A Bioequivalence Study of the Cefuroxime Axetil in Healthy Volunteers

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Abstract

The bioequivalence of 250-mg cefuroxime axetil was evaluated; Furoxime® (by the Siam Bheasach Company, Thailand) as the test and Zinnat® (GlaxoWellcome) as the reference. The two products were administered as a single dose according to a two-way crossover design, 1-week washout period to 12 healthy Thai male volunteers. Thereafter, serial blood samples were collected over a period of 15 hours. Plasma cefuroxime concentrations were measured by HPLC. The pharmacokinetic parameters were analyzed by noncompartmental analysis. RESULTS: The T_{max} [median (range, h)] of Furoxime® and Zinnat® were 1.5 (1.0-3.0) and 1.75 (1.0-3.5), respectively. The T_{max} of Furoxime® was faster than Zinnat® with the mean (90% CI) of difference in T_{max} of -0.5 [(-1.01)-0.01] h. Bioequivalence analysis showed that the $AUC_{0-\infty}$ and the C_{max} of the two products were not significantly different. The point estimator (90% CI) for the ratio [Furoxime®/Zinnat®] of log transformed data of the $AUC_{0-\infty}$ and C_{max} were 1.03 (0.98-1.20) and 1.09 (1.02-1.24), respectively and were within the bioequivalence range of 0.80-1.25.

Key word : Bioequivalence, Cefuroxime Axetil, Zinnat®, Furoxime®

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Cefuroxime axetil is an oral prodrug of cefuroxime, a second-generation cephalosporin antibiotic. The antibacterial activity of cefuroxime is due to its binding to the target protein which results in inhibition of cell wall synthesis[1]. Cefuroxime has a broad bactericidal activity against many beta-lactamase producing pathogens including methicillin-sensitive staphylococci and the common respiratory pathogens such as *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis* and group A *beta-haemolytic streptococci* [2]. It is also active against penicillin-susceptible and -intermediate resistance strains of *S. pneumoniae*[3]. Therefore, the drug is effective in the treatment of upper and lower respiratory tract infections[1-3]. Moreover, it is an effective agent for the treatment of uncomplicated urinary tract infection, skin and soft-tissue infections, as well as erythema migrans associated with early stage of Lyme disease in children[2]. Generally, cefuroxime axetil is well tolerated and the adverse effects are similar to those of other cephalosporins[1,2].

After oral administration, 30-50 per cent of cefuroxime axetil is absorbed from the gastrointestinal tract[4]. Thereafter, the drug is rapidly hydrolyzed by nonspecific esterase enzymes in the intestinal mucosa and the blood to the active form cefuroxime[1]. Cefuroxime is subsequently distributed throughout the extracellular fluids, and the axetil moiety is metabolized to acetaldehyde and acetic acid[1]. Administration of cefuroxime axetil after meals increases its bioavailability from 37 per cent to 52 per cent[4,5]. The peak plasma concentrations (C_{max}, 2-3 mcg/ml for a 125-mg dose, 4-6 mcg/ml for a 250-mg dose and 5-8 mcg/ml for a 500-mg dose) occur approximately 2-3 hours after dosing[4]. The reasons may be due to a delay in the gastric emptying time and gastrointestinal transit time which allows more complete dissolution and prolonged residence at the favorable site of absorption in the intestine[6]. The absolute bioavailability and pharmacokinetic parameters of cefuroxime axetil after fasting and after food showed no differences between the males and females[7]. Nevertheless, the Cmax and the time to the peak concentration (Tmax) varied considerably. The C_{max} and AUC after administration of a 250 mg dose were 4.7 mcg/ml, achieved after 2.1 h and 14.3-14.4 mcg.h/ml, respectively[8]. Approximately 50 per cent of cefuroxime was bound to plasma protein[4]. The mean oral clearances ranged from 20.4-27.0 L/hour and the serum half-lives were 1.3-1.7 h[4,9]. The drug is excreted unchanged in the urine, therefore, the serum half-life is prolonged in patients with impaired renal function[4,10]. Its elimination half-life increased from 4.2 h (creatinine clearance, CLcr 23.0 ml/min) to 22.3 h (CLcr 5.0 ml/min) with a decline in renal function[1]. The apparent volume of distribution ranged from 11.6 to 17.9 L, and increased to 29.6 L in patients with poor renal function[11]. Probenecid elevated its serum levels and prolonged its elimination half-life by 63 per cent[12].

Objective

To test the bioequivalence of the generic oral preparation of 250-mg cefuroxime axetil manufactured by the Siam Bheasach Company, Bangkok, Thailand (Furoxime®) in comparison with the innovator (Zinnat®) after a single oral administration in 12 healthy Thai males.

SUBJECTS, MATERIAL AND METHOD

Drug formulations

Reference product

Zinnat® 250 mg tablet, Glaxo Wellcome (Thailand) Ltd. LOT/C C055367 Mfd 06-10-2001, Exp 05-10-2004.

Test products

Furoxime® 250 mg tablet, the Siam Bhaesach Company, Bangkok, Thailand. LOT 922466 Mfd 19-08-2001 Exp 19-08-2004.

Study design and subjects

The study design was a single dose, two period randomized crossover with one- week washout period. An equal number of subjects (6 in each group) were randomly assigned to the two dosing sequences (test-reference, reference-fest). A total of 12 healthy nonsmoking male volunteers, aged between 20-23 years old and body mass index between 19-23 were enrolled in the present study. All were in good health on the basis of medical history, laboratory finding and physical examination. Any subject with known contraindication or hypersensitivity to cefuroxime and other beta-lactam antibiotics was excluded as well as those with a known history of peptic ulcer disease, dyspepsia, gastrointestinal disease, recent cigarette smoking, alcoholism or drug abuse. No other drug was allowed 1 month before and during the study period.

Dosage and drug administration

After an over night fast for at least 8 hours, at 7:00 a.m., the subjects were given either one tablet of Zinnat® or one tablet of the test drug with 200 ml

water. Thereafter, the subjects remained upright and fasted 2 hours after drug administration. Water and lunch were served at 2 hours and 4 hours, respectively. All the subjects were discharged from the study unit after a 15-hour blood draw was done. The wash-out period between each treatment was 1 week to ensure the total clearance of the drug. After a washout period, the subjects were administered a different brand of cefuroxime in the same manner. An identical meal and fluid intake were served during the two study periods. The subjects were required to refrain from drinking caffeine containing beverages and alcohol in order to standardize experimental conditions.

Plasma sample collections

Venous blood samples (10 ml) was collected into heparin tubes before and at 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 15 h after dose administration. The blood samples will be centrifuged for 10 minutes at 3,000 rpm to separate the plasma. Thereafter, the plasma was immediately kept at -20°C until assay.

Determination of the plasma cefuroxime concentrations

Cefuroxime in plasma was quantified by the high performance liquid chromatography (HPLC) method with UV detection at 275 nm after C18 solid phase extraction (Strata® C18-E, 1 ml, 100 mg, Phenomenex, USA) and was separated on C8 analytical column (Inersil®, 150 x 4.6 mm 5um, GL Sciences Inc., Tokyo Japan) at the temperature of 50°C[13]. The mobile phase was a mixture of 10 mM KH_2PO_4 (pH 4.4)/methanol (500/130, v/v). The retention time for cefuroxime and internal standard (cefoxitin)[14] were approximated at 10.3 and 12.1 minutes, respectively. The calibration curve of cefuroxime ranging from 0.1-5.0 μg/ml was prepared in plasma to establish the calibration curve for validation assay. The linear regression analysis of peak-height ratio of cefuroxime/internal standard (IS) *vs* cefuroxime concentrations consistency gave coefficients of determinant (R^2) of 0.998 or better. Plasma cefuroxime concentrations were calculated from the calibration standard lines using linear regression. The method was validated using a set of control samples, 5 samples from each of 3 different concentrations (0.3, 2.5, 4.5 μg/ml) of quality control samples (QC) and a single calibration curve run concurrently for within-day accuracy and precision. For inter-day assay precision, the 5 sets of three concentrations of QC samples were studied on 5 independent days with 5 concurrent standard calibration curves. The average %CV for within-day and inter-day assay was 3.05 per cent and 5.07 per cent, respectively. The lower limit of quantitative analysis (LLQ) was 10 ng/ml (%CV = 8.55) and the mean recovery of cefuroxime and internal standard which determined from 5 aliquots of each levels of the QC samples were 91.87 and 94.84 per cent, respectively. The stability test of cefuroxime after 3 freeze and thaw cycles presented by percentage of average freeze/thaw was 97.35 per cent.

Data analysis

Pharmacokinetic analysis

Maximal plasma concentration (C_{max}, μg/ml) and time to reach the peak concentration (T_{max}, h) were obtained directly by visual inspection of each subject's plasma concentration-time profiles. The area under the plasma concentration-time curve (AUC) from time 0-infinity ($AUC_{0-\infty}$, μg.h/ml) and half-life ($t_{1/2}$, h) were determined by non-compartmental analysis. The slope of the terminal log-linear portion of the concentration-time profile was determined by least-squares regression analysis and used as the elimination rate constant (K_e). The elimination half-life was calculated as $0.693/K_e$. The AUC_{0-t} from time zero to the last quantifiable point (Ct) was calculated using the trapezoidal rule. Extrapolated AUC from Ct to infinity ($AUC_{t-\infty}$) were determined as Ct/Ke. Total $AUC_{0-\infty}$ was the sum of AUC_{0-t} + $AUC_{t-\infty}$. In the present study, the sampling time was continued for more than 3 times the half-life; therefore, the AUC_{0-t} was sufficient to define at least 80 per cent of the total AUC. The calculation was performed by using the TopFit, pharmacokinetic data analysis program for PC.

Statistical analysis

An analysis of varience (ANOVA) was used to determine the statistical differences of pharmacokinetic parameters (T_{max}, C_{max}, AUC) which represented the rate and extent of drug absorption[15-18]. Statistic analysis of AUC and C_{max} were performed on logarithmically (ln) transformed data. Thereafter, using the variance estimate (S^2) obtained from the ANOVA, the 90 per cent confidence interval for the ratio of AUC as well as C_{max} values of the test preparation over those of the reference product were estimated using the following computational formula:

$$90\%\ CI\ (\mu_T - \mu_R) = (\bar{X}_T - \bar{X}_R) \pm t^{v}_{0.1}\sqrt{\frac{2S^2}{n}}$$

- $\bar{X}_T$, $\bar{X}_R$ were the observed means of the (ln) transformed parameters (either C_{max} or AUC) for the test product (T) and the references (R).
- S^2 was the error variance obtained from the ANOVA
- n was the number of subjects.
- $t^{v}_{0.1}$ was the tabulated two-tail t value for 90 per cent CI.
- v was the number of degree of freedom of the error mean square from the ANOVA.

The antilogarithm of the confidence interval ($\mu_T - \mu_R$) expressed the bioequivalence as a ratio of the test product and the reference product [μ_T/μ_R].

Bioequivalence acceptance criteria

The bioequivalence intervals of 0.8-1.25 for the ratio [$\frac{test}{reference}$] of the average $AUC_{0-\infty}$ and C_{max} were accepted by the Thai FDA[18]. Regarding analysis of T_{max}, the limits for the bioequivalence range were expressed as untransformed data (absolute differences) and the stipulated bioequivalence range of difference T_{max} [test-reference] were ± 20 per cent of the T_{max} of the reference formulation.

RESULT AND DISCUSSION

A single dose administration of 250-mg cefuroxime in healthy male volunteers under a fasting condition was well tolerated and all volunteers completed the study without any adverse effects. The concentration-time profiles were presented using three types of standard plots. Fig. 1 depicts the pairwise of individual concentration-time curves of Zinnat® and the test product while Fig. 2 illustrates their mean plasma concentration-time profiles. Table 1 compares individual calculated pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0-\infty}$ and $t_{1/2}$) of Zinnat® and the test product.

The pairwise concentration-time profiles of the test and the reference were relatively similar, except in volunteers No 1, 3, 4, and 6 who presented with earlier T_{max} and higher C_{max} of the test compared to the reference and vice versa for volunteer No 7 (Fig. 1). Similarly the mean plasma concentration-time curves of the test and the reference products were relatively comparable (Fig. 2), although the average C_{max} and $AUC_{0-\infty}$ of the test (4.16 ± 0.75 μg/ml and 13.03 ± 3.02 μg.h/ml) was slightly higher than that of Zinnat® (3.78 ± 1.05 μg/ml and 12.37 ± 3.81

Table 1. Comparison of cefuroxime pharmacokinatic parameters of individual subjects (n = 12) following oral administration of Furoxime® and Zinnat®.

Subject no.	C_{max} (μg/ml)		$AUC_{0-\infty}$ (@g0h/ml)		F_{rel} (%)	T_{max} (h)		$T_{1/2}$ (h)	
	Furoxime®	Zinnat®	Furoxime®	Zinnat®		Furoxime®	Zinnat®	Furoxime®	Zinnat®
1	4.27	3.50	11.89	14.55	82.0	1.00	3.00	1.40	1.33
2	5.88	5.99	19.59	19.35	101.0	1.50	1.50	1.40	1.27
3	4.17	2.87	12.15	9.85	123.0	1.50	2.50	1.20	1.30
4	4.15	3.02	12.52	13.77	91.0	1.00	3.00	1.38	1.42
5	2.95	2.14	6.93	4.56	152.0	1.00	1.00	0.95	0.97
6	4.95	3.92	14.56	13.33	109.0	2.00	3.50	1.07	1.06
7	4.38	4.72	15.83	15.57	102.0	2.50	1.50	1.98	1.79
8	3.56	3.46	12.65	11.90	106.0	2.00	2.00	1.59	1.37
9	4.06	4.91	12.18	15.12	81.0	1.00	1.50	1.20	1.16
10	4.31	4.09	14.77	11.61	127.0	1.50	1.50	1.50	1.36
11	3.66	3.77	11.51	9.75	118.0	1.50	1.50	1.26	1.06
12	3.54	2.93	11.80	9.09	130.0	3.00	3.00	1.15	1.20
Mean	4.16	3.78	13.03	12.37	110.0	1.63	2.13	1.34	1.27
SD	0.75	1.05	3.02	3.81	21.0	0.64	0.83	0.27	0.22
Median Tmax						1.50	1.75		

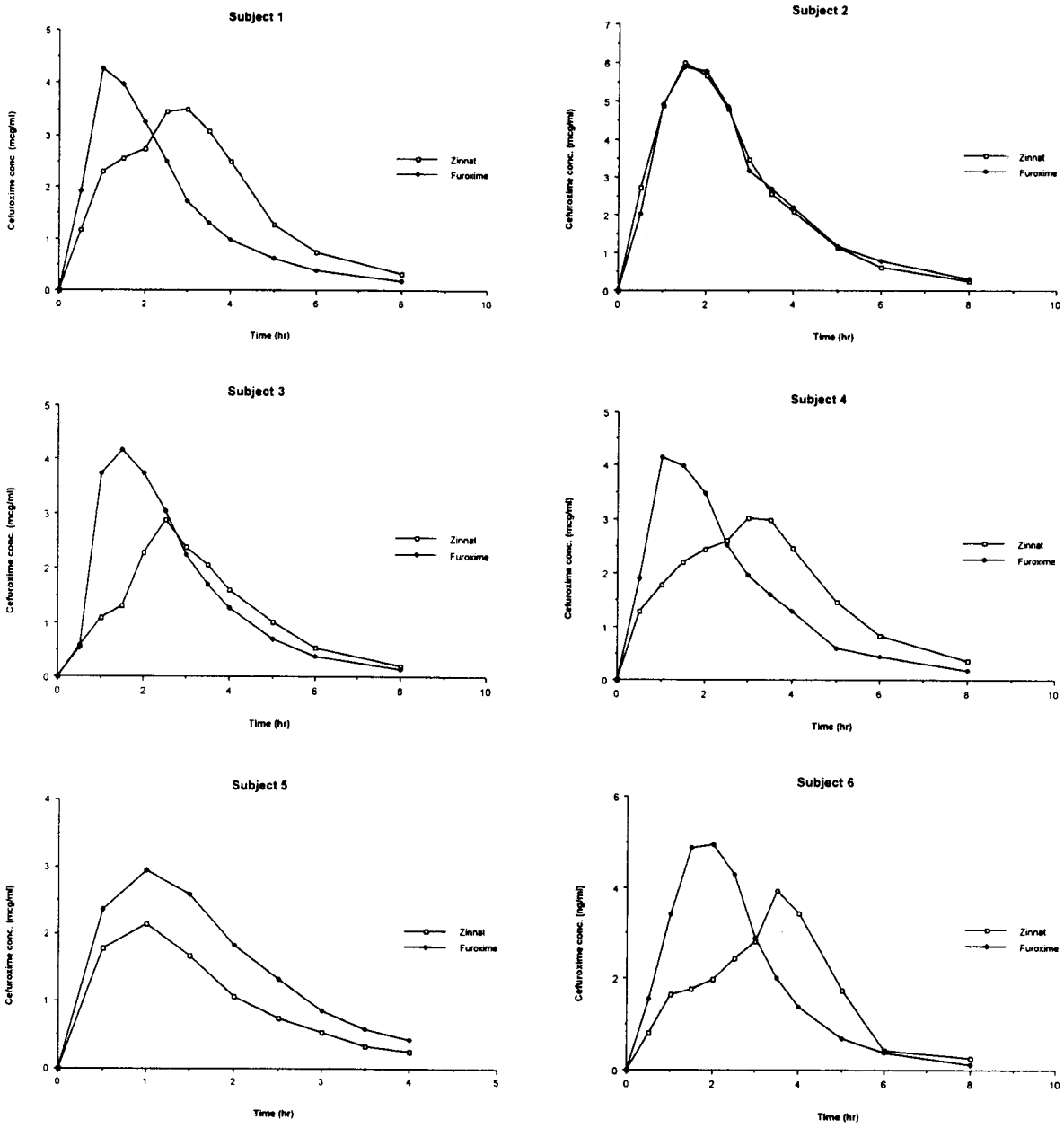
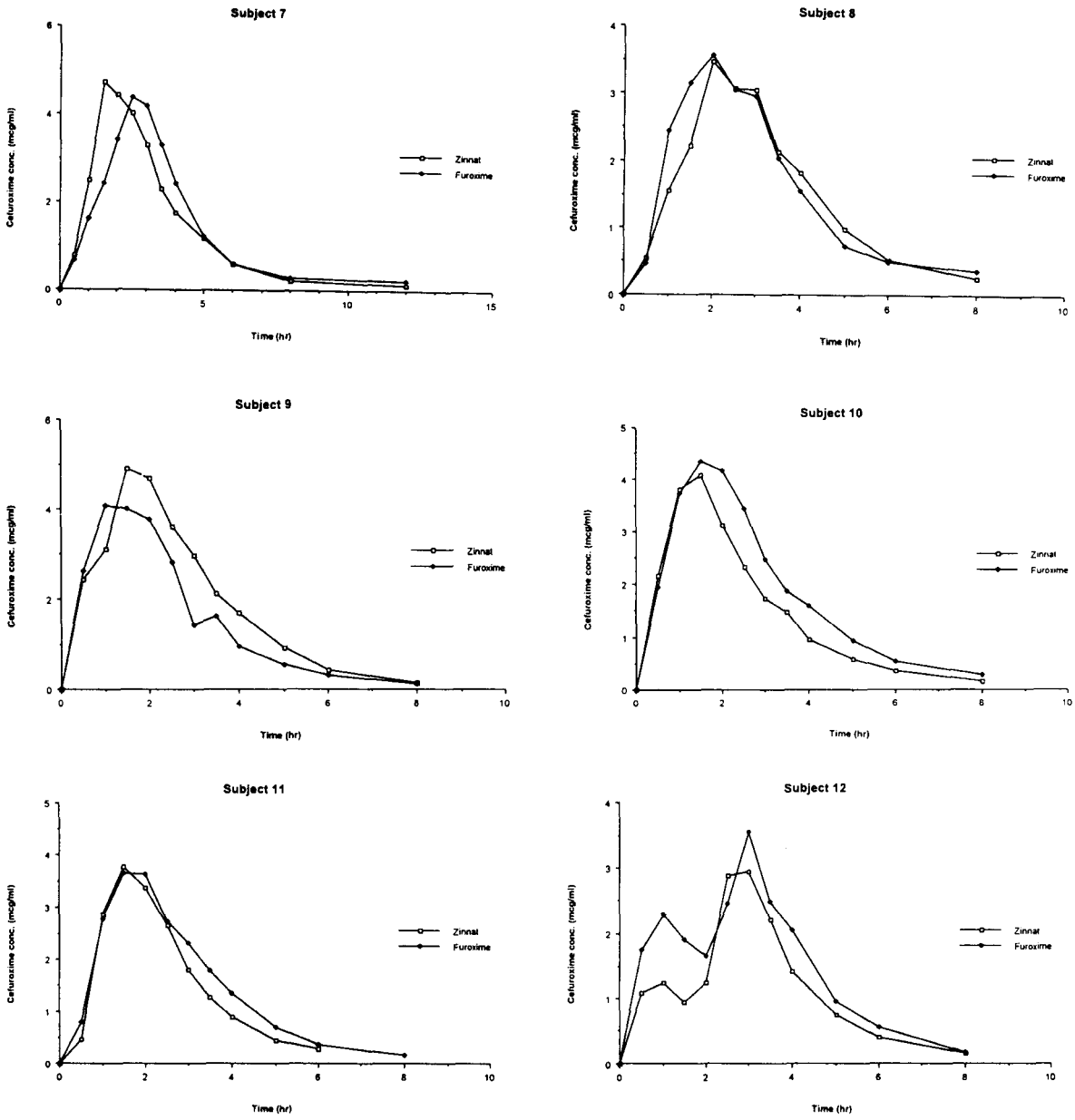


Fig. 1. Pairwise intraindividual comparison of plasma concentration-time profiles after a single oral administration of 250 mg Zinnat® (- -) and Furoxime® (-♦-).



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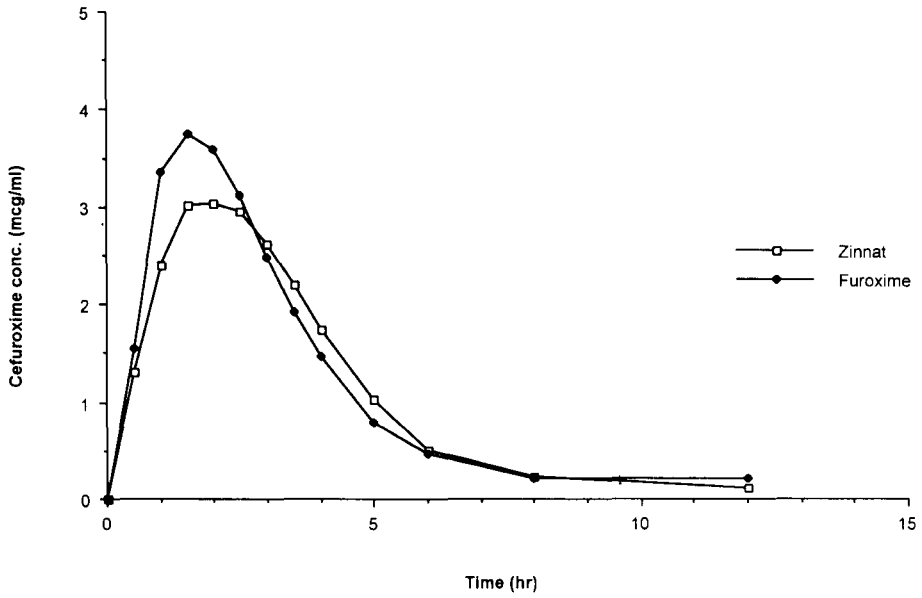

Fig. 2. Mean plasma concentration-time profiles after a single oral administration of 250 mg Zinnat® (- -) and Furoxime® (-♦-).

μg.h/ml) (Table 1). However, cefuroxime peak plasma concentrations and the $AUC_{0-\infty}$ of both formulations were similar to those values reported in the literature (C_{max} = 3.85 ± 1.55, 4.19 ± 0.03, 4.29 ± 0.19 μg/ml and $AUC_{0-\infty}$ = 12.4 ± 3.5, 12.66 ± 1.05, 14.21 ± 0.45 μg.h/ml[19,20]. The relative bioavailability of the test/reference was 110 per cent. Bioequivalence analysis showed that the C_{max} and $AUC_{0-\infty}$ of the two products did not significantly differ (Table 2). The ANOVA after log transformed data showed the point estimator (90% CI) for the ratio [Furoxime®/Zinnat®] of 1.03 (0.98-1.20) and 1.09 (1.02-1.24) for the $AUC_{0-\infty}$ and C_{max}, respectively. These values were within the bioequivalence range of 0.80-1.25, thus the present study demonstrated the bioequivalence of the test and the reference with respect to the rate (C_{max}) and the extent of absorption ($AUC_{0-\infty}$).

After oral administration, the rates of cefuroxime absorption from the two products were relatively variable. The median and the range of time to reach the maximal concentration (T_{max},) for Zinnat® (median 1.75 h, range 1.0-3.5 h) was slightly longer and more variable than Furoxime® (median 1.5 h, range 1.0-3.0 h). Although the upper confidence limit of the T_{max} difference was within the acceptable range of ± 0.43 h (less than ± 20% of the mean T_{max} of the Reference), the point estimate (-0.50 h) and the lower confidence limit of the T_{max} difference (-1.01) were outside the acceptable range (Table 2). However, the values of T_{max} from this study were comparable to those values previously reported (T_{max} = 1.38 ± 0.14, 2.33 ± 0.21, 2.26 ± 0.12)[19]. Similarly, the elimination half-life of the two products (average $t_{1/2}$ = 1.34 and 1.27 h for the test and Zinnat®, respectively) were not different from those values in the literature (average $t_{1/2}$ = 1.08-1.39 h[19], $t_{1/2}$ = 1.24-1.36 h[19]). Since the T_{max}, C_{max}, $t_{1/2}$ and $AUC_{0-\infty}$ from this study were similar to those values reported by James et al[19], whose study showed that the drug concentration-time curves after a single dose of 250 mg cefuroxime axetil exceeded the minimal inhibitory concentration (MIC) of common pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, the statistical difference of the T_{max} was not considered to affect the clinical efficacy and safety of the two products.

From the present study, the intrasubject coefficient of variation (%CV), estimated from S^2 obtained from the ANOVA after logarithmic transfor-

Table 2. Parametric 90% CI of the pharmacokinetic parameters (AUC, C_{max} and T_{max}).

PK parameters	Mean	90% CI	Acceptable range
$AUC_{0-\infty}$ ($\frac{test}{reference}$)	1.03	0.98-1.20	0.80-1.25
C_{max} ($\frac{test}{reference}$)	1.09	1.02-1.24	0.80-1.25
T_{max} (test-reference)	-0.50	(-1.01)-0.01	+ 0.43

(test = Furoxime®, reference = Zinnat®)

mation, for the $AUC_{0-\infty}$, and C_{max} were 14 per cent and 13 per cent, respectively. According to the nomograms and tables of Diletti[21] the power of tests obtained from the present study was 70 per cent for both the $AUC_{0-\infty}$ and C_{max}. To attain a test power greater than 80 per cent the sample size should be approximately 15 subjects. Concerning the duration of sampling time, it should be sufficient to ensure that the area extrapolated beyond the last sample time was less than 20 per cent. Since the guidelines[17,18] recommend that sampling should be continued for at least 3 times the terminal half-life of drug ($t_{1/2}$ approximately 1-2 h), the sampling time in the present study was continue until 15 hours. The AUC analysis in the present study showed that the sampling time was adequate and the calculated AUC-extrapolation was less than 10 per cent.

SUMMARY

The authors conducted a bioequivalence study of 250-mg oral preparations of Cefuroxime manufactured by the Siam Bheasach Company, Bangkok, Thailand in comparison with the innovator Zinnat® in 12 healthy Thai male volunteers. The result demonstrated that the mean (90% CI) of the $AUC_{0-\infty}$ and C_{max} ratios for [$\frac{test}{reference}$] were 1.03 (0.98-1.20) and 1.09 (1.02-1.24), respectively. Since the mean test/reference ratio of the two parameters was close to 1 and its 90 per cent CI fell within the bioequivalence range of 0.80-1.25, it was concluded that the two products were bioequivalent.

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การทดสอบชีวสมมูลของยาสามัญเซฟูรอกซีม อะเซทิล ในอาสาสมัครสุขภาพดี

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บุญเยี่ยม คำสอน, วทม, ชัยชาญ แสงดี, ปรด**

การศึกษาชีวสมมูลของยาเซฟูรอกซีม อะเซทิล ขนาด 250 มิลลิกรัม เปรียบเทียบระหว่างยาทดสอบฟูร็อกซีม® (ผลิตโดยบริษัทสยามเภสัชจำกัดประเทศไทย) กับยาต้นแบบซินแนท® ในอาสาสมัครชายไทยสุขภาพดี 12 คน โดยอาสาสมัครจะได้รับการสุ่มไขว้เพื่อรับประทานยา ทั้งยาต้นแบบและยาทดสอบหนึ่งครั้งหลังจากงดน้ำและอาหาร ระยะเวลาการศึกษาห่างกัน 1 สัปดาห์ ตัวอย่างเลือดจะเก็บตามเวลาที่กำหนดในเวลา 15 ชั่วโมง หลังจากรับประทานยา และนำไปตรวจวัดหาความเข้มข้นของยาเซฟูรอกซีม โดยวิธีโครมาโตกราฟฟี ชนิดของเหลวสมรรถนะสูงและประเมินค่าทางเภสัจลนศาสตร์โดยวิเคราะห์แบบ non-compartment ผลการศึกษาพบว่าค่าเฉลี่ย (มีเดียน) ของเวลาที่ระดับยาในเลือดสูงสุดของยาทดสอบเท่ากับ 1.5 ชั่วโมงเร็วกว่าของยาต้นแบบซึ่งมีค่า 1.75 ชั่วโมง และค่าเฉลี่ย (ช่วงความเชื่อมั่นร้อยละ 90) ของค่าแตกต่างของ ยาทดสอบ–ยาต้นแบบ เท่ากับ –0.5 [(–1.01)–0.01] การวิเคราะห์ชีวสมมูลโดยใช้อะโนวา พบว่า ค่าเฉลี่ย (ช่วงความเชื่อมั่นร้อยละ 90) ของอัตราส่วน [ยาทดสอบ/ยาต้นแบบ] ของพื้นที่ใต้กราฟที่เวลา 0 ถึงอสงไขยและค่าความเข้มข้นสูงสุดของยาในเลือด มีค่าเท่ากับ 1.03 (0.98–1.20) และ 1.09 (1.02–1.24) ตามลำดับ ซึ่งอยู่ในช่วงของชีวสมมูลที่ยอมรับคือ 0.80–1.25

คำสำคัญ : ชีวสมมูล, เซฟูรอกซีม อะเซทิล

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