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Experimentally induced nasal hypersecretion does not reduce the efficacy of intranasal levocabastine*

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SUMMARY

In allergic rhinitis, a nasal H_1-antihistamine spray seems to be well suited for usage on an as-needed basis, because it has a quick onset of action, and many patients prefer to take medicine only when they have symptoms. It is a prerequisite, however, that nasal hypersecretion during a rhinitis episode does not significantly reduce the efficacy of intranasal treatment by washing away the drug before it reaches the H_1-histamine receptors. In order to investigate this problem, we have induced nasal hypersecretion with a methacholine challenge in one experiment and in four experiments we have washed the nasal cavities 0.5 min. before, 5 min. before, 0.5 min. after and 5 min. after intranasal use of the H_1-antagonist, levocabastine. The symptom response to a subsequent histamine challenge was used as the effect parameter. Levocabastine reduced the number of histamine-induced sneezes with 81% ($p < 0.0001$) and the secretion weight with 62% ($p < 0.001$) compared with placebo. Neither methacholine-induced hypersecretion nor washing the nose with saline reduced the efficacy of the antihistamine spray. We conclude that experimentally induced nasal hypersecretion does not reduce the efficacy of the antihistamine spray, and probably the same applies to rhinorrhea during an acute episode of allergic rhinitis.

Key words: allergic rhinitis, rhinorrhea, H_1-antihistamine, levocabastine, methacholine, histamine

INTRODUCTION

Patients, in general, tend to use medicine only when they have symptoms, and H_1-receptor antagonists are the drugs of choice for the symptomatic p.r.n. treatment of allergic rhinitis because of their quick onset of action (Lund et al., 1994). When an antihistamine is used to give quick relief from rhinitis symptoms, it is an advantage if the drug is given topically instead of orally, because it then can reach the H_1-receptors in the nasal epithelium directly. A nasal spray can, therefore, have a quicker onset of action than a tablet.

Efficacy of intranasal treatment, however, will depend on the access of the drug to mucosal H_1-histamine receptors, and when an antihistamine is sprayed into the nose of a patient with ongoing rhinitis symptoms, sneezing, rhinorrhea and blockage may all inhibit drug access to receptor sites and with that reduce or abolish efficacy of the treatment. To our knowledge, this problem has not been investigated earlier, and it is, therefore, not known whether a nasal spray or a tablet is preferable, when an antihistamine is used to give quick relief for allergic rhinitis symptoms.

It is the aim of this study to investigate whether one of the symptoms of rhinitis, nasal hypersecretion, reduces the access of an antihistamine spray to the receptor sites in the nasal mucosa. We examined in an experimental laboratory model whether the inhibitory effect of levocabastine on histamine-induced symptoms is influenced by nasal hypersecretion, induced by a methacholine challenge, and imitated by nasal lavages before and after spraying of the H_1-antihistamine.

The inhibitory effect of the H_1-antihistamine spray on nasal symptoms, induced by a nasal histamine challenge, was used as the effect parameter. As an antihistamine, we have chosen levocabastine, which is a potent H_1-receptor antagonist, widely used for the topical treatment of allergic rhinitis (Dechant and Goa, 1991; Bahmer, 1995; Dahl et al., 1995; Gerth van Wijk, 1995).

MATERIAL AND METHODS

Subjects

Twelve healthy adults (7 women and 5 men) volunteered to take part in the study. Their mean age was 26.8 years (range: 22-32 years). A history of allergy, chronic respiratory or nasal dis-

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eases were exclusion criteria. Volunteers were not included if they had had a common cold within 14 days before start of the study. I
f they got a common cold during the study, they had to wait 14 days after the last day with symptoms, before continuing the study. All volunteers gave informed consent to the study protocol which was approved by the Ethical Committee of Copenhagen County (KF 02-100/97).

Medication
Levocabastine nasal spray, 50 μg/dose (Livostin®), and matching placebo were delivered by Janssen-Cilag, Denmark. A single medication, consisting of two puffs into each nostril (total dose of 200 μg levocabastine) or of placebo, was given in each of the 7 experiments. The nose was blown immediately before medication, and the spray was used according to the written instruction from the manufacturer.

Study design
The design was double-blind, placebo-controlled for medication and histamine challenge (Experiment 1 and 2). The experiments with methacholine (Experiment 3) and with nasal lavages (Experiment 4-7) were not blinded.
Experiment 1 and 2. The volunteers received placebo or levocabastine in a randomised order, and 30 minutes later, they were challenged with histamine.
Experiment 3. A methacholine challenge was performed 5 minutes before levocabastine medication. A histamine challenge was performed 30 minutes after medication.
Experiment 4-7. Each nasal cavity was washed with saline either 5 min. before, 0.5 min. before, 0.5 min. after or 5 min. after the levocabastine medication. A histamine challenge was performed 30 min. after medication.

Histamine challenge
Thirty minutes after medication, 400 μg of histamine was sprayed into each nostril. Histamine was delivered from a metered-dose pump spray, one puff of 0.1 ml into each nostril.
The response to the histamine challenge was measured as the number of sneezes and the weight of blown nasal secretions, produced during a 10 min. period.

Methacholine challenge
In Experiment 3, a nasal challenge with methacholine was performed 5 min. before the levocabastine medication in order to induce nasal hypersecretion. Methacholine, 25 mg, was delivered from a metered-dose pump spray (64 mg/ml), two puffs of 0.1 ml into each nostril.

Nasal lavage
In Experiment 4-7, each nasal cavity was washed with 20 ml of saline (0.9% NaCl) at a fixed point of time, i.e. 5 min. before, 0.5 min. before, 0.5 min. after or 5 min. after levocabastine medication.

Statistics
Friedman's test performs two-way analysis of variance on ranks of objects within the 7 experiments, testing the hypothesis that there is no systematic variation in the rankings across objects. Wilcoxon rank sum test was used to compare two experiments; $p < 0.05$ was considered significant.

RESULTS
The levocabastine nasal spray caused a 81% reduction of histamine-induced sneezing ($p < 0.0001$) and a 62% reduction of the weight of nasal secretion ($p < 0.001$) (Figure 1) compared with placebo.

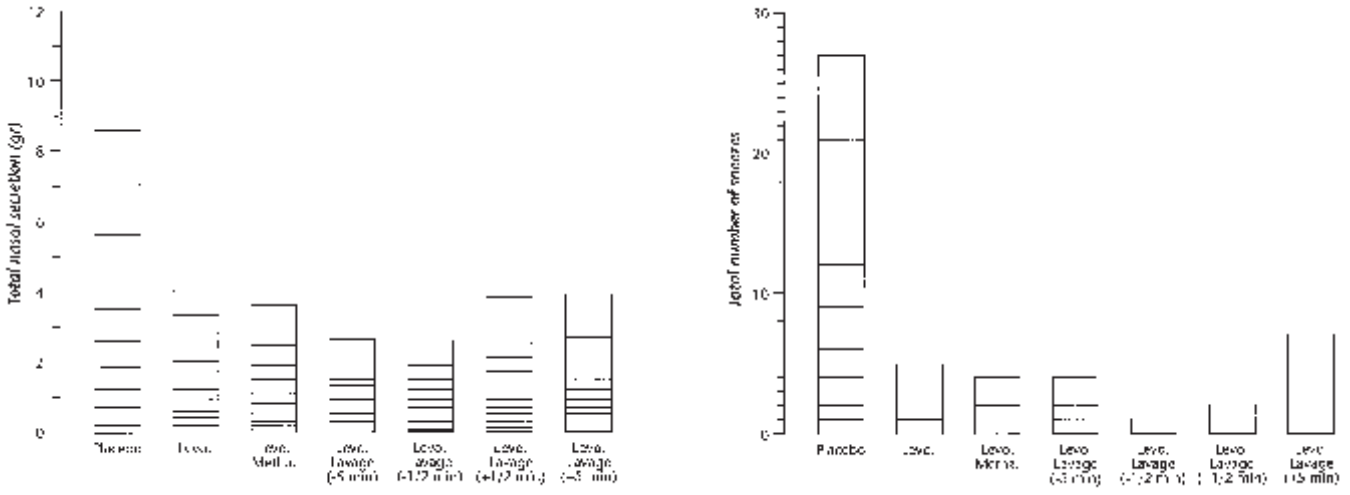

Figure 1. Total amount of histamine-induced nasal secretion (left part) and total number of sneezes (right part) in the 7 experiments. The lines within the bars indicate individual values. Levo. = Levocabastine; Metha. = Methacholine challenge; –5 min. and +5 min. mean nasal lavage 5 min. before and 5 min. after medication.

There was no statistically significant difference between the effect of levocabastine, given alone, and levocabastine given after a methacholine challenge or after/before a nasal lavage with saline (Figure 1). There was not even a tendency of reduced drug effect in the methacholine/lavage experiments. On the contrary, in these experiments, the mean number of sneezes was lower in 4 out of 5 experiments, and that of nasal secretion weight was lower in 5 out of 5 experiments, as compared with the levocabastine experiment without induced rhinorrhea/nasal lavage.

DISCUSSION

A nasal methacholine challenge induces hypersecretion but neither sneezing nor nasal blockage (Borum, 1979). The secretory activity reaches a maximum 5 min. after challenge (Borum, 1979), and for that reason we performed the methacholine challenge 5 min. before levocabastine spraying in the present study. The amount of secretion induced by a methacholine challenge varies from person to person, but an earlier study has shown that the dosage used in this trial produces about 0.4 ml of secretion within 15 min. This corresponds to the degree of rhinorrhea following a mild allergen challenge (Brofeldt et al., 1986), and to an episode of allergic rhinitis that can be expected to be sufficiently severe for a patient to require symptomatic therapy. It is astonishing that the significant hypersecretion, which caused obvious overspill of nasal fluid both to the nostrils and to the throat, did not reduce the efficacy of levocabastine by a wash-away effect. Apparently, the concentration of levocabastine is so high that the dilution in nasal fluid is not critical, and apparently the drug access to the H_1-receptors takes place so rapidly that it is sufficient to have the spray fluid in the nose for a brief period of time only.

This assumption was supported by the lavage experiments. The drug effect was not diminished when the nose was washed with saline as soon as 30 s. after levocabastine spraying, which clearly shows that a maximum drug effect, and with that access to the receptor sites, can occur within 30 s.

As the results were clear with no tendency of reduced drug effect in the methacholine/lavage experiments, intranasal levocabastine can be expected to be fully effective when used by a patient with an acute episode of allergic rhinitis and rhinorrhea. These results are supported by a comparative study showing an advantage of topical levocabastine as compared to oral terfenadine in allergic rhinitis (Davies et al., 1996). It is a prerequisite of topical treatment, however, that drug access to receptor sites is not abolished by nasal blockage. Obviously, a nasal spray will not be effective when used in a completely blocked nose or nostril, but it is apparently not known how a partial blockage will influence the intranasal distribution and the effect of an intranasally applied drug. This question can be investigated in a controlled experiment, using induced blockage instead of induced hypersecretion.

We cannot directly extend our results with the antihistamine, levocabastine to other nasally applied drugs. Firstly, the target receptors for a drug may be located at different levels in the mucous membrane. While an antihistamine may need only to reach sensory nerves superficially in the epithelium, ipratropium bromide, for example, needs to reach cholinergic receptors in submucosal glands. Secondly, the speed of absorption probably depends upon the physicochemical characteristics of a drug, such as its molecular size, hydrophilicity/lipophilicity and electrical charge. In a series of experiments with intranasal application of polypeptides (Drejer et al., 1994) it was the experience of one of us (NM) that watery rhinorrhea before and sneezing immediately after intranasal application precluded the absorption of a peptide drug.

In conclusion, experimentally induced nasal hypersecretion does not reduce the efficacy of a levocabastine spray. This spray can, therefore, also be expected to be fully effective when used on an as-needed basis in order to give quick symptomatic relief to patients with allergic rhinitis symptoms.

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