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Brief communication (Original)

Bioequivalence study of cefepime intramuscular injection

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Background: Cefepime, a fourth generation cephalosporin, is a broad spectrum antibiotic effective against both Gram positive and Gram negative bacteria. It is available from several pharmaceutical firms in southeast Asia. We studied bioequivalence of two products.
Objective: To assess the bioequivalence of two cefepime formulations: Cefamax 1 g intramuscular (Siam Pharmaceutical, Bangkok, Thailand) as the test formulation and Maxipime 1 g (Bristol-Myers Squibb, Bangkok, Thailand) as the reference formulation.
Methods: The study was conducted as an open, randomized, two-period crossover trial with a 1 week washout period in 18 healthy volunteers. Each subject received a single dose of 1 g intramuscular injection of the test or reference formulation. Blood samples were collected via an intravascular catheter at several time points over a 12 h period. Plasma cefepime concentrations were quantified by HPLC with photodiode array detection at 280 nm. The statistical comparisons for pharmacokinetic parameters were made using a paired *t* test.
Results: There was no significant difference in the logarithmically transformed values of C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ between Cefamax and Maxipime using an analysis of variance (ANOVA). The 90% confidence intervals (CIs) of C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ between the two formulations were 91.17–105.78, 90.29–97.63, and 88.89–96.57, respectively. All subjects had good tolerance and no serious adverse events were observed.
Conclusion: Cefamax 1 g intramuscular formulation is bioequivalent to Maxipime 1 g intramuscular formulation based on 90% CIs for $C_{max,}$ AUC_{0-12}, and $AUC_{0-\infty}$ within 80%–125%.

Keywords: Bioequivalence study, Cefamax, cefepime, fourth generation cephalosporin, pharmacokinetics

Among antibiotics, the cephalosporins are the most widely prescribed class because of their broad spectrum of antimicrobial activity and low toxicity [1]. Cefepime, a fourth generation cephalosporin, is a semisynthetic cephalosporin with a broader spectrum of activity than the third generation cephalosporins. This agent has effective activity against Gram-positive bacteria including methicillin-sensitive *Staphylococcus aureus* and *Streptococcus pneumoniae*, and Gram-negative bacteria [2, 3]. Cefepime has been approved for febrile neutropenia, lower respiratory tract infections, bacteremia and septicemia, complicated urinary tract infections, skin or soft-tissue infections, and gynecological and abdominal infections.

This drug is commercially available from at least two manufacturers and this is why we carried out a bioequivalence study of two cefepime formulations: Cefamax and Maxipime.

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Materials and methods

Subjects

The study was conducted in 18 nonsmoking, nonalcohol consuming, and nonobese healthy volunteers. There were six men and twelve women: mean age 30.11 ± 4.19 years (range 23–37); mean weight 53.77 ± 8.59 kg (range 41–72); and mean body mass index 20.67 ± 1.87 kg/m^2 (range 18.22–23.87). They were healthy volunteers, free from significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, and hematological diseases, as assessed by medical history, physical examination, and the following laboratory tests: complete blood count, fasting blood sugar, blood urea nitrogen, creatinine, total bilirubin, SGOT, SGPT, alkaline phosphatase, chest X-ray and ECG. All were serologically negative for human immunodeficiency virus and hepatitis B virus. The protocol for the study was approved by

the Ethics Committee of Songklanagarind Hospital and written informed consent was obtained from each subject before beginning the testing.

Drugs and chemicals

Cefamax (1 g intramuscular injection) was obtained from a local commercial batch marketed by Siam Pharmaceutical Company (Bangkok, Thailand) (lot number 1004200, expiry date 26 Oct 2012). It was used as the test formulation: Maxipime (1 g intramuscular injection) marketed by Bristol-Myers Squibb (Bangkok, Thailand: lot number OM42926, expiry date June 2013) was used as the reference formulation. All of the solvents were HPLC grade.

Study design

The study was an open, randomized, two-period crossover trial with a 1 week washout period between the two tests. The subjects were hospitalized at 7.00 a.m. and a single dose of 1 g of either Cefamax or Maxipime was injected intramuscularly at the buttock. Food was allowed during the study period.

Blood sampling

Blood samples (approximately 5 mL) were obtained via an intravascular catheter at the following times: before (time 0) and at 15, 30, 45 min and 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, and 12 h after drug injection. Blood samples were added to a heparinized tube and centrifuged at 3,000*g* for 15 min, vortexed and stored at –80°C until analysis within 1 week.

Cefepime assay

The concentrations of cefepime were determined by reversed-phase HPLC. Cefadroxil (10 µg/mL) was used as the internal standard and the samples were extracted by the method of Barbhaiya [4]. A portion of the extracted sample (75 µL) was injected using an automated injection system (Waters 717 plus Autosampler, Waters Associates, Milford, MA, USA), onto a Nova-Pak C18 column (Waters Associates). The mobile phase was 0.0023 M 1-octanesulfonic acid sodium salt:acetonitrile (86:14, vol/vol) pH 2.3, at a flow rate of 1 mL/min. The column effluent was monitored by photodiode array detection (Waters 2996, Waters Associates) at 280 nm. The peaks were recorded and integrated on a Waters 746 Data Module (Waters Associates). The limit of detection of cefepime was 0.250 mg/L.

The intraassay reproducibility characterized by CV was 1.9%, 0.7%, and 1.0% for assays of 1, 4, and 16 µg/mL, respectively. The interassay reproducibility precision values calculated by CV were 2.5%, 1.5%, and 1.0% for assays of 1, 4, and 16 mg/L, respectively.

Pharmacokinetic and statistical analysis

The maximum plasma concentration (C_{max}), the time taken to achieve C_{max} (t_{max}), the area under the concentration–time curve between 0 and 12 h ($AUC_{0–12}$) and between 0 and infinity ($AUC_{0–\infty}$), the elimination half-life ($t_{1/2}$), the elimination rate constant (k_e), and the total clearance (CL_{tot}) were determined using WinNonlin software, version 1.1 (Scientific Consulting, Apex, NC, USA). Results were expressed as mean values ± standard deviation (SD) and statistical comparisons were made using a paired *t* test. $P < 0.5$ was considered significant. The 90% confidence intervals (CI) of logarithmic transformation of C_{max}, $AUC_{0–12}$, and $AUC_{0–\infty}$ was performed to compare between Cefamax and Maxipime.

Results

The mean plasma concentration–time data and pharmacokinetic parameters of Cefamax and Maxipime are shown in **Figure 1** and **Table 1**. There were no significant differences in the logarithmically transformed values of C_{max}, $AUC_{0–12}$, and $AUC_{0–\infty}$ between Cefamax and Maxipime using an analysis of variance (ANOVA). The 90% confidence intervals (CI) of the logarithmic transformations C_{max}, $AUC_{0–12}$, and $AUC_{0–\infty}$ between Cefamax and Maxipime are shown in **Table 2**. All subjects had good tolerance and no significant adverse events were observed.

Discussion

The current study showed that the pharmacokinetic parameters for the test formulation, Cefamax, and the reference formulation, Maxipime, are not significantly different, except for CL_{tot} and $AUC_{0–\infty}$. However, based on the 90% CIs for $C_{max,}$ $AUC_{0–12}$, and $AUC_{0–\infty}$ with 80%–125%, Cefamax and Maxipime are essentially bioequivalent and can be used interchangeably.

The pharmacokinetic parameters for Cefamax obtained from the current study were higher than the results from a previous study [2, 5, 6], which may be the result of the lower body weight of the volunteers in this study. Thus, the drug concentrations of Cefamax were higher than recommended levels for treatment of the infections for which this substance is approved.

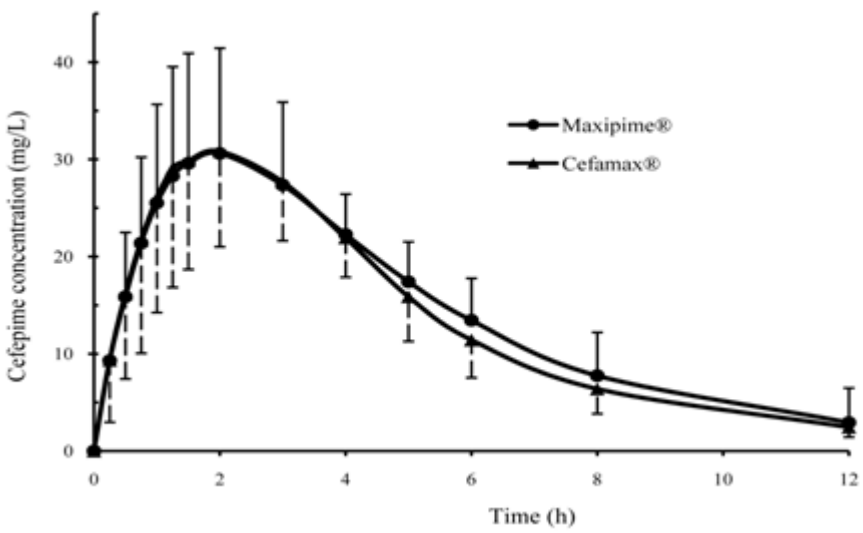

Figure 1. The mean plasma concentration–time profile of cefepime following a single dose of 1 g intramuscular injection of Cefamax and Maxipime in 18 healthy volunteers

Table 1. Pharmacokinetic parameters (mean ± SD) following a single dose of 1 g intramuscular injection of Cefamax and Maxipime in 18 healthy volunteers

Parameter (units)	Product (Mean±SD)	
	Cefamax	Maxipime
C_{max} (mg/L)	32.63 ± 9.96	32.95 ± 8.89
t_{max} (h)	2.14 ± 0.77	2.35 ± 0.93
AUC_{0-12} (mg*h/L)	166.54 ± 36.53	175.47 ± 26.97
$AUC_{0-\infty}$ (mg*h/L)	175.91 ± 37.23	188.48 ± 30.88*
$t_{1/2}$ (h)	2.49 ± 0.51	2.66 ± 0.80
CL_{tot} (L/h)	5.92 ± 1.20	5.45 ± 0.98*
k_e (h^{-1})	0.29 ± 0.07	0.29 ± 0.10

*$P < 0.05$ versus Cefamax, C_{max} = maximum plasma concentration, t_{max} = time taken to achieve C_{max}, AUC_{0-12} = area under the concentration-time curve between 0 and 12 h, $AUC_{0-\infty}$ = area under the concentration–time curve between 0 and infinity, $t_{1/2}$ = half-life, CL_{tot} = total clearance, k_e = elimination rate constant

Table 2. The 90% confidence intervals (CI) of C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ between Cefamax and Maxipime

Pharmacokinetic parameters	confidence interval (90% CI)
C_{max}	91.17–105.78
AUC_{0-12}	90.29–97.63
$AUC_{0-\infty}$	88.89–96.57

C_{max} = maximum plasma concentration, AUC_{0-12} = area under the concentration–time curve between 0 and 12 h, $AUC_{0-\infty}$ = area under the concentration–time curve between 0 and infinity

Conclusion

Cefamax 1 g intramuscular formulation is bioequivalent to Maxipime 1 g intramuscular formulation based on 90% CIs for C_{max}, AUC_{0-12}, and $AUC_{0-\infty}$ within 80%–125%.

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