

Comparison of the efficacy and tolerability of topical levocabastine and sodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children

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Children ($n=110$) with seasonal allergic rhinoconjunctivitis were randomized to receive either twice daily 0.05% levocabastine eye drops and nasal spray plus twice daily topical placebos or 2% sodium cromoglycate eye drops and nasal spray four times daily for a period of 4 weeks. Patients were required to use the nasal sprays as directed and the eye drops only when required. The results obtained suggest that topical levocabastine is at least as effective as sodium cromoglycate for the treatment of this condition. After 2 weeks treatment the effect of therapy on nasal symptoms was considered to be excellent or good in 72% of levocabastine-treated patients and 54% of patients on sodium cromoglycate ($p=0.009$), with corresponding values for ocular symptoms of 81% and 57% in the two groups, respectively ($p<0.05$). Investigator assessments also revealed that the severity of sneezing and lacrimation were significantly lower in the levocabastine group at this time ($p<0.05$). After 4 weeks of treatment, patient diary data revealed that levocabastine was at least as effective as sodium cromoglycate with intergroup differences attaining statistical significance in favor of the topical antihistamine for nasal congestion ($p<0.05$). Both agents were well-tolerated with no significant differences in the incidence or type of adverse reactions in the two treatment groups.

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Seasonal allergic rhinoconjunctivitis, also known as hay fever, is a common allergic condition. Onset typically occurs during childhood and adolescence, with recent studies suggesting a prevalence in children of approximately 15% (1). A wide range of therapeutic approaches are available for the treatment of seasonal allergic rhinoconjunctivitis including oral antihistamines, topical vasoconstrictor/antihistamine combinations, corticosteroids and sodium cromoglycate.

Nasal and ocular challenge studies have demonstrated that the majority of typical symptoms of seasonal allergic rhinoconjunctivitis are mediated by the effects of histamine on H_1 -receptors (2, 3). Consequently, H_1 -receptor antagonism is a logical therapeutic approach. Newer second-generation oral H_1 -receptor antagonists are effective and generally

well-tolerated (4), however the potential for systemic adverse effects clearly exists (5). Topical therapy may be preferable due to the reduced potential for systemic reactions. Topical vasoconstrictor/antihistamine combinations provide effective symptomatic relief but can only be used for a limited period of time, as prolonged therapy is associated with rebound vasodilation which may cause rhinoconjunctivitis medicamentosa. Intranasal corticosteroids are effective and generally well-tolerated (6), however, routine ocular administration is not recommended due to the well-documented potential for severe adverse reactions (7). Sodium cromoglycate is the preferred topical therapy in children due to its favorable adverse-effect profile. Although sodium cromoglycate is an effective prophylactic agent, it has a slow onset of action. While clinical benefits

are observed in the majority of patients within several days of initiation of therapy, up to two weeks treatment are required in some patients to achieve maximum therapeutic effects (8, 9). Treatment should, therefore, preferably be initiated prior to allergen exposure, and maintenance therapy throughout the pollen season is essential. However, patient compliance with the necessary treatment regimen may be problematic.

Levocabastine is an extremely potent H_1 -receptor antagonist which has been specifically developed for topical application (10). Levocabastine eye drops and nasal spray have an extremely rapid onset of action providing relief from symptoms within minutes of administration (11). Furthermore, topical levocabastine has a sufficiently long duration of action to permit a convenient, twice daily dosing schedule (12). Previous studies in a total of 120 children have shown that twice daily levocabastine eye drops are as effective and well tolerated as four times daily sodium cromoglycate for the treatment of allergic conjunctivitis when administered alone (13) and in conjunction with the oral antihistamine terfenadine (14). However, there have been no reports to date of the efficacy and tolerability of levocabastine nasal spray in children. The present study was initiated to compare the efficacy and tolerability of levocabastine nasal spray, with eye drops on demand, with that of sodium cromoglycate for the treatment of children with seasonal allergic rhinoconjunctivitis.

Material and methods

A total of 110 children (age 6 to 15 years) with at least a 1-year history of seasonal allergic rhinoconjunctivitis confirmed by a positive skin prick or radioallergosorbent test (RAST) participated in this multicenter, randomized, double-blind, parallel group trial with a treatment duration of 4 weeks. Fifty-three patients received twice daily 0.05 levocabastine eye drops and nasal spray plus twice daily topical placebos and 57 patients received four times daily 2 sodium cromoglycate eye drops and nasal spray. Patients were required to use the nasal sprays as directed and the eye drops only when required. Rescue medication was not provided and the use of other medications which could interfere with the evaluation of the study drugs (for example, oral antihistamines, vasoconstrictors or corticosteroids) was not permitted. The study design was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki. All children and their parents gave informed consent.

Efficacy assessments

The investigators provided a global evaluation of treatment efficacy for both nasal and ocular symptoms after 2 and 4 weeks of treatment. Treatment efficacy was rated as excellent, good, moderate or poor. Patients with an excellent or good response to treatment were considered to be responders.

Symptoms of sneezing, rhinorrhoea, nasal itching, nasal congestion (blockage), ocular itching, ocular redness, lacrimation and eyelid edema were assessed by the investigator at the start of the trial to obtain baseline measurements and then after 2 and 4 weeks of treatment, as well as by the patients on a daily basis using a four point scale (0 = absent; 1 = mild [noticeable on occasion but not bothersome]; 2 = moderate [(noticeable from time to time and tends to be bothersome); 3 = severe [frequent and bothersome]). Patients also assessed overall severity of rhinoconjunctivitis on a daily basis using a Visual Analogue Scale (VAS).

Blood samples were taken from all patients before initiating therapy and at the end of the trial for routine hematological and biochemical analysis. The post-treatment blood samples were also used to determine plasma concentrations of levocabastine. Total grass and tree pollen counts were recorded daily throughout the study period at both centers. Pollen counts greater than 50/m³ were classed as high.

Statistical analysis

An intention-to-treat analysis was performed for the entire study period. The following parameters were calculated and analyzed after 2 weeks treatment and at the end of the trial: the mean severity score for each individual symptom; the maximum score for nasal symptoms of sneezing, itching and rhinorrhoea (SIR); the mean severity score for all nasal symptoms; and the mean severity score for all symptoms. In addition, the area under the curve (AUC) for symptom severity and the AUC of the VAS rating of overall rhinoconjunctivitis severity were derived from the patient diaries for the first 2 weeks of treatment and for the entire study period. All intergroup comparisons were made using the Mann-Whitney *U*-test or Fischer's exact test (5% level of significance).

Results

As shown in Table 1, patient demographics and baseline symptom severity were comparable in the two treatment groups with the exception of lacrimation which was significantly more severe in the levocabastine group than the sodium cromoglycate group ($p < 0.05$). A total of 6 patients withdrew from

Table 1. Baseline patient demographics

	Levocabastine	Sodium cromoglycate
Number of patients (M/F)	53 (35/18)	57 (35/22)
Mean age in years (range)	8.8 (6–15)	9.2 (6–15)
Mean age in kg (range)	31.7 (15–66)	32.5 (18–66)
Baseline symptom severity (mean $\pm$ SEM)		
Sneezing	2.3 $\pm$ 0.12	1.9 $\pm$ 0.13
Rhinorrhea	2.0 $\pm$ 0.12	1.9 $\pm$ 0.14
Nasal itching	2.5 $\pm$ 0.11	2.5 $\pm$ 0.11
Nasal congestion	2.4 $\pm$ 0.12	2.6 $\pm$ 0.07
Ocular itching	1.2 $\pm$ 0.17	1.0 $\pm$ 0.15
Ocular redness	1.1 $\pm$ 0.15	0.8 $\pm$ 0.14
Lacrimation	0.8 $\pm$ 0.15*	0.4 $\pm$ 0.11
Eyelid edema	0.8 $\pm$ 0.15	0.7 $\pm$ 0.13
Max of SIR	2.7 $\pm$ 0.06	2.7 $\pm$ 0.07
Total nasal symptoms	9.2 $\pm$ 0.35	8.9 $\pm$ 0.33
Total all symptoms	13.1 $\pm$ 0.74	11.8 $\pm$ 0.72

*p<0.05

the study. Reasons for withdrawal were adverse experiences (1 levocabastine-treated patient withdrew due to ocular irritation and another because of headache), lack of symptoms (1 levocabastine-treated patient), intercurrent disease (1 levocabastine-treated patient) and withdrawal of consent (2 patients in the sodium cromoglycate group). All patients used the nasal sprays as directed. The use of eye drops was 57% in the levocabastine group compared with 44% in the sodium cromoglycate group, however, this intergroup difference was not statistically significant.

The investigators' assessments of global therapeutic efficacy are shown in Fig. 1. Statistically significant intergroup differences were observed af-

Table 2. Patient evaluation of symptom severity after 2 weeks treatment and at the end of the trial (mean AUC derived from patient diary data)

Symptom	Levocabastine		Sodium cromoglycate	
	Week 2	Week 4	Week 2	Week 4
Sneezing	32.1	27.6	32.4	29.7
Rhinorrhea	31.1	28.2	35.7	32.0
Nasal itching	36.2	30.1	34.8	30.2
Nasal congestion	39.5*	33.6*	50.5	46.0
Ocular itching	19.9	17.1	17.4	16.2
Ocular redness	19.9	17.2	16.8	15.3
Lacrimation	11.4	9.5	10.5	9.7
Eyelid edema	14.6	11.8	15.3	13.3
Max of SIR	48.6	43.9	48.6	43.5
Total nasal symptoms	34.7	29.9	38.4	34.5
Total all symptoms	25.6	21.9	26.7	24.0

*p<0.05 (levocabastine versus sodium cromoglycate)

ter 2 weeks treatment, when the effect of therapy was considered to be excellent or good in 72% of levocabastine-treated patients compared with 54% of patients who received sodium cromoglycate for nasal symptoms ($p=0.009$) and in 81% and 57% of patients in the two groups, respectively, for ocular symptoms ($p<0.05$). After 4 weeks treatment, 76% of levocabastine-treated patients had an excellent or good response to treatment for nasal symptoms and 78% for ocular symptoms. The corresponding values in the sodium cromoglycate group were 60% and 62%, respectively. Investigator assessments of symptom severity also revealed that the severity of sneezing and lacrimation were significantly lower in levocabastine-treated patients than in those who re-

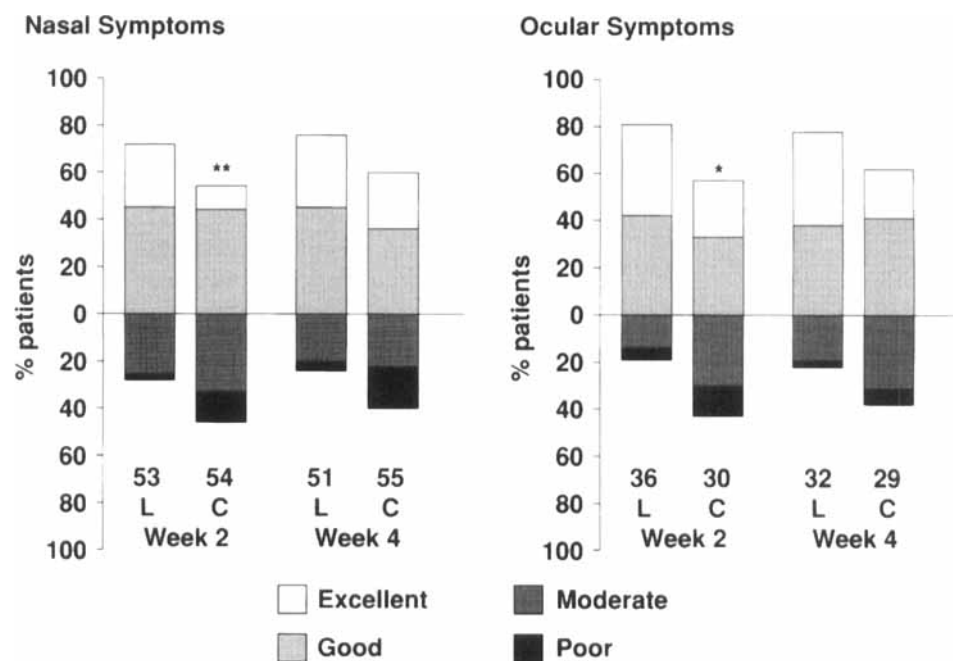


Fig. 1. Investigator assessments of global therapeutic efficacy (L = levocabastine; C = sodium cromoglycate). *p<0.05; **p=0.009.

ceived sodium cromoglycate after 2 weeks treatment ($p < 0.05$).

Patient global evaluations of treatment efficacy revealed a similar trend. In all, 70% of levocabastine-treated patients rated the effect of therapy on nasal symptoms to be excellent or good after 2 weeks treatment compared with 55% of those who received sodium cromoglycate ($p < 0.05$). The corresponding values at the end of the trial were 73% and 60% in the two groups respectively (n.s.). Patient self-evaluation of efficacy for ocular symptoms was not significantly different in the two groups.

Analysis of the data generated in the patients' diaries revealed that symptom severity was generally comparable in the two treatment groups (Table 2), however statistically significant intergroup differences in favour of the topical antihistamine were observed for nasal congestion after 2 weeks of treatment and at the end of the trial ($p < 0.05$). Further analysis revealed that levocabastine-treated patients were completely free from nasal congestion on 38% of treatment days compared with 24% for patients who received sodium cromoglycate ($p < 0.05$). The percentage of days with severe nasal congestion was also lower in the levocabastine treatment group than in the sodium cromoglycate group (30% versus 47%, $p < 0.05$).

Both drugs were well-tolerated and the incidence and type of adverse reactions was comparable in the two treatment groups. A wide range of adverse reactions was reported. Headache was the most common being reported by 6 levocabastine-treated patients and 7 of those who received sodium cromoglycate. Hematology and blood biochemistry tests did not reveal any consistent or clinically significant changes in any of the parameters evaluated during the study period in either of the treatment groups. At the end of the trial, the mean plasma concentration of levocabastine was 3.92 ng/ml, with plasma levocabastine concentrations below the limit of detection in 8 patients.

Discussion

This study was initiated to compare the efficacy and tolerability of topical levocabastine with that of sodium cromoglycate for the treatment of seasonal allergic rhinoconjunctivitis in children. The results suggest that twice daily levocabastine nasal spray with eye drops on demand is at least as effective as sodium cromoglycate four times daily, particularly during the first 2 weeks of therapy. These findings support those of previous comparative studies in children which have shown that levocabastine eye drops are at least as effective as sodium cromoglycate for the treatment of allergic conjunctivitis (13, 14).

Intergroup differences in therapeutic efficacy for a number of parameters attained statistical significance in favour of topical levocabastine after 2 weeks treatment. However, no significant intergroup differences were apparent at the end of the 4-week treatment period. These findings are predicable given the known mechanism of action of the two agents. Previous studies have shown that levocabastine has a rapid onset of action, providing relief from symptoms within minutes of instillation (11). In contrast, sodium cromoglycate is a prophylactic agent typically taking several days to achieve clinical effects (8, 9). It is, therefore, not unexpected that differences in therapeutic efficacy in favour of the topical antihistamine were reported after 2 weeks treatment, but not after 4.

In this study, levocabastine appeared to provide significantly greater relief from nasal congestion than sodium cromoglycate, although no objective measures of the degree of nasal congestion were obtained. Nevertheless, this result is somewhat surprising as clinical experience suggests that oral H_1 -receptor antagonists are not particularly effective for the treatment of this symptom (9, 15). However, it is possible that intranasal administration of a H_1 -receptor antagonist results in higher local concentrations of the active agent than oral dosing producing greater clinical effects.

Drug tolerability is a key factor determining choice of therapy in children. Both levocabastine and sodium cromoglycate were seen to be well-tolerated and the incidence and type of adverse reactions was similar in the two treatment groups. Topical levocabastine has an adverse effect profile comparable with that of placebo (10). Systemic absorption following topical administration of levocabastine appears to be minimal. In this study, the mean plasma concentration of levocabastine after 4 weeks of treatment was found to be 3.92 ng/ml, showing that significant accumulation of the drug does not occur.

In conclusion, twice daily levocabastine eye drops and nasal spray appear to be effective and well-tolerated for the treatment of seasonal allergic rhinoconjunctivitis in children. Topical levocabastine is therefore an attractive alternative to sodium cromoglycate for the treatment of this common condition.

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