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Research Article

Meropenem Determination in Human Plasma by LC-MS/MS and Evaluation for Therapeutic Drug Monitoring in Intensive Care Unit Patients

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ABSTRACT

Meropenem is a broad-spectrum beta-lactam antibiotic widely used in intensive care units (ICUs) for severe bacterial infections. Therapeutic drug monitoring (TDM) is essential to optimize its dosing, ensuring effective bacterial eradication while minimizing toxicity and resistance. This study aimed to determine meropenem concentrations in human plasma using LC-MS/MS and evaluate its application in TDM for ICU patients. Meropenem concentrations in plasma samples from ICU patients were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The study included 40 plasma samples from 20 patients receiving meropenem continuous infusion. Validation followed the guidelines released by the International Council for Harmonization ICH M10 (2022), assessing specificity, accuracy, precision, stability, and dilution integrity. The developed LC-MS/MS method demonstrated high selectivity, sensitivity, and linearity (r^2 = 0.993–0.996) over the 10–2000 ng/mL range. Accuracy and precision met ICH M10 acceptance criteria, with % coefficient of variance (CV) <15%. All ICU patients maintained % time free drug concentration (% fT)>Minimum Inhibitory Concentration (MIC) >40%, ensuring adequate bacterial eradication. Notably, patients with renal impairment required dose adjustments, while those with high creatinine clearance needed increased dosing. The validated LC-MS/MS method is suitable for meropenem TDM in ICU patients, allowing individualized dosing adjustments to optimize therapy.

INTRODUCTION

Bacterial infections present a serious health risk that needs immediate attention. Bacterial infections can lead to severe illnesses and possibly death (Kothekar *et al.*, 2020). Meropenem is a broad-spectrum beta-lactam antibiotic that is often used to treat severe bacterial infections, especially in people who are

in intensive care units (ICU) (Abdul-Aziz *et al*., 2020). Bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Enterobacter spp., Klebsiella spp.,* and *Acinetobacter baumannii* can induce illnesses including meningitis, dermatological infections, gastrointestinal infections, and respiratory tract infections that are susceptible to treatment with meropenem (Barone *et al*., 2023). Meropenem inhibits bacterial cell wall formation, hence restricting growth and causing bacterial cell death. This drug can easily penetrate the bacterial cell wall and bind to the binding proteins (Anggita *et al*., 2022).

Therapeutic Drug Monitoring (TDM) is an approach used to optimize meropenem therapy by monitoring drug levels in the blood and adjusting doses individually (Roberts *et al*., 2014). However, traditional TDM techniques require frequent measurements and involve considerable costs. This research employed a population model to reduce the sample size from ICU patients and to enhance cost efficiency.

Reliable quantification of meropenem plasma concentrations is required for effective therapeutic drug monitoring studies and dosage modifications. This necessitates a highly selective, specific, and efficient analytical approach (Barone e*t al*., 2023). The methods commonly used for compound analysis in the fields of pharmacy, toxicology, and clinical study are immunoassay and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS method), where immunoassays have some issues, such as limited specificity, sensitivity, and lower accuracy in quantification (Yücel *et al*., 2018). Meanwhile, LC-MS/MS has become the most preferred method for determining meropenem concentrations in plasma, according to its high sensitivity and specificity. The development and validation of the analysis methods in this study were conducted to obtain reliable data regarding these preferred methods.

This study aims to determine the meropenem concentrations in blood plasma of the implemented population TDM model. Consequently, individual variances allow for optimization and dose modification to prevent sub-therapeutic results and antibiotic resistance, thereby enhancing the personalization of antibiotic treatment (Abdul-Aziz *et al*., 2020).

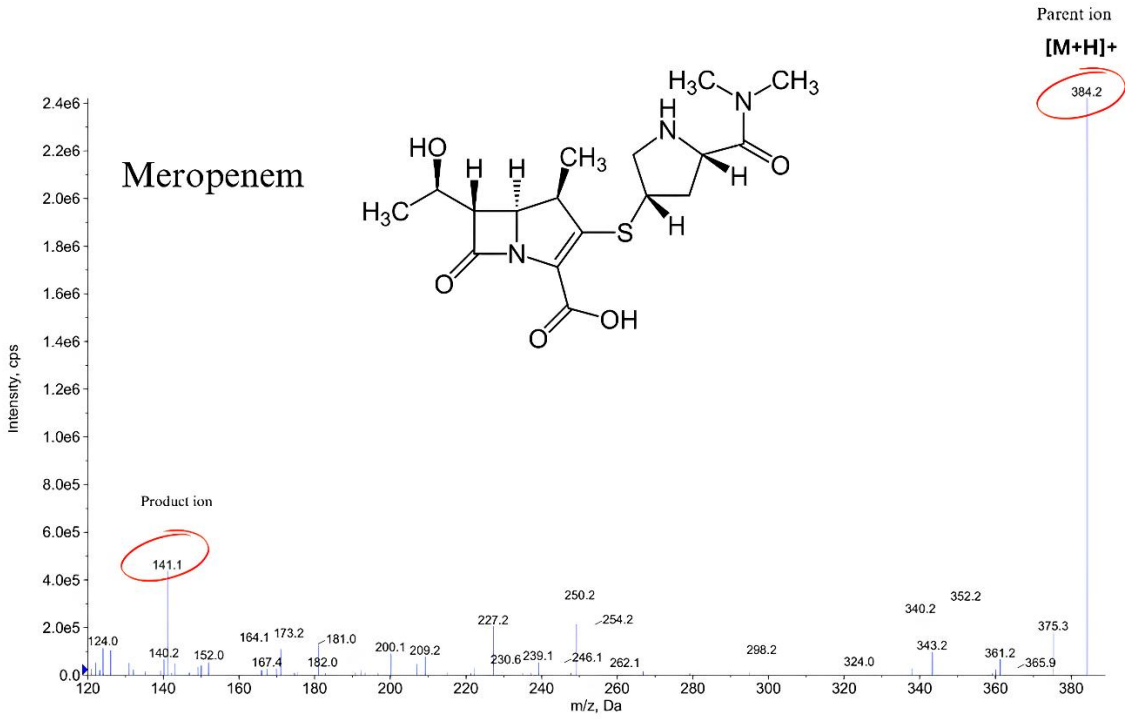


Figure 1. Structural and fragmentation analysis of meropenem based on mass spectrometry method optimization outcomes.

METHODS

Material

Meropenem trihydrate and glibenclamide working standard were obtained from Indonesian Pharmacopeia Standard (BPFI, Indonesia). LC-MS grade of water and formic acid were purchase from Sigma Aldrich (Germany). Blank human plasma was obtained from the Indonesian Red Cross, while sample plasma was from patients of Universitas Gadjah Mada (UGM) Academic Hospital. Human plasma from 40 samples were derived from 20 ICU patients at the UGM Academic Hospital. All patients who participated in this study, represented by their families, have signed informed consent forms in accordance with the clinical trial protocol approved by the Faculty of Medicine, Nursing, and Public Health, Universitas Gadjah Mada, Medical and Health Research Ethics Committee with Ref. No.: KE/FK/0891/EC/2024.

LC-MS/MS conditions

The Sciex 4500 QQQ mass spectrometer with electro-spray ionization was used for this analysis in positive mode. The nitrogen gas used in the nebulization process has the following characteristics: temperature of 500 °C, ion source gas 1 (GS1) of 50.0, ion source gas 2 (GS2) of 60.0, curtain gas (CUR) of 35.0, collision gas (CAD) of 8, and ion spray voltage of 5500 V. The ion monitoring was conducted in multiple reaction monitoring (MRM) mode. The mass spectrometry configuration for meropenem is m/z (M+H)+ 384.2/141.1, obtained from the mass spectrometer tuning results **(Figure 1)** with a Declustering Potential (DP) of 16 V, EP 10 V, CE 23 V, and CXP 8 V, while for glibenclamide it is $(M+H)^+$ 493.9/368.9 with a DP of 131 V, EP 10 V, CE 23 V, and CXP 12 V. A Phenomenex Synergy™ 4 µm Fusion RP18-80 Å, 50 mm x 20 mm column was used in the HPLC procedure. The mobile phase was a mixture of 0.1% formic acid in water (A) and 0.1% formic acid in methanol (B). The gradient elution was carefully programmed to optimize the separation of the analytes; the mobile phase B was eluted from 5% to 95% at a flow rate of 0.6 mL/min for 6.5 minutes run time.

Calibration standards and quality control samples preparation

The stock standard solution of meropenem was prepared at a concentration of 1000 µg/mL, then diluted with methanol to create a calibration curve solution with concentrations of 10, 15, 30, 50, 100, 150, 300, 500, 750, 1000, 1500, and 2000 ng/mL. The internal standard solution of glibenclamide was prepared at a concentration of 100 ng/mL. The 100 µL each calibration curve solution and 100 µL internal standard solutions were spiked into 100 µL blank plasma, then 700 µL methanol was added, and centrifuged at 12,000 rpm at 4°C for 10 minutes. The supernatant was taken and filtered with a 0.45 µm nylon filter membrane.

Quality Control (QC) sample solutions were made with 4 concentrations: LLoQ, Low QC (LQC), Medium QC (MQC), and High QC (HQC). LLoQ was prepared at a concentration of 10 ng/mL, while concentrations of LQC, MQC and HQC were 30 ng/mL, 750 ng/mL and 1500 ng/mL respectively.

Sample preparation

Patient plasma samples containing meropenem were conditioned at room temperature. 100 µL of plasma sample was added to 100 µL of internal standard glibenclamide and 800 µL of methanol and centrifuged at 12,000 rpm at 4°C for 10 minutes. The supernatant was taken and filtered with a 0.45 µm nylon filter membrane.

Method Validation

The validation of the bioanalytical method for meropenem was conducted based on the guidelines by the International Council for Harmonization - ICH M10, (2022) for bioanalytical method validation with validation parameters: specificity and selectivity, lower limit of quantification (LLoQ), calibration curve, accuracy and precision, carry-over, dilution integrity, and stability.

Clinical Application

Procedure for sample administration and collection

Meropenem is administered via continuous intravenous infusion over a duration of 8 hours or via 4 hours intermittent infusion. Meropenem was injected 3x8 hours or 2x12 hours daily. Blood samples were collected at various intervals for each subject, with two samples per subject during a timeframe of 15 minutes to 16 hours after the loading dose during continuous infusion treatment. Blood samples, each measuring 3-5 mL, were collected following the administration of a meropenem dosage. The blood samples were subsequently transferred into tubes containing the anticoagulant ethylene diamine tetra acetic acid (K_2EDTA) and centrifuged at 3000 rpm for 3 minutes to yield blood plasma. Blood plasma samples were

preserved at -80°C until analysis (Cao *et al*., 2022).

RESULTS AND DISCUSSION

Method Validation

The validation of the analytical methods used includes selectivity, lower limit of quantification (LLOQ), linearity of the calibration curve, accuracy, precision, and stability, referring to ICH M10 (2022), Guidelines of Bioanalytical Validation. The results of the validation of the meropenem determination method in plasma can be seen in **Table 1**.

Specificity dan Selectivity

There is no peak interference in the blank plasma at the retention times of meropenem and glibenclamide that was obtained from six different human plasma. **Figure 2** showed the chromatogram of blank, meropenem and glibenclamide as the internal standard in the plasma.

Lower Limit of Quantification (LLoQ)

The lower limit of quantification (LLoQ) was determined by evaluating three concentrations at the lower limit of the calibration curve: 5, 10, and 15 ng/mL. The concentration of 10 ng/mL met the criteria for accuracy and precision, as demonstrated by the resulting mean recovery and % CV values. The mean recovery of meropenem at a concentration of 10 ng/mL was 116.16%, with a coefficient of variation of 2.32%.

Calibration Curves

The calibration curve for meropenem covered ten standard curve points within the range of 10 to 2000 ng/mL. The calibration curves showed linearity over the concentration range, with mean regression coefficients (r^2) between 0.993 and 0.996 with weighing $1/x^2$ for improving accuracy at low concentrations and minimizing bias in the calculation of analyte concentration (Gu *et al*., 2014).

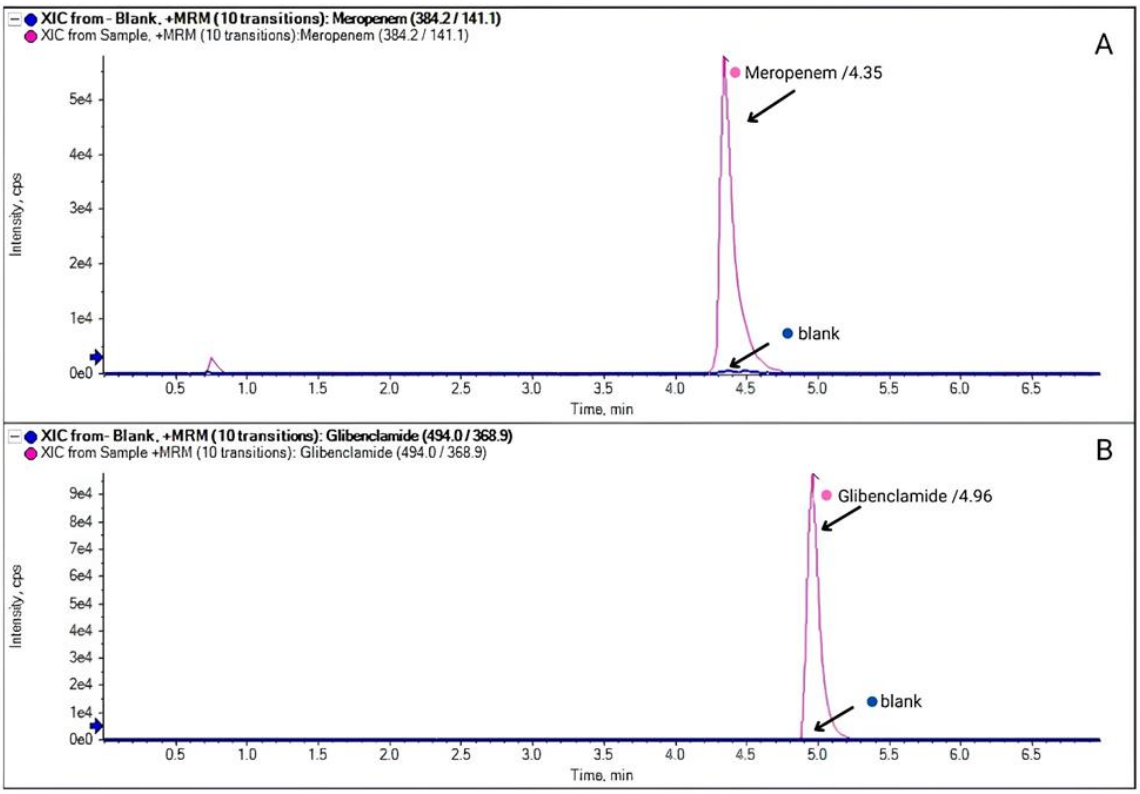


Figure 2. Extracted Ion Chromatogram (XIC) for blank plasma and meropenem in the plasma (A); XIC for blank plasma and glibenclamide internal standard in the plasma (D). This chromatogram was obtained under LC conditions described in the methods section for each respective m/z value.

Table 1. Validation results of meropenem

Parameter			*CV (%)	**RE (%)	Mean Recovery %
LLOQ					
5 ng/mL			1.24	0.69	168.82
10 ng/mL			2.32	0.16	116.16
15 ng/mL			3.08	0.09	90.39
Accuracy and Precision					
LLoQ	Intra-day		9.41	0.11	110.73
	Inter-day		2.96	0.14	114.44
LQC	Intra-day		9.66	0.09	102.23
	Inter-day		10.25	0.01	100.15
MQC	Intra-day		2.05	0.04	107.66
	Inter-day		1.07	0.02	97.65
HQC	Intra-day		3.71	0.08	98.58
	Inter-day		0.71	0.01	98.86
Dilution Factor	2 times		1.74	0.05	94.77
	5 times		3.72	0.01	100.75
	10 times		3.11	0.06	106.76
Stability Condition	T4h	LQC	2.13	0.13	112.58
		HQC	2.72	0.11	110.58
	T24h	LQC	2.40	0.01	101.06
		HQC	1.42	0.12	111.72
	Freeze and Thaw	LQC	1.76	0.06	93.75
		HQC	2.37	0.10	110.11
	24h Autosampler	LQC	11.37	0.06	93.75
		HQC	3.70	0.04	104.05

* CV = Coefficient of Variation. ** RE = Relative Error.

Accuracy and Precision

The accuracy and precision of this analytical method have been evaluated by %RE and %CV at each concentration. The results show that the %CV value is higher at the LQC concentration than at other concentrations, although it remains compliant with ICH M10 (2022) guidelines. This result indicates that the variability of the measured concentration at LQC is elevated. This finding may result from technical influences, including environmental variables such as temperature and humidity variations, analytical instrument performance fluctuations during analysis, human errors in sample solution preparation, or inherent complexities and instabilities of the sample that impact measurement outcomes (Shrivastava and Gupta, 2011).

Mean recovery

The meropenem analytical method has good recovery at all concentration levels. The coefficient of variation (CV) is relatively stable and within acceptable limits (<15%), indicating the reliability of this method for bioanalytical purposes. The highest recovery occurred at LLoQ (114.40%), indicating that this method slightly overestimates the analyte concentration at the lowest detection limit. These results support the validation of the bioanalytical method in accordance with the ICH M10 (2022) guidelines.

Carry-Over

The blank plasma injected following the highest concentration of the standard curve does not cause any interference. The autosampler system is established by designing the needle cleaning mechanism post-injection, utilizing methanol as the washing solution to avoid carryover (Desjardins *et al*., 2019).

Table 2. Demographic and clinical characteristics of patients

ID	Sex	Age (y)	W(kg)	H (cm)	Creatinine (mg/dL)	Urea (mg/dL)	CLCR (mL/min)	Dose	Time sampling (h)	Meropenem Concentration (ug/mL)	Bacterial Culture Results	Diagnose
1	M	70	92.5	171	0.91	33.5	98.82	1g8h	0.25	3.19	*Staphylococcus coagulase* negative	Sepsis
									5	4.68		
2	F	67	34.8	150.1	0.66	44	45.44	1g8h	0.75	5.49	*E. Coli; Enterococcus faecalis*	Sepsis, DM type 2, pneumonia
									6.25	18.27		
3	F	65	58	163	1.31	13.6	39.2	1g8h	1	10.87	*Empirical therapy	Schizophrenia
									7.50	32.17		
4	M	60	70	170	1.97	123.4	39.48	0.5g4h	3	16.11	*Enterobacter Cloacae* complex ESBL	Sepsis
									14	19.27		
5	M	75	57.1	163.4	3.14	75	16.42	1g8h	4	10.06	*Empirical therapy	AKI, pneumonia
									11.75	26.67		
6	M	68	38	158	0.59	39.2	64.41	1g8h	0.25	2.6	*Pseudomonas aeruginosa, E.Coli* ESBL positive	Epilepsy, IHD, pneumonia
									8.75	21.36		
7	M	81	46.8	158	1.75	66.2	21.91	1g8h	1	7.16	*Pseudomonas aeruginosa*	
									10.5	12.88		
8	F	48	60	155	2.02	136	37.95	1g8h	2	38.65	*Enterococcus faecium*	Sepsis, CKD
									15	60.16		
9	M	28	84	174	0.94	41.2	139.01	1g8h	4	3.79	*Empirical therapy	Femur sinistra, motorcycle injury
									10	7.17		
10	M	68	55	165	0.25	44	220	1g8h	0.5	5.96	*Serratia marcescen*	Pneumonia
									5.25	10.14		
11	M	34	58	163	0.99	73.4	86.25	1g8h	1	0.48	*Empirical therapy	Digest
									6.5	5.69		
12	M	56	50.6	169	0.72	61.5	81.99	1g8h	1.5	1.8	*Acinetobacter baumannii*	Aspiration pneumonia
									7.75	9.77		
13	M	67	54	153	1.52	76.4	36.02	1g8h	2	2.93	*Empirical therapy	Ileum
									9	9.19		
14	M	69	60	165	2.81	94.7	21.06	0.5g4h	3	24.82	*Staphylococcus aureus*	Sepsis, CKD stage 5
									14.75	23.89		
15	F	56	62	150.1	0.49	32.4	147.62	1g8h	0.25	1.03	*E. Coli* ESBL positive	
									8.75	5.72	*Acinetobacter baumannii*	
16	F	47	70	157.2	0.75	14.7	120.56	1g8h	0.5	6.7	*Empirical therapy	Ileum, post laparotomy
									9.5	0.4		
17	M	87	61	166	2	73.3	22.45	1g8h	0.75	0.39	*Klebsiella pneumoniae* ESBL positive	Pneumonia
									10.25	26.7		
18	M	84	32	161	1.46	175.3	17.05	1g8h	1	3.9	*Klebsiella pneumoniae* ESBL positive	Pneumonia
									11	24.89		
19	F	81	40	140	0.67	53.8	48.92	1g8h	2.5	27.55	*Enterococcus faecium*	Sepsis
									10	16.83		
20	F	63	59	157	1.02	66.4	52.58	1g8h	0.5	15.89	*Klebsiella pneumoniae* ESBL positive, *Enterobacter cloacae* complex	Sepsis
									9.5	0.34		

*The administration of meropenem was done before the microbiological culture results were available.

Table 3. Minimum Inhibitory Concentration (MIC) and % fT > MIC for different bacterial isolates

Patient ID	Bacterial	MIC (µg/mL)	*% fT > MIC
1	*Staphylococcus*	4	100
2	*E. coli*	2	100
6	*P. aeruginosa*	4	87.5
8	*Enterococcus faecium*	8	100
10	*Serratia marcescens*	16	100
14	*Staphylococcus*	4	100
17	*Klebsiella pneumoniae*	1	97.5
18	*Klebsiella pneumoniae*	1	100
19	*Enterococcus faecium*	8	100

** The percentage of a dosing interval during which the free (unbound) drug concentration in plasma exceeds the MIC (Minimum Inhibitory Concentration) of a pathogen.

Dilution Integrity

Samples diluted at ratios of 1:2, 1:5, and 1:10 remain to meet the accuracy and precision parameters as per ICH M10 (2022) guidelines.

Stability

The stability of plasma spikes maintained in a -80°C freezer for 4 and 24 hours continued to meet the standards for accuracy and precision. The plasma spike that went through the freeze-thaw procedure still met the criterion. During preparation, the standard solution was maintained at room temperature for a maximum of 4 hours, immediately after which it was stored at 2-8°C. The plasma sample solution was stored at 4°C for 24 hours, ensuring it maintained its accuracy and precision standards. This result suggests that a storage temperature of -80°C effectively preserves plasma samples. The deep freezer was maintained at a temperature of -80°C, and daily temperature monitoring was conducted for sample storage. The acceptable temperature variation range is 5°C. We implemented this to prevent sample degradation due to inadequate storage temperature. Additional research is required for sustained stability.

Clinical Application

The validated LC-MS/MS method for quantifying meropenem in blood plasma was applied to determine its concentration in patient plasma. The preparation of patient plasma blood samples required a 1:10 dilution and concentration determinations based on a standard calibration curve. The actual concentration of meropenem in the patient's plasma ranged from 0.34 to 60.16 µg/mL. It is used to check the therapeutic drug meropenem levels in ICU patients. The actual concentration levels in the blood plasma are used to change the dose based on the % time free drug concentration (% fT)>Minimum Inhibitory Concentration (MIC) criteria. Meropenem's ability to kill bacteria depends on how long the free drug concentration is higher than the pathogen's minimum inhibitory concentration (MIC) (Ai *et al*., 2024). The continuous infusion of meropenem antibiotics for 8 hours is anticipated to sustain the blood plasma concentration of meropenem above the MIC for the entire dosing duration. Meropenem kills bacteria most effectively when the concentration of the unbound drug is higher than the MIC for at least 40% of the dosing interval (Boonpeng *et al*., 2022).

The meropenem level data for each patient are shown in the patient demographic table **(Table 2**). TDM is important for patients with low ClCR levels < 30 mL/min, which occurs in patients ID 5, 8, 14, 17, and 18. In patients with sepsis occurring in patients ID 1, 2, 4, 8, 14, 19, and 20. Similarly, TDM was measured in patients with multi-drug resistant/ESBL bacterial infections, patients ID 4, 10, 12, 13, 15, and 20. Measuring the amount of meropenem in patients' blood plasma showed that all of them had % fT > MIC levels higher than 40%, which means they were exposed to enough of the drug to kill the bacteria. This is crucial because meropenem is a time-dependent antibiotic, which means its effectiveness depends on the duration the drug remains above the MIC rather than the peak concentration. Data % fT > MIC can be seen in **Table 3** based on CLSI, 2018. Patients infected with *E. coli*, *Staphylococcus, Klebsiella pneumoniae*, and *Enterococcus faecium* had continuous drug exposure above the MIC, indicating effective therapy. This can reduce the risk of treatment failure and antimicrobial resistance. Patient 6 has a slightly lower % fT > MIC (~87.5%). Although still within the effective range, this may require monitoring, especially for critically ill patients. Patients with a low

creatinine clearance (ClCR) of less than 30 mL/min may require dosage adjustments or prolonged delivery intervals, for example, from 1 g every 8 hours to 500 mg every 12 hours.

Patients with septic shock had lower levels of meropenem in the blood. Sepsis elevates capillary permeability, thereby increasing the transport of meropenem to tissues and leading to lower blood concentrations than anticipated. In contrast, patients with severe sepsis had higher blood levels of meropenem because severe sepsis and organ failure can cause metabolic and drug elimination disturbances, leading to higher levels (Ahmed *et al*., 2020). Patients with ESBL necessitate a combination of additional antibiotics for more intensive treatment.

The administration of meropenem was done before the microbiological culture results were available, also known as empirical therapy, given to patients 3, 5, 9, 11, 13, and 16. This procedure is performed on patients with severe infections, including sepsis, nosocomial pneumonia, meningitis, or intra-abdominal infections, as well as on critically ill individuals in the ICU, such as those who have experienced trauma or undergone surgery. Patient ID 5 with low ClCR < 30 ml/min requires a dose reduction to minimize drug accumulation effects and avoid toxicity. Patient with ID 9 with high ClCR requires a higher dose to increase therapy effectiveness. Bacterial MIC evaluation is conducted after the bacterial culture cell results are available. The ClCR levels must also be monitored regularly.

CONCLUSIONS

The fluctuating concentrations of meropenem necessitate therapeutic drug monitoring contingent upon renal function and the existence of resistant bacterial infections. Continuous infusion of meropenem is recommended for patients with severe infections or high ClCR to maintain meropenem levels within the therapeutic range. A population pharmacokinetic study can be undertaken using the acquired TDM data to optimize dosage, particularly in individuals with sepsis, renal impairment, or multidrug-resistant bacterial infections.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest with any party over the duration of this research.

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