

Levocabastine nasal spray better than sodium cromoglycate and placebo in the topical treatment of seasonal allergic rhinitis

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The efficacy and safety of the nasal administration (twice in each nostril, four times a day) of levocabastine (0.5 mg/ml) were compared with those of sodium cromoglycate (20 mg/ml) and placebo in a 2-week, parallel, double-blind trial in patients with seasonal allergic rhinitis. At the end of treatment, 89% of patients in the levocabastine-treated group rated their treatment as globally good or excellent as compared with 32% ($p = 0.003$) of sodium cromoglycate-treated and 35% ($p = 0.002$) of placebo-treated patients. According to the investigators' ratings, the severest nasal symptom and ocular complaints responded better to levocabastine than to cromoglycate ($p = 0.05$ and $p = 0.03$) or placebo treatment ($p = 0.03$ and $p = 0.001$). Visual analogue scale ratings in patients' diaries indicated that at the end of therapy, nasal symptoms were less severe in the levocabastine-treated group than in the sodium cromoglycate-treated ($p = 0.03$) or placebo-treated group ($p = 0.001$). Total symptom severity as a percentage of the theoretical maximum symptom severity during the treatment period was lower for levocabastine than for sodium cromoglycate ($p = 0.06$) or placebo ($p = 0.004$) for the severest nasal symptom (35% versus 47% and 76%), sneezing (the most frequent symptom) (27% versus 42% and 67%), and itchy nose (18% versus 37% and 67%). The percentage of days at which nasal symptoms were entirely absent was markedly higher in the levocabastine-treated (33%) than in the sodium cromoglycate-treated (9%; $p = 0.006$) or placebo-treated (3%; $p = 0.001$) group. Adverse effects in the levocabastine-treated and sodium cromoglycate-treated group, and, in particular, daytime fatigue, did not occur more frequently than with placebo treatment. It is concluded that levocabastine is an efficacious and well-tolerated drug in the treatment of seasonal allergic rhinitis. (J ALLERGY CLIN IMMUNOL 1991;87:873-8.)

The role of histamine in eliciting symptoms in seasonal AR has been extensively studied during the past decade. Most classic rhinitis symptoms are mediated through effects of histamine via H_1 receptors, whereas both H_1 and H_2 receptors appear to play a role in histamine-induced nasal congestion.¹

Histamine is released locally from mast cells and basophils at the mucosal membranes, exerting its effects through histamine receptors. Theoretically, topical treatment would be ideal in treating such local symptoms. So far, therapy of seasonal AR, when it

Abbreviations used

AR: Allergic rhinitis
VAS: Visual analogue scale
q.i.d.: Four times a day
AUC: Area under the curve

is directed specifically against histamine, has been systemic. When topical treatment was used, it consisted either of nasal decongestants, steroids, or cromoglycate. None of these agents specifically antagonizes histamine. Topical antihistamine treatment was not feasible because none of the antihistamines was potent enough to be administered in small volumes. Recently, nasally instilled azatadine has been reported to suppress allergen-induced nasal symptoms and associated elevations of mediators.²

Levocabastine is a novel pure histamine H_1 antagonist that is 15,000 times more potent than chlor-

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TABLE I. Patient information

	Levocabastine	Cromoglycate	Placebo
No. of patients in efficacy analysis	18	19	20
(M/F)	(10/8)	(7/12)	(11/9)
Median age (yr)	29	26.5	32
(extremes)	(18-41)	(18-42)	(18-41)
Median weight (kg)	63	62	64
(extremes)	(52-85)	(49-82)	(48-80)
Median duration of disease (yr)	3	3	2
(extremes)	(1-10)	(1-10)	(1-6)
Most bothersome symptom*			
Sneezing	15/9	16/7	17/9
Runny nose	12/5	15/6	12/3
Itchy nose	12/1	17/2	17/6
Blocked nose	8/1	8/4	8/2
Ocular symptoms	13/2	12/0	14/0
Hypersensitivity to†			
Grasses	18	19	20
Weeds	0	3	0
Trees	4	6	4
Previously treated patients (total)	14	18	17
Hyposensitization	5	5	6
Medications	14	18	16
Global evaluation of previous treatments (good/moderate/NA‡)			
Sodium cromoglycate	1/1/0	0/5/0	2/4/1
Antihistamines	6/6/1	9/3/1	7/4/0
Topical corticosteroids	0/0/0	2/0/0	3/0/0

*Number of patients presenting symptom/number of patients considering symptom as the most bothersome.

†Number of patients.

‡Not available.

pheniramine in the rat model of 48/80-induced mortality.³ In two nasal provocation studies,^{4,5} levocabastine treatment has been demonstrated to protect atopic patients against allergen-induced nasal symptoms. The drug has no negative effect on ciliary function, as evidenced by ciliary transit times (data on file, Janssen Research Foundation).

The purpose of the present study was to evaluate a nasal spray formulation of levocabastine for efficacy and tolerance against sodium cromoglycate and placebo.

MATERIAL AND METHODS

Patients

Outpatients with clinical symptoms of seasonal AR in the previous hay fever season for whom a diagnosis was confirmed by skin and/or RAST and who presented with the moderate or severe degree of at least one typical symptom of seasonal AR were eligible for the study. Excluded were outpatients who had other forms of rhinitis, who took oral or nasal corticosteroids or any other nasal preparations during the study, or who took the following medications shortly before the investigation: oral or nasal corticosteroids in the last week, astemizole in the last month, and all other

antihistamines and nasal preparations during the last 3 days. In addition, severe renal and other serious diseases were designated as exclusion criteria.

The study was approved by the local ethics committee, and written informed consent was required of the participants.

Of the 77 patients recruited for the investigation, 20 (seven in the levocabastine-treated, seven in the cromoglycate-treated, and six in the placebo-treated group) did not qualify for the efficacy analysis. Of these exclusions, two (one, levocabastine-treated; one, placebo-treated) failed to meet the symptom-severity entry criteria, and the remaining patients withdrew in less than 11 days as follows: 10 (four, levocabastine-treated; three, cromoglycate-treated; three, placebo-treated) because of inefficacy, seven (two, levocabastine-treated; three, cromoglycate-treated; two, placebo-treated) because of adverse experiences, and one patient because of an intercurrent cold. Detailed information on the remaining 57 patients is provided in Table I.

Treatment and method

By means of a computer-generated randomization table, the patients were assigned to either a nasal spray formulation of levocabastine (0.5 mg/ml), sodium cromoglycate (20 mg/ml), or of matching placebo (containing the same in-

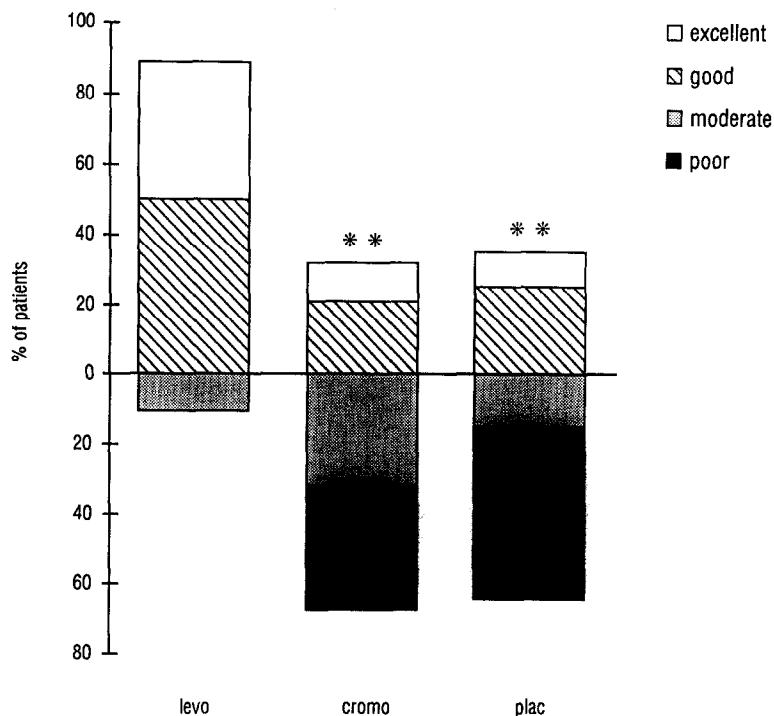


FIG. 1. Global evaluation of treatment for seasonal AR by patients after 2 weeks: $**0.001 < p < 0.01$, levocabastine versus sodium cromoglycate and versus placebo treatment.

gredients as the levocabastine formulation without the active drug) on a double-blind, parallel basis. Two puffs per nostril were applied q.i.d. during 14 days.

Assessments

Both the investigators and the patients rated the severity of the individual symptoms (sneezing, itchy nose, runny nose, blocked nose, and ocular complaints) on a 4-point scale (0, absent; 1, mild; 2, moderate; 3, severe). The investigator assessed at the start of treatment and at 2 weeks, and the patients assessed symptoms daily, from the first to the last day of treatment. Also, the patients evaluated globally the efficacy of their treatment against nasal symptoms by means of a VAS (0%, "no trouble"; 100%, "as bad as it could be") in a diary. At 2 weeks, both investigators and patients gave an overall assessment of the treatments, rating them as excellent (rapid and complete control of symptoms), good (marked overall reduction of symptoms), moderate (discernible but limited improvement), and poor (no appreciable change). Also at 2 weeks, the patients compared the efficacy (better, same, or worse) and the onset of action (faster, same, or slower) of their treatment with those of previous treatment(s). The investigators recorded the adverse experiences spontaneously reported by the patients and, in addition, specifically asked them if they had experienced fatigue during the day or dry mouth.

Whenever it was possible, hematologic and biochemical variables were evaluated at baseline and after treatment. The patient's body weight was also recorded at these time points.

For the analysis of the results, in addition to the score distributions for fixed symptoms, a distribution of the scores

for the most severe symptom (variable over patients and time) was constructed on the basis of the individual symptom scores assigned by the investigator.

From the 2-week diaries, the mean VAS score, the total severity score for each patient (AUC, trapezoidal rule) as a percentage of the maximum possible severity score, the percentage of symptom-free days, and the percentage of days with moderate or severe symptoms were calculated.

Global variance among the three study groups was assessed for significance by means of the Kruskal-Wallis one-way analysis of variance. Intergroup (two groups) comparisons were made with the Mann-Whitney U test.

RESULTS

The three treatment groups were comparable with reference to patient data, allergy characteristics, and pretreatment symptom severity. The most frequently occurring symptom was sneezing, and this complaint was experienced as the most bothersome by the greatest number of patients (Table I).

Of the 57 patients retained for the efficacy analysis, two (levocabastine-treated) failed to complete the 14-day treatment. One of these patients withdrew at day 11 because he was symptom free, and the other patient withdrew at day 14 because of dyspnea. Notwithstanding, these two patients received a global evaluation and are included in the efficacy analysis.

According to the global evaluations by both patients and investigators, the response among the three groups

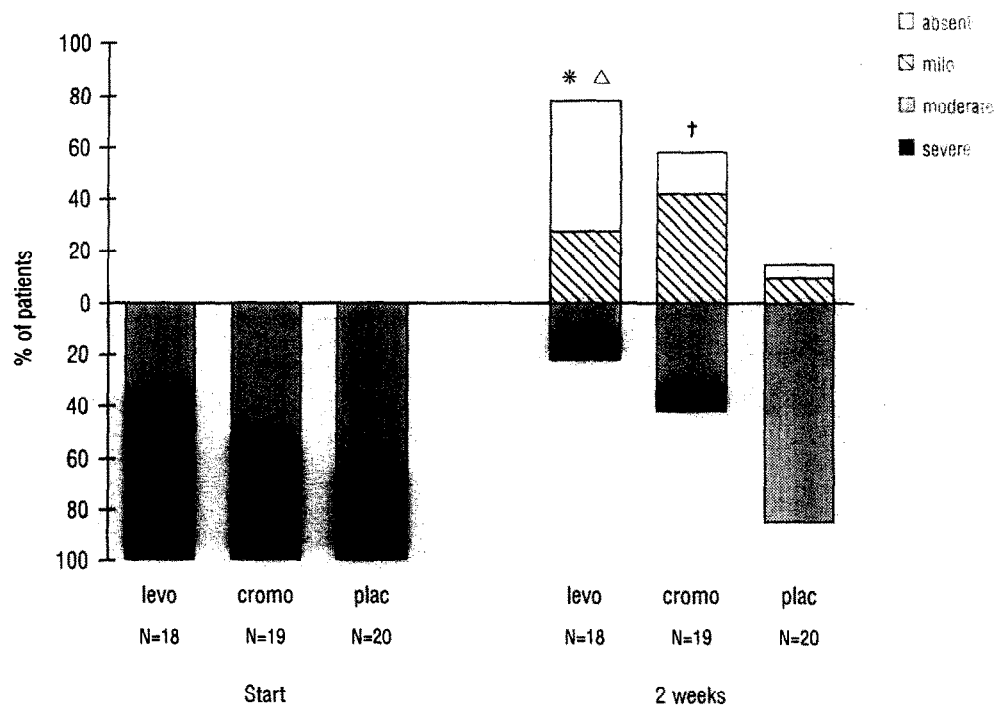


FIG. 2. Severest nasal symptom (for a given patient at a given time point) at the start of the study and after 2 weeks of treatment: * $p < 0.05$, levocabastine versus sodium cromoglycate; $\Delta p < 0.001$, levocabastine versus placebo; † $p = 0.07$, cromoglycate versus placebo; Mann-Whitney U test.

was significantly different ($p = 0.005$, Kruskal-Wallis). The levocabastine-treated patients responded better than both the cromoglycate-treated patients, $p = 0.003$; investigators, $p = 0.02$) and placebo-treated patients ($p = 0.002$), but there was no significant difference between cromoglycate- and placebo-treated patients (Fig. 1). Thus, 16/18 (89%) patients in the levocabastine-treated group rated their treatment as excellent or good as compared with 6/19 (32%) patients in the cromoglycate-treated and 7/20 (35%) patients in the placebo-treated group. The results of the investigators' global evaluation were of the same order (78%, 42%, and 35% of patients with a good or excellent response).

In comparing previously taken antiallergic medications with the study substance, levocabastine-, cromoglycate- and placebo-treated patients found the study substance to be more efficacious in 10/13 (77%), 3/16 (19%), and 4/16 (25%), respectively, of cases. A similar distribution was found for onset of action, levocabastine having been judged to act faster than 77% of the previous medications taken in this group versus 16% and 33% of the previous medications taken in the cromoglycate- and placebo-treated group.

With reference to the investigators' ratings of individual symptoms at 2 weeks, significant variation

($p = 0.004$, Kruskal-Wallis) was found among the three treatment groups in the case of the severest nasal symptom. This parameter, for which the initial mean severity scores were 2.67, 2.47, and 2.35 for the levocabastine-, cromoglycate-, and placebo-treated patients, respectively, responded better to levocabastine (mean change in severity score, -1.83) than to cromoglycate (-1.11 ; $p < 0.05$) or placebo (-0.55 ; $p < 0.001$) (Fig. 2). Mean severity for sneezing, runny nose, itchy nose, and ocular symptoms varied from 1.44 to 1.83 in the levocabastine-treated patients, from 1.42 to 1.79 in the cromoglycate-treated patients, and from 1.20 to 1.80 in the placebo-treated patients. Changes in ocular symptoms (initial severity, 1.56, 1.42, and 1.30, respectively) varied significantly among the three treatment groups ($p < 0.002$) and demonstrated a greater reduction of severity with levocabastine treatment (mean score change, -1.92) than with cromoglycate treatment (-0.69 ; $p = 0.03$) or placebo treatment (-0.19 ; $p < 0.001$). There was also significant intergroup variation with itchy nose ($p = 0.04$), and this symptom improved more markedly with levocabastine than with placebo treatment (mean, -1.39 versus -0.39 ; $p = 0.02$). Mean changes in the symptom severity of sneezing and runny nose were higher but nonsignificantly so with levocabastine treatment (-1.25 and -1.62) than with cromoglycate (-1.00 and -1.00) and placebo treat-

TABLE II. AUC of daily symptom scores according to patients' diaries

	Median AUC*		
	Levocabastine	Cromoglycate	Placebo
Severest nasal symptom	34.5 ($p = 0.002$) [$p = 0.05$]	47 (0.004)	76
Sneezing	26.5 ($p = 0.004$) [$p = 0.06$]	42 ($p = 0.07$)	67
Itchy nose	18 ($p = 0.002$) [$p = 0.05$]	37 ($p = 0.04$)	67
Runny nose	17.5	24	17
Blocked nose	0	0	0
Ocular symptoms	11	29	33

* p Values in parentheses are differences with placebo treatment; p values in brackets are differences between levocabastine and cromoglycate treatment; Mann-Whitney U test.

ment (-0.47 and -1.08). Blocked nose was either absent or mild in most patients (15/18, 12/19, and 12/20) in the levocabastine-, cromoglycate-, and placebo-treated groups, at the start of treatment.

The mean VAS scores calculated from the diaries for nasal symptoms were lower for the levocabastine-treated group (median, 23.5) than for the cromoglycate- (44; $p = 0.03$) and placebo-treated groups (58; $p < 0.001$), and cromoglycate did not do significantly better than placebo in this respect.

The AUC of the symptom-severity scores was significantly lower for levocabastine than for cromoglycate ($p = 0.06$) and placebo ($p = 0.004$) for sneezing, the severest nasal symptom, and itchy nose (Table II).

A similar response pattern was observed in terms of the percentage of symptom-free days. In particular, there was a marked difference between levocabastine and cromoglycate treatment in the percentage of days at which nasal symptoms were completely absent (mean, 33% versus 9%; $p = 0.006$) (Table III). With the less stringent criterion of the percentage of days with moderate or severe symptoms, levocabastine tended to outperform cromoglycate treatment in relieving the severest nasal symptom (41% versus 58%; $p = 0.07$) and itchy nose (17% versus 35%; $p = 0.09$) and was clearly superior to placebo treatment with reference to sneezing (25% versus 62%; $p = 0.02$), the severest nasal symptom (41% versus 86%; $p < 0.001$), and itchy nose (17% versus 60%; $p = 0.004$).

Compliance, as assessed by patient entries in their diaries, was similar in the three treatment groups. On average, 75%, 76%, and 68% of patients reported to

TABLE III. Percentage of symptom-free days according to patients' diaries

	Mean percentage of symptom-free days*		
	Levocabastine	Cromoglycate	Placebo
Severest nasal symptom	33 ($p = 0.001$) [$p = 0.006$]	9 (NS)	3
Sneezing	49 ($p = 0.003$) [$p = 0.03$]	24 (NS)	17
Itchy nose	61 ($p = 0.002$) [$p = 0.03$]	33 ($p = 0.04$)	18
Runny nose	62	44	51
Blocked nose	65	74	69
Ocular symptoms	65	52	32

NS, Not significant.

* p Values in parentheses are differences with placebo treatment; p values in brackets are differences between levocabastine and cromoglycate treatment; Mann-Whitney U test; NS, $p > 0.1$.

have used the nasal spray on a q.i.d. basis in the levocabastine-, cromoglycate-, and placebo-treated groups, respectively.

Of the 77 patients recruited, nine (four, levocabastine-treated; three, cromoglycate-treated; two, placebo-treated) had adverse experiences, six (two, levocabastine-treated; two, cromoglycate-treated; two, placebo-treated) had respiratory disorders (dyspnea, nasal irritation, rhinorrhoea, and excessive sneezing), one (levocabastine-treated) had a headache, one (cromoglycate-treated) had an unspecified adverse experience, and in reply to the investigators' questions, one patient (levocabastine-treated) reported having experienced fatigue. The investigators also elicited that no patient had had dry mouth. Eight (three, levocabastine-treated; three, cromoglycate-treated; two, placebo-treated) of the nine patients withdrew from the study because of their adverse experience.

There were no significant changes or intergroup differences in body weight at the end of treatment. Changes in hematologic values between the start and the end of treatment were random and comparable in the three treatment groups.

DISCUSSION

In this study comparing levocabastine and sodium cromoglycate for the treatment of seasonal AR, all efficacy indicators reflected the superiority of levocabastine. Sneezing and itchy nose were significantly more improved with levocabastine than with cromo-

glycate or placebo treatment. Good or excellent results were obtained in 89% (patient ratings) of the levocabastine-treated patients as compared with 32% and 35% of the cromoglycate-, and placebo-treated patients. While patients were receiving levocabastine, they were free of all symptoms on 1 in 3 days (33%) versus on only 3% of days with cromoglycate treatment. In addition, levocabastine was very well tolerated.

The trend toward improvement in ocular symptoms with levocabastine treatment might suggest absorption. However, such improvement has also been described in other studies with cromoglycate nasal spray.^{6, 7} The improvement in ocular symptoms is probably related to the improved nasal drainage.

Although several studies have been published assessing the efficacy of levocabastine eye drops in the treatment of seasonal allergic conjunctivitis, to date, only one study⁸ and two abstracts^{9, 10} have reported on the effects of levocabastine nasal spray in seasonal AR. In one study,⁸ both levocabastine eye drops and nasal spray were used, and these formulations were compared with naphazoline/antazoline eye drops and flunisolide nasal spray. Levocabastine nasal spray and flunisolide were demonstrated to have similar efficacy, whereas none of the patients had any side effects from levocabastine treatment versus 25% from flunisolide treatment (local irritation). In two studies,^{9, 10} levocabastine nasal spray was compared with cromoglycate nasal spray, given on a q.i.d. basis for 2 weeks. The results of these two studies are similar to results of our study, in favor of levocabastine.

In our study, the poor results with cromoglycate compared to placebo treatment were somewhat surprising. The response rate with cromoglycate treatment (32%) was indeed lower than that in the other two studies reported (44% and 57%). These two studies, however, did not include a placebo-treated group, and our placebo-treated group had a response rate of 35%. It is conceivable that the efficacy of cromoglycate may have been underestimated because of the relatively short duration of treatment (2 weeks). However, the better effects observed with levocabastine treatment make this drug a more suitable choice when fast symptom relief is wanted.

In conclusion, the present study has demonstrated levocabastine to be an efficacious and safe drug in the treatment of seasonal AR, producing better relief and abolition of nasal symptoms than sodium cromoglycate and placebo in a 2-week treatment. Levocabastine thus appears to be an interesting alternative for the topical treatment of patients with seasonal AR.

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