

Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests

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Levocabastine is a new H₁ receptor blocking antihistamine which is intended for topical use in the treatment of allergic conjunctivitis. The protective effect of the drug in conjunctival provocation test (CPT) was evaluated in a double blind study of 25 children aged 9-17 years with confirmed pollen allergy. One drop of levocabastine, cromoglycate or placebo was instilled into the conjunctival sac of both eyes. After 15 min CPT was performed, starting with 320 BU of pollen extract. The allergen dose was increased every 10 min in half 10-log steps in the right eye until a positive reaction occurred, or the top dose 320,000 BU was reached. The lowest dose resulting in a positive CPT reaction, i.e. at least 50 % of the conjunctiva with erythema, was defined as the allergenic threshold dose (ATD). Pretreatment with levocabastine resulted in a median ATD of 32,000 BU, compared with 10,000 after cromoglycate ($P < 0.001$) or placebo ($P < 0.01$). Levocabastine was also superior in reducing subjective itch in the eyes. Determination of the ATD can be used as a relatively quick assessment of drugs intended for the treatment of allergic conjunctivitis.

Key words: allergic conjunctivitis; conjunctival provocation test; levocabastine; sodium cromoglycate; topical antihistamine.

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CLINICAL ASPECTS

In CPT patients are given much more allergen than they are naturally exposed to. Even so, the procedure is useful as a sensitive and relatively quick screening test of drugs intended for treatment of allergic rhinoconjunctivitis.

The conjunctival provocation test (CPT) is a simple, safe and reproducible method for establishing a diagnosis of allergic conjunctivitis (2).

The precision and reproducibility of the CPT is also high enough to allow its use as a research tool, e.g. in evaluation of drugs intended for treatment of allergic conjunctivitis. Repeated provocation tests, even when done once a week do not appear to have any priming effect (2). Topical drugs for the treatment of allergic conjunctivitis, such as sodium cromoglycate

(SCG), have to be instilled into the eyes several times a day to be effective, and the need for frequent administration influences patient compliance negatively. Orally administered classical antihistamines may sedate the patients. Hence there is a need for a drug with the ability to reduce allergic symptoms, mainly ocular itch.

The aim of this study was to evaluate the protective effect of levocabastine in CPT and to compare it with SCG and placebo, given as single doses.

MATERIAL AND METHODS

Twenty-five children, 13 boys and 12 girls, aged 9–17 (mean 12.8) years were included. The inclusion criteria were a history of pollen allergy for one season or more, a positive skin prick test (wheal diameter ≥ 3 mm) and/or a positive RAST ($\geq$ class 2) with the pollen in question. Other allergies should not be significant and no patient with perennial allergy was included. All CPT were performed in the off-pollen season. No concomitant therapy was allowed for at least 1 week prior to each CPT.

The study was designed as a randomized double-blind three-way crossover study. A wash-out period of at least 1 week was interposed between the provocation tests. One drop of levocabastine eyedrops 0.5 mg/ml (Livostin®, Janssen Pharmaceutica, Belgium), so-

dium cromoglycate eyedrops 20 mg/ml (Lomudal®, Intal®, Fisons, Loughborough, UK) or placebo was administered from identically coded, opaque bottles in a randomized way 15 min prior to the CPT. The placebo solution consisted of the vehicle of the levocabastine preparation.

Two batches of standardized allergen, rye grass and birch pollen were used throughout the study (Pharmalgen®, Pharmacia Diagnostics, Uppsala, Sweden). The extracts were delivered freeze-dried for reconstitution and dilution with Albumin Diluent®. The allergen preparations were stored at +4°C and used at room temperature for not more than 7 days after reconstitution.

Skin prick tests (SPT) were carried out with birch and timothy Phazet™ needles (Pharmacia Diagnostics, Uppsala, Sweden) on the volar aspects of the forearms according to Dreborg et al. (1).

All subjects were initially submitted to an open CPT to establish the lowest dose of allergen (allergen threshold dose, ATD) eliciting an allergic response with itching, erythema of at least 50 % of the conjunctiva and swelling of the caruncle (2). When the CPT was regarded as positive the patients filled in a 70 mm visual analogue scale regarding the severity of itch. The scale was divided into seven classes of itch, all 10 mm long. These classes were used in statistical evaluation. The investigator performing the CPT estimated the swelling of the caruncle as either none or as clearly perceivable. The CPT always started with Albumin Diluent instilled into the conjunctival sac of the right eye. If no reaction occurred within 10 min, then one drop of the lowest allergen concentration of either birch pollen ($n = 17$) or rye grass pollen ($n = 8$) was instilled. Itching and erythema were recorded after 2, 5, 8 and 10 min. If no reaction occurred then the CPT was continued at 10 min with a half 10-log increment of allergen concentration in the same eye, until allergic symptoms occurred, or the top concentration (320,000 BU) was reached. When necessary, resulting allergic reactions were reduced by installation of a vasoconstricting drug, containing metaxedrinechloride. Af-

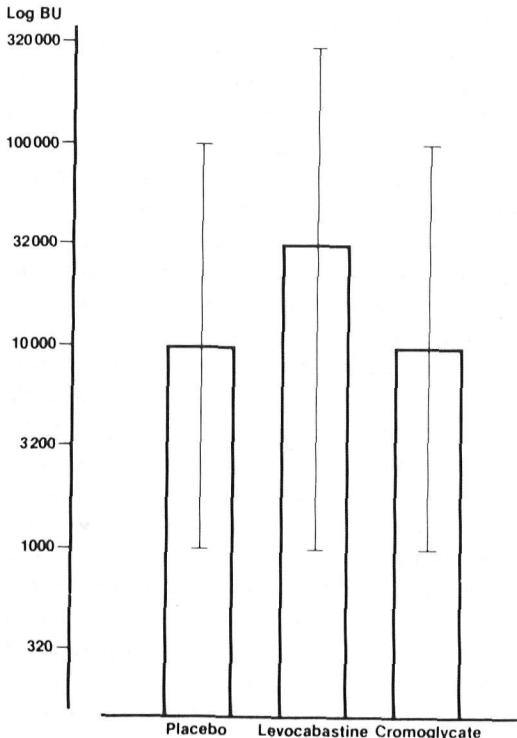


Fig. 1. Median allergen threshold dose (ATD) and range in 25 pollen-allergic individuals subject to CPT after pretreatment with placebo, levocabastine, or sodium cromoglycate. The ATD after levocabastine was significantly higher than after placebo ($P < 0.01$) or SCG ($P < 0.001$).

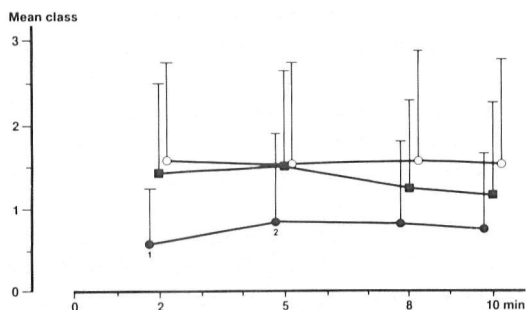


Fig. 2. Mean score for itch and SD as assessed by a 7-graded visual analogue scale at various times after a positive CPT reaction. The difference between levocabastine and placebo was statistically significant after 2 min and vs SCG after 2 and 5 min. Closed circles indicate pretreatment with levocabastine, closed squares SCG, open circles placebo.

ter at least 1 week of wash-out the patient returned for another CPT. At each of the three CPT a study drug was instilled into both eyes 15 min prior to the CPT.

A two-sided sign test was used for statistical assessment of differences in the ATD. Fisher's exact probability test was used when calculating differences in itch scores.

The study was performed according to the Helsinki declaration and approved by the Human Research Ethics Committee at Linköping University. All parents gave informed consent for their children to participate in the study.

RESULTS

The pretreatment with levocabastine resulted in significantly higher ATD than the other pretreatments, i.e. 32,000 BU/ml with levocabastine and 10,000 BU/ml both with SCG ($P < 0.001$) and with placebo ($P < 0.01$) (Fig. 1). The ATD were not significantly different between SCG and placebo.

Itching, as assessed by visual analogue scale, indicated less symptoms after levocabastine than after SCG and placebo (Fig. 2). This was statistically significant compared with placebo ($P < 0.01$) only when assessed 2 min after installation, and compared with SCG 2 and 5 min ($P < 0.05$) after installation. Similarly, itching, as assessed by the investigator, indicated significant-

ly less itch after pretreatment with levocabastine after 5, 8 and 10 min compared with placebo (all $P < 0.05$) and compared with SCG after 5 min ($P < 0.05$) and after 8 and 10 min ($P < 0.01$). No significant differences between SCG and placebo were found either as assessed by the visual analogue scale or by the investigator.

Pretreatment with levocabastine was associated with significantly less swelling of the caruncle 2 and 5 min after a positive CPT compared with placebo ($P < 0.05$) and after 2, 5, 8 and 10 min (all $P < 0.001$) compared with SCG.

The study drugs were all well tolerated and no serious adverse experiences occurred during the study.

DISCUSSION

Topical application of levocabastine 15 min before CPT protected from allergic symptoms better than SCG and placebo. It should, however, be noted that the comparison with SCG in a clinical situation is limited by the fact that ocular SCG should normally be given for several days to produce a clinical effect, while the effects of antihistamines are more rapid. Itching was evaluated separately as it is a major clinical problem, and also in this respect levocabastine was superior to the other pretreatments. No major complaints from use of either drug were received. These results are in accordance with those obtained in other studies of levocabastine (4). It is important to realize that in the CPT more allergen is administered topically than the patient is naturally exposed to during a whole pollen season. For the evaluation of drugs the CPT method should therefore be further refined to better mirror natural exposure. The method is, however, useful as a screening test.

As a consequence, a double-blind trial of seasonal conjunctival symptoms was performed to assess whether two daily doses of levocabastine, topically, could protect from conjunctival symptoms as effectively as SCG given q.i.d. This was confirmed in a 5-week double-blind study of 37 children (3). The results of that study and the present indicate that topical levocabastine with its convenient administration

b.i.d. is an alternative treatment during the pollen season for patients with allergic conjunctivitis.

REFERENCES

1. Dreborg, S., Holgersson, M., Nilsson, G. & Zetterström, O.: The dose response relationship of allergen, histamine and histamine releasers in skin prick test and the precision of the skin prick test method. *Allergy* 42, 117-125, 1987.
2. Möller, C., Björkstén, B., Nilsson, G. & Dreborg, S.: The precision of the conjunctival provocation test. *Allergy* 39, 37-41, 1984.
3. Odelram, H., Björkstén, B., af Klercker, T., Rimås, M. & Kjellman, N.-I. M.: Topical levocabastine versus sodium cromoglycate in birch conjunctivitis. *Allergy* (in press).
4. Pipcorn, U. & Bende, M.: Topical levocabastine, a selective H1 antagonist, in seasonal allergic rhinoconjunctivitis. *Allergy* 42, 512-515, 1987.

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