BIOEQUIVALENCE OF TWO FEXOFENADINE FORMULATIONS IN HEALTHY HUMAN VOLUNTEERS AFTER SINGLE ORAL ADMINISTRATION

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Received: April 24, 2006; Accepted: January 26, 2007

Key words: Fexofenadine/HLPC/AUC/Bioequivalence/Pharmacokinetics

Aim: A randomized, two-way, crossover, bioequivalence study was conducted in 25 fasting, healthy, male volunteers to compare two brands of fexofenadine 180 mg tablets, FEXOFENADINE 180 mg Film Tablet (Drogosan A.S., Ankara, Turkey) as test and Telfast® 180 mg Tablet (Aventis Pharma, Frankfurt am Main, Germany) as a reference product.

Method: One tablet of either formulation was administered after 10 h of overnight fasting. After dosing, serial blood samples were collected during a period of 48 hours. Plasma samples were analysed for fexofenadine by a validated HPLC method. The pharmacokinetic parameters AUC_{0-48} , $AUC_{0-\infty}$, C_{max} , T_{max} , K_{el} , $T_{1/2}$, and CL were determined from plasma concentration-time profiles for both formulations and were compared statistically.

Results and Conclusions: The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90 % confidence intervals (CI) fell within the acceptable range, satisfying the bioequivalence criteria of the FDA. Based on these statistical inferences it was concluded that the two brands exhibited comparable pharmacokinetics profiles and that Drogosan's Fexofenadine is equivalent to Telfast® of Aventis Pharma, Frankfurt am Main, Germany.

INTRODUCTION

Fexofenadine is a selective and peripherally acting H_1 -receptor antagonist. In clinical studies this non-sedating antihistamine has been found to relieve symptoms associated with allergic conditions such as seasonal allergic rhinitis^{1,2}. Results of clinical safety and efficacy trials with fexofenadine HCl doses up to 240 mg twice daily in patients with seasonal rhinitis have further demonstrated its safety, indicating a large therapeutic window for this drug³. The drug effect is seen within 1 hr, achieving maximum effect at 6 hr, and lasting a minimum of 12 hr after medication^{4,5}, and the drug can be used for long periods without evidence of intolerance⁶.

The objective of this study was to evaluate, in healthy volunteers, the bioequivalence (BE) of a test formulation of the 180 mg (tablets) of fexofenadine HCl manufactured by Drogosan A.S., Ankara, Turkey (FEXOFENADINE 180 mg Film Tablet) and a commercial formulation of 180 mg (tablets) of fexofenadine HCl (Telfast® produced by Aventis Pharma, Frankfurt am Main, Germany) used as a reference formulation.

METHODS

Study design and healthy volunteers

Twenty-five healthy adult male volunteers aged between 18 and 50 years (26.3 ± 6.2 years, mean $\pm$ S.D.)

and within 15% of the ideal body weight, weight between 67.0 and 111.0 kg (80.8 ± 10.1), and height between 170 and 198 cm (184.0 ± 7.4), were selected for the study.

All subjects gave written informed consent and the Local Ethics Committee (Hospital and Polyclinic in Mělník) approved the clinical protocol. All volunteers were assessed as healthy based on medical history, clinical examination, blood pressure, ECG and laboratory investigation (hematology, blood biochemistry and urine).

The study was conducted in a randomized, single-dose, two-way, cross-over design with a two-week wash-out period between two doses. During each period, the volunteers were admitted to hospital and after overnight fasting they received a single reference or test 180 mg fexofenadine tablet. Low-carbonate water (240 mL) was given immediately after drug administration. All volunteers fasted 4 h after the drug administration, and then they received a snack. Standardized meals (lunch, afternoon snack, dinner and breakfast) were provided to volunteers 6, 9, 12 and 24 hr after dosing.

The study was performed in accordance with the guidelines of the revised Declaration of Helsinki on biomedical research involving subjects and the requirements of Good Clinical Practice.

Formulations and sample collection

The following formulations were employed: FEXOFENADINE 180 mg Film Tablets (lot number 4100001, expiration date 10/2006) as test formulation,

Fig. 1. Fexofenadine plasma mean concentrations versus time profile obtained after single oral administration of 180 mg of fexofenadine tablet formulation.

and Telfast® 180 mg Tablets (lot number 40D264, expiration date 03/2007) as reference formulation.

Blood (9 ml) was sampled from antecubital or cubital veins and collected into sodium citrate-containing tubes before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours after the administration of each fexofenadine tablet formulation (180 mg). The blood samples were centrifuged at 2500 g for 10 min at 4 °C and the separated plasma was collected and stored at -20 °C until drug analysis. After a wash-out period of 14 days, the study was repeated in the same manner to complete the cross-over design.

Drug analysis

All plasma samples were analysed for fexofenadine concentration according to a sensitive, selective, and accurate high-performance liquid chromatography (HPLC) method, which was developed and validated before the study at the laboratories of I.Q.A..

The chromatographic separations and quantitative determination were performed using a high-performance liquid chromatograph from Agilent Technologies (HPST, Prague, Czech Republic): Model 1100 series, equipped with a degassing unit, quaternary pump, autoinjector, UV detector, and controlled by Agilent Chem. Station software. Chromatographic separation was performed using an Eclipse XDB-C₁₈ (150 × 4.6 mm id.; 5 µm particle

size) HPLC column from Agilent Technologies (HPST, Prague, Czech Republic). The mobile phase consisted of acetonitrile and potassium dihydrogen phosphate (0.05 mol/l, pH 5.0). The mobile phase was eluted at a flow rate of 1.5 ml/min at 50 °C. UV detection of fexofenadine and the internal standard (cetirizine) was performed at 195 nm. Each analysis required a maximum of 12 min. The calibration curves were linear over a range of 10–1000 ng/ml using 1.0 ml plasma samples. All samples from each volunteer were measured on the same day in order to avoid inter-assay variation.

Pharmacokinetic and statistical analysis

Pharmacokinetic analysis was performed by means of a model-independent method using the GraphPad Prism (rev. 2.01), Lotus Approach and Lotus 1-2-3 (rev. 9) computer programs. The maximum fexofenadine plasma concentration ($C_{\max}$) and the corresponding time of peak plasma concentration ($T_{\max}$) were taken directly from the individual plasma data. The elimination rate constant (K_{el}) was estimated from the slope of the semilogarithmic plot of the terminal phase of the plasma concentration-time curve calculated by linear regression, and the elimination half-life ($T_{1/2}$) was generated by dividing $\ln 2$ by the elimination rate constant K_{el} . The area under the plasma concentration-time curve AUC_{0-48} and the area to the infinity $AUC_{0-\infty}$ were calculated using the linear trapezoidal method. Extrapolation of these areas to infinity ($AUC_{0-\infty}$) was done by adding the value $C_{\text{last}}/k_{\text{el}}$ to the calculated AUC_{0-48} (where C_{last} = the last detectable concentration). The clearance (CL) was calculated using the following equation (dose/body wt)/ $AUC_{0-\infty}$.

For the purpose of bioequivalence analysis, a two-way analysis of variance (ANOVA, GLM procedure) was used to assess the effect of formulations, periods, sequences, and subjects on AUC_{0-48} , $AUC_{0-\infty}$ and $C_{\max}$. The difference of two related parameters was considered statistically significant for $p < 0.05$.

RESULTS AND DISCUSSION

Both fexofenadine formulations (FEXOFENADINE and Telfast 180 mg tablets) were well tolerated in all subjects; unexpected serious adverse events that could

Table 1. Arithmetic and geometric means and 90 % confidence intervals (90 % CI) of $C_{\max}$, AUC_{0-48} and $AUC_{0-\infty}$ (log transformed) of fexofenadine during single dose administration of 180 mg test and reference formulations in 25 healthy male subjects.

Fexofenadine	Arithmetic mean		Geometric mean		90 % CI	Acceptable range
	Test	Reference	Test	Reference		
$C_{\max}$ (ng/ml)	625.0	629.5	544.0	550.9	83.72–116.49	80–125
AUC_{0-48} (ng.hr/ml)	2965.0	3028.0	2673.0	2744.0	85.85–110.53	80–125
$AUC_{0-\infty}$ (ng.hr/ml)	2954.0	3012.0	2666.0	2734.0	86.07–110.47	80–125

have influenced the outcome of the study did not occur. There was no drop-out and all subjects who started the study continued to the end and were discharged in good health.

Both medications were readily absorbed from the gastrointestinal tract and fexofenadine was already measurable at the first sampling time (0.5 hr) in all the volunteers. The plasma drug concentration-time curves show that the mean concentrations of fexofenadine were similar for the two formulations over the 48-hr sampling period (Fig. 1).

The results after statistical analysis of the main pharmacokinetic parameters are shown in Table 1. The parametric 90 % confidence intervals for the main pharmacokinetic parameter values of $C_{\max}$, AUC_{0-48} and $AUC_{0-\infty}$ lie entirely within the BE acceptance limits approved by EMEA and FDA (i.e. 80 % to 125 %). The mean fexofenadine values were $T_{\max}$ 1.84 ± 0.87 hr; K_{el} 0.2368 ± 0.0290 1/hr; $T_{1/2}$ 2.97 ± 0.32 hr and CL 76.55 ± 40.01 L/hr for the test formulation, and $T_{\max}$ 1.86 ± 0.77 hr; K_{el} 0.2382 ± 0.0223 1/hr; $T_{1/2}$ 2.94 ± 0.29 hr and CL 76.64 ± 42.7 L/hr for the reference formulation. Based on the nonparametric Wilcoxon test and the paired t-test, there were no significant differences (at $p > 0.05$) in $T_{\max}$, K_{el} , $T_{1/2}$, and CL values for either formulation.

CONCLUSION

The mean bioequivalence of 180 mg fexofenadine tablets of the test formulation compared to the reference formulation was confirmed. Ninety % CI of AUC_{0-48} , $AUC_{0-\infty}$ and $C_{\max}$ ratios of fexofenadine of these two prepa-

rations fell within the 80–125 % interval proposed by the US FDA⁷. Both formulations were equivalent in terms of rate and extent of absorption. Consequently, bioequivalence between the two formulations can be concluded.

ACKNOWLEDGEMENTS

We thank the Hospital and Policlinic Mělník medical and paramedical staff for their valuable contribution.

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