One Year Follow-Up of Patients with Rhinitis Medicamentosa After Vasoconstrictor Withdrawal

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ABSTRACT

The aim of the study was to systematically follow-up 10 patients with rhinitis medicamentosa for at least 1 year after vasoconstrictor withdrawal. During withdrawal of the decongestants the patients used budesonide nasal spray, 400 μg/day, for 6 weeks. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline, and the histamine sensitivity were measured with rhinostereometry during the period. The thickness of the nasal mucosa and the symptom scores of nasal stuffiness were reduced considerably 6 and 12 months after vasoconstrictor withdrawal. The histamine sensitivity reflecting nasal hyperreactivity was still increased after 6 months, but not after 1 year. The decongestive effect of oxymetazoline increased after 6 months, indicating reversible tolerance. We conclude that when given adequate treatment and information about nose-drop overuse, all patients were able to stop using the vasoconstrictors and no one relapsed into a daily long-term overuse of vasoconstrictors during the 1-year follow-up period. (American Journal of Rhinology 11, 67–72, 1997)

The term rhinitis medicamentosa was coined in 1946 for the condition of the nasal membranes resulting from overuse of nasal vasoconstrictors.[1] At that time, these drugs were based on ephedrine and rhinitis medicamentosa, i.e., a rebound congestion, was a common problem.[2,3] With modern decongestants, such as oxy- and xylometazoline, the risk of developing rhinitis medicamentosa was initially considered to be much smaller or even nonexistent.[4–6] However, more recent studies have shown that overuse of these drugs result in a rebound congestion[7–9] and histologic changes of the nasal mucosa including ciliary loss, epithelial ulceration, and inflammatory cell infiltration.[10] The role of the preservative benzalkonium chloride in the development of rhinitis medicamentosa has also been discussed. We have shown that a benzalkonium chloride containing decongestant nasal spray causes more rebound congestion than the same decongestant administered without the preservative for the same length of time.[11] Moreover, the long-term use of benzalkonium chloride alone also induces mucosal congestion.[12]

The various methods for treating rhinitis medicamentosa all have the same aims. The topical decongestant must be discontinued to allow the damaged nasal mucosa to recover. Most authors agree that the vasoconstrictors should be discontinued immediately and completely,[7,13,14] although it has also been suggested to treat one nostril at a time.[15,16] An abrupt cessation induces marked nasal blockage, and various therapies have been suggested to make the withdrawal process less troublesome.[17,18] No controlled studies have been performed to evaluate these treatments objectively, but the success rate on the short-term follow-ups regarding the patient's ability to stop using the decongestants ranges between 72–100%.[14] To our knowledge, there has been no systematic long-term follow-up of patients with rhinitis medicamentosa after vasoconstrictor withdrawal.

The aim of the present study was to systematically follow-up patients with rhinitis medicamentosa for at least 1 year after vasoconstrictor withdrawal. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline, the histamine sensitivity, and symptom scores for nasal stuffiness were studied during the period.

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MATERIALS AND METHODS

The Patients

Ten patients with rhinitis medicamentosa, five women and five men, 18 to 42 years old, were selected from the outpatient department of the ENT Clinic at Södersjukhuset during fall 1993 and spring 1994. They had overused oxy- and/or xylometazolin nasal sprays containing benzalkonium chloride daily for at least 4 months (Table I). A detailed medical history was taken, with special emphasis on the use of nosedrops (Table I). All patients were examined with rhinoscopy and patients with nasal polyps, a deviated nasal septum, or other obvious anatomical causes of nasal obstruction were excluded from the study. They were tested for allergy with the skin prick test Soluprick® (ALK, Denmark) and Phadiatop® (Pharmacia, Uppsala, Sweden). All patients suffered from severe chronic nasal obstruction, and they were unable to stop using the nosedrops. They were informed that the vasoconstrictors were mainly responsible for their nasal blockage and they were urged to stop using the nosedrops without delay. During withdrawal of the nosedrops, the patients' nasal obstruction was alleviated by the administration of budesonide nasal spray, 400 μg/day, for 6 weeks.

Rhinostereometry

The swelling of the nasal mucosa was recorded with rhinostereometry, which is a direct optical noninvasive measuring method employing a surgical microscope placed on a micrometer table fixed to a frame. Because the microscope can be moved in three angular directions, one can set up a three-dimensional coordinate system.

Measurements can be made only by placing the nasal cavity in the coordinate system, so that it resumes the same position with a high degree of precision in repeated measurements. The subject is thus placed in an immobile position and attached to the apparatus by an individually-made plastic tooth splint. The eyepiece, through which the nasal cavity is viewed, has a horizontal millimeter scale. Since the microscope has a small depth of focus, changes in the position of the mucosal surface of the medial side of the head of the inferior turbinate are registered in the plane of focus along the mm scale. The accuracy of the method is 0.2 mm.[19] With respect to the systematic error, the true variation of the mucosal surface is 97% to 102% of the measured variation. The method has shown to be useful in studies when there is a need to record small changes in the nasal mucosa swelling before and after various kinds of nasal challenge.[20,21]

Study Design

On the first day of the examination, the patients were not allowed to use a decongestive nasal spray. The baseline position of the nasal mucosa in both groups was determined by making repeated recordings of the inferior concha in both nasal cavities at noon, after an acclimatization period of 30 minutes. The nasal mucosa was then decongested by the instillation of oxymetazoline nasal spray (0.5 mg/mL, 0.1 mL in each nostril). Thirty minutes later, the position of the decongested mucosa was determined. After decongestion, the nasal mucosa was challenged with 1.0 mg/mL, 2.0 mg/mL, and 4.0 mg/mL of histamine hydrochloride. By means of a syringe, 0.14 mL of the solution was deposited on the mucosa of the medial wall of the inferior concha on one side of the nose during visual inspection, with 5 minutes between doses. On the challenged side, the position of the surface was determined 5 minutes after each provocation.

The patients then began to use budesonide nasal spray, 400 μg/day (100 μg in each nostril in the morning and in the evening) for 6 weeks, but they were not allowed to use any decongestive nasal spray. In the seventh week, budesonide was discontinued. By withholding budesonide treatment in the seventh week and by reevaluating the patients' symptoms and reexamining the patient after that week, we determined the underlying nasal disorder and which patients

TABLE I

Patient Characteristics and Medical History

Patients	Age	Allergy	Time of Use (Years)	Reason for Starting	Drug	Doses/Day	Sprays/Dose	Estimated Duration/Dose
1. Female	18	−	1.5	Common cold	Oxymetazoline	3–8	2–3	0.5–4h
2. Male	38	+	0.5	Common cold	Oxy-/xylometazoline	2	2	6h
3. Male	42	+	6	Common cold	Oxy-/xylometazoline	5–8	4–6	2–3h
4. Female	29	−	0.5	Common cold	Oxymetazoline	6–8	2–3	2–3h
5. Female	33	−	4	Common cold	Oxy-/xylometazoline	5–10	2–3	3–4h
6. Male	28	−	1.5	Sinusitis	Oxymetazoline	5–8	2–4	2–3h
7. Male	25	−	3	Common cold	Oxymetazoline	4–7	2–4	2–3h
8. Female	36	−	6	Common cold	Oxymetazoline	4	2–3	4–5h
9. Male	23	+	1.5	Unknown	Oxy-/xylometazoline	4–5	2	4–5h
10. Female	31	−	4 months	Pregnancy	Oxymetazoline	10	6–8	1.5–2h

needed further corticosteroid treatment (Table II). The patients were followed at the outpatient department for at least 1 year further, six months before the third recording was made. During this period they were instructed not to use any nasal decongestant spray *at all*, and all but two patients succeeded (Table I, patients 1 and 9). After 6 and at least 12 months, the second and third recording was made, again at noon. The patients who had used budesonide during the follow-up period (Table II) were asked to discontinue this medication 14 days before these recordings. On the second recording after 6 months, the baseline position of the nasal mucosa was determined and, after decongestion with oxymetazoline, the position of the decongested mucosa was recorded, followed by another histamine provocation as before. On the third recording after at least 12 months, the baseline position of the nasal mucosa was determined followed by another histamine provocation as before, without previous decongestion with oxymetazolin.

Each patient filled in a questionnaire before treatment with budesonide and at the visit after 6 and 12 months. In the questionnaire, nasal stuffiness was estimated on a visual analogue scale (0–100 symptom scores), which showed states ranging from no nasal stuffiness to very severe stuffiness. The patients also stated whether they had had a cold during the period (Table II).

Statistical Analyses

Trends and spread were analyzed using the means, S.D., and S.E.M. For further statistical analyses, ANOVA and paired *t*-tests were employed. In calculating the mucosal swelling, the baseline position recorded on the first day was considered as the reference position and set at zero. The changes in the mucosal positions in each side of the nose were added and divided by two for each recording. The presence of mucosal swelling induced by histamine challenge was based on data from the challenged nasal cavity alone, the baseline values on each day of provocation being used as reference values.

RESULTS

Patient 5 did not participate in the recordings 6 months after vasoconstrictor withdrawal. The position of the mucosal surface was lower in all patients 6 months after withdrawal of the vasoconstrictor, compared to the reference position, and ranged from -0.5 to -3.0 mm (mean = -1.2, $P < 0.01$) (Fig. 1). Six months later, the corresponding mucosal position ranged from -0.6 to -3.0 mm (mean 1.5, $P < 0.01$) (Fig. 1). On the recording on the first day, the decongestive effect 30 minutes after application of oxymetazoline ranged from -0.65 to -2.4 mm, the mean being -1.6 mm. Six months after vasoconstrictor withdrawal, the corresponding mean decongestion had increased to -2.8 mm, ranging from -2.0 to -4.3 mm ($P < 0.01$) (Fig. 2).

The mean mucosal swelling after histamine provocation on the first day after vasoconstrictor withdrawal was 0.8 mm with a dose of 1.0 mg/mL, 1.1 mm with one of 2.0 mg/mL, and 1.3 mm with 4.0 mg/mL (Fig. 3). At the second recording 6 months later, the corresponding values were 0.5, 0.7, and 1.0 mm (Fig. 3). These values were not significantly lower than the ones on the first day at any histamine provotication level. However, on the third recording at least 12 months after vasoconstrictor withdrawal, the mucosal swelling following 1.0 mg/mL (mean = 0.3 mm, $P < 0.05$) and 2.0 mg/mL (mean = 0.6 mm, $P < 0.05$) were lower than the corresponding values on the first day (Fig. 3). The mean mucosal swelling after challenge with 4.0 mg/mL of histamine was 1.1 mm.

TABLE II

Follow-Up of Patients with Rhinitis Medicamentosa After Vasoconstrictor Withdrawal and Symptom Scores of Nasal Stuffiness

Patients	Age	Follow-Up (Months)	Underlying Disorder	Common Cold During Follow-Up	Use of Topical Decongestants	Use of Budesonide	Symptom scores First Day %	Symptom Scores 6 Months	Symptom Scores >12 Months
1. Female	18	16	Idiopathic rhinitis	3 times	Yes*	Occasional	85	10	10
2. Male	38	19	Allergy	None	No	None	90	10	10
3. Male	42	13	Allergy	None	No	Occasional	100	10	20
4. Female	29	18	Idiopathic rhinitis	None	No	None	100	0	0
5. Female	33	12	Common cold	None	No	None	100	0	0
6. Male	28	14	Sinusitis	3 times	No	None	100	20	10
7. Male	25	14	Common cold	1 time	No	Daily	85	0	0
8. Female	36	15	Idiopathic rhinitis	2 times	No	None	100	0	0
9. Male	23	14	Allergy	None	Yes**	None	95	20	40
10. Female	31	16	Pregnancy	None	No	None	100	0	0

**Use of oxymetazoline for one week on two occasions; **Use of oxymetazoline for one week on one occasion.*

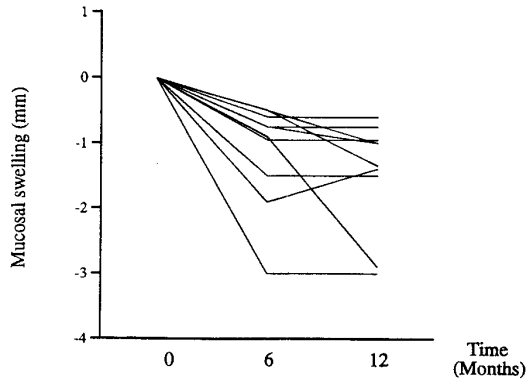

Figure 1. *Mean mucosal surface position recorded with rhinostereometry in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor on the night before the first recording (0), which represents the reference position set at zero. Recordings were also made six and at least 12 months later. Each line represents a different patient.*

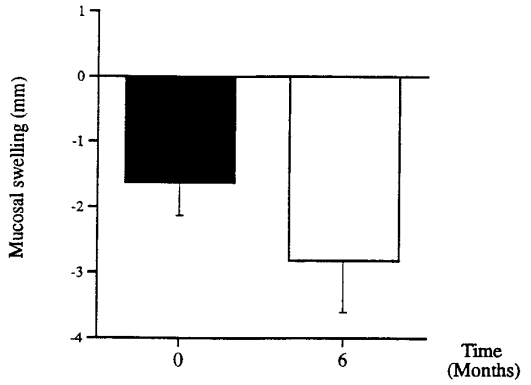

Figure 2. *The mean decongestive effect (± S.D.) 30 minutes after administration of oxymetazoline nasal spray (0.5 mg/mL) in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor on the night before the first recording (0) and 6 months later.*

DISCUSSION

This study shows that the thickness of the nasal mucosa as well as the symptom scores of nasal stuffiness are reduced considerably 6 months after vasoconstrictor withdrawal in patients with rhinitis medicamentosa. These two variables are not further reduced at the follow-up after 12 months. The histamine sensitivity reflecting nasal hyperreactivity is still increased at the follow-up after 6 months, but not after 12 months. Moreover, the decongestive effect of oxymetazoline is considerably increased 6 months after vasoconstrictor withdrawal. When given adequate treatment and information about nose-drop overuse, all patients were able to stop using the vasoconstrictors, and no one relapsed into a daily long-term overuse of vasoconstrictors during the 1-year follow-up period.

Rebound swelling in rhinitis medicamentosa is due either to vasodilatation or to interstitial edema, or a combination of both, and contradictory opinions have been reported.[7,8,22] We have previously reported that overuse of nasal decongestant sprays induces drug tolerance seen both as a reduction of the decongestive response[23] and in the decongestive effect of a single dose of the vasoconstrictor.[22] The present study shows that the decongestive effect after application of oxymetazoline increases significantly 6 months after vasoconstrictor withdrawal. This further supports the theory that the rebound swelling consists, at least partly, of an interstitial edema, since interstitial edema cannot be reduced by application of α_2-agonists.[8,24] Moreover, the fact that the decongestive effect of oxymetazoline has increased shows that the drug tolerance has been reversed, also indicating that the edema is reduced and that the nasal mucosa is recovering. The long-term reduction of the thickness of the nasal mucosa and the symptom score persists during the 1-year follow-up period, despite the relatively short term treatment with budesonide in most patients (Table II). This is clinically important because it is not the intention to turn an overuse of nasal vasoconstrictors into an overuse of topical corticosteroids.

The degree of increased histamine sensitivity is comparable to that seen in patients with vasomotor rhinitis[25] and it reflects the development of nasal hyperreactivity. Histamine provocation is a more sensitive variable for detecting adverse effects of the long-term use of nasal decongestant sprays than the recording of rebound swelling. Thus, an increased histamine sensitivity but no rebound swelling was seen after only 10 days when topical vasoconstrictors containing benzalkonium chloride are used three times daily in healthy volunteers.[26] Likewise, the rebound swelling disappeared 2 days after vasoconstrictor withdrawal, whereas in some subjects the sensitivity to histamine remains increased for more than 1 month after 30 days on this medication.[26] Although the patients in this study had hardly any nasal symptoms at all after 6 and 12 months follow-up, the increased histamine sensitivity lasted for more than 6 months. This is in accordance with a previous study showing long-lasting adverse effect of overuse of a topical decongestant spray containing benzalkonium chloride.[21]

Patients with rhinitis medicamentosa have the same clinical findings as patients who have vasomotor rhinitis with blockage as their main symptom.[2] Both of these groups of patients have an increased histamine sensitivity reflecting nasal hyperreactivity.[22,25] However, the nasal hyperreactivity in patients with rhinitis medicamentosa is more resistant to treatment than in patients with vasomotor rhinitis. Patients with vasomotor rhinitis had a significant reduction in symptom scores and histamine sensitivity after 14 days' treatment with budesonide,[27] unlike patients with rhinitis medicamentosa who still had an unchanged increased histamine sensitivity 2 and 7 weeks after withdrawal from the vasoconstrictors despite budesonide treatment.[22] According

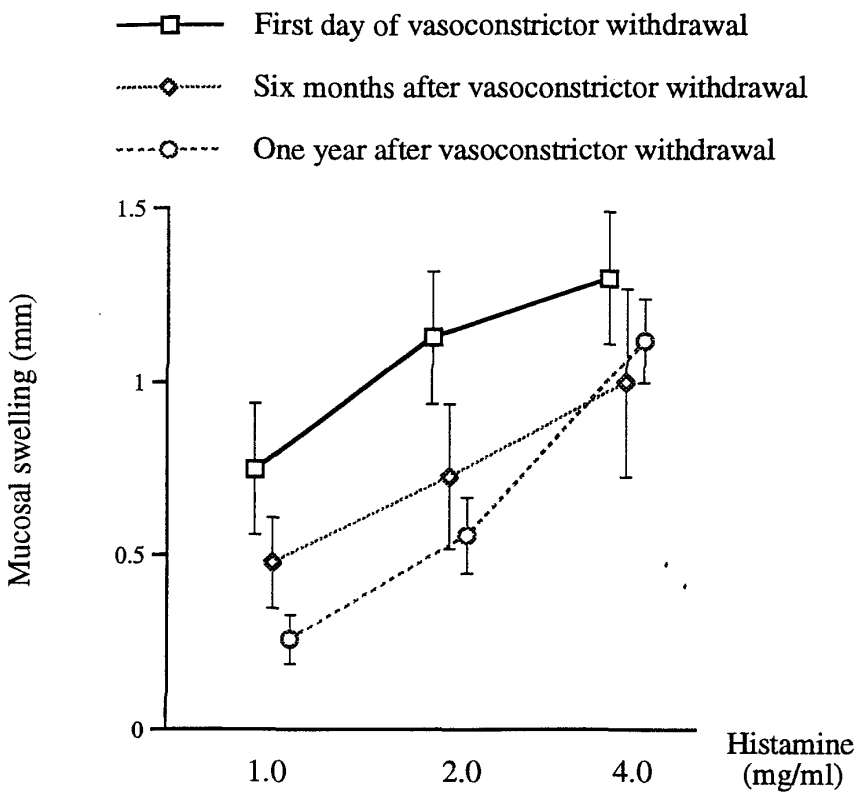

Figure 3. Mean mucosal swelling (± S.E.M.) in 10 patients with rhinitis medicamentosa, after provocation with 1.0 mg/mL, 2.0 mg/mL, and 4.0 mg/mL on one side of the nose. The provocation was performed on the first day after discontinuing the vasoconstrictor and after 6 and 12 months.

to this study, the histamine sensitivity was not significantly reduced until one year after vasoconstrictor withdrawal. Thus, the mechanisms underlying the hyperreactivity probably differ in the two groups.

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