

Effects of H₁-receptor antagonists on nasal obstruction in atopic patients

Horak F, Toth J, Jäger S, Berger U. Effects of H₁-receptor antagonists on nasal obstruction in atopic patients.
Allergy 1993; 48: 226-229. © Munksgaard 1993.

F. Horak, J. Toth, S. Jäger, U. Berger

1st ENT University Clinic, Vienna, Austria

The aim of this study is to investigate whether H₁-receptor antagonists, besides their effect on nasal itching and sneezing, also have a measurable effect on nasal obstruction caused by allergen challenge. The antihistamine used was astemizole (10 mg) versus placebo, in a double-blind, cross-over, randomized study of two groups. Between the two sessions there was a wash-out period of at least 4 weeks. Seven patients of both sexes, with proven allergy to grass pollen, underwent a specific long-term provocation with grass pollen in the Vienna challenge chamber. Using a physiological method of challenge and a sensitive method for evaluating nasal function, we were able to prove H₁-receptor antagonist influence on nasal airway obstruction. The main parameters obtained are nasal flow and nasal resistance at 75, 150 and 300 Pa, evaluated by active anterior rhinomanometry. We also investigated subjective symptom scores (0-3) of nasal, eye, and lung symptoms. It can be shown that the nasal flow under astemizole treatment is statistically significantly higher than the nasal flow under placebo treatment ($P = 0.034$). This is in accordance with the findings in subjective nasal itching and sneezing.

Key words: allergic rhinitis; antihistamine; astemizole; nasal obstruction; rhinomanometry; Vienna challenge chamber.

Dr F. Horak
1st ENT-Univ. Clinic
Lazarettgasse 14
A-1090 Vienna
Austria

Accepted for publication 3 March 1992

Within a few minutes of allergen challenge in atopic volunteers, high amounts of various mediators are released. Previous studies have shown that the appearance of mediators, such as histamine, leukotrienes (B₄, C₄), and prostaglandins (D₂), is followed by the typical hay fever symptoms of rhinorrhea, sneezing, itching, and nasal obstruction (6). These findings are consistent with mast cell degranulation (4). Specific provocation with histamine only also leads to the same symptoms, but within seconds (11). Antihistamines have been tested for their effectiveness in preventing rhinorrhea and sneezing, their onset of action, and their decreasing effect on mediator release.

However, investigations proving the effectiveness of H₁-receptor antagonists in relieving nasal obstruction are still lacking, although recent studies have led to the conclusion that H₁-receptor antagonists can also act as mast cell stabilizers, preventing the activity of other mediators besides histamine (9).

Our aim is to investigate whether it is possible to prove with objective parameters, by a sensitive technique, that modern H₁-receptor antagonists have an effect not only on sneezing and rhinorrhea, but also on nasal obstruction.

Methods

The trial design was double-blind, cross-over, placebo-controlled, with a randomized group of seven volunteers examined in two consecutive sessions with a wash-out period of 4 weeks.

The active treatment used was the H₁-receptor antagonist astemizole (10 mg) and lactic acid as placebo control. Both drugs were administered in visually indistinguishable tablets. Medication was given only 15 min before allergen challenge to simulate an everyday situation.

The 7 patients taking part (3 women and 4 men, mean age 25.3 years, range 22 to 34 years) were allergic to grass pollen, had a positive case history (> 6 years), positive skin prick test and positive nasal provocation test to grass pollen, and positive RAST to g3 and g12 antigen (> class 2.5). Informed consent to this study was obtained. Patients had anatomically normal nasal cavities, no asthmatic case history, and no acute infection of the upper respiratory tract in the 4 weeks prior to the study (Table 1).

Specific allergen challenge was carried out as a physiological long-term challenge with grass pollen, using the Vienna challenge chamber (VCC) for 4 h.

Table 1. Demographic listing of patients

Volunteer (sex)	Age (yr)	Case history (yr)	RAST g3 orchard grass
f	30	28	4.0
m	34	21	3.2
m	20	12	2.5
f	24	11	3.8
m	22	6	2.5
f	22	20	3.3
m	25	21	3.3

This long-term challenge results in a protracted immediate reaction, closely mimicking a period of hours in the course of a day in the pollen season. The VCC is an apparatus which enables us to perform long-term challenge tests under controlled and reproducible conditions (5). It is an enclosed space permitting up to eight persons to be challenged under physiological conditions for several hours. It is charged by indoor air which is cleaned, cooled, and dried. This prepared air is loaded with a qualitatively and quantitatively determined amount of allergens. For this trial, grass pollen (*Dactylis glomerata*) was used in a concentration of 1000 grains/m³ of air, homogeneously dispersed in the chamber (7). The grass pollen is biologically activated by UV light and dispersed slowly through pectinate openings in the ceiling. The used air is removed through four openings in the floor. The indoor pollen concentration is checked every 5 min and counted as grains/m³ of air. The temperature and humidity of the indoor climate is controlled (25°C and 30% humidity) within a small range.

Objective clinical parameters for indicating nasal obstruction, as nasal flow, nasal resistance, and nasal flow increase, are evaluated by active anterior rhinomanometry. This is a very sensitive method for objectively estimating the extent of nasal obstruction. The nasal flow and nasal resistance were observed at pressures of 75, 150, and 300 Pa. The chosen method is active anterior rhinomanometry as described by Bachmann (1), according to the current international standard.

Our rhinomanometry apparatus is connected to a microcomputer system (Fig. 1) for estimating all data within less than a minute, so that a complete measurement takes about 1 min (including calibration). The transducer signals of transnasal airflow and pressure are amplified and digitized, so the measurements can be seen on the computer screen and the results stored for statistical use. With this system, rhinomanometry measurement can be done within 1 min, thus enabling repeated measurements in each patient during the trial time. Nasal secretion is estimated by weighing handkerchiefs before and after use.

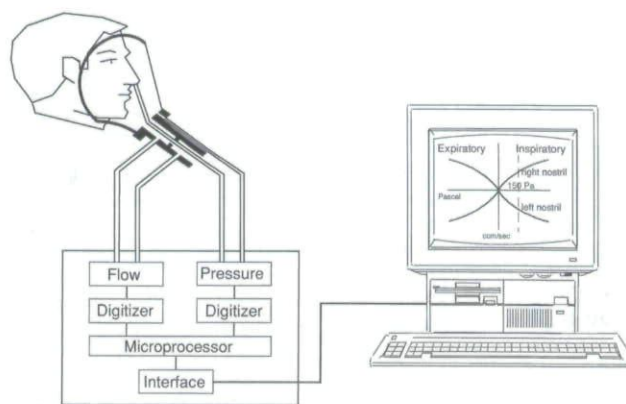


Fig. 1. Computer-assisted rhinomanometry. The patient is breathing through one nostril (mouth closed) to evaluate the nasal flow, while the difference between prenasal and choanal pressure is measured in the other nostril (active anterior rhinomanometry).

In addition to these objective parameters, subjective scores (0–3) of nasal itching, nasal blocking, nasal secretion, and sneezing are recorded. Volunteers are requested to fill in a symptom score sheet. The overall subjective condition is estimated by a 10-cm visual analog scale.

All objective and subjective parameters are recorded every 30 min during a 4-h period of challenge with a physiological concentration of grass pollen.

Statistics

For description of the target aim, the AUC (area under curve) of the nasal flow at 150 Pa was chosen. After testing the presuppositions (normal distribution, homogeneity of variances), we performed a Student's *t* test.

Results

The individual reactions varied not only from person to person but also in the same patient at different challenges. Yet we could see similar reactions in persons undergoing the same treatment. A clear correlation between the amount of reaction and RAST class could not be verified.

The development of nasal flow showed that all patients increased nasal obstruction within 30 min of the start of allergen exposure (Tables 2, 3). About 120 min after the start of the challenge, the trend became biphasic. Obstruction still increased on placebo treatment, while in the actively treated group a decrease in nasal flow stabilized sooner (Fig. 2).

About 120 min after drug administration the obstruction stopped its slight increase in the actively treated group and reached a plateau phase. The placebo group attained this state 30 min later, but it was about two times higher. Statistically significant

Table 2. Change of nasal flow during a 4-h, long-term challenge with orchard grass pollen, in patients ($n=7$) treated with a single dose of 10 mg astemizole

Minutes	Nasal flow in ccm/s at 150 Pa (10 mg astemizole)		
	Mean	Minimum	Maximum
0	860.86	650	1047
30	814.00	611	1010
60	760.00	375	1121
90	711.71	280	1035
120	650.14	309	915
150	689.43	316	911
180	671.29	281	892
210	579.14	298	818
240	650.57	234	880
270	618.14	291	913

Table 3. Change of nasal flow during a 4-h, long-term challenge with orchard grass pollen, in patients ($n=7$) treated with a single dose of placebo

Minutes	Nasal flow in ccm/s at 150 Pa (placebo)		
	Mean	Minimum	Maximum
0	791.71	612	949
30	736.14	545	957
60	599.43	399	756
90	544.14	248	808
120	553.57	297	747
150	457.57	59	666
180	473.86	114	597
210	462.43	87	682
240	498.14	100	770
270	463.86	90	699

differences can be demonstrated for nasal flow ($P=0.034$) from astemizole 10 mg versus placebo.

The production of nasal secretion was not always enough to measure at every interval, so the obtained

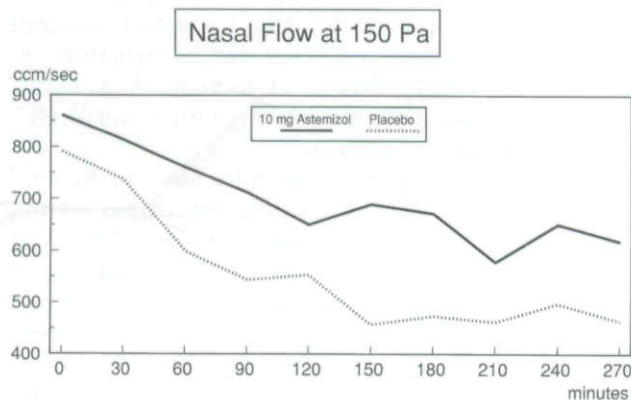


Fig. 2. Change of nasal flow during a 4-h, long-term challenge with grass pollen, in patients ($n=7$) treated with a single dose of 10 mg astemizole vs. placebo. Plot of the mean values shown in Tables 1, 2. Statistical significance (comparing AUC) based on $P=0.03$.

data are not homogeneous but show no visible distinctions. A high amount of nasal secretion was produced in the first 2 h. It is noteworthy that the production declined after 120 min under both treatments.

Evaluation of the subjective scores indicates that the patients used only a very small range on the score scale, and, as the starting point differed from session to session, deviations are sometimes high. This applies to the subjective nasal score (the sum of itching, sneezing, blocking, and subjective rhinorrhea). Nevertheless, subjective itching and sneezing abated after 210 min in the astemizole-treated group but not in the placebo group.

Discussion

The results of this investigation show that the obstructive reaction of nasal mucosa to allergen exposure occurred within 30 min. About 150 min after the start of allergen exposure, a plateau reaction was recognizable in the placebo-treated group. In the astemizole group we could see that the increase in nasal obstruction was definitely less and the plateau phase was reached half an hour earlier. This indicates that active treatment reduced the increase and kept it at a lower range than in the non-treated group.

There was no visible difference in nasal secretion between the two groups, but the individual secretory production can differ widely. The maximum increase in nasal secretion occurred within the first 2 h and abated thereafter. The subjective statements must also be qualified, as previously explained. It is remarkable that the subjective nasal score reached a peak 150 min after the challenge started, while nasal itching and sneezing reached a peak within 60 min, thereby showing a difference between the two groups. The astemizole group had a lower plateau score and a more moderate increase in discomfort. Symptom increase immediately after the start of physiological challenge is in accordance with mediator release, as previously described (8, 10, 13). The minor increase in sneezing and itching in the placebo-treated group was directly due to the effect of histamine antagonism (3). Recent studies (2) could show that under treatment with an H_1 -receptor antagonist (terfenadine) the mediator response is minor and therefore the occurrence of symptoms such as sneezing and itching is reduced. However, nasal obstruction is more dependent on leukotrienes and prostaglandins. Baroody et al. (14) observed a decrease of leukotrienes and prostaglandins in nasal lavage during treatment with cetirizine, terfenadine (systemically administered), and azatadine (topical) and, furthermore, a decrease in albumin and TAME esterase, indicating blood vessel permeability. In recent studies Liu et al. (9) and Naclerio et al. (12) suggest that

H₁-receptor antagonists can also act as mast cell stabilizers. Our results support this assumption, since we find a measurable influence of the antihistamine astemizole on nasal obstruction statistically distinguishable from the influence of placebo.

Conclusion

Even if the effect of H₁-receptor antagonists (astemizole) mainly concerns sneezing and nasal itching, an additional decreasing effect on nasal obstruction can be objectively shown, one that is statistically significant, as compared with placebo.

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