

Changes in skin-test reactivity do not correlate with clinical efficacy of H₁-blockers in seasonal allergic rhinitis

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New-generation H₁-blockers may possess antiallergic properties, and their effect may differ, depending on the target organ. A double-blind, placebo-controlled, parallel-group study was carried out during the pollen season to compare the clinical effect on nasal and conjunctival symptoms of astemizole (10 mg o.d.) and loratadine (10 mg o.d.) with their effect on skin-test reactivity to allergen and histamine. Thirty-eight patients (12–56 years of age) were studied. Nasal and ocular symptoms were recorded daily from days 4 to 7. Skin prick tests with serial concentrations of allergens and one concentration of histamine were carried out before and at the end of the 7-day treatment period. Parallel-line bioassay, analysis of variance, and covariance were used to analyze skin test data. Loratadine and astemizole significantly decreased symptoms from baseline ($P < 0.004$ and $P < 0.006$). Skin-test reactivity to allergen and histamine was more profoundly decreased by astemizole than loratadine. The histamine covariant was more important in the allergen effect of astemizole than in that of loratadine. Two H₁-blockers having the same clinical effect on nasal and ocular symptoms during the pollen season have totally different effects on skin-test reactivity. Skin-test reactivity to allergen or histamine is not predictive of the clinical efficacy of H₁-blockers during seasonal allergic rhinitis.

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H₁-blockers represent the first-line treatment of allergic rhinitis. New-generation H₁-blockers include astemizole, cetirizine, ebastine, loratadine, and terfenadine. Although these molecules vary widely in their structure, they have a similar efficacy in controlling nasal and conjunctival symptoms (1).

H₁-blockers block histamine at the H₁-receptor level, but they have a variable effect on skin tests with histamine. Some block almost completely the wheal and flare reaction, whereas others are much less potent (2). To a large extent, cetirizine (3, 4) and astemizole block histamine- or allergen-induced skin-test reactions (5, 6), whereas loratadine only partially blocks histamine- (7, 8) or allergen-induced reactions (9). However, new-generation H₁-blockers were found to have additional antiallergic properties (10). In particular, loratadine and terfenadine block the release of mediators after *in vitro* (11–13) or *in vivo* allergen

challenge (14), whereas cetirizine blocks the influx of eosinophils in the skin (15–18), but not in the nose (19). Therefore, it is possible that H₁-blockers have a different effect according to the target organ and that the evolution of skin-test reactivity during treatment does not predict the clinical efficacy of the drugs for nasal allergy.

A double-blind, placebo-controlled, parallel-group study was carried out during the pollen season to compare the clinical efficacy of two H₁-blockers, astemizole (10 mg o.d.) and loratadine (10 mg o.d.) with their effect on skin-test reactivity to allergen and histamine.

Material and methods

Patients

Thirty-eight patients ranging in age from 12 to 56 years were enrolled in the study after informed

consent had been obtained and approval of the protocol by the ethics committee. All patients fulfilled the following criteria:

- 1) Patients had presented symptoms of seasonal allergic rhinitis for at least the past 2 years.
- 2) Skin prick tests (SPT) were positive with a standardized orchard grass pollen extract (Stallergènes Laboratories, Fresnes, France). All patients had elevated titers of serum orchard grass pollen IgE (Phadebas RAST, Pharmacia Diagnostics, Uppsala, Sweden).
- 3) Patients were not receiving specific immunotherapy during the current year, and had not been treated with antihistamines, corticosteroids, or ketotifen during the past 2 weeks. None of the patients had received astemizole for the past 2 months.

Before inclusion in the study, patients were carefully evaluated by the physicians for the presence of nasal and ocular symptoms (nasal discharge, sneezing, and itching, itchy eyes, redness of the eyes). By severity, each symptom was scored 0 to 3 according to a previous study (20), and only patients with moderate to severe rhinitis were enrolled in the study.

Patients were assigned to one of the three treatment groups (astemizole, loratadine, or placebo) by random order.

Skin tests

SPT were done with standardized extracts of orchard grass (Stallergènes Laboratories, Fresne, France) (21), as previously described, with end-point titration with seven threefold increasing concentrations (0.045–100 IR/ml). SPT with histamine dihydrochloride (10 mg/ml) were also done. SPT were performed by the modified prick test technique of Pepys. To avoid possible circadian differences in skin reactivity, SPT were performed between 9.00 and 11.00 a.m. The wheals were recorded by the Scotch tape technique 15 min after the performance of the prick.

Evaluation of treatment efficacy

Patients were observed for up to 1 week. During the trial, patients filled in daily a diary card including nasal (nasal discharge, stuffiness, nasal itching, and sneezing) and ocular (itchy eyes) symptoms. The severity of each of the five symptoms was scored from 0 to 3 according to a previous study (0: none, 1: mild, 2: moderate and 3: severe) (20). The maximum symptom score was 15. At each clinic visit, subjective and objective assessments were made by the physicians. Concomitant use of

any other antiallergic medication was not permitted during the trial.

Possible adverse effects of the treatment were carefully checked.

Measurement of efficacy

Skin tests were carried out before treatment and after 7 days of regular treatment. The duration of the treatment period was carefully checked. We assessed whether a 7-day course of astemizole was sufficient to decrease skin-test reactivity with the methods used in the study and found that there was no significant difference between 7 and 14 days (Fig. 1).

The therapeutic effects of astemizole take at most 3 days to be optimal in pollen-induced rhinitis (22–24). Therefore, we did not perform the efficacy analysis over a week but only between days 4 and 7.

Pollen counts

Pollen counts were analyzed during the trial period by means of a filter trap, according to the technique of Cour (25).

Study design

The trial was a double-blind, placebo-controlled, parallel-group study, with patients receiving loratadine (10 mg o.d.), astemizole (10 mg o.d.), or placebo in the morning. The compliance of treatment, was assessed by counting the number of capsules at the end of the trial (drugs were encapsulated to maintain the double-blind). Before and at the end of the treatment the patients had a skin test titration to allergen as described above, and the end point was calculated.

Statistical analysis

Analysis of demographic parameters. For analysis of sex, Fisher's exact test was used. For other demographic parameters, the Mann–Whitney *U*-test with Bonferroni's correction was used.

Analysis of clinical efficacy. For all efficacy parameters, nonparametric tests were used. The Wilcoxon *W* test was used for within-group data, and the Mann–Whitney *U*-test for between-group data. Results are expressed in means $\pm$ SD.

Analysis of skin tests. The analysis of SPT results was performed by two different methods. In the first one, results of the wheal sizes induced by allergen were analyzed by parallel-line bioassay. The linearity of the dose-response curve was checked by regression linear analysis after logarithmic transformation.

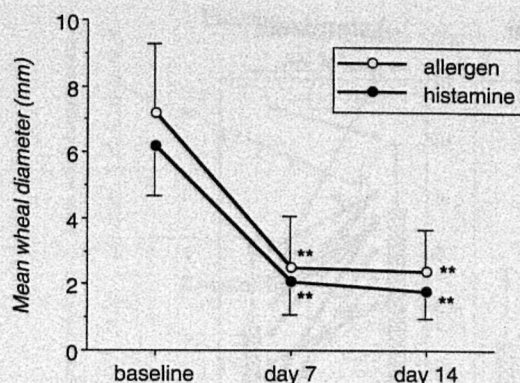


Fig. 1. Evolution of wheals induced by allergen or histamine during astemizole treatment in nine patients allergic to orchard-grass pollen (allergen: orchard-grass pollen; histamine dihydrochloride 9 mg/ml). ** $P < 0.01$, Wilcoxon W test.

The parallelism of the curves (within days and between days) was analyzed by one-way analysis of variance.

The second group of statistical tests was more complex and used three-way analysis of variance with repeated measures. The anticipated effects due to different dilutions or different days (active treatment as opposed to placebo) were evaluated under fairly general assumptions and then removed from the analysis. Simple comparisons were made by nonparametric procedures. The size of the reaction induced by the third allergen concentration was measured on control and treatment days, and data were analyzed by the Wilcoxon W test within the same treatment group and by Mann-Whitney U-test between the treatments. The size of skin tests induced by histamine was analyzed similarly.

Results

Demographic characteristics of the patients

Demographic characteristics of the patients were similar for age, sex, severity, and duration of rhinitis for the three groups (Table 1).

Table 1. Demographic data of three groups of patients

	Treatment			Statistical analysis		
	Loratadine	Astemizole	Placebo	P P/L	P A/P	P A/L
No. of patients	14	12	12			
Age (years)	31.3±10.3	27.4±8.8	35.9±14.2	NS	NS**	NS
Sex (% male)	75.8	76.6	66.6			
Duration of symptoms (years)	9.6±5.9	11.2±4.3	14.2±6.9	NS**	NS	NS
Severity of symptoms at baseline (score)	6.9±1.7	7.5±2.2	7.0±1.8	NS	NS	NS
Allergen skin test at baseline	4.6±1.9	4.9±1.8	4.3±2.4	NS	NS	NS

Results expressed in means±SD or in percentage.

Statistical analysis by Mann-Whitney U-test and Bonferroni's correction.

*Mean wheal diameter for third allergen concentration.

P: placebo; L: loratadine; A: astemizole; NS: not significant; NS**: not significant with Bonferroni's correction.

Dropouts

No patient dropped out of the study.

Clinical efficacy and safety of the treatment

At entry, patients had similar, nonsignificant mean nasal symptom scores in the three groups (Mann-Whitney U-test) (Fig. 2). After 1 week of treatment, placebo patients had a mean symptom score similar to baseline, whereas patients treated with astemizole or loratadine had a significant reduction in mean symptom scores in comparison to baseline values ($P < 0.006$ and $P < 0.004$, respectively, Wilcoxon W test). There was a significant difference between placebo and astemizole ($P < 0.03$, Mann-Whitney U-test) or loratadine ($P < 0.015$). There was no significant difference in mean symptom scores between loratadine- and astemizole-treated patients (Mann-Whitney U-test).

The safety of the three treatment groups was comparable, and only mild side-effects were noticed by the patients.

Pollen counts

Pollen counts were high during the whole study, ranging from 10 grains/m³ to 75 grains/m³ of air. By this method, the number of grains corresponded to an average pollen season.

Evolution of skin-test reactivity to allergens

Parallel-line bioassay showed that the best fit lines for allergen dose-response curves were linear for all six evaluations (Figs. 3 and 4). At entry, all three dose-response lines were parallel (Fig. 3). When control and treatment days were compared (Fig. 4), allergen dose-response lines were parallel for the placebo and loratadine groups ($F = 0.20$ and $F = 4.7$, respectively), but not for the astemizole group ($F = 17.7$). The effect of astemizole was significantly

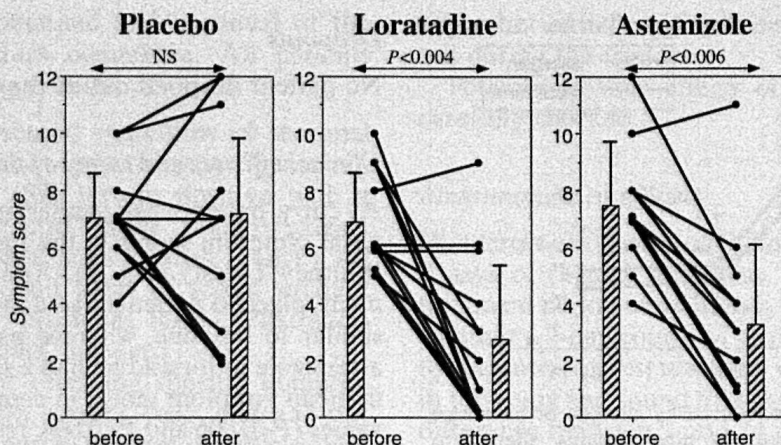


Fig. 2. Nasal symptoms presented by patients before and after treatment. Bars represent mean $\pm$ SD. Statistical analysis was by Wilcoxon W test.

more pronounced for allergen than that of loratadine ($P < 0.01$, Mann-Whitney *U*-test).

The evolution of wheal diameters induced by allergen showed that on the control day, before any treatment, the wheal diameters for each dilution were not significantly different between the three groups ($P = 0.53$), indicating that all three groups were comparable. At day 7, the effect of treatment was significant since there was a decrease in wheal diameters ($P = 0.0001$). The difference between skin-test reactivity performed at days 0 and 7 was not significant for placebo, showing a lack of placebo effect, whereas astemizole and loratadine induced a significant decrease in skin-test reactivity ($P = 0.02$). Astemizole was found to be significantly superior to loratadine ($P = 0.01$).

Evolution of skin-test reactivity to histamine

The intragroup comparison showed that placebo did not significantly modify histamine-induced skin-test reactivity (Fig. 5). Astemizole decreased histamine-induced skin test reactivity in 12/12 patients ($P < 0.01$, Wilcoxon W test). Loratadine decreased histamine-induced skin-test reactivity in

9/14 patients ($P < 0.05$, Wilcoxon W test). The inter-group comparison showed that astemizole induced a significantly ($P < 0.05$, Mann-Whitney *U*-test) greater reduction of histamine-induced skin tests than loratadine.

Discussion

This study shows that two H_1 -blockers having the same clinical effect on nasal and ocular symptoms during the pollen season have totally different effects on the evolution of skin-test reactivity. Thus, the skin-test reactivity to allergen or histamine is not predictive of clinical efficacy of H_1 -blockers during seasonal allergic rhinitis.

The methods used in the present study have been widely validated for the clinical efficacy of both the treatments and the skin tests. Clinical efficacy was expected, and although some placebo effect was observed, both astemizole and loratadine were more effective than placebo in the treatment of seasonal allergic rhinitis. These results agree with previous data already published on astemizole (26–28) and loratadine (20, 29–32). Moreover, there was no significant difference between both treated groups, as observed in previous studies with H_1 -blockers (33).

The study was based on symptoms during the pollen season since clinical trials represent the "gold standard" in assessing the efficacy of anti-allergic drugs. We might have included a nasal challenge study to appreciate better the differences between loratadine and astemizole. However, one study on six patients used a nasal challenge model, and although there were trends to differences between drugs, the differences were not significant (23). Moreover, we have previously carried out a double-blind, placebo-controlled study, comparing the effects of loratadine and cetirizine on nasal and

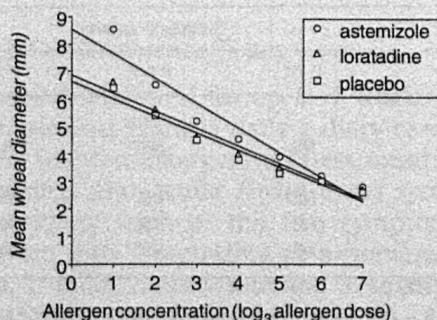


Fig. 3. Dose-response relationship with allergen extracts for three treatment groups before treatment.

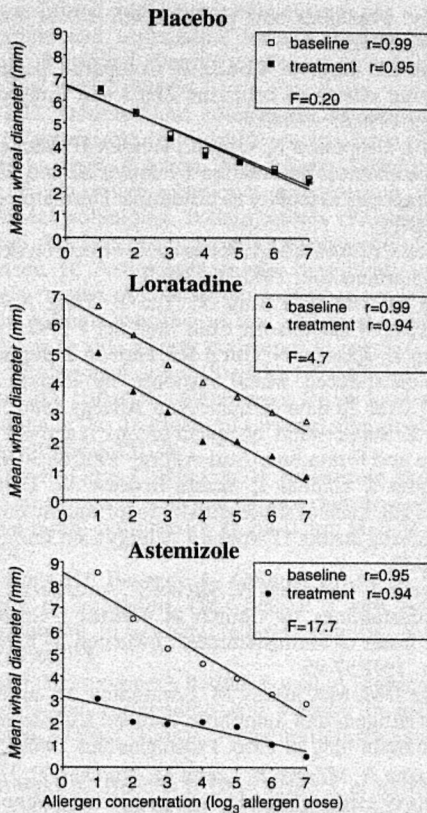


Fig. 4. Dose-response relationship for three treatment groups before (baseline) and after treatment. Statistical analysis by parallel-group bioassay: parallelism of dose-response lines before and after treatment was measured by ANOVA.

skin challenge with allergen (34). We did not find any significant difference in nasal provocation, but we did find a significant difference for skin tests.

The sample size of the study may be too small to appreciate fully the clinical effects of loratadine and astemizole. However, the study was part of a larger multicentric study on over 200 patients and

there was no significant difference between loratadine and astemizole (data on file). Moreover, three other clinical trials have compared these two drugs and did not find any overall significant difference (24, 35, 36). In the last study (36), loratadine was found to be more effective at 1 week. Finally, Fig. 5 suggests that even if the number of patients was increased, there would not be a significant difference between loratadine and astemizole.

The duration of the study was critical. The effect of astemizole on the wheal and flare response to intradermal histamine has been studied in normal volunteers after single dosing, and in patients with urticaria and pruritus after chronic dosing with the drug. Single doses of astemizole (40 mg) in normal volunteers significantly reduced histamine wheal and flare at 24 and 48 h (37). In one study using intradermal skin tests with histamine, it was observed that a 14-day course of astemizole was significantly superior to a 7-day course (38). However, we have investigated whether a 7-day course of astemizole might be sufficient to decrease skin-test reactivity with the methods used in the study and found that there was no significant difference between 7 and 14 days (Fig. 1). Our results agree with those of Malo et al. (39), who found that after 7 days of astemizole treatment, skin-test reactivity to histamine was completely abolished.

The therapeutic effects of astemizole take at most 3 days to be optimal in pollen-induced rhinitis (22, 23). In a double-blind study, 65 patients with hay fever were treated for 14 days with either loratadine 10 mg o.d., astemizole 10 mg o.d., or placebo. On day 3 of treatment, loratadine and astemizole had reached their end-point effect (24). Therefore, we did not perform the efficacy analysis over a week but only between days 4 and 7.

Thus, even though astemizole may require 3 weeks before the accumulation of the active metabolite establishes a steady state, it takes only 3 days

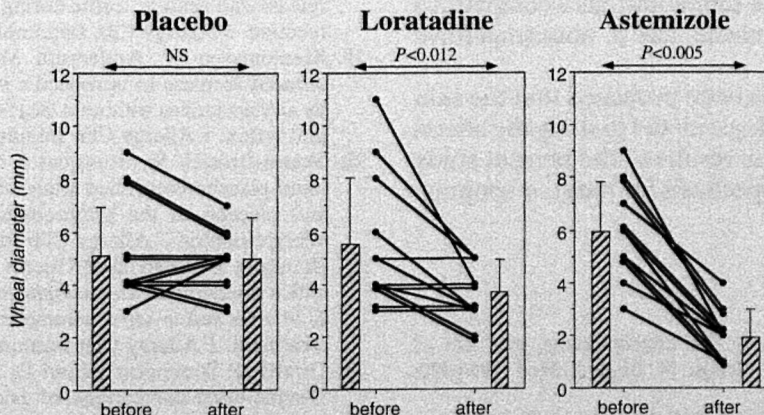


Fig. 5. Histamine skin-test reactivity before and after treatment. Bars represent mean $\pm$ SD. Statistical analysis was by Wilcoxon W test.

to have a full clinical effect, and we have demonstrated that the effects on skin-test reactivity were parallel with the skin-test methods used in the present study.

Skin-test reactivity decreased with both H_1 -blockers and remained unchanged in patients treated with placebo. However, astemizole had a more profound effect on skin test reactivity to histamine and allergen than loratadine. The method of skin-test end point has been widely used in our clinic in immunotherapy trials, and it has been observed that the end-point titer was significantly reduced after treatment in mite (21), mold (40), and pollen immunotherapy (41–44). Moreover, we observed that there was a significant correlation between the decrement in skin-test reactivity and the efficacy of immunotherapy in pollen allergy (43–45). With parallel-line bioassay, it has been observed that immunotherapy decreases skin-test reactivity in a parallel manner (46). In the present study, placebo had no effect on skin-test reactivity, and the parallel-line bioassay showed a remarkable parallelism ($F=0.20$) between control and placebo-treatment days, confirming the reproducibility of the assay. On the other hand, loratadine decreased skin-test reactivity in a parallel manner and astemizole in a nonparallel manner. Comparison of the effects of immunotherapy and H_1 -blockers shows that loratadine reduces skin-test reactivity similarly to immunotherapy, having a global effect on skin reactivity to allergen. However, it must be stressed that the F test was different in the placebo ($F=0.20$) and loratadine groups ($F=4.7$), indicating that besides a global effect on skin-test reactivity, there was some antireceptor effect. On the other hand, astemizole blocks skin-test reactivity more profoundly and in a nonparallel manner, suggesting that this drug has a more potent H_1 -blocking effect than loratadine. Thus, the two antihistamines behave differently in their effects on skin test reactivity, independently of their clinical effect, possibly because loratadine has a competitive action, whereas astemizole has a noncompetitive action.

Thus, although it has been proposed that the skin is a relevant pharmacologic model to study the effects of H_1 -blockers (47), the results of the present study do not confirm this hypothesis for nasal or conjunctival symptoms.

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