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Original article

Pharmacokinetics of meropenem in critically ill patients in Saudi Arabia

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ABSTRACT

Background: Meropenem is commonly used in the ICU to treat gram-negative infections. Due to various pathophysiological changes, critically ill patients are at higher risk of having subtherapeutic concentrations and hence have a higher risk of treatment failure—especially in regions where gram-negative drug resistance is increasing, such as Saudi Arabia. No studies have evaluated the pharmacokinetics of meropenem in critically ill patients in Saudi Arabia. Our primary objective is to assess the percentage of patients achieving the therapeutic target for meropenem.

Methods: This prospective observational study was conducted in the ICUs of King Khalid University Hospital. Patient were included if >18 years-of-age and received meropenem for a clinically suspected or proven bacterial infection. The primary outcome was to assess the percentage of patients who achieved the pharmacokinetic/pharmacodynamic (PKPD) therapeutic target of a free trough concentration four times the MIC. The secondary outcome was to estimate the pharmacokinetics of meropenem. Pharmacokinetic analysis was performed using Monolix Suite 2020R1 (Lixoft, France).

Results: Trough concentrations were highly variable and ranged from <0.5 μg/mL to 39 μg/mL, with a mean ± SD trough concentration of 8.5 ± 8 μg/mL. Only 46% of patients achieved the therapeutic target. The only significant predictor of failing to achieve the PKPD target was augmented renal clearance.

Conclusion: In conclusion, more than half of our patients did not achieve the PKPD target. Thus, there is a need for better dosing strategies of meropenem in critically ill patients in Saudi Arabia such as extended and continuous infusion.

1. Introduction

Meropenem is a broad-spectrum antimicrobial commonly used for the treatment of hospital-acquired infections. Like other β-lactams, the activity of meropenem is time dependent and maximal therapeutic efficacy is achieved by maintaining the free drug concentration above the minimum inhibitory concentration (MIC) (Ambrose et al., 2007). Critically ill patients are at higher risk of sub and supratherapeutic concentrations due to a variety of pathophysiological changes that impact drug pharmacokinetics, such as renal and liver dysfunction, augmented renal clearance, an increased volume of distribution, organ support, renal replacement therapy, and several other factors (Roberts et al., 2014). Several studies have demonstrated that ~40–50% of patients in ICU have subtherapeutic concentrations of meropenem (Taccone et al., 2010, Tröger et al., 2012, Roberts et al., 2014, Scharf et al., 2020). In the study by Scharf et al., 39.3 % of ICU patients had subtherapeutic concentrations (Scharf et al., 2020). In the study by Huttner et al., 90 of ICU patients with augmented renal clearance subtherapeutic concentrations (Huttner et al., 2015). In the study by Roberts et al. 59% of patients had subtherapeutic concentrations (Roberts et al.,

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2014). Therapeutic drug monitoring (TDM) has been recommended as a tool to improve the dosing of β-lactams and meropenem in critically ill patients (de With et al., 2016, Muller et al., 2018, Mabilat et al., 2020). However, TDM for β-lactams is not routinely available at most institutions. The best approach to maximize efficacy would be to optimize initial dosing in combination with TDM. Optimizing the dosing of antibiotics is crucially important due to the increasing rate of drug resistance, limited number of new antibiotics and high mortality associated with hospital-acquired infections especially with gram-negative bacteria (Abdul-Aziz et al., 2020). Several studies in Saudi Arabia have reported over the last 20 years an increased prevalence of multi-drug resistant gram-negative bacteria especially carbapenem-resistant gram-negative bacteria (Al Johani et al., 2010, Balkhy et al., 2012, Yezli et al., 2014, Al-Obeid et al., 2015, Elabd et al., 2015, Zowawi et al., 2015, Zowawi 2016, Zowawi et al., 2018, Alotaibi 2019, Alhifany et al., 2020, Nasser et al., 2020). For example, the susceptibility of *Acinetobacter baumannii* to meropenem decreased from ~70% in 2006 to ~10% in 2012 (Al-Obeid et al., 2015).

When evaluating antibiotics, it is important to take both the drug concentration and susceptibility/MIC into account. Various studies have evaluated the antimicrobial susceptibility of gram-negative bacteria to meropenem in Saudi Arabia, however, to our knowledge, the pharmacokinetics of meropenem have not yet been assessed. Most published pharmacokinetic studies come from Western or east Asian countries. Ethnic differences such as bodyweight, height, fat distribution, genetics and renal function could impact the drugs pharmacokinetics (Johnson 1997, Johnson 2000, Chen 2006). Considering the increasing resistance of gram-negative bacteria and lack of pharmacokinetic studies, it is essential to evaluate and assess if the currently used doses are sufficient to achieve therapeutic concentrations in critically ill patients. Thus, the primary objective of this study is to assess the percentage of critically ill patients in Saudi Arabia achieving the therapeutic target concentration for meropenem. Our secondary objective is to estimate the pharmacokinetic parameters of meropenem in critically ill patients in Saudi Arabia.

2. Methods

2.1. Setting and patient selection

This prospective observational study was conducted in the medical and surgical critical care units of King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. Patients were recruited from July 2019 until March 2020. The KKUH Institutional Review Board approved the study; written consent was obtained from all patients or their appointed guardian. Once consented, the participants' meropenem dose was assessed by critical care clinical pharmacist —short term infusion of 0.5 g, 1 g 2 g over 0.5 or 3 h. All doses were adjusted by the patient's estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation.

Meropenem was started empirically for patients with suspected or confirmed gram negative infection. In the following days, and based on the culture results and the patients' clinical response, the decision for continuation, escalation or de-escalation was made.

Patient were included if >18 years-of-age and received meropenem for a clinically suspected or proven bacterial infection during their ICU stay. All patients with a known allergy to β-lactams, who were pregnant or breastfeeding, with burn injuries, with cystic fibrosis and with inappropriate sample timing were excluded.

2.2. Sample and data collection

We collected two 4 mL blood samples from each patient: a peak sample collected ~1 h after the end of meropenem infusion, and a trough sample collected ~30 min before the next dose. Blood samples were collected into heparinized tubes, centrifuged, and the plasma samples were stored at −80 °C.

Information collected included age, gender, body weight, height, serum creatinine, serum albumin, dosing information, presence or absence of septic shock, mechanical ventilation, and continuous renal replacement therapy (CRRT). Sepsis-3 definition was used to identify patients with septic shock (a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. Creatinine clearance (CrCl) was calculated from serum creatinine using the Cockcroft Gault equation. We also estimated the percentage of patients with augmented renal clearance (ARC), which was defined as a CrCl above 130 mL/min (Udy et al., 2010).

2.3. Analytical assay

Plasma concentrations of meropenem were determined using a validated UPLC assay.

Chromatography was performed on a qualified Waters UPLC system equipped with a photo diode array detector. Stationary phase was waters acquity BEH C18 UPLC column, 1.7 μm, 2.1 × 10 0 mm USA with BEH C-18, 1.7 μm pre-Guard Column Van Guard 2. 1 × 5 mm. Two mobile phases were used, mobile phase "A" was 0.2% H_3PO_4 adjusted to pH = 2.2 and Mobile Phase B was Acetonitrile. Mobile phase was run in an isocratic mannter as follows: 90% mobile phase "A" and 10% mobile Phase "B" at a wavelength of 300 nm using a flow rate of 0.2 mL/min.

For the calibration curve, we spiked 300 μL plasma samples with meropenem and the internal standard (ceftazidime). Proteins were precipitated by adding 700 μL acetonitrile, then the samples were vortexed for 30 s, incubated at room temperature for 5 min, centrifuged for 5 min at 14,000*g*, the supernatants were transferred into a new microcentrifuge tube, 500 μL chloroform was added, vortexed for 30 s, centrifuged for 5 min at 1700*g*, and the supernatants were subjected to UPLC analysis. The calibration curve was linear over the concentration range from 0.5 to 100 μg/mL using 7 points. The standard curves were fitted with 1/y2 -weighted linear regression and assay precision was <15% across all concentrations tested.

2.4. Primary outcome and statistical analysis

The primary outcome was the percentage of patients who achieved the pharmacokinetic/pharmacodynamic (PKPD) therapeutic target of a free trough concentration four folds the MIC. We set the MIC at 2 μg/mL, which is the EUCAST breakpoint for most gram-negative bacteria (EUCAST 2021).

For statistical analysis, continuous covariates were presented as both means + standard deviations (SD) and median (IQR). For categorical variables, they were presented as percentages. For the primary outcome, we used logistic regression to assess the predictors of non-target attainment; predictors with an alpha < 0.05 were entered into the model and predictors with an alpha = 0.01 were retained in the model. All statistical analysis was performed using R statistical software.

2.5. Secondary outcome: Pharmacokinetic analysis

Pharmacokinetic analysis was performed using Monolix Suite 2020R1 (Lixoft, France). Since our data is sparse at the individual level, we used a simple one-compartment model with linear elimination to describe the pharmacokinetics of meropenem. The pharmacokinetic parameters clearance (Cl) and volume of distribution (V) were computed for each individual. We assessed the correla-

tion between these individual pharmacokinetic parameters and covariates. That included effects of age, bodyweight, CrCl, serum albumin and presence of CRRT on the individual pharmacokinetic parameters using stepwise multiple linear regression; values with an alpha < 0.05 were entered into the model and values with an alpha < 0.01 were retained in the model.

3. Results

3.1. Baseline demographics

This study assessed 83 samples from 43 critically ill patients. The mean CrCl (SD) was 139 mL/min (118), mean patient weight was 71 kg (21), and mean age was 49 years (19). Five patients (11%) were on CRRT, and 18 patients had ARC (42%). Only two patients received meropenem as an extended infusion over 3 h; all other patients received a 30-minute bolus dose (Table 1).

Out of the 43 patients, 19 (44.2%) continued on meropenem as targeted therapy by culture, 17 (39.5%) continued based on clinical gestalt due to patients' improvement despite the lack of microbiological evidence, and 7 patients were either de-escalated or placed on a different antimicrobial agent. The identified sites of infection based on meropenem sensitive culture were: pneumonia (8 patients), Intraabdominal (6 patients), UTI (3 patients), central line-associated bloodstream infection (2 patients). The identified microorganisms are shown in table 2. All were susceptible to meropenem with the exception of 1 Acinetobacter baumannii isolate. The patient with the Acinetobacter baumannii resistant culture was treated with a combination of meropenem and colistin.

3.2. Primary outcome: Attainment of target PKPD

Trough concentrations were highly variable and ranged from <0.5 μg/mL to 39 μg/mL, with a mean ± SD trough concentration of 8.5 ± 8 μg/mL (Fig. 1). We did not collect a trough sample for five patients; for those patients, we used the model-predicted concentration 30 min before the next dose as the trough instead. Only 20 (46%) of the patients achieved the therapeutic PKPD target of a free trough concentration four times the MIC. The only significant predictor of not achieving the therapeutic target was augmented renal clearance (chi square test, p-value = 0.016). The effect of ARC was significant in both univariate and multivariate logistic regression analysis. Only 4 of 18 (22%) patients with augmented renal clearance achieved the PKPD target, while 16 of 25 (64%) patients without augmented renal clearance achieved the PKPD target (Fig. 3).

3.3. Secondary outcome: Pharmacokinetic analysis

The one-compartment model adequately described the data (Fig. 2). The only significant covariates were bodyweight for V and CrCl for Cl (Fig. 3). We observed a negative correlation between V and bilirubin, though this trend did not reach statistical significance. The mean V for a 70 kg individual was 30 L and the mean Cl for a patient with a CrCl of 100 was 6.4 L/h (Table 3).

Table 1
Baseline demographics.

N = 43	Mean (SD)	Median (IQR)
Age (years)	49 (19)	49 (33.5–64.5)
Weight (kg)	71 (21)	74 (50.5–84)
Gender	Male n = 24 (55 %)	
CrCl mL/min	139 (118)	95 (48.5–216)
CRRT	5 (11%)	
Augmented renal clearance	18 (42%)	
Albumin g/L	24 (6.5)	25 (19.3–28)
Septic shock	12 (28%)	
ICU location	Medical ICU n = 17 (40%) Surgical ICU n = 26 (60%)	
Dose	Bolus dosing = 41 (95%) Extended infusion = 2 (5%)	

Table 2
Microorganism identified (n = 19).

Microorganism	No of cultures
Pseudomonas aeruginosa	9
Escherichia coli	3
Klebsiella pneumonia	2
Staphylococcus haemolyticus	1
Acinetobacter baumannii	3
Serratia marcescens	1

4. Discussion

In this first study of the PK of meropenem in critically ill patients in Saudi Arabia, more than half of the patients did not achieve the therapeutic target for meropenem. ARC was a major risk factor associated with not achieving this target; another possible factor was higher V, which is commonly observed in patients in ICU (Roberts et al., 2014). The possible causes for not reaching the therapeutic target include hypoalbuminemia, shock and aggressive fluid resuscitation (Roberts et al., 2014, Sjövall et al., 2018, Liebchen et al., 2021). In our analysis, albumin levels correlated negatively with V; however, this trend did not reach statistical significance, possibly because of the small sample size. The only significant covariates for V and Cl were weight and CrCL. Data on fluid resuscitation status was not collected; therefore, this variable was not included in the analysis. In this study, V was 30 L higher than previously reported values for healthy volunteers and patients in ICU (Mouton and van den Anker 1995, Crandon et al., 2011, Dhaese et al., 2019). Higher V combined with ARC leads to lower drug concentrations and failure to achieve the therapeutic PKPD target for meropenem. Additionally—as expected for patients in ICU—PK was highly variable, and further increases the risk of subtherapeutic concentrations.

For patients in ICU, especially those with ARC, the dose of meropenem should be increased or alternative dosing such as extended or continuous infusions should be applied (Abdul-Aziz et al., 2020, Chai et al., 2020). Failure to achieve PKPD targets increases the risk of treatment failure and/or development of resistance (Steffens et al., 2021). This is a particularly important issue in Saudi Arabia due to the rise in carbapenem-resistant gram-negative bacteria (Zowawi 2016). Several meropenem dosing algorithms have been published for critically ill patients. These algorithms take renal function and MIC distributions into account, and can be used to optimize meropenem dosing (Heil et al., 2018, Sjövall et al., 2018, Dhaese et al., 2019, Liebchen et al., 2021). It is important for institutions to develop tailored dosing regimens according to local susceptibility data, preferably based on MIC distributions. MICs should not be viewed in a categorical manner, but as a continuous probability as MIC values within the susceptible range may require different dosing regimens. MICs in the upper end of the susceptible range may require higher and more aggressive dosing, while MICs in the lower range will require lower/standard doses. Therapeutic drug monitoring (TDM) represents another valuable tool for optimization of the dose of meropenem for patients in ICU (Muller et al., 2018, Abdul-Aziz et al., 2020, Mabilat et al., 2020, Scharf et al., 2020). However, to our knowledge, no hospital in Saudi Arabia performs TDM for meropenem or any of the β-lactams.

The limitations of this study include the number of patients assessed which did not allow us to properly assess the impact of CRRT and other variables on the PK of meropenem. Additionally, only a few patients received extended infusion dosing; therefore,

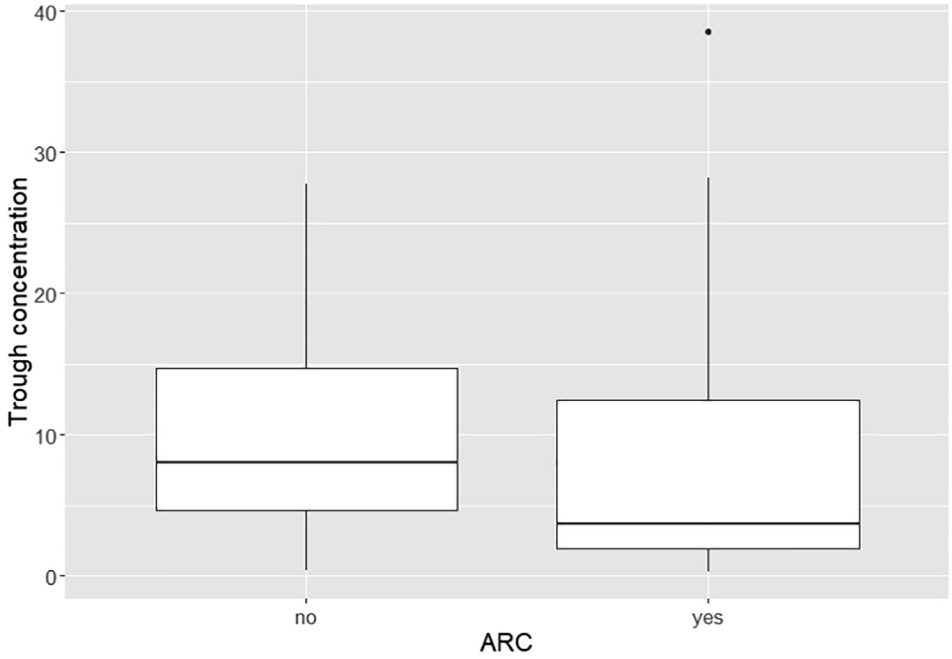

Fig. 1. Boxplot for trough concentrations by augmented renal clearance (ARC) status.

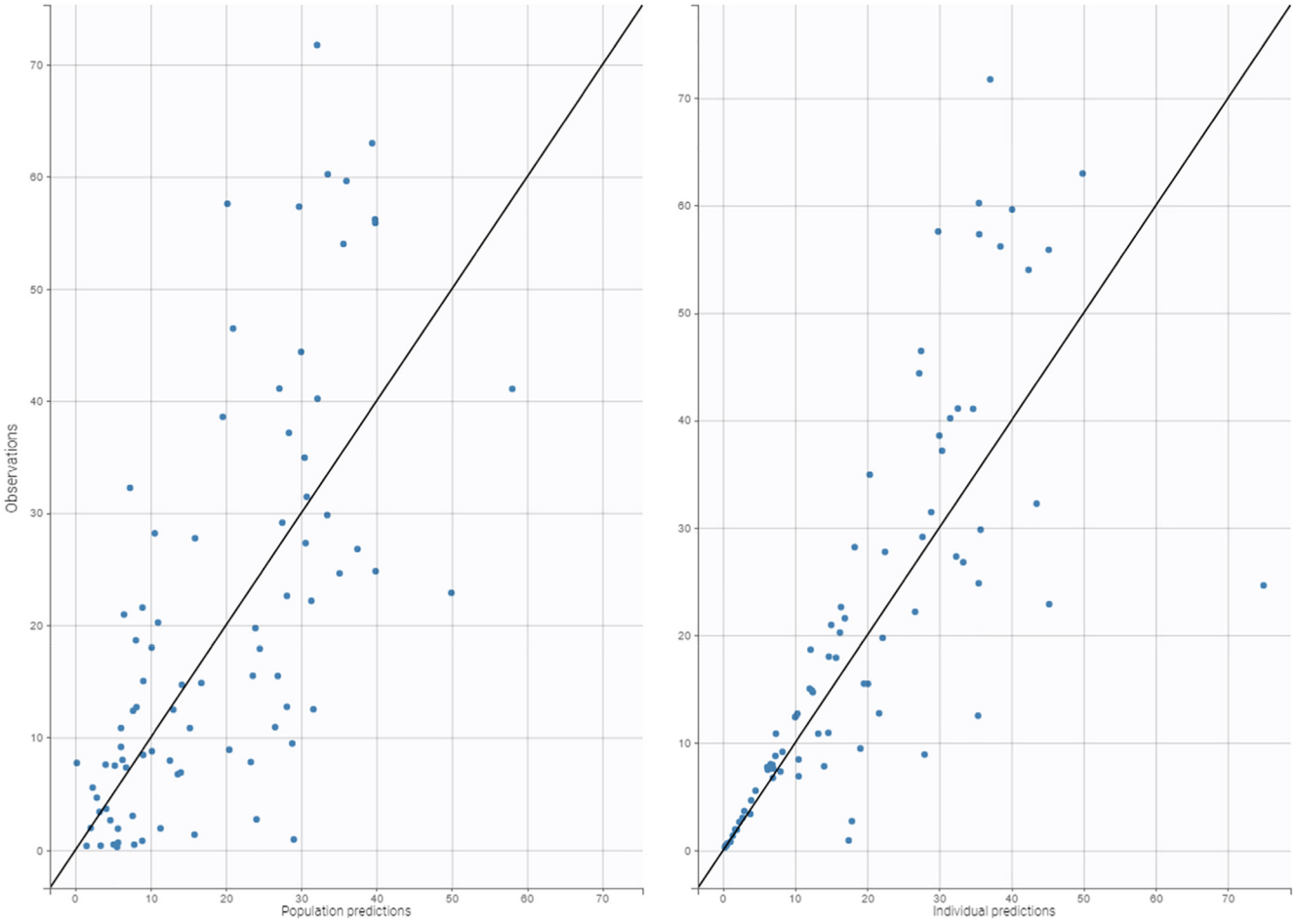

Fig. 2. Goodness-of-fit plot for final population pharmacokinetic model. Right: Individual predictions of meropenem versus observed concentrations. Left: Population predictions of meropenem versus observed concentrations.

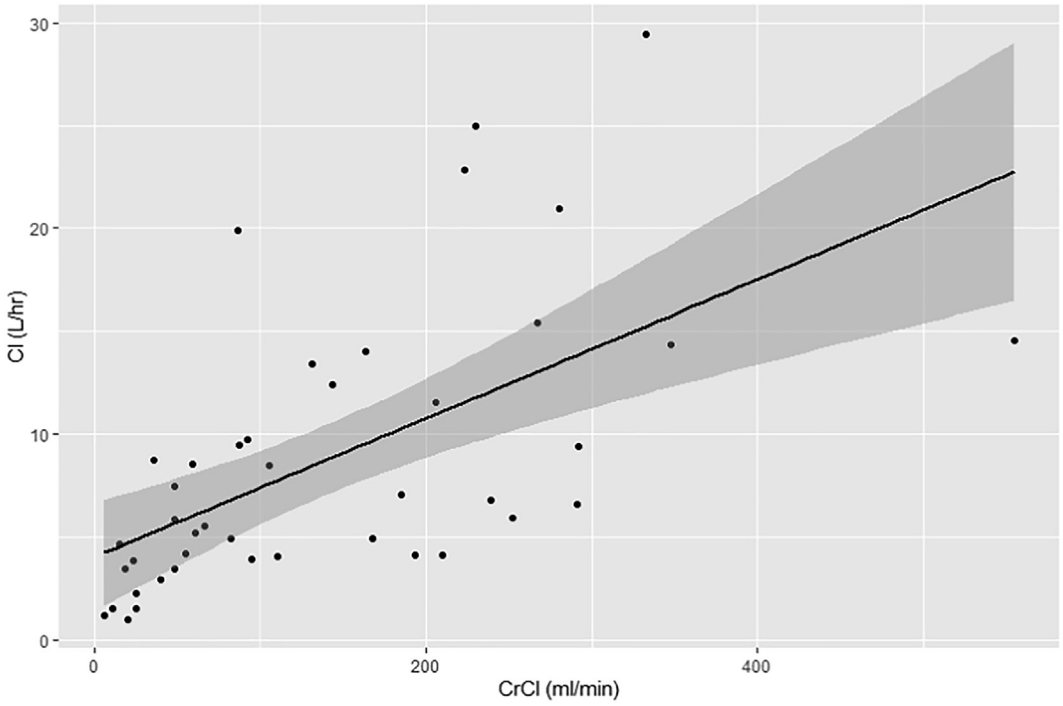

Fig. 3. Meropenem drug clearance (Cl) compared with creatinine clearance (CrCl). Scatter plot showing Correlation between Cl and CrCl (r = 0.6).

Table 3
PK parameter estimates.

	Average (RSE%)	CV% (RSE%)
Cl (L/hr)	6.4 (9.38 %)	48 % (14.6 %)
V (L)	30 (11.4 %)	15.6 % (44 %)

RSE, relative standard error, CV% is variability expressed as the coefficient of variation.
Cl = 6.29 *(CrCl/100) ^0.3.
V = 30.29 *(Weight/70).

we did not determine the PKPD for extended infusion. Moreover, we did not assess clinical outcomes or correlate the clinical outcomes with the drug concentration.

In conclusion, more than half of our patients did not achieve the PKPD target; thus, there is a need to improve the dosing of meropenem for critically ill patients in Saudi Arabia. That would include using extended or continuous infusion of meropenem.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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