Comparative Study of Pharmacokinetics/ Pharmacodynamics of Ciprofloxacin between 400 mg Intravenously Every 8 h and 400 mg Intravenously Every 12 h in Patients with Gram Negative Bacilli Bacteremia

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Objective: *To compare the ratio of the area under the concentration-time curve at 24 hours to the minimum inhibitory concentration value (24-h AUC/MIC) of ciprofloxacin between 400 mg intravenously every 8 h and 400 mg intravenously every 12 h.*

Material and Method: *A prospective, randomized, two-way crossover study of 10 patients with gram-negative bacilli bacteremia was conducted. All patients were randomized to receive ciprofloxacin in both regimens consecutively: (i) 400 mg intravenously every 8 h for four doses; (ii) 400 mg intravenously every 12 h for four doses. Ciprofloxacin pharmacokinetic studies were carried out after the start of both regimens.*

Results: *For the ciprofloxacin 400 mg intravenously every 8 h regimen, the 24-h AUC/MIC at MICs of 0.5 and 1 μg/ml were 218.63 ± 78.75 and 109.31 ± 39.37, respectively. For the ciprofloxacin 400 mg intravenously every 12 h regimen, the 24-h AUC/MIC at MICs of 0.5 and 1 μg/ml were 144.07 ± 57.02 and 72.03 ± 28.51, respectively. After 14 days of ciprofloxacin treatment, the gram-negative bacilli infections were eradicated in all patients. Moreover, during both regimens, no adverse events related to the use of ciprofloxacin were observed.*

Conclusion: *Both ciprofloxacin 400 mg every 8 h and 400 mg every 12 h regimens can provide good coverage for pathogens with the susceptibility breakpoint of ciprofloxacin with an MIC of 0.5 μg/ml. For pathogens with an MIC of 1.0 μg/ml, only ciprofloxacin 400 mg every 8 h regimen can provide a 24-h AUC/MIC ratio greater than 100.*

Keywords: *Ciprofloxacin, Pharmacokinetic/pharmacodynamic, 24-h AUC/MIC, Bacteremia*

J Med Assoc Thai 2010; 93 (7): 784-8
Full text. e-Journal: *http://www.mat.or.th/journal*

The time course of antimicrobial activity varies for different groups of antimicrobial agents. There are two primary patterns of microbial killing. β-lactams for example, have been found to exhibit time-dependent bacterial killing and the time that concentrations in tissue and serum are above the minimum inhibitory concentration (MIC) (t > MIC) is the pharmacokinetic/ pharmacodynamic (PK/PD) index that correlates with efficacy[1-3]. The second pattern is characterized by concentration-dependent killing and increasing the serum during concentration enhances the bactericidal activity of these groups of antibiotics. Therefore, the peak concentration and area under the concentration-time curve (AUC) are the PK/PD indexes that correlate with efficacy. This pattern is observed, for instance, with aminoglycosides and fluoroquinolones[1,4].

Ciprofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity for the treatment of infections caused by gram-positive cocci and gram-negative bacilli[5]. In common with other fluoroquinolones, the main PK/PD index that correlates with its therapeutic efficacy is the 24-h AUC/MIC. The aim of the present study was to assess the pharmacodynamics of ciprofloxacin 400 mg intravenously every 8 h and 400 mg intravenously every 12 h in patients with Gram-negative bacilli bacteremia. The authors conducted the present study to compare the 24-h AUC/MIC of ciprofloxacin in two regimens: i) 400 mg intravenously every 8 h; and ii) 400 mg intravenously every 12 h.

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Material and Method

Subjects

The present study was conducted in patients with Gram-negative bacilli bacteremia. The patients were eligible for the present study if they met the following criteria: (i) older than 20 years; and (ii) documented Gram-negative bacilli bacteremia, defined by at least one positive blood culture. The biochemical and antimicrobial susceptibility tests were used for identifying Gram-negative bacilli and MICs were determined by E-test. The protocol for the present study was approved by the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each patient. None of the patients had a chronic illness or was taking chronic medication. Patients were excluded from the present study if they were pregnant or in circulatory shock (which was defined as a systolic blood pressure of < 90 mmHg and poor tissue perfusion) or had documented hypersensitivity to ciprofloxacin or an estimated creatinine clearance (determined by the Cockcroft-Gault method[6]) of < 60 ml/min.

Drugs and chemicals

Ciprofloxacin (CIPROXYL®) was generously donated by Siam Pharmaceutical, Thailand. All of the solvents were HPLC grade.

Study design

The present study was a prospectively randomized two-way crossover study. Each patient was randomized to receive ciprofloxacin in two regimens consecutively: (i) infusion of 400 mg of ciprofloxacin for 30 min via an infusion pump at a constant flow rate every 8 h for four doses; and (ii) infusion of 400 mg of ciprofloxacin for 30 min via an infusion pump at a constant flow rate every 12 h for four doses. After ciprofloxacin therapy by both regimens for four days in the present study, all patients still received 400 mg every 8 h of ciprofloxacin for 10 more days to complete a course of treatment of 14 days.

Blood sampling

For both regimens, ciprofloxacin pharmacokinetic studies were carried out after the start of each regimen. For the 400 mg every 8 h regimen, blood samples of approximately 2 ml per time were obtained by direct venepuncture from the heparinized catheter at the following times: before (time zero) and at 0.5, 8, 8.5, 16, 16.5, 24, 24.5, 25, 26, 27, 28, 30 and at 32 h after the start of the regimen. For the 400 mg every 12 h regimen, blood samples of approximately 2 ml per time were obtained by direct venepuncture from the heparinized catheter at the following times: before (time zero) and at 0.5, 12, 12.5, 24, 24.5, 36, 36.5, 37, 38, 39, 40, 42, 44 and 48 h after the start of the regimen.

All blood samples were allowed to clot and then centrifuged at 2000 g. The serum obtained was stored at -80°C until analysis.

Ciprofloxacin assay

The concentrations of ciprofloxacin were determined by reversed phase HPLC. Quinine (30 μg/ml) was used as the internal standard and the samples were extracted by the method of Jim et al[7]. For serum preparation, 200 μl of the sample was precipitated with 200 μl of acetonitrile. The mixture was then vortexed and centrifuged at 1,000 g for 15 min; 20 μl of the supernatant was injected using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA, USA), onto a μBondapack C18 Column (Waters Associates). The mobile phase was methanol/KH_2PO_4/Na_2HPO_4/tetrahydrofuran (27: 36.1: 36.1: 0.8, v/v/v/v), pH 3.0, at a flow rate of 1 ml/min. The column eluate was monitored by fluorescence detection (FP-2020 Plus, Jasco). Ciprofloxacin was detected using an excitation wavelength of 277 nm and an emission wavelength of 445 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The quantification range for ciprofloxacin in serum was validated from 0.5 to 16.0 μg/ml. The intra-assay and the inter-assay reproducibility values characterized by coefficient of variation (CV) were 2.9% and 5.12%, respectively.

Pharmacokinetic and statistical analysis

Pharmacokinetic analysis was conducted using a non-compartment model. The maximum serum concentrations (C_{max}), the minimum serum concentrations (C_{min}), the elimination half-lives ($t_{1/2}$), the elimination rate constants (k_{el}), the areas under the concentration-time curve between 0 and 24-h (24-h AUC), the total clearances (CL_{tot}) and the volumes of distribution (V) were determined using WinNonlin version 1.1 (Scientific Consulting Inc., NC, USA). Results were expressed as mean values $\pm$ standard deviation.

Results

Ten patients were enrolled in the present study, five male and five female. The characteristics of all patients and the MICs of ciprofloxacin for the

isolated pathogens are shown in Table 1. The mean serum ciprofloxacin concentration-time data for the two regimens from each patient are shown in Fig. 1. The pharmacokinetic parameters for the two regimens are presented in Table 2. For the ciprofloxacin 400 mg intravenously every 8 h regimen, the 24-h AUC/MIC at MICs of 0.5 and 1 μg/ml were 218.63 ± 78.75 and 109.31 ± 39.37, respectively. For the ciprofloxacin 400 mg intravenously every 12 h regimen, the 24-h AUC/MIC at MICs of 0.5 and 1 μg/ml were 144.07 ± 57.02 and 72.03 ± 28.51, respectively. No adverse effects were observed in any patient during the present study period.

Table1. The characteristics of the 10 patients and the MIC of ciprofloxacin for isolated pathogens from blood cultures

Patient	Sex	Pathogen	MIC (μg/ml)
S-S	Male	*K. pneumoniae*	0.023
P-P	Female	*K. pneumoniae*	0.094
S-P	Female	*K. pneumoniae*	0.094
S-B	Male	*K. oxytoca*	0.094
N-C	Female	*Salmonella* gr D1	0.250
P-S	Male	*S. typhi*	0.023
B-G	Male	*E. coli*	0.032
L-A	Female	*E. coli*	0.012
T-D	Female	*E. coli*	0.016
S-G	Male	*P. mirabillis*	0.032

Table 2. Pharmacokinetic parameters (mean ± SD) of ciprofloxacin administered by 400 mg intravenously every 8 h and 400 mg intravenously every 12 h regimens

Parameter (units)	400 mg q 8 h	400 mg q 12 h
C_{max} (mg/ml)	14.51 ± 6.11	11.86 ± 3.06
C_{min} (mg/ml)	1.73 ± 1.14	1.01 ± 0.64
24-h AUC (μg × h/ml)	109.31 ± 39.57	72.03 ± 28.51
CL_{tot} (liter/h)	9.49 ± 4.22	11.03 ± 4.87
$t_{1/2}$ (h)	4.63 ± 2.91	4.87 ± 1.22
k_{el} (h^{-1})	0.20 ± 0.11	0.15 ± 0.04
V (liter)	52.46 ± 19.25	71.98 ± 24.93
24-h AUC/MIC		
MIC of 2 μg/ml	54.66 ± 19.69	36.02 ± 14.26
MIC of 1 μg/ml	109.31 ± 39.37	72.03 ± 28.51
MIC of 0.5 μg/ml	218.63 ± 78.75	144.07 ± 57.02
MIC of 0.25 μg/ml	437.26 ± 157.49	288.14 ± 114.05

C_{max}, maximum serum concentration; C_{min}, minimum serum concentration; 24-h AUC, area under the concentration-time curve between 0 and 24 h; CL_{tot}, total clearance; $t_{1/2}$, serum half-life; k_{el}, elimination rate constant; V, volume of distribution

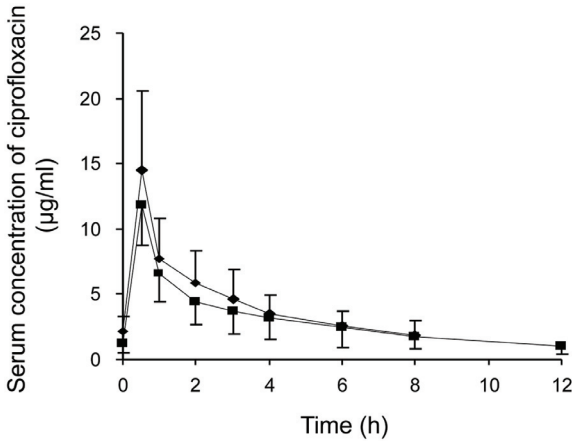

Fig. 1 Mean serum ciprofloxacin concentration-time data of the ten patients with bacteremia following 400 mg intravenously every 8 h (filled diamonds) and 400 mg intravenously every 12 h (filled squares)

Discussion

Ciprofloxacin exhibits a concentration-dependent pattern of antimicrobial activity and has moderate-to-prolonged persistent effects. In both in vitro and *in vivo* infection models, the 24-h AUC/MIC has a strong correlation with the efficacy of fluoroquinolones, as higher concentrations kill pathogens more rapidly and more extensively than lower levels[1,4]. A previous study in non-neutropenic mice infected with *S. pneumoniae* was conducted to demonstrate the relationship between the 24-h AUC/MIC ratio for six fluoroquinolones and the mice survival. The results showed that a 24-h AUC/MIC value of greater than 25 to 34 was associated with a survival rate of greater than 90%[8]. In another study in 121 patients with *S. pneumoniae* respiratory tract infections treated with fluoroquinolones, the microbiological eradication rate was 92.6% when the 24-h AUC/MIC ratio was greater than 34[9]. However, in non-neutropenic mice, the magnitude of 24-h AUC/MIC for fluoroquinolones required for efficacy was approximately three to four folds higher for *K. pneumoniae* when compared with *S. pneumoniae*[10]. A previous study involving seventy-four acutely ill patients with gram-negative bacilli infection treated with intravenous ciprofloxacin

at dosages ranging between 200 mg every 12 h and 400 mg every 8 h was conducted to evaluate the relationship between the PK/PD index of 24-h AUC/MIC of ciprofloxacin and clinical outcome. At a 24-h AUC/MIC above 125, the percentages of clinical and microbiological cures were 80% and 82%, respectively, whereas at a 24-h AUC/MIC below 125, the percentages of clinical and microbiological cures were only 42% and 26%, respectively[11]. Therefore, a 24-h AUC/MIC value of higher 125 was the best predictor of an optimal clinical outcome. A study in 107 nosocomial lower respiratory tract infections treated with ciprofloxacin was conducted to evaluate bacterial resistance during therapy. The present study found that when the 24-h AUC/MIC ratio was below 100, 82.4% of the organisms developed resistance and when the 24-h AUC/MIC ratio was above 100, only 9% of similar organisms developed resistance[12]. Thus, from these results, selection for antimicrobial resistance appeared to be strongly associated with suboptimal antimicrobial exposure, defined as a 24-h AUC/MIC ratio less than 100. For the present paper, the authors conducted a PK/PD study of ciprofloxacin in critically ill patients with bacteremia. For the susceptibility breakpoint of ciprofloxacin for enterobacteriaceae with an MIC of 0.5 μg/ml, the 24-h AUC/MIC ratios were 218.63 ± 78.75 for the ciprofloxacin 400 mg every 8 h regimen and 144.07 ± 57.02 for the ciprofloxacin 400 mg every 12 h regimen. Therefore, from these data, it appears that both ciprofloxacin regimens can provide a 24-h AUC/MIC ratio of more than 100. However, for pathogens with an MIC of 1 μg/ml, only the ciprofloxacin 400 mg every 8 h regimen can provide a 24-h AUC/MIC ratio of greater than 100.

A comparison of the individual outcomes of regimens of ciprofloxacin treatment by 400 mg every 8 h and 400 mg every 12 h could not be evaluated in the present study because the both regimens were administered consecutively in each patient. However, after 14 days of ciprofloxacin treatment, including a 10-day post regimen follow-up, the isolated organisms were eradicated in all patients. Moreover, during both regimens, no adverse events related to the use of ciprofloxacin were observed.

In conclusion, regimens of both ciprofloxacin 400 mg every 8 h and 400 mg every 12 h can provide good coverage for pathogens with the susceptibility breakpoint of ciprofloxacin with an MIC of 0.5 μg/ml. For pathogens with MIC of 1.0 μg/ml, only ciprofloxacin 400 mg every 8 h regimen can provide a 24-h AUC/MIC ratio of greater than 100.

Acknowledgements

The authors wish to thank Mr. David Patterson for checking our English. This work was supported by a faculty grant from the Faculty of Medicine, Prince of Songkla University. Ciprofloxacin (CIPROXYL®) was generously donated by Siam Pharmaceutical, Thailand.

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ศึกษาเปรียบเทียบเภสัชจลนศาสตร์/เภสัชพลศาสตร์ของ ciprofloxacin ระหว่างการบริหารยาในขนาด 400 มิลลิกรัมทางหลอดเลือดดำทุก 8 ชั่วโมง และในขนาด 400 มิลลิกรัม ทางหลอดเลือดดำทุก 12 ชั่วโมงในผู้ป่วยติดเชื้อแบคทีเรียทรงแท่งแกรมลบในกระแสเลือด

พันธ์วศรี แสงสุวรรณ, สุเทพ จารุรัตนศิริกุล, มนชนา จุลลางกูร, นันท์ชนิต เอี่ยนเล่ง

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบค่าสัดส่วนของพื้นที่ใต้กราฟความเข้มข้นของยาใน 24 ชั่วโมง กับความเข้มข้นต่ำสุดของยาปฏิชีวนะในการยับยั้งการเจริญเติบโตของเชื้อ (24-h AUC/MIC) ของ ciprofloxacin ระหว่างบริหารยาในขนาด 400 มิลลิกรัมทางหลอดเลือดดำทุก 8 ชั่วโมง และในขนาด 400 มิลลิกรัมทางหลอดเลือดดำทุก 12 ชั่วโมง*

วัสดุและวิธีการ: *การศึกษาแบบไปข้างหน้าด้วยวิธีการสุ่มแบบข้ามสลับในผู้ป่วยติดเชื้อแบคทีเรียทรงแท่งแกรมลบในกระแสเลือด จำนวน 10 ราย ผู้ป่วยทุกรายจะถูกสุ่มให้ได้รับ ciprofloxacin ก่อนและหลังกัน 2 วิธี โดยให้ติดต่อกันดังนี้ วิธีที่1 บริหารยาในขนาด 400 มิลลิกรัมทางหลอดเลือดดำทุก 8 ชั่วโมง จำนวน 4 ครั้ง และวิธีที่ 2 บริหารยาในขนาด 400 มิลลิกรัม ทางหลอดเลือดดำทุก 12 ชั่วโมง จำนวน 4 ครั้ง ศึกษาทางด้านเภสัชจลนศาสตร์ของ ciprofloxacin หลังบริหารยาทั้ง 2 วิธี*

ผลการศึกษา: *เมื่อบริหารยาในขนาด 400 มิลลิกรัม ทุก 8 ชั่วโมง ค่า 24-h AUC/MIC ที่ MIC 0.5 และ 1 ไมโครกรัม/มิลลิลิตร เท่ากับ 218.63 $\pm$ 78.75 และ 109.31 $\pm$ 39.37 ตามลำดับ เมื่อบริหารยาในขนาด 400 มิลลิกรัม ทุก 12 ชั่วโมง ค่า 24-h AUC/MIC ที่ MIC 0.5 และ 1 ไมโครกรัม/มิลลิลิตรเท่ากับ 144.07 $\pm$ 57.02 และ 72.03 $\pm$ 28.51 ตามลำดับ ภายหลังการรักษาผู้ป่วยต่อจนครบ 14 วัน เชื้อแบคทีเรียทรงแท่งแกรมลบถูกกำจัดออกจากร่างกายของผู้ป่วยทุกราย นอกจากนั้นในระหว่างการบริหารยาทั้ง 2 วิธีไม่พบผลข้างเคียงที่เกี่ยวข้องกับยา ciprofloxacin*

สรุป: *การบริหารยา ciprofloxacin ในขนาด 400 มิลลิกรัม ทุก 8 ชั่วโมง และขนาด 400 มิลลิกรัม ทุก 12 ชั่วโมง สามารถครอบคลุมการติดเชื้อที่เชื้อก่อโรคมีค่า susceptibility breakpoint ที่ MIC เท่ากับ 0.5 ไมโครกรัม/มิลลิลิตร สำหรับเชื้อที่มี MIC เท่ากับ 1 ไมโครกรัม/มิลลิลิตร มีเพียงการบริหารยา ciprofloxacin ในขนาด 400 มิลลิกรัม ทุก 8 ชั่วโมง เท่านั้นที่สามารถทำให้อัตราส่วนของ 24-h AUC/MIC มีค่าสูงกว่า 100*