

Effects of topical treatment with H₁ and H₂ antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis

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Fifteen asymptomatic subjects with allergic rhinitis participated in a double-blind, randomized, crossover, placebo-controlled study. The subjects were pretreated intranasally with a single dose of a selective H₁ receptor antagonist, levocabastine, and/or selective H₂ receptor antagonist, ranitidine, prior to a nasal allergen challenge. The nasal symptoms obtained at the challenge were assessed using a scoring technique 15 min after the allergen exposure. The nasal airway resistance was determined twice prior to and once after the allergen challenge using anterior rhinomanometry. The nasal mucosal blood flow was determined before and 15 min after allergen challenge using the ¹³³Xe wash-out technique. After pretreatment with the H₁ antagonist there was a statistically significant reduction in the number of sneezes and rhinorrhea compared to pretreatment with placebo. Pretreatment with the H₂ receptor significantly decreased the rhinorrhea but not the sneeze. The nasal blockage was unaffected by both the H₁ and the H₂ antagonists. Pretreatment with the H₁ and/or the H₂ antagonists inhibited the reduction in the nasal mucosal blood flow induced by the allergen challenge to a significant degree. The present findings suggest that topical treatment with the highly selective histamine antagonist, levocabastine, inhibits allergen-induced reflex-mediated symptoms. H₁ and H₂ receptors do not appear to be involved in the regulation of the tone of the capacitance vessels. This indicates that a more complex mechanism participates in the induction of nasal blockage than the direct effect of histamine on H₁ and H₂ receptors on the capacitance vessels of the nasal mucosa alone. Both H₁ and H₂ receptors are of importance for the regulation of nasal mucosal blood flow during the allergic reaction.

Key words: allergic rhinitis; blood flow; histamine receptors; levocabastine; nasal mucosa; ranitidine; topical treatment.

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In recent years considerable interest has focused on the role played by mediators such as leukotrienes, platelet activating factor (PAF), neuropeptides and plasma factors in the induction of the signs and symptoms of allergic airway reactions (16, 21). Even so, histamine is still considered the most important mediator of the allergic reactions of the upper airways. This is based on the fact that oral antihistamines have long been the drug of choice in the treatment of allergic rhinitis (6,

13, 14). Furthermore, in the challenge situation, antihistamines given systemically as well as topically inhibit allergen-induced nasal symptoms (12, 18). Moreover, it has recently been shown *in vivo* in the nose that histamine is released following exposure to allergen (16). Thus, histamine is the only mediator which is constantly released after appropriate challenge, producing all the major symptoms of rhinitis.

The recent development of highly selective H₁ and H₂ receptor antagonists such as levo-

cabastine and ranitidine has provided us with interesting pharmacological agents for further evaluation of the role of histamine and different histamine receptors in the induction of the signs and symptoms of the allergic manifestations of the upper airways.

The aim of the present study was to answer the following three questions:

1. Has topical pretreatment with H_1 and/or H_2 receptor antagonists any effect on the provoked symptoms of allergic rhinitis?
2. Are H_1 and H_2 receptors involved in the regulation of the tone of the capacitance vessels and can pretreatment of these receptors influence nasal blockage induced by allergen?
3. Are both H_1 and H_2 receptors of importance for the regulation of the nasal mucosal blood flow during the allergic reaction?

MATERIAL AND METHODS

Study design

The study was designed as a double blind, randomized, crossover, placebo-controlled investigation. Pretreatment was given topically prior to a nasal allergen challenge in asymptomatic hay fever patients. Symptoms and local vascular reactions were monitored.

Subjects

We selected 15 subjects, 11 males and 4 females, ranging in age from 20 to 30 years (mean age 23.2 years). The subjects had a strictly seasonal allergic rhinitis due to birch and/or timothy pollens. All the subjects had a positive skin prick test to 10,000 BU/ml of the antigen extract (PharmalgenTM, Pharmacia) and had a positive nasal allergen challenge. None of the subjects was a smoker and none of the subjects used any medication apart from oral contraceptives. All the subjects had a normal finding at anterior rhinoscopy, i.e. no significant septal deviation or nasal poly-

posis. None of the subjects had any acute nasal disease such as a cold during the study. Every subject gave his/her informed consent to participating in the study which was approved by the Ethics and Isotope Committees of Gothenburg University.

Pretreatment

Each patient was given local intranasal treatment 30 min before the allergen challenge. A double dummy technique was used for the administration of the two drugs. The H_1 receptor antagonist, levocabastine, or an equivalent placebo spray was given initially. This was followed 5 min later by the H_2 receptor antagonist, ranitidine, or an equivalent placebo spray. Both nasal cavities were treated on each occasion. The treatment was randomized in such a way that each individual was given five different treatment alternatives on different days. The alternatives were:

1. Ranitidine placebo + levocabastine placebo
2. Ranitidine 25 mg/nasal cavity (H_2) + levocabastine placebo
3. Levocabastine 0.025 mg/nasal cavity (H_1) + ranitidine placebo
4. Levocabastine 0.05 mg/nasal cavity (H_1) + ranitidine placebo
5. Levocabastine 0.05 mg + ranitidine 25 mg/nasal cavity ($H_1 + H_2$)

The levocabastine solution contained besides drug also benzalkoniumchloride 0.1 mg/ml as a preservative and had a pH between 6 and 8. The corresponding placebo solution was identical to the levocabastine solution but not containing any active drug. The ranitidine solution was prepared as previously described (20). The solution contained 250 mg ranitidine/ml. No preservative was added and the pH was 6.5. The corresponding placebo solution was prepared as previously described containing 1 % kinin chloride, to match the bitter taste, and sodium riboflavine phosphate to match the yellow color of the ranitidine solution. No preservative was added. All solutions

were administered to the nasal cavity with the aid of a mechanical pump spray delivering 0.1 ml per actuation. The dose was 1 puff into each nostril of each of the two sprays.

Nasal allergen challenge

The allergens used for challenge were Pharmalgen[™] (AB Pharmacia, Uppsala, Sweden). They were delivered freeze dried and were diluted to 10⁴ BU/ml using human serum albumin diluent. Between trials they were stored in a refrigerator. One hour before and during trials they were kept at room temperature. The solutions were administered to the nasal cavity with the aid of a mechanical pump spray which is commercially available for delivering DSCG solution (Lomudal Nasal[™], Fisons Ltd., Loughborough, Great Britain). Each spray delivers 0.13 ml of fluid and achieves a widespread distribution in the nasal cavity (15). The subjects stood when the allergen solutions were administered. Both nasal cavities were challenged. The trial was carried out during pollen-free autumn and winter months. At least 1 week elapsed between the challenge occasions which took place between 4.00 p.m. and 8.00 p.m.

Determination of symptoms score

Nasal symptoms were recorded during a 15-min period after each challenge using a scoring technique. Sneezes were counted. Nasal blockage, secretion and itching were rated on a 0-3 scale where: 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms.

Determination of nasal airway resistance

The subjects were examined in a sitting position by means of active anterior rhinomanometry (NR4, Mercury, Glasgow, Scotland) for each separate nasal cavity. Each subject blew her/his nose before every determination whether this was necessary or not. Nasal airway flow was always determined first in the right nasal cavity. Every subject was examined three times in each trial (Fig. 2). An X-Y writer (Recorder 26000 A3,

Bryans, Mitcham, England) provided a hard copy of the results. When the airflow in the right nasal cavity was determined, the left nasal cavity was closed with a piece of adhesive tape (3M, St. Paul, MN, USA) pierced by catheter for pressure determination. Calculations were made of v_2 during expiration and inspiration for each separate nasal cavity according to Broms (4). A higher v_2 value indicates a higher NAR. In the illustration (Fig. 2) the v_2 of expiration for each nasal cavity has been used to calculate the total NAR accordingly (4). The rhinomanometer was calibrated for pressure and flow at each trial and was stable.

Determination of blood flow

Nasal mucosal blood flow was determined using a ¹³³Xenon wash-out method described in detail elsewhere (1). In short, the mean nasal mucosal blood flow in the right inferior turbinate was calculated from the disappearance of an injected isotope, ¹³³Xenon, recorded 5 min after the injection. All blood flow determinations were carried out with the subjects in the supine position.

Procedure

Ten minutes after the last spray of the pretreatment the NAR was determined. This was then followed by a baseline determination of the nasal mucosal blood flow. After the blood flow determination, which takes about 5 min, another 10 min elapse before the next determination of the NAR. The subjects were then challenged with allergen and the symptom scores were assessed after 15 min. Ten minutes after the allergen challenge the NAR was determined for each nasal cavity separately. The nasal mucosal blood flow was then determined 15 min after the allergen challenge. Thus, patients were challenged with allergen 30 min after the administration of the drugs. The last blood flow determination was carried out 45 min after the drug was given.

Statistics

An analysis of variance was performed in order to whether there was a difference between any of the

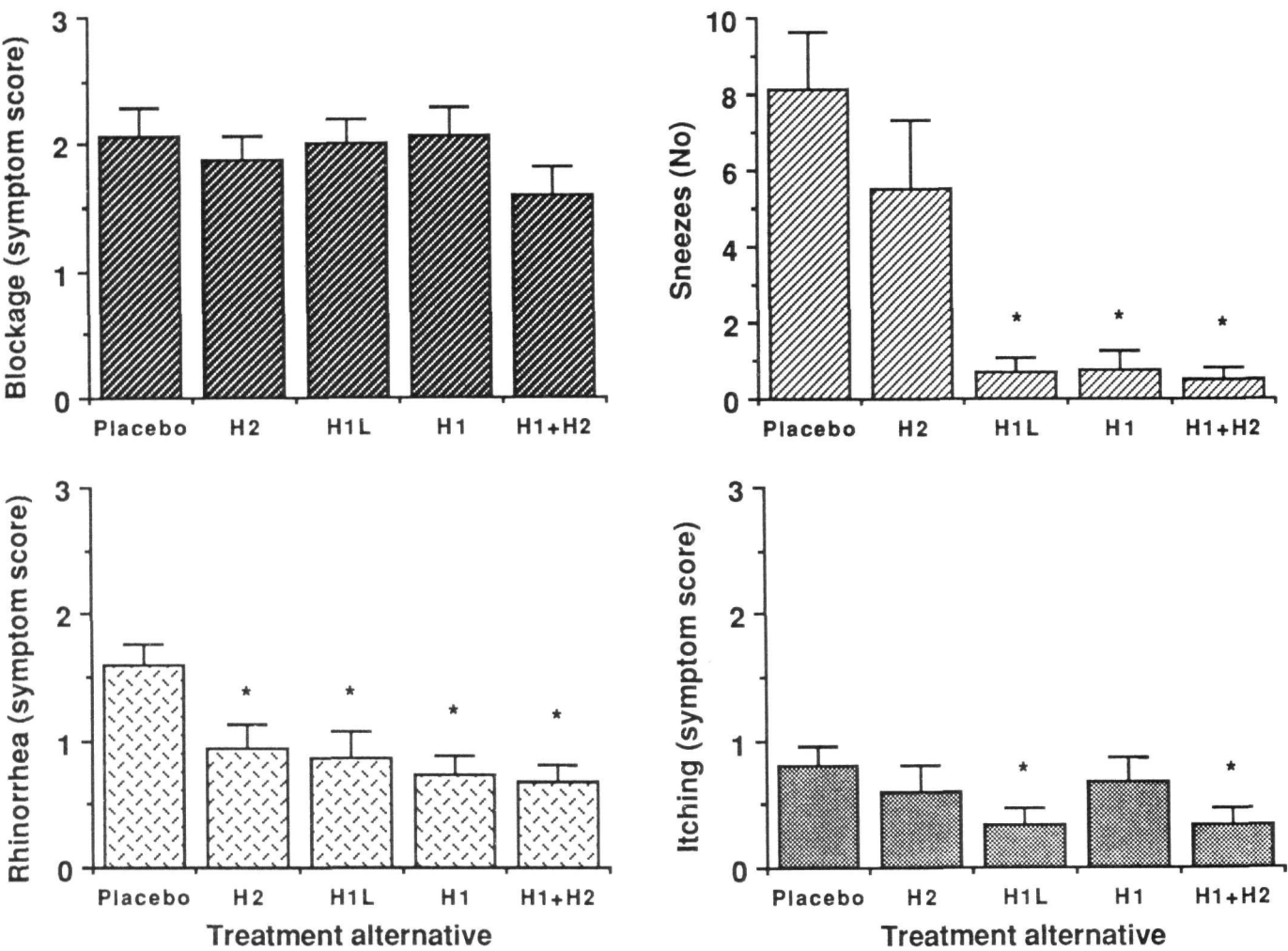


Fig. 1. Symptom score (mean±SEM) for each symptom 0–15 min after allergen challenge in relation to each pretreatment group. (* $P < 0.05$). The treatment alternatives are placebo, H₂ = ranitidine (25 mg/nasal cavity), H₁L = levocabastine (0.025 mg/nasal cavity), H₁ = levocabastine (0.05 mg/nasal cavity) and H₁ + H₂ = levocabastine (0.05 mg/nasal cavity) + ranitidine (25 mg/nasal cavity).

five different treatment alternatives in terms of generation of nasal symptoms, increase in NAR or change in blood flow. If a statistical significance emerged, further analyses were made using Student's t-test for paired data. A two-tailed test was used. P -values of < 0.05 were considered statistically significant.

RESULTS

Symptoms

Topical pretreatment with both a high and low dose of the H₁ antagonist and a combination of the high dose of H₁ and H₂ antagonists significantly ($P < 0.05$) inhibited the number

of sneezes compared to topical treatment with placebo (Fig. 1). Topical treatment with H₁, H₂ and a combination of the antagonists significantly inhibited ($P < 0.05$) rhinorrhea compared to topical treatment with placebo (Fig. 1). Pretreatment with the H₁ low dose and the high dose of H₁ + H₂ had a significant ($P < 0.05$) effect on itching in the nose (Fig. 1).

Nasal airway resistance

The allergen challenge induced a significant increase in NAR as shown after the pretreatment with placebo. The changes in NAR induced by the allergen challenge were unaffected by the pretreatment with H₁, H₂ or a combination of these antagonists as demonstrated in Fig. 2.

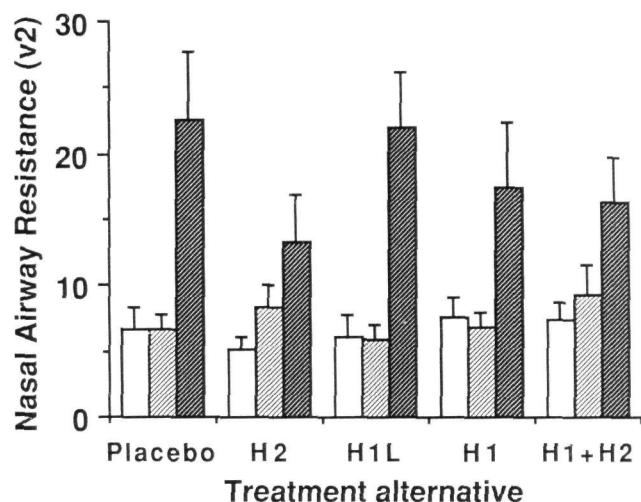


Fig. 2. Nasal airway resistance (v2; mean $\pm$ SEM) in both nasal cavities; the first bar represents v2 10 min after pretreatment, the second bar represents v2 10 min after the first blood flow determination and just before allergen challenge, and the third bar represents v2 10 min after allergen challenge. The pretreatment groups are placebo, H₂ = ranitidine (25 mg/nasal cavity), H₁L = levocabastine (0.025 mg/nasal cavity), H₁ = levocabastine (0.05 mg/nasal cavity) and H₁ + H₂ = levocabastine (0.05 mg/nasal cavity) + ranitidine (25 mg/nasal cavity).

Nasal mucosal blood flow

Following allergen challenge nasal mucosal blood flow was reduced with 16% ($P < 0.05$) after pretreatment with placebo. No allergen-induced changes in blood flow were recorded after the pretreatment with the H₁, H₂ or the combination of these two antagonists, as shown in Table 1.

Table 1

Nasal mucosal blood flow (ml $\times$ min⁻¹ $\times$ 100 g⁻¹) (mean + SEM) before and 15 min after bilateral challenge with allergen and after pretreatment with five different nasal sprays.
H1L = H1 low dose

Pretreatment	Blood flow (ml $\times$ min ⁻¹ $\times$ 100 g ⁻¹)		
	Baseline	After allergen	Change (%)
Placebo	76($\pm$ 3)	64($\pm$ 5)	-16*
H2	71($\pm$ 5)	71($\pm$ 5)	0
H1L	66($\pm$ 5)	73($\pm$ 4)	7
H1	65($\pm$ 4)	72($\pm$ 5)	13
H1 + H2	72($\pm$ 6)	73($\pm$ 4)	-2

* $P < 0.05$

Side effects

In five cases subjects complained that the solutions caused stinging and itching in the nose but in a few cases in the throat. These side effects were not related to any specific treatment alternative. Mainly after the placebo combination a few subjects had protracted nasal symptoms, such as mild or moderate secretion and nasal blockage for up to 3 days. This called for treatment with terfenadine and local decongestant immediately after and within 12 h of the trial as escape medication.

After determining blood flow some subjects occasionally had nosebleed but only after blowing the nose. No special treatment was necessary for these occasional nosebleeds and no one had to withdraw from the trial.

DISCUSSION

In the present study we found that topical intranasal H₁ treatment and a combination of H₁ and H₂ significantly blocked allergen-induced reflex-mediated symptoms but not the allergen-induced changes in NAR. However, the allergen-induced decrease in nasal mucosal blood flow was inhibited after pretreatment with the H₁ and H₂ receptor antagonists.

The inhibition of the allergen-induced reflex-mediated symptoms, sneezes, itching and to some extent rhinorrhea, is in agreement with previous reports (2, 12, 22). Thus, the effect of the topically administered antihistamine, levocabastine, did not differ in its capacity to inhibit these nasal symptoms from previous reports using the same antihistamine when evaluated in a challenge model out of season (12), or when levocabastine was given during seasonal pollen exposure (2). In the present study the low dose of the H₁ receptor antagonist reduced symptoms more or less completely and we could not demonstrate any dose-response relationship as a result of the two different doses of H₁. In other words, the low dose of levocabastine seemed to block all the receptors. Thus, any additive effect from the H₂ antagonist, ranitidine, on the allergen-induced symptoms could not properly be eval-

uated in the present study. However, topical treatment with the H_2 agent alone produced a significant effect on the symptom rhinorrhea, which is in contrast to an earlier report after challenge with histamine (20). This could be due to an indirect effect on the reflex arch or direct effect on the glands, as suggested by Shelhamer et al. (19). The difference between the present findings after allergen challenge with those found after histamine challenge may well be explained by the difference in challenge agents and techniques for the assessment of the rhinorrhea. The finding that more or less all the reflex-mediated symptoms were blocked by the H_1 antihistamine suggests that the effect of the receptor-antagonist is on the afferent side rather than on the efferent reflex arch. The present finding may also indicate the presence of H_1 and H_2 receptors on the nerve endings, presumably "irritant receptors" in the nasal mucosa, is responsible for the induction of the reflex-induced symptoms.

The lack of any effect by both histamine antagonists on the allergen-induced nasal blockage is in agreement with previous experiences from clinical use of antihistamines of the H_1 and H_2 type, where little or no effect has been seen produced by oral antihistamines (5, 18, 22). On the other hand, the findings contrast with a previous report from nasal histamine challenge studies, where a significant inhibitory effect on histamine-induced nasal blockage was reported (7, 20). Furthermore, the reported additive effect of the H_2 receptor antagonist was also absent in the allergen challenge setting.

There are several possible explanations for the discrepancy between the findings from the histamine challenge experiments as compared to the present findings using allergen. Mediators other than histamine are most probably involved in the induction of the nasal blockage. This symptom is largely a vascular phenomenon comprising a mucosal edema as a result of increased vascular permeability and a decrease in the tone of the capacitance vessels leading to an engorgement of blood in the mucosa. Such direct vascular effects are probably also influenced by mediators other than

histamine and this is supported by the findings that the biochemical composition, especially the plasma components in nasal secretions harvested after allergen challenges, differs from secretions harvested after histamine challenge (3). The redundancy of systems involved in the induction of nasal symptoms may overshadow any effect caused by the antihistamines, or there could be an inhibition of the affinity of the H_1 and H_2 receptors of the capacitance vessels for the antagonists during the allergic reaction (11). Nevertheless, it appears less likely that H_1 and H_2 receptors participate in the regulation of the tone of the capacitance vessels during the provoked allergic mucosal reaction.

The regulation of the blood flow in the nasal mucosa during allergic reactions also appears to be complex. It has previously been shown that allergen induces a dose-dependent decrease in nasal mucosal blood flow, a decrease which at least to some extent is reflex-mediated (8). A local challenge with histamine does not induce such a reduction in blood flow (9). However, antihistamines can apparently block the allergen-induced reduction in blood flow. This finding appears to give further support to the notion that the allergen-induced decrease in blood flow is a reflex-mediated phenomenon. Histamine alone might not be able to activate the reflex mechanism which mediates changes in the resistance vessels during the allergic reaction. Allergen releases other vasoactive mediators which, with or without histamine, probably trigger the reflex which decreases blood flow in the mucosa. The inhibition of the reflex might be a much simpler procedure than the reflex activation process, i.e. the reflex mechanism is easily inhibited by local anaesthesia (10).

In conclusion, the present findings suggest that topical treatment with the highly selective histamine antagonist, levocabastine, inhibits allergen-induced reflex-mediated symptoms. H_1 and H_2 receptors do not appear to be involved in the regulation of the tone of the capacitance vessels. This indicates that a more complex mechanism participates in the induction of nasal blockage than the direct effect of

histamine on H₁ and H₂ receptors on the capacitance vessels of the nasal mucosa alone. Both H₁ and H₂ receptors are of importance for the regulation of the nasal mucosal blood flow during the allergic reaction.

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