STABILITY OF MEROPENEM IN NORMAL SALINE SOLUTION AFTER STORAGE AT ROOM TEMPERATURE

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Abstract. The bactericidal activity of meropenem is determined by the time that concentrations in tissue and serum are above the MIC for the pathogens during the dosing interval. Thus, the most effective mode of administering of meropenem is continuous infusion. However, the stability of meropenem reconstituted in solution is influenced by the storage temperature. Until now we have had no data to evaluate the stability of this drug during continuous infusion in a tropical country. The objective of this study was to provide such data. Meropenem 0.5 g and 100 ml normal saline solution were mixed together and stored at room temperature for 8 hours. Half of the solution was stored in a room with air conditioning at 20ºC and the other half of the solution was stored in a room without air conditioning at 32º-37ºC. The concentrations of meropenem in the solution were measured at 0, 1, 2, 3, 4, 6 and 8 hours after the drug was reconstituted. Twelve lots of (0.5 g meropenem in normal saline) solution were evaluated in each temperature condition. The mean meropenem concentrations reconstituted in normal saline solution decreased 1.66%, 3.31% and 5.80% after 2, 4 and 8 hours storage at 20ºC, respectively. Drug concentrations decreased 3.14%, 5.86% and 11.85% after 2, 4 and 8 hours storage at 32º-37ºC, respectively. Therefore, we conclude that this agent should not be administered by 8-hour continuous infusion at room temperature in a tropical country.

INTRODUCTION

The most effective mode of administration to optimize the bactericidal effect of parenteral antibiotics in treating of infections depends up on the drug class (Craig and Ebert, 1992). For instance, the bactericidal activity of a β-lactam antibiotic is not maximized by increasing the peak drug serum concentration to MIC ratio because, the bactericidal activity of these drugs is concentration independent, determined by the time that concentrations in tissue and serum are above the MIC for the pathogen during the dosing interval. If the concentrations of antibiotics decrease to below the MIC, bacterial growth resumes immediately since these drugs have no significant post-antibiotic effect, as seen with aminoglycosides (Craig and Ebert, 1992; Benko *et al*, 1996; Nicolau *et al*, 1996). Therefore, the ideal method to maintain the time that the β-lactam antibiotic is above its MIC for a pathogen would be to administer the agent by continuous infusion (Craig and Ebert, 1992). Moreover, this method of administration allows a reduction in the amount of antibiotic used per day (Craig and Ebert, 1992; Benko *et al*, 1996; Nicolau *et al*, 1996).

Meropenem, a β-lactam antibiotic, is characterized by its ultrabroad spectrum of activity against clinically important aerobic and anaerobic pathogens and is commonly used for the treatment of nosocomial gram-negative bacilli infections, particularly *Pseudomonas aeruginosa* infection (Norrby *et al*, 1997). The stability of meropenem is an important consideration if continuous infusion administration is to be used. From the manufacturer's guidelines, meropenem is stable at room temperature (20ºC) for 8 hours when the drug is reconstituted in isotonic saline solution. Thailand is a tropical country, and temperatures during the daytime are usually above 25ºC. Therefore, this agent may be unstable when administered by continuous infusion. However, until now we have had no data to evaluate the stability of this drug during this mode of administration in a tropical country. The objective of

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this study was to provide such data.

MATERIALS AND METHODS

Drugs and chemicals

Meropenem (Meronem®) was generously donated by AstraZeneca, Thailand and cefepime was generously donated by Bristol Myers Squibb, Thailand, as pure powder. All of the solvents were high-performance-liquid-chromatography (HPLC) grade.

Study design and sample collection

Meropenem 0.5 g and 100 ml normal saline solution were mixed together and stored at room temperature for 8 hours. Half of the solution was stored in a room with air conditioning at 20ºC and the other half of the solution was stored in a room without air conditioning at 32º-37ºC. The concentrations of meropenem in the solution were measured at 0, 1, 2, 3, 4, 6 and 8 hours after the drug was reconstituted. Twelve lots of solution (0.5 g-meropenem in normal saline) were evaluated in each temperature condition. Results were expressed as mean ±SD, and statistical comparisons were made using the Wilcoxon signed-ranks test.

Meropenem assay

The concentration of meropenem was determined by reverse phase HPLC by the modified method of Ip *et al* (1998). The samples were diluted 20-fold by deionized water, and cefepime was used as an internal standard. The diluted samples (20 μl) were injected, using an automated injection system (Waters 717 plus Autosampler, Waters, Milford, MA, USA), onto a μBondapak C18 column (Waters). The mobile phase was composed of 0.01 M 1-heptane-sulphonic acid: acetonitrile (92:8, v/v), at a flow rate of 1 ml/minute. The column effluent was monitored by UV detection (Waters 486) at 280 nm. The standard curve, with meropenem concentrations ranging from 250 to 350 μg/ml, was shown to be linear and the coefficient of variation was 3.62% in the meropenem assay. The limit of detection was 2 μg/ml.

RESULTS

The mean meropemem concentrations, after reconstitution in normal saline solution, gradually decreased after storage at both 20ºC and 32º-37ºC, as shown in Fig 1 and Table 1.

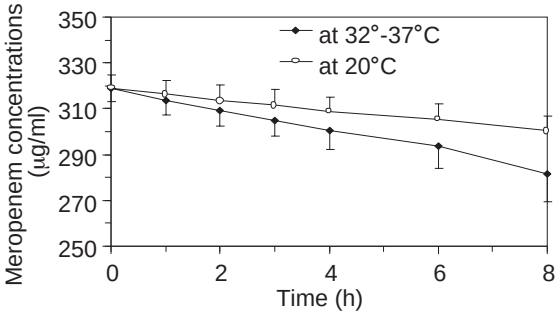

Fig 1–Mean ± SD concentrations of 0.5 g of meropenem in 100 ml normal saline solution after 1, 2, 3, 4, 6 and 8 hours at 20ºC and 32º-37ºC.

Table 1
Meropenem concentrations in normal saline solution (mean ± SD) after storage in a room at 20ºC and 32º-37ºC and % decrease as compared to drug concentration at time 0.

Storage time (hours)	20ºC		32º-37ºC	
	Meropenem concentrations	% Decrease	Meropenem concentrations	% Decrease
0	319.07 ± 5.80	-	319.07 ± 5.80	-
1	316.28 ± 5.99	0.88	313.49 ± 6.34	1.75
2	313.79 ± 6.53	1.66	309.05 ± 6.71	3.14
3	311.49 ± 6.73	2.38	305.07 ± 6.99	4.39
4	308.53 ± 6.71	3.31	300.43 ± 8.39	5.86
6	305.16 ± 7.08	4.36	293.49 ± 9.34	8.03
8	300.57 ± 6.38	5.80	281.32 ± 11.73	11.85

DISCUSSION

Over the last decade, several investigators have attempted to establish the most appropriate administration techniques to optimize the bactericidal activity of parenteral antibiotics for treating infections. For the β-lactams, it is generally accepted that the bactericidal effect of these agents is determined by the time that the serum antibiotic concentrations remains above four or five times the MIC for a pathogen because this drug class has no significant post-antibiotic effect (Craig and Ebert, 1992; Mouton and den Hollander, 1994; Nicolau *et al*, 1996; Lipman *et al*, 1999). From the manufacturer's instructions, β-lactams are usually administered by intermittent injections. However, with this mode of administration, the high peak concentrations cannot enhance the bactericidal activity of these agents and during the dosing interval, drug concentrations may fall below the MIC for the pathogens. Therefore, continuous infusion would be a mode of administration to maintain such concentrations during drug administration for most bacterial pathogens, even though there are several modes of administration to optimize the pharmacodynamic properties of β-lactam antibiotics (Craig and Ebert, 1992; Nicolau and Quintiliani, 1994).

The stability of meropenem reconstituted in solution is influenced by several factors (Patel and Cook, 1997): 1) storage temperature: the drug is stable for a longer time in solutions stored at 4º-5ºC than in solutions stored at 21º-26ºC; 2) concentration of the drug: the drug is stable for a longer time in 1 mg/ml solution than in 20 and 50 mg/ml; and 3) type of fluid for reconstitution: the drug reconstituted in normal saline solution is stable for a longer time than the drug reconstituted in 5% dextose in water. Our present study confirmed that the stability of meropenem in normal saline solution is influenced by storage temperature. Drug concentrations were reduced 1.66%, 3.31% and 5.80% after 2, 4 and 8 hours after storage at 20ºC, respectively, and 3.14%, 5.86% and 11.85% after 2, 4 and 8 hours after storage at 32º-37ºC, respectively. The reduction in drug concentration at the high storage temperature was significant. Therefore, this agent should not be administered by 8-hour continuous infusion at room temperature in a tropical country.

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REFERENCES

Benko AS, Cappelletty DM, Kruse JA, Rybak MJ. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected gram-negative infections. *Antimicrob Agents Chemother* 1996; 40: 691-5.

Craig WA, Ebert SC. Continuous infusion of β-lactam antibiotics. *Antimicrob Agents Chemother* 1992; 36: 2577-83.

Ip M, Au C, Cheung SW, Chan CY, Cheng AFB, A rapid high-performance liquid chromatographic assay for cefepime, cefpirome and meropenem. *J Antimicrob Chemother* 1998; 42: 121-3.

Lipman J, Gomersall CD, Gin T, Joynt GM, Young RJ. Continuous infusion ceftazidime in intensive care: a randomized controlled trial. *J Antimicrob Chemother* 1999; 43: 309-11.

Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. *Antimicrob Agents Chemother* 1994; 38: 931-6.

Nicolau DP, Quintiliani R. Choosing between the new cephalosporin antibiotics : a pharmacodynamic approach. *Pharmacoecon* 1994; 5 (suppl 2): 34-9.

Nicolau DP, Nightingale CH, Banevicius MA, Fu Q, Quintiliani R. Serum bactericidal activity of ceftazidime: continuous infusion versus intermittent injections. *Antimicrob Agents Chemother* 1996; 40: 61-4.

Norrby SR, Faulkner KL, Newell PA. Differentiating meropenem and imipenem/cilastatin. *Infect Dis Clin Practice* 1997; 6: 291-303.

Patel PR, Cook SE. Stability of meropenem in intravenous solutions. *Am J Health Syst Pharm* 1997; 54: 412-21.