Study on Pharmacokinetics and Bioequivalence of Cefdinir Dispersible Tablet in Healthy Chinese Volunteers

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Abstract

Aim: To evaluate the pharmacokinetics and bioequivalence of cefdinir dispersible tablet with cefdinir capsule in healthy Chinese volunteers.

Methods: Cefdinir dispersible tablet and cefdinir capsule were used as the test and reference preparations respectively. Two randomized, comparative two-way crossover studies were conducted in 18 healthy Chinese male volunteers. Test preparation 200mg, reference preparation 200mg were administered once orally to the volunteers fasting overnight, with 5 days washout period between the doses of the test and reference preparations. Before dosing blood sample, after dosing several blood samples were collected for a period of 12 hours. The plasma concentrations of cefdinir at different times were determined by high performance liquid chromatograph (HPLC) with ultraviolet (UV) assay. Pharmacokinetic parameters were calculated. Safety of the drug was evaluated.

Results: The main pharmacokinetic parameters of the test and reference preparations were as follows: Cmax were 1.52±0.48μg/ml and 1.42±0.39μg/ml; Tmax were 3.08±0.73h and 3.22±0.81h; t1/2 were 2.04±0.53h and 1.87±0.29h; AUC appeared were 7.12±1.85 μg•h/ml and 6.86±1.60μg/ml•h; AUC∞ were 7.67±2.01μg•h/ml and 7.38±1.85μg•h/ml respectively. The relative bioavailability of test preparation was 103.53±11.5%. No significant differences between two preparations were found. The parameter mean values of the pharmacokinetic characteristics for test drug were within the bioequivalence acceptable range of 80~125% and 70~143% respectively for AUC and Cmax.

Conclusion: The results indicate that the test preparation is bioequivalent to the reference preparation.

Keywords: Bioequivalence; Pharmacokinetics; HPLC; Cefdinir; Dispersible tablet

Introduction

Cefdinir is one of the third generation cephalosporins which have broad spectrum antibacterial activity. Cefdinir has activity against Gram-positive and Gram-negative bacteria. It is also effective against β-lactamase producing strains of haemophilis and neisseria. This drug is used to treat wide variety of sensitive bacteria infections, especially for mild and moderate infections [1]. To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefdinir, it should be used only to treat or prevent infections that are proven or strongly suspected to be caused bacteria. Cefdinir capsule, tablet and suspension are available in the market for several years [2]. Now, cefdinir dispersible tablet is investigated to determine whether it is bioequivalent to other cefdinir preparations [3-5]. Cefdinir dispersible tablet disintegrates very fast and disperses homogenously, it is easily to be absorbed, and highly effective. The purpose of this study was to determine the pharmacokinetics and bioequivalence between cefdinir dispersible tablet (test preparation) and cefdinir capsule (reference preparation) and to ascertain the safety in medical practice.

Materials and Methods

Drugs and reagents

The test preparation, cefdinir dispersible tablet, was supplied by Tianjin Zhongyang Pharmaceutical Company Ltd.; Batch No.050401 as 100mg per tablet. The reference preparation, cefdinir capsule, was manufactured by Tianjin Zhongyang Pharmaceutical Company Ltd.; Batch No. 050402 as 100mg per capsule. The standard substance of cefdinir was supplied by National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People’s Republic of China, Batch No.130502-200401, purity 98.3%. Internal standard cefadroxil, purity 95.0% was supplied by Nationa Institute for the Control of Pharmaceutical and Biological Products, Beijing, People’s Republic of China, Batch No.0431-9501. Acetonitrile and methanol were HPLC grade. Potassium dihydrophosphate and phosphoric acid were analytical grade. Double distilled water was used in the preparation of all reagents and mobile phase throughout the study.

Approved procedure

The study was conducted in accordance with good clinical practice (GCP) guidelines of State Food and Drug Administration in China [6], and The Declaration of Helsinki (as revised in Edinburgh 2000).

The study was approved by Independent Ethical Committee of Tianjin Medical University. Written informed consent was obtained from all subjects after the medical supervisor of the clinical trial explaining the aim, course, and possible risks of the study prior to participation.

Study subjects

18 healthy Chinese male volunteers were selected in this study. The subjects ranged in age from 20–24 (22±1) years old, height from...
The study consisted of Agilent 1100 HPLC (Agilent Technologies Inc., USA), CAY-1 vortex (Beijing Chang-an Instrument Company), chromatographic column: Kromasil ODS, 250×4.6 mm, 5μm (Dalian Chemical Physics Institute, Academy of Sciences, China), Serial No. C18 B040905.

The mobile phase used was acetonitrile 0.015M-KH₂PO₄ (use phosphoric acid adjust pH=3.8) (V/V 15:85) at flow rate 1 ml/min; wave length of UV detector: 280nm. Injection volume was 20μl. 60μl of 31.35μg/ml internal standard cefadroxil was added to 0.3ml of plasma sample and then 550μl cold methanol was added to the plasma sample. Vortex for 1 min. After mixing well, centrifuged for 15min at 3500rpm. Supernatant was aspirated and transferred into another test tube, then 2ml of dichloro-methane was added. Vortex for 1min, centrifuged for 10min at the speed of 12000rpm. 20μl of the supernatant was injected into HPLC system for analysis.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated from plasma concentration-time by non-compartmental methods. The maximum plasma concentration (Cₘₐₓ) and time to maximum plasma concentration (Tₘₐₓ) were obtained directly from the observed concentration-time profiles. Linear trapezoidal rule was used to estimate the area under the plasma concentration versus time curve (AUC) from 0 to the last measurable concentration (AUCₜₐₜₚₜ). The area under the plasma concentration versus time curve from 0 to infinity (AUC₀→∞) was calculated as AUCₜₐₜₚₜ + Ct/Ke, where Ct was the last measurable concentration. Ke was the elimination rate constant. The terminal elimination half-life (t½) was calculated as 0.693/Ke.

Bioavailability (F) was calculated according the equation: F=[AUC₀→∞(test)/AUC₀→∞(reference)]×100%.

Statistical analysis

All data were expressed as mean±standard deviation (SD), t-test was used as statistical process. AUC₀→∞, AUC₀→tₚₜ, Cₘₐₓ and tₘₐₓ were considered as primary variables for the aim of bioequivalence analysis. The bioequivalence of two products were assessed by means of an analysis of variance (ANOVA) for crossover design, paired two one-sided t-test, and calculating standard 90% confidence intervals of reference drug. The parameter Tₚₜₚₜ was analyzed with Wilcoxon’s rank sum test.

The products were considered bioequivalent, if the difference between two compared parameters was statistically insignificant (P>0.05) and the mean values of the product fall within 90% confidence intervals of the reference drug for AUC and Cₘₐₓ, that are the ranges accepted by State Food and Drug Administration of China [6]. All statistical tests

Figure 1: A. HPLC chromatogram of blank plasma; B. Blank plasma spiked with cefdinir and internal standard; C. Plasma sample of volunteer after administration of cefdinir, and spiked with internal standard.
used a 5% level of significance to determine significance. All P values cited were 2-tails.

Results

Method validity

The analytical method used for measurement of cefdinir in plasma was proved to be accurate and sensitive. The regression equation was described as Y=0.9032X+0.0001 (r=1.0016, n=3) (Y: peak area ratio of cefdinir and internal standard [S/IS], X: plasma concentration of cefdinir), using (1/C) weighted least-square regression. The linear relationship was obtained from the peak area between cefdinir (plasma concentration from 0.065 to 8μg/ml) and internal standard (r=1.0016), the lower limit of quantitation (LOQ) was 0.0625μg/ml. The intra-day and inter-day coefficients of variation (CV%) for these three quality control standard (0.125, 1, 8μg/ml) were 4.41% and 6.01% respectively. The total precision was 5.21%. The intra-day and inter-day accuracy for these three quality control standard (0.125, 1, 8μg/ml) were 105.48±1.98% and 106.90±6.48% respectively. Total accuracy was 106.19±5.57%. The mean absolute recovery was 95.38±4.27%. The retention time for cefdinir dispersible tablet (test) and cefdinir capsule (reference) were 2.04±0.53 and 2.10±0.32 hours. The mean concentration-time profiles of two preparations were closely similar (Figure 2).

The pharmacokinetic parameters of cefdinir after a single oral dose of 200mg cefdinir dispersible tablet (test) and cefdinir capsule (reference) were given to 18 healthy Chinese male volunteers in a randomized, two-treatment, two-period crossover study. The plasma drug concentrations were determined by the validated HPLC with UV assay. It was a specific, sensitive and reproducible procedure and a suitable, valuable tool in the assessment of pharmacokinetics and bioavailability of cefdinir dispersible tablet. The present pharmacokinetic study indicated that both preparations were readily absorbed from gastrointestinal tract with a Tmax of approximately 3 hours. The mean concentration-time profiles of two preparations were closely similar (Figure 2).

The statistic analysis showed that there were no significant difference for pharmacokinetic parameters Cmax, tmax, t1/2, AUC0-t, AUC0-∞ between two preparations (P>0.05). The 90% confidential interval of AUC0-t, AUC0-∞, Cmax of reference drug were 6.28–7.78μg/ml•h, 6.82–8.30μg/ml•h and 1.19–1.84μg/ml respectively. The 90% confidential interval of the AUC and Cmax were within the range of 80%–125% and 70%–143% respectively. The means of AUC0-t, AUC0-∞, and Cmax for the test drug were all within the 90% CIs of reference drug. According to the bioequivalence criteria, these two preparations were bioequivalent [6].

Safety evaluation

Test and reference preparations were well tolerated at the dose administered by all volunteers. No adverse events occurred in this study. During the study none of the changes in laboratory test values and vital signs were considered clinically important and the biochemical parameters were within the reference range. There were no dropouts for the volunteers.

Discussion

A single oral dose of 200mg cefdinir dispersible tablet and cefdinir capsule were given to 18 healthy Chinese male volunteers in randomized, two-treatment, two-period crossover study. The plasma drug concentrations were determined by the validated HPLC with UV assay. It was a specific, sensitive and reproducible procedure and a suitable, valuable tool in the assessment of pharmacokinetics and bioavailability of cefdinir dispersible tablet. The present pharmacokinetic study indicated that both preparations were readily absorbed from gastrointestinal tract with a Tmax of approximately 3 hours. The mean concentration-time profiles of two preparations were closely similar (Figure 2).

The pharmacokinetic parameters of two preparations in this study were similar to that of other reports [3-5]. Compare the pharmacokinetic parameters of other reports with this study, the results were shown in Table 2.

Their tmax, t1/2 were similar. Cmax of same dosage of cefdinir (200mg) were similar, Cmax of 400mg cefdinir dispersible tablet was larger than that of 200 mg and 100mg cefdinir dispersible tablet. AUC0-t of same dosage of cefdinir (200mg) were similar. AUC0-∞ of 400mg cefdinir dispersible tablet was larger than that of 200mg, 100mg cefdinir dispersible tablet. Parameters of cefdinir in healthy volunteers are different from that of hemodialysis patients [9]. The dosage for renal failure patients was 100mg and the dosage for healthy volunteers in this study was 200mg. The mean t1/2, during hemodialysis for the patients was significantly less (2.76± 1.01h) than that in the test without dialysis (16.95± 1.20 h). t1/2 for healthy subjects was shorter (2.04± 0.53h) than that of hemodialysis patients (2.76± 1.01h). AUC0-∞ in the test with dialysis was 43% (30.18± 12.03μg/ml•h ) of that in the test without
hemodialysis. It was still larger than that of healthy volunteers (7.67±2.01 μg/ml•h⁻¹). For the safety of the volunteers, cephalosporin skin testing has been undertaken before volunteers were selected to enroll in this trial. The positive and negative predictive values of the results are less well established than those of penicillin [10]. Throughout the whole study period, there were no adverse events reported.

In the study, $C_{\text{max}}$, $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ of two preparations did not differ suggesting the plasma profiles generated by the test preparation were comparable to those of the reference preparation. ANOVA, after log-tranformation of the data, showed no statistically significant difference between two preparations (P>0.05). From the result of bioequivalence analysis, the parametric mean values of the pharmacokinetic characteristics for test drug were within the bioequivalence acceptable ranges of 80–125% and 70–143% respectively for $\text{AUC}$ and $C_{\text{max}}$. These results were confirmed by Schuirmann’s two one-sided t tests, which indicated that the lower and upper limits of the calculated t value were greater than the critical t value for $\text{AUC}_{0-t}$, $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$. Therefore, two cefdinir preparations can be considered bioequivalent.

PK/PD research for antimicrobial agents is very important and it is same for cefdinir. If we want to evaluate the pharmacologic effects of cefdinir, it is necessary to perform the pharmacodynamics and pharmacokinetics of this drug. The important PK/PD parameters for cefdinir are time over MIC and $\text{AUC}/\text{MIC}$, especially time over MIC, because this drug is time-dependent, but it is not necessary to supply PK/PD parameters for cefdinir BE application in China.

In conclusion, cefdinir dispersible tablet and cefdinir capsule are bioequivalent, and these two preparations can be believed to have same therapeutic effect in medical practice.

References