Pharmaceutical Sciences Asia

Pharm Sci Asia 2024; 51(2), 173-179
DOI:10.29090/psa.2024.02.24.1651

Research Article

Comparative stability of imipenem and meropenem solutions for extended infusion administration

Wasan Katip*, Chuleegone Sornsuvit, Purida Wientong

Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

ABSTRACT

The stability of antibiotic solutions is a critical factor influencing their efficacy during extended infusion administration. This study investigates and compares the stability of imipenem and meropenem solutions in 0.9% sodium chloride at two temperatures—25°C and 30°C—over a 6-hour period. Imipenem and meropenem solutions, each at a concentration of 10 mg/mL, were prepared and incubated, and samples were collected at various intervals. High-performance liquid chromatography (HPLC) was employed to analyze the remaining antibiotic concentrations. Statistical analyses, including t-tests, were conducted to assess stability at different time points and temperatures. Results revealed that, at 25°C, meropenem solutions maintained stability above 90% throughout the 6-hour duration, while imipenem solutions showed a significant decrease after 3 hours. At 30°C, meropenem solutions remained stable for 4 hours, whereas imipenem solutions rapidly declined below 90% within 1 hour. Comparison between the two antibiotics demonstrated that meropenem exhibited significantly higher stability at 4 and 6 hours at both temperatures (p<0.05). In conclusion, this study offers crucial insights into the stability profiles of imipenem and meropenem during extended infusion. Meropenem emerged as the preferred choice due to its superior stability, emphasizing the importance of temperature considerations in administration and the necessity for proper storage and handling to preserve antibiotic stability.

Keywords:
Imipenem, Meropenem, Stability, Extended Infusion, High-Performance Liquid Chromatography, Antibiotic Solutions

1. INTRODUCTION

The rise of multidrug-resistant gram-negative bacterial infections poses a significant challenge in healthcare settings worldwide. Effective antimicrobial agents are essential for combating these infections, and the administration of antibiotics via extended infusion has gained attention as a strategy to optimize therapeutic outcomes[1]. In this study, we focus on two important antibiotics, meropenem and imipenem, which are commonly used for extended infusion administration in the treatment of multidrug-resistant gram-negative infections[1-5].

Meropenem is a broad-spectrum antibiotic that exhibits potent activity against gram-negative pathogens, including multidrug-resistant strains. The percentage of time above the minimum inhibitory concentration (%T > MIC) is a critical pharmacokinetic/pharmacodynamic (PK/PD) parameter that correlates with the therapeutic efficacy of meropenem[2]. Extended or continuous infusion of meropenem has been shown to enhance the %T > MIC, thereby improving treatment outcomes[2]. Previous studies have investigated the stability of meropenem during extended infusion, particularly at room temperature, and have highlighted the importance of maintaining its stability in different concentrations and environmental conditions[3-4].

Imipenem is another valuable antibiotic for the treatment of multidrug-resistant gram-negative infections. It remains active against a wide range of gram-negative and gram-positive pathogens, making it an essential choice for clinicians, particularly in critically ill patients. Similar to meropenem, the %T > MIC is a crucial PK/PD parameter for imipenem, emphasizing the significance of extended infusion administration[5]. However, maintaining the stability of imipenem during extended infusion, especially under specific temperature conditions, poses challenges that need to be addressed.

***Corresponding author:**
*Wasan Katip Email: wasan.katip@cmu.ac.th

Extended infusion, defined as infusion times of three hours or longer[6], is commonly employed in patients with severe infections or those caused by multidrug-resistant bacteria to enhance antibiotic exposure and efficacy. Both meropenem and imipenem are antibiotics frequently administered via extended infusion. Imipenem is typically given as 3- to 4-hour infusions every 6 to 8 hours, while meropenem infusions are usually administered every 8 hours[6]. The stability of meropenem and imipenem solutions during extended infusion is crucial for ensuring optimal therapeutic efficacy. Although previous studies[3-5] have provided valuable insights into the stability of these antibiotics, there is still a need to evaluate their comparative stability, particularly under different temperatures. Understanding the comparative stability profiles of meropenem and imipenem is vital for guiding clinical practice, facilitating informed decision-making, and improving patient outcomes.

Therefore, the objective of this study is to investigate and compare the stability of meropenem and imipenem solutions during extended infusion administration. We aim to assess their stability under various temperatures, simulating real-world clinical conditions. The findings of this study will contribute to a better understanding of the comparative stability profiles of these antibiotics, providing valuable information for healthcare professionals involved in the management of multidrug-resistant gram-negative infections.

2. MATERIALS AND METHODS

2.1. Chemicals and instrumentation

Meropenem for injection product (1 g/vial) in pure powder form was obtained from AstraZeneca and imipenem powder for IV injection was available in 0.5-g vials was from MSD. Both meropenem and imipenem reference standard was from Fluka. For the preparation of solutions and analysis, the following chemicals and reagents were used: 0.9% sodium chloride solution in PVC bags from GHP, Thailand; potassium dihydrogen phosphate from BDH Laboratory Supplies; orthophosphoric acid from Merck. All solutions used in HPLC analysis were HPLC-grade, including acetonitrile and water from RCI Lab Scan.

The analysis of both meropenem and imipenem solutions was performed using a high-performance liquid chromatography (HPLC) system. The HPLC system employed in this study was equipped with an LC-20AD pump, a UV/Vis detector, an autosampler, a column oven, a degassing unit, and an LC solution integrator. The HPLC analysis utilized a reverse-phase technique, employing a C18 column with a particle size of 5 µm and dimensions of 250×4.0 mm for both meropenem and imipenem analysis. The mobile phase was specifically ratio of acetonitrile and buffer, pH and elusion isocratic flow rate for meropenem or imipenem as the following. For meropenem mobile phase consisted of 30 mM monobasic phosphate buffer and acetonitrile (90:10 v/v), adjusted to pH 3.0 with ortho-phosphoric acid, with flow rate of 1.0 ml/min. For imipenem mobile phase flow rate of 1.0 mL/min, consisting of 95:5 v/v ratio of acetonitrile and 1 mM KH2PO4 buffer, pH 6.8. The UV/Vis detectors were set at 298 and 300 nm for meropenem and imipenem, respectively. The HPLC system was operated at a constant temperature of 25°C. Injection volume of both meropenem and imipenem solution were 10 µL. Runtime was 15 minutes for meropenem and 6 minutes for imipenem. A 10.5 minutes and 6 minutes were retention time of meropenem and imipenem, respectively. All samples were incubated at controlled temperatures using a temperature controller cabinet (LHL-112 model) from ESPEC engineering, Amatacity Chonburi Industrial Estate, Thailand.

2.1.1. Preparation of Sample Solutions and Analytical Method

For the meropenem sample solutions, vials containing 1 g of meropenem were reconstituted with HPLC-grade water. The resulting concentration was 100 mg/mL. To prepare the final sample concentrations of 10 mg/mL, the reconstituted vials were further diluted with 0.9% sodium chloride solution in PVC bags. Three replicate solutions were prepared for each concentration, and samples were collected at specific time intervals after incubated at 25 or 30°C in temperature-controlled cabinet.

For the imipenem sample solutions, 0.5-g vials of imipenem were reconstituted with HPLC-grade water. The resulting solutions were further diluted with 0.9% sodium chloride solution to obtain concentrations of 10 mg/mL. Three replicate solutions were prepared for each concentration, and after incubated at 25 or 30°C in temperature controlled cabinet samples were collected at prespecify time intervals.

All collected samples were analyzed using the HPLC system. Aliquots 10 µL of samples were injected into the HPLC column, and the concentration of the injected sample was determined by comparing the peak area against the calibration curve.

2.1.2. Preparation of Reference Standard Solution and Calibration Curve

The HPLC analytical methods used for meropenem and imipenem analysis were validated by determining the linearity, precision, and accuracy. The linearity of the calibration curves was evaluated by calculating the coefficient of determination (r^2). The precision was assessed by determining the % coefficient of variation (% CV), while the accuracy was determined by calculating the mean recovery within the acceptable range. The accep-

tance criteria for imipenem regarding linearity, precision, and accuracy were set as follows: $r^2 > 0.998$, %CV < 10%, and an average recovery of 98-102%[7-8]. For meropenem, the acceptance criteria were defined as $r^2 > 0.998$, %CV < 2%, and a mean recovery of 98-102%[7,9].

Imipenem

A 5.0 mg imipenem reference standard was precisely weighed and added to a 25 mL volumetric flask. The reference standard was dissolved in HPLC-grade water to create a stock solution. From the stock solution, a 0.25 mL aliquot was diluted with 10 mL of HPLC-grade water, resulting in a concentration of 50 µg/mL. To generate the calibration curve, final concentrations of 5, 10, 20, 40, and 50 µg/mL were prepared following the previously described dilution method. The calibration curve was plotted by correlating the peak area against the concentrations of the imipenem reference standard ranging from 5 to 50 µg/mL. To validate the method, the linearity, precision, and accuracy of the calibration curve were determined using the imipenem reference standard with concentra-tions ranging from 5 to 50 µg/mL. The HPLC analytical method for imipenem followed the protocol established by Tissel et al.[10], Srinivasan et al.[11], and Swanson et al.[12].

Meropenem

A total of 10 mg of meropenem reference standard was accurately weighed and added to a 10 mL volumetric flask. The reference standard was dissolved in HPLC-grade water, resulting in a stock solution. From the stock solution, a 0.1 mL aliquot was diluted to 100 mL in HPLC-grade water, yielding a concentration of 20 µg/mL. For the calibration curve, final concentrations of 20, 40, 60, 80, 100, and 120 µg/mL were prepared using the previously described dilution method. The calibration curve was plotted by correlating the peak area against the concentrations of the meropenem reference standard ranging from 20 to 120 µg/mL. The HPLC analytical method for determining meropenem in the solution followed the protocol described by Mendeza et al.[9] To validate the method, the linearity, precision, and accuracy of the calibration curve were determined using the meropenem reference standard with concentrations ranging from 20 to 120 µg/mL.

2.2. Data Analysis

The data analysis involved comparing the stability of imipenem and meropenem at different time points. The results were presented as the mean percentage with standard deviation of imipenem compared to meropenem at each corresponding time point. The stability of the samples was determined by comparing the mean percentage of imipenem and meropenem to the control (0 hour), with samples considered stable if the mean percentage remained higher than 90% according to the U.S. Pharmacopeia[13].

To assess the differences between imipenem and meropenem at each time point, a t-test with equal variance was conducted. Additionally, a T-test was used to compare the percentages of imipenem and meropenem remaining at 6 hours at temperatures of 25 and 30°C.

The significance levels for all analyses were set at <0.05 to determine statistical significance. The data analysis was performed using Stata software, version 14 (Stata Corp, College Station, TX, USA).

3. RESULTS

3.1. Validation analytical method

The analytical method validations for meropenem met the acceptance criteria, with the calibration curve showing linearity in the range of 20-120 µg/mL, $r^2 > 0.999$, %CV of 1.6-2.0%, and an average recovery of 98.18-100.18%.

For imipenem, the analytical method validations also met the acceptance criteria, with the linearity, precision, and accuracy being established as $r^2 > 0.998$, %CV of 3.76-6.24%, and an average recovery of 99.05-101.17%.

3.2. Stability of Imipenem and Meropenem at 25°C

The stability of meropenem and imipenem solutions at a concentration of 10 mg/mL was assessed at 25°C. Results showed that meropenem solutions remained stable (>90%) for up to 6 hours when stored at this temperature (Table 1). In contrast, the 10 mg/mL imipenem solution

Table 1. The mean percentage±SD of imipenem versus meropenem at 25°C compared with the initial concentration.

Time (Hours)	Mean Percentage±S.D.		*p*-value
	10 mg/mL		
	Imipenem	Meropenem	
0	100.00±0.00	100.00	0.000
1	96.42±0.58	97.92±2.08	0.295
2	94.99±1.97	94.87±3.75	0.963
3	93.63±3.06	94.83±2.32	0.617
4	88.63±3.92	95.91±0.52	0.033
6	84.67±0.05	92.34±3.88	0.027

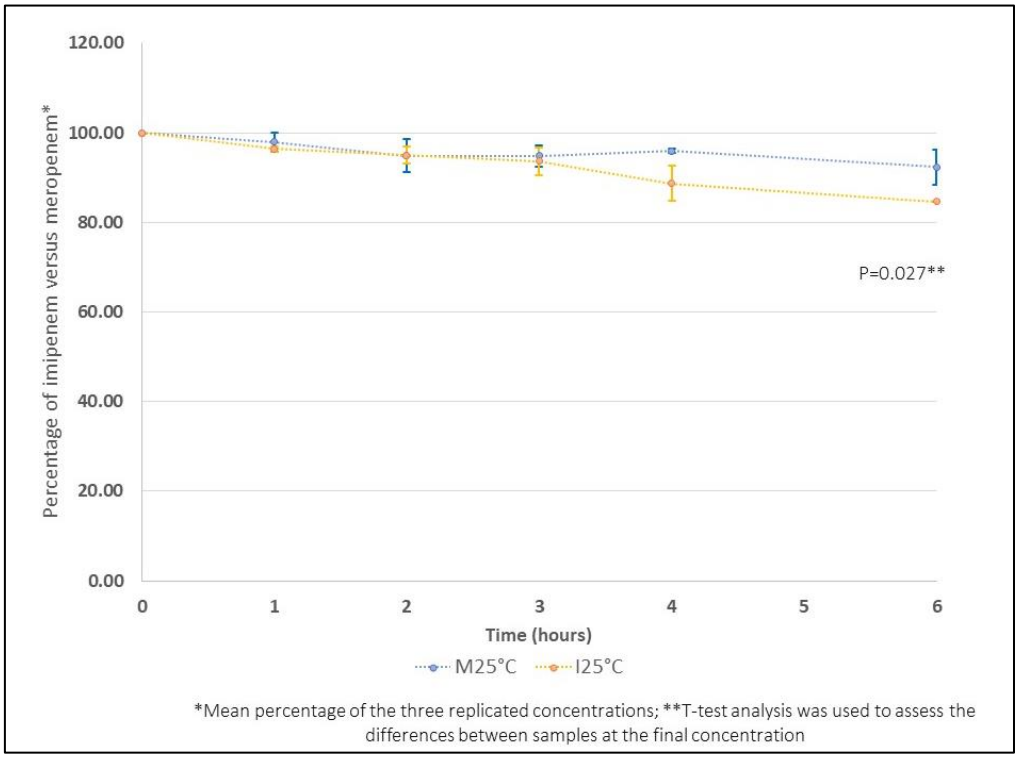

Figure 1. Stability of imipenem (I) (10 mg/mL) and meropenem (M) (10 mg/mL) in 0.9% sodium chloride solution incubated at 25°C for 6 hours.

Table 2. The mean percentage±SD of imipenem versus meropenem at 30°C compared with the initial concentration.

Time (Hours)	Mean Percentage±S.D. 10 mg/mL		*p*-value
	Imipenem	Meropenem	
0	100.00	100.00	
1	84.22±2.29	96.96±0.84	0.001
2	75.00±1.32	92.03±4.10	0.002
3	76.35±0.11	92.07±2.83	0.001
4	71.76±1.95	90.24±2.09	0.001
6	70.07±2.40	84.52±5.04	0.011

Table 3. Differences between percentages of imipenem and meropenem solutions that were stored at 25 and 30°C for 6 hours compared with the initial concentration.

Mean Percentage±S.D.	Temperature (°C)		
	25	30	*p*-value*
Imipenem	92.34±3.88	84.67±0.05	0.027
Meropenem	84.52±5.04	70.07±2.40	0.011

exhibited stability for only 3 hours at 25°C (Table 1) (Figure 1). A comparison between meropenem and imipenem revealed that meropenem exhibited significantly higher stability than imipenem at 4 and 6 hours (p<0.05).

3.3. Stability of Imipenem and Meropenem at 30°C

The stability of meropenem and imipenem solutions at a concentration of 10 mg/mL was evaluated at 30°C. Findings demonstrated that meropenem solutions remained stable (>90%) for up to 4 hours when stored at this temperature (Table 2). Conversely, the 10 mg/mL imipenem solution exhibited stability for less than 1 hour at 30°C (Table 3) (Figure 2). Comparison between meropenem and imipenem indicated that meropenem displayed significantly higher stability than imipenem at 1, 2, 3, 4, and 6 hours (p<0.05) (Table 3).

4. DISCUSSION

These findings highlight the temperature-dependent degradation of imipenem and meropenem solutions. Meropenem displayed superior stability compared to imipenem at both temperatures, indicating its potential for extended infusion administration. At 25°C, both imipenem and meropenem solutions exhibited a gradual decline in stability over time. Meropenem demonstrated higher stability, remaining above 90% for the entire 6-hour

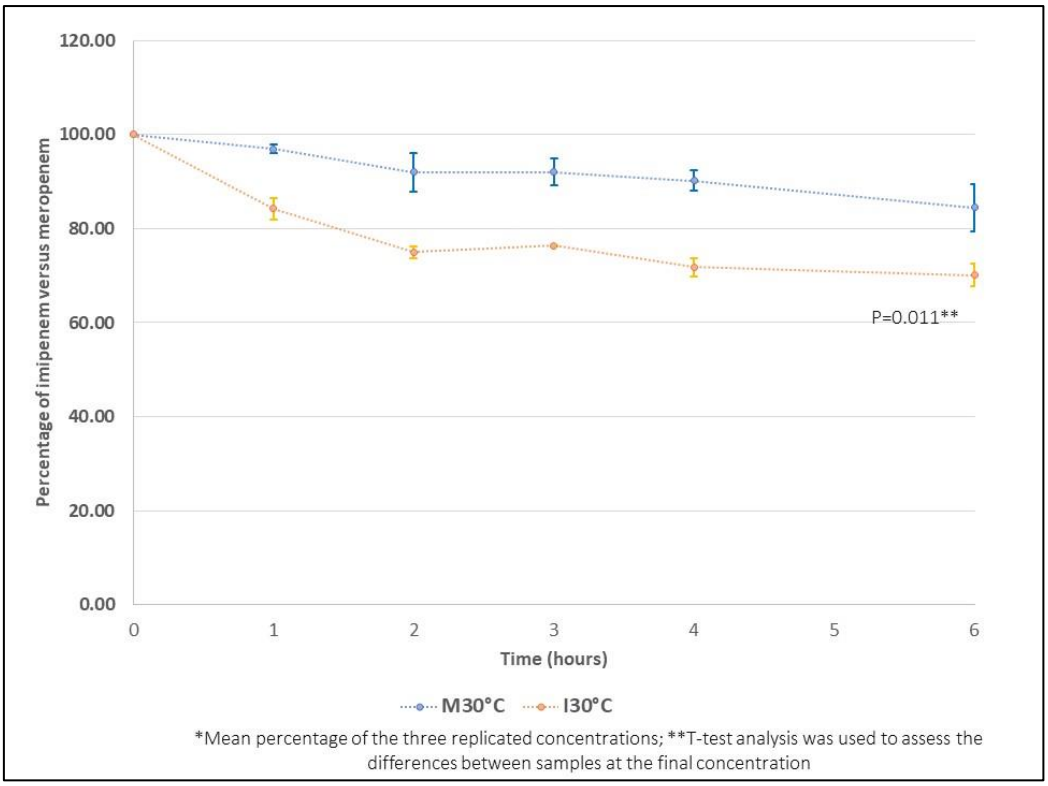

Figure 2. Stability of imipenem (I) (10 mg/mL) and meropenem (M) (10 mg/mL) in 0.9% sodium chloride solution incubated at 30°C for 6 hours.

duration. In contrast, imipenem showed a faster decrease in stability, falling below 90% after 3 hours of incubation. Similarly, at 30°C, the stability of imipenem and meropenem solutions declined over time. Meropenem maintained stability above 90% for 4 hours, whereas imipenem experienced a more rapid decrease, dropping below 90% within 1 hour. These findings highlight the temperature-dependent degradation of imipenem and meropenem solutions. Meropenem displayed superior stability compared to imipenem at both temperatures, indicating its potential for extended infusion administration.

Extended infusion is recommended for meropenem and imipenem to achieve optimal pharmacokinetic/pharmacodynamic (PK/PD) properties and improve therapeutic efficacy[1,2,14]. However, the stability of these antibiotics can be affected by various factors, including temperature[15].

Our study examined the stability of meropenem and imipenem solutions at 25°C and 30°C, focusing on concentrations commonly used in clinical practice. The results revealed significant differences in stability between the two antibiotics at both temperatures. Some studies show the concentration of meropenem in the infusion bag to be 4-8 mg/mL. However, we chose to study the stability of meropenem at a concentration of 10 mg/mL because this concentration is commonly used in clinical practice. In our study, we aimed to mimic real-world conditions by preparing the solutions in a manner consistent with clinical protocols. Specifically, vials containing 1 g of meropenem were reconstituted to achieve a concentration of 10 mg/mL, and these solutions were further diluted with 0.9% sodium chloride solution in PVC bags (100 mL). This concentration reflects the typical range used in clinical settings and allows us to assess the stability of meropenem under conditions that are relevant to its practical use.

Moreover, we chose to study the stability of imipenem and meropenem solutions at 25°C and 30°C because these temperatures are commonly encountered in clinical settings and are relevant for extended infusion administration.

Thailand, being a tropical country, typically experiences temperatures above 25°C during the daytime. While temperatures in a room without air conditioning can reach 32°C to 37°C[4], our selected temperatures represent a range that is both practical and reflective of typical storage conditions in healthcare facilities[4].

Meropenem demonstrated higher stability than imipenem at 25°C. The meropenem solutions remained stable (>90%) for up to 6 hours, whereas the imipenem solution at the same concentration exhibited stability for only 3 hours. These findings are consistent with previous studies that reported the temperature-dependent degradation of meropenem. Berthoin et al.[15] found that meropenem at 40 mg/mL degraded faster at higher temperatures, with a 10% degradation observed in 12 hours at 25°C, but only 6 hours at 37°C[15].

Similarly, at 30°C, meropenem exhibited greater stability than imipenem. The meropenem solutions remained stable (>90%) for up to 4 hours, while the imipenem solution showed stability for less than 1 hour. Keel et al.[16] and Viaene et al.[17] also reported temperature-dependent degradation of imipenem. Keel et al.[16] observed a 10%

degradation of 5 mg/mL imipenem in 6, 4, and 3 hours at 30°C, 35°C, and 40°C, respectively[16]. Viaene et al.[17] found that imipenem experienced a 10% degradation at 25°C and 37°C after 3.5 and 2.75 hours, respectively[17].

A preliminary analysis[18] of meropenem stability using quantitative HPLC at 22°C and 33°C revealed that meropenem concentrations decreased to 90% of their starting concentration after 7.4 and 5.7 hours, respectively. Meropenem may be continuously infused for at least 7 hours if the temperature does not exceed 22°C and for 5 hours if the temperature does not exceed 33°C, even though the results indicate that meropenem should not be continuously infused for more than 24 hours[19]. This aligns with our findings, which suggest that meropenem can be administered for at least 6 hours at 25°C and 4 hours at 30°C but not continuously over a 24-hour period. In a retrospective observational study[19] on the administration of 1% concentration of continuous infusion (CI) meropenem (infused over 8 or 12 hours), the stability experiment using 1% meropenem at room temperature showed that in 22 individuals, a median serum concentration of 17.8 mg/L (interquartile range, 9.3-27.8 mg/L) was obtained with a meropenem daily dose of 6 g/day (range 2-6 g/day). When given as CI, meropenem produced free drug concentrations that were at or above the pathogen's minimum inhibitory concentration (MIC) in 95% of cases. Clinical cure was achieved in 80% of the patients in this review. At the conclusion of the 12-hour dosing interval, the stability experiment showed very little drug breakdown[19]. Regarding the investigation of the effects of temperature and concentration on imipenem stability[20], a 0.9% sodium chloride solution containing 10 mg/mL and 5 mL of imipenem was prepared using imipenem injection powder. PVC bags containing the prepared solutions were kept at 25, 30, and 40°C. At 25°C, imipenem solution remained stable for 3-6 hours at a concentration of 10 mg/mL. Additionally, at 30°C and 40°C, imipenem solutions at a concentration of 10 mg/mL were stable for less than an hour[20]. Our study, consistent with previous studies[18-20] on the stability of imipenem and meropenem solutions, found that increasing temperature resulted in decreased stability of imipenem compared to meropenem, highlighting the importance of considering temperature and concentration when administering this drug by extended infusion.

Our study provides novel insights by comparing the stability of imipenem and meropenem at high temperatures. The data show that imipenem is more susceptible to degradation compared to meropenem. The percentages of imipenem remaining in the 10 mg/mL preparation exhibited more than a 10% reduction after 4 hours of incubation at 25°C and after 1 hour at 30°C, compared to meropenem.

These findings highlight the importance of considering the stability of antibiotics during extended infusion administration, particularly when exposed to higher temperatures. Maintaining the stability of the antibiotic solutions is crucial to ensure adequate drug concentrations and efficacy in clinical settings.

Despite the valuable insights provided by this study, there are certain limitations that should be acknowledged. First, the stability of meropenem and imipenem solutions was assessed only at two specific temperatures, namely 25°C and 30°C. Other temperature conditions that may be encountered in real-world clinical settings were not explored. Therefore, caution should be exercised when extrapolating these findings to other temperature ranges. Moreover, it is important to note the potential for temperatures to fluctuate and exceed 30°C in climate zone IVb. This factor should be acknowledged as it reflects the broader environmental conditions that could affect the stability of these antibiotic solutions, thus potentially limiting our study.

Second, the study focused on the stability of meropenem and imipenem solutions at concentrations commonly used in clinical practice. While this approach provides relevant information, it is important to note that stability may vary for different concentrations. Further investigations involving a wider range of concentrations would provide a more comprehensive understanding of the stability profiles.

Additionally, this study evaluated the stability of meropenem and imipenem solutions over a relatively short duration (up to 6 hours). Longer-term stability beyond this time frame was not investigated. Future studies examining the stability of these antibiotics over extended periods would be valuable in informing clinical practice.

Lastly, it is important to consider that the stability of meropenem and imipenem can be influenced by factors other than temperature, such as pH, light exposure, and specific storage conditions. These factors were not specifically addressed in this study, and their potential impact on stability warrants further investigation.

Despite these limitations, the findings of this study contribute valuable insights into the comparative stability of meropenem and imipenem solutions for extended infusion administration. Further research addressing the aforementioned limitations would enhance our understanding of the stability profiles of these antibiotics and guide their optimal use in clinical practice.

5. CONCLUSION

In conclusion, our study contributes to the understanding of the stability profiles of meropenem and imipenem solutions for extended infusion administration. The results emphasize the superior stability of meropenem compared to imipenem at both 25°C and 30°C. Clinicians should consider these findings when selecting antibiotics for extended infusion regimens and take measures to ensure appropriate storage and handling to maintain stability.

Conflict of interest
None to declare.

Funding
Supported by CMU Junior Research Fellowship Program.

Ethics approval
None to declare.

Article info:
Received January 30, 2024
Received in revised form March 15, 2024
Accepted March 19, 2024

Author contribution
Conceptualization, W.K.; Data curation, W.K., C.S. and P.V.; Formal analysis, W.K. and C.S.; Investigation, W.K., C.S. and P.V.; Methodology, W.K., C.S. and P.V.; Project administration, W.K.; Software, W.K. and C.S.; Validation, P.V.; Writing - original draft, W.K., C.S. and P.V.; Writing - review and editing, W.K. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-resistant gram-negative bacterial infections in the hospital setting: Overview, implications for clinical practice, and emerging treatment options. Microb Drug Resist. 2016;22(5):412-31.
2. Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother. 2007;51(5):1725-30.
3. Patel PR, Cook SE. Stability of meropenem in intravenous solutions. Am J Health Syst Pharm 1997;54(Suppl 4):412-21.
4. Jaruratanasirikul S, Sriwiriyajan S. Stability of meropenem in normal saline solution after storage at room temperature. Southeast Asian J Trop Med Public Health. 2003;34(3):627-9.
5. Lipš M, Siller M, Strojil J, Urbánek K, Balík M, Suchánková H. Pharmacokinetics of imipenem in critically ill patients during empirical treatment of nosocomial pneumonia: A comparison of 0.5-h and 3-h infusions. Int J Antimicrob Agents. 2014;44(4): 358-62.
6. Aboulatta L, Sugita H, Wakabayashi H, Noma H, Sasaki T. Comparison of extended versus intermittent infusion of antipseudomonal beta-lactams for the treatment of critically ill patients with respiratory infections: A systematic review and meta-analysis. Int J Infect Dis. 2020;98:41-50.
7. Shabir GA. A practical approach to validation of HPLC methods under current good manufacturing practices. J Validation Technol. 2004;10(3):210-8.
8. United States Pharmacopeial. Chromatography, validation of compendia preocedures, verification of compendia procedures. USP 36-NF 31. United States Pharmacopeial: Rockville, MD; 2013. p. 621-1226.
9. Mendez AS, Dalomo J, Steppe M, Schapoval EE. Stability and degradation kinetics of meropenem in powder for injection and reconstituted sample. J Pharm Biomed Anal. 2006;4:1363-6.
10. Trissel L, Xu QA. Stability of imipenem-cilastatin sodium in autodose infusion system bags. Hosp Pharm. 2003;38(2);130-4.
11. Srinivasan R, Mary KL, Kumar DR, Chandana P. A new RP-HPLC method for the simultaneous estimation of imipenem and cilastatin in pharmaceutical dosage form. IJFMR 2014;5:2400-4.
12. Swanson DJ, Deangelis C, Smith IL, Schentag JJ. Degradation kinetics of imipenem in normal saline and in human serum. Antimicrob Agents Chemother. 1986;29(5):936-7.
13. United States Pharmacopeial. The United States pharmacopeia, 30th rev., and The National Formulary, 25th ed. The United States Pharmacopeial Convention: Rockville, MD; 2006. p.321-7.
14. Kuti JL, Nightingale CH, Knauft RF, Nicolau DP. Pharmacokinetic properties and stability of continuous-infusion meropenem in adults with cystic fibrosis. Clin Ther. 2004;26(4):493-501.
15. Berthoin K, Le Duff CS, Marchand-Brynaert J, Carryn S, Tulkens PM. Stability of meropenem and doripenem solutions for administration by continuous infusion. J Antimicrob Chemother. 2010;65: 1073-5.
16. Keel RA, Sutherland CA, Crandon JL, Nicolau DP. Stability of doripenem, imipenem, and meropenem at elevated room temperatures. Int J Antimicrob Agents. 2011;37(2):184-5.
17. Viaene E, Chanteux H, Servais H, Mingeot-Leclercq MP, Tulkens PM. Comparative stability studies of antipseudomonal beta-lactams for potential administration through portable elastomeric pumps (home therapy for cystic fibrosis patients) and motor-operated syringes (intensive care units). Antimicrob Agents Chemother. 2002;46(8):2327-32.
18. Fawaz S, Barton S, Whitney L, Swinden J, Nabhani-Gebara S. Stability of meropenem after reconstitution for administration by prolonged infusion. Hosp Pharm. 2019;54(3):190-6.
19. Venugopalan V, Manigaba K, Borgert SJ, Cope J, Peloquin CA, Klinker KP. Training a drug to do new tricks: Insights on stability of meropenem administered as a continuous infusion. Microbiol Insights. 2018;11:1178636118804549.
20. Sornsuvit C, Wientong P, Uitrakul S, Okonogi S, Katip W. Influence of concentration and temperature on stability of imipenem focused on solutions for extended infusion. Dose Response. 2021;19(4):15593258211059325.