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Histamine sensitivity in the nasal mucosa during four-week use of oxymetazoline*

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SUMMARY

In order to objectively study the histamine sensitivity of the nasal mucosa during 30 days of regular use of oxymetazoline nasal spray (0.5 mg/ml; 0.1 ml in each nostril, thrice daily), eight healthy volunteers were examined with rhinostereometry. After 10 days on being treated, the histamine sensitivity was slightly enhanced. After a further 20 days the sensitivity was significantly increased compared to that before the start of the medication ($p < 0.05$). This increase in histamine sensitivity for the group is significantly greater than that of healthy drug-free volunteers, and the level is comparable with that of patients with non-allergic nasal hyperreactivity (NANH). It is concluded that a hyperreactive mucosal reaction develops after a relatively short time on oxymetazoline and that the results of this study are in line with the recommendation that the drug should not be used for more than 10 days.

Key words: nasal hyperreactivity, decongestants, histamine sensitivity, oxymetazoline

INTRODUCTION

Local nasal decongestants in the form of drops and sprays are frequently used drugs. Since 1989 there is no demand for a doctor's prescription for these drugs in Sweden and an increasing sale has been reported (Swedish Drug Statistics, 1991). It has recently been noted by rhinologists that an increased number of patients suffer from therapy-resistent nasal blockage. These patients have often used vasoconstrictors for a long time, often months. On rhinoscopy, mostly no structural cause of the problems can be seen, except for an occasional mucosal congestion. It is suspected that the long-term use of these drugs has caused the blockage which could be due to a rebound congestion when the vasoconstrictor effect has disappeared. In time the patients need to use more vasoconstrictor to get rid of the stuffiness and, therefore, it is difficult to stop using the drugs. This nasal distress has been referred to as "rhinitis medicamentosa", a well-known entity from the use of other vasoconstrictors such as naphazoline (Black et al., 1980). An investigation of healthy volunteers during six-week use of a local vasoconstrictor has been performed, but the study did not show any functional or structural disturbance of the nasal mucosa (Petruson et al., 1982). In another study on guinea pigs, naphthazoline nitrate was applied to the nose for over a period of four months. This study demonstrates both histopathological and histochemical changes in the nasal mucosa (Samy et al., 1983). Twenty patients, who had misused nose drops for more than six months, have been examined; nasal conductivity was increased, the quantity and quality of the cells of the mucous membranes was decreased, and a metaplasia of the mucous membranes was seen (Rijntjes, 1982). The nasal stuffiness in patients with rhinitis medicamentosa can, among different causes, be due to the development of a non-allergic hyperreactivity of the mucosa. The nasal symptoms of patients with non-allergic nasal hyperreactivity (NANH) are difficult to verify objectively (Hallén et al., 1992). However, with rhinostereometry and histamine provocation it has been possible to register an increased sensitivity to histamine in these patients compared to healthy volunteers (Juto et al., 1982; Ohm et al., 1992; Hallén et al., 1992). Patients with rhinitis medicamentosa might have an increased sensitivity to histamine prior to the medication with decongestants. Therefore, to evaluate the impact of these drugs on the nasal mucosa it is at first important to study healthy subjects. As rhinostereometry is the only direct measuring method with a high accuracy to study changes in nasal mucosa swelling, this method was chosen for this study. The aim of this study is to investigate if it is possible to register an increased histamine sensitivity in healthy individuals during long-term medication with oxymetazoline.

MATERIAL AND METHODS

Nine volunteers (4 men and 5 women; 21 to 36 years old) participated in the study which was performed from Autumn 1991 to Spring 92. The subjects were either students at the hospital or belonged to the staff at the department. They were all healthy,

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drug-free, and had no history of allergy or other disease of the nose. On rhinoscopy they were all without signs of mucosal inflammation. Oxymetazoline was obtained from Draco in Sweden in original 10-ml bottles. Recordings of the nasal mucosa swelling were made with rhinostereometry, which is a direct optical non-invasive measuring apparatus. It consists of a surgical microscope placed on a micrometer table. The micrometer table is fixed to a frame and movable in three angular directions to establish a three-dimensional co-ordinate system. The test subject is fixed exactly and reproducibly to the measuring apparatus by an individually-made plastic splint adapted to the teeth. The ocular in the microscope has a horizontal millimeter scale. As the microscope has a small depth of focus, changes of the position of the mucosal surface on the medial side of the inferior concha can be registered along the millimeter scale. The method has an accuracy of 0.2 mm. After an acclimatization period of 30 min the mucosal surface on the medial side of the inferior concha in both nasal cavities was determined repeatedly during a 15-min period to establish a mucosal baseline position for the test procedure that day. Thereafter, a solution of normal saline with 0.5% phenol was applied to one side in the nose and 5–10 min later recordings were made of the mucosal surface position of the inferior concha on both sides. Then, 0.14 ml of histamine hydrochloride solution in a concentration of 0.1 mg/ml in the diluent was applied to the mucosal surface on the same side as before and recordings were made 5–10 min later. The provocation and recording procedures were continued, gradually increasing the concentrations of histamine hydrochloride up to 32 mg/ml, or until the volunteer was too troubled to be willing to continue with the provocation. Likewise, the provocation was stopped if the nasal mucosal congestion was so pronounced that the nose was totally obstructed. One to five days later, the volunteers were asked to spray 0.1 ml (2 puffs) of oxymetazoline in each nostril. After 50–70 min the mucosal baseline position of the day was determined after the volunteers had been in the test locality for at least 30 min. The histamine provocation procedure was then performed as before, this time from a decongested baseline position. The volunteers were then asked to continue to spray 0.1 ml of the test drugs in each nostril thrice a day, for 30 days. From 10 and 30 days on, the mucosal baseline position was again established after drug administration and a new histamine provocation procedure was performed as before. The statistical calculations were made with paired t-tests.

RESULTS

One subject had a bacteriologically verified streptococcal tonsillitis after nine days on the drug and was therefore excluded from the study. The remaining eight subjects performed the tests the first two days. All of them had on both these tests a mucosal swelling not more than 0.5 mm from the baseline position of the day at histamine concentrations up to 2 mg/ml. The mean values for the group were significantly below 0.5 mm, up to a histamine concentration of 2 mg/ml on both test occasions, and did not differ from each other on any histamine concentration level (Figure 1). After 10 days on oxymetazoline, one subject had a mucosal swelling over 0.5 mm at a histamine concentration of 1.0 mg/ml. At 2 mg/ml that subject's mucosal swelling remained above 0.5 mm along with three others'. The remaining four subjects reacted as before with an increased mucosal swelling over 0.5 mm first at 4 mg/ml. The mucosal congestion for the group on the 2-mg/ml level exceeded that of the earlier tests indicating an increased sensitivity to histamine (Figure 2). This increase was not significant. After 30 days on the drugs two subjects had a mucosal swelling above 0.5 mm compared with the baseline position of the day already at a histamine concentration of 0.1 mg/ml. At histamine concentrations of 0.5 and 1.0 mg/ml, they continued above the 0.5-mm level together with three and five other subjects, respectively. At 2.0 mg/ml and higher histamine concentrations all subjects were above the 0.5-mm level. The mean value for the group was different from that at the start of the medication already at the 0.1 mg/ml level showing a pronounced increased sensitivity to histamine (Figure 2). The increase is statistically significant ($p < 0.05$) at all provocation levels, except at 10 min after 0.5 mg/ml ($p = 0.0548$).

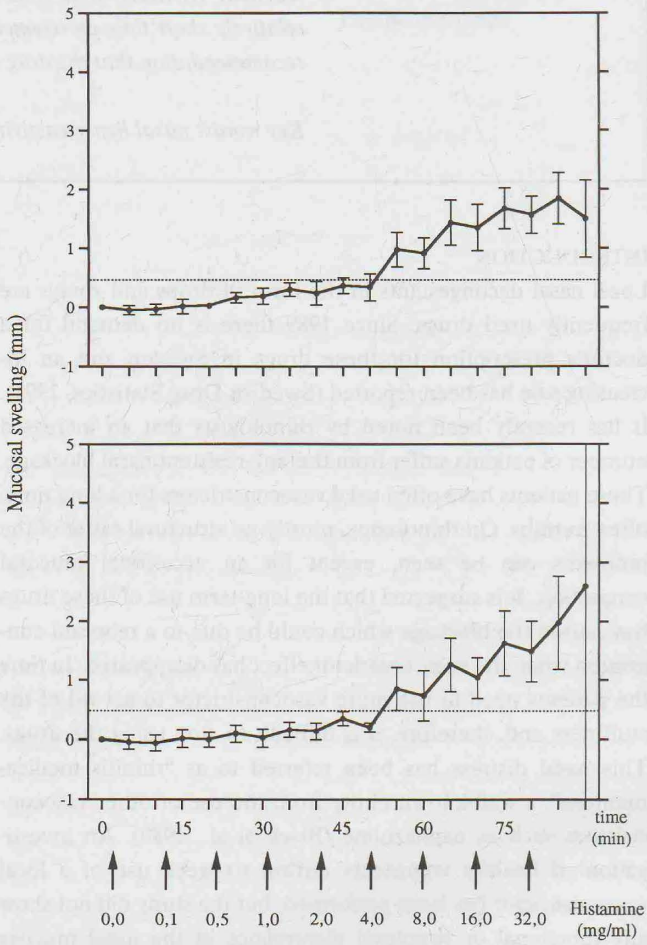

Figure 1. The mean mucosal swelling of the nose in eight healthy subjects after application of histamine in raising concentrations every 10 min (arrows). The zero level indicates the mucosal baseline position before provocation. Error bars denote 95% confidence intervals. Provocation was performed without oxymetazoline (upper graph) and 50–70 min after oxymethazoline (0.5 mg/ml; 0.1 ml) was sprayed in each nostril (lower graph).

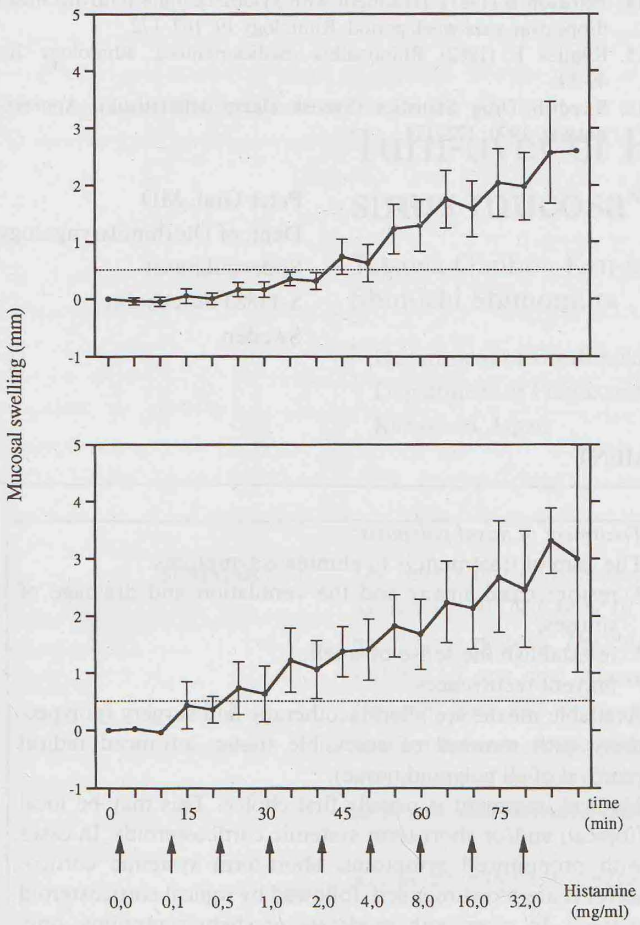

Figure 2. The mean mucosal swelling of the nose in eight healthy subjects using oxymetazoline (0.5 mg/ml: 0.1 ml in each nostril thrice a day for 10 days, upper graph, and 30 days, lower graph) after application of histamine in raising concentrations every 10 min (arrows). The zero level indicates the mucosal baseline position before provocation which was performed 50–70 min after oxymetazoline was sprayed in each nostril. Error bars denote 95% confidence intervals.

DISCUSSION

Due to a possible rebound swelling of the nasal mucosa after 10 and, indeed, after 30 days the histamine provocation could be difficult or impossible to perform as the space between the inferior concha and the septum then could be too narrow. Therefore, the mucosa was pre-treated with oxymetazoline to gain more space. The first part of this study was to investigate if the mucosal reaction upon histamine provocation was changed by a single dose of oxymetazoline before the provocation. The shapes of the two curves are not different from each other, but the mucosa is in a decongested position when the vasoconstrictor is used before provocation. This fact implies that histamine and oxymetazoline have different pathways of action in the nasal mucosa. This is in line with the theory that histamine directly stimulates the H_1- and H_2-receptors on the nasal blood vessels (Mygind et al., 1983) and that local vasoconstrictors act upon α1- and α2-receptors (Bende et al., 1984). As the histamine sensitivity in the individual after oxymetazoline during 10 and 30 days could be changed in any direction, complete histamine provocation series were performed. The increased sensitivity could be due to a cumulative dose effect of histamine and, if so, a pathological reaction as this has not been seen in healthy volunteers (Hallén, 1992). The registered increased sensitivity could also be due to a shortened duration of the drug effect. This is unlikely, however, as after 30 days the threshold level for the group (0.5 mm) was reached already within 2 h after the administration of oxymetazoline. Moreover, in another study it is reported that the decongestion effect of xylometazoline remained unchanged during 4 h after six weeks on xylometazoline (Petruson, 1981). The sensitivity to histamine in the group was gradually increased during the month of medication. As the volunteers investigated were all free from infections during the study, the increased histamine sensitivity, therefore, must be due to the use of oxymetazoline. This drug consists of a vasoconstrictor as well as preservative and bulks. The design of this study does not answer which of these components actually causes the increased sensitivity to histamine.

The group of subjects were at the end of the month troubled by nasal blockage, especially in the mornings and in the evenings. The blockage was relieved after drug administration. This description is the same as that of the patients with rhinitis medicamentosa. An increased histamine sensitivity has previously been seen in patients with non-allergic nasal hyperreactivity (NANH) contrary to healthy volunteers (Ohm et al., 1992; Hallén et al., 1992). Thus, the increased histamine sensitivity in the investigated group must be regarded as the development of a pathological mucosal reaction as the subjects also complained of nasal blockage. The small increase in sensitivity to histamine already seen after 10 days on the drug indicates that adverse effects of vasoconstrictors develops after a relatively short time of medication. This is in line with some authors, but in opposition with others who argue that rhinitis medicamentosa develops after a longer period on vasoconstrictors (Feinberg et al., 1971; Mabry, 1982; Petruson et al., 1982). The results of this study, therefore, support the recommendation that local vasoconstrictors should not be used regularly for more than 10 days. In this study all subjects were healthy volunteers. The long-term users of these drugs are patients with nasal blockage. Some of them have anatomical defects in the nose, but the majority have allergic and non-specific rhinitis and, therefore, already at the start of medication an increased sensitivity to histamine. Probably these patients develop an even more pronounced increase in histamine sensitivity than seen in this study, but to verify this further investigations are necessary.

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ANNOUNCEMENT

POSITION STATEMENT ON NASAL POLYPS

A group of international scientists and clinicians has been assembled in Fredensborg, Denmark, on June 18-19, 1994, to discuss current problems on research, diagnosis and treatment of nasal polyps. The meeting was made possible by a grant from Astra Pharmaceuticals.
The following 16 persons have participated: Jerry Dolovich (Canada), Adrian Drake-Lee (United Kingdom), Roger Jankowski (France), Nobuo Kubo (Japan), Jan Kumlien (Sweden), Knud Larsen (Denmark), Per Larsen (Denmark), Torben Lildholdt (Denmark), Ian S. Mackay (United Kingdom), Lars Malm (Sweden), Niels Mygind (Denmark), Hans Rundcrantz (Sweden), Guy Settipane (USA), Heinz Stammberger (Austria), Pontus Stierna (Sweden), Olle Zetterström (Sweden).
The discussions have resulted in the following statements.

Definitions
Nasal polyps are a protrusion of benign oedematous mucosa from the meatus into the nasal cavity. They may present at any stage ranging from a single polyp to diffuse polyposis.

Pathogenesis
The aetiology is not yet known. Nasal polyps are the result of a chronic inflammatory process. This is supported by the fact that a large number of inflammatory cells and mediators have been identified. Accumulation of eosinophilic granulocyres is a frequent finding. There is an association with systemic diseases such as asthma and NSAID intolerance.

Diagnosis
The diagnosis of nasal polyps requires appropriate inspection of the nasal cavities, this may require decongestion and endoscopy. Neoplasia should be excluded.

Staging
* Unilateral polyps,
* Bilateral polyps (nasal polyposis):

  - no known associated diseases (to be staged by CT),
  - with asthma,
  - with asthma plus NSAID intolerance,
  - local or systemic host defence deficiency.

Treatment of nasal polyposis
The aim of treatment is to eliminate symptoms:
* restore nasal airway and the ventilation and drainage of sinuses,
* re-establish the sense of smell,
* prevent recurrences.

Available means are pharmacotherapy and surgery (polypectomy with removal of accessible tissue, advanced radical removal of all polypoid tissue).
Medical treatment is usually first choice. This may be local (topical) and/or short-term systemic corticosteroids. In cases with pronounced symptoms, short-term systemic corticosteroids are recommended, followed by topical corticosteroid therapy. In cases with moderate or slight symptoms, only topical corticosteroid should be used.
After about one month the patient should be reviewed and a decision made whether the given therapy has been sufficient. If this regimen has failed, surgery should be considered. If the result is satisfactory, the topical treatment should be continued. Antibiotic treatment may be indicated.

Future research
The research on nasal polyposis may focus on a variety of subjects. A very important problem is the *causes* for the infiltration of eosinophilic granulocytes and the consequences of their presence.
On the humoral level the study of cytokines should be given high priority. The promising studies in *animal models* have to be further evaluated. *Research in surgical* treatment should be focussed on long-term efficacy, especially considering the safety of repeated procedures.
The research in pharmacotherapy should preferably define the necessary dosage and duration of corticosteroids, evaluation of side effects and testing new compounds such as LT-antagonists and synthetase inhibitors. This also applies to delivery systems.
Clinical research should be performed in order to predict responders to medical and surgical treatment.
Finally, it is of utmost importance to study various combinations of surgical and medical treament in order to individualize the therapy.

Comments are invited, please write to:
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