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Relative Bioavailability Study of Cefuroxime Axetil Tablets

K. C. SUNG[1]*, YA-CHING CHANGCHEIN[2], PON-CHUANG CHEN[3], CHUNG-LUNG LU[3], ROUGH-YEE HAN[1] AND YU-YING LIN[1]

[1.] *Chia-Nan College of Pharmacy & Science, 60, Sec. 1, Erh-Jen Road, Pao-An Tsun, Jen-Te Hsiang, Tainan Hsien, Taiwan, R.O.C.* [2.] *Standard Chemical & Pharmaceutical Co. Ltd., Tainan Hsien, Taiwan, R.O.C.*
[3.] *Sin-Lau Christian Hospital, Tainan, Taiwan, R.O.C.*

ABSTRACT

The study was to assess the bioequivalence of two cefuroxime axetil tablets. The test product was Cefxin tablet; the reference product was Zinnat tablet. Twelve healthy adult male volunteers participated in the study. Every subject received each formulation according to a completely double-blind randomized cross-over design with a one-week washout period before the second dose. Following oral administration of two cefuroxime axetil tablets, blood samples were drawn thirteen times over a period of ten hours. These samples were analyzed for cefuroxime concentrations using a sensitive and specific high performance liquid chromatography. Statistical assessments were performed, including ANOVA, power analysis and 90% confidence interval of ratio on various pharmacokinetic parameters derived from the plasma drug concentration-time profiles. The results indicated that the AUC_{0-t} , AUC_{0-inf}, peak concentration and mean resident time for the two products were not statistically significant different, i.e., the two products showed no difference in the rate and extent of drug absorption. Namely, there is no statistically significant difference between the bioavailability of Cefxin and Zinnat.

Key words: **cefuroxime axetil, cefuroxime, relative bioavailability, pharmacokinetics, bioequivalence.**

INTRODUCTION

Cefuroxime axetil, the 1-acetoxyethyl ester of cefuroxime, is a broad-spectrum oral cephalosporin antibiotic. This ester prodrug of cefuroxime increases the lipophilicity of the parent compound and its oral bioavailability[(1)]. It is the first oral β-lactam to combine high intrinsic activity with stability to β-lactamase enzymes from most Gram-positive and Gram-negative organisms[(2)]. Cefuroxime axetil is often used to treat pharyngitis, tonsillitis, bronchitis, urinary tract infections, uncomplicated gonorrhea and some skin infections[(3,4)].

After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolyzed by non-specific esterase in the intestinal mucosa and blood to release cefuroxime

Correspondence to: K. C. Sung

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into circulation[5]. The oral bioavailability of cefuroxime axetil is around 34% (23-44%) following an oral dose on an empty stomach[2]. Peak plasma cefuroxime concentrations after a 500 mg dose (i.e., equivalent to 500 mg cefuroxime) are around 4.2 μg/ml while the peak time is approximately 2.4 hours. The terminal half-life and renal clearance were reported to be 1.56 hours and 12.58 l/hour, respectively[6, 7]. When cefuroxime axetil was given with food, a significant higher AUC and peak cefuroxime concentration were observed[2, 5-6], however, the clinical responses were independent of food intake[3]. After drug absorption, the axetil moiety is metabolized to acetaldehyde and acetic acid; cefuroxime is excreted unchanged in the urine.

The purpose of this project was to assess the bioequivalence of two cefuroxime axetil tablets. The test product was Cefxin tablet (equivalent to 250 mg cefuroxime per tablet) manufactured by Standard Chemical & Pharmaceutical Co. Ltd.; the reference product was Zinnat tablet (equivalent to 250 mg cefuroxime per tablet) made by Glaxo, Inc.. In addition to detailed physical examinations, clinical studies, assay validation and pharmacokinetic data analysis, statistical assessments on various pharmacokinetic parameters were used to determine the bioequivalence of these two products.

MATERIALS AND METHODS

I. *Materials*

Cefxin tablet (equivalent to 250 mg cefuroxime per tablet, manufactured by Standard Chemical & Pharmaceutical Co. Ltd., Lot NO. TC-12075) and the reference product Zinnat tablet (equivalent to 250 mg cefuroxime per tablet, made by Glaxo Inc., Lot NO. B6865LE) were obtained from the manufacturers. The other chemicals were all purchased from the Sigma Chemical Company and used as received.

II. *Subject*

Twelve volunteers enrolled in the study were all citizens of Taiwan. Informed consent was provided and signed for each volunteer prior to entry into the study . The volunteers were deemed to be in good health on the basis of interview, physical examination, chest X-ray, complete blood count, urinalysis and several other laboratory evaluations. No medication was permitted for all volunteers for two weeks prior to dosing and during the course of the study. Drinks containing caffeine were not allowed before drug administration. No vitamin supplement was taken for 48 hours prior to each dosing. Volunteers with a history of drug or alcohol abuse or drug sensitivity were excluded. The ages of those volunteers ranged from 20 to 30 years old (25.3 ± 2.57). Their body weights ranged from 61 to 87 kg (72.5 ± 7.68) and heights ranged from 160 to 187 cm (173 ± 7.01), respectively.

III. *Study Design*

This study was a double-blind crossover comparison with subjects randomly assigned to two-treatment phases. Twelve healthy adult male volunteers participated in the study. The experimental drug was Cefxin tablets and the reference drug was Zinnat tablets. Identical procedures used for both phases are described as follows: the subjects were refrained from taking any foods or fluids for ten hours prior to dosing. At approximately 7:30 am on the day of dosing, subjects entered the clinical study unit and were checked for normal vital signs of pulse rate and blood pressure. Between 7:30 am to 8:00 am, an indwelling catheter were placed in a forearm antecubital vein and 20 ml blood were drawn. This sample was designated as the zero hour sample. At approximately 8:00 am, the subjects were given either formulation and 240 ml water. Other than the 240 ml water, water intake was not allowed from one hour predose to one hour postdose. The administered dose were two cefuroxime axetil tablets (equivalent to 500 mg cefuroxime). A sample of 10 ml of blood was collected at 20 minutes, 40 minutes, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours after drug dosing. The actual blood collection time was recorded on the report form. During the study, volunteers were

ambulatory but were not permitted to engage in strenuous exercise. Lunch was served at four hours post dosing. Subjects were confined to a monitor center for ten hours after dosing. Seven days after the initial drug administration, the volunteers returned to the testing center for the second phase of study. The procedures of the second phase were identical to those of the phase one as described previously. At the end of the study, the participants received the same physical and laboratory evaluations as in the beginning of the study with the exception of a chest x-ray. Following blood collection, the samples were transferred to a heparinized vacutainer and centrifuged immediately. After centrifugation, biosamples were stored at about -20°C pending further chemical analysis.

IV. *Assay Method*

The assay method was modified from methods described in the literature[7-9]. 100 μl of cephaloridine (30 μg/ml) was added into 1 ml plasma samples as the internal standard. The 1 ml plasma samples were deproteined with 0.5 ml of trichloroacetic acid (10% w/w). The mixture was vortexed for 1 minute and centrifuged at 1080 g for 10 minutes. The upper aqueous layer was transferred into insert and 100 μl of the sample was injected into HPLC.

The assay for cefuroxime concentration was performed at ambient temperature using reverse phase column. The chromatographic system consisted of a pump (HITACHI 655-A40), an autosampler (HITACHI L6000), a UV detector (HITACHI L4000) and an integrator (HITACHI D2500). The detector was set at UV 273 nm. The stationary phase was ODS 4.6*150 mm, 5μm (Inertsil, USA) whereas the mobile phase was 0.04 M phosphate buffer (pH=7.0)/acetonitrile (85/15). The flow rate and the injection volume were 1.5 ml/min and 100 μl, respectively. Drug concentrations were determined by measuring the peak area ratio and comparing with the calibration curve. The calibration curve was constructed by fitting the peak area ratios and known standard concentrations to a straight line. The concentrations used in establishing calibration curves were 0.1, 0.4, 1, 3, 6 and 10 μg/ml. The accuracy (and thus the error %) was assessed by comparing the peak area of cefuroxime in aqueous solutions to the peak area in plasma samples (n=6) when both sets of samples were spiked with equivalent amounts of cefuroxime; the precision (CV %) was obtained by calculating the coefficient of variation of the six sets of data.

V. *Pharmacokinetic and Data Analysis*

The area under the plasma concentration-time curve from 0 to infinity ($AUC_{0\text{-}inf}$) was calculated for each subject after each treatment by the equation:

$$AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/k_{el}$$

where $AUC_{0\text{-}t}$ is the area under the plasma concentration-time curve estimated from time 0 to time t using the trapezoid rule and t is the last sampling time. The elimination rate constant (K_{el}) was obtained from the terminal slope of the curve using the WINNONLIN program. The maximum plasma concentration (C_{max}) achieved and the time to maximum plasma concentration (T_{max}) was obtained from the measured plasma concentration-time curve following drug administration. The mean resident time (MRT) is defined by the following equation:

$$MRT = \frac{\int_0^\infty tCdt}{\int_0^\infty Cdt}$$

Where C is the plasma cefuroxime concentration in μg/ml, and t is the time in hour after oral administration. The mean resident time reported in this study was also obtained using the WINNONLIN program.

The pharmacokinetic parameters were compared by two-way ANOVA by isolating the variance into subjects, formulations, order and error. The 90% confidence interval of the ratio of test parameters was calculated by:

$$Mean_{Cefxin} / Mean_{Zinnat} \pm (T_{n\text{-}2}\,(2*MSE/n)^{1/2}) / Mean_{Zinnat}$$

where n is the number of subject and MSE is the mean square of error from the ANOVA table as the estimate of variance.

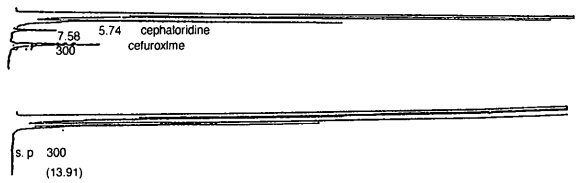

Figure 1a. Representative chromatograms of plasma spiked with cefuroxime and cephaloridine. **1b.** Representative chromatograms of blank plasma.

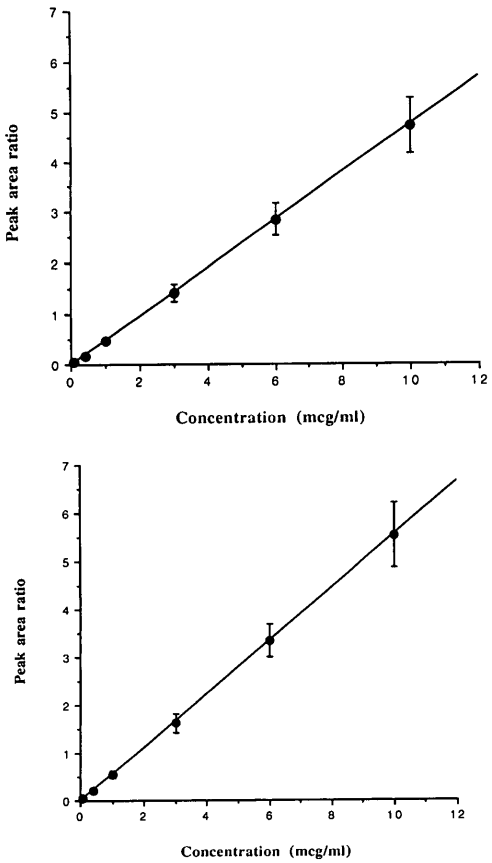

Figure 2a. Interday standard curves of cefuroxime in plasma (n=6). **2b.** Interday standard curves of cefuroxime in plasma (n=6).

RESULTS AND DISCUSSION

All the volunteers were in good conditions and none developed any adverse symptoms after dosing. No volunteer showed abnormalities on physical and clinical examination at completion of the study. Since all the volunteers were in healthy conditions and the randomized cross-over experimental design was used, intersubject variation was minimized.

The assay of cefuroxime (the parent compound) in plasma was validated by examining the specificity, limit of quantitation (LOQ), intraday error % and precision (CV %), interday error % and precision (CV %) as well as calibration linearity. Figure 1a and 1b show the representative chromatograms of plasma spiked with cefuroxime and cephaloridine as well as blank plasma, respectively. The blank plasma samples from the test subjects indicated no interfering chromatographic peaks for cefuroxime and cephaloridine. The HPLC assay for the plasma samples was sensitive down to 0.1 μg/ml (LOQ), which is adequate for this study. Figures 2a and 2b show the intraday and interday standard curves (n=6) of cefuroxime in plasma, respectively. The overall intraday precision (CV %) observed in the standard curves was less than 10 % and the intraday error was within 2 % and 8 % between the concentrations of 0.1 μg/ml and 10 μg/ml (Table 1). The response of detector to cefuroxime was linear in the concentration range of 0.1 μg/ml to 10 μg/ml. The correlation coefficients were all higher than 0.99 and the CV % of slope was 3.26%. For the interday validations, the overall interday precision (CV

Table 1. The intraday and interday validation data: error (%) and precision (CV %) (n=6)

Concentration (μg/ml)	Intraday error (%)	Intraday precision (CV %)	Interday error (%)	Interday precision (CV %)
0.10	4.41	2.70	8.52	9.78
0.40	5.23	10.0	9.65	0.74
1.00	6.89	1.53	6.76	2.58
3.00	7.11	0.46	5.64	2.80
6.00	2.06	2.86	2.62	2.90
10.0	5.73	0.59	8.73	1.95

%) observed in the standard curves was less than 9.78 % and the interday error was 2 % to 10 % between the concentrations of 0.1 μg/ml and 10 μg/ml (Table 1). The response of the detector to cefuroxime was also linear with correlation coefficients higher than 0.99. The CV % of slope was 5.67 %.

The change of mean cefuroxime plasma concentration versus time (± standard deviation) in twelve healthy volunteers following the treatment are shown in Figure 3. The two concentration-time profiles overlap, suggesting the performance of the two products in those volunteers were similar. However, pharmacokinetic and statistical analysis are needed to be performed in this study to ensure the bioequivalent of the two products. Based on the concentration-time data of the twelve volunteers (Table 2), a series of pharmacokinetic parameters were obtained. Those parameters, including the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, MRT and K_{el}, are shown in Table 3. According to those pharmacokinetic data, statistical results are also calculated and summarized in Table 3.

Statistical comparison of $AUC_{0\text{-}inf}$ of the products using two-way ANOVA, the F value (0.53) indicates that there was no statistically significant difference (α=0.05) for the $AUC_{0\text{-}inf}$ of the two products. The power of ANOVA tests was greater than 0.8, demonstrating that the test was able to detect a 20% difference between two products. The 90% confidence interval of ratio was 84 to 107%, which is within the acceptable range of 80-120%. According to those statistical tests, it can be concluded that the difference in the extent of drug absorption of the two products is not statistically significant.

The ANOVA test on C_{max} shows that the difference between the two products was not statistically significant (α=0.05) (Table 3). The power of

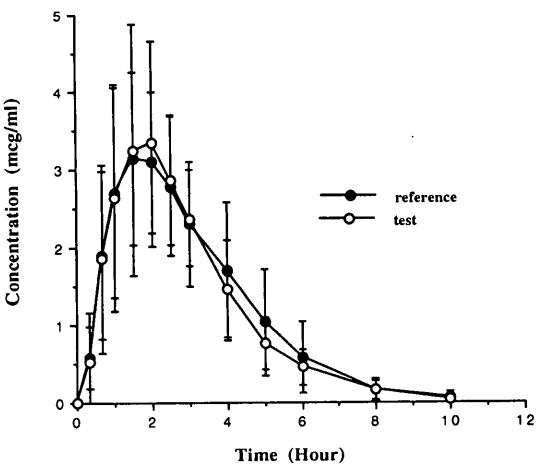

Figure 3. Change of plasma cefuroxime concentration versus time in 12 volunteers (mean ±s.d.).

Table 2. Mean and standard deviation of cefuroxime plasma concentrations after oral administration of cefuroxime axetil tablets in twelve volunteers

Time (Hour)	Reference drug (μg/ml, Zinnat)	s.d. (Zinnat)	Test drug (μg/ml, Cefxin)	s.d. (Cefxin)
0	0.000	0.000	0.000	0.000
0.33	0.631	0.376	0.569	0.644
0.67	1.979	1.111	1.961	1.219
1	2.731	1.416	2.752	1.482
1.5	3.083	1.149	3.324	1.683
2	3.064	0.937	3.348	1.387
2.5	2.801	0.937	2.861	0.871
3	2.351	0.830	2.395	0.660
4	1.774	0.886	1.468	0.654
5	1.080	0.704	0.765	0.350
6	0.619	0.467	0.458	0.235
8	0.165	0.138	0.162	0.132
10	0.073	0.082	0.043	0.052

Table 3. Summary of pharmacokinetic parameters (mean ± s.d.) and statistical results for cefuroxime axetil bioequivalence study

Parameter	Reference drug (Zinnat)	Test drug (Cefxin)	Ratio of means (test/reference)	ANOVA α=0.05 (F value)	90% Confidence interval of ratio
AUC_{0-t} (μg*hr/ml)	12.20±3.28	11.68±3.03	0.98±0.21	n.s. (0.45)	84-107 %
AUC_{0-inf} (μg*hr/ml)	12.32±3.37	11.76±3.02	0.97±0.21	n.s. (0.53)	84-107 %
C_{max} (μg/ml)	3.69±0.75	3.93±1.08	1.09±0.30	n.s. (0.78)	93-120 %
T_{max} (hr)	1.76±0.99	2.00±0.77	1.50±1.04	n.s. (0.37)	74-153 %
MRT (hr)	2.98±0.65	2.93±0.72	1.01±0.24	n.s. (0.06)	84-113 %
K_{el} (hr^{-1})	0.89±0.49	0.92±0.37	1.11±0.28	n.s. (0.18)	91-114 %

this ANOVA test was 0.7. The 90% confidence interval of ratio were 93-120%, which is within the range of 80-120%. Although the power of the ANOVA test was slightly lower than 0.8, the ANOVA test and 90% confidence interval results still support the equivalent peak drug concentration for both products.

The ANOVA results on Table 3 show that the difference in T_{max} of the two products were not statistically significant (α=0.05). However, the 90% confidence interval of ratio did not fall in the range of 80-120% (Table 3) and the power of analysis was poor. From those statistical results, it would be difficult to obtain conclusive results on the rate of absorption of the two products. In order to draw more definitive conclusions on the rate of drug absorption, MRT was evaluated in this study. MRT in a relative bioavailability study is the sum of the true mean residence time and the mean absorption time. If the drug disposition is similar, MRT can be used to indicate the rate of drug absorption[9]. From Table 3, both the ANOVA test and 90% confidence interval of ratio (84-113%) indicate that the MRT of the two products were not statistically different. Those results support that the two products have the same rate of absorption.

In conclusion, since these two products are so similar with respect to both the rate and the extent of cefuroxime axetil absorption following oral administration, the results of this study clearly demonstrate that there is no statistically significant difference between the bioavailability of reference drug Zinnat and test drug Cefxin.

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Cefuroxime Axetil錠劑相對生體可用率之研究

宋國峻[1*] 張簡雅青[2] 陳本全[3] 陸重隆[3] 韓若怡[1] 林瑜瑩[1]

[1.]嘉南藥理學院 台南縣仁德鄉71710保安村二仁路一段60號
[2.]生達製藥股份有限公司
[3.]基督教新樓醫院

摘 要

本研究旨在評估兩種cefuroxime axetil錠劑之生體相等性。試驗品爲Cefxin錠，參考品爲Zinnat錠。十二位健康成年男性自願者，以隨機雙盲交叉之實驗設計方式給予cefuroxime axetil錠，兩次給藥間有一星期的間隔時間。每位受試者口服兩粒cefuroxime axetil 錠後，於十小時內抽血十三次，此血液樣本透過高效液相層析儀分析其中cefuroxime之濃度。由藥物血中濃度-時間之數據得到藥物動力學參數後作ANOVA、統計能力分析、90%信賴區間等統計比較。結果顯示兩種cefuroxime axetil錠之$AUC_{0\text{-}t}$，$AUC_{0\text{-}inf}$，尖峰血中濃度及平均滯留時間，在統計學上均沒有顯著之差異；亦即兩種藥品之吸收程度和吸收速率沒有差異。根據以上之結果，可證明Cefxin和Zinnat之生體可用率在統計學上沒有顯著之差異。

關鍵詞：cefuroxime axetil，cefuroxime，相對生體可用率，藥物動力學，生體相等性。