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Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity*

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SUMMARY

It has been suggested but never confirmed, that the severity of the rebound swelling and rhinitis medicamentosa are directly proportional to the period during which the drug is used, to the frequency of its use, and to the amount of drug administered. However, no studies have been performed to evaluate the effects of various amounts of the vasoconstrictors on the development of rhinitis medicamentosa. Moreover, no in vivo studies have yet been performed to investigate whether benzalkonium chloride in nasal decongestant solutions affects the development of rhinitis medicamentosa. This study shows that rhinitis medicamentosa is a condition of nasal hyperreactivity, mucosal swelling and tolerance induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative.

Key words: nasal hyperreactivity, oxymetazoline, rhinitis medicamentosa, rhinostereometry, xylometazoline

INTRODUCTION

Local decongestants for the nose have been used since the beginning of this century. Even then it was well known that prolonged use of these drugs could result in nasal stuffiness and tolerance, an entity known as *rhinitis medicamentosa* (RM). The nasal stuffiness caused by overuse of nasal vasoconstrictors has been ascribed to rebound swelling when the decongestive effect of the drug disappears. This phenomenon may be due to an alteration in the vasomotor tone with increased parasympathetic activity, vascular permeability and oedema formation (Elwany et al., 1983; Osguthorpe et al., 1987). Similar results have been reported by Talaat et al. (1981). However, no such histological changes were found either in a study on healthy subjects who received xylometazoline nasal sprays for six weeks (Petruson et al., 1982), or in patients with RM (Rijntjes, 1985).

With modern vasoconstrictors, such as oxy- and xylometazoline, the risk of developing RM and tolerance has been considered to be much smaller or even non-existent. Since 1981, it has been possible to purchase nosedrops in single-dose pipettes containing oxymetazoline over the counter in Sweden and, since April 1, 1989, there has been no need for a doctor's prescription of nasal sprays containing oxy- and xylometazoline.

In contrast to nosedrops in single-dose pipettes, all nasal decongestant sprays on the Swedish market contain the preservative benzalkonium chloride (BC) to prevent bacterial contamination. Since 1989 the sales of these drugs have increased tremendously in Sweden and the number of patients with therapy-resistant nasal blockage has also increased. It has been suspected that some of these patients suffer from RM and the roles of vasoconstrictors and preservatives have therefore been discussed in this context.

Using rhinomanometry, no rebound swelling has been found in healthy subjects after the long term use of xylometazoline nosedrops (Petruson, 1981; Åkerlund et al., 1991). Moreover, opinions vary as to whether tolerance exists with modern decongestants (Petruson, 1981; Lekas, 1991) and systematic follow-up of patients with RM after vasoconstrictor withdrawal has been lacking. There is therefore a great need for objective, long-term studies regarding RM in healthy volunteers and in patients. Rhinostereometry is a relatively new, direct, non-invasive optical method, nasal mucosal swelling can be recorded with a high degree of accuracy (Juto et al., 1982). With this method, one can assess the degree of nasal reactivity, after histamine provocation tests in healthy volunteers and in patients with vasomotor rhinitis (Hallén et al., 1993a, 1993b, 1994).

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The aim of these studies (I, II, III; *vide infra*; Graf, 1994) was to investigate how the long-term use of oxy- and xylometazoline nasal sprays with and without benzalkonium chloride influences the nasal mucosa in terms of congestion, decongestion, histamine sensitivity and drug duration as measured with rhinostereometry. A further aim was to investigate these variables in patients with RM during seven weeks after vasoconstrictor withdrawal.

MATERIAL AND METHODS

Rhinostereometry

Nasal mucosal swelling was recorded with rhinostereometry, which is a direct optical method. A surgical microscope is placed on a micrometer table fixed to a frame. The microscope can move in three angular directions, establishing a three-dimensional coordinate 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. As 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 (Juto and Lundberg, 1982).

Histamine challenge

Histamine was dissolved in 0.5% phenol and NaCl, and 0.14 ml of the solution was applied to the nasal mucosa in concentrations of 0, 0.1, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, and 32.0 mg/ml (Study I). By means of a syringe, the solution was deposited on the head of the inferior concha on the mucosa of the medial wall on one side of the nose during visual inspection. The position of the nasal mucosa was recorded with rhinostereometry 5 and 10 min after each application. In Studies II and III the nasal mucosa was challenged only with 1.0, 2.0, and 4.0 mg/ml.

Assessment of nasal stuffiness

Throughout the month of medication, each subject filled in a diary card in the morning and the evening, just before using the nasal spray (Studies II and III). Nasal stuffiness was estimated on a 100-mm visual analogue scale. The scale ranged from 0 mm (nose completely clear) to 100 mm (nose completely blocked).

Study design of study I

Eighteen healthy subjects (13 women and 5 men; aged 17–41 years) entered the trial. Oxymetazoline (0.5 mg/ml) nasal spray (Nezeril®; Draco Lakemedel AB, Sweden) and xylometazoline (1.0 mg/ml) nasal spray (Otrivin®; Ciba-Geigy, Sweden) were supplied in original 10-ml bottles with covered labels. Nine subjects were randomly chosen to receive oxymetazoline (0.5 mg/ml; 2 puffs equalling 0.1 ml, in each nostril, on each administration) and nine to receive xylometazoline (1.0 mg/ml; 2 puffs equalling 0.28 ml, in each nostril on each administration). The baseline position of the nasal mucosa was determined with rhinostereometry at noon followed by a histamine provocation on one side in the nose (Figure 1; A). One to five days later, the mucosal baseline position was again recorded at noon. Thereafter, the subjects sprayed two puffs of their nasal spray into each nostril, and 1 h later the position of the decongested mucosa was determined (Figure 1; B). The subjects then began to use their nasal spray. They sprayed two puffs into each nostril, three times daily at fixed hours for 30 days. After 10 and 30 days, the morning spray was discontinued. At noon on these days, 14–17 h after the last dose on the night before, the mucosal baseline position was determined and, 1 h after drug administration, the mucosal positions were again recorded followed by histamine provocations in one side of the nose (Figure 1; B). Two, seven, and 14 days after they had stopped using this medication, the location of the mucosa was determined again at noon (Figure 1; C).

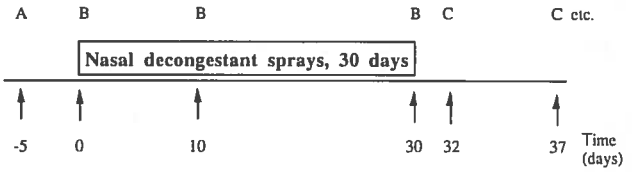

Figure 1. Design of study I. (A) The mucosal baseline was established with rhinostereometry and then a histamine provocation series (0–32 mg/ml) was performed on one side of the nose. (B) The mucosal baseline was established, decongestion was induced with the nasal spray and 1 h later a histamine provocation series (0–32 mg/ml) was performed from the decongested mucosal position on one side of the nose. (C) The mucosal baseline was established and then histamine provocation was performed with 2.0 mg/ml. If the mucosal swelling was 0.5 mm or more after challenge with 2.0 mg/ml, the nasal mucosa was considered to be hyperreactive, and another provocation was performed one week later.

Decongestive responses before and after 4-week use of nasal decongestants

From the same group of healthy volunteers, in the same session, 11 subjects (seven women and four men; aged 18–41 years) were randomly selected to participate in this part of the trial. Seven subjects received xylometazoline and four had oxymetazoline nasal spray. The mucosal baseline position was recorded 1 and 6 h after administration of the nasal sprays before starting the medication. Subsequently, after 29 days on the nasal sprays, the subjects were asked to use their nasal spray as usual in the morning, and 5 h later the mucosal baseline position was recorded.

1. Study II

Thirty healthy volunteers (23 women and 7 men; aged 19–41 years) entered the trial. This was a parallel randomized, double-blind study, with 10 subjects in each group. In two groups, the subjects were randomly selected for treatment with Nezeril® (oxymetazoline; 0.5 mg/ml), 0.1 ml in each nostril three times daily for 30 days, with or without 0.1 mg/ml BC. The third group received oxymetazoline (0.5 mg/ml; 0.1 ml in each nostril) with BC (0.1 mg/ml) at night for 30 days. "Dummies" containing placebo without oxymetazoline and BC were used in the morning and at noon. The study drugs, all in a new type of

nasal spray bottle shown to withstand bacterial contamination, were supplied by Draco Lakemedel AB (Lund, Sweden). Before the treatment with the nasal spray, the baseline position of the nasal mucosa was determined with rhinostereometry at noon. The nasal mucosa was then challenged with 0.14 ml of a solution containing 1.0, 2.0, or 4.0 mg/ml of histamine hydrochloride, with 5 min between doses. After 30 days on the nasal sprays, the morning spray was discontinued. At noon, 14–17 h after the last dose on the night before, the mucosal baseline positions were recorded. Then a histamine provocation was performed as before.

2. Study III

Ten patients (5 women and 5 men; aged 18–41 years) who had overused nasal decongestant sprays daily for at least four months, were selected from the out-patient department of the ENT Clinic at Södersjukhuset. They all suffered from chronic nasal obstruction and were unable to stop using nosedrops. The patients were informed that nosedrops were mainly responsible for their nasal obstruction and they were urged to stop using them immediately. One hypothesis of the study was that the decongestive effect of a vasoconstrictor is less in patients with RM than in healthy volunteers.

For this reason, 10 healthy subjects (6 women and 4 men; aged 22–42 years) formed the control group. On the first day of examination, the patients were not allowed to use any decongestive nasal spray. The mucosal baseline position of the nasal mucosa was determined in both nasal cavities with rhinostereometry at noon. The nasal mucosa was then decongested with Nezeril® (oxymetazoline) nasal spray (0.5 mg/ml; 0.1 ml in each nostril). Thirty minutes later, the decongested mucosal position was determined. The rest of the study was only performed in the patient group. After decongestion, the nasal mucosa was challenged with 1.0, 2.0, and 4.0 mg/ml of histamine hydrochloride in one side of the nose. The patients then began to use budesonide nasal spray (Rhinocort Aqua®), 100 µg in each nostril in the morning and in the evening, but they were not allowed to use any decongestive nasal spray. Fourteen days later, the second recording was made as before. The patients then continued to use budesonide nasal spray for a further four weeks. In the fifth week, budesonide was discontinued and the third recording was performed in the same way as before.

RESULTS

Healthy subjects who use topical vasoconstrictors containing BC in the recommended dose for 30 days develop rebound swelling. The use of twice the recommended dose of vasoconstrictors for 30 days does not further increase the amount of rebound swelling. Two days after stopping the medication, the rebound swelling disappears. No rebound swelling is present after 10 days on the nasal sprays.

In healthy subjects, nasal hyperreactivity, in terms of increased histamine sensitivity, is induced by 10 days' treatment with topical vasoconstrictors containing benzalkonium chloride three times daily. After 30 days on a vasoconstrictor nasal spray, using the recommended or twice the recommended dose, histamine sensitivity increases further, and to the same extent. In some subjects, when the nasal spray is stopped, the increased histamine sensitivity persists for more than one month.

Presence of rebound swelling, as evidenced by the symptom scores of nasal stuffiness and increased histamine sensitivity is ascribed to the development of RM induced by decongestant nasal sprays. Healthy volunteers also develop RM when using oxymetazoline three times daily without BC for 30 days. However, the long-term use of BC in oxymetazoline nasal spray aggravates RM (Figures 2–3).

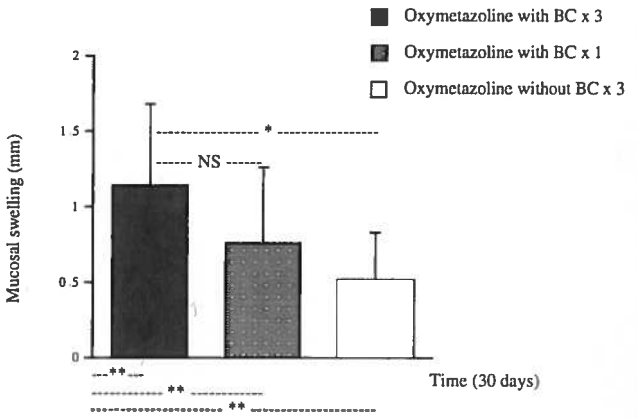

Figure 2. Mean mucosal swelling of both inferior conchae after 30 days on the nasal sprays. Baseline values were set at zero before the medication was started. The recordings after 30 days on the nasal sprays were performed 14–17 h after drug administration. Error bars denote 95% confidence intervals. The level of statistical significance is indicated by asterisks (NS: not significant; *: $p < 0.05$; **: $p < 0.01$).

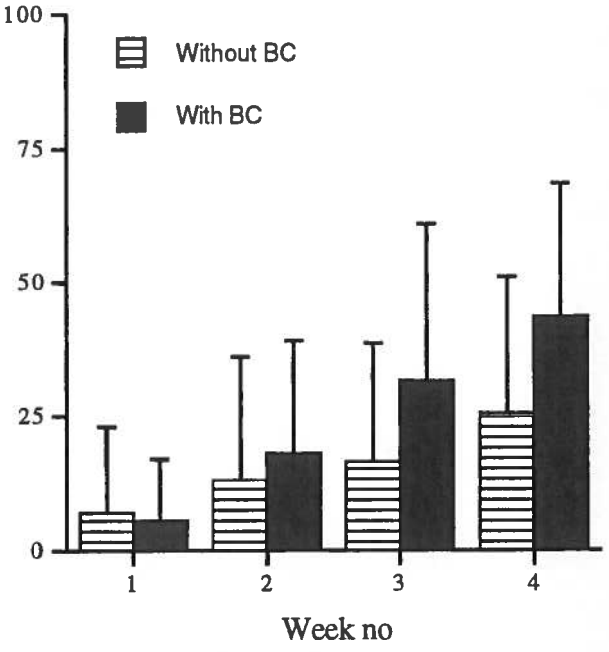

Figure 3. Mean evening nasal stuffiness during 4 weeks' treatment with oxymetazoline nasal spray with and without BC, respectively.

The results strongly suggest that in healthy volunteers rebound swelling after 4 weeks' use of nasal decongestant sprays with BC three times daily is due to vasodilatation, since the decongestive effect of the vasoconstrictor remains unchanged. However,

in patients with RM, the decongested mucosal position is significantly lower 14 days after vasoconstrictor withdrawal than at the start of the study which suggests that the rebound swelling is partly due to interstitial oedema (Figure 4).

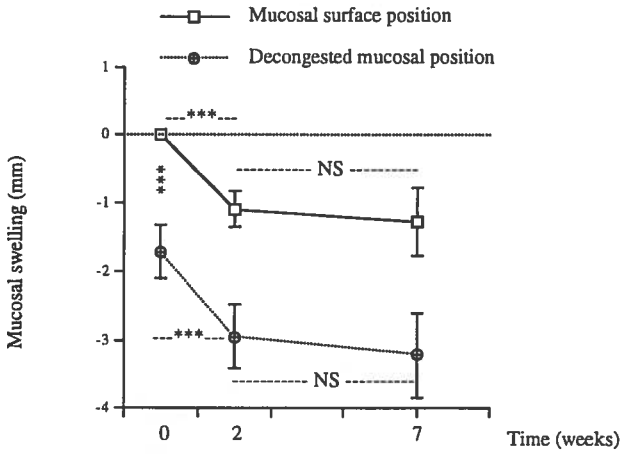

Figure 4. Mean mucosal surface position in 10 patients with RM after immediate cessation of vasoconstrictor overuse on the night before the first recording (0), which represents the reference position set at zero. The patients then started to use budesonide nasal spray, 400 µg/day for 6 weeks. Recordings were also taken after two and seven weeks. After each recording, oxymetazoline was applied and the mean decongested mucosal position was recorded 30 min later. Error bars denote 95% confidence intervals. The level of statistical significance is indicated by asterisks (NS: not significant; ***: $p < 0.001$).

Healthy volunteers develop RM when they use oxymetazoline nasal spray with BC once daily at night for 30 days. This is true whether they use the decongestant once or three times daily (Figure 2). Symptom scores show that, regardless of the frequency of administration of the spray, the subjects are particularly bothered by nasal obstruction in the evenings (mean estimated figures for stuffiness were 43 in the fourth week for both groups).

In healthy subjects, long-term use of decongestant nasal sprays induces tolerance, meaning a reduction in the duration of the decongestive response (Figure 5). In patients with RM, tolerance consists of a reduction in the duration of the decongestive response (patient history) and in the decongestive effect of a single dose of the vasoconstrictor since the decongestive effect was significantly less in the patient group then in the controls ($p < 0.001$).

All patients with RM were able immediately to stop using the vasoconstrictors and they all denied using any topical vasoconstrictor during the 7-week study period. The thickness of the nasal mucosa were reduced considerably 14 days after vasoconstrictor withdrawal (Figure 5). The mean symptom scores for nasal obstruction was 90.5 on the first day, and two weeks later it was 31 ($p < 0.0001$). However, the design of the study does not take up the question whether this improvement is due to the vasoconstrictor withdrawal or to the treatment with budesonide. Seven weeks after vasoconstrictor withdrawal, the patients still had an increased histamine sensitivity reflecting nasal hyperreactivity.

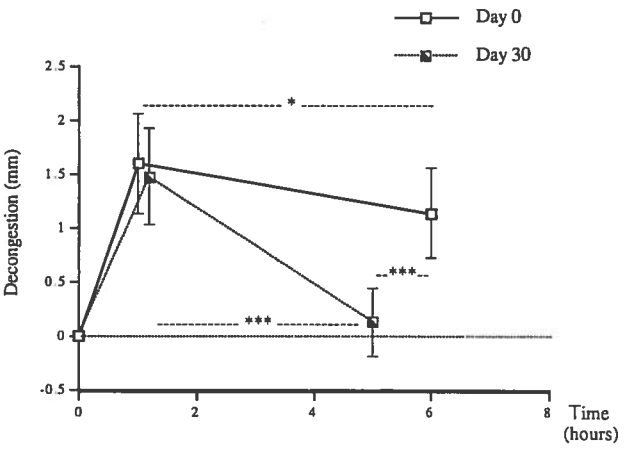

Figure 5. The mean decongestion in both inferior conchae in 11 healthy subjects who used decongestant nasal sprays for 30 days. The zero level represents the reference position before starting the medication. Open squares represent the mean decongestion 1 and 6 h after administration of the sprays before starting the medication. Partly filled squares indicate the corresponding decongestion, 1 and 5 h after 30 days on the nasal sprays. Error bars denote the 95% confidence intervals. The level of statistical significance is indicated by asterisks (*: $p < 0.05$; ***: $p < 0.001$).

DISCUSSION

Although patients who overuse topical vasoconstrictors are clinically identical with patients having vasomotor rhinitis with nasal blockage as their main symptom, there is no doubt that RM is an entity in itself. Studies have shown that patients with allergic and non-allergic rhinitis experience an excellent decongestive effect with topical α_2-agonists with a duration exceeding 6 h (Åkerlund et al., 1989). However, subjects with nasal blockage and hyperreactivity induced or aggravated by the long-term use of nasal decongestant sprays show a reduction in the decongestive response. This does not mean that all patients who overuse vasoconstrictors actually increase the number of daily doses. Hitherto, it has not been possible to determine a patient's "nasal status" before the overuse of topical decongestants and a definition of RM must therefore be based on the findings in healthy subjects. Thus, RM is a condition of nasal hyperreactivity, mucosal swelling and tolerance induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative. Moreover, the increase in the number of patients with RM in Sweden may reflect the increase in the total use of nasal decongestants. However, in accordance with the results of this study, it may also be due to the switch from the use of preservative-free to BC-preserved solutions.

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