

A Double-Blind Evaluation of Topical Levocabastine, a New Specific H₁ Antagonist in Patients with Allergic Conjunctivitis

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Forty patients suffering from allergic conjunctivitis, due to birch pollen, participated in a double-blind parallel group comparison between levocabastine (a potent new specific histamine (H₁) antagonist) and placebo, both given as eye drops. Symptom scores were recorded during a 4-week period. A 1-week run-in period was followed by a 3-week treatment period. To enable a fair evaluation of the treatment effect on the ocular symptoms only, all patients were treated with topical nasal glucocorticoids for possible rhinitis symptoms during the whole study period. Plasma levels of levocabastine were determined in all subjects at the end of the 3 weeks' treatment period. Pollen counts for birch pollen were followed simultaneously. The evaluation of the symptom score cards revealed a significant reduction of ocular symptoms following use of the active compound. The resorption of the active substance through the conjunctiva was low. In accordance with the present trend of more topical treatment for allergic rhinitis, levocabastine may constitute a valuable compound for the topical treatment of allergic conjunctivitis.

Key words: allergic; conjunctivitis; H₁-blocker, levocabastine.

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Allergic rhinitis is often associated with conjunctival symptoms. At present there is trend towards the use of topical glucocorticoids in the treatment of allergic rhinitis (23). Such treatment, however, does not influence the often associated conjunctival symptoms, while, in contrast, systemic treatment with antihistamines often does (17). Thus, there is a need for better treatment alternatives for conjunctival symptoms. Topical vasoconstrictors (2, 6) and antihistamines (7), or a combination of these (18) have been used for decades. Presently available antihistamines have moderate efficacy and have side-effects, such as local irritation, and carry the risk of rebound phenomena (20). The more recently available addition to our local therapeutics for allergic conjunctivitis, disodium cromoglycate (DSCG) eye drops, although ef-

ficacious, has the disadvantage of requiring frequent administration (9, 10). Levocabastine is a new, pure histamine₁ (H₁) antagonist (14). In animal studies this drug has been shown to be approximately 65 times more potent than astemizole, which up to now has been the most potent oral H₁ antagonist (14). Pharmacokinetic studies in humans have shown that the peak plasma level is reached within 1-2 h of oral administration. The oral bioavailability is high (100 %) and the plasma half-life has been determined to 35-40 h. This implies that a once or twice daily administration would be sufficient to treat symptoms when given orally.

The purpose of the present investigation was to evaluate topically administered levocabastine in the treatment of allergic conjunctivitis due to birch pollen.

MATERIAL AND METHODS

Study design

The study was designed as a double-blind parallel group comparison between topical levocabastine and placebo. Symptom score technique was utilized. A 1-week run-in period was followed by a 3-week treatment period.

Patients

Subjects consisted of 40 patients, 20 males and 20 females, aged 18–47 years (mean age 29 years) who had given their informed consent to participate in the study. All patients had at least a 2-year history of hay fever during the birch pollen season with both conjunctival and rhinitis symptoms. The birch pollen allergy had been confirmed by means of a skin-prick test. All patients with clinical or biochemical evidence of significant renal, hepatic, gastrointestinal or other disease requiring chronic and/or variable medication were excluded. Patients under 16 years, pregnant women, or those actively seeking pregnancy, were not accepted for the study either. The study was approved by the Ethics Committee of the University of Göteborg.

Methods

Before entry into the trial each subject was interviewed and examined. All patients were provided with a diary card on which they were to record the following symptoms daily: itchy eyes, runny eyes, watery eyes and redness. They were graded on a scale 0–3 where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. In addition, an overall assessment of ocular symptoms was made on a visual analogue scale once daily. Any side effect experienced was also to be noted on the diary card. All patients started their ratings on May 1, 1984. Treatment was started on May 8 for a 3-week period. The patients were then seen on their last treatment day, when a renewed clinical examination was performed. On this occasion a blood sample

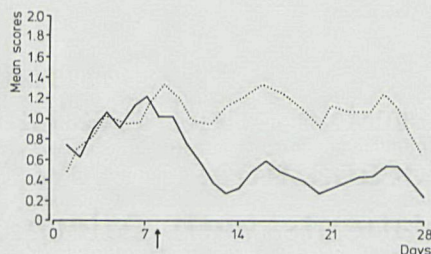


Fig. 1. Mean of daily recorded symptom score for itchy eyes. Max score is 3. Placebo treatment (-----) and active treatment (——). The reduction in the actively treated group day 0–7 versus 8–28 is statistically significant ($P < 0.05$). The difference between active treatment and placebo is significant ($P < 0.05$).

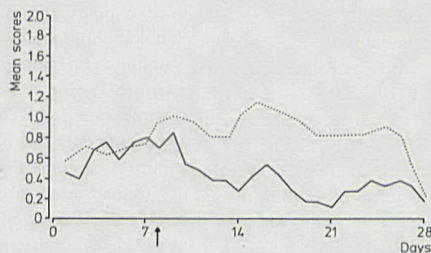


Fig. 2. Mean of daily recorded symptom score for runny eyes. Max score is 3. Placebo treatment (-----) and active treatment (——). The reduction in the actively treated group day 0–7 versus 8–28 is statistically significant ($P < 0.05$). The difference between active treatment and placebo is significant ($P < 0.05$).

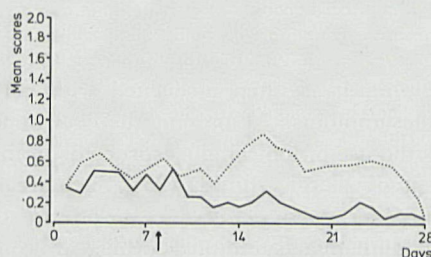


Fig. 3. Mean of daily recorded symptom score for eye redness. Max score is 3. Placebo treatment (-----) and active treatment (——). The reduction in the actively treated group day 0–7 versus 8–28 is statistically significant ($P < 0.05$). The difference between active treatment and placebo is significant ($P < 0.05$).

was taken for determination of the drug plasma level. In addition to the study drug all patients received topical glucocorticoid treatment for nasal symptoms (budesonide 400 µg/day, Rhinocort®, AB DRACO, Lund, Sweden, a

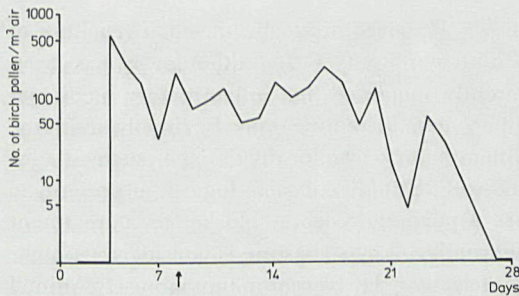


Fig. 4. Daily recordings of birch pollens in the air. No. of pollen grains/m³ of filtered air.

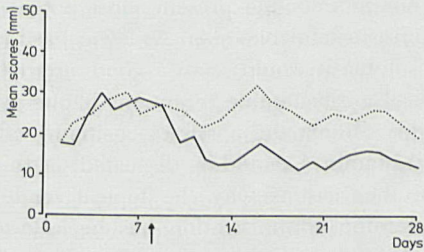


Fig. 5. Mean daily recorded total ocular score. Max score is 10. Placebo treatment (-----) and active treatment (—). The reduction in the actively treated group day 0–7 versus 8–28 is statistically significant ($P < 0.05$). The difference between active treatment and placebo is significant ($P 0.05$).

subsidiary of ASTRA Sweden) which was started before May 1 and maintained throughout the study period. No other treatments were allowed. Pollen counts for birch pollens were followed during the study.

Drugs

Levocabastine was supplied in a water solution as eye drops in a concentration of 0.5 mg/ml. The dosage was 1–2 drops into each eye twice daily. The matching placebo was supplied in identical bottles.

Determination of plasma level

The blood sample taken (10 ml) was centrifuged, the plasma separated and stored at -80°C until analysed. Within 6 months the samples were analysed for unchanged levocabastine using a RIA method. The detection limit for plasma analyses with this method is 0.1 ng/ml.

Statistical methods

The data obtained from the diary cards were analysed by Wilcoxon's rank sum test and Mann-Whitney U test.

RESULTS

Thirty-seven patients completed the study. Three patients were classified as drop outs because of ocular irritation due to treatment (active treatment), lack of treatment efficacy after 1 weeks' treatment (placebo) and lack of cooperation (did not return to the follow-up visit). The average daily scores for the different ocular symptoms are presented in Figs. 1–3, the pollen counts for birch pollens in Fig. 4, and the results from the visual analogue scale determinations in Fig. 5. A similar pattern was found in all symptoms recorded, which also led to similar statistical significances. In the run-in period without any treatments, there was no statistical difference between the two patient groups. After start of treatment, only the

Table 1

Significance levels for the different ocular symptoms recorded

Symptom	Run-in Active/ Placebo	Run-in Active	Run-in Placebo	Treatment Active/ Placebo
Itchy eyes	N.S.	$P < 0.05$	N.S.	$P < 0.05$
Runny eyes	N.S.	$P < 0.05$	N.S.	$P < 0.05$
Eye redness	N.S.	$P < 0.05$	N.S.	$P < 0.05$
Overall symptoms	N.S.	$P < 0.05$	N.S.	$P < 0.05$

Table 2

Plasma concentration of levocabastine in the individual patients

1.	< 0.1 ng/ml	9.	0.40 ng/ml
2.	< 0.1 ng/ml	10.	0.48 ng/ml
3.	< 0.1 ng/ml	11.	0.49 ng/ml
4.	< 0.1 ng/ml	12.	0.51 ng/ml
5.	< 0.1 ng/ml	13.	0.55 ng/ml
6.	< 0.1 ng/ml	14.	0.58 ng/ml
7.	0.28 ng/ml	15.	1.07 ng/ml
8.	0.38 ng/ml	16.	1.24 ng/ml

patient group receiving active treatment showed a significant reduction in symptoms compared with pretreatment symptoms. Also during the double-blind treatment period there was a significant difference between active and placebo treatment. The different levels of statistical significance are presented in Table 1. Two patients, both in the actively treated group, reported ocular irritation as a side effect due to treatment. No other side effects were reported. Most patients stated that the eye drops, whether of placebo or active substance, were non-irritating and gave relief, and the twice daily schedule was convenient.

It was possible to obtain plasma for determination of levocabastine levels in 34 patients, 18 of whom had received placebo and 16 active drug. The plasma concentration was 0.35 ± 0.09 ng/ml (mean $\pm$ SEM). The individual values are presented in Table 2.

DISCUSSION

The main trend in allergic rhinitis therapy during the last decade has been to use topical treatments, glucocorticoids and disodium cromoglycate (DSCG), instead of systemic antihistamines, systemic glucocorticoids or hyposensitization. This has revealed the need for a more intensive treatment of the often associated ocular symptoms. Presently available topical treatments for ocular symptoms (vasoconstrictors/antihistamines/DSCG) have several drawbacks, such as local irritation, moderate efficacy and short duration (10, 18). Local administration of glucocorticoids was tried soon after the introduction of these agents (11) and found to be very effective in the treatment of ocular symptoms. However, ocular topical glucocorticoids have been shown to induce cataracts and glaucoma, and should not be a routine treatment for allergic ocular symptoms (1, 8, 12). Therefore, more effective alternatives for the treatment of allergic conjunctivitis symptoms would be desirable.

The role of different histamine receptors in eliciting symptoms in the eyes is not fully evaluated. In the nose H_1 and H_2 receptors appear to have an additive effect on nasal congestion (24). An ocular challenge study has

shown H_1 receptors to be the main elicitors of ocular symptoms (15). Although it has been recently suggested that inflammatory mediators other than histamine may be involved in the inflammatory reaction in the eye, such as substance P (SP) (13), it seems logical, at present, to use a pure H_1 receptor blocker as a treatment alternative. Levocabastine is considered a highly selective H_1 receptor antagonist. Animal experimental data has shown that, on a molar basis, this compound is more than 65 times more potent than the present most potent H_1 antagonist (astemizole) (14). As levocabastine is water soluble it would seem a good alternative to topical antihistamine treatment in the eyes.

In this context the possible sensitizing effect of antihistamines should be discussed, as this is one of the reasons why the topical mode of antihistamine administration has been largely avoided. A sensitizing effect was reported after dermal application of the early antihistamines (19). However, topical application of antihistamines to the eye has now been used for nearly 40 years without any serious side effects (21).

In the present study the majority of patients receiving the active drug had no, or only minor, conjunctivitis symptoms during the pollen season, while the placebo-treated patients had ocular symptoms that related to the pollen counts. Although the placebo eye drops may have a cooling and comforting effect (placebo effect), by washing out any pollens present in the conjunctiva, the active treatment showed positive statistical significance. To maintain the patients' rhinitis symptoms of hay fever at a minimum and thus, facilitate their assessment of the ocular symptoms, all patients received active nasal treatment with a topical glucocorticoid (budesonide), previously shown to be highly efficacious in the treatment of allergic rhinitis (3, 22). The daily dose of budesonide used has previously been shown to have no influence on ocular symptoms (25).

The comparatively long-lasting effect of levocabastine made a twice-daily dosage possible. As patients with allergic conjunctivitis are usually within the active age group, this is an important factor, since more frequent dosage

regimens require that the drug is constantly available instead of only being needed when at home. It is always possible that a drug given locally in the eye may have some systemic activity, particularly since it has been shown that topical glucocorticoids are rapidly absorbed and found in the systemic circulation (16). To assess this possibility, the plasma concentration of the drug was determined at steady state condition on the last day of the trial. The determination of the plasma concentrations showed that there was a minor absorption of the drug from the conjunctiva. The level measured was 1/30 of the steady state therapeutic level achieved by giving 0.5 mg orally once daily (14). To allow a fair evaluation of the therapeutic effect, all patients started recording their symptoms on the same day. The run-in week demonstrated that, as expected, symptoms began in both patient groups at the start of the birch pollen season. During the run-in week and throughout the rest of the study period, the symptoms in the placebo-treated patients were reflected in the birch pollen count. This is one of the advantages of having a simultaneous pollen count. Moreover, it is interesting to speculate that the eye may be the first organ to react to airborne pollens.

Conclusion

Topical levocabastine, a new specific H_1 antagonist, may provide a valuable addition to our therapeutic armoury for the treatment of allergic conjunctivitis.

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