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FACTORS AFFECTING MEROPENEM TROUGH LEVELS IN CRITICALLY ILL PATIENTS: A THERAPEUTIC DRUG MONITORING STUDY

KRİTİK HASTALARDA MEROPENEM SEVİYELERİNİ ETKİLEYEN FAKTÖRLER: TERAPÖTİK İLAÇ İZLEME ÇALIŞMASI

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ABSTRACT

Objective: *This study primarily aimed to determine meropenem the trough level (C_{min}) in intensive care unit (ICU), with an exploratory secondary aim of evaluating factors influencing C_{min} and clinical cure.*
Material and Method: *This prospective study included adult ICU patients receiving meropenem for ≥48 hours, and C_{min} levels were measured using a ready-to-use ELISA kit.*
Result and Discussion: *The study included 38 patients, 26 of whom were male. Mean meropenem C_{min} value was found to be 0.40 ± 0.07 mg/l which is statistically different than the target value of 8 mg/l ($p < 0.001$). We found no statistically significant difference in mean C_{min} between the patient groups whose creatinine clearance was smaller than 50 ml/min and not. Erythrocyte and hemoglobin values decreased after meropenem treatment compared to baseline ($p < 0.05$). C-Reactive Protein (CRP) decreased, and Sequential Organ Failure Assessment (SOFA) values increased after meropenem treatment ($p < 0.001$). Logistic regression in patients with Systemic Inflammatory Response Syndrome (SIRS) showed that only SOFA reduced the clinical cure rate (OR 0.534, 95% CI 0.311–0.917). In this study, the target 100% fT > MIC < 4×MIC was not achieved with standard or extended meropenem infusion, potentially limiting clinical cure in ICUs with resistant pathogens, highlighting the need for alternative dosing strategies.*
Keywords: *Drug trough level, intensive care unit, meropenem, therapeutic drug monitoring*

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ÖZ

Amaç: *Bu çalışmanın öncelikli amacı yoğun bakım ünitesinde (YBÜ) meropenem çukur seviyesini (C_{min}) belirlemek, ikincil amacı ise C_{min} ve klinik iyileşmeyi etkileyen faktörleri değerlendirmektir.*
Gereç ve Yöntem: *Bu prospektif çalışmaya, ≥48 saat meropenem alan yetişkin yoğun bakım hastaları dahil edildi ve Cmin düzeyleri hazır kullanıma uygun ELISA kiti ile ölçüldü.*
Sonuç ve Tartışma: *Çalışmaya 26'sı erkek toplam 38 hasta dahil edildi. Ortalama meropenem Cmin değerinin 0.40 ± 0.07 mg/l olduğu bulundu; bu değer, hedef değer olan 8 mg/l'den istatistiksel olarak farklıdır ($p < 0.001$). Kreatinin klirensi 50 ml/dk'dan az olan ve olmayan hasta grupları arasında ortalama C_{min} açısından istatistiksel olarak anlamlı bir fark bulunmadı. Meropenem tedavisi sonrası eritrosit ve hemoglobin değerleri başlangıç değerlerine göre azaldı ($p < 0.05$). Meropenem tedavisi sonrasında C-reaktif protein (CRP) azaldı ve Sekansiyel Organ Yetmezliği Değerlendirmesi (SOFA) değerleri arttı ($p < 0.001$). Sistemik İnflamatuvar Yanıt Sendromu (SIRS) olan hastalarda yapılan lojistik regresyon analizinde yalnızca SOFA'nın klinik iyileşme oranını düşürdüğü görüldü (OR 0.534, %95 CI 0.311–0.917). Çalışmamızda, standart veya uzatılmış meropenem infüzyonu ile hedeflenen 100% $fT > MIC < 4 \times MIC$ sağlanamadı; bu durum, dirençli patojenlerin sık görüldüğü yoğun bakım ünitelerinde klinik iyileşmeyi sınırlayabilir ve alternatif dozlama stratejilerinin geliştirilmesi gerektiğini göstermektedir.*

Anahtar Kelimeler: *İlaç çukur düzeyi, meropenem, terapötik ilaç izlemi, yoğun bakım ünitesi*

INTRODUCTION

Most mortality rates in the intensive care unit (ICU) are due to the infection itself and the worsening of infection-induced sepsis in inpatients. Sepsis is a life-threatening organ dysfunction caused by a host's dysregulated response [1]. Adults at high risk of septic shock or sepsis should receive antimicrobials within an hour of diagnosis, according to the Sepsis Survival Campaign [2]. Mortality is substantially increased by even a one-hour delay in administering effective antimicrobial therapy following the onset of hypotension caused by septic shock [3].

Sepsis can alter the pharmacokinetics (PK) of many antimicrobials [4]. Broad-spectrum antibiotics, like meropenem-a carbapenem with broad activity and low toxicity-are commonly used. This antibiotic is widely used in hospitalized patients for severe and hospital-acquired infections due to its broad-spectrum activity [5]. Time-dependent drugs like meropenem are more effective when their concentration remains above the minimum inhibitory concentration (MIC) for longer durations [6]. The pharmacodynamic index for beta lactams was established as the percentage of time during a 24-hour period that the concentration of the unbound drug stayed above the minimum inhibitory concentration ($fT > MIC$) [7]. For infections caused by infecting microorganisms with higher MICs in critically ill patients, continuous infusion provides an alternative strategy to maintain a $fT > MIC$ of 100% [8].

It is common practice to administer large volumes of resuscitation fluids that significantly increase interstitial volume to treat hypotension in critically ill patients. This fluid load may increase the volume of distribution (V_d) of hydrophilic drugs such as meropenem, resulting in lower plasma and tissue antimicrobial concentrations [9]. In patients with impaired renal function, the drugs may increase to supratherapeutic levels because they cannot be excreted; in patients with normal renal function, fluid therapy increases the V_d, so the drug may remain at subtherapeutic levels because it leaves the body more quickly [10].

The reasons for performing therapeutic drug monitoring (TDM) include avoiding drug toxicity, checking whether the drug is at subtherapeutic concentrations in cases of deficiency in response to treatment, evaluating treatment after changes in the dosing regimen, and providing individualized dosing [11,12]. As a result of all the changes that occur in critically ill patients, it is extremely important to know the factors that may affect the trough level (C_{min}) of meropenem, which is hydrophilic and frequently used in critically ill patients.

The aim of this study was to determine the C_{min} of meropenem in critically ill patients. The secondary, exploratory aim was to assess factors affecting C_{min} and determinants of clinical cure with meropenem.

MATERIAL AND METHOD

Study Setting

This prospective study included patients hospitalized in the Anesthesiology and Reanimation ICU of Inonu University Turgut Ozal Medical Centre who received meropenem for the treatment of any infection. The study was conducted between May 9, 2022, and March 9, 2023, in an ICU with a capacity of 26 beds. The ethics committee approval required for the research was obtained from Malatya Clinical Research Ethics Committee on 02.03.2022 with the decision numbered 2022/16.

Inclusion and Exclusion Criteria

During the study period, patients who received intravenous meropenem for at least 48 hours initiated in accordance with the opinion of a specialist physician due to any infectious disease in the ICU, who were 18 years of age or older, and for whom a written consent form was obtained from themselves, or their relatives were included in the study. Patients whose blood sample was found to be hemolyzed despite sampling were excluded from the study. Written informed consent was obtained from all the patients' relatives because our patient group was sedated or comatose.

Definition of Target Value

For critically ill patients, a target of 100% *f*T > MIC < 4xMIC is recommended for drugs with time-dependent antimicrobial activity, such as beta-lactams [13]. Studies have reported that 4 times the MIC value should be targeted for the treatment of resistant pathogens. Therefore, in the current study, 8 mg/l, which is 4 times the MIC value of 2 mg/l, was determined as the target C_{min} for meropenem resistance by European Committee on Antimicrobial Susceptibility Testing (EUCAST) [14-16].

Sample Size

Sample size was calculated using G*Power for Mac, version 3.1.9.6 (Düsseldorf, Germany). In this study, we assumed that critically ill patients receiving the conventional meropenem dosing regimen had a mean meropenem C_{min} different from 8 mg/l. The minimum required sample size was calculated as 19 patients using a two-way one-sample t-test with an alpha error of 0.05 and power of 0.80. As the sample size calculation was based on detecting a difference in mean C_{min}, the study was not specifically powered for multivariable analyses; therefore, the results of the factor analysis should be interpreted as hypothesis-generating rather than confirmatory.

Data Collection

Demographic data, obesity status (body mass index (BMI) more than 30 kg/m^2) laboratory results, all medications used during hospitalization, Acute Physiology and Chronic Health Evaluation II (APACHE II), Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), meropenem infusion strategy and duration, source of infection, routine biochemistry, hematology, hormone and serology panel, mechanical ventilation status, patient's vitals during hospitalization, patient files and data obtained through verbal communication between the patient and the physician were recorded by the clinical pharmacist on the data collection form. After meropenem treatment was started, information such as doses, duration of administration, date, time, and status of administration were recorded.

Meropenem Treatment Scheme

Although meropenem dosing was determined at the discretion of the attending physician, the general regimen was as follows: 1 g every 8 hours (q8h) for patients with creatinine clearance (CrCL) >50 ml/min, 1 g every 12 hours (q12h) for those with CrCL between 25–50 ml/min, 500 mg q12h for CrCL between 10–25 ml/min, and 500 mg every 24 hours (q24h) for patients with CrCL < 10 ml/min.

Sample Collection and Analysis

The decision to collect samples on the 3rd day of meropenem treatment was made after a literature review with infectious disease specialists. Since we only looked at meropenem C_{min}, the blood sample was taken at a single time. A 5 ml blood sample was collected approximately 30 minutes before drug

administration on the third day of meropenem treatment from a consenting participant [4]. Samples were centrifuged at 3500 rpm for 10 minutes as specified in the kit user manual and stored at -80°C until analyzed. Enzyme-Linked Immunosorbent Assay (ELISA) ready-to-use kits and a reader device were used for quantification.

Clinical Cure

Clinical cure was assessed among patients with Systemic Inflammatory Response Syndrome (SIRS) at the beginning of the meropenem therapy and was defined as follows: a decrease in C-reactive protein (CRP) values by at least 30% from baseline, resolution of SIRS at the end of the treatment, and having no radiological evidence of active infection and no other clinical signs and symptoms of infection [17].

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM corp., USA) version 27.0.1 software. The Kolmogorov-Smirnov test was used to determine whether the continuous data were normally distributed. In hypothesis testing, parametric or non-parametric tests were used accordingly. Pearson's correlation test was used to examine the correlation between two continuous data if they were normally distributed, while Spearman's correlation test was used if they were not normally distributed. A logistic regression analysis was performed to determine attainment of clinical cure at the end of the meropenem treatment in the patient group in who has SIRS at the beginning of the therapy. If the significance level was less than 0.05, the result of the statistical test was accepted as significant.

RESULT AND DISCUSSION

A total of 54 patients were initially included in the study, 16 of whom were excluded from the study due to death, discharge, or transfer to another ward before blood sampling or hemolysis after sampling. Male was 68.42% of the patients. The mean age of the patients was 66.68 ± 16.27. The SOFA score at admission (mean ± standard deviation) was 8.03 ± 3.63, indicating a mortality prediction of 33.3%. Most patients were transferred from the emergency to the ward and the majority passed away at discharge. Other characteristics of the patients are given in Table 1.

Table 1. Patient characteristics

Patient (n, %)	38 (100.0)
Gender (n, %) Male Female	 26 (68.42) 12 (31.58)
Age, years (mean ± standard deviation)	66.68 ± 16.27
Body Mass Index, (kg/m^2) (mean ± standard deviation)	26.17 ± 4.05
Comorbidities (mean ± standard deviation)	4.47 ± 2.82
Duration of hospitalization, days (median, [25. percentile – 75. percentile])	26.50 [13.00 – 58.50]
Meropenem treatment duration, days (mean ± standard deviation)	9.74 ± 4.79
Operation status, (n, %)	15 (39.47)
GCS at admission (median, [25. percentile – 75. percentile])	7.00 [3.00 – 11.50]
APACHE II score at admission (mean ± standard deviation)	22.53 ± 8.10
SOFA at admission (mean ± standard deviation)	8.03 ± 3.63
Daily fluid balance, ml (median, [25. percentile – 75. percentile])*	1176.50 [527.50 – 2057.50]

Table 1 (*continue*). Patient characteristics

CrCL, ml/min, (n, (%))*	
CrCL<10	1 (2.63)
10≤ CrCL≤25	5 (13.16)
25< CrCL≤50	9 (23.68)
50< CrCL<130	15 (39.47)
CrCL≥130	8 (21.05)
Type of admission (n, %)	
Emergency	23 (60.53)
Transfer between wards	9 (23.68)
Transfer between hospitals	6 (15.79)
Type of discharge (n, %)	
Death	31 (81.58)
Transfer between hospitals	6 (15.79)
Discharge home	1 (2.63)

APACHE II: Acute Physiology and Chronic Health Evaluation II
CrCL: Creatinine clearance, GCS: Glasgow Coma Scale, SOFA: Sequential Organ Failure Assessment
* Data from day 3rd of the meropenem treatment was used

A total of 177 comorbidities and 51 hospitalizations were diagnosed. The most common diagnoses during hospitalization were multiple fractures (15.79%), cardiac arrest (13.16%), and subarachnoid hemorrhage (10.53%); the most common comorbidities were essential (primary) hypertension (55.26%), atherosclerotic heart disease (44.74%), hyperlipidemia (36.84%), and type 2 diabetes mellitus (36.84%).

A total of 91 cultures were obtained from patients during meropenem treatment. It was recorded that 41.76% of the cultures obtained from the patients were respiratory tract secretions. The meropenem resistance rate of the pathogens isolated in this study was 96.55%. The distribution of sites of infection and causative microorganisms detected in the patients is given in Table 2.

Table 2. Identified sites of infection and causative microorganisms

Sites of Infection	Number of Cultures, n	Microorganism, (n, %) *
Respiratory tract secretion	38	*Acinetobacter baumannii* (20, 52.63) *Pseudomonas aeruginosa* (7, 18.42) *Klebsiella pneumoniae* (3, 7.89) *Stenotrophomonas maltophilia* (3, 7.89)
Blood	16	*Acinetobacter baumannii* (2, 12.50) *Enterococcus faecalis* (2, 12.50) *Klebsiella pneumoniae* (2, 12.50)
Urine	13	*Candida albicans* (5, 38.46) *Escherichia coli* (4, 30.77) *Enterococcus faecium* (1, 7.69) *Enterococcus sp.* (1, 7.69) *Candida sp.* (1, 7.69) *Klebsiella pneumoniae* (1, 7.69)
Wound	11	*Acinetobacter baumannii* (5, 45.45) *Klebsiella pneumoniae* (2, 18.18) *Citrobacter koseri* (1, 9.09) *Enterococcus faecium* VRE (1, 9.09) *Escherichia coli* ESBL (1, 9.09) *Pseudomonas aeruginosa* (1, 9.09)
Sputum	3	*Pseudomonas aeruginosa* (2, 66.67) *Acinetobacter baumannii* (1, 33.33)
Cerebrospinal fluid	2	*Acinetobacter baumannii* (1, 50.00) *Staphylococcus epidermidis* (1, 50.00)
None	8	

ESBL: Extended-spectrum beta lactamase, VRE: Vancomycin-resistant Enterococcus
* The top three most frequently isolated microorganisms are given

The mean meropenem C_{min} value of our sample was tested against our recommended target value of 8 mg/l for resistant pathogens. Mean meropenem C_{min} value was found to be 0.40 ± 0.07 mg/l which is statistically different than the target value of 8 mg/l ($p < 0.001$).

We analyzed the relationship between meropenem C_{min} and patient characteristics and ICU scores and found no significant correlation between these factors and meropenem C_{min}. These values are given in Table 3.

Table 3. Correlation values between meropenem trough level and some factors related to patients

Factors	***p***
Age, (years)[a]	0.547
Admission APACHE II score[a]	0.693
Admission SOFA score[a]	0.785
Mean corpuscular volume, (fL)[a, **]	0.355
Duration of hospitalization, (day)[b]	0.771
Intensive care unit day when meropenem treatment was started, (day)	0.562
Admission GCS[b]	0.764
GCS[b, **]	0.857
SOFA score[b, **]	0.651
Meropenem dose before sample, (mg) [b]	0.730
CrCL, (ml/min)[b, **]	0.331
Albumin, (mg/dl)[b, **]	0.546
Mean norepinephrine dose, (µg/kg/min)[b, **]	0.759

APACHE II: Acute Physiology and Chronic Health Evaluation II
CrCL: Creatinine clearance
GCS: Glasgow Coma Scale
SOFA: Sequential Organ Failure Assessment
[a]Pearson correlation test was used.
[b]Spearman correlation test was used.
** Data from day 3rd of the meropenem treatment was used.

Since the renal dose adjustment of meropenem started at the 50 ml/min limit, we divided the patients into two groups using creatinine clearance (CrCL) values on the 3rd day of treatment as the 50 ml/min limit. The mean meropenem C_{min} was 0.39 ± 0.09 mg/l in the group with a CrCL value of 50 ml/min or less and 0.40 ± 0.06 mg/l in the group with a CrCL value greater than 50 ml/min (p=0.651).

Patients were divided into two groups according to their obesity status, and the differences between meropenem C_{min} were analyzed. Patients with a body mass index (BMI) of more than 30 kg/m^2 were considered obese, and those with a BMI of less than 30 kg/m^2 were considered non-obese. Meropenem C_{min} in obese and non-obese patients were 0.41 ± 0.05 and 0.40 ± 0.08, respectively (p = 0.809).

Some laboratory parameters of the patients before and after meropenem treatment were compared. Among these values, erythrocyte count, hemoglobin and CRP values were found to decrease after treatment, while SOFA value was found to increase ($p < 0.05$). The results of this test are given in Table 4.

Meropenem dosing was adjusted based on renal function. Patients were grouped by their last dose before C_{min} sampling, but no significant association was found between dose and C_{min}. According to the doses received, the mean meropenem C_{min} was 0.41 ± 0.06 mg/l for 500 mg, 0.39 ± 0.07 mg/l for 1000 mg and 0.41 ± 0.08 mg/l for 2000 mg, respectively (p=0.659).

Table 4. The relationship between some values of patients before and after meropenem treatment

	Parameter	Before Treatment	After Treatment	p
Biochemistry Panel	Serum creatinine (mg/dl)**	1.05 [0.60 – 1.95]	1.10 [0.60 – 2.13]	0.993
	Serum ALT (IU/l)**	30.50 [19.75 – 52.75]	24.50 [14.00 – 81.75]	0.298
	Serum AST (IU/l) **	39.50 [28.50 – 113.00]	48.00 [30.75 – 97.25]	0.900
	Serum albumin (g/dl)*	2.78 ± 0.53	2.46 ± 0.43	0.946
	Serum sodium (mmol/l)*	140.82 ± 8.36	130.34 ± 6.40	0.141
	Serum potassium (mmol/l)*	4.00 ± 0.65	3.98 ± 1.04	0.599
Hematology Panel	WBC ($x10^3/\mu l$) **	11.92 [8.37 – 16.82]	10.39 [7.58 – 21.19]	0.902
	Neutrophil count ($x10^3/\mu l$) **	9.92 [6.31 – 15.77]	7.87 [4.67 – 16.78]	0.637
	Erythrocyte count ($x10^6/\mu l$) **	3.39 [3.14 – 4.07]	3.18 [2.95 – 3.64]	0.032
	Hemoglobin (g/dl)**	9.80 [8.70 – 12.00]	9.30 [8.38 – 10.35]	0.044
	Hematocrit (%)*	31.96 ± 5.38	29.55 ± 4.84	0.115
	MCV (fl)*	89.04 ± 5.45	90.31 ± 7.10	<0.001
	Platelet ($x10^3/\mu l$)**	209.00 [132.50 – 272.75]	185.50 [95.00 – 292.75]	0.792
Infection Panel	PCT (ng/ml)**	1.08 [0.20 – 4.25]	0.66 [0.21 – 2.88]	0.078
	CRP (mg/dl)*	16.47 ± 11.28	11.71 ± 7.78	<0.001
ICU Scores	SOFA*	8.55 ± 3.48	9.00 ± 4.97	<0.001
	Total GCS**	7.00 [4.00 – 10.00]	7.00 [3.00 – 14.00]	0.933

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
WBC: White Blood Cell
MCV: Mean Corpuscular Volume
PCT: Procalcitonin
CRP: C-Reactive Protein
ICU: Intensive Care Unit
GCS: Glasgow Coma Scale
SOFA: Sequential Organ Failure Assessment
* Paired-sample t-test was used.
** Wilcoxon signed-rank test was used

The effect of receiving mechanical ventilation, sedation and norepinephrine on the sampling day on meropenem C_{min} was analyzed. The results of this test are given in Table 5.

A logistic regression analysis was performed to determine attainment of clinical cure at the end of the meropenem treatment in the patient group in who has SIRS at the beginning of the therapy (n=26). Among 26 patients, 4 (15.38%) patients attained clinical cure. The trough level of meropenem belonging to the 3rd day of the treatment, SOFA score belonging to the first day of the treatment and duration of the meropenem treatment were included in the model. The model was statistically significant X2(3) =11.788, p=0.008. The model explained 50.3% of the variance of the dependent variable (Nagelkerke R2). The Hosmer-Lemeshow test showed that the data fit the model well X2(7) =8.398, p=0.299. It was seen that the only variable that significantly influenced the clinical cure rate was SOFA score belonging to the first day of the treatment and the analysis showed that an increase of one unit in the SOFA score decreases the likelihood of the clinical cure 0.534 times (95% CI 0.311-0.917).

Table 5. The relationship between meropenem C_{min} and some factors related to patients

Factor	n (%)	Meropenem C_{min} (mg/l)	p^*
Mechanical ventilation status			
Yes	31 (81.58)	0.39 ± 0.07	0.321
No	7 (18.42)	0.42 ± 0.08	
Sedation status			
Yes	22 (57.89)	0.38 ± 0.05	0.061
No	16 (42.11)	0.43 ± 0.09	
Average Administered Norepinephrine Dose (µg/kg/min)			
≤0.1	27 (71.05)	0.39 ± 0.07	0.188
>0.1	11 (28.95)	0.42 ± 0.08	

* Independent sample t-test was used

In this study, the targeted 100% *f*T > MIC < 4xMIC index was not achieved when meropenem was administered by standard or extended infusion, which may make it difficult to achieve clinical cure, especially in the ICU environment where resistant pathogens are common. Different dosing strategies need to be developed to reach the targeted index. Many guidelines recommend using TDM to assess the adequacy and efficacy of antimicrobial therapy. TDM maximizes the efficacy and minimizes the toxicity of antimicrobial therapy [18].

MIC values of bacteria vary among themselves. Accordingly, some may be resistant. In one study, the most frequently isolated microorganisms were *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* [19]. The fact that Acinetobacter baumannii was the most frequently isolated organism in our study may indicate that there are infections that are relatively difficult to treat in the ICU where we conducted the study. Furthermore, it is important to consider that organisms may be localized to ICUs in such cases. The resistance rate of this organism to meropenem was found to be as high as 96.55%.

In a study conducted on patients in the ICU, over 50% of the patients failed to achieve the desired therapeutic level for meropenem. In this study, C_{min} levels varied between less than 0.5 mg/l to 39 mg/l [19]. A study comparing the C_{min} of meropenem administered through intermittent and continuous infusion indicated that the C_{min} were 0.5 (0-1.0) in the group getting intermittent infusion, and 11.2 (7.6-11.7) in the group receiving continuous infusion [20]. In this study, the mean meropenem C_{min} value was 0.40 ± 0.07 mg/l. The highest meropenem C_{min} value was 0.63 mg/l, and it was determined that only the patient from whom this sample was taken was given an extended infusion. The fact that C_{min} levels were so far from the target value in our study may also be interpreted because of the low sensitivity of the ELISA method. Validation studies with more sensitive high-performance liquid chromatography methods are available in the literature [21-23]. One of the limitations of the study is that these more sensitive chromatographic methods were not used. Since TDM is difficult to perform in resource-limited settings, dosing protocols can be developed according to the renal and hepatic functions of patients in such centers.

We have found significantly lower meropenem C_{min} compared to the MIC values determined for meropenem in the EUCAST system. It is important that institutions develop specific dosing regimens based on local susceptibility data, preferably based on MIC distributions. MICs should not be viewed in a categorical way but as a continuous probability because MIC values in the susceptible range may require different dosing regimens [24]. MICs at the upper end of the sensitive range may require higher dosing, while MICs in the lower range will require lower dose [4,25,26].

Augmented renal clearance (ARC) is a major risk factor associated with failure to reach the target; another possible factor is inadequate drug dosing in patients [10]. One study found that the only significant predictor of failure to reach the PK target for meropenem was ARC [19]. In our study, CrCL ≥ 130 ml/min was found in 21.05% of the patients and this limit is accepted as ARC in the literature [27]. Failure to achieve PK targets increases the risk of treatment failure and/or development of resistance [5]. Considering that the meropenem resistance rate was 96.55% in the ICU where the study was conducted, it can be said that subtherapeutic meropenem C_{min} levels make it difficult for patients to

achieve clinical cure. To improve the chances of reaching therapeutic targets, higher doses and extended infusion strategies—with or without loading doses—have been used to address subtherapeutic antibiotic levels, particularly in the early stages of severe sepsis [28].

In a study investigating the factors affecting meropenem C_{min}, infusion time, age, albumin, creatinine, and procalcitonin showed a significant positive correlation with the meropenem C_{min} value, while hemoglobin, red blood cells, alanine aminotransferase, and CrCl showed a negative correlation [29]. Our study investigated the association between meropenem C_{min} and different characteristics in patients. However, we couldn't find any significant correlation between these factors and C_{min}. The limited sample size in our study likely influenced the correlation results.

Continuous dosing of meropenem was established as an independent predictor of microbiological success by multivariate logistic regression (OR = 2.977; 95% CI = 1.050-8.443; p= 0.040) [30]. Another study showed that continuous infusion of beta-lactam antibiotics caused a significant difference in the fT > MIC value and led to higher clinical cure rates compared to intermittent administration in critically ill patients with severe sepsis [31]. Keeping in mind that only four patients had established clinical cure, this study showed that a one-unit increase in SOFA score on the first day of meropenem treatment decreased the probability of clinical improvement by 0.534-fold (95% CI 0.311-0.917). The results of this logistic regression should be interpreted with caution due to the small sample size. This regression analysis needs to be repeated with larger participants. In another study, the use of a loading dose prior to continuous or extended infusion increased clinical cure rates in carbapenem treatment [32]. These findings support the routine use of continuous or extended carbapenem infusions in critically ill patients with severe infections, particularly when preceded by a loading dose.

In one study, 13 patients, 12 of whom received extended infusion meropenem, failed to reach the target meropenem concentration. Eight of these patients had an estimated glomerular filtration rate (eGFR) below 50 ml/min [33]. In this current study, using 50 ml/min CrCl values as a cutoff, we divided patients into two groups and observed no statistically significant difference in mean C_{min}. No difference in meropenem C_{min} between groups in our study may be due to renal dosage modification approved by infectious diseases specialists from the start of treatment. Renal function determined the dose; therefore, patients with impaired renal function received a lower dose and those with normal renal function received a greater dose. Thus, the two groups were not significantly different. Ensuring adequate antibiotic therapy within the first 48 hours of critical illness is of paramount importance in the effective treatment of infectious diseases; therefore, unnecessary dose reduction within the first 48 hours may contribute to increased clinical failure of antibiotics [34]. Another study did not recommend adjusting initial doses of meropenem during the first 48 hours in septic critically ill patients to achieve the desired goal [35].

There was a significant difference in the erythrocyte count, hemoglobin value, CRP, and SOFA levels before and after meropenem treatment. When erythrocyte and hemoglobin values were examined after the treatment, a decrease was observed compared to the pre-treatment period ($p < 0.05$). No direct effect of meropenem has been found in the literature and it is thought that the decrease in hemoglobin and erythrocyte values is due to the nature of critical illness. In addition, changes in CRP and SOFA are not sufficient to precisely evaluate the success of meropenem treatment. We think that they may have been affected by factors other than meropenem (mechanical ventilation status, trauma, hospitalization diagnoses...). However, the CRP value appeared to be lower than the value before therapy ($p < 0.001$). This may be due to patients' antimicrobial responses. Meropenem may not have caused this condition alone because patients also used other antibiotics.

SOFA values were found to be increased after treatment compared to pretreatment ($p < 0.001$). The increase in SOFA values indicates the progression in organ failure of the patients. This was not assumed to be related to meropenem treatment, but rather to fluid therapy, difficult-to-treat infections, and unresponsiveness of blood pressure to vasopressors.

A study conducted in a substantial group of very ill patients showed no statistically significant difference in meropenem C_{min} values between obese and non-obese patients [36]. In our study, obese and non-obese patients had similar meropenem C_{min}. A larger patient cohort may change the results.

The investigation revealed no statistically significant relationship between the patients' mechanical ventilation, sedation status, mean norepinephrine dose (µg/kg/min), and meropenem C_{min} (p

> 0.05). No pertinent study was found in the literature review, suggesting additional research. The link of these parameters with meropenem C_{min} can be shown with larger populations and more sensitive chromatographic methods since the patient population of the study and analytical method may alter the results.

Limitations of our study include the small number of patients compared to similar studies and the inability to perform dose optimization based on simultaneous C_{min} levels. In addition, a homogeneous distribution could not be obtained to compare extended infusion and standard infusion strategies. This may be explained by the decision of the responsible infectious disease's specialist.

One of the strengths of this study is that although there is a study investigating meropenem trough levels in Türkiye, ours is the first study reporting meropenem trough levels obtained in a critically ill patient sample. In addition, the fact that the factors affecting C_{min} levels are limited in the literature reveals the unique aspect of our study.

In this study, the target index of 100% $fT > MIC < 4\times MIC$ was not achieved with either standard or extended infusion of meropenem. This limitation may impede clinical progress, particularly in ICU environments where resistant pathogens are prevalent. Alternative dosing regimens are required to achieve the optimal pharmacodynamic targets. Larger-scale studies incorporating blood sample collection at multiple time points throughout the meropenem dosing interval are warranted. Expanding TDM studies using more sensitive chromatographic techniques is also of significant importance for accurately assessing treatment response.

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AUTHOR CONTRIBUTIONS

Concept: A.Ç., H.M.; Design: A.Ç., H.M., Z.Ü.G.; Control: - ; Sources: D.D., M.B., Ç.K.; Materials: D.D., M.B., Ç.K.; Data Collection and/or Processing: A.Ç., H.M., D.D., M.B.; Analysis and/or Interpretation: A.Ç., H.M., Z.Ü.G., E.D., Ç.K.; Literature Review: A.Ç.; Manuscript Writing: A.Ç., H.M., E.D.; Critical Review: Z.Ü.G., E.D.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The ethics committee approval required for the research was obtained from Malatya Clinical Research Ethics Committee on 02.03.2022 with the decision number 2022/16.

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