

Pharmacokinetic and Bioequivalence Studies of Oral Cefuroxime Axetil 250 mg Tablets in Healthy Human Subjects

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Abstract

The objective of this study was to determine the bioequivalence of two Cefuroxime oral 250 mg tablet formulation. One was the innovators brand (Zinnat®), was taken as reference brand (REF) and the other was a newly developed, optimized and cost effective formulation (TEST). A single dose, open, random sequence, cross over, two treatment study with a one week washout period in between was carried out in 12 healthy male Pakistani young volunteers. Reference and Test tablets were administered to these volunteers with 150 mL of water after an overnight fast. Blood samples were drawn 15 min prior to the administration of dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours post dose. The cefuroxime concentrations in the plasma were determined by a modified, simple HPLC method in which the mobile phase was 10 mM solution of ammonium acetate and acetonitrile, pH was adjusted to 5 ± 0.2 with glacial acetic acid. The wavelength of detection was 254 nm having a flow rate of 1ml/min and the retention time of 5.8 min. The method was validated as per the ICH requirements. Both compartmental and non-compartmental methods were used to determine the various PK parameters such as C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, AUMC, MRT, $t_{1/2}$, K_{el} , V_d and Cl using Kinetica® ver 4.4.1 The bioequivalence between the REF and TEST cefuroxime axetil 250mg formulations was established as the Latin square design of ANOVA does not show any significant difference with a $p \geq 0.05$ for period and the 90% confidence interval lies within the acceptable range (80-125%) for the log transformed data of C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$, AUMC, MRT, V_d and Cl, showing a comparable plasma profiles generated by both the formulations. It is, thus concluded that both the formulations were bioequivalent.

Keywords: Bioequivalence; Pharmacokinetics; Bioavailability; Cefuroxime axetil

Introduction

Cefuroxime is a second-generation broad-spectrum cephalosporin antibiotic and is a mixture of two equally active isomers having 50% of each [1,2]. Cefuroxime is a bactericidal antibiotic that inhibits bacterial cell wall synthesis like other β -lactam antibiotics. As with other -lactam antibiotics, cefuroxime interferes with the transpeptidation process binding the cell wall, weakening the cell wall to produce non-viable filaments. Cefuroxime also binds with Penicillin-binding protein 3, which is involved in the formation of the peptidoglycan bacterial cell wall, leading to lysis of the organism.

Cefuroxime axetil, CA is the acetoxyethyl ester of cefuroxime and a prodrug. Chemically, cefuroxime axetil is the 1-(acetyloxy) ethyl ester of cefuroxime, is (RS)-1-hydroxyethyl (6R,7R)-7-[2-(2-furyl) glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate, 7Z-(Z)-(O-methyl-oxime), 1-acetate 3-carbamate. Its molecular formula is $C_{20}H_{22}N_4O_{10}S$, and has a molecular weight of 510.48 [1] (Figure 1). After oral administration, cefuroxime axetil is deesterified in the intestinal mucosa and absorbed into the bloodstream as cefuroxime moiety. It has activity against *Staphylococcus aureus* and other Gram-positive cocci, certain members of the family *Enterobacteriaceae*, and β -lactamase-positive and β -lactamase-negative strains of *Haemophilus influenzae* [3]. Cefuroxime axetil oral formulations are indicated in the treatment of upper and lower respiratory tract infections, in community acquired pneumonia and in intensive care units [4].

On oral administration, the bioavailability of the drug is 37% only [3,5], and the absorption of tablet is greater when taken after food i.e. 37% to 52% [6]. Approximately 38-50% of serum cefuroxime is bound

to protein [7] and almost the entire drug is metabolized into active form and 50% can be recovered in urine [8-10].

Cefuroxime axetil pharmacokinetics (PK) and clinical efficacy has been reported in various literature. The objective of this study was to determine the Bioequivalence of the newly developed and optimized formulation (TEST) [11], after comparing it with the innovator brands Zinnat (REF). The other PK parameters beside C_{max} , T_{max} and AUC was also reported in this study.

Material and Methods

Study design

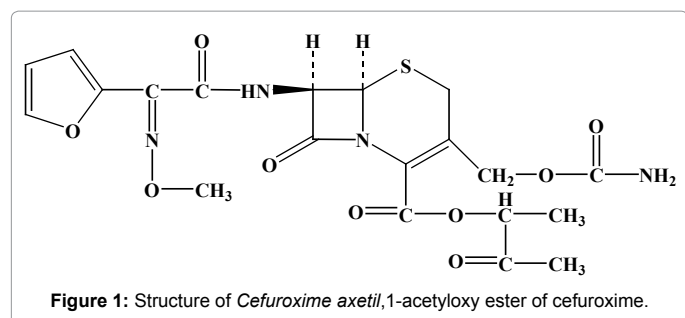
The study design was a single dose, open, random two sequence, two treatment, cross over, study with a one week washout period in between, in which the innovator brand, (Zinnat® of GlaxoSmithKline, Pvt. Ltd. Karachi), was taken as reference brand (REF) and compared with the newly developed and optimized formulation (TEST). Details of formulation, its optimization and stability study has been reported earlier [11]. Study was conducted on 12 healthy male Pakistani young

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volunteers who were thoroughly worked up for clinical and general health. A written informed consent was obtained from the participants. The study was conducted as per the ethical guidelines of Helsinki declaration for studies on human subjects [12] and the International Conference on Harmonization [13]. The study was conducted in the Research Laboratory, Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi, after being ethically approved by the Institutional Review Board and the Board of advanced studies and Research, University of Karachi. Inclusion criteria for study were healthy subjects of age limit from 18-45 years of age and having weight within 10% ideal body weight and height and with all physical, medical and mental examination within normal limits and with no allergy history. While the exclusion criteria for the volunteers were:

1. Participation in any other clinical studies during the last three months
2. Intake of any medicines, including herbal and/or nutritional supplements within a month before or during the study period, or had
3. Any known allergy to the cephalosporins.

The participants had an average age of 23.166 ± 1.193 years (22-26), average weight of 63.416 ± 9.199 Kg (53-81) and average height of 168.173 ± 11.211 cm (155.448-185.928).

Drug administration and blood sampling

The cefuroxime axetil 250 mg REF and TEST tablet formulations were administered to the volunteers who were randomized to receive either formulation with 150 mL of water after an overnight fast. No food or dietary items were allowed until 4 hours after the drug administration, after which a standard diet was given. The volunteers were confined to the study venue for 12 hours following the drug administration. Venous blood was withdrawn from the elbow fold 15 min prior to dosing, then at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours after dosing. The plasma was separated and the samples were stored at -20°C in the laboratory refrigerator/chiller cabinet (LG Electronics, Korea).

Drug analysis

Mobile phase: A modified HPLC method was used for determining the cefuroxime concentrations in the plasma [14]. The mobile phase was 10 mM ammonium acetate (pH adjusted to 5.2 ± 0.2 with glacial acetic acid) and acetonitrile in the ratio of 85:15. The mobile phase was filtered using Sartorius filtration assembly (Sartorius, Goringen, Germany) and sonicated (Clifton, Nickel Electro Ltd. Somerset, England) before use.

Sample preparation: Volunteer plasma was deproteinated in a ratio of 1:1 ratio with acetonitrile (Merck, Darmstadt, Germany), vortexed (Whirl mixer, England) for 5 minutes and then centrifuged (Heraeus,

Osterode, Germany) at 4000 rpm for 10 minutes. The supernatant was removed and filtered using 0.45μ membrane filter (Schleicher & Schuell, Dassel, Germany) in a swinney assembly (Millipore, England). The sample was kept in clean dirt free test tube and was kept covered by an aluminum foil till the end of analysis.

Chromatographic conditions: The HPLC system comprised on Shimadzu Corporation system controller Pump, LC 10 AT VP, Spectrophotometric Detector, SPD-10 A, Communication Bus Module CBM 102. For processing the data, HPLC Software Class GC 10 version 2.0 (Shimadzu Corp. Kyoto, Japan) was used.

Aliquot of 100 μL of the sample was injected using a microliter syringe (Hamilton, Switzerland) in Supelcosil[®] column LC-18-DB 250 \times 4.6 mm, 5 μm (Supelco, Bellefonte, PA, USA) protected with a Guard column C18, 4.0 \times 2 mm (Phenomenex, Torrance, CA, USA). The detection wavelength was 254 nm and the flow rate was 1ml/min and the retention time was 5.8 min. The method was validated as per the ICH requirements [15], wherein, the lower limit of quantitation for cefuroxime was 0.260 $\mu\text{g/ml}$ of plasma with accuracy of 89.121% and precision of 1.488%. The range of detection was 0.173–50 $\mu\text{g/ml}$ with a R^2 of 0.998. The accuracy and precision for intra-assay and inter-assay QC samples of two higher and two lower concentrations were run in triplicate. The mean intra-assay accuracy for concentrations of 25, 6.25, 3.125 and 0.781 $\mu\text{g/ml}$ were 97.04%, 94.27%, 86.61% and 87.34%, while precision was 1.47%, 1.68%, 1.62% and 1.91% respectively. The inter-assay accuracy and precision for the same set of concentrations were 98.49%, 95.56%, 88.21% and 88.91% and precision 1.95%, 2.57%, 3.15% and 5.08% respectively. The absolute and the relative recovery of the drug was 80.85% and 100.16%, 79.90 and 91.01%, 79.05 and 88.78% for the concentrations of 25, 6.25 and 0.781 $\mu\text{g/ml}$ respectively. The method selectivity was determined by spiking the blank plasma sample and plasma with the drug at concentrations used for linearity. No plasma interference was observed with the drug. The specificity was determined by spiking the drug with internal standard, IS, which was cefoperazone. The stability of cefuroxime was observed by carrying three freeze-thaw cycles in plasma. Short-term stability of cefuroxime in plasma was at least 4 hours at room temperature and long-term stability was at least for three weeks at -20°C . The details of validation parameters are mentioned in Table 1.

Pharmacokinetic and statistical analysis: Compartmental and non-compartmental analysis was used to determine the PK properties of cefuroxime using Kinetica[®] software (version 4.4.1, Thermoelectron Corp., USA). In the data, the observed peak plasma concentration (C_{max}) and the time to achieve the peak concentration, (T_{max}) were obtained from the plasma concentration-time profiles for the REF and TEST formulations. The area under the plasma concentration-time curves, AUC_{0-t} and $AUC_{0-\infty}$ were estimated by linear trapezoidal rule and extrapolation using equation $AUC_{0-t} + C_t/K_{el}$ where C_t is the measurable last concentration at time t and K_{el} is first order elimination rate constant. Other parameters measured were, K_{el} , $t_{1/2}$, V_d , CL, AUMC, and MRT. K_{el} was obtained by linear regression of log-transformed data; $t_{1/2}$ was calculated by $0.693/K_{el}$. MRT was calculated by $AUMC/AUC$ and CL by $Dose/AUC_{0-t}$, all the data were generated by the software.

The bioequivalence between the REF and TEST cefuroxime axetil 250 mg formulations was established using its means and 90% CI by Latin square design ANOVA and students t -test with significance level at $p < 0.05$ on log transformed data of C_{max} , T_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Equivalence was also estimated for other pharmacokinetic parameters

| | | | | | |
|--|--------------------------|-------------------|-------------|-------------------|-----------------------|
| Sensitivity / LLOQ (µg/ml) | 0.260 | | | | |
| Linear range (µg/ml) | 0.173-50 | | | | |
| Coefficient R ² | 0.998 | | | | |
| Back calculated concentration precision (6.25-0.173 µg/ml) | 1.488 | | | | |
| Back calculated concentration Accuracy (6.25-0.173 µg/ml) | 89.121 | | | | |
| Intra-assay precision for QC samples, RSD (%) | QC Samples Conc. (µg/ml) | After 4 hr. | After 7 hr. | After 9 hr. | Mean of Three periods |
| | 25 | 3.53 | 0.24 | 0.64 | 1.47 |
| | 6.25 | 1.72 | 3.23 | 0.09 | 1.68 |
| | 3.125 | 2.31 | 0.11 | 2.43 | 1.62 |
| Intra-assay accuracy for QC samples (%) | 25 | 97.12 | 96.76 | 97.23 | 97.04 |
| | 6.25 | 94.23 | 94.54 | 94.03 | 94.27 |
| | 3.125 | 86.03 | 87.78 | 86.03 | 86.61 |
| | 0.781 | 86.76 | 87.23 | 88.02 | 87.34 |
| Inter-assay precision for QC samples, RSD (%) | | Day 1 | Day 2 | Day 3 | Mean of Three days |
| | 25 | 1.55 | 2.38 | 1.93 | 1.95 |
| | 6.25 | 1.51 | 2.76 | 3.45 | 2.57 |
| | 3.125 | 2.46 | 5.08 | 1.90 | 3.15 |
| Inter-assay accuracy for QC samples (%) | | Day 1 | Day 2 | Day 3 | Mean of Three days |
| | 25 | 98.49 | 98.18 | 98.79 | 98.49 |
| | 6.25 | 95.41 | 95.68 | 95.58 | 95.56 |
| | 3.125 | 88.51 | 88.61 | 87.50 | 88.21 |
| Recovery | | Absolute n=5 | | Relative n=5 | |
| | 25 | 80.85 | | 100.16 | |
| | 6.25 | 79.90 | | 91.01 | |
| | 0.781 | 79.05 | | 88.78 | |
| Stability of Cefuroxime at room temperature (4 hr.) n= 5 | | Accuracy n=5 | | Precision n=5 | |
| | 25 | 98.42 | | 1.36 | |
| Mean of 3 Freeze-thaw cycles n=5 | 25 | 93.05 | | 3.26 | |
| | 0.781 | 87.09 | | 1.34 | |
| Long Term Stability at -20°C | | After 2 weeks n=5 | | After 3 weeks n=5 | |
| | | Accuracy | Precision | Accuracy | Precision |
| | 25 | 95.70 | 1.54 | 88.95 | 0.80 |
| | 0.781 | 87.40 | 1.81 | 86.04 | 1.31 |

Table 1: Bio-analytical method validation parameters.

such as $t_{1/2}$, AUMC, Vd and MRT. Bioequivalence was considered if the 90% CI lied between 80-125% [16].

Result

Cefuroxime drug was well tolerated by the volunteers without any unexpected outcomes. The mean concentration vs. time profile of both the formulations of 250 mg cefuroxime axetil is shown in the Figure 2 while the Pharmacokinetic parameters are summarized in Table 2. The ANOVA analysis with 90% CI for C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and AUMC, on log transformed data of both the formulations, is mentioned in Table 3. The PK parameters were in agreement to the previously published data [17-20].

Discussion

The pharmacokinetics of *Cefuroxime axetil* was studied in fasted healthy male Pakistani volunteers in order to observe any interethnic variation in the pharmacokinetics of the drug and the pharmacokinetic data was compared with a developed immediate release formulation of CA to establish bioequivalence against the reference brand. The in-vivo study was completed with no subject drop-out with good tolerance to the formulations. The drug quantification was observed in the first and the last sample time with measureable amounts of the drug. Pharmacokinetic parameters such as C_{max} , T_{max} , and $AUC_{0-\infty}$ were found to be slightly different with that of reported one i.e. Sung et al. in 1999 observed C_{max} value of $3.69 \pm 0.75 \mu\text{g/ml}$, T_{max} and $AUC_{0-\infty}$ values of $1.76 \pm 0.99 \text{ hr}$ and $12.20 \pm 3.28 \text{ mg/L.hr}$ [21], similarly James et al. in 1991 reported C_{max} , T_{max} and AUC values of $4.19 \pm 0.30 \mu\text{g/ml}$, $1.39 \pm 0.14 \text{ hr}$ and $12.66 \pm 0.67 \text{ mg/L.hr}$ [19]. The relative bioavailability was 93.89%. Variation was also observed for the PK data reported among fed state subjects [6,20] and with those given a 500 mg dose [18,21,22]. The other parameters like volume of distribution (V_d), Clearance, elimination rate constant and $t_{1/2}$ were in agreement with the

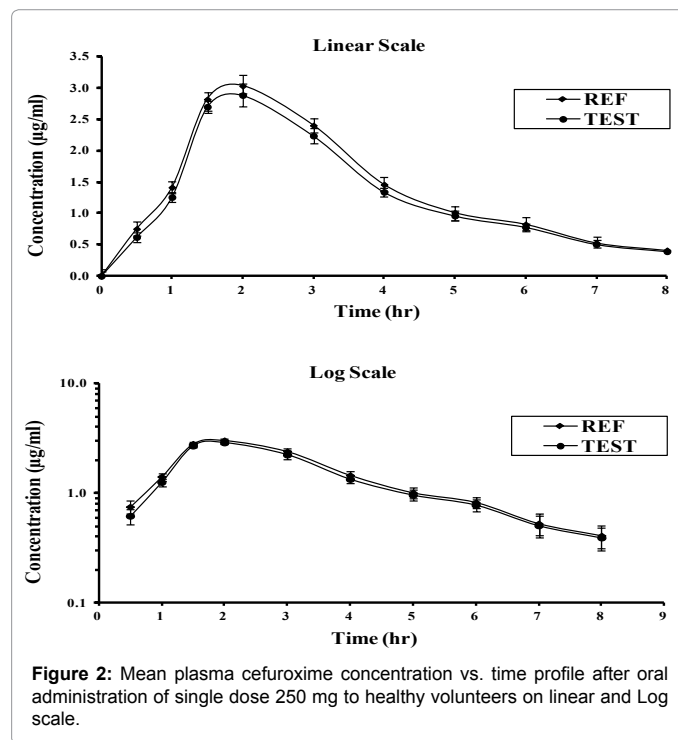


Figure 2: Mean plasma cefuroxime concentration vs. time profile after oral administration of single dose 250 mg to healthy volunteers on linear and Log scale.

| Pharmacokinetics Parameter | TEST | REF |
|--------------------------------|------------------|------------------|
| C_{max} (µg/ml) | 2.88 ± 0.09 | 3.03 ± 0.09 |
| T_{max} | 2.22 ± 0.04 | 2.24 ± 0.03 |
| $t_{1/2}$ | 1.35 ± 0.25 | 1.35 ± 0.19 |
| AUC_{0-t} (mg/L.hr) | 9.60 ± 0.38 | 10.23 ± 0.44 |
| $AUC_{0-\infty}$ (mg/L.hr) | 10.75 ± 0.47 | 11.42 ± 0.46 |
| AUMC (mg/L.hr) ² | 32.42 ± 3.68 | 36.51 ± 7.14 |
| Relative Bioavailability (% F) | 93.89 | |
| K_{el} (hr ⁻¹) | 0.52 ± 0.10 | 0.52 ± 0.07 |
| V_d (L) | 49.05 ± 8.27 | 46.00 ± 7.15 |
| CL (L/hr) | 25.13 ± 1.13 | 23.50 ± 1.26 |
| MRT (hr.) | 4.21 ± 0.25 | 4.18 ± 0.25 |

Table 2: Pharmacokinetic parameters of TEST and REF for *Cefuroxime Axetil* 250mg tablets in 12 healthy fasting male Pakistani volunteers (Mean \pm SD).

| Statistical Analysis | C_{max} | T_{max} | AUC_{0-t} | $AUC_{0-\infty}$ | $t_{1/2}$ | AUMC | MRT | CI | V_d |
|----------------------|-------------|--------------|-------------|------------------|--------------|-------------|-------------|-----------|-------------|
| ANOVA (p value)* | 0.235 | 0.882 | 0.372 | 0.531 | 0.9238 | 0.849 | 0.546 | 0.539 | 0.8073 |
| 90% CI | 91.34-99.82 | 97.74-100.27 | 91.33-96.55 | 92.04-96.31 | 88.21-112.16 | 90.56-98.99 | 96.69-104.4 | 103.7-110 | 93.95-120.5 |
| Two one sided t-test | 1.8125 | | | | | | | | |

* p value for period

Table 3: Statistical Analysis of log transformed pharmacokinetic data for Bioequivalence.

published data [17-20]. Although some reports in the literature shows similar studies, but pharmacokinetic studies of 250 mg cefuroxime axetil oral formulation among fasted healthy Pakistani volunteers was not reported. The present study would be helpful to obtain kinetics data to rectify any inter-ethnic variations among this ethnic population.

There was no significant difference between the TEST and REF formulation with respect to the mean and standard deviation for C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and AUMC, showing a comparable plasma profiles generated by both the formulations. The natural log-transformation of the data showed no statistically significant difference between the two formulations with a p -value greater than 0.05 for period, while the 90% CIs were between 80-125%, as per the FDA acceptable range to establish bioequivalence, statistical analysis of log transformed pharmacokinetic data for bioequivalence is shown in Table 3. It is, thus concluded that both the formulations stands bioequivalent on the basis of C_{max} , T_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Both of the products are also bioequivalent for the other PK parameters such as $t_{1/2}$, AUMC and MRT, V_d and CI. Although some reports in the literature shows similar studies, but pharmacokinetic studies of 250 mg cefuroxime axetil oral formulation among fasted healthy Pakistani volunteers was not reported. The present study would be helpful to obtain kinetics data to rectify any inter-ethnic variations among this ethnic population.

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