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Original Article

THE STABILITY OF GENERIC MEROPENEM IN TROPICAL COUNTRIES

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ABSTRACT

Objective: To evaluate the stability of two brands of generic meropenem at high ambient temperatures and various concentrations in solution.

Methods: Generic meropenem brand A and brand B vials were used to prepare 10 mg/mL and 20 mg/mL solutions in PVC bags. The prepared solutions were incubated at 25, 30 and 35 °C. Three mL of each solution were with drawn at 0, 4, 8 and 12 hours and subjected to HPLC analysis.

Results: Generic meropenem (Brand A) as a 10 mg/mL solution was stable for up to 10 hours at 25°C, 5 hours at 30°C and 4.5 hours at 35°C. A. 20 mg/mL solution was stable for 6 hours at 25°C, 5 hours at 30°C and 3 hours at 35°C. Generic meropenem (Brand B) as a 10 mg/mL solution was stable for up to 9 hours at 25°C, 5 hours at 30°C and 3 hours at 35°C. A. 20 mg/mL solution was stable for 5 hours at 25°C,10 hours at 30°C and 5 hours at 35°C.

Conclusion: The stability of the generic meropenem solutions was affected by temperature and concentration. Higher the temperatures and higher the drug concentrations, show lower the stability of generic meropenem.

Keywords: stability, Meropenem, Extended infusion, High temperatures, Tropical country.

INTRODUCTION

The incidence of multidrug-resistant *Pseudomonas aeruginosa* and *Acenetobactor buamanii* is likely to rise in several regions world wide [1, 2]. Meropenem is commonly used to treat multi drug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections [3]. Animal models have suggested that the pharmacokinetic/ pharmacodynamic parameter of meropenem is the percentage of time above minimum inhibition concentration (T>MIC). Therefore, the drug is administered to optimize the bactericidal effect [4].

In the higher ambient temperatures of tropical countries, the stability of meropenem is an important consideration, if administering via extended infusion [4]. Understanding meropenem's stability profile is critical for clinical practice. Furthermore, Patel et al. [5] have shown that the stability of meropenem was influenced by its concentration [5]. However, data on meropenem concentrations used in clinical practice are limited. Jaruratanasirikul et al. [6] suggested 1 g (10 mg/mL) as a 3-hour infusion results in greater *T*>MICs than a bolus injection. In addition, a 3-hour infusion of 2 g (20mg/mL) of meropenem was the appropriate treatment for infections caused by highly resistant pathogens. However, meropenem may not be stable enough to use for extended infusions at high ambient temperatures. This study evaluated the stability of meropenem at elevated temperatures (25, 30 and 35°C) and various concentrations (10, 20 mg/mL) to assess the feasibility of administering as an extended infusion at higher ambient temperatures in non-climate controlled settings in the tropics (i. e. , non-air conditioned clinical settings).

MATERIAL AND MEDTHOD

Drugs, chemicals and instruments

This study used meropenem tri hydrate as a pure powder commercially available in 0.5 g vial (Brand A) and 1 g vial (Brand B)from two local Thai companies. The meropenem tri hydrate used as the reference standard was a product of Fluka. The sterile normal saline solution in PVC bag was a product of GHP, Thailand. The HPLC grade acetonitrile and water used to prepare all solutions for HPLC analysis were obtained from RCI Labscan, Thailand. Potassium dihydrogen phosphate and orthophosphoric acid were obtained from BDH Laboratory Supplies and Merck, respectively.

Instruments and analytical conditions were as the following. The HPLC method was performed on a LC-20AD Prominence model HPLC (Shimadzu, Japan), equipped with a model LC-20AD pump, a UV/Vis detector SPD-20A, a model SIL-20AHT auto sampler, a model CTO-20AC column oven, a DGU-20A5R degassing unit and a LC solution integrator(Shimadzu, Japan). The method was performed using a reversed-phase technique [7]. A. 5 μm particle size C18Fortis column of dimension 250x4.0 mm (Fortis technologies) was used. Meropenem was eluted isocratically using a mobile phase consisting of 30 mm monobasic phosphate buffer and acetonitrile (90:10; v/v), adjusted to pH 3.0 with ortho-phosphoric acid data flow rate of 1.0 ml ml/min. The UV/Visdetector was set at 298 nm. The mobile phase was freshly prepared, filtered through a 0.45 mm membrane filter and degassed before use. The HPLC system was operated at 25°C. An Espec temperature and humidity controller cabinet (LHL-112 model) was used to create the controlled temperature conditions [7].

Preparation of meropenem solutions and analytical method

Generic meropenem 0.5 g/vial (Brand A) and 1g/vial(Brand B) were used to prepare 10 and 20 mg/mL solutions.

To produce the 10 mg/mL solution (Brand A), two vials (0.5g each)were reconstituted with 10 mL of HPLC grade water to yield a concentration of 50 mg/mL. Then each 10 mL of reconstituted meropenem (2 vials for 20 mL) was combined with 80mL mL of 0.9% sodium chloride (NS) in the PVC bags. Meropenem 20 mg/mL solutions were prepared by combining four reconstituted meropenem 0.5 g vials (40mL mL) with 60 mL of NS in the PVC bags.

To produce the 10 mg/mL solution (Brand B), each 1g vial was reconstituted with 10 mL of HPLC grade water to yield a meropenem concentration of 100 mg/mL. Then 10 mL of reconstituted meropenem was combined with 90 mL of 0.9% sodium chloride (NS) in PVC bags. Meropenem 20 mg/mL solutions were prepared by combining two reconstituted meropenem1g vials (20 mL mL) with 80 mL of NS in the PVC bags.

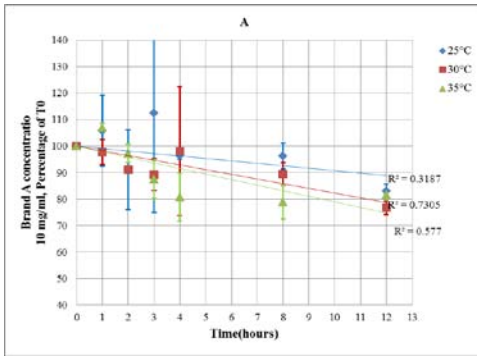
Three replicate solutions were prepared for each concentration and temperature. Prepared solutions in the PVC bags were incubated in the temperature controlled cabinet (at 25, 30 and 35 °C). Three mL of each solution were with drawn at 0, 4, 8, 12 hours and subjected to HPLC analysis at concentrations of 50 and 100 μg/mL.

Data analysis

Results were reported in the mean percentage ± SD of the initial concentration. Meropenem was considered stable if solutions maintained ≥ 90% of the initial concentration [8].

RESULTS

Fig. 1 and 2 show the stability of the meropenem preparations for 12 hours at three elevated temperatures (25, 30 and 35 °C). The degradation of the brand A generic meropenem solutions (fig. 1) was both time and temperature dependent. For brand A, the 10 mg/mL solution was stable (maintained more than 90% of its initial concentration) for up to 10 hours at 25°C, 5 hours at 30°C and 4.5 hours at 35°C. The 20 mg/mL solution was stable for 6 hours at 25°C, 5 hours at 30°C and 3 hours at 35°C. For brand B (fig. 2), the 10 mg/mL solution was stable for up to 9 hours at 25°C, 5 hours at 30°C and 3 hours at 35°C. The 20 mg/mL solution was stable for 5 hours at 25°C, 10 hours at 30°C and 5 hours at 35°C.



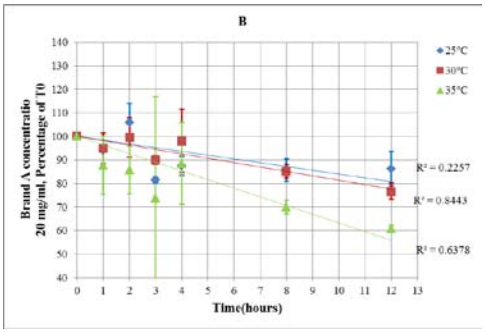
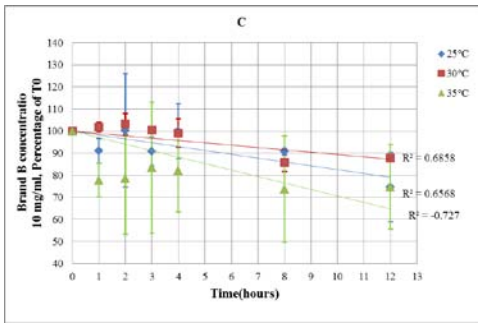


Fig. 1: The stability of generic meropenem (brand A) in NS solutions - 10(A) and 20(B) mg/mL - incubated for up to 12 hours at various temperatures. Data are presented as mean of duplicate samples at each time set



DISCUSSION

The efficacy of meropenem correlated with the time that the concentrations in serum were above the MIC for the pathogens during the dosing interval. The 3-hour infusion was shown to provide benefits over bolus injection, 3-hour infusion of 1 g of meropenem achieved higher % time above MIC values for MICs of 1–4 mg/L than did a bolus injection of 1 g of meropenem. Based on the data, meropenem should be administered by extended infusion [9].

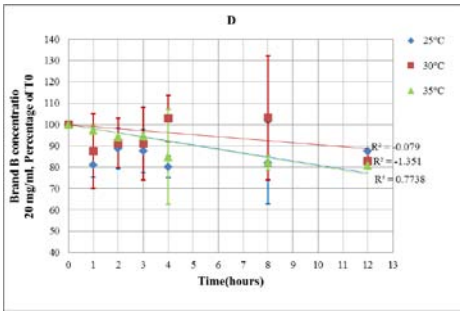


Fig. 2: The stability of generic meropenem (brand B)in NS solutions –10(C) and 20(D) mg/mL - incubated for up to 12 hours at various temperatures. Data are presented as mean of triplicate samples at each time set

However, the stability of meropenem reconstituted in solution was influenced by temperature. Viaeneet al.[10] showed that the degradation of brand meropenem in concentrated aqueous solutions (6.4 g/100 mL) resulted in 10% degradation after 5.15 hours when incubated at 25°C. Franceschi et al.[11] demonstrated that the generic meropenem formulation in a concentration of 5 mg/ml in normal saline solution did not change when add into new buffers or salts. They suggested that in clinical settings with ambient temperatures below 35°C, continuous infusion of meropenem may be applied, even for this generic version of the drug, provided that the 5 mg/mL aqueous solution is reconstituted at most after 6–8 hours. However, at 40°C, generic solutions degraded by 5 hours. These previous results were similar with our study that showed that two brands of generic meropenem(at 10 mg/mL) were stable(less than10% degradation)for 10 hours (Brand A) and 5.5 hours (Brand B) at 25°C. However, when the temperature was increased to 35°C, the meropenem degraded more quickly (within 4.5and 3 hours for Brand A and B, respectively). Berthoinet et al.[12] confirmed that the degradation of the 4 g/100 mL solution was both time and temperature dependent (10% in 12 hours at 25°C; in 6 hours at 37°C). This corresponded with Jaruratanasirikul et al.[3] who showed that the original brand of meropenem, reconstituted in normal saline solution, was unstable when stored at room temperature in a tropical country (32 to 37°C) for 8 hours. Drug concentrations decreased 3.14%, 5.86% and 11.85% after 2, 4 and 8 hours after storage at 32-37°C, respectively. Moreover, we found that the concentration of the drug was affected to their stability. Patel et al.[5] showed that the stability of meropenem was influenced by the drug concentration. Meropenem was stable for a longer time in the 1mg/mL (0.7% degradation) solution than in the 20 and 50 mg/mL (2.7% degradation) solutions at 4-5 °C after 4 hours.

Our study confirmed that the stability of meropenem (Brand A) in normal saline solution is influenced by drug concentration. Drug concentrations were reduced by 10%after 4.5(10 mg/mL) and 3 (20 mg/mL) hours after storage at 35°C. However, our study also showed that brand B was less affected by drug concentration.

Our study has some limitations. First, the stability of the original meropenem was not assessed directly, so the comparison was based on initial concentration. Second, triplicate samples were performed on the different of PVC bag, so it may have inter individual variability.

CONCLUSION

The stability of generic meropenem solutions was affected by their concentration and ambient temperature. Higher temperatures and drug concentration as a result to decreased the stability of generic meropenem. We conclude that these agents should not be

administered by infusions for more than 3 hours at ambient room temperatures in a tropical country.

Moreover, we should be aware when these drugs are used in high concentrations.

CONFLICT OF INTERESTS

Declared None

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REFERENCES

1. Taccone FS, Cotton F, Roisin S, Vincent JL, Jacobs F. Optimal meropenem concentrations to treat multidrug-resistant Pseudomonas aeruginosa septic shock. Antimicrob Agents Chemother 2012;56(4):2129-31.
2. Ikonomidis A, Pournaras S, Maniatis AN, Legakis NJ, Tsakris A. Discordance of meropenem versus imipenem activity against Acinetobacter baumannii. Int J Antimicrob Agents 2006;28(4):376-7.
3. 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.
4. Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. Clin Infect Dis 2008;47(1):32-40.
5. Patel PR, Cook SE. Stability of meropenem in intravenous solutions. Am J Health Syst Pharm 1997;54(4):412-21.
6. Jaruratanasirikul S, Sriwiriyajan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administrationby 3-hour Infusion or bolus injection. Antimicrob Agents Chemother 2005;49(14):1337-9.
7. Mendez AS, Dalomob J, Steppe M, Schapoval EE. Stability and degradation kinetics of meropenem in powder for injection and reconstituted sample. J Pharm Biomed Anal 2006;41(4):1363–6.
8. Smith DL, Bauer SM, Nicolau DP. Stability of meropenem in polyvinyl chloride bags and an elastomeric infusion device. Am J Health Syst Pharm 2004;61(16):1682-5.
9. Jaruratanasirikul S, Sriwiriyajan S. Comparison of the pharmacodynamics of meropenem in healthy volunteers following administrationby intermittent infusion or bolus injection. J Antimicrob Chemother 2003;52(3):518–21.
10. 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.
11. Franceschi L, Cojutti P, Baraldo M, Pea F. Stability of generic meropenem solutions for administration by continuous infusion at normal and elevated temperatures. Ther Drug Monit 2014;36(5):674-6.
12. 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(5):1073–5.