

Treatment of hay fever with loratadine – a new non-sedating antihistamine

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The efficacy and safety of loratadine, a new orally active specific H₁-receptor blocking antihistamine with poor penetration into the CNS, was evaluated in a double blind comparative study. One hundred and seven hay fever patients, sensitive to birch pollen, were randomized into three parallel groups receiving loratadine 40 mg once daily, clemastine 1 mg twice daily, or placebo during the birch pollen season. Both active treatments showed reduction of symptoms in comparison with placebo, but the results were more pronounced with loratadine treatment, which significantly reduced the overall allergic condition as well as all separate allergic rhino-conjunctivitis symptoms except nasal stuffiness. Compared with placebo the sedation rate was significantly higher with clemastine treatment ($P < 0.05$) but not with loratadine. Loratadine was thus concluded to be efficacious in hay fever treatment with a sedation rate not differing from placebo.

Key words: allergic rhino-conjunctivitis; clemastine; loratadine; seasonal allergy.

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CLINICAL ASPECTS

Loratadine is a new orally effective antihistamine, with good efficacy in allergic rhino-conjunctivitis given in once daily dosage. A dose of 40 mg shows a sedation rate not differing from placebo.

In many allergic disorders, including hay fever, there is a need for H₁-receptor blocking antihistamines with good efficacy but with fewer side effects than are associated with the classic antihistamines. Astemizole and terfenadine, both introduced in recent years, are non-sedating antihistamines (19, 22). Loratadine is a new antihistamine, which has been shown to be efficacious, long-acting and without significant activity on the central nervous system (5, 7).

The aim of this study was to evaluate the efficacy and safety of loratadine in comparison with clemastine, an efficacious conventional antihistamine, and placebo in the treatment of seasonal allergic rhino-conjunctivitis.

PATIENTS AND METHODS

Patients of either sex were included on a voluntary basis if they were over the age of 18, presented a history of rhino-conjunctivitis during the birch pollen season for at least two preceding seasons, and showed a positive skin prick test to birch pollen extract (Pharmalgen 10,000 BU/ml, DHS prick test lancet, wheal diameter 3 mm > negative control).

Patients with asthma, perennial rhinitis, polyps, marked deviation of the nasal septum, or those taking drugs that could influence the results, were excluded from the study, as were pregnant and lactating women.

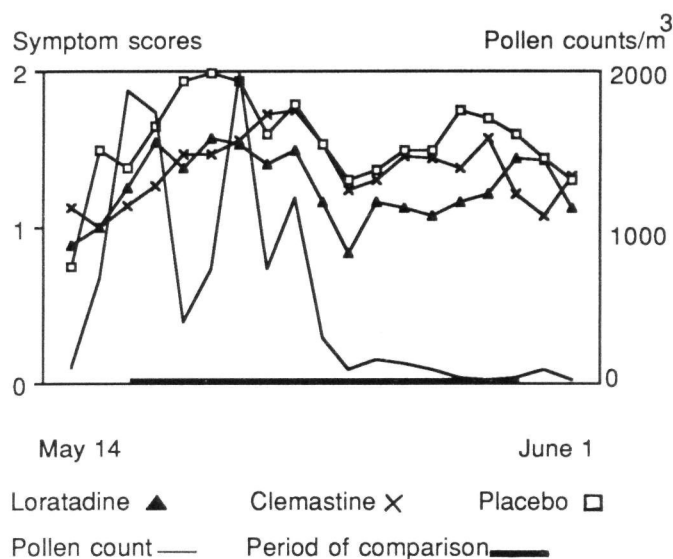


Fig. 1. Daily mean symptom scores for the overall allergic condition in relation to birch pollen counts.

Loratadine, clemastine and placebo were identically encapsulated. To blind the treatments the following alternatives were given: a) loratadine 40 mg once daily with placebo as the second dose, b) clemastine 1 mg twice daily, or c) placebo twice daily.

Eight rhino-conjunctivitis symptoms including sneezing, itching, discharge and stuffiness of the nose, itching, tearing and redness of the eyes and itching of the palate, were scored individually on a scale of 0 (none) to 3 (severe) each evening by the patient, as was an overall estimation of the allergic condition. Patients entered their symptom scores daily on diary cards.

Daily birch pollen counts for the local area were obtained from the Swedish Meteorological and Hydrological Institute (SMHI).

The study was approved by the Regional Ethics Committee for Human Research at the University Hospital of Linköping and was conducted by two ENT centers (Linköping and Västjör).

The study had a double-blind design with patients randomized into three parallel groups receiving loratadine, clemastine, or placebo, respectively.

Only patients with moderate or severe rhino-conjunctivitis were eligible for the study. The treatment period was 2 consecutive weeks. The patients were seen at entry and on treatment days 3, 7, and 14. At the follow-up visits the

diary cards were collected and the eight rhino-conjunctivitis symptoms, the overall allergy condition, and the therapeutic response, were evaluated by the physician. The patients were also questioned about adverse experiences and consumption of other drugs. A physical examination of the nose and eyes was performed, and vital signs including pulse rate, blood pressure, respiration rate and body temperature were recorded at all visits. Hematology, blood chemistry and urinalysis were performed and body weight was measured before the start of treatment and at the last visit.

For evaluation of efficacy the unpaired t-test was used to compare the three treatment groups. The chi-square test was used in the evaluation of sedation.

RESULTS

One hundred and seven patients were enrolled in the study (47 and 60 patients in Linköping and Västjör, respectively). As all patients had to be symptomatic in order to become eligible, they entered the study on different days. The demographic data, such as age, body weight, duration of allergic condition, and total symptom scores at entrance, did not differ significantly among the three treatment groups.

Efficacy evaluation

Eleven patients, three in the loratadine group, four in the clemastine and four in the placebo groups, required one or more additional drugs for systemic use or locally in the nose and eyes in order to reduce their allergy symptoms during peak pollen periods. Symptom scores recorded on those days when intake of additional drugs could have influenced the results were excluded from the efficacy evaluation.

The daily mean symptom scores from patients on therapy were calculated from the patients' diary cards. The values for the overall allergic condition are shown together with the pollen concentrations in Fig. 1.

Statistical differences between the results from the three treatment groups were based on

symptom scores obtained during 15 consecutive days with the largest number of patients on treatment: 30 patients in the loratadine group, 29 in the clemastine group and 32 patients in the placebo group. The mean score values for all separate symptoms are shown in Fig. 2.

There were no statistical differences as regards clinical efficacy of the same treatment drug between the two centres. Statistical differences between the three treatment groups are shown in Table 1. Loratadine significantly reduced all symptoms in comparison with placebo except nasal stuffiness, which showed only a tendency to reduction. The efficacy of clemastine in comparison with placebo was less pronounced, demonstrating significant reduction

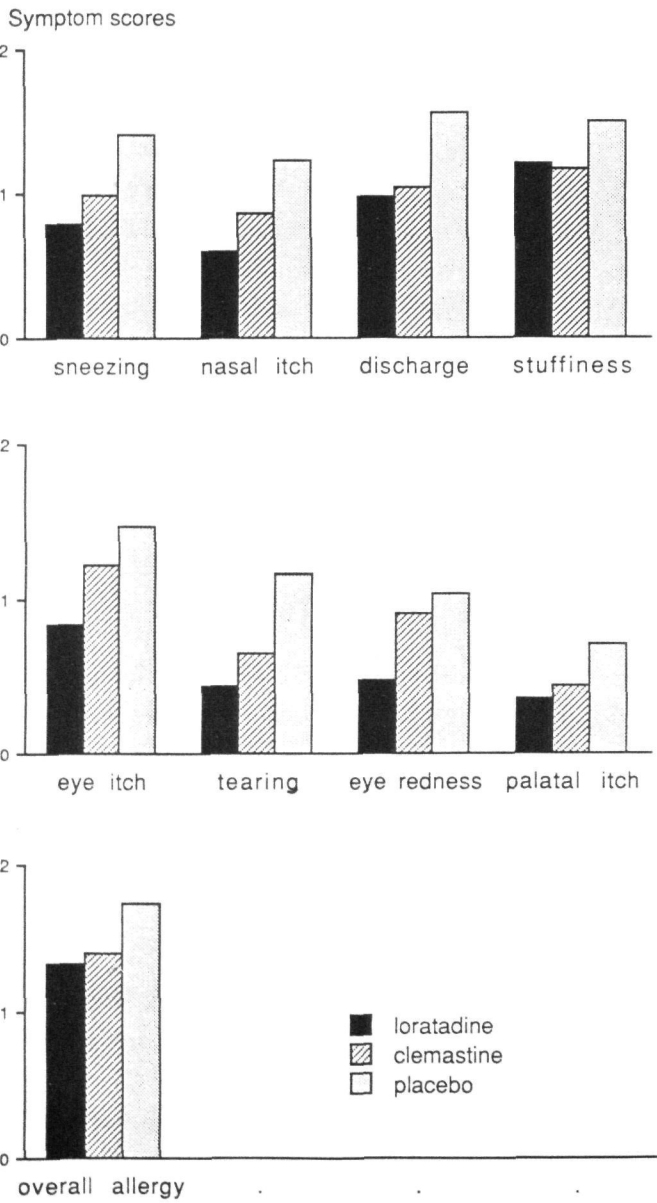


Fig. 2. Mean score values for all separate symptoms.

Table 1
Statistical comparison between mean symptoms scores from the treatment groups. NS = not significant

	Lorata- dine vs Clemastine	Lorata- dine vs Placebo	Clemastine vs Placebo
Nasal symptoms			
Sneezing	NS	$P < 0.001$	$P < 0.05$
Itching	NS	$P < 0.001$	NS
Discharge	NS	$P < 0.01$	$P < 0.01$
Stuffiness	NS	NS	NS
Eye symptoms			
Itching	$P < 0.05$	$P < 0.001$	NS
Tearing	NS	$P < 0.001$	$P < 0.01$
Redness	$P < 0.05$	$P < 0.01$	NS
Palatal itching	NS	$P < 0.05$	NS
Overall condition	NS	$P < 0.01$	$P < 0.05$

only for sneezing, nasal discharge, tearing and for the overall allergic condition with only a tendency to reduction of the remaining symptoms. When the two active treatment groups were compared, significant differences were found for itching and redness of the eyes in favour of loratadine. The physicians' evaluation scores were in agreement with those of the patients.

Safety evaluation

All patients were evaluated for safety. When considering "probably" and "possibly" related adverse reactions, the incidence was 12/35 in

Table 2
Numbers of reported adverse experiences (a and b = symptoms occurring in one patient)

	Loratadine <i>n</i> = 35	Clemastine <i>n</i> = 36	Placebo <i>n</i> = 36
Sedation	10(a)	16	5(b)
Dizziness	1	-	-
Headache	1(a)	-	2(b)
Insomnia	-	-	1(b)
Mouth dryness	1	-	1
Nausea	-	-	1
Weight gain	-	-	-

the loratadine group, 16/36 in the clemastine group and 8/36 in the placebo group (Table 2).

Sedation of varying severity was predominant among the adverse reactions. Compared with placebo there was no statistical difference in sedation rate with loratadine treatment, but a significantly higher incidence was noted with clemastine treatment ($P < 0.05$).

Dizziness, headache, insomnia, dryness of the mouth and nausea were reported rarely and weight gain was not observed. None of the laboratory parameters or vital signs were affected in any of the three treatment groups.

Discontinuation

Twenty-six patients discontinued treatment before completing the 2-week study period. Twenty patients discontinued due to treatment failure, 13 patients in the placebo group, three in the loratadine group and four in the clemastine group. One patient in the placebo group discontinued due to drowsiness, and one in the clemastine group due to concomitant illness. One patient in the clemastine group and three in the placebo group withdrew for personal, non-specified reasons.

DISCUSSION

When allergen elimination in allergic rhinoconjunctivitis is impossible or gives inadequate relief, symptomatic improvement can be achieved by various drugs, such as antihistamines, ephedrinergic substances, mast cell stabilizing agents or steroids. The introduction of topical steroids for intranasal use constituted an important milestone in ameliorating nasal symptoms, but does not rule out the need for antihistamines.

An "ideal" antihistamine should have good efficacy, rapid onset and optimal duration of action, and should be free of troublesome adverse effects such as sedation. This implies rapid absorption, specific H_1 -receptor affinity, no interaction at peripheral cholinergic receptors and no penetration into the central nervous system.

In recent years, a new class of non-sedating antihistamines has been introduced. Astemizole is efficacious but not entirely free from side effects. Its onset time is slow, accumulation of the drug in plasma is observed, the elimination rate is prolonged, and increased appetite and weight gain have been reported (12, 16, 18, 23). Terfenadine has a rapid onset of action and with an efficacy comparable to or less than other antihistamines (8, 13, 15).

Loratadine is a new, orally effective and long-acting antihistamine with minimal CNS and anticholinergic effects (1, 2, 3, 4, 14). It was shown to possess a mast cell stabilizing effect as well as a selective antagonistic property on histamine-induced reactions including bronchospasm (17). The drug is rapidly absorbed with peak concentrations in serum reached within 2 h. The half-life of loratadine is 8–11 h and 17–24 h for the biologically active metabolite descarboethoxy-loratadine (9). Renal impairment has no effect on the pharmacokinetics (10).

The birch pollen concentrations during this study showed pronounced variations from day to day with very high intermittent peaks, the magnitude of which were approximately the same when measured at different places in the region of Sweden, to which the two conducting centers belong.

To confirm a manifest allergy, the patients did not enter this study until the symptoms were moderate or severe. As a consequence, the patients did not start simultaneously, which might affect the efficacy evaluation due to pronounced day to day variations in pollen counts. To elude this problem the mean values over a long treatment period were calculated before comparing the results from the three groups. For the same reason the time to onset of symptom relief was not studied. At the time of our study, the optimal dose of loratadine was not established. Actually, this study with loratadine given in a single daily dose of 40 mg was one part of a multicentre study, where loratadine was compared at various doses with various antihistamines by other centres. The dose-response curve in the efficacy evaluation of the rhinoconjunctivitis treatment turned out to be

flat, justifying the choice of 10 mg to be the relevant dose for future clinical use (personal communication with Schering Corporation).

Our study clearly showed loratadine to be significantly more efficacious than placebo in alleviating all rhino-conjunctivitis symptoms except nasal stuffiness, albeit this was partially reduced. Loratadine thus exhibited similarities to other antihistamines in terms of differences in reducing individual rhino-conjunctivitis symptoms (12). The efficacy of clemastine was more modest, although significant in comparison with placebo for a number of symptoms. The sedation rate of loratadine given as a single daily dose of 40 mg did not differ from placebo, and other adverse effects were few and mild.

Further reports have shown the efficacy and safety of loratadine in comparison with placebo and other antihistamines. Loratadine, given to patients with allergic rhinitis, as a single daily dose of 10 mg was comparable with clemastine 1 mg twice daily (6), with mequitazine 5 mg twice daily (21) and with terfenadine 60 mg twice daily (11), and was significantly more efficacious than placebo in all studies. Loratadine given in increasing doses was shown to reduce histamine-induced wheal responses more effectively than chlorpheniramin maleate in a dose-related fashion (20). The sedation rate did not differ from placebo in any of these comparative studies.

In conclusion, our study showed loratadine, given in a dose of 40 mg, to be an antihistamine with good efficacy in allergic rhino-conjunctivitis, with a duration that permits once daily dosage and a sedation rate comparable to placebo and with no signs of toxicity, which implies a wide safety margin, when using the recommended dose of 10 mg once daily for clinical use.

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