Effects of acrivastine, loratadine and cetirizine on histamine-induced wheal and flare responses

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Summary

It is accepted that studies evaluating histamine-induced wheal and flare reactions in the skin represent a simple and reliable method for demonstrating pharmacodynamic activity and pharmacokinetics of the H_1-receptor antagonists. In this study, the effects of single oral doses of acrivastine (8 mg), loratadine (10 mg) and cetirizine (10 mg) on the histamine-induced wheal and flare reactions were compared in 60 healthy volunteers. The wheal and flare responses were produced by prick test using 1% histamine solution. Measurements were performed before the ingestion of antihistamines (baseline values) and afterwards at 15, 30, 90, 240, 360 min and 24 h. The values obtained for each antihistamine were compared with each other and with baseline values. Cetirizine was found to be superior to acrivastine and loratadine for the suppression of wheal and flare responses at 240, 360 min and 24 h ($P<0.05$) and acrivastine was superior to the other two antihistamines for the suppression of flare response at 30 min ($P<0.05$). Our results indicate that a single dose of cetirizine provides a more effective and long acting suppression on wheal and flare reactions in urticaria when compared to acrivastine and loratadine.

Introduction

Oral antihistamines are the most widely used drugs for the treatment of allergic disorders.[1–5] The first generation H_1-receptor antagonists that was discovered more than 50 years ago are poorly tolerated by most patients because of sedative and anticholinergic effects.[5,6] The second generation H_1-receptor antagonists were developed to reduce significantly the incidence of centrally mediated side-effects while maintaining the effectiveness of their predecessors.[4,6]

The aim of present investigator-blinded, cross-over study was to compare the effects of single oral doses of acrivastine (8 mg), loratadine (10 mg), and cetirizine (10 mg) on the histamine-induced wheal and flare reactions in healthy volunteers.

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Materials and methods

Subjects

This investigator-blinded, single dose, cross-over study was performed in 60 healthy volunteers between May and September 1997. Thirty male and 30 female adults aged 22–52 years (mean, 28.68 ± 0.74 years) were included in the study. The mean weight of the study population was 64.78 ± 13.34 kg. Ethical approval was granted for all experiments carried out in the study and all volunteers gave informed consent to the procedures performed.

Haematological and biochemical tests were normal in all subjects. Subjects were excluded if they had any acute or chronic illness, if they had taken an H_1 or H_2-receptor antagonist, systemic corticosteroid, mast cell stabilizator

or tricyclic antidepressan drug within the previous month, or if they had a known history of idiosyncratic reaction to histamine or antihistamines. The study population was divided into three groups of 10 females and 10 males volunteers. Group 1 received an 8 mg single oral dose of acrivastine (Semprex, Glaxo Wellcome); group 2 received a 10 mg single oral dose of loratadine (Claritine, Schering-Plough); group 3 received a 10 mg single oral dose of cetirizine (Zyrtec, UCB).

Study design

The study was performed during a 3-day period. On day 1, the wheal and flare responses were produced by the first investigator and the baseline values were established. On day 2, the medications were administrated by a second investigator with a glass of water 2 h after breakfast. Afterward the wheal and flare responses were produced, at 15, 30, 90, 240 and 360 min after drug ingestion, by the first investigator. On day 3, 24 h after antihistamine ingestion, wheal and flare responses were produced again by the first investigator. The first investigator had no knowledge of the drugs at any stage of the investigation.

After performing each skin test, subjects were questioned about adverse effects such as sedation, disorientation, dizziness, drowziness, dry mouth, visual changes, nausea, vomiting and diarrhoea.

Assessment of epicutaneous tests

The wheal and flare responses were produced by an epicutaneous test with histamine phosphate 1 mg/mL (Hal Allergenes Lab. BV., Haarlem) on the volar aspect of the forearms at sites separated from each other by ≤ 4 cm. The size of the response was marked on the skin 10 min after each injection and then traced to measure the area involved and to quantify the skin responses; the longest diameter and the perpendicular diameter were measured separately after each application: a measurement of the response was calculated as the mean of these two values.

Wheal and flare responses obtained at 0, 15, 30, 90, 240, 360 min and 24 h were compared with each other and with baseline values; percentage inhibition was calculated according to the following equation: percentage inhibition = (wheal/flare $\text{area}_{\text{baseline}}$ − wheal/flare $\text{area}_{\text{time t}}$) / (wheal/flare $\text{area}_{\text{baseline}}$) × 100

Statistical analysis

Results were expressed as the means ± SEM. Statistical significance of differences between groups was determined by one-way analysis of variance followed by posthoc LSD test or unpaired student's *t*-test when appropriate. $P < 0.05$ was taken to indicate statistical significance.

Results

There was no significant difference among the treatment groups in terms of age, sex and weight.

At baseline there was no significant difference among the groups in mean wheal and flare responses (Table 1). Percentage inhibition of wheal and flare responses by the three test drugs is shown in Figs 1 and 2.

There were no significant differences among the three antihistamines for the suppression of wheal and flare responses at 15 min. For acrivastine, loratadine and cetirizine, 17.4%, 10%, 12.4% inhibition in mean flare responses and 11.6%, 9.8%, 6.1% inhibition in mean wheal responses were obtained, respectively.

Acrivastine suppressed the mean flare response more than loratadine and cetirizine whereas there were no significant differences bewteen the drugs for the suppression of wheal response at 30 min. The inhibition in mean flare responses was 37.8%, 13.2%, and 17.1% for acrivastine, loratadine and cetirizine, respectively.

Table 1 Mean wheal and flare responses (mm ± SEM) at baseline and after antihistamine ingestion.

Group	*n*	Baseline	15min	30min	90min	240min	360min	24 h
Wheal								
Acrivastine	20	7.32 ± 0.46	6.47 ± 0.43	5.58 ± 0.37	4.28 ± 0.37	4.03 ± 0.42	4.60 ± 0.32	7.11 ± 0.47
Loratadine	20	7.43 ± 0.40	6.70 ± 0.54	5.97 ± 0.40	5.03 ± 0.45	4.97 ± 0.47	4.21 ± 0.32	6.42 ± 0.46
Cetirizine	20	6.96 ± 0.48	6.53 ± 0.56	5.71 ± 0.46	3.03 ± 0.30	1.79 ± 0.30	1.33 ± 0.39	3.67 ± 0.21
Flare								
Acrivastine	20	39.60 ± 1.81	32.70 ± 1.96	24.61 ± 1.56	15.63 ± 1.82	18.97 ± 2.23	24.45 ± 1.78	34.42 ± 1.94
Loratadine	20	36.70 ± 1.80	33.02 ± 1.59	31.85 ± 1.79	29.00 ± 1.85	24.28 ± 1.84	21.96 ± 1.27	27.52 ± 1.98
Cetirizine	20	35.95 ± 1.65	31.47 ± 1.80	29.80 ± 1.44	20.12 ± 1.30	10.12 ± 1.47	6.82 ± 1.25	15.55 ± 1.23

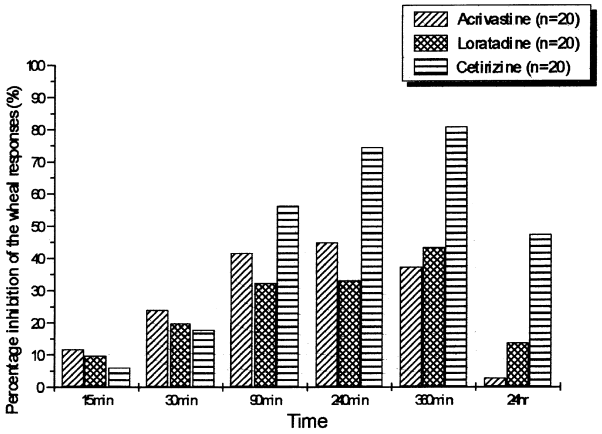


Figure 1 Percentage inhibition of wheal responses to the three antihistamines.

The inhibition in mean wheal responses was 23.7%, 19.7% and 17.9% for the three test drugs, respectively.

Acrivastine and cetirizine were superior to loratadine for the suppression of flare response at 90 min whereas cetirizine was superior to acrivastine and loratadine for the suppression of wheal response. The inhibition in mean flare and wheal responses was 60.5%, 20.9%, 41.2% and 41.4%, 32.2%, 56.3% to acrivastine, loratadine and cetirizine, respectively.

Cetirizine suppressed the flare and wheal responses significantly more than acrivastine and loratadine at 240 min. Acrivastine was superior to loratadine for the suppression of flare response whereas no significant difference was present among these drugs for the suppression of wheal response at this time. For acrivastine, loratadine and cetirizine, 52%, 33.8%, 71.8% inhibition in mean flare responses and 44.9%, 33.1%, 74.1% inhibition in mean wheal responses were obtained, respectively.

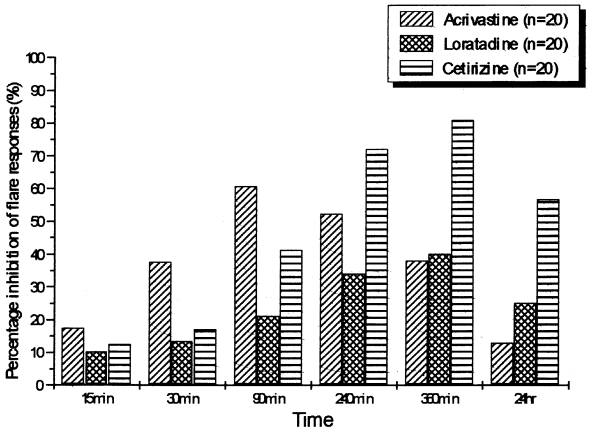


Figure 2 Percentage inhibition of flare responses to the three antihistamines.

Cetirizine suppressed both the flare and wheal responses significantly more than acrivastine and loratadine but there was no significant difference between acrivastine and loratadine at 360 min. The inhibition in mean flare and wheal responses was 38.2%, 40.1%, 81% and 37.2%, 43.3%, 80.8% for acrivastine, loratadine and cetirizine, respectively.

Cetirizine was superior to acrivastine and loratadine for the suppression of flare and wheal responses at 24 h. Loratadine was superior to acrivastine for the suppression of flare response whereas no difference was present for the suppression of wheal response at 24 h between these two antihistamines. The inhibition in mean flare responses was 13%, 25%, 56.7% for acrivastine, loratadine and cetirizine, respectively. The inhibition in mean wheal responses was 2.9%, 13.6%, 47.2% for the three test drugs, respectively.

Sedation was reported by three subjects and drowsiness by one subject receiving acrivastine and loratadine, respectively.

Discussion

The use of histamine-induced wheal and flare reactions to demonstrate the antihistamine activity of H_1-receptor antagonists is a widely accepted and well established method.[1,7–9]

The aim of this study was to evaluate and compare the effects of the most widely used nonsedative antihistamines (acrivastine, loratadine, cetirizine) on the skin quantitatively. For this purpose, the ability of these antihistamines to suppress the histamine-induced wheal and flare responses were assessed in 60 healthy volunteers.

It was found that acrivastine was superior to loratadine and cetirizine at 30 min, acrivastine and cetirizine were superior to loratadine at 90 min and cetirizine was superior to acrivastine and loratadine at 240, 360 min and 24 h for the suppression of flare reactions. For the suppression of wheal responses, cetirizine was found to be superior to acrivastine and loratadine at all other time-points whereas there were no differences among the groups at 15 and 30 min.

Marks[10] *et al.* reported that a single oral dose of 8 mg acrivastine inhibited the flare response by 63% of the peak inhibition and the wheal response by 55% of the peak inhibition when compared with the placebo at 30 min. The results of this study are similar: acrivastine inhibited the flare response by 62.5% and the wheal

response by 53% of the peak inhibition at 30 min. Although Simons[11] *et al.* reported 25% inhibition in the flare and wheal responses in the first 20 min after oral administration of cetirizine, we obtained 17% inhibition in the flare and wheal responses at 30 min with cetirizine.

Kontou-Fili[12] *et al.* reported that a single oral dose of 10 mg cetirizine inhibited the mean flare and wheal responses by 40% at 120 min and by 70–75% at 240 min. In our study a similar level of inhibition—71–74%—of flare and wheal responses were obtained at 240 min. In the same study, 12% inhibition in mean wheal response at 120 min and 30% inhibition at 240 min, by an oral dose of 10 mg loratadine, were reported.[12] We confirmed this finding by showing 33% inhibition of flare and wheal responses with loratadine at 240 min.

In our study, the inhibition in mean flare responses at 360 min were approximately 40% and 81% for loratadine and cetirizine, respectively. Kontou-Fili[12] *et al.* reported that inhibition in mean flare and wheal responses at 360 min were approximately 30% and 80% for loratadine and cetirizine, respectively.

We obtained 13%, 25% and 56.7% inhibition in mean flare responses at 24 h for acrivastine, loratadine and cetirizine, respectively. There were 2.9%, 13.6% and 47.2% inhibition in mean wheal responses to acrivastine, loratadine and cetirizine, respectively.

Simons *et al.*[7] reported that cetirizine was the only antihistamine which inhibited the mean wheal responses over 50% at 24 h when compared with placebo, terfenadine, loratadine, astemizole and chlorpheniramine. In this study we obtained 47.2% inhibition in mean wheal responses at 24 h with cetirizine, approximately equal to the results of Simons *et al.*, and a significantly greater inhibition than that induced by loratadine or acrivastine.

In various studies comparing single oral doses of antihistamines, cetirizine was found to be superior to astemizole,[7,13,14] terfenadine,[7,13,15] loratadine,[7,14] chlorpheniramine[7] and placebo[7] in suppressing histamine-induced flare and wheal responses. In the present study, cetirizine was also found to be superior to acrivastine and loratadine at 240, 360 min and 24 h for the suppression of flare responses, and at 90, 240, 360 min and 24 h for the suppression of wheal responses.

The superiority of cetirizine over most other antihistamines can be attributed to some of its properties other than its antiallergic effects. Cetirizine has been shown to have anti-inflammatory effects not seen with most other second generation antihistamines.[5,11,16–19] It has also been shown that cetirizine inhibited not only the early allergic response but also the late inflammatory cell recruitment after IgE-mediated reactions in human skin.[20]

Although antihistamines are the mainstay of urticaria treatment most patients do not use their antihistamines regularly. Moreover, when they use them they expect fast symptomatic relief. Many studies have assessed the relative potency of antihistamines by measuring their ability to suppress the histamine-induced wheal and flare reactions on the skin. To the best of our knowledge, there has been no report comparing acrivastine, loratadine and cetirizine. We found that cetirizine suppressed the wheal and flare responses more effectively over 24 h as compared with acrivastine and loratadine. Our findings indicate that a single dose of cetirizine is more potent and provides longer suppression of urticarial wheal and flare reactions than both acrivastine and loratadine. Like all single-dose studies, this study does not reflect the dynamic equilibrium of repetitive maintenance dosing but it does have clinical implications for the relief of symptoms in patients presenting with urticaria.

References

1 Juhlin L. A comparison of the pharmacodynamics of H_1-receptor antagonists as assessed by the induced wheal-and-flare model. *Allergy* 1995; **50:** 24–30.

2 Gendreau-Reid L, Simons KJ, Simons FER. Comparison of the suppressive effect of astemizole, terfenadine, and hydroxyzine on histamine-induced wheals and flares in humans. *J Allergy Clin Immunol* 1986; **77:** 335–40.

3 Volkerts ER, van Laar M. Specific review of the psychometric effects of cetirizine. *Allergy* 1995; **50:** 55–60.

4 Passalacqua G, Bousquet J, Bachert C *et al.* The clinical safety of H_1-receptor antagonists. *Allergy* 1996; **51:** 666–75.

5 Simons FER. H_1-receptor antagonists: clinical pharmacology and therapeutics. *J Allergy Clin Immunol* 1989; **84:** 845–61.

6 Monroe EW. Safety and efficacy of loratadine in urticaria. *Int J Dermatol* 1996; **35:** 837–41.

7 Simons FER, McMillan J, Simons KJ. A double blind, single-dose, crossover comparison of cetirizine, terfenadine, loratadine, astemizole, and chlorpheniramine versus placebo: Suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol* 1990; **86:** 540–7.

8 Kassem N, Roman I, Gural R *et al.* Effects of loratadine (SCH 29851) in suppression of histamine-induced skin wheals. *Ann Allergy* 1988; **60:** 505–7.

9 Roman IJ, Kassem N, Gural RP *et al.* Suppression of histamine-induced wheal response by loratadine (SCH 29851) over 28 days in man. *Ann Allergy* 1986; **57:** 253–6.

10 Marks P, Manna VK, Gibson JR. Acrivastine—an evaluation of initial and peak activity in human skin. *J Int Med Res* 1989; **17** (Suppl. 2): 3B–8B.

11 Simons FER. A new classification of H_1-receptor antagonists. *Allergy* 1995; **50:** 7–11.
12 Kontou-Fili K, Paleologos G, Herakleous M. Suppression of histamine-induced skin reactions by loratadine and cetirizine diHCl. *Eur J Clin Pharmacol* 1989; **36:** 617–9.
13 Ghys L, Rihoux JP. Pharmacological modulation of cutaneous reactivity to histamine: a double blind acute comparative study between cetirizine, terfenadine and astemizole. *J Int Med Res* 1989; **17:** 24–7.
14 Humphreys F, Hunter JAA. The effects of astemizole,-cetirizine and loratadine on the time course of wheal and flare reactions to histamine, codeine and antigen. *Br J Dermatol* 1991; **125:** 364–7.
15 Pechadre JC, Vernay D, Trolese JF *et al*. Comparison of the central and peripheral effects of cetirizine and terfenadine. *Eur J Clin Pharmacol* 1988; **35:** 255–9.
16 Jinquan T, Reimerd CM, Deleuran B *et al*. Cetirizine inhibits the in vitro and ex vivo chemotactic response of T lymphocytes and monocytes. *J Allergy Clin Immunol* 1995; **95:** 979–86.
17 Cheria-Sammari S, Aloui R, Gormand F *et al*. Leukotriene B4 production by blood neutrophils in allergic rhinitis effects of cetirizine. *Clin Exp Allergy* 1995; **25:** 729–36.
18 Roch-Arveiller M, Tissot M, Idohou N *et al*. In vitro effect of cetirizine on PGE2 release by rat peritoneal macrophages and human monocytes. *Agents Actions* 1994; **43:** 13–6.
19 Bagnasco M, Canonica GW. Influence of H_1-receptor antagonists on adhesion molecules and cellular traffic. *Allergy* 1995; **50:** 17–23.
20 Michel L, De Vos C, Rihoux JP *et al*. Inhibitory effect of oral cetirizine on in vivo antigen-induced histamine and PAF-acether release and eosinophil recruitment in human skin. *J Allergy Clin Immunol* 1988; **82:** 101–9.