flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2023;28(3):540-551 • doi: 10.5578/flora.20239726

Are Given Doses of Meropenem Adequate for Elderly Patients?

Yaşlı Hastalara Verilen Meropenem Dozları Yeterli mi?

Esra NURLU TEMEL[1](İD), Onur ÜNAL[1](İD), Kağan ŞEVİK[1](İD), Pınar KARABACAK[2](İD), Mehtap SAVRAN[3](İD), Özgür ÖNAL[4](İD), Onur KAYA[1](İD), Gül Ruhsar YILMAZ[1](İD), Füsun Zeynep AKÇAM[1](İD)

[1] Department of Infectious Diseases and Clinical Microbiology, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye
[2] Department of Anesthesiology and Reanimation, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye
[3] Department of Pharmacology, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye
[4] Department of Public Health, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye

Cite this article as: *Nurlu Temel E, Ünal O, Şevik K, Karabacak P, Savran M, Önal Ö, et al. Are given doses of meropenem adequate for elderly patients? FLORA 2023;28(3):540-551.*

ABSTRACT

Introduction: *Infections are major contributing factors to morbidity and mortality in the elderly. Aging affects various aspects of antibiotic pharmacokinetics, including absorption, distribution, and elimination. Maintaining adequate antibiotic concentrations is crucial in elderly individuals due to the heightened risk of treatment inadequacy. In this study, our objective was to investigate the plasma concentrations of meropenem, a commonly utilized antibiotic in elderly populations, and assess the impact of age on these measurements.*

Materials and Methods: *In this prospective observational study, we analyzed meropenem levels in a total of 177 blood samples obtained from 59 patients aged 65 and older. These patients were under the care of inpatient services outside the intensive care unit. Meropenem treatment was administered through intermittent infusions of 1 g in 0.5 hours every eight hours. A total of three blood samples were collected from each patient. These samples were collected on the third day of meropenem treatment, just before the next dose, at 30 and 120 minutes after the first dose. Plasma meropenem level was quantified using high-performance liquid chromatography-ultraviolet analysis. To determine the effect of age on the results, the obtained data were compared with the patient characteristics and laboratory parameters.*

Results: *Our results showed that in the first samples (C_{trough}) plasma antibiotic concentrations exceeded the MIC in 20.3% of patients, while 79.7% remained at the subtherapeutic level. In the second (C_{max}) and third samples (C_{mid}) 5.1% and 1.7% of patients remained at the subtherapeutic level, respectively. The plasma meropenem level was 8 mg/L and above in participants with four and more comorbidities, and this result demonstrated statistical significance ($p< 0.05$).*

Conclusion: *Current guidelines for beta-lactam antibiotics do not provide predictable trough antibiotic concentrations in older adults hospitalized for infections. There is a need for predictive factors to inform antibiotic dosing in the elderly population, and a greater emphasis on therapeutic drug monitoring of beta-lactams in these patients would be beneficial.*

Key Words: *Meropenem; Elderly; Minimum inhibitory concentration; Therapeutic drug monitoring*

Received/Geliş Tarihi: 23/08/2023 - Accepted/Kabul Ediliş Tarihi: 16/09/2023

Available Online Date: 20.09.2023

ÖZ

Yaşlı Hastalara Verilen Meropenem Dozları Yeterli mi?

Esra NURLU TEMEL[1], Onur ÜNAL[1], Kağan ŞEVİK[1], Pınar KARABACAK[2], Mehtap SAVRAN[3], Özgür ÖNAL[4], Onur KAYA[1], Gül Ruhsar YILMAZ[1], Füsun Zeynep AKÇAM[1]

[1] Süleyman Demirel Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Isparta, Türkiye
[2] Süleyman Demirel Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Isparta, Türkiye
[3] Süleyman Demirel Üniversitesi Tıp Fakültesi, Farmakoloji Anabilim Dalı, Isparta, Türkiye
[4] Süleyman Demirel Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, Isparta, Türkiye

Giriş: *İnfeksiyonlar yaşlılarda morbidite ve mortaliteye katkıda bulunan başlıca faktörlerdir. Yaşlanma; antibiyotik farmakokinetiğini emilim, dağılım ve eliminasyon dahil birçok farklı açıdan etkiler. Yaşlı bireylerde yetersiz tedaviye yol açabilmesi nedeniyle düşük antibiyotik konsantrasyonları kritik öneme sahiptir. Bu çalışmada yaşlı bireylerde meropenemin plazma konsantrasyonlarını ve yaşın bu değerlere etkisini araştırmayı amaçladık.*

Materyal ve Metod: *Prospektif gözlemsel olarak yürütülen çalışmada yoğun bakım ünitesi dışında yataklı servislerde takip edilen 65 yaş üstü 59 hastadan alınan 177 kan örneğinde meropenem düzeyleri araştırıldı. Hastalara sekiz saatte bir yarım saatte gidecek şekilde 1 g aralıklı infüzyonla meropenem tedavisi uygulandı. Her hastadan toplam üç kan örneği alındı. Kan örnekleri meropenem tedavisinin üçüncü gününde, ilk dozdan hemen önce, ilk dozdan 30 ve 120 dakika sonra alındı. Plazma meropenem düzeyi yüksek performanslı likit kromatografisi-ultraviyole ile belirlendi. Yaşın sonuçlara etkisini belirlemek için elde edilen veriler hastaların özellikleri ve laboratuvar parametreleriyle karşılaştırıldı.*

Bulgular: *Sonuçlarımız hastaların ancak %20.3'ünde ilk örnekte (C_{trough}) plazma antibiyotik konsantrasyonunun MİK'i aştığını, %79.7'sinin ise subterapötik düzeyde kaldığını gösterdi. İkinci numuneleri (C_{max}) ve üçüncü numuneleri (C_{mid}) takiben hastaların sırasıyla %5.1 ve %1.7'sinde meropenem düzeyi subterapötik seviyede kaldı. Komorbiditesi dört ve üzerinde olan katılımcılarda plazma meropenem düzeyi 8 mg/L ve üzerindeydi, sonuç istatistiksel olarak anlamlıydı ($p< 0.05$).*

Sonuç: *Beta-laktam antibiyotiklere ilişkin mevcut kılavuzlar, infeksiyon nedeniyle hastaneye yatırılan yaşlı yetişkinlerde öngörülebilir antibiyotik konsantrasyonları sağlamamaktadır. Yaşlılarda antibiyotik dozunu yönlendirmek için prediktörlere ihtiyaç vardır ve bu hastalarda beta-laktamların terapötik ilaç takibinin artan kullanımı yardımcı olacaktır.*

Anahtar Kelimeler: *Meropenem; Yaşlı; Minimum inhibitör konsantrasyon; Terapötik ilaç takibi*

INTRODUCTION

The global population of older adults has increased rapidly worldwide, especially in developed countries. The general population profile is shifting towards old age, and there is almost a "demographic revolution". Hence, one of the paramount concepts emerging in the 21st century is the aging of populations. Based on World Health Organization (WHO) data, in 2019, the number of people aged 60 years and older was one billion. This number will increase to 1.4 billion by 2030 and 2.1 billion by 2050. This increase is occurring at an unprecedented pace and will accelerate in the coming decades, particularly in developing countries[1].

Due to factors such as ongoing physiological changes in organ function and the complexity of polypharmacy, striking a satisfactory balance between antibiotic efficacy, safety, and tolerability is a challenging task in the elderly population. These factors can cause considerable changes in antibiotic pharmacokinetics (PK) and pharmacodynamics (PD), resulting in altered therapeutic efficacy, safety, and tolerability[2]. It is difficult to decide on the optimal antibacterial treatment for the elderly.

Aging affects various aspects of antibiotic pharmacokinetics, including absorption, distribution, and elimination[3]. Antibiotic doses and dosing intervals may need to be adjusted depending on the origin and severity of the underlying infection and the elimination pathway of the antibiotic itself[3]. Due to the risk of inadequate treatment efficacy, low concentrations are the most critical concern. Therefore, therapeutic drug monitoring (TDM) is recommended for individualizing antimicrobial drug doses in a special patient population[4]. Meropenem is characterized by a

low volume of distribution and a minimal (2%) extent of protein binding[5]. Since meropenem has time-dependent antimicrobial activity, the primary parameter indicating its antimicrobial activity is the percentage of time intervals during which the plasma concentration persists above the minimum inhibitory concentration (MIC) of the pathogenic microorganism (%T> MIC)[5].

The available studies that confirm the attainment of sufficient antibiotic concentrations in older adults using current dosing regimens of intravenous β-lactam antibiotics are extremely limited[6,7]. Furthermore, due to the absence of well-established clinical pharmacology practices in our country, there is also a notable insufficiency in studies conducted in this domain. The main objective of this preliminary study was to ascertain the plasma meropenem levels, aiming to enhance the quality of drug-oriented healthcare. The secondary aim is to observe and evaluate the possible effects of age on the pharmacokinetics of meropenem.

MATERIALS and METHODS

Study design

This prospective cross-sectional study was conducted at the Süleyman Demirel University Research and Application a tertiary care hospital in Isparta, Türkiye. The study was performed between January and June 2022.

Study population

The study included individuals aged 65 and older who had received a preliminary diagnosis of either community-acquired or hospital-acquired infection. These individuals were being treated in hospital departments other than the intensive care unit. To be eligible, participants were required to have an estimated glomerular filtration rate (eGFR) greater than 50 mL/min and to have been started on meropenem treatment under the guidance of an infectious diseases specialist. Furthermore, only those who had completed a minimum of 48 hours of meropenem treatment were considered for inclusion in the study. Patients with a documented history of meropenem allergy, an eGFR below 50 mL/min, concurrent use of probenecid, vasopressors/inotropes and valproic acid that could potentially interact with meropenem, and those undergoing renal replacement therapy were excluded from the study.

Data collection

Patient data were collected, encompassing demographic information such as age, sex, body weight, height, body mass index (BMI), and comorbidity status. Additionally, microbiological results, biochemical parameters, C-reactive protein (CRP) levels, procalcitonin values, clinical outcomes over a 28-day period (patients were evaluated in four groups according to their clinical outcomes), length of hospital stay, timing of dosing and sampling, as well as the drug treatment information of the patients, were included in the data collection process. Biochemical parameters, CRP and procalcitonin values were analyzed in first week, between 8^{th}-14^{th} day (second week) and after 15^{th} day (third week) of the meropenem therapy.

Meropenem dosing and administration

The dosing of meropenem was ultimately determined based on the professional judgment of the infectious disease specialist. In this study, meropenem was given intravenously at 1 gram in 0.5 hours every eight hours through intermittent administration.

Blood sampling

Measurements during the initial and subsequent days of treatment were omitted to attain steady-state-like trough concentrations. After six doses of meropenem were given, blood samples (3 mL of whole blood/sample in an ethylenediaminetetraacetic acid tube) were collected just before the next dose of meropenem (C_{trough}) and at 30 minutes (C_{max}) and 120 minutes (C_{mid}) after starting meropenem administration. [C_{trough}= unbound plasma meropenem concentrations at end-dosing intervals; C_{max} (peak concentration)= the maximum drug concentration measured in the blood following the administered dose; C_{mid}= unbound plasma meropenem concentrations at mid-dosing intervals]. Blood samples were centrifuged at 3000 rpm for 10 minutes. Plasma samples were evaluated immediately without freezing. The samples were analyzed by high-performance liquid chromatography-ultraviolet

(HPLC-UV) at Süleyman Demirel University, YETEM (Innovative Technologies Application and Research Center).

Determination of plasma meropenem concentrations

Meropenem concentrations were measured at Süleyman Demirel University, YETEM, using the HPLC-UV detection method, as previously described[8]. 500 µL of saline was added to the 500 µL plasma sample and mixed by vortexing. 400 µL of phosphoric acid solution prepared by adding 75 µL of phosphoric acid to 10 mL of methanol was added and vortexed for two minutes. After vortexing, it was centrifuged at 14.000 rpm for 10 minutes. The supernatant was taken and placed in HPLC-UV (SHIMADZU, Japan). The specifications of the HPLC-UV device used are given in the appendix.

Evaluation of meropenem concentration measurements

In our research, meropenem efficacy is described by the plasma concentration exceeding the MIC (fT%> MIC)[7]. This is why we have established our target concentration for C_{trough} at 8 mg/L. For reference, the MIC breakpoints established by EUCAST[9] for meropenem plasma concentrations were adopted (the MIC value determined for *Pseudomonas* spp. was selected similarly to those in the previous studies, >8 mg/L).

According to several publications, the maximal killing of bacteria is observed when serum concentrations remain four to five times higher than the MIC of the pathogen that is causing the infection (fT> 4-5 X MIC)[10]. Hence, we established our second target concentration value at 32 mg/L for C_{max} and C_{mid}. Serum meropenem concentrations in the 8-32 mg/L range were determined as the therapeutic target[10,11]. As a result, the obtained concentrations were then interpreted about the known or presumed MIC of the pathogen (Table 2)[12].

Statistical Method

Statistical Package for Social Sciences (SPSS) 28.0 Windows (IBM Corporation, Armonk, New York, USA) software was used to analyze the research data statistically. Numbers and percentages were used to represent nominal data, and median (med) and interquartile ranges (IQR) were used to describe measurement values. The conformity of the metric values to the normal distribution was examined with the Shapiro-Wilk test. Mann-Whitney U test, Wilcoxon test, Freidman analysis of variance, and Chi-square test were used for comparisons. Bonferroni correction was applied in post hoc tests. Statistical significance was defined as a p-value of <0.05.

RESULTS

Seventy-five patients who were followed up in the clinics and started on meropenem treatment were included in the study. Meropenem treatment was started empirically in 45 (76.3%) patients and based on microbiological data in 14 (23.7%) patients. Sixteen patients were excluded from the study as nine of them were de-escalated by switching to different antibiotics, five patients required dialysis while under meropenem treatment, and two patients were transferred to other centers.

Ultimately the plasma meropenem levels of 59 patients were evaluated. The mean age of the study population was 73.20 ± 8.83, 32.2% of the participants were female, and 47.5% were older than 75. The BMI was ≤25 kg/m^2 in 47.5% of the patients, while it was >25 kg/m^2 in 52.5%. More than 70% of the patients receiving meropenem treatment had two or more comorbidities. The mean number of comorbidities was 1.9 ± 0.09, and the most common diseases in patients (heart diseases, respiratory diseases, stroke, anemia, diabetes mellitus, peripheral vascular disorders, gastrointestinal diseases, musculoskeletal diseases, non-vascular neurological diseases such as Parkinson's and Alzheimer's, malignancies) were determined as comorbidity types[13]. When the indications for meropenem treatment were examined, it was found that pneumonia (40.7%), urinary tract infection (16.9%), and intra-abdominal infection (15.3%) were the most common.

Microorganism growth was not detected in the cultures (blood, catheter, urine, abscess, and cerebrospinal fluid) obtained from 55.9% of the participants. In other patients, the most

Table 1. Demographic characteristics of patients aged 65 and above in the study

	Number	%
Sex		
Female	19	32.2
Male	40	67.8
Age		
<75 years	31	52.5
≥75 years	28	47.5
BMI		
≤25 kg/m^2	28	47.5
>25 kg/m^2	31	52.5
Number of comorbidities*		
0-1	17	28.8
2-3	31	52.5
≥4	11	18.6
Site of infection		
Pneumonia	24	40.7
Urinary tract infection	10	16.9
Intraabdominal infection	9	15.3
Bloodstream infection	3	5.1
Central nervous system infection	2	3.4
Soft tissue infection	2	3.4
Cholecystitis	2	3.4
Prosthesis infection	2	3.4
Surgical-site infection	1	1.7
Osteomyelitis	1	1.7
Cholangitis	1	1.7
Pancreatitis	1	1.7
Empyema	1	1.7
Microorganisms		
Escherichia coli	9	15.3
Pseudomonas aeruginosa	7	11.9
Klebsiella spp.	4	6.8
Acinetobacter spp.	4	6.8
Enterobacter spp.	2	3.4
No growth	33	55.9
Clinical outcomes		
Clinical improvement	34	57.6
Exitus	11	18.6
Other group**	7	11.9
Transfer to ICU	7	11.9

* Some patients have more than one comorbidities.
**Duration of meropenem therapy was prolonged or second antibiotic was added.
ICU: Intensive care unit, BMI: Body mass index.

Table 2. Meropenem plasma concentrations before the next dose of meropenem, 30 minutes, and 120 minutes after treatment

	MCP	Number	%
Pretreatment (C_{trough})	<8 mg/L	47	79.7
	8-31.99 mg/L	11	18.6
	≥32 mg/L	1	1.7
30 minutes after treatment ($C_{maximum}$)	<8 mg/L	3	5.1
	8-31.99 mg/L	20	33.9
	≥32 mg/L	36	61.0
120 minutes after treatment ($C_{mid-dosing}$)	<8 mg/L	1	1.7
	8-31.99 mg/L	28	47.5
	≥32 mg/L	30	50.8

MCP: Meropenem concentration in plasma (mg/L EUCAST values were referenced).

prevalent identified microorganisms were multi-drug resistant (MDR) *Escherichia coli* (15.3%), MDR *Pseudomonas aeruginosa* (11.9%), and MDR *Klebsiella* spp. (6.8%), respectively. The participants were assessed for clinical outcomes at the end of the meropenem treatment period. The mean duration of meropenem treatment was 18.1 ± 1.79 days. While clinical improvement occurred in 57.6% of the participants, a mortal course was observed in 18.6%. Demographic data are shown in Table 1.

In three samples from participants on the third day of meropenem treatment, measured plasma meropenem concentrations were evaluated according to the time of collection of samples and MIC value (Table 2).

The meropenem level was below 8 mg/L in 79.7%, above 8 mg/L in 18.6%, and above 32 mg/L in 1.7% of the first samples (C_{trough}).

The meropenem level was below 8 mg/L in 5.1%, between 8 mg/L and <32 mg/L in 33.9%, and above 32 mg/L in 61.0% of the second samples (C_{max}).

The meropenem level was below 8 mg/L in 1.7%, between 8 mg/L and <32 mg/L in 47.5%, and above 32 mg/L in 50.8% of the third samples (C_{mid}).

The effect of the descriptive variables of the participants on the meropenem concentration in plasma (MCP) is analyzed in Table 3. It was determined that the participant's sex, age, clinical outcomes, length of hospital stay, and BMI values did not affect plasma meropenem levels. In the group with four and more comorbid diseases, the number of people with an MCP value of 8 mg/L and above was higher (p= 0.039). Additionally, the patients with 2-3 comorbid diseases, number of people with an for $C_{through}$ MCP value of 32 mg/L and above was higher for C_{max} (p= 0.015).

Biochemical, CRP, and procalcitonin values of the patients were recorded once a week (for three weeks) during the first three weeks of the 28-day follow-up period. The results were evaluated weekly in terms of the relationship between both themselves and the plasma meropenem level (Table 4).

There were no alterations observed in the values (creatinine, AST, and ALT) indicative of the renal and hepatic functions of the patients during the first three weeks of the 28-day follow-up period. However, when evaluated according to the plasma meropenem level measured in the first week of meropenem treatment, creatinine level in the second week was significantly higher in patients with MCP≥ 8 mg/L compared to those with MCP< 8 mg/L (p< 0.05) in C_{trough} group.

Weekly significant reductions in CRP and procalcitonin levels were observed, except for the patient group whose plasma meropenem concentration was ≥8 mg/L before next dose of meropenem ($C_{through}$). Procalcitonin level was also higher in patients with MCP≥ 8 mg/L than those with MCP< 8 mg/L in all three measurements in the $C_{through}$ group [(p< 0.01), (p< 0.01) and (p< 0.05) respectively, Table 4].

Table 3. The descriptive variables of the patients and their impact on PMC values.

			C trough*		C max*		C mid*	
		Total**	MCP< 8 n (%)	MCP≥ 8 n (%)	MCP< 32 n (%)	MCP≥ 32 n (%)	MCP< 32 n (%)	MCP≥ 32 n (%)
Sex	Female	19 (32.2)	15 (78.9)	4 (21.1)	9 (47.4)	10 (52.6)	6 (31.6)	13 (68.4)
	Male	40 (67.8)	32 (80.0)	8 (20.0)	14 (35.0)	26 (65.0)	23 (57.5)	17 (42.5)
	p		0.925		0.363		0.063	
Age (years)	<75	31 (52.5)	27 (87.1)	4 (12.9)	12 (38.7)	19 (61.3)	17 (54.8)	14 (45.2)
	≥75	28 (47.5)	20 (7.4)	8 (28.6)	11 (39.3)	17 (60.7)	12 (42.9)	16 (57.1)
	p		0.135		0.964		0.358	
Clinical outcome	CI	34 (57.6)	29 (85.3)	5 (14.7)	15 (44.1)	19 (55.9)	20 (58.8)	14 (41.2)
	OG	7 (11.9)	5 (71.4)	2 (28.6)	4 (57.1)	3 (42.9)	3 (42.9)	4 (57.1)
	Ex	11 (18.6)	7 (63.6)	4 (36.4)	3 (27.3)	8 (72.7)	4 (36.4)	7 (63.6)
	TICU	7 (11.9)	6 (85.7)	1 (14.3)	1 (14.3)	6 (85.7)	2 (28.6)	5 (71.4)
	p		0.414		0.287		0.349	
Number of comorbidities***	0-1	17 (28.8)	16 (94.1)	1 (5.9)	11 (64.7)	6 (35.3)	9 (52.9)	8 (47.1)
	2-3	31 (52.5)	25 (80.6)	6 (19.4)	7 (22.6)	24 (77.4)	17 (54.8)	14 (45.2)
	≥4	11 (18.6)	6 (54.5)	5 (45.5)	5 (45.5)	6 (54.5)	3 (27.3)	8 (72.7)
	p		**0.039**		**0.015**		0.272	
Length of hospital stay (day)	≤14	19 (78.9)	15 (78.9)	4 (21.1)	5 (26.3)	14 (73.7)	8 (42.1)	11 (57.9)
	14-28	29 (72.4)	21 (72.4)	8 (27.6)	15 (51.7)	14 (48.3)	16 (55.2)	13 (44.8)
	>28	11 (100.0)	11 (100.0)	0 (0.0)	3 (27.3)	8 (72.7)	5 (45.5)	6 (54.5)
	p		0.053		0.139		0.650	
BMI (kg/m^2)	<25	28 (47.5)	20 (71.4)	8 (28.6)	12 (42.9)	16 (57.1)	16 (57.1)	12 (42.9)
	≥25	31 (52.5)	27 (87.1)	4 (12.9)	11 (35.5)	20 (64.5)	13 (41.9)	18 (58.1)
	p		0.197		0.602		0.301	

*Row percentage is used.
**Column percentage is used.
***Some patients may have more than one comorbidities.
BMI: Body mass index, CI: Clinical improvement, OG: Other group, TICU: Transfer to intrensive care unit, Ex: Exitus, MCP: Meropenem concentration in plasma (mg/L), C_{trough}: Unbound plasma meropenem concentrations at end-dosing intervals, C_{max} (peak concentration): The maximum drug concentration measured in the blood following the administered dose C_{mid}: Unbound plasma meropenem concentrations at mid-dosing intervals.

The study also found that CRP was higher in patients with MCP≥ 8 mg/L in the third week than those with MCP< 8 mg/L in the $C_{through}$ group (p< 0.05).

DISCUSSION

Optimizing antibiotic therapy entails selecting the appropriate antibiotic and administering the correct dose to ensure efficacy and minimize the risk of side effects. Dosage recommendations are frequently based on data from adults, and healthy volunteers, but they are generalized to all people. Nevertheless, a majority of antibiotics are administered to older adults within hospital settings, and there is a scarcity of information available regarding the assessment of antibiotic concentrations within this demographic. Most of the studies on blood antibiotic levels were performed on critically ill patients in the intensive care unit, where the continuous infusion of meropenem treatment was recommended, and studies on patients followed in clinical services are scarce[14,15]. In clinical practice, it's imperative to bear in mind that age is linked to significant alterations in drug metabolism.

The key factor linked to the therapeutic effectiveness of meropenem is the duration during which its levels remain above the MIC. Insufficient meropenem levels can result in treatment failure and increase the risk of bacterial resistance development. Pharmacodynamics employs the

Table 4. Weekly change in procalcitonin. liver enzymes. creatinine. and C-reactive protein during meropenem treatment and the effect of plasma meropenem concentration on this change

	C trough			C Max			C mid		
	MPC< 8 Med (IQR)	MPC≥ 8 Med (IQR)	p*	MPC< 32 Med (IQR)	MPC≥ 32 Med (IQR)	p*	MPC< 32 Med (IQR)	MPC≥ 32 Med (IQR)	p*
Procalcitonin 1 (1st week)	0.7 (3.4)	6.2 (11.8)	**<0.01**	0.4 (1.9)	1.9 (8.2)	>0.05	1.0 (6.5)	0.8 (3.7)	>0.05
Procalcitonin 2 (2nd week)	0.2 (0.7)	1.2 (5.1)	**<0.01**	0.2 (0.7)	0.6 (2.1)	>0.05	0.5 (1.3)	0.4 (0.8)	>0.05
Procalcitonin 3 (3rd week)	0.1 (0.3)	0.5 (2.3)	**<0.05**	0.1 (0.2)	0.2 (0.7)	>0.05	0.1 (0.5)	0.2 (0.9)	>0.05
p**	**<0.001**	0.174		**0.001**	**0.043**		**0.005**	**0.015**	
AST 1 (1st week)	36.0 (33.0)	30.0 (17.3)	>0.05	36.0 (29.0)	32.0 (32.3)	>0.05	32.0 (25.0)	33.0 (36.3)	>0.05
AST 2 (2nd week)	39.0 (32.0)	32.5 (20.8)	>0.05	33.0 (25.0)	26.5 (29.0)	>0.05	26.0 (31.0)	30.0 (28.8)	>0.05
AST 3 (3rd week)	30.0 (28.0)	39.0 (56.5)	>0.05	33.0 (23.0)	330.0 (51.5)	>0.05	30.0 (32.0)	34.0 (43.3)	>0.05
p**	0.382	0.059		0.924	0.092		0.706	0.261	
ALT 1 (1st week)	23.0 (37.0)	18.5 (12.5)	>0.05	26.0 (27.0)	20.0 (12.8)	>0.05	22.0 (19.5)	22.0 (17.8)	>0.05
ALT 2 (2nd week)	21.0 (31.0)	19.0 (15.8)	>0.05	23.0 (36.0)	21.0 (26.8)	>0.05	24.0 (34.0)	20.0 (23.0)	>0.05
ALT 3 (3rd week)	20.0 (38.0)	24.0 (26.5)	>0.05	21.0 (38.0)	19.0 (28.0)	>0.05	21.0 (37.0)	19.0 (19.8)	>0.05
p**	0.533	0.917		0.926	0.504		0.782	0.209	
Creatinine 1 (1st week)	0.7 (0.3)	0.8 (0.5)	>0.05	0.7 (0.3)	0.7 (0.4)	>0.05	0.7 (0.3)	0.6 (0.3)	>0.05
Creatinine 2 (2nd week)	0.6 (0.3)	0.8 (0.4)	<0.05	0.6 (0.3)	0.7 (0.4)	>0.05	0.6 (0.3)	0.7 (0.4)	>0.05
Creatinine 3 (3rd week)	0.7 (0.5)	0.8 (0.8)	>0.05	0.6 (0.4)	0.7 (0.8)	>0.05	0.6 (0.2)	0.8 (0.8)	>0.05
p**	0.056	0.779		0.344	0.406		0.355	0.188	
CRP 1 (1st week)	136.0 (132.0)	168.0 (107.5)	>0.05	110.0 (126.0)	172.0 (144.3)	>0.05	135.0 (118.5)	159.5 (160.5)	>0.05
CRP 2 (2nd week)	89.0 (87.0)	86.2 (118.8)	>0.05	77.0 (81.0)	94.0 (88.0)	>0.05	89.0 (76.5)	91.0 (86.5)	>0.05
CRP 3 (3rd week)	44.0 (70.0)	87.0 (120.3)	<0.05	43.0 (68.0)	66.5 (123.3)	>0.05	36.0 (68.0)	67.0 (118.9)	>0.05
p**	**<0.001**	0.368		**<0.001**	**<0.001**		**<0.001**	**<0.001**	

p*: Row comparison, p**: Column comparison, MPC: Meropenem concentration in plasma (mg/L).

MIC to establish parameters of antibacterial activity, thereby determining whether an antibiotic has an impact on the target microorganisms[7]. Meropenem TDM targets used in studies vary[2,4].

In the present study, the primary PK outcome under analysis for treatment was the maintenance of plasma antibiotic concentrations above the MIC on day three[16]. Three blood samples were obtained from each patient during a single dosing interval. However, in the first samples (C_{trough}) plasma antibiotic concentrations exceeded the MIC in 20.3% of patients, while 79.7% remained at the subtherapeutic level. In the second samples (C_{max}) and third samples (C_{mid}) 5.1% and 1.7% of patients remained at the subtherapeutic level, respectively.

Our results showed that in some elderly patients who received intermittent meropenem infusion, C_{mid}, C_{max}, and especially the C_{trough} values could not exceed the MIC. Hence, the plasma meropenem concentration remained at the subtherapeutic level. Again, when the maximum drug concentration was reached at the 30^{th} (C_{max}) and 120^{th} (C_{mid}) minutes, it was determined that the MIC value could not be exceeded in 5.1% and 1.7% of the patients, respectively. These results may be related to the failure to administer meropenem as a continuous infusion or it may be due to not administering loading doses in geriatric patients. In a study conducted by Dulhunty et al., it was demonstrated that continuous administration of beta-lactam antibiotics led to higher plasma antibiotic concentrations and better clinical improvement compared to intermittent administration[17]. Furthermore, continuous infusion has been proven to result in elevated blood and interstitial fluid concentrations, as well as faster killing of bacteria, especially for bacteria with elevated MIC values[18]. Similar to our study, Hatti et al. found that meropenem trough antibiotic concentrations were generally low in relation to the target range in elderly patients hospitalized for infection[6]. Previous studies on elderly patients demonstrated that age-related changes in organ dysfunction, co-morbidity, and critical infections (e.g., severe sepsis) are associated with variations in beta-lactam concentration levels[7,12,19,20]. In our study, patients with a eGFR 50 mL/min and above were included, but metabolic changes due to old age, which have not yet been determined, may have contributed to our results.

Given the established fact that older individuals experience a heightened mortality risk from infections, the foremost concern lies in low concentrations, primarily due to the potential of inadequate treatment outcomes. For this reason, continuous or long-term infusion and loading doses of antibiotics may be applied to elderly patients, as in intensive care patients. However, therapeutic drug level monitoring is essential to follow-up toxic doses that may occur due to decreased functional reserve capacity and comorbidities.

Upon assessing the connection between certain descriptive variables of the participants and plasma meropenem levels, it was observed that the number of comorbidities was notably higher in patients whose meropenem concentration levels were at therapeutic and supratherapeutic levels. Unlike our results, in the study of Hatti et al., no association was found between comorbidities and plasma meropenem concentrations in elderly individuals[6]. This elevation may be associated with decreased elimination of meropenem due to the burden placed on renal functions by comorbidities, polypharmacy, and infection[21]. In conclusion, two different results in our study show that the risk of meropenem level being affected by different variables should be investigated. Comorbidities that primarily affect drug pharmacokinetics rather than the number of comorbid diseases may be effective on meropenem levels.

Participants were categorized into two groups based on age. There was no significant difference in meropenem concentrations between patients 65 and 75 years of age and patients over 75 years of age. Furthermore, it was determined that sex did not impact the meropenem levels in elderly patients. Among the descriptive characteristics of the patients, it was noted that BMI did not influence plasma meropenem levels. Similar to our findings, two studies that specifically assessed the influence of body weight on meropenem pharmacodynamics and pharmacokinetics demonstrated that BMI

was not a determining factor in achieving the target concentration level[22,23]. However, elderly individuals were not included in these studies, unlike in the current study.

In patients followed during meropenem treatment, the most common indications for β-lactam therapy were pneumonia (40.7%), similar to the findings of Hatti et al[6]. The most frequently identified bacteria were *Escherichia coli* (15.3%) and *Pseudomonas aeruginosa* (11.9%), respectively. As no reproduction occurred among all the study participants, MIC data were sourced from the literature and employed in the modeling process to attain the pharmacodynamic target[7].

A significant association was not found between plasma meropenem concentrations and the length of hospital stay, as well as seven, 14 and 28 day mortality. Contrary to our results, Hatti et al. reported that high concentrations of meropenem in elderly patients were associated with 28-day mortality and increased length of stay[6]. In elderly patients treated with meropenem, subtherapeutic and supratherapeutic doses may affect mortality. Therefore, therapeutic monitoring of meropenem in elderly individuals is essential. However, there is a limited number of studies on this subject.

No significant changes were not observed in creatinine, AST, and ALT values during their three-week clinical follow-up. With this, when laboratory data was evaluated according to the plasma meropenem level measured in the first week of treatment, creatinine level in the second week was higher in patients with MCP≥ 8 mg/L in the C_{trough} group. Usman et al., similar to the results of our study, reported that meropenem treatment at different doses and durations applied to elderly patients did not affect renal functions[19]. In addition, significant decreases were observed in CRP and procalcitonin levels during their three-week clinical follow-up, except for the patient group whose trough meropenem concentration was above 8 mg/L in $C_{through}$ group. Again, when procalcitonin and CRP values were evaluated according to the plasma meropenem level measured in the first week of treatment, procalcitonin level was also higher in patients with MCP≥ 8 mg/L in all three measurements. At the same time, CRP was more elevated in patients with MCP≥ 8 mg/L in the third week in the $C_{through}$ group. All of these results may be related to the more severe clinical course of infections or comorbid diseases of the participants in this group, hence the later decrease in CRP and procalcitonin responses. Yet, no other study was found in which CRP and procalcitonin levels were evaluated to plasma meropenem concentrations in geriatric patients.

With this study, a validated plasma meropenem determination method applicable to clinical practice was successfully established in our own center. The study's findings underlined the potential for subtherapeutic levels of meropenem in older individuals, even plasma in susceptible pathogens. In addition, our study draws attention to the fact that age-related comorbid conditions may be associated with subtherapeutic and supratherapeutic doses of meropenem. Therefore, these data need to be supported by further studies.

However, the study also has limitations. The most critical limitations were that patients with the same infectious disease diagnosis were not included in the study, no disease severity scoring specific to infectious diseases (for service patients), and geriatric comorbidity scoring could not be performed, respectively. The second limitation of the study did not include patients with severe acute kidney injury or those receiving renal replacement therapy. Furthermore, the effects of loading dose and infusion time on blood meropenem levels in geriatric patients could not be evaluated since patients given meropenem with prolonged infusion were not included in the study.

The third limitation of the study is that it could not be designed to measure fT> MIC or perform appropriate pharmacokinetic simulations requiring a larger number of samples per patient and the scale of the study was limited.

In conclusion, current guidelines for beta-lactam antibiotics do not provide predictable trough antibiotic concentrations in older adults hospitalized for infections. There is a need for predictive factors to inform antibiotic dosing in

the elderly population, and a greater emphasis on therapeutic drug monitoring of beta-lactams in these patients would be beneficial.

CONCLUSION

Optimizing the management of older patients with infectious diseases necessitates an understanding of the principal age-related changes in the patient's organism. Tailoring pharmacotherapy to align with the distinctive characteristics of elderly patients might lead to attaining an optimal PK/PD target and, consequently, treatment success.

ETHICS COMMITTEE APPROVAL

This study was approved by the Süleyman Demirel University Clinical Research Ethics Committee (Decision no: 28/394, Date: 21.12.2020).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: ENT, MS, OÜ, OK, GRY, FZA

Analysis/Interpretation: ÖÖ, ENT

Data Collection or Processing: ENT, KŞ, PK

Writing: ENT

Review and Correction: OÜ, OK, GRY, FZA

Final Approval: ENT, OÜ, KŞ, PK, MS, ÖÖ, OK, GRY, FZA

REFERENCES

1. *World Health Organization (WHO). December 2, 2022. Available from: https://www.who.int/health-topics/ageing#tab=tab_1.*
2. *Pea F. Pharmacokinetics and drug metabolism of antibiotics in the elderly. Expert Opin Drug Metab Toxicol 2018;14:1087-100. https://doi.org/10.1080/17425255.2018.1528226*
3. *Bradley SF. Principles of antimicrobial therapy in older adults. Clin Geriatr Med 2016;32:443-57. https://doi.org/10.1016/j.cger.2016.02.009*
4. *Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 2012;73:27-36. https://doi.org/10.1111/j.1365-2125.2011.04080.x*
5. *Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. Clin Infect Dis 2008;47:S32-S40. https://doi.org/10.1086/590064*
6. *Hatti M, Solomonidi N, Odenholt I, Tham J, Resman F. Considerable variation of trough β-lactam concentrations in older adults hospitalized with infection-a prospective observational study. Eur J Clin Microbiol Infect Dis 2018;37:485-93. https://doi.org/10.1007/s10096-018-3194-x*
7. *Butranova OI, Ushkalova EA, Zyryanov SK, Chenkurov MS, Baybulatova EA. Pharmacokinetics of antibacterial agents in the elderly: The body of evidence. Biomedicines 2023;11:1633. https://doi.org/10.3390/biomedicines11061633*
8. *Dincel D, Sagirli O, Topcu G. A high-performance liquid chromatographic method for the determination of meropenem in serum. J Chromatogr Sci 2020;58:144-50. https://doi.org/10.1093/chromsci/bmz087*
9. *European Committee on Antimicrobial Susceptibility Testing. March 8, 2023. Available from: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_13.0_Breakpoint_Tables.pdf*
10. *Steffens NA, Zimmermann ES, Nichelle SM, Brucker N. Meropenem use and therapeutic drug monitoring in clinical practice: A literature review. J Clin Pharm Ther 2021;46:610-21. https://doi.org/10.1111/jcpt.13369*
11. *Bostancı Y, Kara E, Demirkan K, Topeli A, Ünal S. Yoğun bakım hastalarında antimikrobiyal ilaçların kan düzeyi izlemi. FLORA 2022;27:1-10. https://doi.org/10.5578/flora.20229901*
12. *Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: Defining antibiotic levels in intensive care unit patients: Are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;5:1072-83.*
13. *Hafızoğlu M, Odacı Cömertoğlu E, Öztürk Y, Kahyaoğlu Z, Çavuşoglu Ç, Balcı C, et al. Which comorbidity index is more appropriate for geriatric patients from the frailty perspective? Eur Geriatr Med 2023. https://doi.org/10.1007/s41999-023-00851-5*
14. *Sjövall F, Alobaid AS, Wallis SC, Perner A, Lipman J, Roberts JA. Maximally effective dosing regimens of meropenem in patients with septic shock. J Antimicrob Chemother 2018;73:191-8. https://doi.org/10.1093/jac/dkx330*
15. *Abdulla A, Ewoldt TMJ, Hunfeld NGM, Muller AE, Rietdijk WJR, Polinder S, et al. The effect of therapeutic drug monitoring of beta-lactam and fluoroquinolones on clinical outcome in critically ill patients: The DOLPHIN trial protocol of a multi-centre randomised controlled trial. BMC Infect Dis 2020;20:57. https://doi.org/10.1186/s12879-020-4781-x*
16. *Magréault S, Jauréguy F, Carbonnelle E, Zahar JR. When and How to Use MIC in Clinical Practice? Antibiotics 2022;11:1748. https://doi.org/10.3390/antibiotics11121748*

17. *Dulhunty JM, Roberts JA, Davis JS, Webb SA, Bellomo R, Gomersall C, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: A multicenter double-blind, randomized controlled trial. Clin Infect Dis 2013;56:236-44. https://doi.org/10.1093/cid/cis856*

18. *Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: Intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009;64:142-50. https://doi.org/10.1093/jac/dkp139*

19. *Usman M, Frey OR, Hempel G. Population pharmacokinetics of meropenem in elderly patients: Dosing simulations based on renal function. Eur J Clin Pharmacol 2017;7:333-42. https://doi.org/10.1007/s00228-016-2172-4*

20. *Zhou QT, He B, Zhang C, Zhai SD, Liu ZY, Zhang J. Pharmacokinetics and pharmacodynamics of meropenem in elderly chinese with lower respiratory tract infections: Population pharmacokinetics analysis using nonlinear mixed-effects modelling and clinical pharmacodynamics study. Drugs Aging 2011;28:903-12. https://doi.org/10.2165/11595960-000000000-00000*

21. *Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: A retrospective study of β-lactam concentration-toxicity relationships. J Antimicrob Chemother 2017;72:2891-7. https://doi.org/10.1093/jac/dkx209*

22. *Luque S, Benítez-Cano A, Larrañaga L, Sorlí L, Navarrete ME, Campillo N, et al. Pharmacokinetics and pharmacodynamics of meropenem by extended or continuous infusion in low body weight critically ill patients. Antibiotics (Basel) 2021;10:666. https://doi.org/10.3390/antibiotics10060666*

23. *Alobaid AS, Wallis SC, Jarrett P, Starr T, Stuart J, Lassig-Smith M, et al. Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. Antimicrob Agents Chemother 2016;60:4577-84. https://doi.org/10.1128/AAC.00531-16*

Address for Correspondence/Yazışma Adresi

Dr. Esra NURLU TEMEL

Department of Infectious Diseases and Clinical Microbiology, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye

E-posta: dresratemel@gmail.com