

Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis

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The aim of this study was to evaluate the effect of levocabastine, a new H₁-blocking antihistamine for topical use, in comparison with sodium cromoglycate on conjunctival symptoms of birch pollinosis. The two drugs were compared in a randomized double-blind comparative study over 5 weeks in 37 children and adolescents (6-19 years of age) with birch pollen conjunctivitis. Nasal symptoms occurred in 31 of the children and were treated with beclomethasone dipropionate nasal spray. An oral antihistamine was offered as rescue medication for eye symptoms. Initially, the patients received placebo four times a day for a 7-day run-in period. Conjunctival symptoms were recorded daily on diary cards on a 100 mm visual analogue scale. The pollen counts indicated a short but intensive birch pollen season. There was no statistically significant difference between the two treatment groups with regard to eye symptom scores before and during active treatment. However, the patients' evaluation of the efficacy of the therapy was in favour of levocabastine ($P < 0.01$). Topical levocabastine, an H₁-blocker, applied twice daily, seems to protect from symptoms of allergic conjunctivitis as favourably as sodium cromoglycate applied four times a day. There was no difference in number or character of reported adverse reactions between the two treatment groups.

Key words: allergic conjunctivitis; children; adolescents; topical antihistamine; sodium cromoglycate.

Accepted for publication 13 March 1989

Pharmacological treatment of conjunctivitis associated with pollinosis is at present mainly limited to vasoconstricting agents, antihistamines and sodium cromoglycate (SCG). Vasoconstrictors and SCG are taken topically and they have to be instilled frequently during the day, which may reduce patient compliance. Most antihistamines are taken orally, but their use is often hampered by such adverse experiences as somnolence. The only presently available antihistamine for topical use is combined with a vasoconstrictor and is therefore not suitable for long-term treatment. Thus, there is a need for an effective topical drug for the treatment of allergic conjunctivitis that can be administered

less frequently and is not hampered by adverse systemic effects.

The aim of the present study was to evaluate the effect of levocabastine, a new H₁-blocking antihistamine for topical use (1, 2, 5), in comparison with SCG on conjunctival symptoms of birch pollinosis.

MATERIAL AND METHODS

Patients

A total of 39 children and adolescents (mean age 12 years, range 6-19 years) with birch polli-

Table 1
Patients characteristics

	Levocabastine	Cromoglycate
No. patients	21	16
Male/Female	7/14	9/7
Age (years):		
mean $\pm$ SD	12.0 $\pm$ 3.9	11.9 $\pm$ 3.1
median (range)	12.0 (6-19)	11.5 (6-16)
Weight (kg):		
mean $\pm$ SD	43.4 $\pm$ 16.2	39.5 $\pm$ 13.8
median (range)	45.0 (17-67)	37.0 (23-72)

nosis were recruited at three out-patient clinics (Linköping, Motala and Mjölby, County of Östergötland, Sweden). They all had a history of conjunctivitis for at least one previous pollen season. The diagnosis of birch pollen allergy was confirmed by positive skin prick tests (PhazetTM, Pharmacia, Uppsala, Sweden) and demonstration of circulating IgE antibodies to birch pollen (Phadebas RAST[®], Pharmacia, Uppsala, Sweden). All topical eye therapy was withdrawn at least 1 week prior to study start.

Records from 37 of the 39 patients could be used. Two patients, both belonging to the SCG group, were excluded from the efficacy analysis due to missing diaries. There was no significant difference between the groups with regard to

age, weight and sex of the 37 remaining patients (Table 1).

Study design and procedures

The study design was double-blind. The patients were randomized to either treatment with levocabastine (Janssen Pharmaceutica, Beerse, Belgium) eyedrops 0.5 mg/ml ($n = 21$) or SCG (Lomudal, Fisons) eyedrops 20 mg/ml ($n = 18$). Initially, all patients received placebo four times a day (q.i.d.) for a 7-day run-in period. The medication was then given for 5 weeks in the spring of 1987 (from April 27 to and including May 31). The two placebos used were identical with the real preparations minus drug. The run-in period was included to familiarize the participating children and their parents with regular administration of eye drops and diary card recording. Further, the placebo period was used as a base line of symptom scores before the start of active treatment.

All patients had two bottles each; one for administration in the morning and evening and a second for use at noon and in the afternoon. One drop of levocabastine, corresponding to 0.025 mg, was given in each eye twice daily (b.i.d) with two doses of placebo added to mimic q.i.d. The second group received one drop of SCG in each eye q.i.d. Clemastine, 1-2 mg per dose b.i.d., was used as "rescue medication" in the event of severe symptoms in the

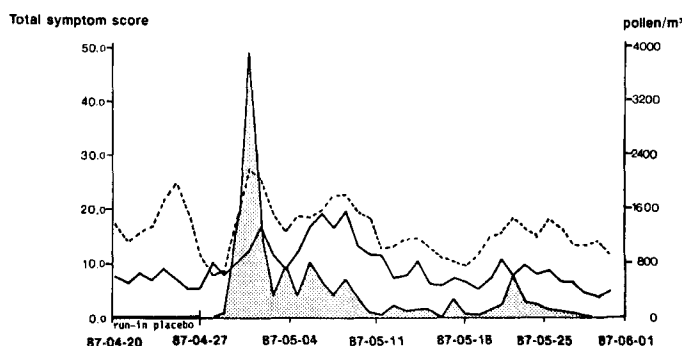


Fig. 1. Total eye symptom scores of patients who completed the entire study period. Unbroken lines denote patients receiving levocabastine b.i.d. and placebo b.i.d. and broken line patients on SCG q.i.d. The daily pollen counts are indicated by the hatched area.

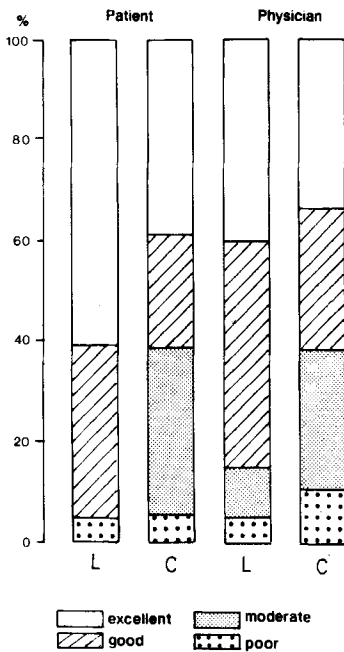


Fig. 2. Global evaluation of the efficacy of treatment (L = levocabastine, C = sodium cromoglycate) by patients and investigators. The difference in the patient assessment was statistically significant ($P < 0.01$).

eyes and nose. No other oral medication was allowed. For nasal symptoms topical beclomethasone dipropionate, 50 µg per dose, was given when needed as 1 or 2 puffs in each nostril b.i.d. Patients suffering from asthma used beta-2-agonist inhalation during the study as required.

Conjunctival symptoms as itching, erythema and tearing or their absence were recorded daily on diary cards. The severity of the different symptoms was recorded on 100mm visual analogue scales. The extremes of these scales were "no symptoms" and "very severe symptoms". Concomitant illnesses as well as the whereabouts of the patients were also continuously recorded. Type and severity of adverse experiences were recorded daily, using a four-grade scale. Particular emphasis was placed on sedation.

The patients underwent medical examination before the run-in period and after the end of the study period. Blood samples were obtained on these occasions for analysis of hemoglobin levels, liver enzymes (ASAT, ALAT) and creatinine concentrations.

After the study two global evaluations of the therapy were made, one by the investigator and the other by the patient. These evaluations were done independently using a four-graded scale; excellent, good, moderate and poor. During both the run-in period and the treatment period continuous birch pollen counts were performed in Linköping and expressed as the number of pollen grains/m³ (mean per day).

Calculations and statistics

The Mann-Whitney U-test was used for comparisons of symptom scores and use of drugs. Tests for differences in distribution of patients

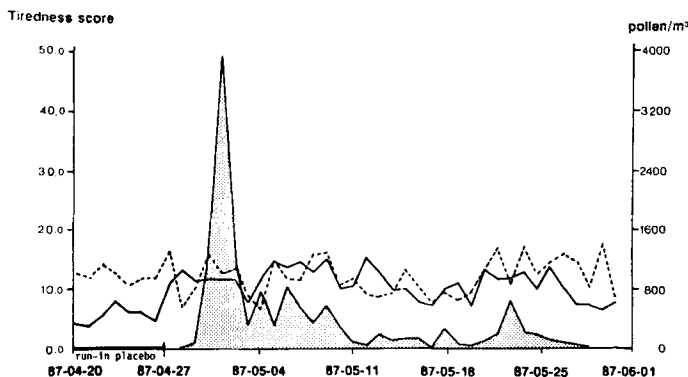


Fig. 3. Symptom scores for tiredness in the two treatment groups in relation to daily pollen counts. Cf Fig. 1 for explanation.

between categories were done with the chi-square test. Fisher's exact probability test was used to test for statistical differences in the global evaluations.

The study was approved by the Human Research Ethics Committee, Linköping, and reported to the National Board of Health and Welfare, Uppsala, Sweden. All parents gave their informed consent to participation.

RESULTS

The birch pollen season started at the end of the run-in period with very high daily pollen counts during the first treatment week. Later on more moderate pollen counts were recorded (Fig. 1).

The mean daily eye symptom scores, i.e. the cumulative scores for conjunctival itching, erythema and tearing, were similar in the two treatment groups (Fig. 1), as also when the symptoms were assessed separately (data not shown).

The global evaluation done by the patients showed preference for levocabastine as the most effective treatment (Fig. 2, $P < 0.01$). There was a similar non-significant trend for the global evaluation done by the investigators.

There were several reports of possible adverse reactions in both treatment groups. The experiences were scattered over a broad spectrum of symptoms, each of them occurring only in a few patients and they were equally distributed over the two treatment groups. The symptoms included topical symptoms, such as burning sensation, dry and itchy eyes, eye discharge, swollen eyes and eye ptosis and general reactions as headache, itch other than in the eyes, nausea, nose bleeding and tiredness. However, scores for sedation were low in both treatment groups (Fig. 3).

A few patients suffered from gastroenteritis or upper respiratory tract infections during the run-in period as well as during the treatment period with no difference between the groups.

Only one patient (on SCG) needed oral antihistamine as rescue medication. Antiasthmatic drugs were used by a few patients in both groups. The results of safety data were normal in every patient prior to, as well as after the study period.

DISCUSSION

This study shows that topical levocabastine in the treatment of allergic conjunctivitis is as effective as topical SCG. No drop-outs due to treatment failure occurred in either of the treatment groups. The global assessments by the families were in favour of levocabastine. The twice daily administration of levocabastine is convenient compared with other regimens where drugs are administered more frequently. We chose not to include a placebo group, as in previous studies levocabastine was found superior to placebo (3, 4, 5).

Unfortunately for the study, the birch pollen season did not begin until the end of the run-in period. Thus the purpose of using placebo in all subjects during that period was lost to a certain extent, i.e. there was no possibility of establishing a base-line of conjunctival symptom scores during placebo treatment with birch pollen present in the air.

The pollen sampler being placed in Linköping, i.e. in the neighbourhood of 60 % and not more than 60 km from the homes of any of the participating patients, probably means that pollen counts were representative. The pollen counts received in Linköping were in accordance with those officially recorded at the Swedish Meteorological and Hydrological Institute in Norrköping, 50 km from Linköping.

During the run-in period there was a slight, but not significant, difference in total conjunctival symptom scores between the treatment groups (Fig. 1). Both groups had only minor symptom scores during this run-in week (total possible score for each symptom = 100!).

Although the birch pollen season was short, but with intensive pollen occurrence during the first week, the mean conjunctival symptom scores remained low in both groups. This indicates good treatment efficacy of both eye drops, especially since most of the patients in both groups had nasal symptoms during the pollen season (15 of 21 in the levocabastine group and 16 of 16 in the SCG-group) requiring treatment with topical beclomethasone propionate. Despite the massive pollen exposure during the first treatment week none of the

patients had to use oral steroids or any treatment which would have excluded them from further participation. Concomitant diseases did not appear to influence the result of the study.

A disturbing factor in a study as this is that whatever eye drop is used against conjunctivitis, even placebo, it will help. It is possible that differences between the treatment groups would have been disclosed by an ophthalmologist examination, but unfortunately this could not be accomplished.

In conclusion, topical levocabastine, an H_1 -receptor blocking agent b.i.d. appears to be equally effective as sodium cromoglycate q.i.d. against symptoms of allergic conjunctivitis. Patient preference in this double-blind study was for levocabastine.

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