SYNOPSIS

INN: FEXOFENADINE

Study number: M016455I/1114

Study title: A Multicenter Study of the Pharmacokinetics of Oral Fexofenadine Hydrochloride Administered as a Granulation Powder in Applesauce to Children from 2 through 5 Years of Age

CSR date: 15 December 2003

The study results and synopsis are supplied for informational purposes only.

Not all of the study results have necessarily been reviewed by the Regulatory Authorities.

The decision to prescribe and take a product should always be made on the basis of the most recent version of the product information and product package insert in the country of prescription.
STUDY SYNOPSIS

**Study number**  M016455I/1114

**Title**
A multicenter study of the pharmacokinetics of oral fexofenadine hydrochloride administered as a granulation powder in applesauce to children from 2 through 5 years of age

**Investigator(s), study site(s)**
Multicenter, three sites participating in the Pediatric Pharmacology Research Unit network

**Study duration and dates**
The first subject was enrolled on 14 March 2000 and the last subject completed the study on 28 June 2000.

**Phase** I

**Objectives**

**Primary objective:** To characterize the pharmacokinetics of fexofenadine following a single oral dose of fexofenadine HCl 30 mg and following twice a day dosing for 4 to 7 days in children 2 through 5 (≥ 2, <6) years of age.

**Secondary objective:** To characterize the safety and tolerance of fexofenadine HCl 30 mg administered twice a day for 4 to 7 days in children 2 through 5 (≥ 2, <6) years of age.

**Study design**
This study was a multicenter, open-label, multiple-dose study with pharmacokinetic sampling after a single dose and after twice-a-day dosing for 4 to 7 days.

**Population**
This study was conducted in children 2 through 5 years of age who were candidates for antihistamine therapy or who had tolerated a therapeutic course of antihistamine therapy within the preceding 12 months without adverse effects. A total of 26 subjects were enrolled in the study.

**Treatments**
Fexofenadine HCl 30 mg was to be given orally as a granulation powder in applesauce once daily on day 1, followed by fexofenadine HCl 30 mg given orally twice daily for an additional 4 to 7 days.

All subjects were to receive the same treatment. Subjects were assigned a subject number at the time they received the first dose of study medication. Based on their subject number, subjects were assigned to one of two groups for sparse pharmacokinetic sampling on the last day of multiple dosing. Subjects with an odd subject number were assigned to Group I for pharmacokinetic sampling predose and 2 hours postdose and subjects with an even subject number were assigned to Group II for pharmacokinetic sampling predose and 4 hours postdose.
Pharmacokinetic data

Serial pharmacokinetic blood samples were to be collected in all subjects prior to and at various intervals up to 24 hours after administration of the first dose on day 1. After twice daily administration of fexofenadine for an additional 4 to 7 days, blood samples were to be drawn for pharmacokinetic analysis according to one of two sampling schemes: immediately prior to the last dose and at 2 hours postdose (Group I), or immediately prior to the last dose and at 4 hours postdose (Group II).

Safety data

Age-appropriate physical exams, vital signs, and clinical laboratories were to be performed at the screening visit and within 3 days following collection of the final pharmacokinetic blood sample. Adverse events were to be monitored throughout study conduct.

Statistical procedures

In the first report (Report No. K2000CLN0016), fexofenadine plasma concentrations following the first dose were analyzed using noncompartmental techniques. All subjects completing serial sampling were to be included in the noncompartmental analysis. Subjects with partial data were to be evaluated on a case-by-case basis to determine if sufficient data were available for meaningful analysis. Pharmacokinetic parameters calculated included, but were not limited to, $C_{\text{max}}$, $t_{\text{max}}$, AUC(0-\(\infty\)) , AUC(0-\(z\)) , and $\text{CL}_{po}$. Pharmacokinetic parameters and plasma concentrations were summarized descriptively.

In this report, population pharmacokinetic parameters, including intrasubject and intersubject variability, were estimated from the fexofenadine plasma concentrations collected following the first dose and at steady state using nonlinear hierarchical models. The goal of the population analysis was to compare the steady-state data to single dose. All subjects who completed at least 4 days of multiple dosing and who had at least 2 pharmacokinetic samples after multiple dosing were included in the population analysis. Subjects were to be excluded on a case-by-case basis if it was determined that the subject was not compliant in dosing to the extent that it would bias the pharmacokinetic analysis.

The modeling approach followed the guidelines set forth in Ette and Ludden (1995) and Bruno et al. (1996). Model selection was based on physiological and pharmacological rationale and the principle of parsimony – simpler models were chosen over more complex models when statistically justified (Wade et al., 1994). First, exploratory data analysis was undertaken to examine the basic structure of the concentration-time data and to identify any outliers. Second, population pharmacokinetic models were developed without covariates. Using conditional estimation methods, individual pharmacokinetic parameter estimates were obtained. Third, individual covariates were screened to determine if there was any relationship between individual pharmacokinetic parameter estimates and individual covariates. Fourth, any significant covariates identified previously were entered into the population model to identify the population model that best described the data. Lastly, once the final model was identified, individual pharmacokinetic parameter estimates were again estimated and summarized by descriptive statistics.

The frequency of adverse events was tabulated. Baseline, end-of-study, and change from baseline clinical laboratories and vital signs were summarized.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.1.
Interim analysis

On 5 May 2000, following approximately 7 weeks of recruitment, data from available subjects were cleaned and finalized. Report number K2000CLN0016, dated 5 July 2000, presented the noncompartmental analysis of fexofenadine plasma concentrations following the single oral dose of study medication as well as all safety data collected for that interval. As this was an open-labeled study, review of interim data did not bias the final analysis.

Results – Study subjects and conduct

Twenty-six subjects (14 males and 12 females) from 2 through 5 years of age were enrolled in this study and received study medication on day 1. Subjects were equally distributed across age groups with 7 subjects in the 2 to <3 year old group; 5 subjects in the 3 to <4 year old group; 7 subjects in the 4 to <5 year old group; and 7 subjects in the 5 to <6 year old group. One subject discontinued the study for personal reasons on day 1. Thus 25 subjects completed the study according to the protocol. There were no major protocol deviations for the study. Concomitant illnesses ongoing at study start included allergic rhinitis in 11 subjects; asthma in 10 subjects; eczema, allergies, and sinusitis in 2 subjects each. A total of 10 subjects received concomitant medication while taking study medication. Three subjects received counteractive treatment for an adverse event. A total of 8 subjects received continuing treatment of asthma as follows: 4 subjects received treatment with both albuterol and Flovent® (fluticasone propionate) inhalers, 2 subjects received treatment with albuterol in normal saline, 1 subject received treatment with Azmacort® (triamcinolone acetonide), albuterol, and Intal® (cromolyn sodium) in nebulizer, and 1 subject received treatment with Intal®.

Results – Pharmacokinetics

Nonlinear mixed-effects (NONMEM) models examined were the one- and two-compartment pharmacokinetic models with instantaneous (i.v. models) or first-order (oral models) absorption. A two-compartment oral model with intersubject variability on apparent oral clearance, apparent central volume and apparent peripheral volume was selected as the BASE MODEL. The intersubject variability of different pharmacokinetic parameters was found independent of each other. The typical value of population clearance in children from 2 to 5 years of age under the base model from this study was 39.7 L/h with CV% of 31.9%. The typical population values of apparent central volume and peripheral volume were 26.2 L and 484 L.

The potential covariates screened for use in the population pharmacokinetic model included age, weight, height, body surface area, body mass index, sex, race, presence of concurrent medication, and presence of on-going disease. The influence of steady state was tested as covariate in the model as well.

The inclusion of body surface area as a predictor of apparent oral clearance significantly improved the goodness of fit and predictability of the model. Apparent oral clearance increased with body surface area at the rate of 54.8 L/h.m². No other covariate was found significant to be included in the model. Age was not identified as a significant covariate to fexofenadine pharmacokinetics in children from 2 to 5 years of age. There is no significant change in fexofenadine pharmacokinetics from single dose of 30 mg to steady state after twice daily doses of 30 mg.
Results – Safety

Of the 26 subjects exposed to study medication, 13 (50.0%) reported TEAEs in a total of 8 system organ classes. The system organ class with the highest incidence of TEAEs was gastrointestinal disorders. The most common TEAE was rhinorrhea and was reported in 3 (11.5%) fexofenadine HCl subjects.

Following the current ICH guidelines for reporting of serious TEAEs, there were no serious TEAEs reported. There were no discontinuations from the study due to adverse events and no deaths reported during the study.

There were 7 occurrences in 6 subjects of predefined change abnormal laboratory values at poststudy: 1 occurrence each of a decrease in albumin, potassium, and absolute neutrophils; and 1 occurrence each of an increase in alkaline phosphatase, absolute lymphocytes, absolute eosinophils, and potassium. There were no clinically meaningful changes observed in mean laboratory values from baseline to poststudy.

No trends or clinically relevant changes were observed in vital sign data.

The medication given in this study (30 mg fexofenadine hydrochloride) was well tolerated in 2- through 5-year-old pediatric subjects.

The recoding of adverse events data in MedDRA did not change the safety profile of fexofenadine HCl, and the nature of adverse events reported remain consistent with those reported in the original study report.

Conclusions

- The population pharmacokinetic model best describing the data (base model) was a two-compartment oral model having an exponential residual error and intersubject variabilities on apparent oral clearance, apparent central volume and apparent peripheral volume.

- Base model population parameter estimates agreed with previous fexofenadine pharmacokinetic studies in children from 6 to 11 years of age. The typical value of population clearance in children from 2 to 5 years of age under the base model from this study was 39.7 L/h with CV% of 31.9%. The typical population values of apparent central volume and peripheral volume were 26.2 L and 484 L, respectively.

- Inclusion of body surface area as covariate to apparent oral clearance under the base model significantly improved the goodness of fit and predictability of the model. Apparent oral clearance increased with body surface area at the rate of 54.8 L/h.m².

- Age was not found to have a significant influence on the population pharmacokinetics of fexofenadine in children from 2 to 5 years of age.

- Fexofenadine pharmacokinetics in children from 2 to 5 years of age did not change significantly from single dose of 30 mg to steady state after twice daily doses of 30 mg from 5 to 7 days.

- The medication given in this study (30 mg fexofenadine hydrochloride) was well tolerated in 2- through 5-year-old pediatric subjects.

- The recoding of adverse event data did not change the safety profile of fexofenadine HCl.