Pharmacodynamics of Meropenem in Critically Ill Patients with Ventilator-Associated Pneumonia

Sutep Jaruratanasirikul MD*,
Narongdet Kositpantawong MD*, Monchana Jullangkoon MPharm*,
Nanchanit Aeinlang MPharm*, Wibul Wongpoowarak MPharm**

** Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
*** Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Background: *Pharmacokinetic changes have been found in critically ill patients, including ventilator-associated pneumonia (VAP) when compared with healthy volunteers leading to fluctuation of plasma concentrations.*
Objective: *To compare the probability of target attainment (PTA) and cumulative fraction of response (CFR) for meropenem between administration by a bolus injection and a 3-hour infusion.*
Material and Method: *The study was a randomized three-way crossover in nine patients with VAP. Each patient received meropenem in three regimens consecutively: (i) a bolus injection of 1 g every eight hours (q8h) for 24 hours; (ii) a 3-hour infusion of 1 g q8h for 24 hours; and (iii) a 3-hour infusion of 2 g q8h for 24 hours. The pharmacodynamic analysis of meropenem was performed to determine the PTA by using the Monte Carlo simulation and the study used susceptibility patterns obtained from EUCAST and MYSTIC for assessment of CFR.*
Results: *For an MIC of 4 µg/ml, the PTAs achieving 40% T>MIC following a bolus injection of 1 g q8h, a 3-hour infusion of 1 g q8h, and a 3-hour infusion of 2 g q8h were 87.71%, 98.80%, and 99.90%, respectively. Only the 3-hour infusion regimens were predicted to achieve a CFR ≥90% against E. coli, Klebsiella spp., P. aeruginosa, and Acinetobacter spp.*
Conclusion: *A 3-hour infusion of 2 g of meropenem regimen was predicted to have the highest PTA rates. Only the prolonged infusion regimens achieved a high CFR against E. coli, Klebsiella spp., P. aeruginosa, and Acinetobacter spp.*

Keywords: *Meropenem, Population pharmacokinetic, Pharmacokinetics/pharmacodynamics, Pharmacodynamics, Carbapenems, Ventilator-associated pneumonia*

J Med Assoc Thai 2013; 96 (10): 1283-9
Full text. e-Journal: *http://jmat.mat.or.th*

Ventilator-associated pneumonia (VAP) is a common cause of nosocomial infection with a high mortality rate[1] and meropenem is still one of the most commonly used antibiotics for empirical therapy of highly resistant nosocomial infections in VAP[2]. In common with other β-lactams, this agent exhibit primarily time dependent killing, therefore, the time that concentrations in serum are above the MIC (T>MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) index that correlates with efficacy[3]. Our previous studies revealed that a 3-hour infusion of carbapenem give greater values for T>MIC than those after a bolus injection. Therefore, in an attempt to improve the efficacy of present β-lactam antimicrobial agents such as meropenem, a prolonged infusion would be the appropriate mode for administration to promote the maximal bactericidal effect[4].

PK changes have been found for several hydrophilic antimicrobial agents in critically ill patients[5]. Therefore, the aim of the present study was to assess the PD of meropenem in patients with VAP, comparing administration by a bolus injection or a 3-hour infusion. The authors compared the probability of target attainment (PTA) and cumulative fraction of response (CFR) for meropenem in three regimens: (i) a bolus injection of 1 g; (ii) a 3-hour infusion of 1 g; and (iii) a 3-hour infusion of 2 g.

Material and Method

Subjects

The patients with VAP were eligible for the study if they met the following criteria: (i) older than 18 years; (ii) were intubated and receiving mechanical ventilation; and (iii) clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography

Correspondence to:
Jaruratanasirikul S, Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
Phone: 074-451-452, Fax: 074-429-385
E-mail: jasutep@medicine.psu.ac.th

associated with at least one of the following: purulent tracheal secretions, temperature of 38.3°C or higher or a leucocyte count higher than 10,000 cells/mm^3. Patients were excluded from the study if they were pregnant or in circulatory shock (systolic blood pressure <90 mmHg) or had documented hypersensitivity to meropenem or an estimated creatinine clearance (determined by the Cockcroft-Gault method)[6] of <60 ml/min. The protocol for the study was approved by the Ethics Committee of Songklanagarind Hospital, and written informed consent was obtained from each subject's legally acceptable representative before enrolment.

Drugs and chemicals

Meropenem (Meronem®) was purchased from AstraZeneca, Bangkok, Thailand. Meropenem standard powder was generously donated by AstraZeneca, Macclesfield, UK and cefipime standard powder (internal standard) was donated by Bristol-Myers Squibb, Sermoneta, Italy as pure powder. All solvents were of high-performance liquid chromatography (HPLC) grade.

Study design

The study was a randomized three-way crossover study. Meropenem was reconstituted according to the manufacturer's guidelines. It was then diluted into two preparations: 1 g in 50 ml of normal saline solution and 2 g in 50 ml of normal saline solution. Each subject received meropenem in three regimens at room temperature (32 to 37°C) consecutively: (i) a bolus injection of 1 g of meropenem over 10 minutes every eight hours (q8h) for 24 hours, (ii) a 3-hour infusion of 1 g of meropenem via an infusion pump at a constant flow rate q8h for 24 hours, and (iii) a 3-hour infusion of 2 g of meropenem via an infusion pump at a constant flow rate q8h for 24 hours. After completion of meropenem therapy for three days, all patients were appropriately treated with other antibiotics for 10 days.

Blood sampling

The meropenem PK studies were carried out during administration of the third dose of each regimen (16 to 24 h after the start of each regimen). Blood samples (~3 ml) were obtained by direct venepuncture at the following times: before (time zero) and 10 and 30 minutes and 1, 1.5, 2, 2.5, 3.5, 4, 4.5, 5, 6, and 8 hours after the third dose of each regimen. The blood samples were added to a heparinized tube and immediately stored on ice, centrifuged at 1,000 g for 10 minutes within five minutes, vortexed and then stored at -80°C until analysis within one week.

Meropenem assay

Concentrations of meropenem were determined by reverse-phase HPLC. Cefepime (100 µg/ml) was used as the internal standard and the samples were prepared by the method of Ozkan et al[7]. An aliquot of the extracted sample (50 µl) was injected using an automated injection system (Waters 717 Plus Autosampler; Waters Associates, Milford, MA) onto a µBondapak C18 column (Waters Associates; 3.9x300 mm). The mobile phase was 15 mM KH_2PO_4-acetonitrile-methanol (84:12:4, v/v/v), pH 2.8, at a flow rate of 1 ml/min. The column effluent was monitored by ultraviolet detection (Waters 486; Waters Associates) at 308 nm. Peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The limit of detection of meropenem was 0.05 µg/ml and the limit of quantitation was 0.08 µg/ml. The intra-assay reproducibility values characterized by coefficients of variation (CVs) were 2.58%, 1.77% and 3.45% for samples containing 2, 32 and 128 µg/ml, respectively. The interassay reproducibility precision values, calculated by CVs, were 3.21%, 2.98% and 3.74% for samples containing 2, 32 and 128 µg/ml, respectively.

PK analysis

To perform Monte Carlo simulation, the model should be able to represent the whole concentration-time profile. Data analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA) spreadsheets. Preliminary data analysis indicated that a 1- or 2-compartment model would not be adequate for describing the distribution phase discrepancy, so a 3-compartment model was used, as shown in Fig. 1, after review of the goodness of-fit plots. The objective of non-linear regression is to minimize the sum of the squares of the errors. The error is defined as the difference in concentrations on a geometric scale, i.e. error = (ln calculated Concentration-ln actual concentration). On a normal scale, a high concentration value in the distribution phase would affect the parameters too strongly and would lead to biased predictions in the excretion phase. Such a geometric scale should prevent unrealistic predictions in the excretion phase, which is very important for the calculation of T>MIC in a simulation study.

The 3-compartment PK model for this study was solved numerically using the Runge order 2 method[8]. This is a stiff differential equation for which the calculation instabilities depend on the selected Δt value, the time step increment in the calculation. In this study, the value of Δt was set to 0.001 hour, which had good numerical stability in this situation. We validated the suitability of this Δt and found that it could be used as an optimal value.

Minimization of the sum of squares error (SSE) in this study was performed by the random heuristic optimization method[9,10]. This method has good convergence speed and can be easily implemented manually in a spreadsheet. In brief, various random sets of parameters were generated and used for calculation of SSE, and only satisfactory sets were selected and recorded. From these recorded sets, the average and standard deviation (SD) were computed and used as seeds in generating new random sets of normal distribution parameters with the same averages and SD. The whole process was repeated continuously until convergence was achieved, which usually occurred within a thousand iterations.

Validation of suitability of Δt for Runge order 2 calculations

In post hoc analysis of 500 Monte Carlo simulations of concentration-time profiles, computation differences between using $\Delta t = 0.001$ and $\Delta t = 0.0001$ provided maximum differences of 0.15%, with the median of the differences being 0.07%. Since the algorithm was a second-order method, the error of computation varied with $(\Delta t)^2$ and computations at $\Delta t = 0.0001$ should be 100-fold more precise than at $\Delta t = 0.001$. This implied that the calculated concentration differed from theoretical value by less than 0.15% at $\Delta t = 0.001$. We thus considered $\Delta t = 0.001$ to be the optimum value to be used with the Runge order 2 calculations in spreadsheet data analysis.

Pharmacodynamic assessment using a Monte Carlo simulation

Since the values of PK parameters are not normally distributed, their behavior can be represented more properly using logarithmic scales and logarithmic scales for all parameters were used in the Monte Carlo simulation calculations. From the low correlation matrix between the PK parameters, we determined that it was unnecessary to use a covariate Monte Carlo simulation.

In brief, a set of logarithmic PK parameters was simulated by the log-and-trig formula[11] (synonym, Box-Muller transform) and were converted back to normal-scale values. Since there has been a report that random number behavior may lead to severely spurious results in Monte Carlo simulations[12], the log-and-trig formula was validated to be working properly for its cosine formula (data not shown). From the PK parameters obtained in this study (Table 1), PK parameters were simulated that mimicked the parameters obtained from the clinical study, and these parameters were used to simulate the concentration-time profiles using the Runge-Kutta order 4 algorithm[8]. For the infusion studies, drug stability in vitro was also

Table 1. PK parameters of meropenem in nine patients with VAP after administration by a bolus injection and a 3 h infusion

Parameter	Geometric mean	Geometric SD	Median	95% CI
k_{12} (/h)	2.091	2.667	2.704	(0.48822-7.42779)
k_{21} (/h)	2.582	3.028	2.984	(0.32910-9.49118)
k_{13} (/h)	1.459	3.294	0.967	(0.34102-9.75465)
k_{31} (/h)	2.993	3.079	4.731	(0.40678-8.15546)
k_e (/h)	1.517	1.544	1.201	(0.94441-3.05977)
CL (l/h)	11.793	1.699	15.585	(5.45548-20.84850)
V (l)	7.774	1.419	7.523	(4.78534-14.25540)
V (l)*60 kg	8.792	1.499	8.730	(4.49543-15.89919)

k_{12}: intercompartmental transfer rate constant from compartment X1 to X2
k_{21}: intercompartmental transfer rate constant from compartment X2 to X1
k_{13}: intercompartmental transfer rate constant from compartment X1 to X3
k_{31}: intercompartmental transfer rate constant from compartment X3 to X1
k_e: elimination rate constant from X1
PK = pharmacokinetic; VAP = ventilator-associated pneumonia; CL = total clearance; V = volume of distribution

modeled. The degradation rate constant of meropenem in vitro in an ambient environment of 0.01/h was used as determined in a previous study[13]. This earlier study used n = 10,000 simulations to determine the behavior of % T>MIC at four different target levels, i.e. 20% and 40% attainment. The simulated concentrations were compared with the MIC values and the results were recorded in an external text file for later use. The cross-tabulation relationship in the MIC versus % T>MIC attainment represents the whole spectrum of microbial behavior.

Results

Nine patients were enrolled in the study, six males and three female. Their mean age was 38.00±15.05 years (range 16-61) and their mean weight was 55.52±9.95 kg (range 42.0-70.0). The PK parameters of meropenem for the three regimens are shown in Table 1. The PTAs for the three meropenem regimens achieving 20% and 40% T>MIC at specific MICs are shown in Table 2 and Fig. 1. The assessment of CFR for patients who achieved a target of 40% T>MIC for the three meropenem regimens against *E. coli*, *Klebsiella* spp., *P. aeruginosa* and *Acinetobacter* spp. are shown in Table 3.

Discussion

The current study in critically ill patients with VAP found that a prolonged infusion of 2 g of meropenem q8h was predicted to have the highest PTA rates. Only the prolonged infusion regimens of meropenem had high probabilities of achieving optimal exposure against *E. coli*, *Klebsiella* spp., *P. aeruginosa*, and *Acinetobacter* spp.

Meropenem, a β-lactam antibiotic, is one of the most important and commonly prescribed drugs for the treatment of nosocomial infections in critically ill patients with VAP. This agent is hydrophilic antimicrobial agent, which is characterized by its wide distribution into the extracellular fluid. The drug concentrations in the pulmonary epithelial lining fluid (ELF) for the extracellular respiratory pathogen should be the primary determinants for therapeutic efficacy[14,15]. However, antibiotic concentrations at

Table 2. PTA for meropenem regimens achieving 20% T>MIC and 40% T>MIC in nine patients with VAP after administration of: 1 g bolus injection; 1 g, 3 h infusion; and 2 g, 3 h infusion

MIC (µg/ml)	PTA 20% T>MIC			PTA 40% T>MIC		
	Bolus injection	3 h infusion		Bolus injection	3 h infusion	
		1 g	2 g		1 g	2 g
1	99.96	99.95	99.95	99.07	99.94	99.94
2	99.82	99.95	99.95	96.84	99.87	99.94
4	99.08	99.85	99.91	87.71	98.80	99.90
8	91.68	95.99	99.83	62.60	83.75	98.55
16	61.13	65.94	95.94	23.47	37.08	83.30

PTA = probability of target attainment; MIC = minimum inhibitory concentration

Table 3. CFR (%) for bolus injection of 1 g; 1 g, 3 h infusion; and 2 g, 3 h infusion of meropenem against *E. coli*, *Klebsiella spp.*, *P. aeruginosa* and *Acinetobacter* spp. at PTA achieving 40% T>MIC in nine patients with VAP

	CFR for EUCAST[a], %			CFR for MYSTIC[b], %		
	Bolus injection	3 h infusion		Bolus injection	3 h infusion	
		1 g	2 g		1 g	2 g
E. coli	99.98	99.98	99.99	100.17	100.19	100.19
Klebsiella spp.	99.70	99.81	99.94	99.66	99.73	99.92
P. aeruginosa	89.81	93.13	97.47	92.62	94.64	96.55
Acinetobacter spp.	86.27	89.92	95.91	89.08	91.23	94.42

CFR = cumulative fraction of response; PTA = probability of target attainment

[a] CFR determined using MIC distribution of 2010 EUCAST

[b] CFR determined using MIC distribution of 2002 MYSTIC Program in North America

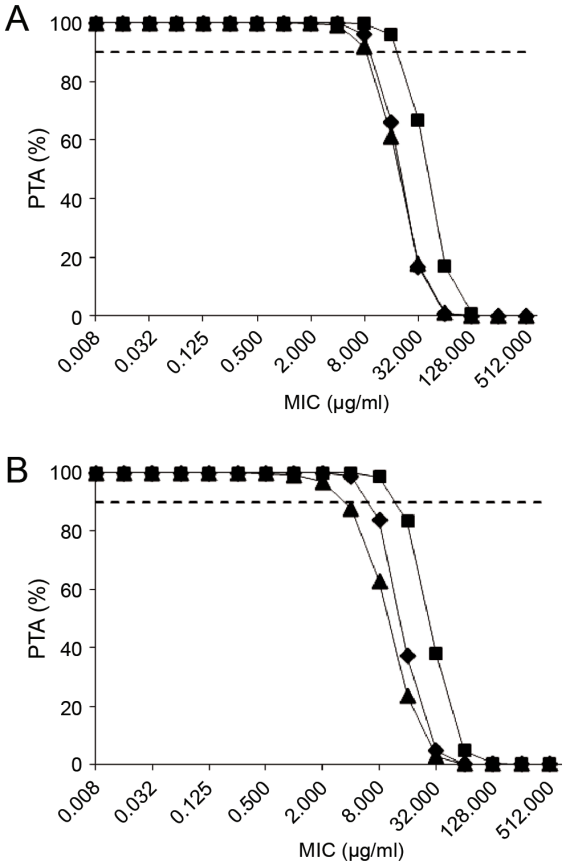

Fig. 1 PTA for meropenem regimens achieving 20% T>MIC (A) and 40% T>MIC (B) in nine patients with VAP after administration of: bolus injection of 1 g (filled triangles); 1 g, 3 h infusion (filled diamonds); and 2 g, 3 h infusion (filled squares). The broken line represents 90% PTA.

ELF are very difficult to obtain and the correlation between the PK/PD index in the ELF and antimicrobial effect is less well understood[16]. Therefore, serum concentrations are most commonly used as a surrogate measure for determining the PK/PD indices and T>MIC is the best parameter that correlates with the bactericidal activity of meropenem.

Our previous PK/PD study of meropenem in patients with VAP found that a 3-hour infusion of meropenem resulted in greater T>MIC values than a bolus injection, suggesting that a 3-hour infusion may be an appropriate mode of administration for meropenem in tropical countries, and a 3-hour infusion of 2 g of meropenem q8h provided mean concentrations in serum >4x the MIC of 4 µg/ml for almost 60% of an 8-h interval[4]. In the current study, we examined the PK/PD in patients with VAP and MCS was performed to determine the probability of attaining a specific PD target at various regimens. The probability of 3-hour infusion regimens achieving a target of 20% T>MIC and 40% T>MIC were all superior to a bolus injection of meropenem regimen and the highest PTA rates were obtained with a 3-hour infusion of 2 g of meropenem q8h. The high PTA (≥90%) achieving 40% T>MIC for MICs of 2 µg/ml was observed when meropenem was administered by all three regimens. For pathogens with MICs of 4 µg/ml, the high PTA was achieved when meropenem was administered as a prolonged infusion. However, only a 3-hour infusion of 2 g meropenem q8h regimen achieved >98% PTA of 40% T>MIC for a MIC of 8 µg/ml. Therefore, from the data, it appears that a prolonged infusion of 1 g of meropenem q8h can provide good activity for pathogens with MICs of ≤4 µg/ml. However, against less susceptibility pathogens to meropenem with MIC >4 µg/ml, the dosage regimen should be increased to a maximum of a prolonged infusion of a 2 g q8h to achieve almost 100% PTA for a MIC of 8 µg/ml.

Previous PD modeling studies in both healthy volunteers and patients with bacterial infections have found that a 3-hour infusion of imipenem and meropenem improved the CFR for several pathogens compared to a 30 minutes infusion[17]. The current study used susceptibility patterns obtained from EUCAST and MYSTIC for assessment of CFR. A prolonged infusion of all regimens had an advantage over a bolus injection and only the prolonged infusion regimens of meropenem achieved high probability targets (CFR ≥90%) against *E. coli*, *Klebsiella* spp., *P. aeruginosa* and *Acinetobacter* spp. The results from our study indicate that against the less susceptible *Acinetobacter* spp., only a prolonged infusion regimen can achieve the high cumulative probability of target attainment. Therefore, for the treatment of severe infections in critically ill patients with highly resistant pathogens, we recommend that meropenem should be administered by a prolonged infusion of 2 g q8h. Our study was conducted in only a small number of patients, which could be considered a potential limitation. However, in the absence of data from a larger sample size, a MCS based on a small number of patients such as in our study can be instructive in illuminating the effects of different dosing approaches.

Conclusion

A prolonged infusion of meropenem from all three regimens resulted in higher PTA rates than after

a bolus injection, and the highest PTA rates were obtained with a 3-hour infusion of 2 g q8h. Moreover, the prolonged infusion regimens of meropenem had high probabilities of achieving optimal exposure against *E. coli*, *Klebsiella* spp., *P. aeruginosa*, and *Acinetobacter* spp.

Competing interests

The authors declare that they have no competing interests.

Acknowledgement

Meropenem was generously donated by Astrazeneca, Bangkok, Thailand and cefipime (internal standard) was donated by Bristol-Myers Squibb, Sermoneta, Italy as pure powder. We thank Mr. David Patterson for checking our English.

Potential conflicts of interest

None.

References

1. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. Am J Respir Crit Care Med 1996; 153: 1711-25.
2. Wiseman LR, Wagstaff AJ, Brogden RN, Bryson HM. Meropenem: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. Drugs 1995; 50: 73-101.
3. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995; 22: 89-96.
4. Jaruratanasirikul S, Sriwiriyajan S, Punyo J. Comparison of the pharmacodynamics of meropenem in patients with ventilator-associated pneumonia following administration by 3-hour infusion or bolus injection. Antimicrob Agents Chemother 2005; 49: 1337-9.
5. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005; 44: 1009-34.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
7. Ozkan Y, Kucukguzel L, Ozkan SA, Aboul-Enein HY. A rapid, sensitive high performance liquid chromatographic method for the determination of meropenem in pharmaceutical dosage form, human serum and urine. Biomed Chromatogr 2001; 15: 263-6.
8. Wylie CR, Barrett LC. Advanced engineering mathematics. Auckland, New Zealand: McGraw-Hill; 1982.
9. Li J, Rhinehart RR. Heuristic random optimization. Comput Chem Eng 1998; 22: 427-44.
10. Worakul N, Wongpoowarak W, Boonme P. Optimization in development of acetaminophen syrup formulation. Drug Dev Ind Pharm 2002; 28: 345-51.
11. Daykin CD, Pentikainen T, Pesonen M. Practical risk theory for actuaries. London, UK: Chapman and Hall; 1994.
12. Ferrenberg AM, Landau DP, Wong YJ. Monte Carlo simulations: hidden errors from 'good' random number generators. Phys Rev Lett 1992; 69: 3382-4.
13. 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: 627-9.
14. Kikuchi E, Kikuchi J, Nasuhara Y, Oizumi S, Ishizaka A, Nishimura M. Comparison of the pharmacodynamics of biapenem in bronchial epithelial lining fluid in healthy volunteers given half-hour and three-hour intravenous infusions. Antimicrob Agent Chemother 2009; 53: 2799-803.
15. Baldwin DR, Honeybourne D, Wise R. Pulmonary disposition of antimicrobial agents: methodological considerations. Antimicrob Agents Chemother 1992; 36: 1171-5.
16. Mouton JW, Ambrose PG, Kahlmeter G, Wikler M, Craig WA, Applying pharmacodynamics for susceptibility breakpoint selection and susceptibility testing. In: Nightingale CH, Ambrose PG, Drusano GL, Murakawa T, eds. Antimicrobial pharmacodynamics in theory and clinical practice. New York: Informa Healthcare, 2007.
17. Lee LS, Kinzig-Schippers M, Nafziger AN, Ma L, Sörgel F, Jones RN, et al. Comparison of 30-min and 3-h infusion regimens for imipenem/cilastatin and for meropenem evaluated by Monte Carlo simulation. Diagn Microbiol Infect Dis 2010; 68: 251-8.

เภสัชพลศาสตร์ของ meropenem ในผู้ป่วยที่อยู่ในภาวะวิกฤตปอดอักเสบจากการใช้เครื่องช่วยหายใจ

สุเทพ จารุรัตนศิริกุล, ณรงค์เดช โฆษิตพันธวงศ์, มนชนา จุลลางกูร, นันท์ชนิต เอี่ยนเล่ง, วิบุล วงศ์ภูวรักษ์

ภูมิหลัง: ผู้ป่วยที่อยู่ในภาวะวิกฤต รวมทั้งผู้ป่วยปอดอักเสบจากการใช้เครื่องช่วยหายใจ (VAP) จะมีการเปลี่ยนแปลงทางด้านเภสัชจลนศาสตร์ไปจากผู้ที่มีสุขภาพแข็งแรง ทำให้ระดับความเข้มข้นของยาในพลาสมามีการเปลี่ยนแปลงไปด้วย

วัตถุประสงค์: เพื่อเปรียบเทียบ probability of target attainment (PTA) และ cumulative fraction of response (CFR) ของ meropenem ระหว่างการบริหารยาเข้าหลอดเลือดดำทันทีในระยะเวลาสั้นและ 3 ชั่วโมง

วัสดุและวิธีการ: การศึกษาเป็น randomized three-way crossover ในผู้ป่วย VAP 9 ราย ผู้ป่วยทุกรายจะได้รับ meropenem 3 วิธีติดต่อกันดังนี้ 1) บริหารยาเข้าหลอดเลือดดำ 10 นาที ในขนาดยา 1 กรัม ทุก 8 ชั่วโมง เป็นเวลา 24 ชั่วโมง 2) บริหารยาเข้าหลอดเลือดดำ 3 ชั่วโมง ในขนาดยา 1 กรัม ทุก 8 ชั่วโมง เป็นเวลา 24 ชั่วโมง 3) บริหารยาเข้าหลอดเลือดดำ 3 ชั่วโมง ในขนาดยา 2 กรัม ทุก 8 ชั่วโมง เป็นเวลา 24 ชั่วโมง ค่า PTA จะถูกคำนวณโดย Monte Carlo simulation และ CFR จะถูกประเมินโดยใช้ MIC จาก EUCAST และ MYSTIC

ผลการศึกษา: สำหรับ MIC 4 ไมโครกรัม/มิลลิลิตร ค่า PTA 40% T>MIC หลังการบริหารยาทันทีในระยะเวลาสั้น ในขนาดยา 1 กรัม หลังการบริหารยา 3 ชั่วโมง ในขนาดยา 1 กรัม และหลังการบริหารยา 3 ชั่วโมง ในขนาดยา 2 กรัม มีค่าเท่ากับร้อยละ 87.71, 98.80 และ 99.90 จากการประเมินค่า CFR ≥90% มีเพียงการบริหารยา 3 ชั่วโมง เท่านั้น ที่สามารถครอบคลุมเชื้อ E. coli, Klebsiella spp., P. aeruginosa และ Acinetobacter spp.

สรุป: การบริหาร meropenem 3 ชั่วโมง ในขนาด 2 กรัม สามารถทำให้ได้ค่า PTA สูงสุด จากการประเมินค่า CFR พบว่ามีเพียงการบริหารยา 3 ชั่วโมงเท่านั้น ที่สามารถครอบคลุมเชื้อ E. coli, Klebsiella spp., P. aeruginosa และ Acinetobacter spp.