

H₁-antihistaminic activity of cetirizine and fexofenadine in allergic children

Simons FER, Semus MJ, Goritz SS, Simons KJ. H₁-antihistaminic activity of cetirizine and fexofenadine in allergic children. *Pediatr Allergy Immunol* 2003; 14:207–211. ©2003 Blackwell Munksgaard

The clinical pharmacology of H₁-antihistamines has not yet been optimally studied in children and other special groups of patients. Our objective was to determine the onset, extent, and duration of H₁-antihistaminic activity of cetirizine and fexofenadine in the pediatric population. We performed a prospective, randomized, placebo-controlled, double-blind, crossover, single-dose study of these H₁-antihistamines in 15 allergic children, mean $\pm$ SEM age 8.8 ± 0.5 years. We used suppression of the histamine-induced wheal and flare as the primary outcome. Compared with pre-dose baseline, cetirizine 10 mg suppressed the wheals significantly ($p \leq 0.05$) from 2 to 24 h and the flares significantly from 1 to 24 h, achieving $77 \pm \text{SEM } 10\%$ to $86 \pm 9\%$ suppression of the wheal from 2 to 7 h and $85 \pm 6\%$ to $88 \pm 6\%$ suppression of the flare from 2 to 24 h, inclusive. Compared with baseline, fexofenadine 30 mg did not suppress the wheals or flares significantly at any time, achieving $40 \pm 9\%$ to $54 \pm 9\%$ wheal suppression from 2 to 7 h and $45 \pm 11\%$ to $68 \pm 9\%$ flare suppression from 2 to 7 h, inclusive. Compared with placebo, cetirizine suppressed the wheals and flares significantly from 2 to 24 h. Compared with placebo, fexofenadine suppressed the wheals significantly at 4 and 6 h, and the flares from 4 to 7 h. Cetirizine suppressed the wheals and flares significantly more than fexofenadine at 2 h (wheals), and at 3 and 24 h (flares). Placebo did not suppress the wheals and flares significantly at any time. In children age 6–11 years, cetirizine 10 mg has a rapid onset of H₁-antihistaminic activity, a 24-h duration of action, and greater H₁-activity than fexofenadine 30 mg. Higher doses of fexofenadine should be tested in children.

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Key words: cetirizine; fexofenadine; H₁-antihistamine;
histamine; wheal; flare; children

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Accepted 2 September 2002

H₁-antihistamines are widely used for the treatment of allergic disorders in children. The evidence base for their use is strongest in allergic rhinoconjunctivitis and in urticaria (1). Clinical pharmacology studies of H₁-antihistamines provide objective information about the onset of action, duration of action, and the relative amount of H₁-activity of these medications (2).

We hypothesized that the H₁-antihistamine cetirizine, which is well studied in infants and children (3–13) and is widely available in a pediatric formulation, as well as the newer H₁-antihistamine fexofenadine (14–16), for which a pediatric formulation is being developed, would have similar clinical pharmacology profiles in children. Here, we report a prospective, randomized, placebo-controlled, double-blind, crossover,

single-dose study of cetirizine and fexofenadine in children, using suppression of the histamine-induced wheal and flare as the primary outcome.

Methods

The study protocol was approved by the University of Manitoba Research Ethics Board. Before enrollment, written consent for each child's participation was obtained from his/her caregiver, and written assent was obtained from the child. Children were eligible for inclusion if they were age 6–11 years, non-obese, non-smokers, and in good health except for allergic rhinitis with or without mild asthma. For 30 days before, and during, the study, the only oral medications permitted were the test doses of cetirizine and

fexofenadine. Low-dose intranasal or inhaled glucocorticoids (≤ 400 $\mu\text{g/day}$ total inhaled and intranasal glucocorticoids) and as-needed inhaled salbutamol, which do not suppress histamine skin tests, were allowed.

Cetirizine 10 mg (Reactine[®], Pfizer Canada Inc., Kirkland, QC, Canada), fexofenadine 30 mg (Allegra[®] 60 mg tablet [halved using a precision tablet cutter] Aventis Pharma, Inc., Laval, QC, Canada) (17), or placebo was administered in a Latin Square design crossover sequence. On study days at least 1 week apart, and after an overnight fast, the encapsulated H_1 -antihistamine or placebo, with up to 180 ml of clear liquid, was administered by the research nurse coordinator. A standardized breakfast was given 2 hours after dosing and a standardized lunch was served 4–5 h after dosing.

Epicutaneous tests with histamine phosphate 1 mg/ml were performed on the volar surfaces of the forearms using sterilized, disposable straight needles (Coates & Clark, Greer, SC, USA) and the prick-through drop technique. The sequence of test sites was identical in all participants. Tests were performed before medication or placebo was administered at approximately 0800 h, at 15-min intervals during the first hour afterwards, at hourly intervals thereafter for 7 h, and at 24 h. At baseline, and at 1 and 24 h, the tests were performed in duplicate to assess reproducibility of the test, and the test results at these times were averaged.

Each time the skin tests were performed, children were asked how they felt and were observed for possible adverse effects. All information obtained was noted in the case record forms.

Wheal and flare circumferences were traced at 10 min with a fine-tipped pen and transferred to

paper using transparent tape. Under double-blind study conditions, all skin tests and tracings of wheal and flare circumferences were made by the same nurse, and all wheal and flare tracings were digitized and the areas calculated by the same investigator (MS) (6).

The histamine-induced wheal and flare areas were analyzed as absolute values and as percent decrease compared with baseline. For all comparisons, we used two-way analysis of variance (ANOVA) and the Tukey and Bonferroni multiple-range tests, using wheal and flare areas at each time, within medication and between medication, by time as the criteria of classification. Differences within and between medications were considered to be significant at $p \leq 0.05$.

Results

Fifteen children (8 boys, 7 girls) with allergic rhinitis, mean age $8.8 \pm 0.5 \pm \text{SEM}$ years and mean weight 30 ± 2 kg completed the study. There were no dropouts. There was no significant difference in the pre-dose baseline wheal and flare areas on the cetirizine, fexofenadine, and placebo treatment days (Figs 1 and 2).

Compared with pre-dose baseline, cetirizine 10 mg produced significant suppression of the wheals from 2 to 24 h (Fig. 1), with 77 ± 10 to $86 \pm 9\%$ suppression from 2 to 7 h, inclusive (Fig. 3), and significant suppression of the flares from 1 to 24 h (Fig. 2), with 85 ± 6 to $88 \pm 6\%$ suppression from 2 to 24 h, inclusive (Fig. 4). Compared with pre-dose baseline, fexofenadine 30 mg did not produce significant suppression of the wheals or flares, but achieved a maximum of 40 ± 9 to $54 \pm 9\%$ suppression from 2 to 7 h (Fig. 3), and 45 ± 11 to $68 \pm 9\%$ suppression of

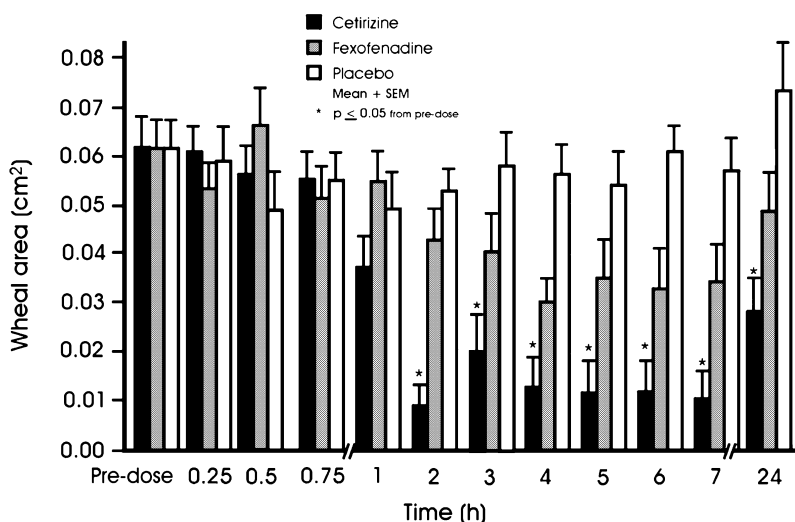


Fig. 1. Mean + SEM wheal areas after epicutaneous histamine phosphate 1 mg/ml: suppression by cetirizine, fexofenadine, and placebo. *Indicates a significant difference ($p \leq 0.05$) from pre-dose baseline wheal areas.

Fig. 2. Mean + SEM flare areas after epicutaneous histamine phosphate 1 mg/ml: suppression by cetirizine, fexofenadine, and placebo. *Indicates a significant difference ($p \leq 0.05$) from pre-dose baseline flare areas.

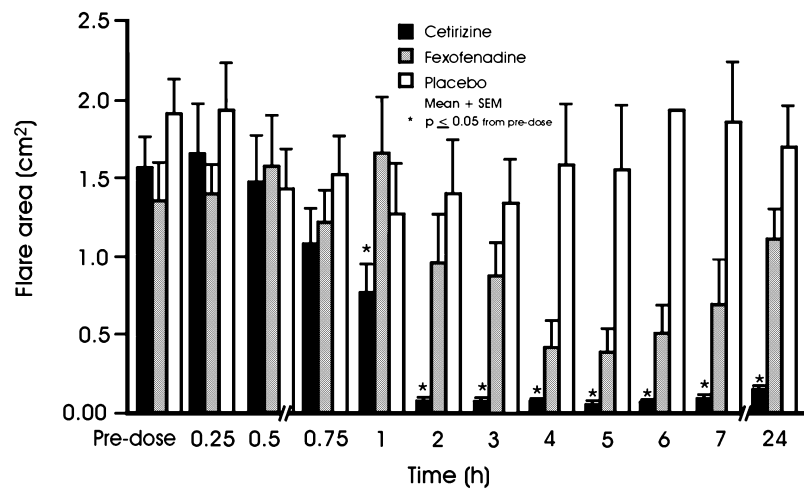


Fig. 3. Mean + SEM percent suppression of histamine-induced wheals by cetirizine, fexofenadine and placebo, compared with pre-dose baseline values. *Indicates a significant difference ($p \leq 0.05$) from placebo; **indicates a significant difference ($p \leq 0.05$) from fexofenadine.

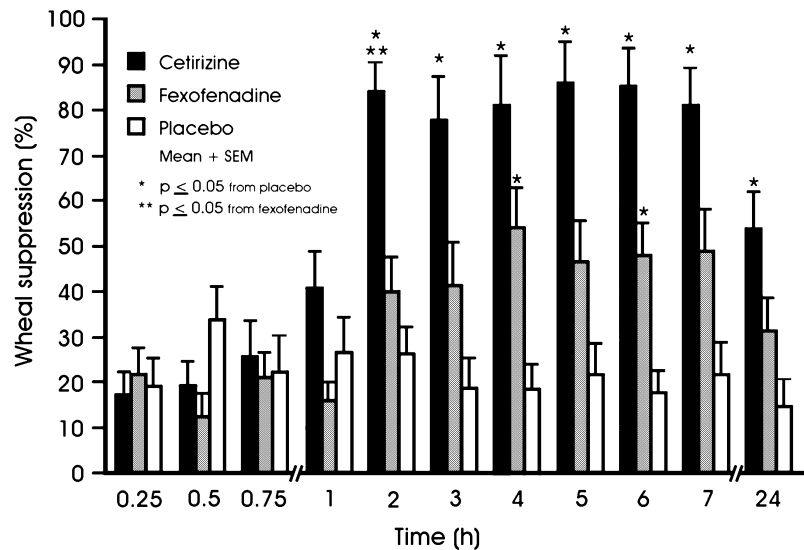
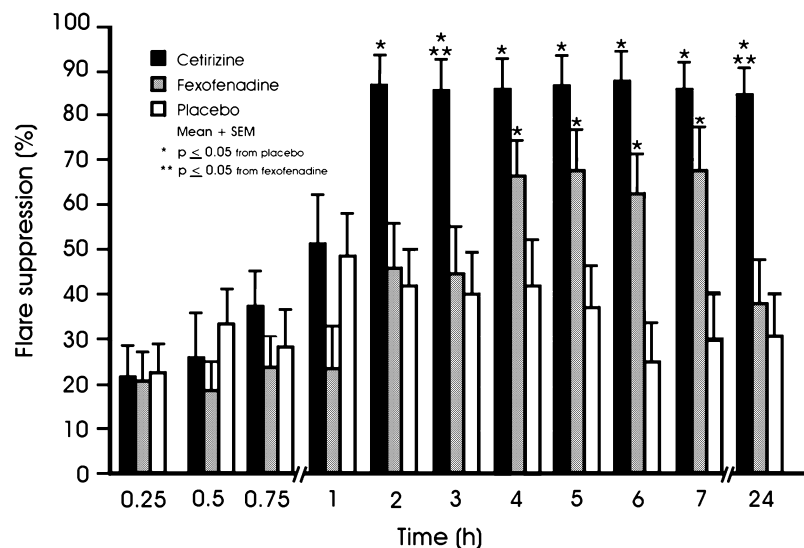


Fig. 4. Mean + SEM percent suppression of histamine-induced flares by cetirizine, fexofenadine and placebo, compared to pre-dose baseline values. *Indicates a significant difference ($p \leq 0.05$) from placebo; **indicates a significant difference ($p \leq 0.05$) from fexofenadine.



the flares from 2 to 7 h, inclusive (Fig. 4). Compared with pre-dose baseline, placebo did not produce any significant suppression of the wheals, with a maximum suppression of 26% at 2 h (Fig. 3), or any significant suppression of the flares, with a maximum suppression of 49% at 1 h (Fig. 4).

Compared with placebo, cetirizine suppressed the wheals and flares significantly from 2 to 24 h. Compared with placebo, fexofenadine suppressed the wheals significantly at 4 and 6 h, and the flares from 4 to 7 h. Cetirizine suppressed the wheals significantly more than fexofenadine at 2 h, and suppressed the flares significantly more than fexofenadine at 3 and 24 h.

No serious adverse effects occurred. Mild transient fatigue occurred in nine children on the cetirizine treatment day, nine on the fexofenadine treatment day, and seven on the placebo treatment day. Mild transient headache occurred in three children on the cetirizine treatment day, four on the fexofenadine treatment day, and three on the placebo treatment day.

Discussion

Clinical pharmacology research in children presents unique challenges. During recruitment to the study, truly informed consent about the nontherapeutic nature of the research must be obtained from the parents, and assent must be obtained from the child. Caregiver concerns regarding potential side-effects of medications, inclusion of a placebo day, absence from school because of study participation, and frequent performance of procedures must be addressed (18). During the study itself, presence/absence, severity and onset/offset of subjective symptoms, including adverse effects, must be ascertained and interpreted by the caregiver and the medical personnel involved (19). Special expertise is required for performance of technical procedures, even minimally invasive ones such as epicutaneous tests, and for interpretation of tests. The medical staff must be alert and responsive to the possibility of withdrawal of consent from the caregiver, or withdrawal of assent from the child, as evidenced by tearfulness or reluctance to have a test or procedure performed.

Despite these challenges, the clinical pharmacology of some first-generation H₁-antihistamines [chlorpheniramine (20), brompheniramine (21), diphenhydramine (22), hydroxyzine (23), ketotifen (24)] and some non-sedating, second-generation H₁-antihistamines [cetirizine (3–6), fexofenadine (14), ebastine (25), and loratadine (6, 26, 27)] has been documented in children.

Cetirizine, the best-studied H₁-antihistamine in children (3–13), is approved for use in patients aged 2 years and older, and has been widely available in a pediatric formulation for several years. The manufacturers' recommended dose for children age 6–11 years is 5 or 10 mg once daily (17). Fexofenadine, a newer H₁-antihistamine, now also being studied in children (14–16), is approved for use in patients aged 6 years and older, and a pediatric formulation is being developed. The manufacturers' recommended dose for children age 6–11 years is 30 mg twice daily (17).

Here, for the first time, we compare the H₁-activity of cetirizine and fexofenadine in a pediatric population, in a three-way crossover study. We used a relatively painless bioassay involving objective epicutaneous tests with histamine phosphate, which were performed with careful attention to detail. We have obtained clinically useful information with regard to the onset of H₁-activity and duration of H₁-activity of cetirizine and fexofenadine. Cetirizine suppressed the wheals and flares promptly and had a duration of action of 24 h after administration of a single dose, confirming that once-daily dosing is a reasonable recommendation for children aged 6–11 years. The onset, duration, and amount of H₁-activity of cetirizine found in this study were similar to those reported previously in a comparative clinical pharmacology study of cetirizine and loratadine in children (6).

The results of the present study confirm that the currently recommended pediatric dose of fexofenadine, 30 mg, does indeed need to be administered twice daily as per the manufacturer's instructions, as there was no significant suppression of the histamine-induced wheal and flare 24 h after a single 30 mg dose of this medication. Although fexofenadine 30 mg twice daily has been proven to be safe and effective in children with seasonal allergic rhinitis (15, 16), our data suggest that higher doses should be investigated in children. It is of interest that the fexofenadine dose currently recommended by the manufacturer for children ages 6–11 years, 30 mg twice daily, is only one-third to one-half of the 'adult' fexofenadine doses recommended worldwide (60 mg bid, 120 mg od, or 180 mg od). In contrast, based on clinical pharmacology studies (3) and clinical trials (1, 7), 'adult' doses of cetirizine, 5–10 mg od (17), are recommended for children aged 6–11 years.

In summary, clinical pharmacology studies such as this offer a unique opportunity to determine the ideal pediatric dose and dose regimen of H₁-antihistamines.

Acknowledgments

This study was funded by a research grant from Pfizer Inc., New York, NY. We acknowledge the assistance of Dr X. Gu.

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