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

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Background: *Drug dispositions are altered in critically ill patients, including ventilator-associated pneumonia (VAP) when compared with healthy subjects leading to fluctuations of plasma concentrations.*
Objective: *To compare the probability of target attainment (PTA) and cumulative fraction of response (CFR) for imipenem between administration by 0.5-hour and 2-hour infusions.*
Material and Method: *The present study was a randomized three-way crossover in nine patients with VAP. Each patient received imipenem in three regimens consecutively: (i) a 0.5-hour infusion of 0.5 g every six hours for 24 hours; (ii) a 2-hour infusion of 0.5 g every six hours for 24 hours; and (iii) a 2-hour infusion of 1 g every six hours for 24 hours. Monte Carlo simulation was performed to determine the PTA at various regimens and the study used susceptibility patterns obtained from EUCAST and MYSTIC for assessment of CFR.*
Results: *For an MIC of 2 μg/ml, the PTAs achieving 40% T>MIC following a 0.5-hour infusion of 0.5 g, a 2-hour infusion of 0.5 g, and a 2-hour infusion of 1 g were 90.93%, 98.97%, and 100%, respectively. Only a 2-hour infusion of 1 g achieved 98.75% of the PTA of 40% T>MIC for an MIC of 4 μg/ml. All regimens were predicted to achieve CFR >99% against E. coli and Klebsiella spp.*
Conclusion: *A 2-hour infusion of 1 g regimen was predicted to have the highest PTA rates. All regimens achieved a high CFR against E. coli and Klebsiella spp.*

Keywords: *Pharmacokinetics/pharmacodynamics, Pharmacodynamics, Population pharmacokinetics, Imipenem, Carbapenems, Ventilator-associated pneumonia*

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In the current era of increasing highly resistant pathogens in nosocomial infections, the empirical treatment of these organisms is becoming more difficult and only a few novel antimicrobial agents are currently in development with activity against these highly resistant Gram-negative bacilli infections. Imipenem is still one of the most commonly used antibiotics for empirical therapy of highly resistant nosocomial infections in ventilator-associated pneumonia (VAP). In common with other β-lactams, imipenem exhibits 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[1]. Previous studies the authors performed found that a 2-hour infusion of carbapenem antibiotics gave greater values for T>MIC than a 0.5-hour infusion[2,3]. Therefore, a prolonged infusion would be the appropriate mode for administration to promote the maximal bactericidal effect.

PK changes have been found for several hydrophilic antimicrobial agents in critically ill patients[4]. Therefore, the aim of the present study was to assess the PD of imipenem in VAP patients, comparing administration by 0.5-hour infusion or 2-hour infusion. The authors compared the probability of target attainment (PTA) and cumulative fraction of response (CFR) for imipenem in three regimens: (i) a 0.5-hour infusion of 0.5 g, (ii) a 2-hour infusion of 0.5 g, and (iii) a 2-hour infusion of 1 g.

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Material and Method

Subjects

The patients with VAP were eligible for the present 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 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 present study if they were pregnant, in circulatory shock (systolic blood pressure <90 mmHg), or had documented hypersensitivity to imipenem or an estimated creatinine clearance (determined by the Cockcroft-Gault method)[5] of <60 ml/min. The protocol for the present 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

Imipenem (Tienam®) was purchased from MSD, Bangkok, Thailand. Imipenem was generously donated by Merck & Co, Inc., Elkton, VA, USA, as pure powder.

Study design

The present study was a randomized three-way experimental study. Imipenem was reconstituted in 100 ml of normal saline solution according to the manufacturer's guidelines. Each subject received imipenem in three regimens at room temperature (32-37°C) consecutively: (i) a 0.5-hour infusion of 0.5 g of imipenem every six hours for 24 hours; (ii) a 2-hour infusion of 0.5 g of imipenem every six hours for 24 hours; and (iii) a 2-hour infusion of 1 g of imipenem every six hours for 24 hours.

Blood sampling

The imipenem PK studies were carried out during administration of the fourth dose of each regimen (18 to 24 hours after the start of each regimen). Blood samples (~3 ml) were obtained by direct venepuncture at the following times: before (time zero) and 0.5, 1, 2, 3, 4, 5, and 6 hours after the fourth dose of each regimen. The blood samples were added to a heparinized tube, immediately stored on ice, and centrifuged at 1,000 g for 10 minutes within five minutes. An equal volume of stabilizing solution (0.5 M MOPS/water/ethylene glycol, 2:1:1, v/v/v) was added to each plasma sample, vortexed and then stored at -80°C until analysis within one week.

Imipenem assay

The concentrations of imipenem were determined by reversed-phase HPLC[6]. A 10 ml aliquot of the sample was injected onto a Nova-Pak C18 column (Waters Associates), using an automated injection system (Waters 717 plus Autosampler, Waters Associates). The mobile phase was 0.2 M borate buffer, pH 7.2, at a flow rate of 1 ml/minute. The column effluent was monitored by UV detection (Waters 486, Waters Associates) at 300 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The limit of detection of imipenem was 0.125 μg/ml.

PK analysis

The data of imipenem from the authors' previous study was used to perform the population PK and the Monte Carlo simulation (MCS)[3]. Previous pharmacokinetic analyses have found that a two-compartment model is adequate for describing distribution phase discrepancies[7,8], and this was the model employed in the present study. Due to the high values of the rate constants in the differential equations, computation instabilities were expected for most numerical algorithms, and the Taylor series expansion method[9] was used to solve the differential equations, computing them until convergence of the final results was achieved.

Data analysis was performed using Visual Basic programming in Microsoft Excel (Microsoft Corp.) spreadsheets.

The PK parameters were obtained by non-linear regression to minimize the objective function of the sum square errors (SSEs), with the following equation:

$$obj = \min \left(\sum_{i=1}^{N} (\ln y_{actual} - \ln y_{calc})_i^2\right)$$

The logarithmic scale of computational errors was used in order to properly represent the lower concentration regions near the MIC. This is important in the case of β-lactam antibiotics where the lower concentration behavior is vital if its full efficacy is to be realized. The algorithm for minimization of the SSEs in the present study was random heuristic optimization, as has been described elsewhere[10,11]. This method has good convergence speed and can be conveniently implemented in a spreadsheet.

PD assessment using a MCS

The authors found that the values of PK parameters obtained were not normally distributed, and

their behavior could be represented more accurately using logarithmic scales, thus logarithmic scales for all parameters were used in the authors MCS calculations.

The simulations were performed using the Visual Basic language program. A set of PK parameters were simulated from each parameter median and its standard deviation. The algorithm for a normal distribution generator is a Box-Muller Transform[12]. From the PK parameters obtained in the present study (Table 1), a MCS was performed to achieve concentration-time profiles. The parameters were used to solve the differential equations describing a two-compartment model, and by comparing the results of these equations with the given MICs,% time above MIC (% T>MIC) could be determined. The authors used 10,000 simulations to see the behavior of % T>MIC at 2 different target levels, 20% and 40% attainment. The cross-tabulation relationship in the MIC vs. % T>MIC attainment represented the whole spectrum of microbial behavior in the present study.

Results

Nine patients were enrolled in the present study, eight males and one female. Their mean age was 63.33±14.86 years (range 33-38) and their mean weight was 66.61±10.44 kg (range 50.5-81.5). The PK parameters of imipenem for the three regimens are shown in Table 1. The PTAs for the three imipenem 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 imipenem regimens against *E. coli*, *Klebsiella* spp., *P. aeruginosa* and *Acinetobacter* spp. are shown in Table 3.

Discussion

Several β-lactam antibiotics have been shown to distribute into the extracellular fluid rapidly[4] and the concentration levels of these agents in the pulmonary epithelial lining fluid (ELF) at the site of infections in patients with VAP should be the primary determinants for therapeutic effect[13,14]. However, antibiotic concentrations at ELF are difficult to obtain and the correlation between the PK/PD index in ELF and antimicrobial activity is less well understood[15]. 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 β-lactams. Increasing peak concentrations do not enhance the bactericidal activity of these agents and if the concentration of antibiotics decreases to below the MIC, bacterial growth resumes immediately[1]. In addition, T>MIC is the best predictor of bacterial eradication or clinical success[16].

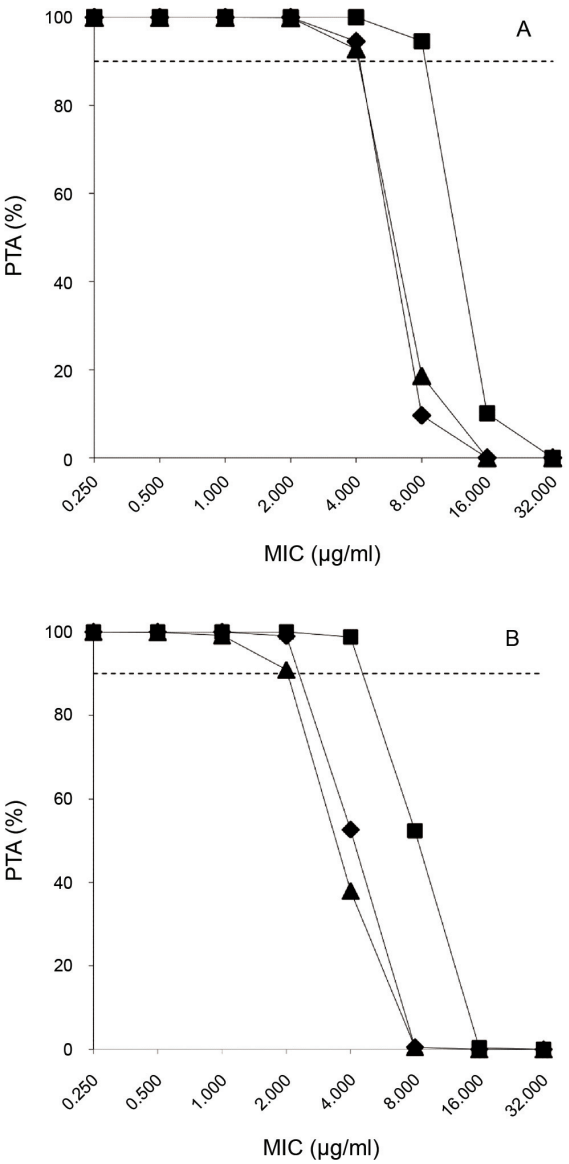

Fig. 1 Probability of target attainment (PTA) for imipenem regimens achieving 20% T>MIC (A) and 40% T>MIC (B) in nine patients with VAP after administration of: 0.5 g, 0.5 h infusion (filled triangles); 0.5 g, 2 h infusion (filled diamonds); and 1 g, 2 h infusion (filled squares). The broken line represents 90% PTA.

Table 1. Pharmacokinetic parameters of imipenem in nine patients with VAP after administration by a 0.5 h infusion and a 2 h infusion

Parameter	Geometric mean	Geometric SD	Median	90% CI
k_{12} (/h)	2.819	1.448	2.661	(0.908-5.032)
k_{21} (/h)	5.598	5.283	3.971	(0.945-13.759)
k_e (/h)	0.901	0.283	0.851	(0.574-1.251)
CL (l/h)	20.86	6.130	22.68	(12.39-27.17)
V (l)	23.59	5.070	22.14	(19.57-32.44)
V (l/kg)	0.368	0.123	0.328	(0.253-0.566)

k_{12} = intercompartmental transfer rate constant from X_1 to X_2 compartment; k_{21} = intercompartmental transfer rate constant from X_2 to X_1 compartment; k_e = elimination rate constant from X_1; CL = total clearance; V = volume of distribution; X_1 = central compartment; X_2 = peripheral compartment

Table 2. PTA for imipenem regimens achieving 20% and 40% T>MIC in nine patients with VAP

MIC (µg/ml)	PTA 20% T>MIC			PTA 40% T>MIC		
	0.5 h infusion	2 h infusion		0.5 h infusion	2 h infusion	
		0.5 g	1 g		0.5 g	1 g
1	100.00	100.00	100.00	99.10	99.99	100.00
2	99.90	100.00	100.00	90.93	98.97	100.00
4	92.78	94.53	99.99	37.98	52.61	98.75
8	18.62	9.61	94.59	0.53	0.53	52.34
16	0.00	0.00	10.10	0.00	0.00	0.38

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

Table 3. CFR of imipenem against the pathogens at PTA achieving 40% T>MIC in nine patients with VAP

	CFR for EUCAST[a], %			CFR for MYSTIC[b], %		
	0.5 h infusion	2 h infusion		0.5 h infusion	2 h infusion	
		0.5 g	1 g		0.5 g	1 g
E. coli	99.64	99.75	99.86	99.85	99.90	99.90
Klebsiella spp.	99.56	99.67	99.82	99.51	99.61	99.80
P. aeruginosa	74.48	77.43	84.21	81.54	84.27	88.88
Acinetobacter spp.	79.43	81.12	85.56	87.96	89.05	91.35

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

The authors' previous PK/PD study of imipenem in patients with VAP found that a 2-hour infusion of imipenem resulted in greater T>MIC values than a 0.5-hour infusion[3], suggesting that a prolonged infusion may be an appropriate mode of administration for imipenem in tropical countries. A previous study in healthy volunteers showed that prolonging the infusion rate of imipenem from 30 minutes to three hours resulted in greater PTAs for achieving the target of 20% T>MIC, 30% T>MIC and 40% T>MIC[17]. Moreover, in another previous pharmacodynamics study in patients with intensive care unit acquired pneumonia, a 90% PTA for achieving the target of 40% T>MIC was observed at an MIC of 1 to 2 µg/ml when imipenem was administered by an intermittent 40 minutes infusion of 1 g every eight hours, while, a continuous infusion at a lower total daily dose of 2 g of imipenem had a 90% PTA for achieving the target

of 40% T>MIC at an MIC of 2 to 4 μg/ml[8]. In the current study, the authors examined the PK/PD in patients with VAP and a MCS was performed to determine the probability of attaining a specific PD target at various regimens. Prolonged infusion of imipenem from 0.5-hour to 2-hour improved the PTA of 20% T>MIC and 40% T>MIC in an equivalent daily dosage and the highest PTA rates were obtained with a 2-hour infusion of 1 g of imipenem every six hours. For pathogens with an MIC of 2 μg/ml, the PTAs achieving 40% T>MIC following the administration of imipenem by a 0.5-hour infusion of 0.5 g every six hours, a 2-hour infusion of 0.5 g every six hours, and a 2-hour infusion of 1 g every six hours were 90.93%, 98.97%, and 100%, respectively. Only a 2-hour infusion of 1 g achieved 98.75% of the PTA of 40% T>MIC for an MIC of 4 μg/ml. Therefore, from these data, it appears that a 2-hour infusion of 1 g of imipenem every six hours can provide good coverage for pathogens with MICs of ≤4 μg/ml.

Previous pharmacodynamic modeling studies in both healthy volunteers and patients with bacterial infections have found that a three hours infusion of imipenem and meropenem improved the CFR for several pathogens compared to a 30 minutes infusion[17]. The present study used susceptibility patterns obtained from EUCAST and MYSTIC for assessment of CFR. All three regimens of imipenem achieved high probability targets (CFR ≥90%) against *E. coli* and *Klebsiella* spp., and the prolonged infusion of imipenem regimens did not have significant advantage over the 0.5-hour infusion regimens. These results indicate that for mild to moderate infections caused by pathogens with low MICs, the 0.5-hour infusion regimen may be as effective as the prolonged infusion regimens. Meanwhile, against the less susceptible *P. aeruginosa* and *Acinetobacter* spp., the present study predicts that only a prolonged infusion of 1 g regimen can achieve the high cumulative probability of target attainment. Therefore, for the treatment of severe infections in critically ill patients with highly resistant microorganisms, the authors recommend that imipenem should be administered by prolonged infusion of 1 g regimen.

The authors' 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 the present study can be instructive in illuminating the effects of different dosing approaches.

Conclusion

It was predicted that the PTAs from all three regimens were improved when imipenem was administered by prolonged infusion and the highest PTA rates were observed with a 2-hour infusion of 1 g every six hours. Moreover, the three regimens of imipenem had high probabilities of achieving optimal exposure against *E. coli* or *Klebsiella* spp.

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Potential conflicts of interest

None.

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เภสัชพลศาสตร์ของ imipenem ในผู้ป่วยที่อยู่ในภาวะวิกฤตปอดอักเสบจากการใช้เครื่องช่วยหายใจ

สุเทพ จารุรัตนศิริกุล, นันท์ชนิต เอี่ยนเล่ง, มนชนา จุลลางกูร, วิบุล วงศ์ภูวรักษ์

ภูมิหลัง: กระจายและการกำจัดยาในผู้ป่วยที่อยู่ในภาวะวิกฤต รวมทั้งผู้ป่วยปอดอักเสบจากการใช้เครื่องช่วยหายใจ (VAP) จะมีการเปลี่ยนแปลงไปจากผู้ที่มีสุขภาพแข็งแรง ทำให้ระดับความเข้มข้นของยาในพลาสมามีการเปลี่ยนแปลงไปด้วย

วัตถุประสงค์: เพื่อเปรียเทียบ probability of target attainment (PTA) และ cumulative fraction of response (CFR) ของ imipenem ระหว่างการบริหารยาเข้าหลอดเลือดดำโดยวิธี 0.5 และ 2 ชั่วโมง

วัสดุและวิธีการ: การศึกษาเป็น randomized three-way crossover ในผู้ป่วย VAP 9 ราย ผู้ป่วยทุกรายจะได้รับ imipenem 3 วิธีติดต่อกันดังนี้ 1) บริหารยาเข้าหลอดเลือดดำ 0.5 ชั่วโมง ในขนาดยา 0.5 กรัม ทุก 6 ชั่วโมง เป็นเวลา 24 ชั่วโมง 2) บริหารยาเข้าหลอดเลือดดำ 2 ชั่วโมง ในขนาดยา 0.5 กรัม ทุก 6 ชั่วโมง เป็นเวลา 24 ชั่วโมง 3) บริหารยาเข้าหลอดเลือดดำ 2 ชั่วโมง ในขนาดยา 1 กรัม ทุก 6 ชั่วโมง เป็นเวลา 24 ชั่วโมง ค่า PTA จะถูกคำนวณโดย Monte Carlo simulation และ CFR จะถูกประเมินโดยใช้ MIC จาก EUCAST และ MYSTIC

ผลการศึกษา: ค่า PTA 40% T>MIC หลังการบริหารยา 0.5 ชั่วโมง ในขนาดยา 0.5 กรัม หลังการบริหารยา 2 ชั่วโมง ในขนาดยา 0.5 กรัม และหลังการบริหารยา 2 ชั่วโมง ในขนาดยา 1 กรัม มีค่าเท่ากับร้อยละ 90.93, 98.97 และ 100 สำหรับ MIC 2 ไมโครกรัม/มิลลิลิตร ตามลำดับ มีเพียงการบริหารยา 2 ชั่วโมง ในขนาดยา 1 กรัม ที่ทำให้ค่า PTA 40% T>MIC เท่ากับร้อยละ 98.75 สำหรับ MIC 4 ไมโครกรัม/มิลลิลิตร การบริหารยาทั้ง 3 วิธี โดยประเมินจากค่า CFR สามารถครอบคลุมเชื้อ E. coli และ Klebsiella spp.

สรุป: การบริหารยา 2 ชั่วโมง ในขนาด 1 กรัม สามารถทำให้ได้ค่า PTA สูงสุด การบริหารยาทั้ง 3 วิธี สามารถครอบคลุมเชื้อ E. coli และ Klebsiella spp.