The Effect of Concentration and Temperature on Stability of Meropenem Solution Administered by Extended Infusion

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บทคัดย่อ

วัตถุประสงค์: เพื่อประเมินความคงตัวทางเคมีของยา Meronem® (meropenem trihydrate) ตามความเข้มข้นที่ใช้โดยทั่วไป ใน 3 อุณหภูมิ ณ เวลาต่าง ๆ **วิธีการศึกษา:** นำผลิตภัณฑ์ยา Meronem® ชนิดฉีด (บริษัท Astra Zeneca) ละ ละลายด้วย 0.9% sodium chloride ใน PVC bags จนได้สารละลายความเข้มข้น 10 และ 20 มิลลิกรัม/มิลลิลิตร เก็บสารละลายดังกล่าวในตู้ควบคุมอุณหภูมิที่ 25, 30 และ 35 องศาเซลเซียส จากนั้นเก็บตัวอย่างสารละลายมาวิเคราะห์ปริมาณด้วย วิธี HPLC ที่เวลา 0, 1, 2, 3, 4, 8 และ 12 ชั่วโมง แล้วพิจารณาความสัมพันธ์ ระหว่างความคงตัวของยากับอุณหภูมิและความเข้มข้นที่เปลี่ยนแปลงไป โดยใช้ เกณฑ์ความคงตัวที่ 90% ของตัวยาที่เหลือ **ผลการศึกษา:** สารละลายยาฉีด Meronem® ความเข้มข้น 10 มิลลิกรัม/มิลลิลิตร มีความคงตัวเป็นระยะเวลา 8 ชั่วโมงที่อุณหภูมิ 25 องศาเซลเซียส แต่พบว่าความคงตัวดังกล่าวลดลงเมื่อ อุณหภูมิเพิ่มสูงขึ้น (4 ชั่วโมงที่ 30 องศาเซลเซียส และ 1 ชั่วโมงที่ 35 องศา เซลเซียส) ส่วนกรณีความเข้มข้น 20 มิลลิกรัม/มิลลิลิตรพบว่ายายังคงตัวที่ < 8, 3 และ < 1 ชั่วโมงที่อุณหภูมิ 25, 30 และ 35 องศาเซลเซียส ตามลำดับ **สรุป:** ความ คงตัวของผลิตภัณฑ์ยา Meronem® ชนิดฉีดขึ้นกับอุณหภูมิและความเข้มข้น การ เพิ่มอุณหภูมิและความเข้มข้นของยาที่สูงขึ้นจะทำให้ความคงตัวของยาลดต่ำลง ดังนั้นอุณหภูมิและความเข้มข้นของยาที่เหมาะสมจึงมีความสำคัญในกรณีที่ ต้องการหยดยาแบบยืดระยะเวลา (extended infusion)

คำสำคัญ: ความคงตัว, มีโรพีเนม, การหยดยาแบบยืดระยะเวลา, อุณหภูมิ, ความเข้มข้น

Abstract

Objective: To evaluate chemical stability of Meronem® (meropenem trihydrate) in two commonly used concentrations when stored in 3 temperatures over time. **Methods:** Meronem® injection (Astra Zeneca) was used to prepare 10 mg/mL and 20 mg/mL of meropenem in 0.9% sodium chloride solution. The final solutions in PVC bags were stored at 25, 30, and 35 °C. The solutions were determined for concentration at 0, 1, 2, 3, 4, 8 and 12 hours by means of HPLC analysis. The associations between drug stability, temperature and concentration were determined. Stability was set with a cut-off of 90%. **Results:** Meronem® 10 mg/mL solutions was stable for up to 8 hours at 25°C. Its stability was lower at higher temperatures, specifically, 4 hours at 30 °C and 1 hour at 35 °C. For 20 mg/mL solutions, the solution was stable in < 8, 3 and < 1 hours at 25, 30 and 35 °C, respectively. **Conclusion:** The stability of Meronem® injection solution was affected by temperature and concentration where high temperature and concentration resulted in less stability. Suitable temperature and drug concentration should be concerned when this drug is given by extended infusion.

Keywords: stability, meropenem, extended infusion, temperature, concentration

Introduction

The multidrug-resistant gram-negative bacterial infection continues to rise in several regions worldwide.[1,2] Meropenem is active against gram-negative pathogenic bacteria including multidrug-resistant gram-negative bacterial infection.[3] The percentage of time above the MIC (%T > MIC) is the most important pharmacokinetic/pharmacodynamic (PK/PD) parameter correlating with therapeutic efficacy of meropenem, so extended or continuous infusion of meropenem is the key to success.[4]

According to a previous study, the results suggested that extended infusion of 1 g (10 mg/mL) and 2 g (20 mg/mL) of meropenem could provide serum concentrations above the MIC of multidrug-resistant gram-negative pathogenic bacteria.[5] Thus, the stability of meropenem in the extended infusion in the two concentrations (10 and 20 mg/mL) is important, especially when it is given at room temperature in tropical countries (32 to 37 °C).[5,6] However, information about stability of meropenem in the extended infusion at high temperature and concentration used in clinical practice is limited. The objective of this study therefore was to evaluate the meropenem stability of the extended infusion in various concentrations and temperatures.

Methods

Drugs, chemicals and instruments

Meropenem (1g/vial) as pure powder was from Astra Zeneca. Meropenem trihydrate as reference standard was a product of Fluka. Sodium chloride solution (0.9%) in PVC bag was a product of GHP, Thailand. Potassium dihydrogen

phosphate was obtained from BDH Laboratory Supplies. Orthophosphoric acid was from Merck. HPLC-grade acetonitrile and water were obtained from RCI Lab Scan, Thailand, and were used to prepare all solutions for the HPLC analysis.

Instruments and analytical conditions were as follows. The HPLC machine was an LC-20AD Prominence model HPLC, Shimadzu, Japan, equipped with a model LC-20AD pump, a UV/Vis detector SPD-20A, a model SIL-20AHT autosampler, a model CTO-20AC column oven, a DGU-20A5R degassing unit and an LC solution integrator (Shimadzu, Japan). The analyses were performed by using reverse-phase technique.[7] A 5-µm particle size C18 Fortis column with a dimension of 250 x 4.0 mm (Fortis Technologies) was used. Meropenem injection 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 an orthophosphoric acid flow rate of 1.0 ml/min. The UV/Vis detector was set at 298 nm. The mobile phase was prepared freshly, filtered through a 0.45-mm membrane filter and degassed before use. The HPLC system was operated at 25 °C. An ESPEC's temperature and humidity controller cabinet, LHL-112 model, was used to study under three temperature conditions.[7]

Preparation of meropenem sample solution

To prepare sample solutions at final concentrations of 20 mg/mL and 10 mg/mL, meropenem 1 g/vial was diluted as follows. First, each 1-g vial was reconstituted with 10 mL of HPLC-grade water to yield a meropenem concentration of 100 mg/mL. To prepare a final 20 mg/mL sample, two reconstituted vials (i.e. 2 g in 20 mL) were further diluted with 80 mL of 0.9% sodium chloride in a PVC bag. With the same method, one reconstituted vial (1 g in 10 mL) was further diluted with 90 mL of 0.9% sodium chloride in a PVC bag to prepare a final 10 mg/mL sample. A total of three replicate solutions were prepared for each concentration and temperature.

Regarding temperature, prepared meropenem solutions in PVC bags were incubated at three controlled temperatures, specifically 25, 30 and 35 °C. A sample of 3 mL of each incubated solution was collected at 0, 1, 2, 3, 4, 8 and 12 hours and kept on ice until it was subject to analysis. At the analysis, all incubated samples with concentrations of 10 and 20 mg/ml were further diluted with

HPLC-grade water to concentrations of 50 and 100 µg/mL, respectively. An aliquot of 20 µL was injected into the HPLC column. The concentration of injected sample was calculated from the calibration curve.

Preparation of reference standard solution and calibration curve

A total of 10 mg of meropenem reference standard was weighted accurately and added to a 10-mL volumetric flask and dissolved in HPLC grade water, as a stock solution. A 0.1-mL aliquot of stock solution was diluted to 100 mL in HPLC grade water, and yielded a concentration of 20 µg/mL. The final concentrations of 20, 40, 60, 80, 100 and 120 µg/mL were prepared by the dilution method previously described and used for plotting standard curves. The calibration curve was plotted between peak area against meropenem reference standard with concentrations of 20 to 120 µg/mL.

The analytical method for determining meropenem in the solution by HPLC method was the one of Mendeza et al.[7] To verify the method, linearity, precision and accuracy of the calibration curve were determined with meropenem reference standard with concentrations ranging from 20 to 120 µg/mL. The acceptance criteria of linearity, precision and accuracy were $r^2 > 0.998$, % CV < 2% and mean recovery of 98 - 102%, respectively.[8,9]

Data analysis

Results were reported as mean percentage with standard deviation of meropenem concentrations compared to that at the initial time point. Samples were considered stable if mean percentage of meropenem concentrations remained higher than 90% of the control (0 hour) according to the U.S. Pharmacopeia.[10]

Results

The calibration curve shows a linearity in the concentration range of 20 - 120 µg/mL, with $r^2 \geq 0.99$. The standard curve between peak area and concentration is shown in Figure 1. The within-run precision (% CV) was in a range of 0.0 - 0.4% and the between-run precision ranged from 3.2% to 4.9%. The within-run accuracy was 96.13 - 100.18% with the between-run accuracy of 97.18 - 100.18%.
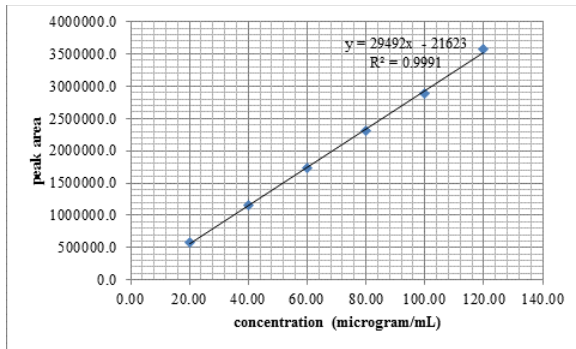
Figure 1 Calibration curve for determining meropenem concentration, and peak area versus meropenem concentration demonstrating linearity.

Stability of meropenem in 0.9% sodium chloride solution incubated at 25, 30 and 35 °C for up to 12 hours is shown in Figure 2 (meropenem 10 mg/mL) and Figure 3 (meropenem 20 mg/mL). Based on a criterium of 90% remaining as being stable, meropenem at a concentration of 10 mg/mL was stable for 8 hours (90%) when stored at 25 °C. Shorter duration was found with higher temperature where the solution was stable at 4 hours (92%) and 1 hours (91%) when stored at 30 °C and 35 °C, respectively. For meropenem 20 mg/mL solution, the stable duration was shorter. After stored at 25 °C for 8 hours, while 90% of the 10 mg/mL meropenem was found, only 87% of the 20 mg/mL solution was detected. Similar to the 10 mg/mL meropenem solution, the higher the temperature, 30 °C and 35 °C, the lower the stable duration of the 20 mg/mL solution, i.e. 3 hour (91%) and less than 1 hour (79%), respectively.
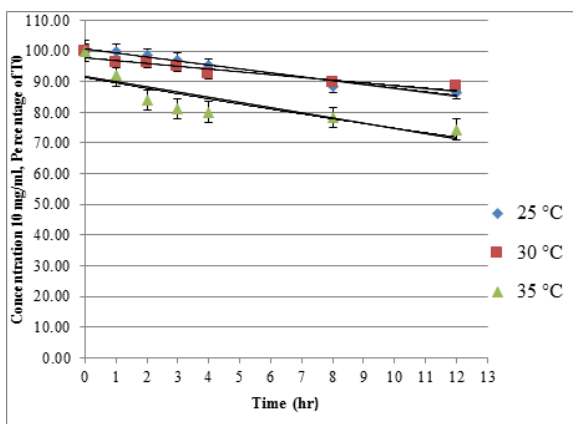

Figure 2 Stability of 10 mg/mL meropenemin in 0.9% sodium chloride solution incubated at three different temperatures for up to 12 hours.
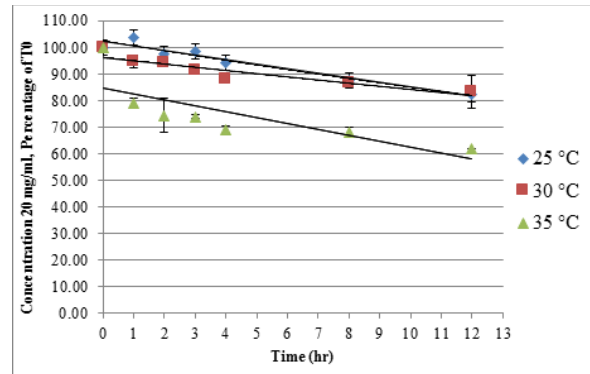

Figure 3 Stability of 20 mg/mL meropenem in 0.9% sodium chloride solution incubated at three different temperatures for up to 12 hours.

Discussions and Conclusion

Based on our definition of stability, admixtures were stable if the mean percentages of meropenem remained greater than 90%. Meropenem 10 mg/mL solution was stable for 8, 4 and 1 hours at 25, 30 and 35 °C, respectively. In addition, 20 mg/mL solution was stable for < 8, 3 and < 1 hours at 25, 30 and 35 °C, respectively.

To achieve an adequate time above the MIC (%T > MIC), the extended infusion of meropenem has been recommended in clinical practice.[11] The recommendation is however not free of limitation as the stability of meropenem solution was temperature and concentration-dependent. Our study found that the stability of reconstituted meropenem was lessened with higher temperature. A previous study by Berthoin et al[12] indicated that 40 mg/mL meropenem in water for injection was degraded faster in a higher temperature where a 10% degradation was found in 12 hours when stored at 25 °C, but 6 hours at 37 °C. Furthermore, our finding that the degradation of meropenem was concentration-dependent were also supported by the works of Viaene et al and Franceschi et al.[13,14] In these two studies, higher concentration of meropenem in water for injection resulted in a faster rate of degradation at 25 °C. This was evident as 10% degradation was found after 5 hours in the high concentration of meropenem (64 mg/mL) and 8 hours in a low one (5 mg/mL).[13,14] The study by Patel and colleagues also found that the stability of meropenem was influenced by the drug concentration.[6] After stored at 4 – 5 °C for 4 hours, more degradation (2.7%) was found in the 20 mg/mL meropenem in sterile water for injection, while

a less degradation (0.7%) in the 1 mg/mL solution.[6] Although results from these studies agreed with the one in our study, concentrations tested in their studies were considerably different from ours.[6,13,14] In our study, the concentrations of and solvents for meropenem were mostly identical to the ones in the real practice. In addition, our finding also suggested that at a high practical concentration (20 mg/mL) and a relatively high temperature (35 ℃) which could be found in most medical wards in tropical countries almost throughout the year, 10% degradation of meropenem was found as fast as after 1 hour.

Based on this study and other studies,' findings factors influencing the stability of meropenem in normal saline solution were drug higher concentration and higher temperature. Practically, when meropenem is given by extended infusion, we therefore recommend that it should be diluted to a low concentration (10 mg/mL) and infused in an air conditioned room (≤ 25 °C) if possible, especially in tropical countries.

This study was no exception regarding limitations. First, this experiment was performed at the indicated temperatures, i.e. 25, 30, and 35 °C, so our results should not be extrapolated to out-of-range temperatures such as those less than 25 °C or greater than 35 °C. Moreover, based on a range of normal room temperature of 32 – 37 °C in tropical countries, we suggest more stability tests on higher temperature in further studies. Lastly, our results were based on the test of the product named Meronem® injection solution. Stability profiles of other various brands of meropenem for injection could be different attributable to differences in salts or other ingredients. Application of stability profile from this experiment to other brands of meropenem should be done with care, and studies on stabilities of other brands should also be done.

Conclusions

Meropenem solution for injection was less stable with higher temperature and concentration. Based on a pharmacokinetic/ pharmacodynamic profile of meropenem where adequate time above the MIC (%T > MIC) could be achieved by the extended infusion, we recommend that the solution should be diluted to the lowest possible concentration infused in a low temperature, such as in an air conditioned room.

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