

FACTORS INFLUENCING PHARMACOKINETIC/PHARMACODYNAMIC INDEX OF MEROPENEM IN CRITICALLY ILL PATIENTS

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ABSTRACT

*There is a growing consensus that, in critically ill patients, meropenem dosing should aim to achieve 100% fT > MIC. The primary objective of our study was to evaluate the frequency of meropenem underdosing—considering its widespread use in this population—and to identify factors associated with such underdosing. This prospective, cross-sectional study included two groups of critically ill patients: a control group, comprising patients who received optimal meropenem dosing (100% fT > MIC), and a case group, consisting of patients who were underdosed (fT > MIC < 100%). A validated high-performance liquid chromatography (HPLC) method was employed to measure meropenem concentrations in plasma. The effects of various independent and confounding variables on the dichotomous dependent variable were assessed using univariate and multivariate logistic regression analyses. We recruited a total of 63 critically ill patients. The results of our study demonstrated that the majority of critically ill patients (n = 52; 82.5%) received an adequate meropenem dose, achieving fT > MIC of 100%, whereas 11 patients (17.5%) were underdosed, with fT > MIC below 100%. Finally, *Acinetobacter* spp. and *Pseudomonas aeruginosa*, as causative pathogens of bacterial infections, were identified as significant risk factors for meropenem underdosing in critically ill patients. Clinicians should exercise caution when selecting the meropenem dosage for critically ill patients with infections caused by *Acinetobacter* spp. and *Pseudomonas aeruginosa*.*

Keywords: Meropenem, critically ill patients, PK/PD index, fT > MIC.

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INTRODUCTION

Meropenem is a broad-spectrum carbapenem antibiotic widely used in the treatment of severe and hospital-acquired infections in hospitalized patients, particularly those caused by most Gram-negative and certain Gram-positive bacteria (1-3). Its advantages stem primarily from its broad-spectrum antibacterial activity, notable efficacy against resistant Gram-negative strains, and excellent tissue penetration (4). Notably, meropenem remains effective against extended-spectrum β -lactamase (ESBL)-producing and AmpC β -lactamase-producing *Enterobacteriaceae*, as well as against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (5,6). It is administered via intravenous infusion and is generally associated with a favorable safety profile.

Meropenem is a time-dependent antibiotic, and the pharmacokinetic/pharmacodynamic (PK/PD) index that most accurately reflects its bactericidal efficacy is the proportion of the dosing interval during which free plasma concentrations exceed the minimum inhibitory concentration (MIC) of the target pathogen ($ft > MIC$) (1,7). To achieve optimal antibacterial activity, $ft > MIC$ values should be maintained at $\geq 40\%$ of the dosing interval (8). However, dosing meropenem is particularly challenging in critically ill patients, for whom some clinicians advocate dose adjustments aimed at achieving $100\% ft > MIC$ (9-12).

Antibiotic dosing recommendations for critically ill patients often differ substantially from those for the general population (13). This is primarily due to profound pathophysiological alterations in critically ill individuals, which can significantly affect drug pharmacokinetics (13,14). Moreover, inadequate antimicrobial therapy is a well-established risk factor for in-hospital mortality in this patient population (15). Accordingly, the aim of our study was to assess the frequency of meropenem underdosing—given that it is among the most frequently used antibiotics in critically ill patients—and to identify the factors contributing to such underdosing.

MATERIAL AND METHOD

Study design

This prospective, cross-sectional study included two groups of critically ill patients: a control group, comprising patients who received optimal meropenem dosing ($100\% ft > MIC$), and a case group, consisting of patients who were underdosed ($ft > MIC < 100\%$) (9-12).

Study population

The study population comprised critically ill patients with severe, life-threatening infections treated in the intensive care units of the University Clinical Center Kragujevac (UCCKG) between June 2021 and October 2022. Critically ill patients in our study had the diagnoses of meningitis, pneumonia, sepsis, septic shock, and febrile neutropenia caused by multidrug-resistant gram-negative bacteria, including *Enterobacteriaceae*, *Klebsiella pneumoniae*, *Pseudomonas*

aeruginosa, and strains of *Escherichia coli* that produce extended-spectrum beta-lactamases. We recruited only critically ill patients in whom steady-state meropenem levels were achieved, that is, those in whom meropenem had been administered for at least 3 days before recruitment. On the other hand, we excluded all patients who were not critically ill, those in whom steady-state meropenem was not achieved, pregnant women, lactating women, and patients who refused to participate in the study. We recruited patients by the principles of consecutive convenience sampling.

Before initiating the study, we secured approval from the Ethics Committee at the UCCKG (No. 01-21-63). Written informed consent was obtained from all participants prior to their inclusion in the study.

Study variables

Main study outcome was achieved value of $ft > MIC$ PK/PD index of meropenem that was dichotomized to $< 100\%$ and $> 100\%$. To calculate $ft > MIC$ of meropenem, we measured at least two plasma concentrations of meropenem in dose interval, and based on the authors-made calculator in Excel (available on demand from the corresponding author) the plasma concentration / time curve was reconstructed and used for determining value of $ft > MIC$. The concentrations of meropenem in plasma were measured by a validated high-performance liquid chromatography (HPLC) method. Details of the equipment, reagents, and the HPLC method used to measure the concentration are presented in the publication Rančić et al (16).

We obtained data on MIC values in patients in two ways: by reviewing the medical documentation of those patients in whom these values were previously measured in the microbiology laboratory of the UCCKG or by reviewing data from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (17).

The following independent and confounding variables were taken into account for adjustment of their effects on the study outcome: gender, age, body weight, body height, body mass index, dose of meropenem, meropenem dosage interval, values of laboratory parameters (creatinine, aspartate aminotransferase, alanine transaminase, red blood cell count, white blood cell count, platelet count, hemoglobin), causative agent of infection (*Klebsiella spp.*, *Staphylococcus aureus*, *Proteus mirabilis*, *Acinetobacter spp.*, *Pseudomonas aeruginosa*, *Enterobacter* and *Escherichia coli*), type of bacterial infection (pneumonia, urinary tract infection, intra-abdominal infection), comorbidities (hypertension, chronic renal insufficiency, cerebral infarction, neoplasma), concomitant administration of other antibiotics (vancomycin, colistin).

Statistical analysis

Data were initially analyzed using descriptive statistical methods. Categorical variables were presented as frequencies (percentages), while continuous variables were summarized

using means, standard deviations, and ranges. The effects of various independent and confounding variables on the dichotomous dependent variable were assessed using univariate and multivariate logistic regression analyses. Potential risk factors were evaluated based on their regression coefficients (B), along with corresponding 95% confidence intervals (CIs). A p-value of <0.05 was considered statistically significant. Results were reported as crude and adjusted odds ratios (ORs) with their respective 95% CIs.

RESULTS

We recruited a total of 63 critically ill patients whose socio-demographic and clinical characteristics are shown in Table 1.

Table 1. Basic socio-demographic and clinical characteristics of recruited patients

Variable	Mean $\pm$ standard deviation (range) or number (%)
Gender (M/F)	37 (58.7%) / 26 (41.3%)
Age (years)	63.92 $\pm$ 1.62
Body weight (kg)	78.46 $\pm$ 12.73
Charlson comorbidity index	4.25 $\pm$ 2.66
Hypertension	20 (31.7%)
Chronic renal insufficiency	8 (12.7%)
Cerebral infarction	11 (17.5%)

M-male; F-female

The most common reasons for the use of meropenem in our patients were complicated urinary tract infections (n=23; 36.5%) and pneumonia (n=20; 31.7%), while in the remaining 20 patients (31.7%), meropenem was used to treat other severe bacterial infections. Table 2 shows a list of the most common bacteria causing infections in our patients. The vast majority of patients received meropenem in a total daily dose of 3 grams (n=53; 84.1%); 8 patients (12.7%) received meropenem in a total daily dose of 2 grams, while in one patient (3.25) meropenem was administered in a total dose of 6 grams per day.

Meropenem was most commonly administered three times daily (n=55; 87.3%), while in 12 patients (12.7%) the dosing regimen involved administering meropenem twice daily.

Table 2. The most common causes of infections in our patients

Bacteria	Number (%)
<i>Klebsiella spp.</i>	17 (27%)
<i>Staphylococcus aureus</i>	12 (19%)
<i>Proteus mirabilis</i>	12 (19%)
<i>Acinetobacter spp.</i>	9 (14.3%)
<i>Pseudomonas aeruginosa</i>	6 (9.5%)
<i>Enterobacter</i>	4 (6.3%)
<i>Escherichia coli</i>	3 (4.8%)

The results of our study showed that in most of our critically ill patients (n=52; 82.5%), the administered dose of meropenem was adequate (fT>MIC =100%), while 11 patients (17.5%) were underdosed (fT>MIC <100%). In the group of underdosed critically ill patients, there were significantly more female patients ($\chi^2=3.982$; p=0.046) and those whose infection was caused by *Acinetobacter spp.* ($\chi^2=21.849$; p=0.000) compared to the group of optimally dosed patients. The study patient groups did not differ significantly from each other in terms of other characteristics.

Table 3 shows the results of univariate and multivariate logistic regression, which we used to identify factors that predispose to meropenem underdosing in critically ill patients. In the final logistic regression model, we entered the following variables: age, gender, pneumonia, urinary tract infection, *Acinetobacter spp.*, and *Pseudomonas aeruginosa*. Our multivariate logistic regression model (enter method) showed satisfactory goodness of fit (Cox & Snell R Square 0.383, Nagelkerke R Square 0.634). Finally, *Acinetobacter spp.* and *Pseudomonas aeruginosa*, as causative agents of bacterial infections, have been identified as risk factors for the occurrence of meropenem underdosing in critically ill patients.

Table 3. Crude and adjusted odds ratios (OR) of the risk factors for meropenem underdosing in critically ill patients

Risk factors	Univariate model Crude OR with 95% CI p	Multivariate model Adjusted OR with 95% CI p
Gender	5.037 (1.188-21.359) p=0.028*	4.505 (0.562-36.087) p=0.156
Age	1.004 (0.954-1.057) p=0.878	0.988 (0.891-1.095) p=0.818
<i>Acinetobacter spp.</i>	3.778 (1.942-6.725) p=0.000*	4.637 (1.365-14.961) p=0.000*
<i>Pseudomonas aeruginosa</i>	1.812 (1.147-5.125) p=0.044*	2.938 (1.392-7.116) p=0.035*

Risk factors	Univariate model	Multivariate model
	Crude OR with 95% CI p	Adjusted OR with 95% CI p
Pneumonia	1.286 (0.329-5.021) p=0.718	4.945 (0.393-62.148) p=0.216
Urinary tract infection	0.600 (0.142-2.532) p=0.487	0.676 (0.075-6.088) p=0.727

*-statistically significant; CI- confidence interval; p- statistical significance

DISCUSSION

Hydrophilic drugs such as meropenem exhibit considerable pharmacokinetic variability in critically ill patients, primarily due to pathophysiological alterations including capillary leak and augmented renal clearance (18). These changes often lead to reduced systemic drug concentrations, thereby diminishing therapeutic efficacy (19). Numerous studies have demonstrated that beta-lactam antibiotic levels frequently fall below therapeutic thresholds in a substantial proportion of critically ill patients (19). Underdosing of antibiotics has been linked to increased mortality in patients with sepsis or septic shock (19) and plays a critical role in the emergence of antibiotic resistance among various bacterial species (20). Consequently, therapeutic drug monitoring (TDM) is increasingly advocated to optimize dosing of meropenem and other beta-lactam antibiotics in this population (21-24). Several analytical techniques are currently available for the detection and quantification of meropenem in biological fluids (25). The majority of validated methods employ chromatographic approaches coupled with ultraviolet or mass spectrometry detection (25), which was the methodology utilized in our study.

The results of our study demonstrated that meropenem was underdosed in approximately 20% of critically ill patients. Similarly, Angelini et al. reported a 26% underdosing rate in this patient population (26). The lower incidence of underdosing observed in our study may be attributed to the standard practice at UCCKG, where clinical pharmacologists are routinely involved in dosing calculations for critically ill patients (27). The involvement of clinical pharmacologists in treatment planning has been shown to improve clinical outcomes in this vulnerable population (27).

Our findings indicate that the treatment of infections caused by *Acinetobacter* species is associated with an increased risk of meropenem underdosing in critically ill patients, likely due to the elevated minimum inhibitory concentrations (MICs) observed in these infections. The role of carbapenems in managing infections caused by *Acinetobacter baumannii* and related species has undergone substantial changes (28). *Acinetobacter baumannii* is a Gram-negative, aerobic, non-fermenting bacterium responsible for severe healthcare-associated infections, including pneumonia, bacteremia, and urinary tract infections (29,30). For many years, carbapenems were considered the treatment of choice for multidrug-resistant *A. baumannii* infections (30). However, this organism has developed multiple mechanisms of resistance to carbapenems (30,31). In some regions, up to 75%

of *A. baumannii* strains exhibit resistance to meropenem (28). The predominant resistance mechanisms involve the production of OXA-type β -lactamases and metallo- β -lactamases (31). Carbapenem-resistant *Acinetobacter baumannii* (CRAB) represents a significant nosocomial threat due to the high mortality rates associated with infections caused by these strains (30,31). Two randomized clinical trials have demonstrated that meropenem, even when combined with colistin, is no longer effective against CRAB infections (32,33). Furthermore, the addition of vaborbactam—a β -lactamase inhibitor—to meropenem does not improve clinical outcomes in *A. baumannii* infections, as the β -lactamases produced either do not hydrolyze the parent carbapenem or are inadequately inhibited by vaborbactam (17).

In contrast to infections caused by *Acinetobacter baumannii*, meropenem remains highly effective against *Pseudomonas aeruginosa* infections (34). Nevertheless, meropenem-resistant strains of *P. aeruginosa* are increasingly reported (34). Consequently, combination therapy with meropenem and either colistin or amikacin is recommended for infections caused by these resistant strains (35). A key determinant of meropenem's efficacy in treating *P. aeruginosa* infections is the minimum inhibitory concentration (MIC) (35). According to EUCAST breakpoints, resistant *P. aeruginosa* strains exhibit elevated meropenem MICs (>8 mg/L) (17). This necessitates the administration of high meropenem doses to achieve optimal pharmacokinetic/pharmacodynamic (PK/PD) targets. Accordingly, doses as high as 12 grams per day have been suggested for the treatment of septic shock caused by *P. aeruginosa* (36).

This study has several limitations. First, it was conducted at a single center and involved a relatively small sample of critically ill patients, which may limit the generalizability of the findings. Additionally, we were unable to identify cases of meropenem overdose, as the minimum (trough) concentrations of the drug were not measured.

In conclusion, clinicians need to pay special attention when administering meropenem to treat infections caused by *Acinetobacter spp.* and *Pseudomonas aeruginosa* in critically ill patients. Given the elevated MIC values, particularly among resistant bacterial strains, there is a substantial risk of meropenem underdosing, which may lead to unfavorable clinical outcomes in patients.

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CONFLICT OF INTEREST

None.

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