

Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis

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Background: This study was designed to compare the efficacy and tolerability of a new topical (nasal spray and eye drops) H_1 -receptor antagonist, levocabastine, with that of orally administered terfenadine for the prophylaxis and treatment of seasonal allergic rhinoconjunctivitis.

Methods: A total of 115 patients with documented birch pollen allergy were enrolled in this randomized, double-blind, double-dummy, parallel-group trial. Treatment was initiated immediately before the birch pollen season started and continued for a total of 8 weeks. Xylometrazoline (Otrivin) nasal spray was permitted as rescue medication.

Results: The investigator's evaluation of symptoms showed similar effects for levocabastine and terfenadine. Both the patients' and the investigator's global evaluations of ocular and nasal symptoms disclosed a somewhat higher percentage of good or excellent results for levocabastine, but the differences were not statistically significant. Visual analog scale ratings from the patients' diaries showed better results for levocabastine. Levocabastine was significantly more effective than terfenadine in relieving sneezing, rhinorrhea, lacrimation, itch, and burning sensation ($p < 0.05$). For some symptoms, levocabastine was significantly more effective than terfenadine on days when the pollen count was high. There were no statistically significant differences in the use of rescue medication or in the incidence of adverse reactions reported in each treatment group.

Conclusions: In the present study topical levocabastine was frequently more effective than orally administered terfenadine for the treatment of seasonal allergic rhinoconjunctivitis. Both drugs were well-tolerated. (*J ALLERGY CLIN CLIN IMMUNOL* 1993;92:73-81.)

Key words: Allergic rhinoconjunctivitis, levocabastine, topical antihistamine, H_1 -receptor antagonist

The vast majority of allergic reactions in the eye and nose are mediated through the effects of histamine on H_1 -receptors.¹ Consequently, it is not surprising that antihistamines are a cornerstone for the treatment of ocular and nasal allergies. Indeed, the emergence of potent yet non-sedating antihistamines has largely been responsible for an increase in the use of this particular class of

Abbreviations used

VAS: Visual Analog Scale
AUC: Area under the curve

drugs for this indication. This trend has recently been enhanced by the development of levocabastine, a long-acting, potent, and highly selective H_1 -antagonist, designed for topical use.²

Topical antihistamines may have a number of potential advantages over orally administered antihistamines. First, a topical agent will most likely provide more rapid relief from symptoms because it is administered directly to the affected site and is, consequently, immediately available. Second, a topical antihistamine is less likely to produce systemic side effects because the amount of active

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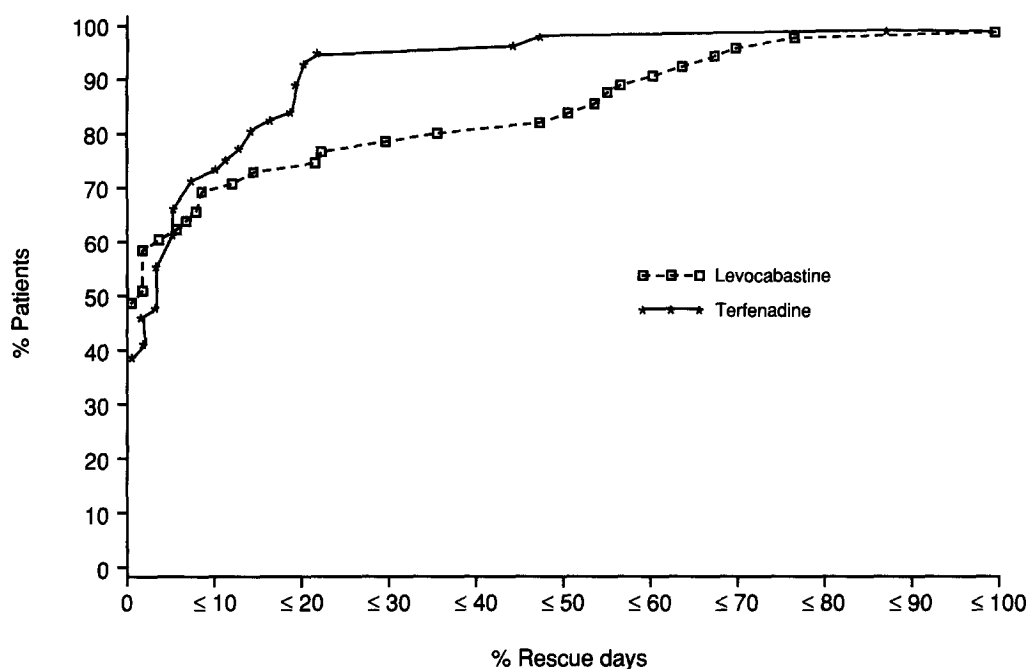


FIG. 1. Frequency of use of rescue medication in the two treatment groups.

drug reaching the circulation will be much less than that of an orally administered drug.

Other topical agents used for the treatment of allergic rhinoconjunctivitis include corticosteroids, vasoconstrictors, and sodium cromoglycate. Although topical corticosteroids provide effective relief from nasal symptoms, these agents cannot be used for the routine relief of ocular symptoms because of the potential risk of long-term complications such as steroid-induced cataracts and glaucoma.^{3, 4} Moreover, topical corticosteroids have a slow onset of action and take several days to achieve maximum effect. Topical vasoconstrictors are also unsuitable for long-term administration. Furthermore, they are limited by the need for frequent instillation, a feature which is known to affect patient compliance adversely. Although topical vasoconstrictor-antihistamine combinations are available, such preparations have similar limitations. Sodium cromoglycate is an effective agent for the treatment of allergic rhinoconjunctivitis. However, this agent must be instilled four times daily, and treatment should preferably be initiated before allergen exposure.

Levocabastine has a rapid onset of action. Studies have shown that levocabastine eye drops provide relief from symptoms within 15 minutes of instillation.⁵ Furthermore, a number of comparative trials have demonstrated that this topical antihistamine is at least as effective as topical

sodium cromoglycate for the treatment of allergic rhinoconjunctivitis,⁶⁻¹¹ and as effective as vasoconstrictor-antihistamine combinations in providing relief from symptoms of allergic conjunctivitis.¹²

The aim of the present study was to compare the efficacy and tolerability of levocabastine eye drops and nasal spray with that of orally administered terfenadine for the prophylaxis and treatment of seasonal allergic rhinoconjunctivitis in patients with birch pollen allergy.

METHODS

Patients

A total of 115 patients were enrolled in the study (59 men and 56 women). All patients had at least a 1-year history of birch pollen allergy and positive skin prick test results for birch pollen only or both birch pollen and timothy grass pollen within the last year. Exclusion criteria included: participation in a hyposensitization program; diseases that might complicate evaluation of the study drug such as large, obstructive nasal polyps or symptomatic septal deviations; concurrent therapy with corticosteroids, sodium cromoglycate, decongestants, and antihistamines; and use of soft contact lenses. Pregnant, nursing, and fertile women without adequate contraception were also ineligible for participation in this trial.

The trial was approved by the regional ethics committee, and all patients gave their written informed consent.

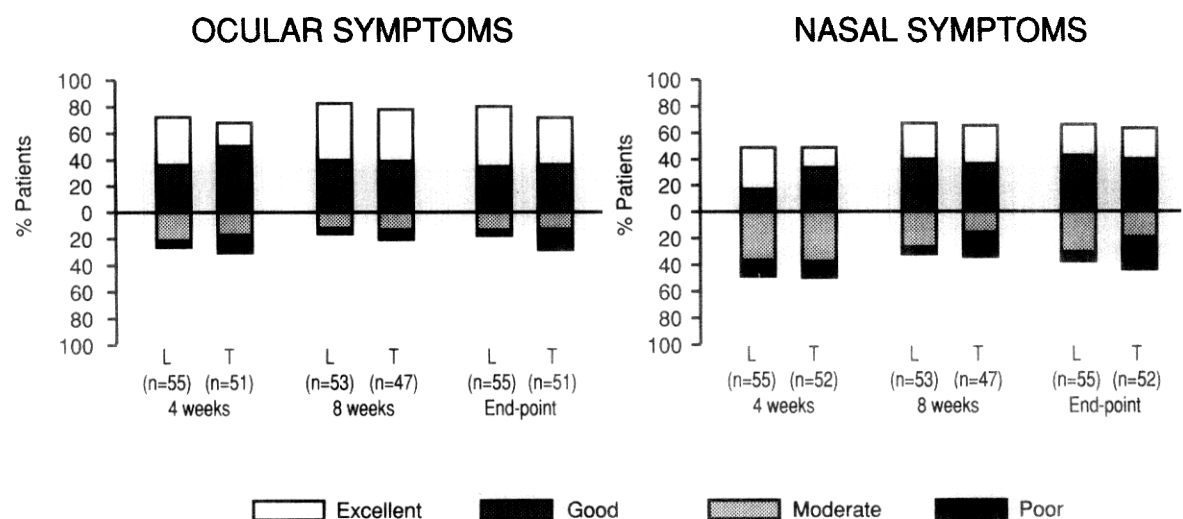


FIG. 2. The patients' global efficacy evaluations for ocular and nasal symptoms throughout the entire study period. L, Levocabastine; T, terfenadine.

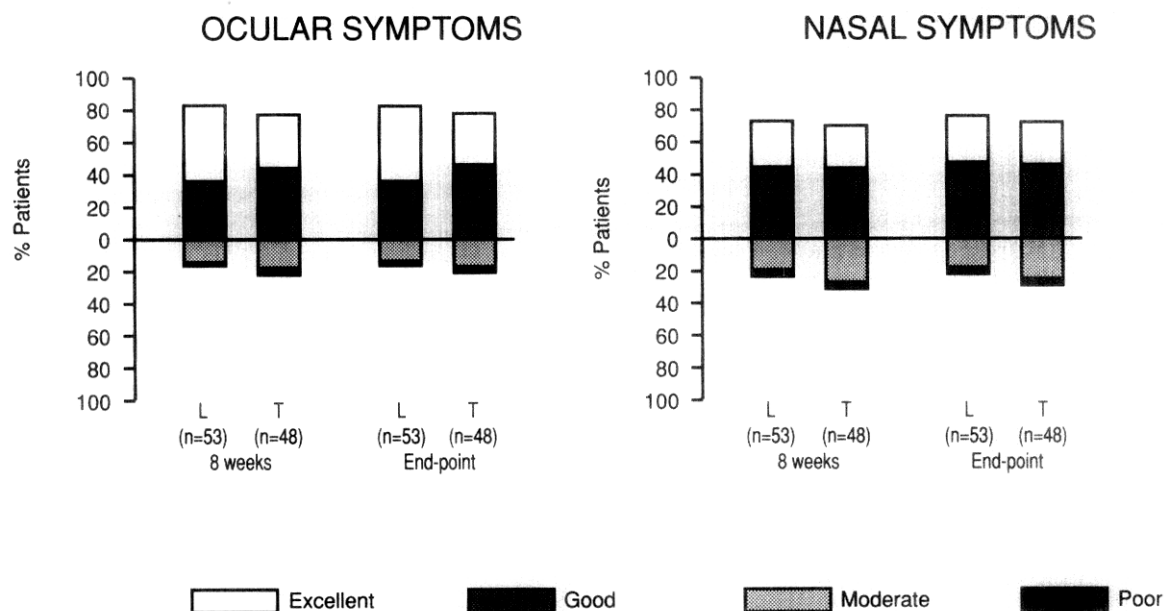


FIG. 3. The investigator's global efficacy evaluations for ocular and nasal symptoms throughout the entire study period. L, Levocabastine; T, terfenadine.

Study design

The study was a multicenter, randomized, parallel-group, double-blind, double-dummy trial in patients allergic to birch pollen only or to both birch and grass pollen. The patients were stratified into these two allergy subgroups. The patients were then randomized in blocks of four within each subgroup to receive either levocabastine eye drops (0.5 mg/ml, 1 drop in each eye) and nasal spray (0.5 mg/ml, 2 puffs in each nostril) plus

orally administered placebo twice daily or placebo eye drops and nasal spray with orally administered terfenadine, 60 mg twice daily. The placebos used were identical to the active treatments minus the study drugs.

All previous antiallergic treatment was discontinued before randomization. Furthermore, patients were required to complete a wash-out period of 7 days if they had received oral corticosteroids orally and a wash-out period of 3 days for other drugs excluded by the study

TABLE I. Investigator assessments of symptom severity: Mean scores

Symptom	Levocabastine				Terfenadine			
	Start	Week 4	Week 8	End point	Start	Week 4	Week 8	End point
Sneezing	0.69	0.53	0.39	0.39	0.49	0.51	0.31	0.29
Itchy nose	0.39	0.40	0.40	0.39	0.21	0.26	0.35	0.33
Rhinorrhea	0.67	0.62	0.45	0.47	0.53	0.55	0.49	0.47
Congestion	0.66	0.89	0.59	0.62	0.60	0.67	0.74	0.73
Red eyes	0.45	0.22*	0.21	0.20	0.44	0.57	0.29	0.33
Lacrimation	0.26	0.20	0.13	0.13	0.30	0.20	0.14	0.14
Lid edema	0.05	0.07	0.06	0.06	0.12	0.12	0.14	0.14
Itchy eyes	0.50	0.36	0.28	0.27	0.53	0.35	0.33	0.31
Burning sensation	0.35	0.27	0.19	0.20	0.25	0.20	0.18	0.18
Worst nose symptom	1.05	1.20	0.79	0.82	0.97	1.10	0.86	0.84
Worst eye symptom	0.76	0.66†	0.49	0.49	0.83	0.90	0.47	0.51
Worst of all symptoms	1.26	1.35	0.89	0.91	1.21	1.45	0.98	1.02

**p* < 0.01, levocabastine versus terfenadine.†*p* < 0.05, levocabastine versus terfenadine.

protocol. Treatment was initiated immediately before the start of the birch pollen season, as predicted from experience in previous years, and the study lasted for a total of 8 weeks.

The only rescue medication allowed was xylometazoline (Otrivin) nasal spray (1 puff in each nostril three times daily for a maximum of 7 consecutive days), which was only permitted in cases of severe nasal congestion. If absolutely necessary, rescue medication could also be used during the first 2 days of the trial to ensure adequate exposure to the levocabastine nasal spray.

Efficacy assessments

Ocular symptoms of redness, itching, burning sensation, lacrimation, and lid edema and nasal symptoms of sneezing, itch, congestion, and rhinorrhea were assessed by the investigator immediately before the start of the trial and after 4 and 8 weeks. Symptom severity was graded on a scale from 0 to 3 (0 = absent, 1 = mild [noticeable only on occasion but not bothersome], 2 = moderate [noticeable from time to time and tending to be bothersome], 3 = severe [frequently noticeable and bothersome]). The same symptoms were assessed by the patients on a daily basis with the Visual Analog Scale (VAS) where 0 = absence of symptoms and 100 = very severe symptoms.

All patients performed a global evaluation of treatment efficacy at weeks 4 and 8. Therapy was graded as excellent, good, moderate, or poor. After 8 weeks, the investigator also performed a global evaluation of therapeutic efficacy using the same criteria.

Pollen counts were performed daily by the Norwegian National Weather Report Institute. Pollen counts greater than 50/m³ were classed as high; pollen counts of less than or equal to 50/m³ were classed as low.

Adverse reactions were recorded after 4 and 8 weeks

of treatment. A routine blood biochemical and hematologic examination was performed at the start of the trial and after 8 weeks of treatment.

Statistical analysis

In addition to the nine ocular and nasal symptoms listed above, the worst (most severe) ocular symptom, the worst nasal symptom, and the worst of all symptoms were analyzed for each patient before the start of the trial and after 4 and 8 weeks of treatment. The following parameters were derived from the patients' diaries: daily VAS ratings of symptom severity, the area under the curve (AUC) for the different VAS scores (expressed as a percentage of the maximal AUC and calculated with the trapezoidal rule), the percentage of days with severe symptoms (VAS ≥ 50%) and the percentage of symptom-free days (VAS ≤ 10%).

Further analysis of symptom scores was performed with a penalization technique. In this analysis use of rescue medication resulted in addition of a penalty point to the original symptom severity scores. The rationale behind this technique is that symptom severity and use of rescue medication may be evaluated as a single entity, rather than as two unrelated parameters, because symptom severity scores may be influenced by the use of rescue medication.

Intergroup differences in these parameters, the investigator's rating of symptoms and the global efficacy assessments were analyzed by means of the Mann-Whitney U test. An analysis was conducted over the entire study period for the entire patient population for those days when the pollen count was recorded as high and, alternatively, for those days when the pollen count was low. All parameters were analyzed on an intention-to-treat basis; that is, all available data from all patients were used.

TABLE II. Patient evaluation of symptom severity on VAS

Symptom	Levocabastine		Terfenadine	
	Severe days (%)	Symptom-free days (%)	Severe days (%)	Symptom-free days (%)
Congestion	10	51	11	44
Rhinorrhea	6*	64	8	55
Sneezing	5*	56	8	49
Itchy nose	3	71*	6	60
Burning sensation	3	79*	4	75
Itchy eyes	4	63	6	55
Red eyes	3	77	5	71
Lacrimation	1	83†	3	73
Lid edema	1	84	3	81
Worst nose symptom	17	37	16	29
Worst eye symptom	8	57*	9	44
Worst of all symptoms	19	34	18	23

Scores were calculated as percentage of the maximal possible score: percent of severe days (VAS score $\geq 50\%$), percent of symptom-free days (VAS score $\leq 10\%$).

* $p \leq 0.05$, levocabastine versus terfenadine.

† $p \leq 0.01$, levocabastine versus terfenadine.

RESULTS

A total of 115 patients were enrolled in the trial, 58 (28 women and 30 men) in the levocabastine group and 57 (28 women and 29 men) in the terfenadine group. The mean age was 32.5 years (SEM = 2.6 years) for the women and 31.2 years (SEM = 2.6 years) for the men in the levocabastine group, and 30.2 years (SEM = 2.9 years) for the women and 31.3 years (SEM = 2.6 years) for the men in the terfenadine group. Baseline symptom severity was low in both treatment groups.

A total of 13 patients failed to complete the study: eight patients withdrew because they found the treatment ineffective (two from the levocabastine group and six from the terfenadine group), and another four patients (two from each treatment group) were excluded because they failed to comply with the study protocol. Another patient in the terfenadine group withdrew from the study for unspecified reasons.

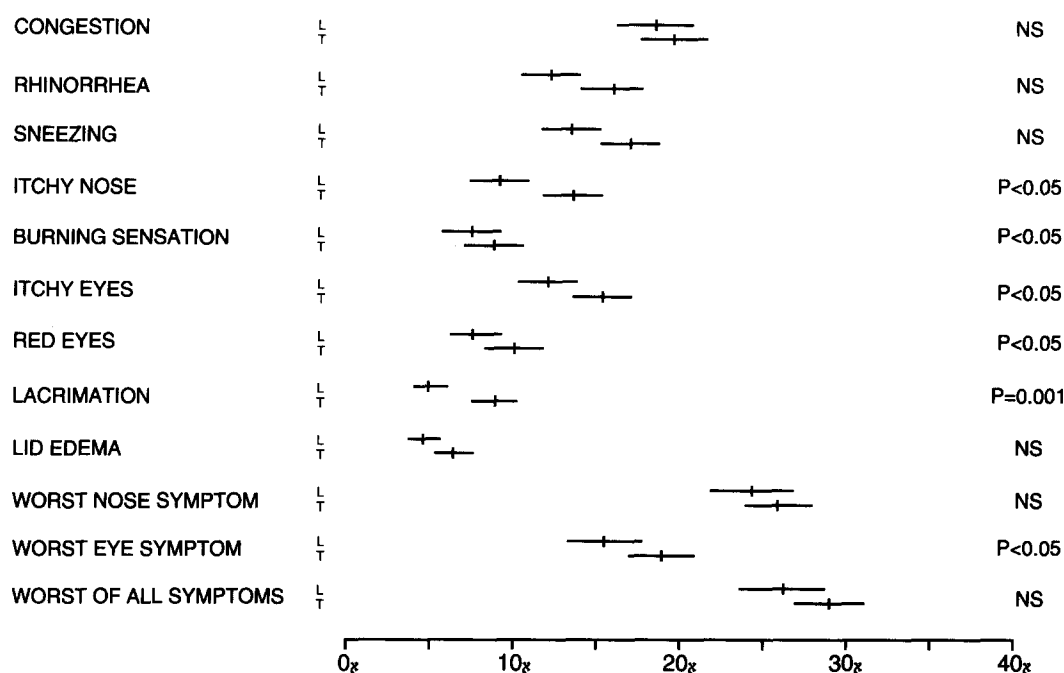
Analysis of pollen counts revealed that the aim to initiate treatment before the start of the birch pollen season had been achieved. The pollen counts began to rise shortly after initiation of therapy and remained elevated for the remainder of the study period. High pollen counts were recorded during a period of 2 consecutive weeks, which permitted analysis of therapeutic efficacy as a function of the pollen count.

As shown in Fig. 1, the frequency of use of

rescue medication was lower in the levocabastine group than in the terfenadine group. The mean frequency of use was 9% and 16% of treatment days in the two groups, respectively. However, this intergroup difference did not attain statistical significance.

The results of the global efficacy evaluations for both ocular and nasal symptoms showed no statistically significant differences between the two treatment regimens (Figs. 2 and 3). The investigator rated the effect of therapy on ocular symptoms to be excellent or good in 89% of patients treated with levocabastine and in 83% of the patients treated with terfenadine. The therapeutic effect on nasal symptoms was rated excellent or good in 74% of patients treated with levocabastine compared with 69% of patients treated with terfenadine. After 4 weeks of treatment, 73% of patients treated with levocabastine rated the effect on ocular symptoms to be excellent or good. By week 8 the proportion had increased to 85%. The corresponding values for the terfenadine group were 69% and 81%, respectively. The effect of treatment on nasal symptoms was rated to be excellent or good in 51% of patients treated with levocabastine and 50% of patients treated with terfenadine at week 4. By week 8, the corresponding values were 68% and 66%, respectively.

Investigator assessments of symptom severity at weeks 4 and 8 are shown in Table I. The scores



L=Levocabastine (n=57); T=Terfenadine (n=55)

FIG. 4. AUC of symptom severity over entire study period in both treatment groups (derived from the patient diaries).

TABLE III. Patient evaluation of symptom severity on VAS

Symptom	Levocabastine				Terfenadine			
	Severe days (%)		Symptom-free days (%)		Severe days (%)		Symptom-free days (%)	
	High	Low	High	Low	High	Low	High	Low
Congestion	9	12	49	52	13	8	37	48
Rhinorrhea	6	4	59	66	9	7	48	59
Sneezing	5	4	55	56	9	7	45	50
Itchy nose	3	2*	69*	72	6	7	55	66
Burning sensation	3	4	77	81	5	3	71	79
Itchy eyes	5*	3	57*	67	9	5	43	61
Red eyes	2	2	71	78	5	4	65	77
Lacrimation	1*	1	81†	85*	5	3	66	78
Lid edema	1	1	79	88*	3	3	76	84
Worst nose symptom	16	16	32	38	19	14	21	33
Worst eye symptom	8	6	48*	60	11	7	33	51
Worst of all symptoms	19	18	28*	36	22	16	13	28

Scores were calculated as percentage of the maximal possible score on high and low pollen days: percent of severe days (VAS score $\geq 50\%$), percent of symptom-free days (VAS score $\leq 10\%$).

* $p \leq 0.05$, levocabastine versus terfenadine.

† $p \leq 0.01$, levocabastine versus terfenadine.

are similar in the two treatment groups, with the exception of red eyes, for which the score was significantly lower in the levocabastine group at week 4 ($p < 0.01$). The calculated score for the worst eye symptom was also significantly lower in

the levocabastine group at the same visit ($p < 0.05$).

Table II, which is derived from the patients' diaries, shows the percentages of severe and symptom-free days in the two treatment groups.

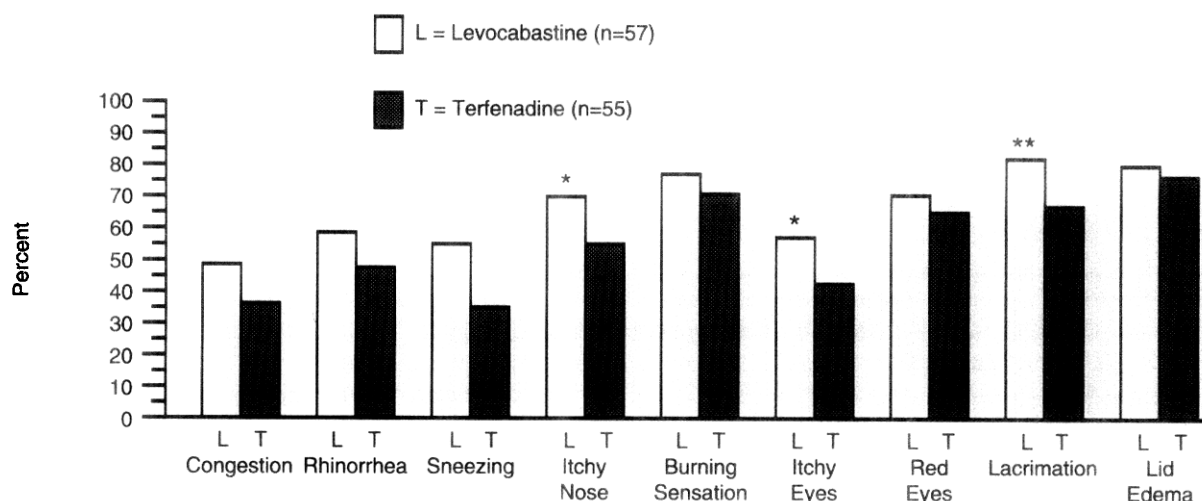


FIG. 5. Percentage of symptom-free days in the two treatment groups on days with high pollen counts (* $p \leq 0.05$; ** $p \leq 0.01$, levocabastine vs terfenadine).

The percentage of symptom-free days was generally higher in the patients treated with levocabastine. The intergroup differences were significant for itchy nose ($p < 0.05$), burning sensation ($p < 0.05$), lacrimation ($p < 0.01$), and the worst eye symptom ($p < 0.05$). The percentage of days on which symptoms were severe also tended to be lower in the levocabastine group. This was statistically significant for rhinorrhea ($p < 0.05$) and sneezing ($p < 0.05$).

The AUC for symptom severity over the entire treatment period, which was also derived from the patients' diaries, was significantly lower in the levocabastine group than in the terfenadine group for itchy nose ($p < 0.05$), burning sensation ($p < 0.05$), itchy eyes ($p < 0.05$), lacrimation ($p = 0.001$), and the worst eye symptom ($p < 0.05$) as shown in Fig. 4.

Separate analyses of intergroup differences on high and low pollen days (Table III) revealed that the percentage of high pollen days when symptoms were severe also tended to be lower in the levocabastine group for all symptoms studied (Fig. 5). The findings were statistically significant for lacrimation ($p < 0.05$) and itchy eyes ($p < 0.05$). The percentage of low pollen days with severe symptoms was also lower in the levocabastine group, with the exception of congestion and burning sensation. Findings were of significance for itchy nose ($p < 0.05$). In addition, the percentage of symptom-free days was higher in the levocabastine group on both low and high pollen days. On high pollen days, this was significant for itchy nose ($p < 0.05$), itchy eyes ($p < 0.05$), and lacrimation ($p < 0.01$). On low pollen days, the intergroup differences attained

significance for lacrimation ($p < 0.05$) and lid edema ($p < 0.05$).

Analysis of symptom severity scores with the penalization technique did not appear to affect study outcome; the only difference was that intergroup difference in percentage of days on which symptoms of rhinorrhea were severe was no longer statistically significant in favor of levocabastine.

Adverse experiences were reported by a total of 16 patients in the levocabastine group and 12 in the terfenadine group. A wide range of adverse reactions was reported. Three patients in the levocabastine group complained of drowsiness and seven complained of tiredness, compared with one and two patients in the terfenadine group, respectively. However, this difference was not statistically significant. It should be noted that in both treatment groups, the vast majority of adverse events occurred during the first week of treatment.

No clinically significant changes were observed in any of the blood biochemical and hematologic parameters investigated.

DISCUSSION

The primary aim of this trial was to compare the efficacy and tolerability of the topical H_1 -receptor antagonist levocabastine with that of the systemic antihistamine terfenadine in the treatment of seasonal allergic rhinoconjunctivitis. The study was timed to start with the onset of the birch pollen season. Subsequent analysis of pollen counts revealed that this aim had been achieved. Initial symptom severity was low, so both prophylaxis and the ability of the two agents to relieve symptoms could be evaluated.

Both drugs were well tolerated. There were no statistically significant differences in the incidence of adverse reactions in the two treatment groups. Although more patients who were receiving levocabastine reported tiredness and drowsiness, the difference compared with terfenadine was not statistically significant and, importantly, did not lead to withdrawal of the drug. Contact sensitization is a particular concern with any topical therapy. However, extensive studies of the local tolerance of levocabastine eye drops and nasal spray in nonatopic and atopic subjects for periods of up to 4 months have shown that the incidences of ocular and nasal irritation associated with levocabastine are no different from those observed with placebo.¹³

The only rescue medication permitted was a vasoconstrictor nasal spray (xylometazoline, Otrivin) for relief of nasal congestion. This was deemed to be necessary in order to ensure adequate exposure of the nasal mucosa to the study medications, because there is evidence to suggest that H₁-receptor antagonists are not particularly effective at relieving nasal congestion.^{14, 15} The use of rescue medication was lower in the levocabastine group than in the terfenadine group, although the difference did not attain statistical significance. Analysis of the trial data with a penalization technique for use of rescue medication did not affect the results, which suggests that use of rescue medication did not influence study outcome in any way.

Overall, the global efficacy assessments performed by both the investigator and patients indicated that topical levocabastine tended to be more effective than orally administered terfenadine for the prophylaxis and treatment of both ocular and nasal symptoms. However, intergroup differences were not statistically significant. The investigator's evaluation of symptoms showed similar effects for levocabastine and terfenadine, with the exception of red eyes, for which the score was significantly lower in the levocabastine group after 4 weeks of treatment. VAS ratings in the patients' diaries consistently indicated better results for levocabastine, and statistically significant differences were demonstrated in favor of levocabastine for several symptoms.

Topical levocabastine appeared to be more effective than orally administered terfenadine on high pollen days. Symptom severity was generally lower in the levocabastine group than in the

terfenadine group on days when the pollen count was high, and the percentage of symptom-free days was higher.

Because this was a double-blind trial and patients in the terfenadine group benefitted from the use of placebo eye drops and nasal spray, it is possible that the high placebo response rate associated with the use of a topical placebo may have masked the true difference in efficacy between the two therapeutic approaches. Placebo response rates as high as 40% have been reported for eye drops and nasal sprays.¹³

In conclusion, there is now a considerable body of clinical evidence to suggest that levocabastine is a well-tolerated and effective agent for the treatment of seasonal ocular and nasal allergies.⁶⁻¹² In the present study topical levocabastine was frequently more effective than orally administered terfenadine for the prophylaxis and treatment of seasonal allergic rhinoconjunctivitis.

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