Relative Bioavailability of a Generic Cefuroxime 500mg Capsule Versus the Innovator Brand 500 mg Tablet

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Abstract

Objective: This study was performed to determine the bioequivalence between a generic capsule formulation of cefuroxime and the innovator product which is a tablet.

Materials and Methods: Twenty two healthy male subjects received a single 500 mg oral dose of generic cefuroxime axetil as the capsule and the 500 mg tablet (Zinnat, GSK) which is the innovator brand or standard comparator under fasting conditions in a randomized, 2-way crossover study with a wash-out period of 13 days. Fifteen blood samples were collected from each volunteer over 14 hours and plasma concentrations of cefuroxime were assayed using a validated high performance liquid chromatography method. All data analyses were completed prior to unblinding of the product codes.

Results: The ratio of mean maximum concentration (C max) of the generic cefuroxime compared to the innovator cefuroxime was 108.1% and with 90% confidence limits was within 82.2% to 134.0%. In terms of geometric means, the ratio of the mean maximum concentration (Cmax) was 106.8% and with 90% confidence limits was within 81.8% to 139.5%. The ratio of mean AUC0-t of the generic cefuroxime compared to the innovator was 90.3% which at 90% confidence limits was within 56.9% to 123.7%. In terms of geometric means, the ratio was 89.5% and with 90% confidence limits was within 64.1% to 126.0%. When the mean AUC0-Inf was compared between the two treatments and the ratio was 86.9% and with 90% confidence limits was within 33.5% to 140.3%. In terms of geometric means, the ratio was 69.6%, and with 90% confidence limits was within 46.3% to 104.7%. The 90% confidence limits of the ratio of the Cmax, AUC0-t, AUC0-Inf were not within the prescribed limits of 80% to 125%.

Conclusion: This single dose study found that the generic cefuroxime did not meet the criteria for bioequivalence in these fasting male volunteers.

Keywords: Generic cefuroxime axetil, Innovator cefuroxime axetil, bioequivalence, bioavailability, 2nd generation cephalosporin

Introduction

Cefuroxime is a second generation cephalosporin which attach to penicillin binding proteins and prevents the final transpeptidation steps of the peptidoglycan synthesis. This inhibits bacterial cell wall synthesis and result is bacterial cell death. It has similar or slightly less activity against gram-positive organisms as compared to first generation cephalosporins but greater stability to hydrolysis by beta-lactamases produced by gram-negative bacteria. Cefuroxime is more active against E. coli, K. pneumoniae, P. mirabilis, H. influenzae, some enterobacter, Serratia, anaerobes, Neisseria compared to first generation cephalosporins. It has no activity against Pseudomonas and Enterococci.

It is used for infections due to susceptible organisms such as in respiratory tract infections, urinary tract infections, skin and soft tissue infections, and bone and joint infections.

Cefuroxime is generally well-tolerated. Most common adverse events include gastrointestinal disturbances and hypersensitivity reactions. Rarely, hepatitis and elevated blood urea nitrogen and creatinine may occur. Since its introduction in the mid-1980s, over 200 million patients in 128 countries have received cefuroxime axetil and it has come to be recognized as one of the leading agents in its class (1).

Cefuroxime is absorbed from the gastrointestinal tract and peak plasma concentrations are reached within 2-3 hours after ingestion. Its bioavailability is 37-52%. About 66-100% is excreted as unchanged drug in the urine.

It has been a common practice since the introduction of its generic counterparts to substitute for the innovator mainly due to cost reduction issues. Having established the clinical benefits by the innovator brand, the generic copies need not pass through the same rigorous clinical trials. In some settings however, there is concern regarding efficacy and safety of the generic forms (2). Thus, a number of studies internationally have been conducted and published to determine if indeed locally available cefuroxime axetil have the same bioavailability as the originator brand (3-5). These studies showed that the generic formulations were bioequivalent to the innovator product.

To date, there are about 25 generic versions of Cefuroxime axetil (in the Philippines) (6). However, there are currently no local published data showing comparative performance of the generic product against the innovator brand, especially in terms of bioequivalence. Information
obtained from such study would be essential in validating the quality and therapeutic efficacy of generic cefuroxime at its currently marketed form. The present study was conducted to compare the bioavailability of the test drug, generic cefuroxime axetil 500 mg capsule, with the reference drug, innovator brand cefuroxime axetil 500 mg tablet in healthy Filipino males aged 21 to 45 after single dose administration in fasting conditions.

Materials and Methods

The clinical phase of the study was performed at the facilities of the Philippine General Hospital. The analytical laboratory work was performed at the laboratory facilities of the Department of Pharmacology and Toxicology of the University of the Philippines College of Medicine.

The test formulations employed were as follows: generic Cefuroxime 500 mg capsule manufactured by Asian Antibiotics Inc (Batch no 88739A, Manufacture date September 2006.); and for the reference formulation: Innovator Brand 500 mg tablet, manufactured by Glaxo Wellcome Operations (Batch no. C274, Manufacture date October 2006).

Subjects

Twenty-two (22) healthy male subjects were selected for this study. Potential subjects were screened prior to inclusion into the study and underwent the following procedures: A thorough medical history, physical examination and routine laboratory examinations. Volunteers were excluded as subjects if any one of the following was elicited or observed: recent or chronic smoking history, recent or chronic alcoholic beverage intake, recent or past history of drug abuse, current or recent (i.e., preceding 2 weeks) use of any other systemic drug or medication, any history of chronic or recent illnesses, such as viral hepatitis, liver disease, kidney disease, anemia, cardiac disease, recent infection, dyslipidemia, or allergy to study drugs. Their hematologic, liver function profile all should be within normal limits.

Intervention and Measurements

The biostatistician generated a series of random numbers which will determine which treatment the subject will receive in the first treatment period. One group of subjects received one 500 mg capsule of generic Cefuroxime while the other group received the innovator Cefuroxime 500 mg tablet.

Dinner was provided the night before followed by 10 hours of fasting. Treatments (generic or innovator cefuroxime) were administered around 6:00 AM with 200 mL of water. Breakfast was provided 4 hrs after drug administration while lunch and supper were served 12 noon and 6 pm respectively. Meals were uniform for all the subject participants. Subjects were ambulatory during the study but were prohibited from engaging in any strenuous activity.

Seven mL of blood were extracted at the following 15 time points: 0 hour (pre-dose), 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.5, 5.5, 7.5, 9.5, 11.5, and 13.5 hours after dosing. Blood samples were drawn into evacuated heparinized glass tubes. These samples were transported to the analytical laboratory in cold canisters and centrifuged at 2000 rpm at room temperature for 10 minutes. Plasma was kept frozen at -20°C until assayed. Analysts were blinded to the treatment allocation of the subjects.

After 13 days, the groups were subjected to a complete crossover of the treatment allocations on the next and last session. Hence there were a total of 360 blood samples from the first experiment and an expected 360 number of blood samples from the second experiment after the crossover.

Analysis

The plasma samples were assayed for cefuroxime concentration according to a sensitive, selective and accurate High Performance Liquid Chromatography (HPLC) method. An isocratic reverse-phase liquid chromatography was developed for the determination of cefuroxime axetil in plasma. The method used a direct precipitation separation technique.

The chromatographic system consisted of a Waters Model 510 pump, Waters model 481 variable ultraviolet wavelength absorbance detector connected to ChromJet integrator, Rheodyne injector and a 150 mm stainless steel C18. Peaks were monitored at 225nm. Known amounts of Carbamazepine used as the internal standard was spiked into each blood sample to monitor the accurate recovery of the cefuroxime concentrations from the HPLC determination.

The mobile phase consisted of a mixture of acetonitrile and 0.02M phosphate buffer (72:28) having a pH of 3, passed through a 0.45um glass filter and degassed for 10 minutes. Quantitation was achieved by measuring the peak height ratio of the drug to that of the internal standard. This method was validated according to international guidelines. The limit of quantitation was 1 ug/mL. The coefficient of variation of the intraday, interday and total assay precision was less than 20%.

Pharmacokinetic Parameters and Tests

A bioavailability curve was drawn based on chromatographic data. The following parameters were derived: Area Under the Plasma Concentration Curve (AUC), Maximum Plasma Concentration (Cmax), Time to reach maximum plasma concentration (Tmax), half-life (T1/2) and Elimination Rate Constant (Ke).

Statistical analysis using a parametric general linear model (GLM) was made with the use of a computer program, SAS™ GLM procedure. Using the least square means of the different pharmacokinetic parameters, a standard confidence interval symmetric about the difference between the two means was calculated. At 90% confidence intervals, that limits that were considered bioequivalent were ≥80%-≤125%. The bioequivalence test will be done by comparing the confidence intervals about
the difference between pharmacokinetic measurements of two drugs with a confidence limit constructed from WHO standards. If the confidence interval is entirely within the confidence limit of \( \pm 80\% - \pm 125\% \), the drugs are declared bioequivalent.

## Ethical Considerations

The study was approved by the Ethics Committee of the Research Implementation and Development Office (RIDO) which serves as the institutional review board (IRB) of the University of the Philippines College of Medicine and was conducted in adherence to the Principles of the Declaration of Helsinki and its amendments (7). Informed consent was secured from each and every participant prior to entry into the study.

## Results

Twenty-four (24) healthy adult male volunteers from a total of forty-four (44) screened volunteers were deemed fit to participate in the study based on the set inclusion and exclusion criteria. The 24 volunteers were initially randomized into 2 treatment sequences; all of the 24 qualified volunteers were available for the 1st session, but only 22 returned for the second session. The final number of evaluable study subjects was 22. Table 1 shows the patient characteristics of the population studied.

### Table I. Demographic Data of subjects of the Cefuroxime bioequivalence study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>27.45</td>
<td>±6.61</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.93</td>
<td>±7.07</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.49</td>
<td>±5.85</td>
</tr>
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</table>

Both the innovator and generic cefuroxime were well tolerated by the subjects and no adverse effects were reported. The participants were closely observed by the physicians tasked to monitor the occurrence of any adverse event.

The mean maximum plasma concentrations (\( C_{max} \)) for the generic cefuroxime and the innovator cefuroxime were comparable to the innovator cefuroxime. The \( C_{max} \) of the generic cefuroxime was 30.33 mcg/mL and the \( C_{max} \) of the innovator drug was 28.05 mcg/mL and were not significantly different (p=0.5952). The mean time to reach maximum concentration (\( T_{max} \)) for the generic cefuroxime and the innovator cefuroxime were 3.68 hrs and 4.11 hrs respectively and were not significantly different (p=0.5952). The mean area under the curve to last reading (\( AUC_{0-t} \)) for the generic cefuroxime and the innovator cefuroxime were 185.30 mcg/mL and 205.11 mcg/mL respectively and were not significantly different (p=0.0943). The mean area under the curve extrapolated to infinity (\( AUC_{0-\infty} \)) for the generic cefuroxime and the innovator cefuroxime with values of 459.55 mcg/ml and 528.97 mcg/ml respectively (p=0.6761).

There was no significant difference (p=0.2512) between the treatments when mean half-life (\( t_{1/2} \)) was compared. The mean half-lives which were 12.00 and 19.05 hours respectively for generic cefuroxime and the innovator cefuroxime did not differ significantly although the half-life of the latter appeared relatively longer. There were significant differences in mean rate of elimination (\( K_e \)) between the two treatments (p=0.0030) with generic cefuroxime having a \( k_e \) of 0.12/hr and innovator cefuroxime having a \( K_e \) of 0.06/hr respectively.

Using the innovator cefuroxime as reference (Table 3), the ratio of mean maximum concentration (\( C_{max} \)) of the generic cefuroxime was 108.1% and with 90% confidence limits was within 82.2% to 134.0%. In terms of geometric means (Table 3), the ratio of the mean maximum concentration (\( C_{max} \)) was 106.8% and with 90% confidence limits was within 81.8% to 139.5%. The ratio of mean \( AUC_{0-t} \) was 90.3% which at 90% confidence limits was within 56.9% to 123.7%. In terms of geometric means, the ratio was 89.5% and with 90% confidence limits were within 64.1% to 125.0%. When the mean \( AUC_{0-\infty} \) was compared, the ratio was 86.9% with 90% confidence limits was within 33.5% to 140.3%. In terms of geometric means, the ratio was 69.6%, and at 90% confidence limits, was within 46.3% to 104.7%.

### Table II. Summary of Mean (± SD) Pharmacokinetic Parameters of the Generic Cefuroxime and the Innovator Cefuroxime

| Parameters | Generic Cefuroxime | Innovator Cefuroxime | Mean Ratio | 90% confidence interval for % mean ratio | Pr>|t| | Power (%) |
|------------|-------------------|---------------------|------------|----------------------------------------|------|--------|
| Tmax ± SD (hrs) | 3.68±0.85 | 4.11±0.87 | 90.3% | 56.9% to 139.5% | 0.6761 | 0.1332 |
| Cmax ± SD (mcg/mL) | 30.33±18.63 | 28.05±20.69 | 86.9% | 56.9% to 123.7% | 0.6234 | 0.1524 |
| AUC0-t ± SD (mcg-h/mL) | 185.30±136.61 | 205.11±172.57 | 89.5% | 64.1% to 125.0% | 0.5738 | 0.2299 |
| AUC0-∞ ± SD (mcg-h/mL) | 459.55±645.92 | 528.97±531.39 | 90.3% | 46.3% to 140.7% | 0.2512 | 0.0827 |
| Kel ± SD (hrs) | 0.12±0.07 | 0.06±0.04 | 88.1% | 64.1% to 125.0% | 0.6736 | 0.1875 |

## Table III. Summary of statistical analysis with treatment B (innovator) as the reference

| Parameter | Generic Cefuroxime | Innovator Cefuroxime | Mean Ratio | 90% confidence interval for % mean ratio | Pr>|t| | Power (%) |
|------------|-------------------|---------------------|------------|----------------------------------------|------|--------|
| Cmax (mcg/mL) | 30.33 | 28.05 | 108.1% | 82.2% to 134.0% | 0.6761 | 0.1332 |
| GLCMax (mcg/mL) | 23.70 | 22.19 | 106.8% | 81.8% to 139.5% | 0.6736 | 0.1875 |
| GLCMax (mcg/mL) | 185.30 | 205.11 | 90.3% | 64.1% to 125.0% | 0.5738 | 0.2299 |
| GLAUC (mcg/mL) | 138.64 | 154.85 | 90.3% | 64.1% to 125.0% | 0.6234 | 0.1524 |
| GLAUC (mcg/mL) | 459.55 | 528.97 | 88.1% | 64.1% to 125.0% | 0.5738 | 0.2299 |
| Kem (mcg/mL) | 0.12 | 0.06 | 88.1% | 64.1% to 125.0% | 0.6736 | 0.1875 |
| Half-life (hrs) | 12.00 | 9.0-117.0 | 90.3% | 56.9% to 123.7% | 0.2512 | 0.0827 |
Discussion and Conclusion

Two orally administered medicinal products are considered bioequivalent if they are pharmaceutically equivalent and their rate and extent of availability after administration in the same molar dose are similar to such a degree that their effects can be expected to be essentially the same.

This study showed that the test drug Cefuroxime 500 mg capsule was not bioequivalent to the innovator Cefuroxime 500 mg tablet. Although the values of the mean $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ of the generic cefuroxime were not statistically different from those of the innovator cefuroxime, the generic cefuroxime showed a shorter half-life as well as a faster rate of elimination as compared to the innovator product. Since cefuroxime is a time-dependent antibiotic and maximizing the duration of exposure of the bacteria to the drug is a determinant of efficacy, the above mentioned differences may result in decreased bacterial eradication and possible clinical failure. Also, the confidence intervals for the ratios of the mean $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$ indicated that these values are not within the bioequivalence accepted range of 80-125%.

This single dose study found that the generic cefuroxime did not meet the criteria for bioequivalence in these fasting male participants.

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References

6. MIMS Philippines 120th edition 2009