

Effect of topical levocabastine on allergic and non-allergic perennial rhinitis

A double-blind study, levocabastine vs. placebo, followed by an open, prospective, single-blind study on beclomethasone

P. H. VAN DE HEYNING,¹ J. VAN HAESENDONCK,¹ W. CRETEN² & N. ROMBAUT¹

¹Dept. of ENT and Head and Neck Surgery and ²Laboratory of Biophysics and Medical Physics, University of Antwerp, Belgium

Forty-four patients, with symptoms of nasal obstruction, sneezing, itching and/or rhinorrhea, were entered into a placebo-controlled, double-blind study to evaluate the clinical efficacy of a topical antihistamine drug, levocabastine, applied 4 times a day for 14 days. At the end of the treatment the placebo patients were treated with levocabastine and the levocabastine patients were treated with beclomethasone dipropionate in a single-blind design for another 14 days. This study showed that levocabastine is significantly more active than placebo with reference to nasal discharge and sneezing. Placebo application improved the symptom score. Levocabastine could not be proved to be more effective against nasal obstruction than placebo in the double-blind trial. In the single-blind set-up, levocabastine resulted in an additional improvement in the score for obstruction, after the placebo period. Although the allergic group tended to respond better, no statistically significant difference could be detected between allergic and non-allergic patients. After treatment with levocabastine, beclomethasone dipropionate administration could not improve the results for nasal discharge and sneezing. For nasal congestion, beclomethasone dipropionate proved to be superior to levocabastine.

Key words: allergic and non-allergic perennial rhinitis; beclomethasone dipropionate; levocabastine; topical antihistamines.

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Allergic and non-allergic rhinitis have been treated by many drugs with different modes of action (15). In various studies topical disodium cromoglycate and ipratropium bromide have been shown to be less than entirely satisfactory for all symptoms (3, 4, 11). It has been demonstrated that systemic antihistamine and corticosteroid drugs are active against allergic and non-allergic rhinitis (6, 7, 10, 15, 18). Topical corticosteroids, such as beclomethasone dipropionate (BDP), have largely replaced the systemic approach in the treatment of allergic and non-allergic rhinitis to reduce side effects (13).

Some authors have previously emphasized the

rationale for the topical, intranasal use of antihistamines in patients (12, 19, 20, 23). Topical antihistamine agents are administered in an attempt to avoid the side effects of systemically applied medications, such as sleepiness, and to reach higher local drug concentrations (18, 23). H₁ receptors of the nasal mucosa have been proven to play an important role in the pathophysiology of allergic and non-allergic rhinitis (5, 9, 15, 23). Levocabastine is a potent H₁-antagonist and topical application has already yielded good results in allergic conjunctivitis (21) and seasonal allergic rhinoconjunctivitis (2).

The aim of the present investigation was to

evaluate the efficacy of topical levocabastine in the treatment of allergic and non-allergic perennial rhinitis and to investigate whether topical BDP was able to further decrease the symptoms after levocabastine treatment.

MATERIAL AND METHODS

Patients

Forty-nine patients (20 males and 29 females) entered the clinical trial, 5 were later excluded as they did not complete the study. Of the remaining 44 patients, 23 suffered from a non-allergic rhinitis, presenting complaints of nasal obstruction, sneezing, aqueous rhinorrhea and itching. They had negative allergic skin tests for grass- weed- and tree pollens, house dust, *D. pteronyssinus*, animals and moulds and had negative RAST scores for the same allergens. Twenty-one patients had an atopic rhinitis to *D. pteronyssinus*. They had almost the same complaints as the non-allergic rhinitis group but had positive allergic skin tests for *D. pteronyssinus* and a positive RAST score for this allergen.

The study was undertaken from December 1985 to March 1986.

Study design

The study comprised two phases. Phase 1 was a double-blind placebo-controlled trial of topical levocabastine. The patients were instructed to use a metered dose pump spray, applying two puffs into each nostril 4 times a day. The sprays with active product delivered 0.05 mg levocabastine per application. The placebo sprays contained only the solvent* used in the levocabastine solution. The treatment lasted for a period of 14 days. The placebo and levocabastine sprays were packed in sealed and

numbered identical boxes, supplied by the pharmaceutical company (Janssen Pharmaceutica, Beerse, Belgium). The boxes were then randomly distributed.

Phase 2 followed phase 1 in a continuous fashion after the patient's code had been broken by an independent person. Patients receiving placebo in phase 1 were given 2 puffs of levocabastine in each nostril 4 times a day. The patients receiving levocabastine in phase 1 were further treated for another 14 days with 1 puff of BDP in each nostril 4 times a day (total daily dose 400 µg).

Symptom scoring

The patients were given a diary card to record the medication intake and the daily severity of the following items: sneezing, itching, nasal discharge and nasal obstruction. The scale employed for symptom scoring was 0 = no symptoms; 1 = slight symptoms; 2 = moderate symptoms; 3 = severe symptoms.

Due to the different physiopathological mechanisms involved, symptoms can be divided into rhinorrhea/sneezing and obstruction (4, 26).

A total symptom score was calculated using the above-mentioned scale and on the basis of the different items mentioned.

In addition, the score for nasal obstruction and the combined score for rhinorrhea and sneezing were also used for further analysis. These two symptom scores and the total symptom score, assessed before treatment, at the end of phase 1 and the end of phase 2, were taken into account in the statistical analysis.

Statistical analysis

Because the data only consist of symptom scores, non-parametric statistical procedures were applied (Mann-Whitney U-test and Wilcoxon signed-ranks test) (22). Mean scores were only used for visual representation.

RESULTS

The results of the double-blind, placebo-controlled study, i.e. phase 1, are shown in Fig. 1.

*Composition of the solvent: propyleneglycol 50 mg, polysorbate 80 1 mg, dibasic sodiumphosphate (anhydrous) 8.66 mg, monobasic sodiumphosphate (monohydrate) 5.38 mg, benzalkoniumchloride 0.1 mg, disodium EDTA 0.1 mg, hydroxypropylmethylcellulose 2910 4000 CPS 2.5 mg, purified water q.s.ad 1 mg.

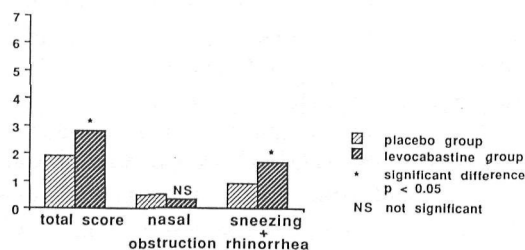


Fig. 1. Mean score improvement at end of the double-blind study, (phase 1) placebo versus levocabastine.

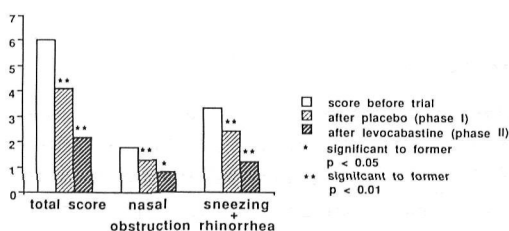


Fig. 2. Mean scores before and after treatment with placebo (phase 1) and after treatment with levocabastine (phase 2).

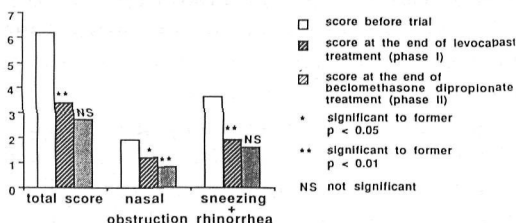


Fig. 3. Mean score before the trial, at the end of levocabastine treatment (phase 1) and at the end of beclomethasone dipropionate treatment (phase 2).

Mean score amelioration is represented for the total symptom score, nasal obstruction and the combined assessment of sneezing and rhinorrhea. There was a statistically significant effect of levocabastine for the total score and the combined score of sneezing and rhinorrhea. The score for nasal obstruction was not able to demonstrate levocabastine to be efficacious.

To demonstrate the effect of the placebo, the results of the mean scores before and after pla-

cebo treatment in phase 1 are shown in Fig. 2. There is a clear statistically significant improvement for the three scores.

Fig. 2 also shows the mean score at the end of the open, single-blind treatment with levocabastine. Total assessment and the symptoms obstruction and sneezing plus nasal discharge, all improved significantly.

The eventual additional effect of BDP in phase 2 after levocabastine is shown in Fig. 3. An additional improvement could only be achieved for symptoms of nasal obstruction.

When symptom scores for allergic and non-allergic rhinitis patients were considered separately (Fig. 4a, b, c, d), no additional conclusions could be drawn. Although atopics and non-atopics appeared to respond similarly to placebo, levocabastine and beclomethasone dipropionate, a trend emerged that allergics responded better than non-allergics.

No adverse drug effects were reported in the levocabastine group. It must be noted that 3 of the patients, who did not complete the study and whose files were excluded for further analysis, received placebo and stopped therapy during phase 1 due to local irritation.

DISCUSSION

Levocabastine has been introduced as a specific H_1 antagonist without an antiserotonine or anticholinergic effect. It has been shown to be 65 times more potent than astemizole (1). Systemic use of levocabastine in allergic rhinitis patients has produced good results but with a dose-related sedative effect (25). In clinical practice, topical levocabastine application has proved to be very successful in allergic conjunctivitis (21) and seasonal allergic rhinoconjunctivitis (2). However, Zellweger et al. (27) concluded that the addition of the aerosolized antihistamine drug levocabastine in low doses to the bronchodilator treatment in light perennial asthma has no obvious clinical advantage. Our study is apparently the first clinical trial of intranasally administered levocabastine in perennial rhinitis.

Analysis of the results of the double-blind, placebo-controlled study of the efficacy of levocabastine (phase 1 of our study design),

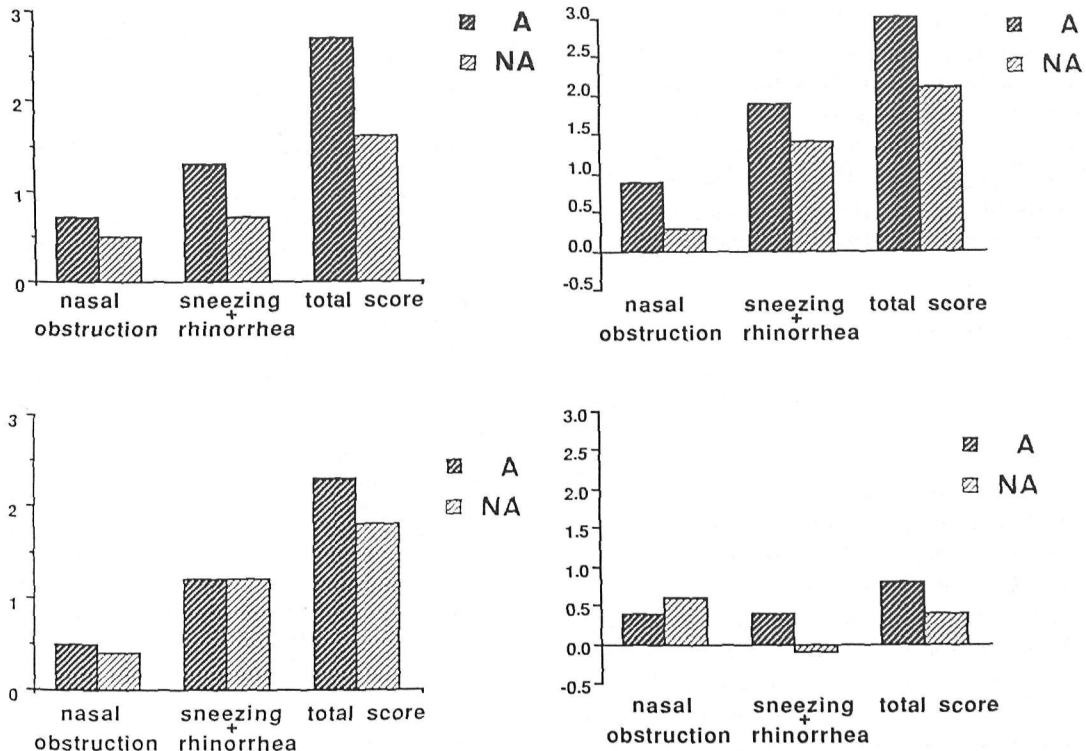


Fig. 4. Mean score changes in allergic (A) and non-allergic (NA) patients (intragroup comparison). Positive mean indicates clinical improvement and negative mean clinical deterioration. Results after placebo, end of phase 1 (Fig. 4a); after levocabastine, end of phase 1 (Fig. 4b); after levocabastine given after placebo, end phase 2 versus end phase 1 (Fig. 4c); and after beclomethasone given after levocabastine, end phase 2 versus end phase 1 (Fig. 4d).

revealed that levocabastine improved the total symptom score and, in particular, the combined score for sneezing and rhinorrhea (Fig. 1). Analysis of the symptom nasal obstruction failed to disclose any statistically significant effect.

These findings are in agreement with other investigators who have tested the efficacy of local antihistamines *in vivo* by nasal histamine provocation test in normal volunteers and patients (12, 19, 20). Even the peroral treatment with antihistamines has showed this same trend (5, 26): in particular, nasal discharge and sneezing were improved and nasal obstruction was affected to a lesser degree.

The inadequate response to antihistamine therapy in some patients indicates the participation of other mediators in rhinitis (15, 18), hypothetically via H_2 receptors in capacitance

vessels in the nose (5, 8, 23). On the other hand, nasal irritant receptors presenting at or near the surface of the nasal epithelium are thought only to contain H_1 receptors.

In our study, we could not detect any significant difference between allergic rhinitis patients and non-allergic rhinitis patients (Fig. 4a-d). This finding is due to the common physiological mechanisms involved and the fact that histamine and mast cells participate in non-allergic rhinitis (14, 16, 26). When considering that the allergic group tended to respond better, the finding that an intranasally applied antihistamine, azatadine, was able to block the antigen-induced mediator release, should be noted (17).

The improvement of symptom score by placebo is clearly shown in Fig. 2. This beneficial effect of topical placebo application on rhinitis

symptoms has already been noted by other authors (24). It has to be stressed that the placebo used is not mere saline. Some of the components of this placebo have been used with success in preparations for nasal lavage.

It is also noted that levocabastine significantly improved nasal obstruction, when used after placebo in a single-blind study design (Fig. 2)

In the same type of design (single-blind, phase 2) BDP appeared to be capable of significantly improving nasal obstruction symptom score after treatment with levocabastine (Fig. 3). The symptom scores for sneezing and rhinorrhea as well as the total symptom score showed no statistical improvement as a result of BDP topical application, although a 14-day treatment period might be too short to evaluate the full corticosteroid effect.

Summarizing, it may be stated that a typical H_1 antagonist effect was demonstrated using topical levocabastine, which improved especially the symptoms of sneezing and running nose, when treating allergic and non-allergic perennial rhinitis.

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Address:

P. van de Heyning, M.D. Ph.D.
Dept. of ENT and Head and Neck Surgery
University Hospital Antwerp
Wilrijkstraat 10
2520 Edegem
Belgium

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