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Effect of systemically administered H_1- and H_2-receptor antagonists on nasal blood flow as measured with laser Doppler flowmetry in a provoked allergic reaction*

S. Juliusson[1], M. Bende[2]

[1] Department of Chest Medicine, Vifilstadir, Gardabaer, Iceland
[2] Department of Otorhinolaryngology, Central Hospital, Skövde, Sweden

SUMMARY

Twelve subjects with seasonal allergic rhinitis were challenged topically with birch pollen extract in a double-blind, double-dummy, placebo-controlled, randomized cross-over study. Pre-treatment was performed with either a selective histamine-1 (H_1-) antagonist (terfenadine), a selective H_2-antagonist (cimetidine), a combination of these drugs or a placebo. Nasal mucosa microcirculatory blood flow was measured with the use of laser Doppler flowmetry. The allergen challenge induced a decrease in the microcirculatory blood flow of the nasal mucosa. Pre-treatment with the H_1-antagonist inhibited this effect and allergic symptoms, while pre-treatment with the H_2-antagonist did not. No signs of an additive effect were seen after combination of the antagonists. Thus, H_1-receptors but not H_2-receptors, seem to be of importance in the pathophysiology of the allergic rhinitis.

Key words: antihistamines, laser Doppler flowmetry, microcirculation, nasal allergy, humans

INTRODUCTION

The pathophysiology of allergic rhinitis is for the most part unknown, especially regarding the regulation of blood flow in the vascular bed of the mucosa. Several vasoactive mediators are involved and, among these, histamine is the most important in the pathogenesis during the acute phase of the allergic inflammation. Histamine acts on both H_1- and H_2-receptors, and if H_2-receptors play a role in the allergic reaction, a selective H_1-receptor antagonist may be less effective in relieving the allergic symptoms. This suggestion is supported by the findings that treatment with a combined H_1-/H_2-antagonist gave an additional effect on the symptoms of allergic rhinitis as compared to an H_1-antagonist alone during pollen season (Carpenter et al., 1983). The effect was found, however, only during the week with the highest pollen counts. Furthermore, an additional effect on nasal airway resistance of a combined H_1-/H_2-antagonist was found as compared with separate H_1- and H_2-antagonist treatments after histamine challenge in healthy subjects (Secher et al., 1982). By selectively blocking the histamine receptors during the allergic reaction, information can be obtained on the differences between histamine receptors on blood flow-regulating resistance vessels. Furthermore, by combining H_1- and H_2-antagonists, a possible additional or synergistic effect can be revealed. Holmberg et al. (1989a) measured the nasal mucosal blood flow with a ^{133}Xe wash-out technique and found that the H_1- and/or H_2-antagonist inhibited to a significant degree the reduction in blood flow induced by the allergen challenge. They concluded that both H_1- and H_2-receptors were of importance for the regulation of nasal mucosal blood flow during the allergic reaction.

The aim of this study was to evaluate possible effects of different histamine antagonists on nasal mucosal blood flow as measured with laser Doppler flowmetry in the allergic reaction.

MATERIAL AND METHODS

Study design

The study was designed as a double-blind, double-dummy, randomized, placebo controlled cross-over comparison of the effects of selective H_1- and H_2-antagonists on nasal microcirculation during an acute allergic reaction. The study was approved by the Ethics Committee of the Medical Faculty at the University of Göteborg. The study was performed in the pollen-

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free winter months of January and February. The patients were examined four times with at least two weeks between each examination. Thus, a comparison between the effect of a H_1-antagonist, a H_2-antagonist, a combination of the H_1- and the H_2-antagonist, and a placebo was done. Each investigation consisted of an oral intake of the test-drug, measurement of the microcirculatory blood flow with laser Doppler flowmeter after nasal allergen provocation, and evaluation of symptoms.

Patients

Twelve patients (3 women and 9 men; aged 19–36 years; mean age: 25 years) voluntarily entered the study and gave their informed consent. None was on any medication with known influence on allergic symptoms and none had received previous immunotherapy. All were asymptomatic at the start of the study, but had a history of hypersensitivity to birch pollen, which was confirmed by a positive skin prick test. In order to obtain symptoms of allergic rhinitis, the volunteers were provoked in the nose with a highly purified birch pollen extract (Pharmalgen®; Pharmacia, Uppsala, Sweden). The challenge applications commenced with the diluent and then proceeded with the birch pollen extract 15 min later, on the nasal mucosa in front of the laser Doppler probe as previously described (Juliusson and Bende, 1988). A 5-min stable registration period before each application was required to give a baseline value.

Pre-treatment drugs

About two hours prior to the allergen challenge the patients were given one of four drugs: (1) 60 mg terfenadine, a selective H_1-receptor antagonist (Teldanex®; Draco, Lund, Sweden); (2) 400 mg cimetidine, a selective H_2-receptor antagonist (Tagamet®; SmithKline and French, Welwyn Garden City, U.K.); (3) a combination of these drugs; or (4) a placebo in a randomized order with double-blind, double-dummy technique.

Measurement of nasal mucosal bloodflow

The blood flow of the nasal mucosa was investigated by means of a laser Doppler flowmeter (Periflux PF1d; Perimed, Stockholm, Sweden), which is a sensitive non-invasive method of studying the microcirculation, as described previously (Juliusson and Bende, 1987, 1988). The tip of the probe was fixed, under visual guidance, 1-3 mm from the mucosal surface of the anterior part of the inferior turbinate. The output signal was registered on a pen-recorder throughout the 15 min after application of the test solutions. The results were evaluated by calculating the area under the curve during that time period.

Symptom registration

Sneezes were counted and graded (0-4) according to the following scale: 0: no sneezes; 1: 1–2 sneezes; 2: 3–4 sneezes; 3: 4–6 sneezes; and 4: >6 sneezes. The patients' symptoms of irritation, blockage, and secretion were pooled and evaluated at the end of each examination by following rating scale: 0: no symptoms; 1: minimal; 2: mild; 3: moderate; and 4: severe symptoms.

Statistics

Analysis of variance was carried out among the different treatments to test for differences in response. If significance was found, Duncan's Multiple Range Test was used to detect the treatments producing different responses. P-values less than 0.05 were considered significant. Results are expressed as mean±SEM.

RESULTS

The diluent did not induce any statistically significant changes of the microcirculatory flow as compared to the baseline registrations. Therefore, the effect of the allergen provocation was calculated as a percentage of the registration curve obtained after the diluent. After allergen provocation and treatment with placebo the blood flow decreased to 90.3±4.2% ($p < 0.05$; paired t-test). The H_1-antagonist inhibited the decrease in blood flow obtained after the allergen provocation (100.5±3.2% in relation to the diluent). The H_2-antagonist *per se* did not inhibit the decrease in blood flow (decrease to 85.9±3.0%). The combination of the H_1-antagonist and the H_2-antagonist inhibited the blood flow decreasing effect of the allergen provocation (96.5±3.2% of the diluent effect). Thus, no additional or synergistic effect could be seen of the H_2-antagonist (Figure 1). The effect of the H_1-antagonist and the

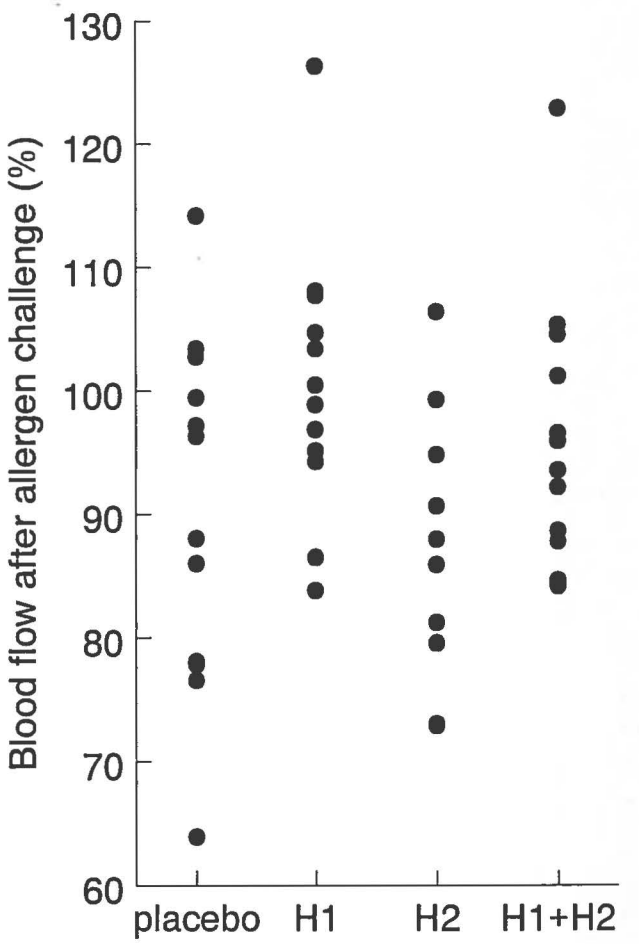

Figure 1. The effect of pre-treatment with a selective H_1-antagonist (terfenadine), a selective H_2-antagonist (cimetidine), a combination of these drugs or a placebo on the microcirculatory blood flow in the nasal mucosa after allergen challenge in 12 subjects with birch pollen allergy.

combination of the H_1-antagonist and the H_2-antagonist differed significantly from the placebo and the H_2-antagonist alone ($p < 0.05$). The H_1-antagonist differed significantly from the H_2-antagonist on the 1% level.

In Figure 2, the effects of the drugs on the sneezes and nasal symptoms are plotted. Similarly as for the blood flow, the symptoms were significantly inhibited by the H_1-antagonist, but no effects were seen after the H_2-antagonist.

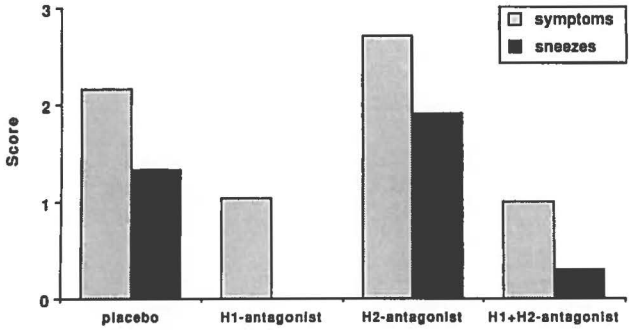

Figure 2. The effect on nasal symptoms (irritation, blockage and secretion) and on sneezes of pre-treatment with either a placebo, a selective H_1-antagonist, a selective H_2-antagonist, and a combination of these antagonists after allergen challenge in 12 patients with birch pollen allergy.

DISCUSSION

The present study shows that systemically given H_1-antagonist but not H_2-antagonist, significantly inhibited the allergen-induced nasal symptoms and microcirculatory blood flow in the mucosa as measured with laser Doppler flowmetry.

When comparing the laser Doppler flowmeter with other methods for studying the blood flow in the nasal mucosa, it is obvious that differences exist (Olsson, 1986; Lacroix and Lundberg, 1989). When speaking about "blood flow in the nasal mucosa," it should be defined which method and what species have been used. Laser Doppler flowmeters measure the product of the number of moving cells and their mean velocity (flux) in the tissue that is illuminated by laser light. The penetration depth of laser light varies with different tissues and with the state of the tissue. The output signal is expressed as a voltage and data obtained from the laser Doppler is presented on a scale ranging from 0–100%. Some investigators have presented the laser Doppler registrations from the nasal mucosa in quantitative terms (Druce et al., 1984, 1989; Rangi et al., 1990). This approach could only be recommended if the Doppler output-signal could be calibrated against other established methods for measuring blood flow in that specific tissue. Such a calibration has not been performed in the nasal mucosa. Bearing this in mind, and because of the complex vascular anatomy in the nasal mucosa with its large sinusoid system and arteriovenous shunts, we prefer to present our laser Doppler flowmetry data from the inferior turbinate in arbitrary units.

There have been several investigations performed concerning nasal mucosal blood flow in allergy using various techniques during the last decade. With the hydrogen clearance method, a bilateral increased mucosal blood flow was found after unilateral allergen challenge in most subjects (Konno et al., 1982). With the ^{133}Xe wash-out method a decreased mucosal blood flow has been found after allergen challenge (Bende et al., 1984; Holmberg et al., 1988, 1989a, b, c). As measured by laser Doppler flowmetry, an increased blood flow has been found after challenge with antigens (Juliusson and Bende, 1987, 1988; Rangi et al., 1990). These differences in results are due to the fact that close to the site of allergen challenge of the nasal mucosa there is a decreased blood flow, but in the surrounding tissues the blood flow is increased (Tanimoto et al., 1983), a phenomenon similar to the weal-and-flare reaction seen at skin prick testing.

Oral antihistamines have long been an important drug in the treatment of allergic rhinitis. According to the present study the H_1-receptor antagonist *per se* was effective both in inhibition of the nasal symptoms and effect on microcirculation accompanying the allergic reaction. The H_2-antagonist had no effect *per se* and no additive effect.

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REFERENCES

1. Bende M, Elner Å, Ohlin P (1984) The effect of provoked allergic reaction and histamine on nasal mucosal blood flow in humans. Acta Otolaryngol (Stockh) 97: 99–104.
2. Bisgaard H, Olsson P, Bende M (1986) The effect of leukotriene D_4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. Clin Allergy 16: 289–297.
3. Carpenter GB, Bunker-Soler AL, Nelson HS (1983) Evaluation of combined H_1- and H_2-receptor blocking agents in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 71: 412–417.
4. Druce HM, Bonner RF, Patow C, Choo P, Summers RJ, Kaliner MA (1984) Response of nasal blood flow to neuro hormones as measured by laser Doppler velocimetry. J Appl Physiol 57: 1276–1283.
5. Druce HM, Kaliner MA, Ramos D, Bonner RF (1989) Measurement of multiple microcirculatory parameters in human nasal mucosa using laser Doppler velocimetry. Microvasc Res 38: 175–185.
6. Holmberg K, Bake B, Pipkorn U (1988) Nasal mucosal blood flow after intranasal allergen challenge. J Allergy Clin Immunol 81: 541–547.
7. Holmberg K, Bake B, Pipkorn U, Blychert L-O (1989a) Effect of topical treatment with H_1 and H_2 receptor antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis. Allergy 44: 281–287.
8. Holmberg K, Bake B, Pipkorn U (1989b) Reflex activation of allergen induced nasal mucosal vascular reactions. Acta Otolaryngol (Stockh) 108: 130–135.
9. Holmberg K, Bake B, Pipkorn U (1989c) The effect of topical anaesthesia on allergen-induced symptoms, obstruction and blood flow. Clin Exp Allergy 19: 443–447.
10. Juliusson S, Bende M (1988) Priming effect of a birch pollen season studied with laser Doppler flowmetry in patients with allergic rhinitis. Clin Allergy 18: 615–618.
11. Juliusson S, Bende M (1987) Allergic reaction of the human nasal mucosa studied with laser Doppler flowmetry. Clin Allergy 17: 301–305.
12. Konno A, Togawa K, Nishihira S (1982) Participation of vascular reflex in mucosal swelling in nasal allergy. Acta Otolaryngol (Stockh) 94: 131–140.
13. Lacroix J-S, Lundberg JM (1989) Sympathetic vascular control of the pig nasal mucosa: Adrenoceptor mechanisms in blood flow and volume control. Br J Pharmacol 97: 1075-1084.

14. Olsson P (1986) A comparison between the ^{133}Xe washout and laser Doppler techniques for estimation of nasal mucosal blood flow in humans. Acta Otolaryngol (Stockh) 102: 106–112.
15. Rangi SP, Serwonska MH, Lenahan GA, Pickett WC, Blake VA, Sample S, Goetzi EJ (1990) Suppression by ingested eicosapentaenoic acid of the increases in nasal mucosal blood flow and eosinophilia of ryegrass-allergic reactions. J Allergy Clin Immunol 85: 484–489.
16. Secher C, Kirkegaard J, Borum P, Maansson A, Osterhammel P, Mygind N (1982) Significance of H_1 and H_2 receptors in the human nose: Rationale for topical use of combined antihistamine preparations. J Allergy Clin Immunol 70: 211–218.
17. Tanimoto H, Okuda M, Yagi T, Ohtsuka H (1983) Measurement of the blood flow of the nasal mucosa by the hydrogen clearance method. Rhinology 21: 59–65.

Mats Bende
Dept. of Otorhinolaryngology
Central Hospital
S-54185 Skövde
Sweden

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