, and eGFR is the individual's estimated glomerular filtration rate based on the CKD-EPI equation (in mL/min).

Characteristics	All patients (N = 37)
Age (in years)	52 (40–62)
Female, n (%)	17 (46)
Weight (in kg)	63 (60–70)
BMI (in kg/m^2)	24 (21–26)
Serum creatinine (μmol/L) on ICU admission	97 (60–118)
Estimated renal function on ICU admission	
Cockroft–Gault CLcr (in mL/min)	68.6 (41.4–99.6)
CKD-EPI eGFR (in mL/min/1.73 m^2)	78.2 (48.7–112.9)
MDRD eGFR (in mL/min/1.73 m^2)	68.2 (44.0–106.7)
Albumin on ICU admission (in g/L)	23 (19–27)
Hypoalbuminaemia[b], n (%)	21 (57)
APACHE II score on ICU admission	14 (12–20)
SOFA score on ICU admission	6 (4–9)
Mechanical ventilation, n (%)	28 (76%)
Primary site of infection, n (%)	
Lungs	25 (67.6)
Genitourinary	4 (10.8)
Intraabdominal	3 (8.1)
Skin and soft tissue	3 (8.1)
Others	2 (5.4)
Meropenem dosing regimens, n (%)	
0.5 g q8H	2 (5)
1 g q8H	32 (86)
2 g q8H	1 (3)
1 g q12H	1 (3)
2 g q12H	1 (3)
Meropenem administration method, n (%)	
Extended infusion[c]	20 (54)
Continuous infusion[d]	17 (46)

Table 1. Baseline demographic, clinical characteristics, and treatment details[a]. APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaborative, CLcr = creatinine clearance, eGFR = estimated glomerular filtration rate, ICU = intensive care unit, MDRD = Modification of Diet in Renal Disease, q8H = every 8 h, q12H = every 12 h, SOFA = Sequential Organ Failure Assessment. [a]Data are presented as medians (interquartile range) or counts (percentage). [b]Hypoalbuminaemia was defined as a plasma albumin level of less than 25 g/L. [c]Extended infusion was defined as meropenem infusion between 3 to 4 h. [d]Loading dose of 1 g of meropenem infused over 30 to 60 min was administered prior to continuous infusion.



EI = extended infusion (3 – 4 hours); CI = continuous infusion.

Fig. 1. Total meropenem concentrations by sampling occasion. EI = extended infusion (3–4 h); CI = continuous infusion.

	Occasion 1[a]			Occasion 2[b]		
Patient characteristic	**Target attainment (n = 24)**	**Non-target attainment (n = 5)**	**p value[c]**	**Target attainment (n = 21)**	**Non-target attainment (n = 5)**	**p value[c]**
Age (in years)	57 (42–62)	56 (46–68)	0.795	52 (44–64)	46 (37–62)	0.435
Weight (in kg)	64 (60–70)	70 (60–70)	0.727	60 (45–65)	65 (60–70)	0.358
Body mass index (in kg/m^2)	23.5 (21–27.5)	26 (24–27)	0.338	23 (20–25)	24 (23–26)	0.180
Female, n (%)	11 (46)	1 (20)	0.286	7 (33)	2 (40)	0.778
APACHE II (on admission)	13.5 (12–19)	17 (17–17)	0.434	14 (13–20)	14 (9–17)	0.472
SOFA score (on sampling day)	6 (4–9.5)	7 (7–7)	0.839	6 (5–10)	3 (2–7)	0.124
Plasma albumin (in g/dL)	21.5 (18–25)	27 (23–29)	0.125	22 (19–26)	30 (27–31)	**0.013***
Estimated renal function						
Cockroft–Gault CLcr (in mL/min)	54.5 (34.5–98.5)	77 (68–122)	0.225	48 (40–100)	114 (76–155)	**0.025***
CKD-EPI eGFR (in mL/min/1.73 m^2)	59 (38.5–104.5)	97 (66–116)	0.341	80 (45–113)	108 (101–123)	0.097
MDRD eGFR (in mL/min/1.73 m^2)	57.5 (37.5–134.5)	105 (62–135)	0.402	72 (43–125)	179 (105–185)	0.054
Pre-ICU stay (in days)	1 (1–3)	1 (1–15)	0.683	1 (1–2)	1 (1–15)	0.426

Table 2. Patient characteristics and treatment-related variables differences by pharmacokinetic/pharmacodynamic (PK/PD) target attainment. APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, CKD-EPI = Chronic Kidney Disease Epidemiology Collaborative, CLcr = creatinine clearance, eGFR = estimated glomerular filtration rate, ICU = intensive care unit, MDRD = Modification of Diet in Renal Disease, SOFA = Sequential Organ Failure Assessment. [a]For non-target attainment, 3 patients demonstrated sub-optimal concentrations and 2 patients demonstrated toxic concentrations. [b]For non-target attainment, all patients demonstrated sub-optimal concentrations. [c]Continuous data were compared using the Mann–Whitney U-test, and categorical data were compared using the Pearson chi-square test or Fisher's exact test as appropriate. The value in bold with an asterisk (*) indicates statistical significance.

	Occasion 1[a]			Occasion 2[b]		
Characteristic	**Target attainment (n = 24)**	**Non-target attainment (n = 5)**	**p value[c]**	**Target attainment (n = 21)**	**Non-target attainment (n = 5)**	**p value[c]**
Mechanical ventilation, n (%)	17 (71)	3 (60)	0.634	18 (86)	3 (60)	0.190
Surgery in previous 24 h of the first PK sampling, n (%)	6 (25)	2 (40)	0.495	5 (24)	4 (80)	**0.018***
Presence of shock (on sampling day), n (%)	12 (50)	3 (60)	0.684	9 (43)	1 (20)	0.345
Use of inotrope (on sampling day), n (%)	12 (50)	3 (60)	0.684	8 (38)	1 (20)	0.445
Administration method, n (%)						
Extended infusion	14 (82)	3 (18)	0.945	9 (64)	5 (36)	**0.021***
Continuous infusion	10 (83)	2 (17)		12 (100)	0 (0)	
Dosing regimen, n (%)						
0.5 g q8H	0 (0)	1 (100)	0.244	0 (0)	2 (100)	**0.010***
1 g q8H	21 (84)	4 (16)		20 (87)	3 (13)	
2 g q8H	1 (100)	0 (0)		0 (0)	0 (0)	
1 g q12H	1 (100)	0 (0)		0 (0)	0 (0)	
2 g q12H	1 (100)	0 (0)		1 (100)	0 (0)	

Table 3. Infection severity and treatment-related variables differences by pharmacokinetic/pharmacodynamic (PK/PD) target attainment. PK = pharmacokinetic, q8H = every 8 h, q12H = every 12 h. [a]For non-target attainment, 3 patients demonstrated sub-optimal concentrations and 2 patients demonstrated toxic concentrations. [b]For non-target attainment, all patients demonstrated sub-optimal concentrations. [c]Continuous data were compared using the Mann–Whitney U-test, and categorical data were compared using the Pearson chi-square test or Fisher's exact test as appropriate. The value in bold with an asterisk (*) indicates statistical significance.

$$CLsurgery = CLpop * e^{0.51}$$

where $CL_{surgery}$ is the estimated meropenem clearance in a given individual who underwent surgery in the previous 24 h (in L/hr), and CL_{pop} is the typical value of meropenem clearance in the population. The model building process is summarised in Supplementary Tables 1 and 2, and typical pharmacokinetic parameter estimates from the final model are presented in Table 4.

Basic goodness-of-fit (Figs. 2 and 3) and visual predictive check (Fig. 4) plots demonstrated that the final model adequately described the data. Results from the 1000 bootstrap runs demonstrated bootstrap median

Parameter	Estimate (%RSE)	Bootstrap median (95% CI)
Fixed effects		
CL (L/hr)	7.40 (8.75)	7.4 (6.27 to 8.92)
V1 (L)	7.5 (38.2)	7.43 (0.33 to 15.16)
V2 (L)	17.92 (12.1)	19.28 (12.31 to 27.8)
Q (L/h)	28.29 (10.64)	24.09 (8.47 to 58.28)
CKD-EPI eGFR effect on CL	0.58 (17.2)	0.5 (0.23 to 0.79)
Surgery effect on CL	0.51 (26.9)	0.58 (0.37 to 0.87)
Between-subject variability		
CL (%)	27.15 (25.2)	24.35 (3.8 to 36.10)
V1 (%)	95.93 (31.1)	94.68 (18.15 to 732.11)
Q (%)	93.49 (35.3)	79.52 (19.17 to 277.11)
Between-occasion variability		
CL (%)	28.93 (18.0)	34.12 (0.17 to 0.43)
Random error		
Additive (mg/L)	1.33 (17.0)	1.32 (0.33 to 2.82)
Proportional (%)	0.17 (7.23)	0.17 (0.11 to 0.22)

Table 4. Typical population parameter estimates from the final model and the 1000 bootstrap runs. CI = confidence interval, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CL = clearance, eGFR = estimated glomerular filtration rate, Q = intercompartmental clearance, RSE = relative standard error, V1 = volume of distribution of central compartment, V2 = volume of distribution of peripheral compartment.

values close to typical pharmacokinetic parameter estimates from the final model with narrow confidence intervals (Table 4).

Monte Carlo simulations

Two comprehensive color-coded heatmaps were generated for Occasion 1 (Supplementary Table 3) and Occasion 2 (Supplementary Table 4) to visually represent the performance of each dosing regimen, stratified by the MIC and eGFR values. In the heatmaps, green indicates a PTA of 90% or higher, yellow indicates a PTA of 80–89%, while orange and red indicate PTAs of 50–79% and less than 50%, respectively.

Continuous infusion consistently demonstrated the highest probability of optimal target attainment (i.e., ≥ 90% PTA) on both occasions (Supplementary Tables 3 and 4). This strategy achieved an optimal PTA of 73% of the simulated scenarios of various MIC values and eGFRs for both occasions. In comparison, the rates were 54.4% for both occasions for extended infusion, while intermittent infusion achieved the rates of 45.0% for Occasion 1 and 45.2% for Occasion 2 for the simulated scenarios. Notably, all simulated continuous infusion regimens achieved the optimal PTA against MIC of up to 4 mg/L at various eGFRs. The strategy was also associated with the highest likelihood of toxic meropenem concentrations, with increased rates of toxicity observed in patients with lower eGFRs and those receiving higher daily doses of meropenem. Our simulations also demonstrated that surgery within 24 h of PK sampling influenced the PTA in a "typical" patient with an CKD-EPI eGFR of 97 mL/min (Supplementary Table 5). The rates of optimal PTA attainment were 34.4% (55 of 160 simulated scenarios) in both occasions for patients who underwent surgery, compared to 51.3% (82 of 160 simulated scenarios) for patients who did not undergo the procedure. Continuous infusion consistently reached the optimal PTA against MIC values of up to 4 mg/L in both groups.

Discussion

Our study found significant variability in meropenem concentrations among patients in the local ICU population. We identified that renal function and recent surgery significantly influence meropenem clearance. Additionally, these factors, along with meropenem dosing and infusion strategies, were found to be crucial in influencing PK/PD target attainment during the first three days of therapy. Continuous infusion was the most effective strategy for achieving PK/PD targets in our simulations, but the strategy might require monitoring to avoid potential nephrotoxicity and neurotoxicity, especially when higher daily doses are used or in patients with reduced renal function.

Numerous studies have estimated population PK parameters for meropenem, with the estimated mean or median clearance for meropenem that ranged between 4.2 and 13.7 L/h, and the volume of distribution ranged between 26.0 and 43.9 L[15–19]. Therefore, the estimated clearance (7.37 L/h) and volume of distribution (28.41 L) in our study fall within these ranges. Nevertheless, there remain significant differences. For instance, Gijsen et al. reported clearance and volume of distribution of 13.7 L/h and 37.9 L respectively, despite recruiting patients without significant renal impairment similar to ours[17]. However, the study cohort was sicker, reflected by the higher median APACHE II and SOFA scores. Furthermore, our study highlights the significant impact of surgical procedures on meropenem clearance, with patients who underwent surgery demonstrating higher estimated clearance rates (12.26 L/hr) compared to those who did not (7.4 L/hr). In our study, "surgery" was defined as any surgical procedure occurring within 24 h before the first PK sampling. No patients underwent

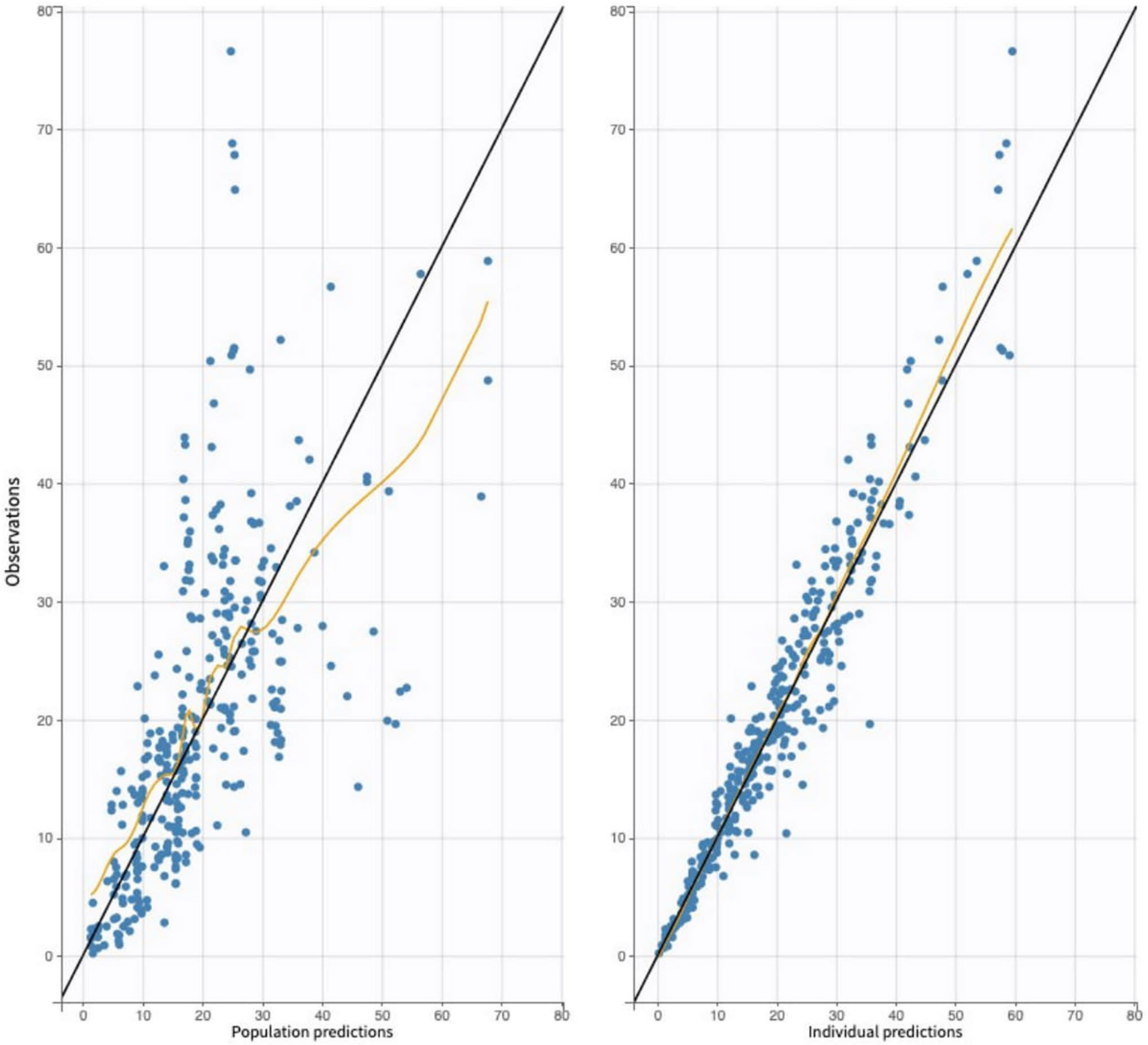


Fig. 2. Observations versus population (left) and individual (right) predictions.

surgery within 24 h of the second sampling occasion, and therefore the effect of surgery was not tested on between-occasion variability. The higher clearance observed in post-surgical patients may reflect several early postoperative physiological changes. These include a hyperdynamic circulatory state, aggressive fluid resuscitation and hemodynamic support, and increased catecholamine release due to surgical stress[20,21], all of which may contribute to augmented renal clearance (ARC). ARC, in turn, can lead to subtherapeutic drug concentrations, especially for renally eliminated agents like meropenem[22].

This observation aligns with previous reports suggesting that surgery can enhance drug elimination. For instance, Adnan et al. reported that 3.8% (2.8–5.4%) of meropenem was cleared via abdominal surgical drains, with a drain to plasma AUC ratio of 0.2[23]. Similarly, a larger study involving 384 adult patients found that surgical procedures was associated with the nonattainment of PK/PD targets for various beta-lactam antibiotics, including meropenem[24].

The conventional dosing strategy will likely result in suboptimal plasma concentrations in ICU patients[2,5,25]. To address the issue, alternative strategies of extended and continuous infusion of meropenem and other beta-lactams have been proposed[5]. Several studies have demonstrated improved attainment of optimal PK/PD targets for meropenem with these strategies, particularly with continuous infusion[12,26,27]. Despite the two most recent randomized controlled trials (RCTs), namely BLING III and MERCY, not showing a statistically significant mortality difference with continuous infusion of meropenem[13,28], there were notable positive outcomes. BLING III reported a higher rate of clinical cure in the continuous infusion group compared to the intermittent infusion group, suggesting that while the mortality benefit was not achieved, there may still be clinical advantages to continuous infusion. Moreover, the observed absolute reduction in mortality of around 2% with continuous

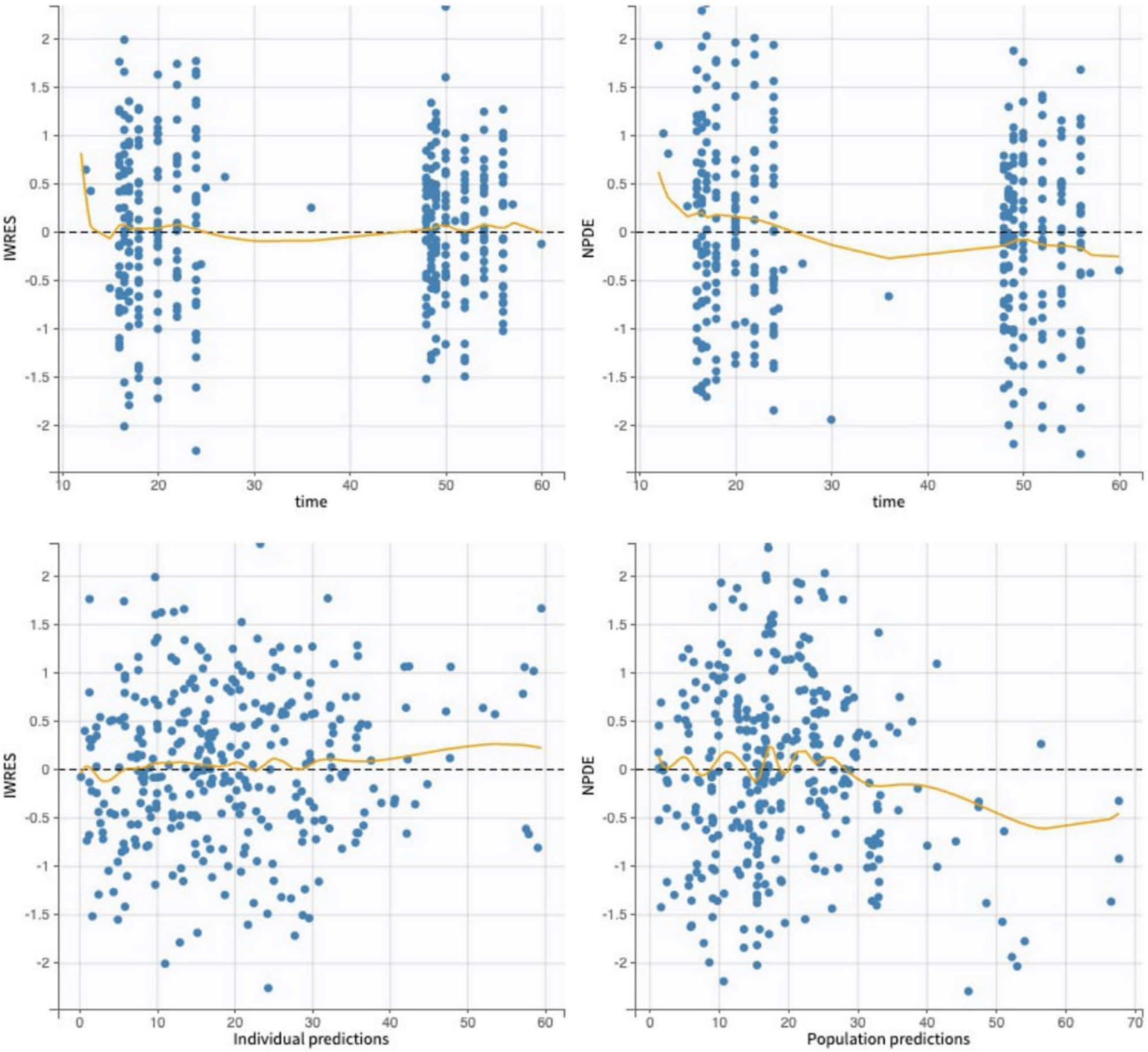


Fig. 3. Scatter plot of the residuals.

infusion in this study corresponds to a number needed to treat of 50 patients to prevent 1 death, highlighting the potential clinical significance of the strategy. The associated meta-analysis corroborates this benefit, showing a reduced risk of 90-day mortality with the strategy compared to intermittent infusion[14]. This analysis included 18 trials, with 17 comparing continuous with intermittent infusions while one comparing extended with intermittent infusions of beta-lactam antibiotics. Notably, meropenem was studied in 11 of these trials.

An et al. presented similar findings, showing improved PK/PD target attainment with continuous infusion, particularly at higher meropenem doses, but also projecting increased neurotoxicity and nephrotoxicity risks[15]. Our study offers greater detail by including more eGFR levels and additional simulations on the impact of surgical procedures on PTA rates, providing practical guidance for optimizing therapy post-surgery. These heatmaps can be invaluable for ICUs in low- and middle-income countries (LMICs) where TDM for beta-lactam antibiotics is not routine and access to new beta-lactam beta-lactamase inhibitors is limited, leading to reliance on high-dose continuous infusion meropenem-based regimens for carbapenem-resistant Gram-negative bacterial infections[29]. They would allow LMIC physicians to move the needle across the MIC values and eGFRs for specific regimen while considering the potential for toxic meropenem levels in the absence of TDM.

The study is not without limitations. First, the population models are derived from 3 local ICUs, which limits its generalizability, a known issue of published meropenem models, where their predictive performance vary considerably[30]. Second, we only assessed a conservative PK/PD target of 100%$fT_{>MIC}$. However, even with such a target, we have already demonstrated limited performance of traditional infusion strategy, where less than 50% of patients receiving intermittent infusion would meet the target. Third, surgery was recorded as

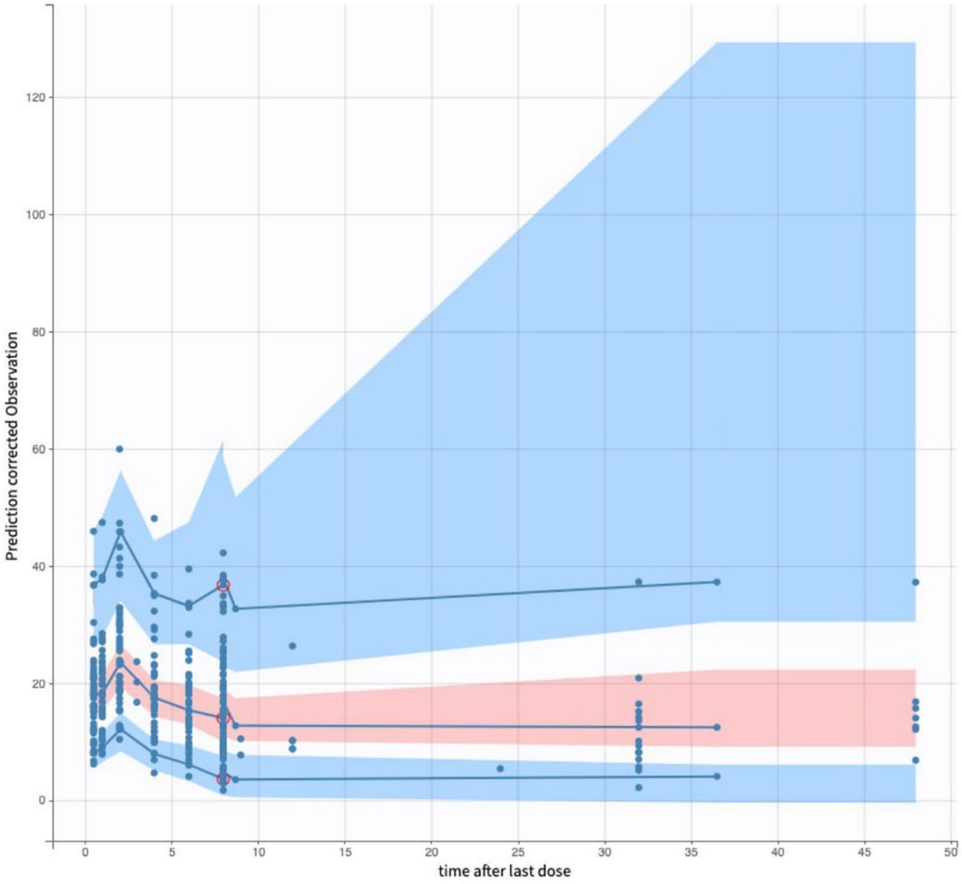


Fig. 4. Visual predictive check plot of the final population pharmacokinetic model for meropenem. The solid blue circles represent the observed data, the solid blue lines represent the 5th, 50th, and 95th percentile of the observed data, and the shaded areas represent the 95% confidence intervals of the 5th, 50th, and 95th percentiles of the simulated concentrations.

a binary variable reflecting any procedure within 24 h before the first PK sampling, without stratification by surgical type due to small subgroup sizes. The effect was only assessed at the first sampling and not evaluated for between-occasion variability. Future studies should explore the differential and temporal impacts of specific surgical procedures on meropenem pharmacokinetics. Finally, we did not assess the clinical evidence for toxicity in our patients, limiting the interpretation of the toxic concentrations projected in the study. Moreover, the threshold of 45 mg/L used as the upper limit for neurotoxicity was derived from intermittent dosing regimens[31] and may not be directly applicable to continuous infusion. However, it represents the best available evidence to date linking meropenem concentrations with the likelihood of neurotoxicity. This potential limitation has been acknowledged, and future studies are warranted to define toxicity thresholds specific to different dosing strategies.

In conclusion, our study highlighted significant variability in meropenem concentrations among ICU patients, with renal function and recent surgery being key factors influencing its clearance. While continuous infusion shows promise in meeting PK/PD targets, careful consideration of renal function and potential toxicity is crucial.

Methods

Study design and settings

A multicentre, prospective pharmacokinetic study was conducted in three ICUs in Malaysia–(i) Sultan Ahmad Shah Medical Centre (SASMEC), (ii) Hospital Universiti Sains Malaysia (USM), and (iii) University of Malaya Medical Centre (UMMC) between March 2017 and March 2018. Eligible participants were adult (≥ 18 years old) ICU patients receiving meropenem who met the Sepsis-3 criteria[32], had confirmed or suspected infections, and had a central venous or arterial line for blood collection. Patients suspected or known to be hypersensitive to beta-lactam antibiotics, pregnant patients, lactating mothers, or those with preexisting renal impairment defined as either receiving extra-corporeal renal support or having an estimated creatinine clearance of less than 30 mL/min or plasma creatinine concentration above 200 µmol/L were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice (ICH-GCP) guidelines, and local regulatory requirements. Informed consent was obtained from all participants or a legally authorized representative before they participated in the study. Individual institutional ethical approvals were obtained according to local protocols (UMMC Medical Research Ethics Committee Reg. No 2016725-4020; USM Human Research Ethics Committee Reg. No USM/JEPeM/16110528; IIUM Research Ethics Committee Reg. No IREC 2017-062). The study was registered and also approved by the Medical Research Ethics Committee Malaysia (NMRR-16237231675).

Meropenem dosing and sample collection

Meropenem dosing regimens were determined by the treating physician based on standard prescribing practices and the clinical assessment of each patient. Meropenem was typically administered as an intermittent infusion (II) over 30–60 min, extended infusion (EI) over 3–4 h, or continuous infusion (CI) over the entire dosing interval (8 h). Pharmacokinetic sampling was conducted on day 1 (Occasion 1) and day 3 (Occasion 2) of antibiotic therapy. Each patient had up to seven blood samplings on each occasion from a central line into heparinized tubes. These sampling points were distributed evenly across the dosing interval. For patients receiving meropenem every 8 h, the sampling points were immediately before the antibiotic dose was administered (T_0), followed by 30, 60, 90, 120, 240, 360, and 480 min after the start of antibiotic infusion. For patients receiving meropenem every 12 h, the sampling points were immediately before the antibiotic dose was administered (T_0), followed by 30, 60, 180, 360, 540, and 720 min after the start of antibiotic infusion.

All samples were promptly refrigerated at 4 °C and centrifuged at 3000 rpm for 10 min within 1 h to separate plasma. Subsequently, these samples were frozen at − 80 °C within 24 h of collection and were stored locally at participating institutions. The frozen plasma samples were shipped on dry ice and were then assayed at the central bioanalysis laboratory at the University of Queensland Centre for Clinical Research (UQCCR), Brisbane, Australia.

Data collection

A standardized case report form was used to collect relevant clinical data including patients' demography, baseline biochemistry results (e.g., plasma albumin and creatinine), estimated renal function (via creatinine clearance, CLcr and glomerular filtration rates, eGFR), infection site, baseline disease severity (assessed using the Acute Physiology and Chronic Health Evaluation II [APACHE II] and the Sequential Organ Failure Assessment [SOFA] scores)[24,33] and antibiotic dosing details (e.g., meropenem dosing regimen, administration method, and length of therapy). The Cockcroft-Gault CLcr[34], CKD Epidemiology Collaboration (CKD-EPI)[35], and Modification of Diet in Renal Disease (MDRD)[36] eGFR equations were used to estimate renal function. Inotrope use was defined as the administration of any inotropic agent (e.g., norepinephrine, dopamine) on the same day of meropenem PK sampling. "Surgery" in this study refers to any surgical procedures occurring within 24 h prior to the first PK sampling (Occasion 1).

Bioanalysis

Total meropenem plasma concentrations were measured using a validated ultra-high performance liquid chromatography-MS/MS (UHPLC-MS/MS) method on a Nexera UHPLC connected to an 8030 + triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan). The analysis was performed in batches, and samples were analysed concurrently with calibration standards and quality-control replicates at high (80 mg/L), medium (4 mg/L), and low (0.6 mg/L) concentrations. The assay limit for meropenem in plasma was 0.2 mg/L and linearity was established within a range of 0.2 to 100 mg/L. Precision and accuracy at three different concentrations were all within 10%. The analysis was performed in accordance with the U.S Food and Drug Administration's guidance for industry on bioanalysis[37].

PK/PD target attainment analysis

In this study, a composite PK/PD target was used, aiming to achieve 100% of the time above the minimum inhibitory concentration (100%$fT_{>MIC}$) while ensuring that a predefined toxic trough concentration thresholds was not exceeded[38]. An MIC value of 2 mg/L was chosen as this corresponds to meropenem susceptibility breakpoint for *P. aeruginosa* according to the 2024 guidelines from the Clinical and Laboratory Standards Institute (CLSI)[39] and the 2024 European Committee on Antimicrobial Susceptibility Testing (EUCAST)[40]. Therapeutic meropenem trough concentrations were defined as those between 2 and 45 mg/L, with concentrations below 2 mg/L deemed suboptimal and those above 45 mg/L considered toxic. These thresholds were chosen because 2 mg/L is the MIC breakpoint for susceptibility, and concentrations exceeding 45 mg/L were associated with neurotoxicity and nephrotoxicity[31,38]. Meropenem total concentrations were corrected for the protein binding value of 2% to determine its free concentrations[41].

Population pharmacokinetic analysis

Structural model development

Population PK analysis was performed using the nonlinear mixed-effect modeling approach using the Monolix software (version 2021R2, LIXOFT, Antony, France). This software utilizes the stochastic approximation expectation maximization (SAEM) algorithm for parameter estimation[42]. Individual estimates for PK parameters were assumed to be log-normally distributed. The between-subject variability (BSV or ω) was described using an exponential model according to the equation $\theta_j = \theta_p \times \exp(\eta_j)$, where θ_j is the estimate for a PK parameter in the jth patient as predicted by the model, θ_p is the typical population PK parameter value, and η_j is a random variable from a normal distribution with zero mean and variance ω^2, which is estimated. One- and two-compartment models with first-order elimination were compared. Several error models (constant, proportional, or combined error model) were tested to describe the residual variability (ε). An exponential variability model evaluated between-subject variability (BSV) and between-occasion variability (BOV). Model selection was based on visual inspection of goodness-of-fit (GOF) plots and numerical assessment of objective function value (OFV) and the corrected Bayesian information criteria (BICc). A reduction in the OFV of > 3.84 for one degree of freedom was considered a statistically improvement ($p < 0.05$) for a model.

Covariate model development

From the structural model, the effects of fifteen potential covariates on meropenem PK parameters were evaluated. These covariates were age, gender, weight, body mass index, APACHE II and SOFA[24] scores on sampling occasions, plasma albumin, estimated renal function by Cockcroft-Gault, CKD-EPI, and MDRD equations, pre-ICU stay before sampling, mechanical ventilation, surgery in the previous 24 h before the first sampling, septic shock, and the use of inotropes during sampling.

The continuous covariates were centered on their median values and categorical covariates were introduced as $\theta_j = \theta_{\mathrm{jTPV}} * e^{\theta_{\mathrm{COVi}} * COVi}$, where θ_j is the value of the PK parameter *j*, θ_{jTPV} is the median value of *j*, and θ_{COVi} is the parameter estimated to represent the effect of the *i*th covariate (*COVi*) when the value is 1. A stepwise covariate modelling approach was used, consisting of forward inclusion and backward elimination steps. A reduction in −2LL of at least 3.84 ($p < 0.05$) was required for inclusion, and an increase of greater than 10.83 ($p < 0.001$) for elimination. The covariate model-building process was applied systematically to all pre-specified covariates.

Model evaluation

Evaluation of the model was based on goodness-of-fit (GOF) plots, including observations versus individual and population predictions, weighted individual residuals versus individual predictions and time (IWRES), and plots of normalized prediction distribution error (NPDE) versus population predictions and time. The visual predictive check (VPC) was performed using 500 simulations with the final model. This plot shows the time course of the simulated profiles' 5th, 50th, and 95th percentiles and compares them with observed data. The accuracy of the final model was also examined using a bootstrap method. A 1000-run bootstrap resampling procedure was performed in Monolix using the Rsmlx (R Speaks 'Monolix', version 4.0.2) package in R software (version 4.1.3). The median, 2.5%, and 97.5% values obtained from the 1000 bootstrap runs for each parameter were calculated and compared to the estimates from the original data.

Dosing simulation

Based on the final population PK model parameter estimates, the probability of target attainment (PTA) for a meropenem dosing regimen to achieve 100% $fT_{>\mathrm{MIC}}$ were assessed on Occasion 1 and Occasion 2 using Monte Carlo simulations ($n = 1000$). Moreover, the simulation also examined the proportion of patients reaching potentially toxic meropenem concentrations, defined as 45 mg/L or higher.

Sixteen meropenem dosing regimens were simulated and these regimens ranged from intermittent infusion of 0.5 g meropenem every 8 h to extended infusion of 2 g meropenem every 12 h and continuous infusion of 6 g meropenem over 24 h. The PTA of each regimen was assessed for 60 possible scenarios across ten MIC values ranging from 0.125 to 64 mg/L and six levels of eGFR by the CKD Epidemiology Collaboration (CKD-EPI) at 30, 50, 70, 90, 110, and 130 mL/min. Additional dosing simulations were planned to incorporate covariates that improve the models during covariate testing. Similar to other relevant papers[15], color-coded categories were applied to visualize PTA across dosing regimens: green (≥ 90%), yellow (80–89%), orange (50–79%), and red (< 50%). These thresholds were selected based on interpretive benchmarks commonly used in PK/PD literature, where ≥ 90% PTA is considered optimal, 80–89% acceptable, and values < 80% increasingly associated with suboptimal exposure and reduced likelihood of clinical efficacy.

Statistical analysis

The data were presented as counts and percentages for categorical variables and as median values with interquartile ranges for continuous variables. Patient characteristics and treatment-related variables were evaluated for their impact on PK/PD target attainment using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. A two-sided p value of < 0.05 was considered statistically significant. All analyses were performed using Stata version 18.

Data availability

The de-identified datasets generated in this study can be accessed upon reasonable request from the corresponding author. Interested parties must submit a formal proposal and agree to the terms outlined in a data access agreement before data sharing is granted.

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Author contributions

Dr. Helmi Sulaiman and Dr Mohd H. Abdul-Aziz had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis Concept and design: Sulaiman, Abd Rahman, Hasan, Mat-Nor, Roberts, Abdul-Aziz Acquisition, analysis, or interpretation of data: all authors Drafting of manuscript: Sulaiman, Roberts, Abdul-Aziz Critical review of manuscript for important intellectual content: all authors Statistical and pharmacokinetic analysis: Sulaiman, Liu, Roberts, Abdul-Aziz Bioanalysis: Adiraju, Wallis Obtained funding: Sulaiman, Abd Rahman, Hasan, Jamal, Mat-Nor, Mazlan, Salmuna, Roberts, Abdul-Aziz Administrative, technical, or material support: Hasan, Mat-Nor, Roberts, Abdul-Aziz Supervision: Roberts, Abdul-Aziz.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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