

Allergens, IgE, mediators, inflammatory mechanisms

The clinical pharmacology of fexofenadine in children

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Fexofenadine, a newly synthesized H₁-receptor antagonist that is also the active metabolite of terfenadine, is reported to be free of adverse cardiovascular and central nervous system effects.¹ Here, we report a double-blind, two-way crossover study of its clinical pharmacology.

METHODS

This study was approved by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research. Assent from the child and written informed consent from the parents were obtained.

Except for a history of allergic rhinitis with or without mild asthma, subjects were healthy, as assessed by history, physical examination, 12-lead electrocardiogram, complete blood count, blood chemistry tests, and urinalysis. Before and during the study, medications other than low-dose inhaled glucocorticoids and albuterol were restricted for an appropriate length of time.

On 2 different study days 1 week apart, after fasting overnight, the children received 30 or 60 mg of fexofenadine in capsule form with 150 ml water. No placebo was given because of the crossover study design and the need to limit the number of invasive tests. A two-lead electrocardiogram and measurement of vital signs were performed before dosing and 2.5 hours afterward.

On each study day, a blood sample for plasma fexofenadine quantitation was collected from an indwelling intravenous catheter before and 1, 2, 3, 6, 8, 24, and 48

hours after the dose was given. Fexofenadine concentrations were determined by using a validated liquid chromatography/mass spectrometry assay with a lower limit of quantitation of 1 ng/ml and a precision of 5.5% to 9.7%.¹ Calibration curves were linear over the range of 1 to 500 ng/ml. Before each fexofenadine dose was given and at 1, 2, 3, 6, 8, and 24 hours afterwards, epicutaneous tests with histamine phosphate (1.0 and 10.0 mg/ml) were performed, as previously described.² Pharmacokinetic data and wheal and flare areas were analyzed.² Safety was assessed subjectively and by evaluation of electrocardiogram rhythm strips.

RESULTS

Fourteen children (13 boys) with a mean age of 9.8 ± 1.8 years, a mean height of 134 ± 12.6 cm, and a mean weight of 32.1 ± 9.3 kg received fexofenadine.

Fexofenadine was rapidly absorbed, with maximum plasma concentrations of 178 ± 22 ng/ml and 286 ± 34 ng/ml ($p < 0.05$) after the 30 and 60 mg doses, respectively, occurring at 2.4 ± 0.2 hours (Fig. 1, A). After administration of 30 and 60 mg of fexofenadine, the areas under the plasma fexofenadine concentration versus time plot from time 0 to time of final measurable plasma concentration were, respectively, 1090 ± 125 ng/ml/hr and 1892 ± 129 ng/ml/hr ($p < 0.05$), indicating no dose-dependent kinetics in the dose range studied.

The mean clearance rates did not differ ($p > 0.05$) after the 30 and 60 mg doses and were, respectively, 14.4 ± 2.0 ml/min/kg and 18.4 ± 2.4 ml/min/kg. Also, the mean terminal elimination half-life values did not differ ($p > 0.05$) after the 30 and 60 mg doses and were, respectively, 18.3 ± 2.0 hours and 17.6 ± 1.0 hours. In calculating these values, plasma fexofenadine concentrations measured at 24 and 48 hours were included. The apparent volumes of distribution at steady state were 5.4 ± 0.7 L/kg and 5.8 ± 0.7 L/kg ($p > 0.05$), after the 30 and 60 mg doses, respectively.

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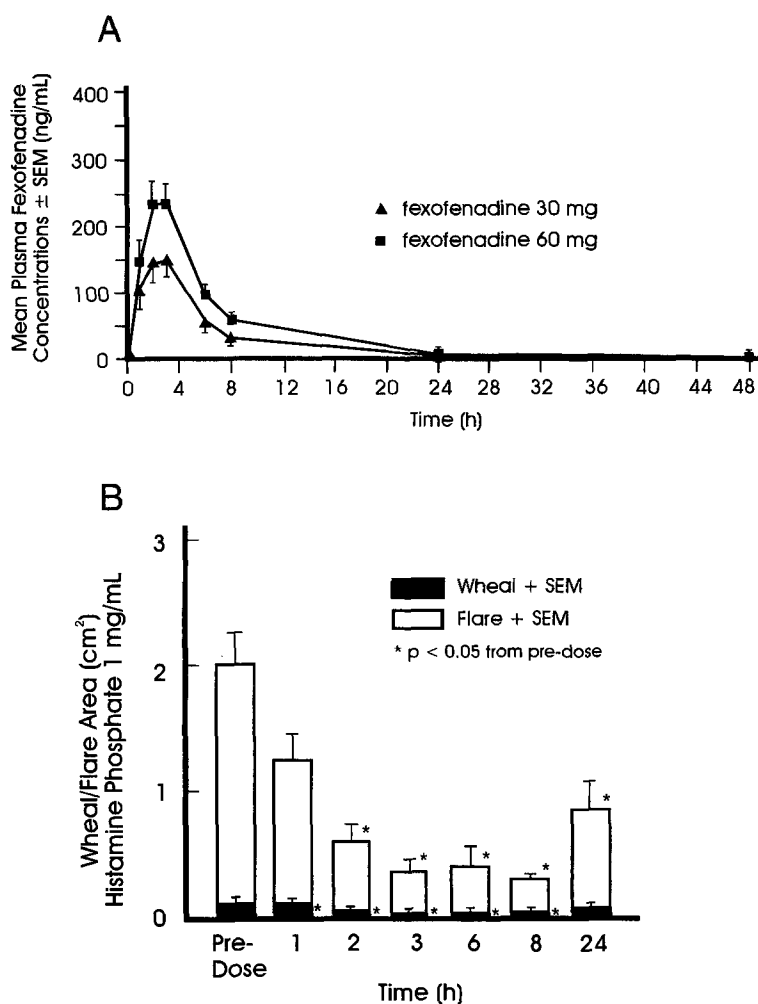


FIG. 1. A, Mean $\pm$ SEM plasma fexofenadine concentration versus time plots after administration of 30 mg or 60 mg of fexofenadine by mouth. **B,** After ingestion of 30 mg of fexofenadine, wheals induced by 1 mg/ml histamine phosphate were significantly suppressed from 1 through 8 hours, and flares were suppressed from 2 through 24 hours.

After ingestion of 30 mg of fexofenadine, wheals induced by 1 mg/ml histamine phosphate were suppressed ($p < 0.05$) from 1 to 8 hours, and flares were suppressed ($p < 0.05$) from 2 to 24 hours (Fig. 1, B); when 10 mg/ml histamine phosphate was tested, wheals and flares were suppressed ($p < 0.05$) from 2 to 8 hours. After ingestion of 60 mg of fexofenadine, wheals induced by 1 mg/ml histamine phosphate were suppressed ($p < 0.05$) from 1 to 24 hours, and flares were suppressed ($p < 0.05$) from 2 to 8 hours; when 10 mg/ml histamine phosphate was tested, wheals were suppressed ($p < 0.05$) from 1 to 8 hours, and flares were suppressed ($p < 0.05$) from 2 to 24 hours.

DISCUSSION

The pharmacokinetics of fexofenadine found in children are similar to those reported in adults, in whom the mean terminal elimination half-life is 14 hours (plasma concentrations monitored for only 12 hours).¹ This is not surprising, because 80% of a dose is eliminated unchanged in the feces, and about 10% is eliminated unchanged in the urine.³ In contrast, H_1 -receptor antagonists, which are extensively metabolized in the hepatic cytochrome P450 system, usually have shorter terminal elimination half-life values in children than in adults.⁴

In our study fexofenadine, 30 or 60 mg, suppressed the histamine-induced wheal-and-flare within 1 to 2 hours. Depending on the fexofena-

dine dose administered and the histamine concentration used in the skin tests, suppression was significant in three of the eight tests at 24 hours. The mean maximal suppression produced by the 30 and 60 mg doses was similar. Dosing regimens of fexofenadine 60 mg once daily or 30 mg twice daily would be expected to produce sustained effective peripheral H₁-histamine receptor blockade in children.

No child experienced any serious adverse effects, although one reported somnolence 10 hours after ingestion of 30 mg of fexofenadine. No abnormalities were found in any electrocardiogram rhythm strip performed as a safety precaution at times of peak plasma concentrations. Fexofenadine, unlike its parent compound, terfenadine, has not been reported to cause prolongation of the QTc interval in human beings. In vitro, on a cloned delayed rectifier K⁺ channel from human heart, the blocking effect of fexofenadine is 583-fold less potent than that of terfenadine.⁵

In summary, in children administration of 30 or 60 mg of fexofenadine is effective in suppressing the wheal-and-flare and is well tolerated. Further studies of its efficacy and safety are in progress.

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