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Skin reactivity to vasomotor agents in non-eosinophilic and eosinophilic non-allergic rhinitis

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Abstract

The aim of this prospective study was to examine skin reactivity to four vasomotor agents and to determine whether non-eosinophilic rhinitis patients differ from patients with eosinophilic rhinitis. Nasal cytology enabled us to classify 74 rhinitis patients into a non-eosinophilic (n = 63) and an eosinophilic group (n = 11). Skin reactivity to intradermal tests with papaverine, metacholine, histamine and compound 48/80 was measured. No significant difference for papaverine, metacholine, histamine and compound 48/80, singly, was found between the non-eosinophilic and eosinophilic group.The frequency of the total pathological skin reactivity to vasomotor agents, singly and in combinations, was greater in the eosinophilic (91 per cent) then in the non-eosinophilic group (78 per cent) but intergroup difference was not significant. These findings suggest that pathologic skin reactivity to vasomotor agents is a feature of non-eosinophilic as well as eosinophilic non-allergic rhinitis patients and indicate that no difference is noticed in the skin reactivity between these groups.

Key words: Skin Tests; Rhinitis; Vasomotor System; Drug Effects

Introduction

Non-allergic rhinitis a heterogeneous syndrome consisting of at least two groups: non-eosinophilic and eosinophilic.[1] The non-specific nasal reactivity to metacholine and histamine in non-allergic rhinitis patients is well known,[2,3] but the skin reactivity to non-specific agents in these patients is less examined.[4,5] Our prior study of intradermal tests with vasomotor agents suggests that a difference in skin reactivity between healthy subjects and perennial non-allergic rhinitis patients is noticed.[6] It is not clear whether skin reactivity to vasomotor agents in non-eosinophilic rhinitis patients differs from eosinophilic rhinitis patients.

The aim of this study was to examine the skin reactivity to papaverine, metacholine, histamine and compound 48/80 and to determine whether non-eosinophilic rhinitis patients differ significantly from eosinophilic rhinitis patients.

Materials and methods

A prospective study with 74 non-allergic rhinitis patients was carried out in the Department of Rhinology and Allergology, Institute of Otorhinolaryngology and Maxillofacial Surgery in Belgrade. Before entering the study, all patients gave their written informed consents.

The criteria for selection of rhinitis patients were: nasal obstruction and/or rhinorrhoea and sneezing of three months duration or more;[7] a negative history of allergen exacerbation that was supported by definite negative skin prick results and negative Phadiatop results; no evidence of other types of non-allergic rhinitis, e.g. rhinitis induced by hormones, drugs, emotions or mechanical trauma;[8] and no evidence of other diseases and conditions, that could interfere with vasomotor activity of the nasal mucosa.

The diagnosis of non-allergic rhinitis was based on history, physical, microbiological and radiological examination and a skin prick test with a battery of routine respiratory and nutritive allergens (Institute of Immunology and Virology, Torlak, Belgrade) and Phadiatop determination (Pharmacia, Upsala).

The main exclusion criteria were: asthma and other chronic pulmonary diseases, liver and renal diseases, skin diseases, systemic disorders, intolerance of non-steroid anti-inflammatory drugs, autoimmune diseases and tumours, emotional stress, trauma of the nose and paranasal sinuses and usage of drugs interfering with vasomotor activity (e.g.

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antihypertensives, topical/systemic steroids and decongestants).

Nasal smears for eosinophils were taken with cotton swabs in order to obtain cells from the posterior part of the nose. Three smears were performed on each patient. The specimens were transferred to a slide and stained by the May Grünvald-Giemsa method. One hundred cells were counted and the number of eosinophils per 100 cells was expressed as a percentage. Nasal eosinophilia was regarded as significant when 20 per cent or more of the cells in nasal smear were eosinophils.[9,10] Nasal cytology enabled us to classify 74 rhinitis patients into a non-eosinophilic (n = 63) and an eosinophilic group (n = 11).

The skin testing in rhinitis patients was conducted according to the modified skin test with vasomotor agents[6] proposed by Wayoff *et al.*[4,5] The skin reactivity was examined with papaverine hydrochloride (5 mg/ml; ICN, Belgrade), metacholine chloride (0.02, 0.2 and 2 mg/ml; Sigma-Aldrich, Steinheim), histamine phosphate (0.01, 0.1, 1 and 10 μg/ml; Sigma-Aldrich, Steinheim) and the compound 48/80 (0.01, 0.1, 1 and 10 μg/ml; Sigma-Aldrich, Steinheim). The saline solution control was used because the patients with dermographic skin react to trauma itself and in the case of a positive skin reaction to the saline, this value was subtracted from each value measured for each vasomotor agent. Vasomotor agents were dissolved in saline, stored at 4°C and used at room temperature. The solutions of metacholine were renewed every two weeks.[2]

Each intradermal test consisted of the injection of 0.1 ml of the vasomotor agents or saline into the dermis. The application of the vasomotor agents resulted in the appearance of wheal-and-flare skin reactions. These tests were performed on the skin of the back, symmetrically around the backbone. The measurement of wheal-and-flare skin reactions was optimal after 10 minutes. Pathological skin reactions are hyporeactivity to papaverine and hyper-reactivity to metacholine, histamine and/or compound 48/80, singly and in combinations.[4,5]

According to the results of the modified skin test with vasomotor agents, the pathological skin reactivity was: hyporeactivity to papaverine, with a wheal-and-flare skin reaction diameter less than 15 mm; hyperreactivity to metacholine (0.02, 0.2 and 2.0 mg/ml), when two of three wheal-and-flare skin reaction diameters were greater than 15, 25 and 31 mm, respectively, hyperreactivity to histamine (0.01, 0.1, 1.0 and 10.0 μg/ml), when three of four wheal-and-flare skin reaction diameters were greater than 7, 13 25 and 40 mm, respectively; and hyperreactivity to compound 48/80 (0.01, 0.1, 1.0 and 10.0 μg/ml), when three of four wheal-and-flare skin reaction diameters were greater than 9, 16, 26 and 38 mm, respectively. The normal skin reactivity was: for papaverine (5 mg/ml), when wheal-and-flare skin reaction diameter was greater than 15 mm; for metacholine (0.02, 0.2 and 2.0 mg/ml), when wheal-and-flare skin reaction diameters were less than 15, 25 and 31 mm, respectively; for histamine (0.01, 0.1, 1.0 and 10.0 μg/ml), when wheal-and-flare skin reaction diameters were less than 7, 13, 25 and 40 mm, respectively; and for compound 48/80 (0.01, 0.01, 1.0 and 10.0 μg/ml), when wheal-and-flare skin reaction diameters were less than 9, 16, 26 and 38 mm, respectively.[6] The skin tests were performed early in the morning throughout the study period.

To compare the frequencies of the pathological and normal skin reactivity to vasomotor agents between the non-eosinophilic and eosinophilic groups of rhinitis patients, the Chi-square test statistic values, calculated by Pearson formula for general case and Mood formula for the 2×2 contingency tables were used. All statistical calculations were performed by means of the IMSL Problem-Solving Software Systems (IMSL Inc., 1989).

Results

This study included 74 non-allergic rhinitis patients. A significant percentage of eosinophils was found in 15 per cent of these patients and they were classified into the eosinophilic group (n = 11). In this group, The percentage of eosinophils varied from 20 to 80 per cent (mean ± SD, 35 ± 21 per cent). In the non-eosinophilic group (n = 63), it ranged from 0 to 10 per cent (mean ±SD, 1 ± 2 per cent). No significant difference concerning sex ($p = 0.445$) and age ($p = 0.076$) between the two groups of rhinitis patients was observed (Table I).

No significant intergroup difference for pathological skin reactivity to papaverine ($p = 0.588$), metacholine ($p = 0.456$), histamine ($p = 0.210$), compound 48/80 ($p = 0.923$) and saline ($p = 0.727$) was found (Table II).

The total pathological skin reactivity to vasomotor agents, singly and in combinations, was found in 78 per cent (49/63) of non-eosinophilic and in 91 per cent (10/11) of eosinophilic rhinitis patients. In both the non-eosinophilic and eosinophilic group, the frequency of total pathological skin reactivity to vasomotor agents was significantly greater than the frequency of normal skin reactivity ($p = 1.1 \cdot 10^{-5}$ and $p = 0.007$, respectively). The intergroup difference of total pathological skin reactivity to vasomotor agents was not significant ($p = 0.552$).

TABLE I
CHARACTERISTICS OF THE NON-EOSINOPHILIC (NE) AND EOSINOPHILIC RHINITIS PATIENTS (E)

	NE (n = 63)	E (n = 11)
Sex		
females	45	6
males	18	5
Age (years)		
range	18–73	18–57
mean ± SD	40 ± 13	33 ± 13

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TABLE II
FREQUENCIES OF PATHOLOGICAL SKIN REACTIVITY TO SINGLE VASOMOTOR AGENTS AND SALINE IN NON-EOSINOPHILIC (NE) AND EOSINOPHILIC GROUP (E)

Pathological skin reactivity	NE	E
	N^0 (%)	N^0 (%)
Papaverine	20 (31.7)	5 (45.4)
Metacholine	22 (34.9)	2 (18.2)
Histamine	14 (22.2)	5 (45.4)
Comound 48/80	13 (20.6)	3 (27.3)
Saline	12 (19.0)	2 (18.2)

Discussion

This study demonstrated that pathological skin reactivity to intradermal tests with papaverine, metacholine, histamine and compound 48/80 agents is a feature of both non-eosinophilic and eosinophilic non-allergic rhinitis patients.

The changes in the vasomotor activity of the nasal mucosa represent one of the fundamental mechanisms responsible for the well-known symptoms of non-allergic rhinitis. The examination of skin reactivity to vasomotor agents in rhinitis patients is based on the morphological and functional similarities of nasal mucosa blood vessels and skin blood vessels,[11–13] suggesting that established reactivity of skin blood vessels to vasomotor agents could represent similar or just the same reactivity of nasal mucosa blood vessels.

Papaverine, metacholine, histamine and compound 48/80 are vasoactive substances with different pharmacological mechanisms of vasodilatation. The main action of papaverine is to relax the smooth muscle in blood vessels by phosphodiesterase inhibition and blockade of calcium channels.[14] The dilatation of blood vessels by metacholine is due to the presence of muscarinic receptors located on the endothelial cells.[15] The release of histamine from mast cells is a result of the action of immunological and non-immunological factors (drugs, physical stimulus and chemical substances) on the mast cells. It causes the dilatation of the blood vessels, increase of capillary permeability and stimulation of sensory nerve endings.[16] Compound 48/80 stimulates the release of histamine from mast cells directly and without prior sensitization. The exact mechanism of its action is not clear, but it seems to involve the mobilization of intracellular calcium or the activation of G-protein.[17]

The intradermal tests with different vasomotor agents in patients with non-allergic rhinitis provide data of skin reactivity and suggest that several forms of skin reactivity be involved. Also, a certain number of positive skin reactions to the saline and false negative results confirm well-known difficulties in performing reliable tests in non-allergic rhinitis patients.

Our results suggest that the non-eosinophilic group of rhinitis patients is characterized by pathological skin reactivity to papaverine, singly, and metacholine and histamine, singly and in combination. Even though the number of eosinophilic rhinitis patients (n = 11) was small, we could notice that the pathological skin reactivity to papaverine singly, and histamine, singly and in combinations, is characteric of these patients. Monaret-Vautrin *et al.*[9,10] also demonstrated pathological skin reactivity to paraverine in eosinophilic rhinitis patients. On the other hand, the pathological skin reactivity to metacholine, singly, was not found in this group. In the case of coexisting pathological skin reactivity to metacholine, histamine and/or compound 48/80, it is important to emphasize that histamine stimulates sensory nerve endings and produces parasympathetic and axon reflexes.

The pathological skin reactivity to vasomotor agents suggests that both non-eosinophilic and eosinophilic non-allergic rhinitis patients may be heterogeneous groups. Also, the study of nasal challenge tests with metacholine and histamine demonstrated that non-allergic rhinitis patients were not a homogeneous group.[3]

These findings suggest that the pathological skin reactivity to vasomotor agents is a feature of non-eosinophilic as well as eosinophilic non-allergic rhinitis patients.

In spite of some specific features of skin reactivity to vasomotor agents, no difference in the skin reactivity between non-eosinophilic and eosinophilic rhinitis patients was observed.

More studies are needed to determine whether there are different subgroups of non-eosinophilic and eosinophilic rhinitis patients and to characterize possible subgroups of these patients.

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