Bioequivalence Evaluation of Two Brands of Cefixime 100 mg Capsule (Suprax and Alpha-Cefixime) in Korean Healthy Volunteers

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Abstract – Cefixime is an orally absorbed cephalosporin with a broad spectrum of activity against Gram-negative bacteria and is highly resistant to beta-lactamase degradation. The purpose of the present study was to evaluate the bioequivalence of two cefixime capsules, Suprax capsule (Dong-A Pharmaceutical Co., reference drug) and Alpha-Cefixime capsule (Alpha Pharmaceutical Co., test drug), according to the guidelines of Korea Food and Drug Administration (KFDA). Twenty-four normal subjects, 23.5±3.72 years in age and 68.3±8.89 kg in body weight, were divided into two groups and a randomized 2×2 cross-over study was employed. There was a one week washout period between the doses. After one capsule containing 100 mg of cefixime was orally administered, plasma was taken at predetermined time intervals and the concentrations of cefixime in plasma were determined using HPLC with UV detector. The pharmacokinetic parameters such as AUC₀–₉, C₉₀₀₉ and T₉₀₀₉ were calculated and ANOVA test was utilized for the statistical analysis of the parameters. The results showed that the differences in AUC₀–₉, C₉₀₀₉ and T₉₀₀₉ between two products were -3.91%, -2.23% and -3.18%, respectively, when calculated against the reference drug. The 90% confidence intervals using logarithmically transformed data were within the acceptance range of log0.8≤δ≤log1.25 (e.g., log0.8786≤δ≤log1.0523 and log0.8889≤δ≤log1.0512 for AUC₀–₉ and C₉₀₀₉, respectively). The 90% confidence intervals using untransformed data was within ±20% (e.g., -10.37%≤δ≤6.73% for T₉₀₀₉). All parameters met the criteria of KFDA for bioequivalence, indicating that Alpha-Cefixime capsule (Alpha Pharmaceutical Co.) is bioequivalent to Suprax capsule (Dong-A Pharmaceutical Co.).

Key words □ bioequivalence, cefixime, suprax, cross-over study

INTRODUCTION

Cefixime is an oral third-generation cephalosporin antibiotic. The drug has been clinical effective in treating otitis media, respiratory tract infections and uncomplicated urinary tract infections due to susceptible organisms (Lacy et al., 1993; Sweetman, 2002). Cefixime has bioavailability of about 50%. Following oral administration of cefixime with food, the total amount absorbed is not altered but the time to maximal concentration is increased by 0.8 hours (Faulkner et al., 1988; Montay et al., 1991). Therapeutic plasma concentrations for cefixime have not been defined, but depending on the dose, peak plasma concentrations of 1-4 µg/mL or 19-77 µg/mL were measured with single or multiple doses of 200 mg and 400 mg, respectively (Faulkner et al., 1988; Montay et al., 1991). Peak plasma concentrations normally occur within 2-6 hours after single oral doses (Faulkner et al., 1988; Montay et al., 1991). The drug has a half-life of 3-4 hours, and a relatively low proportion (15-20%) of a dose is excreted by the renal route (Faulkner et al., 1988; Mamzoridi et al., 1996).

The purpose of this study was to evaluate the bioequivalence of two cefixime capsules, Suprax capsule (reference drug) and Alpha-Cefixime capsule (test drug) in 24 Korean healthy volunteers, according to the guidelines of Korea Food and Drug Administration (Korea Food and Drug Administration, 2005). Typical bioavailability, including AUC₀–₉, the area under the plasma concentration-time curve from 0 until the last sampling time, 12 hr), C₉₀₀₉ (the maximum plasma concentration) and T₉₀₀₉ (time to reach C₉₀₀₉) parameters were compared.

MATERIALS AND METHODS

Test and reference products

The test product was Alpha-Cefixime capsule (100 mg of
cefixime, lots no. 338501, Alpha Pharmaceutical Co., Seoul, Korea). The reference product was Suprax capsule (100 mg of cefixime, lots no. 5285, Dong-A Pharmaceutical Co., Seoul, Korea).

Subjects

This bioequivalence study involved 24 Korean healthy subjects. The mean age of subjects was 23.5±3.72 years, with a range of 21–30 years, mean body weight was 68.3±8.89 kg, with a range of 52–91 kg, mean height was 173.0±19.4 cm, with a range of 159–183 cm. All the subjects were enrolled after passing a clinical examination, including a physical examination and laboratory tests (plasma analysis: hemoglobin, hematocrit, WBC, platelets, WBC differential, blood urea nitrogen, total bilirubin, cholesterol, total protein, albumin, alkaline phosphatase, glucose, ALT, AST, and AST; and urine analysis: specific gravity, color, pH, sugar, albumin, bilirubin, RBC, WBC, and casts). Any with potential hypersensitivity to this type of medication, a history of the hepatic, renal, or cardiovascular disease, of chronic alcohol consumption or other medications was excluded. This criteria was applied to eliminate the source of variation which can influence the pharmacokinetics of the drug. All the subjects were restricted not to take using other drugs from at least one week before the study and until the completion of the study. They also refrained from alcoholic beverages and xanthine-containing foods and beverages 48 h after the study, until the completion of the study. They also refrained from alcoholic beverages and xanthine-containing foods and beverages 48 h after the study, until the last sampling time.

Each subject received an oral dose of 100 mg of cefixime in a standard 2×2 cross-over design with one-week washout period between each treatment phase. Subjects were randomly divided into two equal groups and assigned to one of the two sequences between each treatment phase. Subjects were randomly divided and assigned to one of the two sequences of drug administration. The study was approved by a local ethics committee. All the subjects signed a written informed consent, in accordance with the Korea Guidelines for Bioequivalence Tests.

Drug administration and sample collection

The subjects were hospitalized (Chosun University Hospital, Gwangju, Korea) at 7:00 p.m. the day before drug administration. At 7:00 a.m., the median cubital vein was cannulated and 1 mL of heparinized injectable normal saline solution was flushed into the cannula to prevent blood clotting. The doses were taken at 8:00 a.m. on each dosing day with 240 mL of drinking water. Four hours after oral administration, all the subjects were given standard meals. The subjects were not allowed to take a supine position or to sleep until 4 h after drug administration. Approximately 5 mL blood samples were collected before and 1, 2, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 h after drug administration. The cannula was flushed with 1 mL of heparinized injectable normal saline solution after each blood sampling. The blood sample was centrifuged immediately, and the plasma was frozen at -70°C until the HPLC analysis. After one week period washout, the study was repeated in the same way to complete cross-over study.

HPLC analysis of cefixime in plasma

The concentrations of cefixime in plasma were performed using a reported HPLC method (Falkowski et al., 1987) on a Shimadzu chromatographic system (Kyoto, Japan). The mobile phase involved a mixture of phosphate buffer (10 mmol/L), pH=2.6 and acetonitrile (86:14 v/v), pumped at a flow rate of 1.0 mL/min through the column (Capcell Pak C18 MG 4.6×100 mm, Shiseido, Tokyo, Japan) at room temperature. Peaks were monitored by UV absorbance at 280 nm. Cefixime stock solution (1 mg/mL in methanol) was serially diluted with methanol and added at drug-free plasma to obtain concentrations of 100, 200, 500, 1000, 2000, and 5000 ng/mL. These standard solutions were employed for the preparation of calibration graphs. To assess the intra-day coefficient of variation (CV) and accuracy for plasma samples, samples of cefixime were spiked into human plasma at final concentrations of 100–5000 ng/mL. Limit of detection (LOD) was determined from signal to noise ratio (S/N)=3 and lower limit of quantitation (LLOQ) from S/N=10. The precision and accuracy for inter-day assay were assessed at the same concentration and repeated for five different days. After thawing at room temperature, an aliquot of each sample (500 µL) was pipetted into an eppendorf tube and 20 µL of internal standard solution (7-hydroxycoumarin, 100 µg/mL in water) was added. After vortexing briefly, 500 µL of 6% trichloroacetic acid was added to each sample. The mixture was shaken and centrifuged at 13,000 rpm for 5 min. A 50 µL of the supernatant was injected into the HPLC system.

Pharmacokinetic analysis

Each subject received oral dose of 100 mg of cefixime in a standard 2×2 cross-over model in a randomized order. Pharmacokinetic parameters such as $AUC_{0\rightarrow\infty}$, $C_{max}$ and $T_{max}$ were calculated from plasma concentration-time curve. $C_{max}$ and $T_{max}$ were calculated by trapezoidal formula in 0–12 h using Excel program.