

Clinical pharmacology of the H₁-receptor antagonists cetirizine and loratadine in children

Simons FER, Johnston L, Simons KJ. Clinical pharmacology of the H₁-receptor antagonists cetirizine and loratadine in children.

Pediatr Allergy Immunol 2000; 11: 116–119. © Munksgaard, 2000

H₁-receptor antagonists are widely used in children but are not as well-studied in children as they are in adults. Our objective was to determine the onset and duration of action and the relative potency of the H₁-receptor antagonists cetirizine and loratadine in children. We performed a prospective, randomized, placebo-controlled, double-blind, crossover, single-dose study of cetirizine and loratadine using suppression of the histamine-induced wheal and flare as the primary outcome. In 15 allergic children, mean age 9 years, compared with baseline, cetirizine (10 mg) suppressed the wheals and flares significantly from 0.25 to 24 h, achieving nearly 100% of flare suppression from 2 to 24 h, inclusive, and loratadine (10 mg) suppressed the wheals and flares significantly from 0.75 to 24 h, inclusive. Cetirizine suppressed the wheals and flares significantly more than loratadine from 0.25 to 1 h, inclusive, and at 0.5, 1, 2, 3, 5, 6, 7, and 24 h, respectively. Placebo also suppressed the wheal and flare significantly at some assessment times. Cetirizine and loratadine both have excellent antihistaminic activity in children, with a rapid onset of action and a 24-h duration of action in this population.

**F. Estelle R. Simons^{1,2},
Lana Johnston¹ and
Keith J. Simons^{2,3}**

¹Health Sciences Clinical Research Center,
²Faculty of Medicine, ³Faculty of Pharmacy,
University of Manitoba, Winnipeg, Manitoba,
Canada

Key words: cetirizine; loratadine; H₁-receptor antagonist; antihistamine

Dr F.E.R. Simons, 820 Sherbrook Street,
Winnipeg, Manitoba, Canada, R3A 1R9
Tel.: 204-787-2440
Fax: 204-787-5040

Accepted 8 December 1999

During the past 50 years, H₁-receptor antagonists have been widely used to relieve symptoms of allergic disorders in children, especially the nasal itching, discharge, congestion and sneezing of allergic rhinitis, the itching, redness and tearing of allergic conjunctivitis, and the itching and whealing of urticaria (1). Their primary mechanism of action is blockade of H₁-receptors on post-capillary venules, leading to decreased vasodilation, vascular permeability, and tissue edema (2). They also block H₁-receptors on the thin, unmyelinated, extensively branching afferent C-fibres in the skin, leading to relief of itching (3).

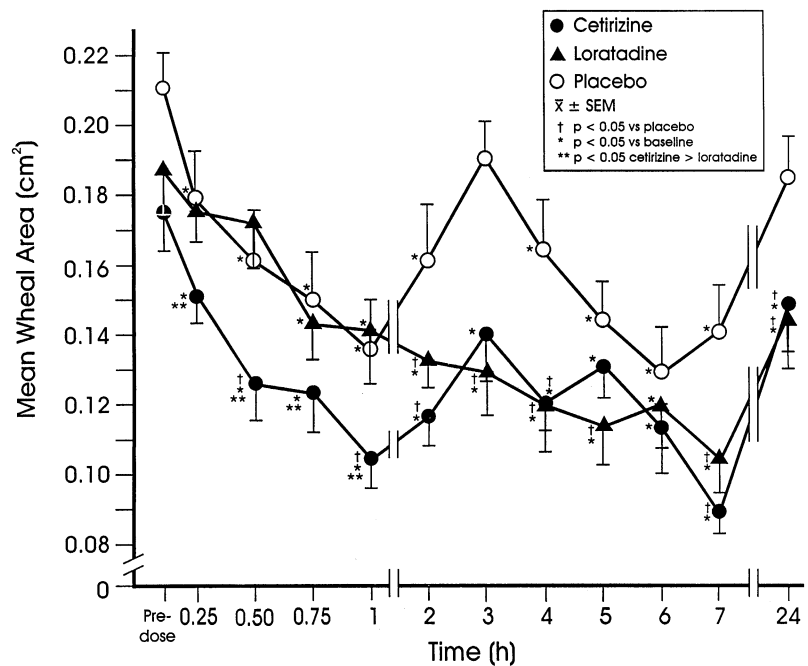
Clinical pharmacology studies of H₁-receptor antagonists are useful for determining the onset and duration of action and the relative potency of these medications (4–10). Here we report a prospective, randomized, placebo-controlled, double-blind, crossover, single-dose study of cetirizine and loratadine in children, using the ability of these H₁-antagonists to suppress the histamine-induced wheal and flare as the primary outcome.

Methods

The study protocol was approved by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research. Before enrolment, written consent for each child's participation was obtained from his/her parent, and written assent was obtained from the child. Children were eligible for inclusion in the study if they were light-skinned, age 6–11 years, non-obese, non-smokers, and in good health except for allergic rhinitis with or without mild asthma. Before the study or during the study, ketotifen or astemizole were not permitted for 90 days, and all other oral medications were not permitted for 30 days. Low-dose intranasal or inhaled glucocorticoids (≤ 400 µg/day total inhaled intranasally and orally) and as-needed inhaled albuterol, which do not suppress skin tests (11, 12), were allowed.

Cetirizine (10 mg) (Reactine[®], Pfizer Canada Inc., Kirkland, QC, Canada), loratadine (10 mg) (Claritin[®], Schering Canada, Inc., Pointe-Claire, QC, Canada), or placebo was administered in a

Fig. 1. Mean $\pm$ SEM wheal areas after epicutaneous histamine phosphate 1 mg/ml: suppression by cetirizine, loratadine, and placebo. † indicates significant difference from placebo ($p \leq 0.05$); * indicates significant difference from predose baseline wheal area ($p \leq 0.05$); ** indicates significant difference between cetirizine and loratadine ($p \leq 0.05$).



crossover sequence designated by a computer-generated random code. On study days at least one week apart and after an overnight fast, encapsulated medication or placebo was administered by the research nurse, with up to 180 ml clear liquid permitted at the time of dosing. A standardized breakfast was given two 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 administration at around 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, and at these times the results were averaged.

Each time skin tests were performed, children were asked to assess the amount of itching in the wheals and flares as absent, present and mild, or present and severe by selecting a happy, neutral, or sad 'face', respectively, from a picture code. At these times, they were also asked about sleepiness, dry mouth and other possible adverse effects of the medications. 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. All skin tests and

tracings of wheal and flare circumferences were made by the same investigator. All wheal and flare tracings were digitized, and the areas calculated, by the same investigator (4, 6–9).

The histamine-induced wheal and flare areas were analyzed as absolute values. The two-way analysis of variance, using skin-test time by subject as the criteria of classification, and the Tukey and Bonferroni multiple-range tests were used for all comparisons. Differences were considered significant at $p < 0.05$.

Results

Fifteen children (13 boys, 2 girls) with allergic rhinitis, mean age 9 ± 0.4 (SEM) years and mean weight 32 ± 3 kg completed the study. There were no dropouts. Compared with predose baseline, cetirizine (10 mg) produced significant suppression of the wheals from 0.25 to 24 h, with a maximum of 49% at 7 h (Fig. 1), and significant suppression of the flares from 0.5 to 24 h, with nearly 100% suppression from 2 to 24 h, inclusive (Fig. 2). Compared with baseline, loratadine (10 mg) produced significant suppression of the wheals from 0.75 to 24 h, with a maximum of 46% suppression at 7 h, and significant suppression of the flares from 0.75 to 24 h, inclusive, with a maximum of 90% suppression at 4 h. Compared with baseline, placebo produced significant suppression of the wheals from 0.25 to 2 h and from 4 to 7 h, and significant suppression of the flares from 0.5 to 1 h.

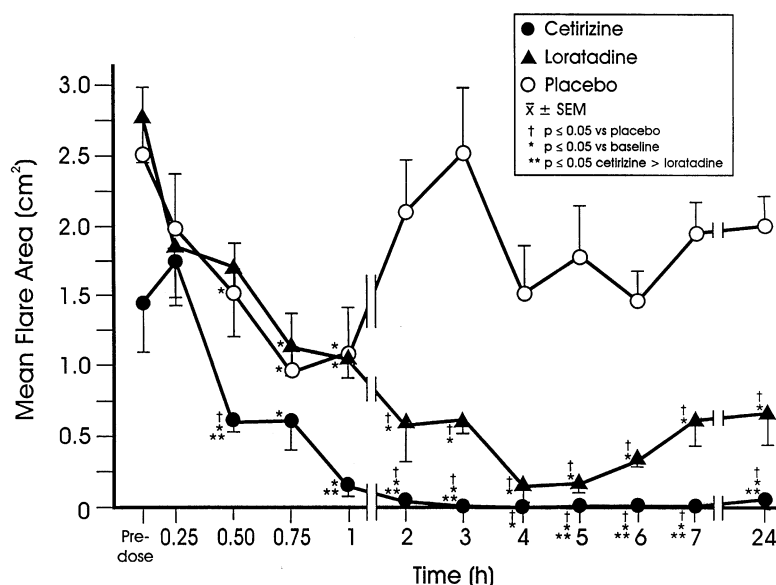


Fig. 2. Mean $\pm$ SEM flare areas after epicutaneous histamine phosphate 1 mg/ml: suppression by cetirizine, loratadine, and placebo. † indicates significant difference from placebo ($p \leq 0.05$); * indicates significant difference from predose baseline flare area ($p \leq 0.05$); ** indicates significant difference between cetirizine and loratadine ($p \leq 0.05$).

Cetirizine suppressed the wheals significantly more than loratadine from 0.25 to 1 h inclusive, and suppressed the flares significantly more than loratadine at 0.5, 1, 2, 3, 5, 6, 7 and 24 h.

In six children who did not consistently experience itching of the wheals and flares in the predose baseline tests, suppression of itching could not be assessed. In the remaining children, cetirizine completely suppressed itching from 0.75 to 7 h, inclusive; loratadine completely suppressed itching at 3 and 5 h; and placebo did not completely suppress itching at any time.

No adverse effects attributable to the H_1 -receptor antagonists, including sedation, light-headedness, dizziness, dry mouth, visual changes and difficulty in urinating, were noted.

Discussion

New, non-sedating H_1 -receptor antagonists such as cetirizine or loratadine are gradually replacing old, sedating H_1 -receptor antagonists in the treatment of allergic rhinitis and urticaria (10). In this 3-way crossover study, using a relatively non-invasive bioassay involving epicutaneous tests with histamine phosphate, we have obtained clinically useful information with regard to onset and duration of cetirizine and loratadine, and their relative potency. All skin tests were performed with careful attention to detail; predose baseline was obtained at around 0800 h; an identical test site sequence was used on all study days; one investigator performed and traced all the skin tests; and one investigator digitized all the wheals and flares. A strong placebo effect was observed, as is typical not only

of clinical pharmacology studies in which wheal and flare suppression by H_1 -receptor antagonists is the primary outcome (8, 9), but also of intervention studies in which suppression of symptoms is the primary outcome (13–19).

Both cetirizine and loratadine suppressed the wheals and flares promptly. The suppression lasted for 24 h after administration of a single dose of both medications, thus confirming that once-daily dosing in children age 6–11 years is optimal. Cetirizine appeared to have a more rapid onset of action in suppressing whealing, flaring, and itching than loratadine did. This would more likely be clinically relevant during sporadic use than during regular use. The objective findings in this pharmacodynamic study are a useful adjunct to the subjective descriptions of the symptom relief produced by cetirizine (13–18) and loratadine (19–22) in clinical trials in children with allergic disorders.

References

1. SIMONS FER. H_1 -receptor antagonists in children. In: SIMONS FER, ed. *Histamine and H_1 -Receptor Antagonists in Allergic Disease*. New York: Marcel Dekker Inc., 1996: 329–56.
2. CLOUGH GF, BENNETT AR, CHURCH MK. Effects of H_1 antagonists on the cutaneous vascular response to histamine and bradykinin: a study using scanning laser Doppler imaging. *Br J Dermatol* 1998; 138: 806–14.
3. SCHMELZ M, SCHMIDT R, BICKEL A, HANDWERKER HO, TOREBJÖRK HE. Specific C-receptors for itch in human skin. *J Neurosci* 1997; 17: 8003–8.
4. WATSON WTA, SIMONS KJ, CHEN XY, SIMONS FER. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1989; 84: 457–64.
5. LIN CC, RADWANSKI E, AFFRIME MB, CAYEN MN.

- Pharmacokinetics of loratadine in pediatric subjects. *Am J Therapeutics* 1995; 2: 504–8.
6. SIMONS FER, WATSON WTA, SIMONS KJ. Pharmacokinetics and pharmacodynamics of ebastine in children. *J Pediatr* 1993; 122: 641–6.
 7. SIMONS FER, BERGMAN JN, WATSON WTA, SIMONS KJ. The clinical pharmacology of fexofenadine in children. *J Allergy Clin Immunol* 1996; 98: 1062–4.
 8. SIMONS FER, LUKOWSKI JL, BECKER AB, SIMONS KJ. Comparison of the effects of single doses of the new H_1 -receptor antagonists loratadine and terfenadine versus placebo in children. *J Pediatr* 1991; 118: 298–300.
 9. SIMONS FER, WATSON WTA, BECKER AB, SIMONS KJ. Histamine blockade after astemizole in children: a single-dose, placebo-controlled study. *Pediatr Allergy Immunol* 1994; 5: 214–7.
 10. SIMONS FER, SIMONS KJ. The pharmacology and use of H_1 -receptor antagonist drugs. *N Engl J Med* 1994; 330: 1663–70.
 11. DEMOLY P, MICHEL F-B, BOUSQUET J. In vivo methods for study of allergy skin tests, techniques, and interpretation. In: MIDDLETON E Jr, REED CE, ELLIS EF, ADKINSON NF Jr, YUNGINGER JW, BUSSE WW, eds. *Allergy Principles and Practice* (5th edn). St. Louis: Mosby-Year Book Inc., 1998: 430–9.
 12. FREW AJ. Skin tests. In: KAY AB, ed. *Allergy and Allergic Diseases*. Oxford: Blackwell Science Ltd, 1997: 1007–11.
 13. MASI M, CANDIANI R, VAN DE VENNE H. A placebo-controlled trial of cetirizine in seasonal allergic rhinoconjunctivitis in children aged 6–12 years. *Pediatr Allergy Immunol* 1993; 4 (Suppl.): 47–52.
 14. BAELEDE Y, DUPONT P. Cetirizine in children with chronic allergic rhinitis. A multicentre double-blind study of two doses of cetirizine and placebo. *Drug Invest* 1992; 4: 466–72.
 15. JOBST S, VAN DEN WIJNGAART W, SCHUBERT A, VAN DE VENNE H. Assessment of the efficacy and safety of three dose levels of cetirizine given once daily in children with perennial allergic rhinitis. *Allergy* 1994; 49: 598–604.
 16. PEARLMAN DS, LUMRY WR, WINDER JA, NOONAN MJ. Once-daily cetirizine effective in the treatment of seasonal allergic rhinitis in children aged 6–11 years: a randomized, double-blind, placebo-controlled study. *Clin Pediatr* 1997; 36: 209–15.
 17. LA ROSA M, RANNO C, MUSARRA I, GUGLIELMO F, CORRIAS A, BELLANTI JA. Double-blind study of cetirizine in atopic eczema in children. *Ann Allergy* 1994; 73: 117–22.
 18. WAHN U for the ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. *Pediatr Allergy Immunol* 1998; 9: 116–24.
 19. SERRA HA, ALVES O, RIZZO LF, DEVOTO FM, ASCIERTO H. Loratadine-pseudoephedrine in children with allergic rhinitis, a controlled double-blind trial. *Br J Clin Pharmacol* 1998; 45: 147–50.
 20. BONER AL, MIGLIORANZI P, RICHELLI C, MARCHESI E, ANDREOLI A. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. *Allergy* 1989; 44: 437–41.
 21. BONER AL, RICHELLI C, CASTELLANI C, MARCHESI E, ANDREOLI A. Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis. *Allergy* 1992; 47: 98–102.
 22. LUTSKY BN, SCHULLER JL, CERIO R, et al. Comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of chronic allergic skin diseases in a pediatric population. *Arzneim-Forsch/Drug Res* 1993; 43: 1196–9.