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Changes in Nasal Reactivity in Patients with Rhinitis medicamentosa after Treatment with Fluticasone Propionate and Placebo Nasal Spray

Key Words
Rhinitis medicamentosa
Rhinostereometer
Acoustic rhinometer
Nasal reactivity
Fluticasone propionate

Abstract

Aim of the Study: To study the changes in nasal reactivity in patients with rhinitis medicamentosa during treatment with placebo or fluticasone propionate, in order to better understand the mechanisms of nasal congestion in such patients. **Study Design:** A parallel, double-blind study. Twenty patients with rhinitis medicamentosa were randomized to either placebo or fluticasone treatment during 14 days. **Material and Methods:** Nasal mucosa reactivity was studied with a histamine challenge model using three concentrations of histamine to challenge the nasal mucosa (1, 2 and 4 mg histamine/ml). Recordings of the nasal mucosa response were made 5 min after each challenge, using rhinostereometry and acoustic rhinometry, before and after the period of treatment. **Results:** The fluticasone group had a significantly increased histamine sensitivity after treatment, unlike the placebo group who had an unchanged or slightly decreased histamine sensitivity after treatment. **Conclusions:** The results of this study support the theory that the nasal obstruction in rhinitis medicamentosa is due to interstitial oedema rather than to vasodilatation. On the first day of vasoconstrictor withdrawal, the inferior concha was congested and oedematous with a limited capacity to respond to histamine challenge. However, after 14 days of treatment with a corticosteroid nasal spray, the oedema was reduced and the increase in histamine sensitivity reflected the persistence of nasal hyperrreactivity. In the placebo group, histamine sensitivity remains unchanged with the measuring technique we used. This probably indicates that oedema was still present after treatment.

Introduction

Rhinitis medicamentosa is a condition characterized by symptoms of rhinitis caused by the long-term use of decongesting nosedrops or sprays [1]. Vasoconstrictors temporarily induce vasoconstriction and subsequent decongestion of the nasal mucosa via α-receptors in the nasal erectile tissues [2, 3]. When the vasoconstrictive action disappears, there is a compensatory vasodilatation with subsequent swelling of the nasal mucosa [3]. Together, these factors involve a great risk with prolonged use of the vasoconstrictors and rebound nasal congestion. Rhinos-

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Table 1. Patient characteristics

Patients	Sex	Age years	Allergy test	Time of use years	Reason for starting	Drug	Doses/ day	Other medication
A. Fluticasone group								
1	female	28	–	3	common cold	oxymetazoline	2–5	
2	female	23	–	4	common cold	oxymetazoline	2–10	citalopram
3	female	29	–	4	unknown	xylometazoline	3–5	
4	female	28	–	4	unknown	oxymetazoline	3–4	
5	female	31	dog	10	unknown	xylometazoline	7–10	
6	female	37	–	3	pregnancy	oxymetazoline	8–15	
7	female	38	HDM	5	unknown	oxymetazoline	3–5	omeprazole
8	male	35	–	4	unknown	oxymetazoline	6–7	
9	male	29	cat	10	unknown	oxy-/xylometazoline	1–2	
10	female	30	–	15	unknown	oxy-/xylometazoline	10–15	
B. Placebo group								
1	male	39	–	4	common cold	oxymetazoline	3–4	citalopram
2	male	41	cat	5	unknown	xylometazoline	3–4	
3	female	39	–	7	pregnancy	oxymetazoline	7–8	
4	male	32	–	7	common cold	xylometazoline	3–4	
5	female	34	–	10	pregnancy	xylometazoline	5–6	
6	female	38	–	6	sinusitis	xylometazoline	3–5	
7	male	35	–	10	unknown	oxymetazoline	4–5	paroxetine
8	female	22	birch	5	SOM	oxymetazoline	6–8	
9	female	40	–	7	unknown	xylometazoline	3–5	
10	male	48	–	6	rhinoplasty	oxymetazoline	3–4	

SOM = Secretory otitis media; HDM = house dust mite.

copy shows a boggy and swollen nasal mucosa, but this is also seen in patients with vasomotor rhinitis. Patients having vasomotor rhinitis and those with rhinitis medicamentosa also complain of the same symptoms, which makes them hard to distinguish unless they are asked about decongesting nosedrops.

Swelling of the nasal mucosa is mainly due to oedema or swelling of the erectile tissue. Patients with vasomotor rhinitis have a greater nasal mucosa reactivity than healthy subjects, when such reactivity is defined as sensitivity to histamine challenge [4]. The increase in nasal mucosa swelling is probably due mainly to the local effects of mediators acting directly on blood vessels and causing swelling of the nasal erectile tissue [5–7]. In patients with rhinitis medicamentosa however, we find indications that swelling of the nasal mucosa is due largely to the formation of oedema [8].

This study was performed to increase understanding of the mechanisms in rhinitis medicamentosa. It aimed to determine whether there are any changes in nasal reactivity, in patients having rhinitis medicamentosa, after withdrawal of the decongestant nosedrops/spray, and whether there are any differences if they are treated with nasal steroids or placebo. This study is a part of a project studying treatment of rhinitis medicamentosa.

Material and Methods

Study Design

The study was designed as a parallel randomized, double-blind trial. Two groups of 10 patients each having rhinitis medicamentosa (table 1) stopped overusing their nasal vasoconstrictor spray immediately and were treated with either fluticasone propionate nasal spray or placebo nasal spray once daily for 14 days. Nasal mucosal swelling as measured with rhinostereometry and acoustic rhinometry was recorded before and after treatment.

On the first day of the study, day 0, the patients were not allowed to use any decongestant nasal spray. After an acclimatization period of 30 min, the position of the nasal mucosa of the inferior concha in both nasal cavities was recorded repeatedly to establish the baseline mucosal position with rhinostereometry and acoustic rhinometry.

Then the nasal mucosa was challenged with 1, 2 and 4 mg/ml of histamine hydrochloride, where 0.14 ml of the solution was syringed over the inferior concha in one side of the nose. The position of the mucosal surface was determined 5 min after each histamine provocation with rhinostereometry, and the minimal cross-sectional area (MCA 2) was determined with acoustic rhinometry. The first dose of the study drug was taken after completion of the nasal measurements on day 0, and patients were instructed not to use any decongestants. After 13 days on the study drugs (day 14), the measuring procedure was repeated. Written informed consent was obtained from all patients before any procedure was performed. The study was approved by the local Ethics Committee and the Medical Products Agency.

Subjects

Twenty volunteers suffering from nasal blockage, 12 women and 8 men, mean age 33 years, entered the trial. All of them had overused topical decongestants for at least 2 years using their spray 1–15 times a day (table 1). A skin test, Soluprick® (ALK, Denmark), performed on all patients, showed that 5 of them were allergic (table 1). The skin test contained the following allergens: birch, hazel, timothy, mould *(Alternaria, Cladosporium),* house-dust mite *(Dermatophagoides pteronyssinus, D. farinae),* cat, dog, horse, rabbit and guinea pig. Rhinoscopy revealed no signs of a structural basis for the nasal symptoms. All patients were selected from the out-patient department of the ENT clinic at Söder Hospital, Stockholm. They were informed that the vasoconstrictors were mainly responsible for their nasal blockage and they were urged to stop using them immediately.

Methods of Measurements

The nasal mucosal swelling was recorded with rhinostereometry and acoustic rhinometry. Rhinostereometry is an optical, direct, non-invasive method for measuring nasal mucosal swelling with a high degree of accuracy. A surgical microscope is placed on a micrometer table fixed to a frame. The microscope can be moved in three angular directions, establishing a three-dimensional co-ordinate system. The subject is fixed exactly to the apparatus by a plastic, individually made tooth splint. The eyepiece has a horizontal millimetre scale. The nasal cavity is viewed through the eyepiece. Since the microscope has a short depth of focus, changes in the position of the mucosal surface of the medial side of the head of the inferior concha are registered in the plane of focus along the millimetre scale. The accuracy of the method is 0.2 mm [9].

Acoustic rhinometry is a method for recording an acoustic pulse that enters the nose via a tube equipped with an adapter tightly fitted to the nostril. Changes in the cross-sectional area are digitised by a computer and numerical values of the cross-sectional area are registered. The minimal cross-sectional area, MCA 2, is that cross-sectional area between the anterior portions of the concha inferior and the septum. This method has been described elsewhere [10] and in previous studies it seemed to be accurate [11]. The apparatus used in this study was a RHIN 2100 (SR Electronics APS, Lynge, Denmark).

Study Drugs

All patients in both groups sprayed two puffs of the aqueous nasal spray into each nostril every morning. One group was randomized for treatment with Flutide Nasal® fluticasone propionate aqueous nasal spray, a 50 µg/spray puff giving a total of 200 µg a day. The other group received placebo aqueous nasal spray (vehicle). The study drugs were supplied by Glaxo Wellcome AB, Mölndal, Sweden.

Statistical Analyses

Trends and spread were analysed using the mean and standard deviation. The Student's paired and unpaired t tests were employed, for further statistical analyses.

Results

No patient admitted that they used any decongestant nasal spray or other drugs affecting the nasal mucosa during the study period. All patients completed the study. The results from 1 patient were excluded because of a common cold during the study period.

Rhinostereometric Measurements

In the fluticasone group the mean mucosal swelling following histamine challenge before treatment was 0.6 mm using a dose of 1 mg/ml, 1.0 mm using a dose of 2 mg/ml and 1.13 mm using a dose of 4 mg/ml. After 14 days of treatment the corresponding values for mucosal swelling were 1.2, 1.6 and 1.7 mm (fig. 1). The increase in mucosal swelling was not significant at any histamine provocation level. In the placebo group the mean mucosal swelling following histamine challenge before treatment was 0.8 mm using a dose of 1 mg/ml, 1.1 mm using one of 2 mg/ml and 1.3 mm using 4 mg/ml. After 14 days of treatment the corresponding values for mucosal swelling were 0.5, 0.8 and 1.1 mm (fig. 1). The decrease in mucosal swelling was not significant at any histamine provocation level.

When comparing the changes after treatment, an increase in nasal reactivity was observed in the fluticasone group and a decrease in the reactivity in the placebo group. However, no significant difference was detected at any histamine provocation level.

Acoustic Rhinometric Measurements

In the fluticasone group the mean MCA 2 values following histamine challenge before treatment were -0.06 cm^2 with a dose of 1 mg/ml, -0.15 cm^2 with one of the 2 mg/ml and -0.16 cm^2 with 4 mg/ml. After 14 days of treatment the corresponding MCA 2 values were -0.19, -0.26 and -0.23 cm^2 (fig. 2). The decreases in MCA 2 were significant after 1 and 4 mg/ml ($p < 0.01$) but not after challenge with 2 mg/ml. In the placebo group, the mean MCA 2 values following histamine challenge before treatment were -0.1 cm^2 with a dose of 1 mg/ml, -0.2 cm^2 with one of 2 mg/ml and -0.23 cm^2 with 4 mg/ml. After

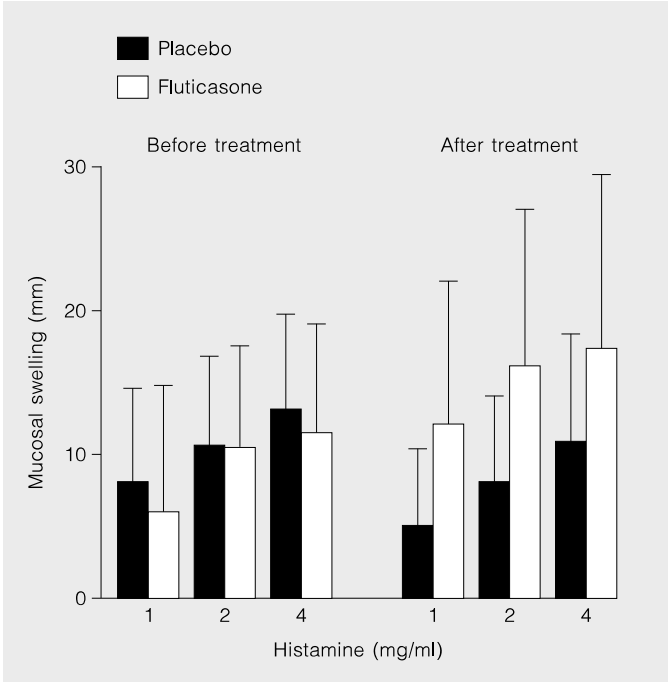

Fig. 1. The mean and SD mucosal swelling following histamine challenge of the nasal mucosa after treatment with fluticasone propionate or placebo nasal spray as measured with rhinostereometry. Challenge of the nasal mucosa was made using a dose of 1, 2 and 4 mg histamine/ml applied to one side of the nose. Recordings were made before and 5 min after each challenge.

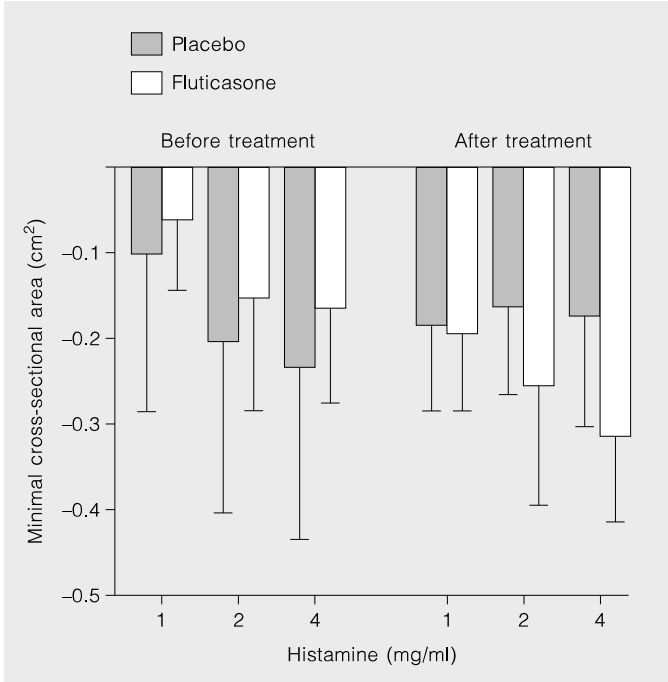

Fig. 2. The mean and SD minimal cross-sectional area (MCA 2) following histamine challenge of the nasal mucosa after treatment with fluticasone propionate or placebo nasal spray as measured with acoustic rhinometry. Challenge of the nasal mucosa was made using a dose of 1, 2 and 4 mg histamine/ml applied to one side of the nose. Recordings were made before and 5 min after each challenge.

14 days of treatment, the corresponding values for MCA 2 were –0.18, –0.16 and –0.17 cm^2 (fig. 2). The changes in MCA 2 were not significant at any histamine provocation level.

When comparing the changes after treatment, one finds a significant increase in nasal reactivity in the fluticasone group compared to the placebo group after challenge with 4 mg/ml ($p < 0.05$). No significant difference was noted after challenge with the other histamine provocation levels.

Discussion

This study shows that nasal reactivity increases after 14 days of treatment with fluticasone propionate nasal spray in patients with rhinitis medicamentosa, but not in patients treated with placebo nasal spray, where reactivity remained unchanged or tended to decrease. These results were confirmed with rhinostereometry and with acoustic rhinometry.

We have previously shown that healthy subjects treated with oxymetazoline nasal spray for 30 days developed a pronounced increase in nasal reactivity, which was significantly greater than that induced by placebo nasal spray [12]. When the vasoconstrictor was withdrawn, the increase in histamine sensitivity gradually normalized after 14–30 days without any further treatment [13]. In this study, the histamine sensitivity was significantly increased after 14 days of treatment with a corticosteroid nasal spray which was not the case after treatment with placebo. It should be pointed out that the patients in both groups were able to stop using the decongestants immediately and that no one used any decongestant medication during the study period. The results of this study therefore support the theory that the nasal obstruction in rhinitis medicamentosa is due to interstitial oedema rather than to vasodilatation. On the first day of vasoconstrictor withdrawal, the inferior concha was congested, and if we assume that there is an oedema, the concha has a limited capacity to respond to histamine challenge. However, after 14 days of treatment with a corticosteroid nasal

spray, the oedema had diminished. The increase in histamine sensitivity reflects the persistence of nasal hyperreactivity. In the placebo group, the histamine sensitivity remained unchanged with the measuring technique we used. This is probably because oedema was still present after treatment. In two other studies it has also been suggested that the rebound congestion in rhinitis medicamentosa results from interstitial oedema, because of incomplete decongestion after the application of an α-agonist [1, 14]. Patients with rhinitis medicamentosa are clinically identical with patients having vasomotor rhinitis with nasal blockage as their main symptom. We have previously reported that 14 days of treatment with budesonide nasal spray significantly reduced the histamine sensitivity in patients with vasomotor rhinitis [14].

It seems that the pathophysiologies of the two diseases differ considerably. The pathophysiology of patients with vasomotor rhinitis seems to consist of a dysfunction in vasomotor tone, resultling in nasal hyperreactivity without the development of interstitial oedema [14]. Rhinitis medicamentosa on the other hand is a disease where the overuse of topical decongestants seems to induce the formation of oedema, nasal hyperreactivity and tolerance to decongestants.

In conclusion, this study shows that in patients with rhinitis medicamentosa, but not in those treated with placebo nasal spray, nasal reactivity increases after 14 days of treatment with fluticasone propionate nasal spray. It is not shown that there is an oedema, but the data support the theory that the nasal obstruction in rhinitis medicamentosa is due to interstitial oedema rather than to vasodilatation. An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and a topical corticosteroid to alleviate the withdrawal process.

Acknowledgement

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