Seven-Week Follow-Up of Patients with Rhinitis Medicamentosa after Vasoconstrictor Withdrawal

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Abstract

An objective systematic follow-up of patients with rhinitis medicamentosa after vasoconstrictor withdrawal has hitherto been lacking. With this in mind, we selected ten patients with rhinitis medicamentosa who had used topical vasoconstrictors daily for at least 4 months and promptly discontinued them. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline and the histamine sensitivity were measured with rhinostereometry during 7 weeks after vasoconstrictor withdrawal. Symptom scores were also estimated. All patients were immediately able to stop using the vasoconstrictors and they all denied using any topical vasoconstrictor during the study period. The symptom scores of nasal stuffiness and the thickness of the nasal mucosa were reduced considerably 14 days after vasoconstrictor withdrawal. Seven weeks after the withdrawal of vasoconstrictors, the patients still had an increased histamine sensitivity reflecting nasal hyperreactivity. The results support the theory that the rebound swelling recorded in this group of patients is partly due to interstitial oedema. Moreover, the presence of tolerance, as reflected by a reduction in the duration of the decongestive response and in the decongestive effect of a single dose of the vasoconstrictor, was noted.

Introduction

Local decongestants for the nose have been used since the beginning of this century. As far back as the 1940s, it was well known that the prolonged use of these drugs, which then contained ephedrine, could induce nasal stuffiness and drug addiction.[1] This phenomenon has been called rhinitis medicamentosa. The nasal stuffiness is caused by rebound swelling when the decongestive effect of the drug has disappeared. To alleviate the stuffiness, patients gradually starts using larger doses of the vasoconstrictor more frequently- i.e., as a result of tolerance. In many cases, they are

unaware of the cause of nasal stuffiness and the vicious circle cannot be broken without professional help.[2]

Hitherto, the knowledge about rhinitis medicamentosa has been based on a few surveys and case reports. *In vitro* studies have also been reported. However, to our knowledge, only one objective investigation has been performed on patients with rhinitis medicamentosa- i.e., that of Rijntjes who investigated 20 patients who had overused nosedrops for more than 6 months.[3] They were treated with a combination of topical and oral corticosteroids during withdrawal from the decongestants and had metaplasia of the mucous membranes during the overuse. Moreover, the nasal conductivity, measured with rhinomanometry, improved in all patients 4 to 6 months after the overuse stopped.

The pathophysiology of the rebound swelling in rhinitis medicamentosa is not understood. It may be due either to vasodilatation or interstitial oedema and conflicting results have been reported.[3-5] Moreover, some authors question whether tolerance can occur with modern decongestants, such as oxy- and xylometazoline.[4,6] Since it has not been possible to measure accurately the thickness of the nasal mucosa, no studies have been done to evaluate tolerance and rebound swelling in patients having rhinitis medicamentosa.

The various methods for treating rhinitis medicamentosa all have the same aims. The patient must stop using topical decongestants to allow the damaged nasal mucosa to recover and then the underlying nasal disease must be treated. Most authors agree that vasoconstrictors should be discontinued immediately and completely.[7,8] However, there has been no systematic follow-up of symptoms after the withdrawal of vasoconstrictors.

The aim of the present study was to investigate the thickness of the nasal mucosa, the decongestive effect of oxymetazoline, the histamine sensitivity and symptom scores during 7 weeks after vasoconstrictor withdrawal in patients with rhinitis medicamentosa. To investigate whether the decongestive effect of oxymetazoline was reduced on the first day of withdrawal, we compared the results with the decongestive effect in a control group of 10 healthy volunteers. On the basis of the findings in this study, some aspects of the treatment, tolerance and the pathophysiology of rhinitis medicamentosa will be discussed.

Material and methods

Ten patients, 5 men and 5 women, who had overused nosedrops daily for at least 4 months, were selected from the outpatient department of the ENT Clinic at Södersjukhuset during the autumn of 1993. They all suffered from 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 were urged to stop using the nosedrops immediately. A detailed medical history was taken, with special emphasis on the use of nosedrops (Table 1). All patients were tested for allergy with the

skin prick test Soluprick® (ALK, Denmark) and Phadiatop® (Pharmacia, Uppsala, Sweden). The patients received budesonide nasal spray, 400 µg daily for 6 weeks during withdrawal from the topical vasoconstrictors.

The control group comprised 10 healthy volunteers, 6 women and 4 men (22 to 42 years old). They were all healthy, had no history of allergy or other rhinological disease and had normal rhinoscopic findings. The volunteers were students or staff members of the Department.

Table 1. Patient characteristic and medical history

Patient no	Age	Allergy	Time of use	Reason for starting	Nasal sprays	Doses/ day	Sprays/ dose	Estimated duratic dose (hours)
1	18	-	1.5 years	common cold	oxy	3-8	2-3	0.5-4
2	38	+	0.5 years	common cold	oxy + xylo	2	2	6
3	41	-	6 years	sinuitis	oxy + xylo	2-5	2	3-4
4	29	-	0.5 years	common cold	oxy	6-8	2-3	0.5-2
5	31	-	4.5 years	common cold	oxy	4-5	2	3-4
6	28	-	1.5 years	sinuitis	oxy	5-8	2-4	2-3
7	25	-	3 years	common cold	oxy	4-7	2-4	2-3
8	36	-	6 years	common cold	oxy	4	2-3	4-5
9	23	+	1.5 years	unknown	oxy + xylo	4-5	2	4-5
10	31	-	4 months	pregnancy	oxy	8-10	6-8	1.5-2

oxy = oxymetazoline, xylo = xylometazoline

The swelling of the nasal mucosa was recorded with rhinostereometry, which is a direct optical non-invasive measuring method employing a surgical microscope placed on a micrometer table fixed to a frame. Since the microscope can be moved in three angular directions, one can set up a three-dimensional coordinate system. The subject is placed in an immobile position and attached carefully to the apparatus by an individually-made plastic tooth splint. The eyepiece, through which the nasal cavity is viewed, has a horizontal millimetre 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.[9]

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.

The rest of the study was performed only on the patient group. 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), but they were not allowed to use any decongestive nasal spray. Fourteen days later, the second recording was made, again at noon. The patients were instructed to discontinue budesonide on the day before the second recording and on the morning of that day. 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. The patients then continued to use budesonide nasal spray for a further 4 weeks. In the 5th week, budesonide was discontinued and the third recording was done in the same way.

Each patient filled in a questionnaire on the first day after withdrawal of the vasoconstrictor and after 2, 6 and 7 weeks. 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 reported whether they had had a cold during the period.

Trends were analysed using the mean. Analysis of variance (ANOVA) was employed to test the statistical significance. The unpaired t-test was used to compare the patient group to controls, as regards the decongestive effect of oxymetazoline. The amount of mucosal swelling was calculated by determining the mean value of the mucosal baseline position on each side of the nose before starting treatment with budesonide. This value, set at zero, served as the reference position. The findings pertaining to mucosal swelling resulting from histamine challenges were based on data in only one nasal cavity, the baseline values on each day of the recording were used as reference values.

Results

All the patients denied using any decongestant nasal spray during the study period. One patient did not participate in the recordings 7 weeks after discontinuing the vasoconstrictor and two patients had a common cold during the withdrawal period.

In the patient group, the position of the mucosal surface was lower in all patients 2 weeks after withdrawal of the vasoconstrictor, compared to the reference position, and ranged from -0.5 to -1.6 mm (mean = -1.1 mm, $p<0.001$) (Fig. 1). Five weeks later, the

corresponding mucosal position ranged from -0.2 to -2.3 mm, the mean being -1.3 mm ($p<0.001$) (Fig. 1). On the recording on the first day, the decongested mucosal position ranged from -0.9 to -2.5 mm, compared to the reference position (mean = -1.72 mm, $p<0.001$) (Fig. 1). Two weeks later, the decongested mucosal position was still lower compared to the reference position, ranging from -1.9 to -4.0 mm (mean = -2.9 mm), and it was significantly lower than the decongested mucosal position on the first day ($p<0.001$) (Fig. 1). Five weeks later, the corresponding decongested mucosal position ranged from -2.25 to -4.75 mm (mean = -3.2 mm, $p<0.001$) (Fig. 1).

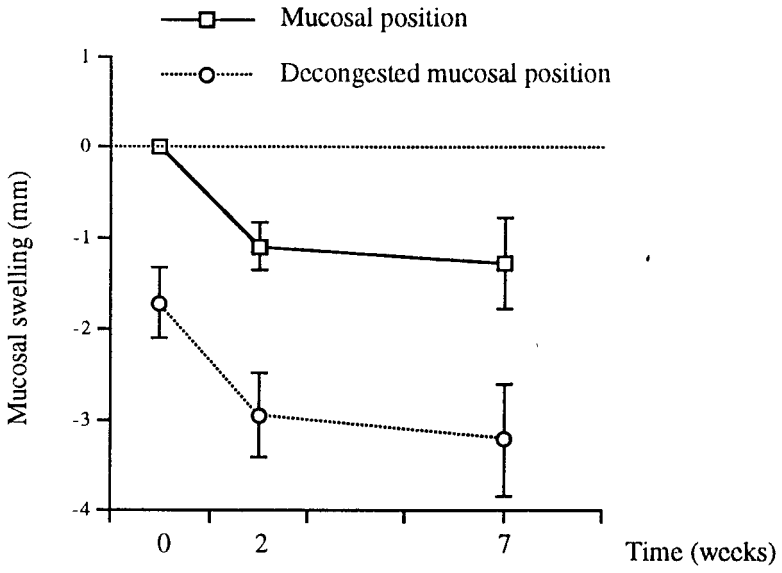

Fig. 1. Mean mucosal surface position in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor overuse on the night before the first recording, which represents the reference position set at zero. The patients then started to use budesonide nasal spray, 400 µg/day, for 6 weeks. Recordings were also taken after 2 and 7 weeks. After each recording, the nasal mucosa was decongested with oxymetazoline and the mean decongested mucosal position was recorded 30 min later. Error bars denote 95% confidence intervals.

On the first day, the mean estimated symptom score was 90.5 and two weeks later it was 31 ($p<0.001$). Compared to the symptom score 14 days after discontinuing the vasoconstrictor, the symptom scores were still lower 4 weeks later (mean = 10.5, $p<0.05$). One week later, the mean symptom score was 19 (Fig. 2) (Table 2).

Table 2. Symptom scores after vasoconstrictor withdrawal and probable underlying disorder

Patient no	Age	Sex	Day 1	2 Weeks	6 Weeks	7 Weeks	Underlying disorder
1	18	F	85	45	0	45	NANH
2	38	M	90	20	20	20	Allergy
3	41	F	95	30	0	0	Sinuitis
4	29	F	60	50	45	45	NANH
5	31	M	100	25	0	0	Common cold
6	28	M	90	40	0	0	Sinuitis
7	25	M	85	15	10	10	Common cold
8	36	F	100	30	0	30	NANH
9	23	M	100	30	30	40	Allergy
10	31	F	100	25	0	0	Rhinitis with pregnancy

NANH = Non allergic nasal hyperreactivity

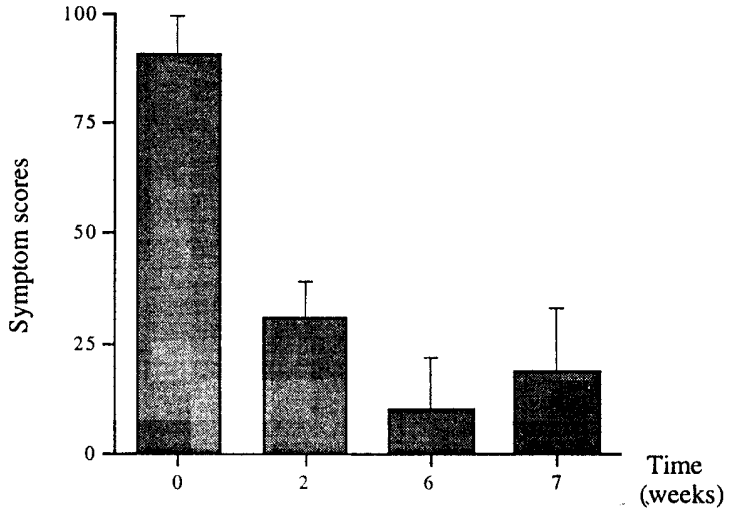

Fig. 2. Mean estimated nasal symptom scores in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor overuse on the night before the first estimate (0). The other estimates were made 2, 6 and 7 weeks later. After the first estimate (0), the patients had budesonide nasal spray, 400 µg/day, for 6 weeks. Error bars denote 95% confidence intervals.

The mean mucosal swelling following histamine challenge on the first day was 0.6 mm with a dose of 1.0 mg/ml, 1.0 mm with one of 2.0 mg/ml and 1.4 mm with 4.0 mg/ml. After 14 days on budesonide, the corresponding values for mucosal swelling were 0.6, 0.9 and 1.1 mm. Five weeks later, the values for mucosal swelling on histamine provocation were 1.0, 1.2 and 1.4 mm, using these three doses (Fig. 3).

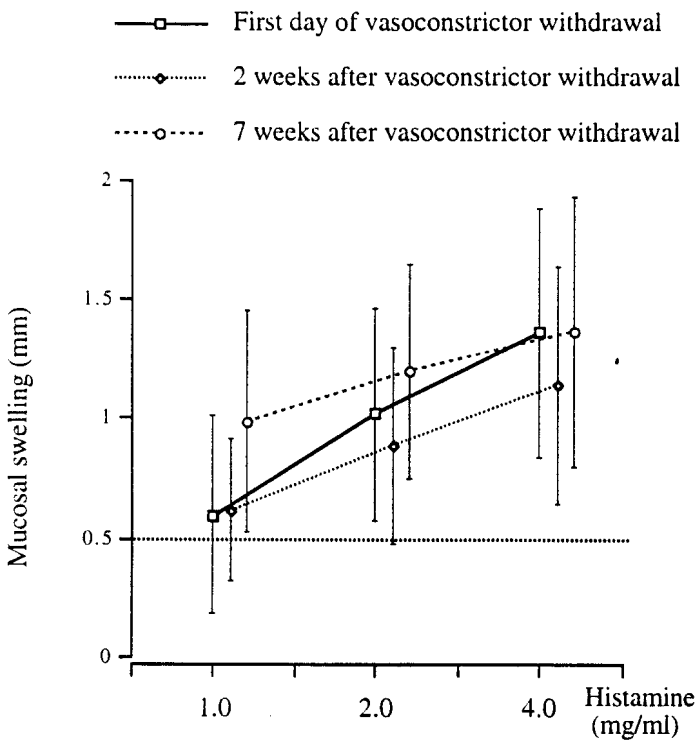

Fig. 3. Mean mucosal swelling in 10 patients with rhinitis medicamentosa. The provocations were performed with 1.0 mg/ml, 2.0 mg/ml and 4.0 mg/ml of histamine on one side of the nose, 30 min after decongestion with oxymetazoline, on the first day after discontinuing the vasoconstrictor, and after 2 and 7 weeks. Error bars denote 95% confidence intervals.

In the patient group, the mean decongestive effect after the instillation of oxymetaxoline was -1.7 mm the first day, -1.9 mm two weeks later and -1.8 mm at the end of the study. In the control group, the decongestive effect ranged from -2.1 to -3.9 mm (mean = -2.75 mm) over this period. In the patient group the decongestive effect on the first day was significantly less than in the controls ($p<0.001$) (Fig. 4).

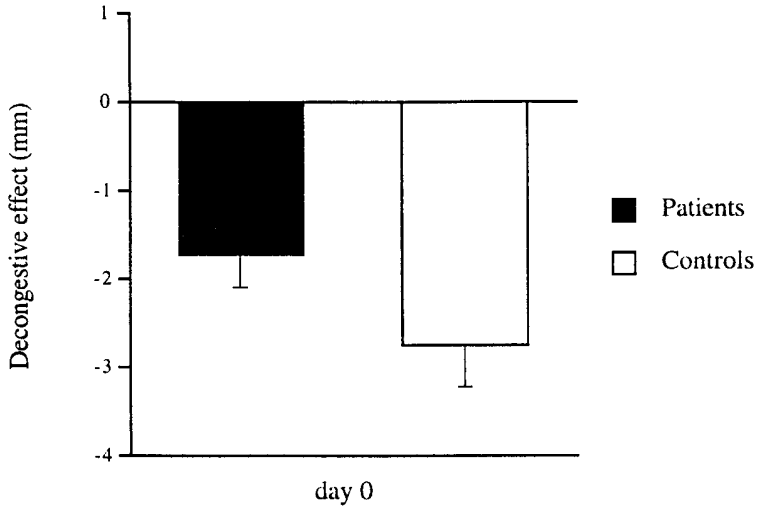

Fig. 4. Mean decongestive effect 30 min after oxymetazoline in 10 healthy volunteers and in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor overuse on the night before the recording. Error bars denote 95% confidence intervals.

Discussion

In a study aiming to measure the amount of mucosal swelling and facilitate comparison of the results obtained from repeated measurements during the treatment of patients with rhinitis medicamentosa, it is essential to use a reproducible measuring technique and obtain a reliable individual value before treatment with budesonide. The occurrence of reciprocal swelling in the nose [10] was taken into account by calculating the mean amount of mucosal swelling in both nasal cavities.

Rebound swelling and decongestion

Rebound swelling is due either to vasodilatation or interstitial oedema or a combination of both. Rijntjes studied patients with rhinitis medicamentosa during and after their overused of nosedrops for more than 6 months.[3] Metaplasia of the mucous membranes was seen during the overuse, but no oedema was found. It was concluded that rhinitis medicamentosa was probably caused by vasodilatation. Since interstitial oedema is almost impossible to measure [11], the evidence indicating the occurrence of oedema was indirect. It was therefore postulated that oedema does not respond to treatment with α-agonists and that an incomplete decongestion indicates the occurrence of interstitial oedema.[4] In a study of patients with vasomotor rhinitis, increased nasal airway resistance was found after three weeks' use of xylometazoline nasal spray. The

decongestive effect of the drug was incomplete and it was suspected that rhinitis medicamentosa might be due to oedema.[4] In this study, all patients had a significant reduction in rebound swelling as shown by the mucosal baseline position and symptom scores after 14 days on budesonide. The design of the study does not take up the question whether the reduction in rebound swelling is due to the vasoconstrictor withdrawal or to treatment with budesonide. However, the fact that the *decongested mucosal position* is significantly lower 14 days after vasoconstrictor withdrawal than at the start of the study suggests that the rebound swelling is partly due to interstitial oedema. The finding that the decongestive effect is less in the patient group than in the controls also accords with the theory that rebound swelling is due to interstitial oedema, since oedema cannot be treated with α-agonists. In this context it should be emphasized that budesonide has no vasoconstrictor effect.[12]

Three studies on healthy volunteers have reported that the same single dose of a vasoconstrictor had the same decongestive effect after 3, 4 and 6 weeks´ use of vasoconstrictors, indicating that no interstitial oedema had developed.[4-6] Therefore, it probably takes more than 6 weeks´ use of vasoconstrictors for oedema to develop. On the other hand, it is possible, as suggested [4], that only predisposed persons with some underlying nasal disease, such as vasomotor or allergic rhinitis, develop interstitial oedema after prolonged use of vasoconstrictors. This would agree with the results of the present study. However, four patients probably had no underlying nasal disease other than a common cold or sinusitis (Table 2), and yet all the patients developed oedema.

Tolerance

By definition, tachyphylaxis is a rapid reduction in the effect of a drug after the administration of only a few doses. Tolerance, on the other hand, is a hyporeactivity acquired as a result of prior exposure to the drug,[13] which means that the decongestive effect fades after sustained use of the vasoconstrictor. However, in the literature on rhinitis medicamentosa, the term tachyphylaxis has frequently been used instead of tolerance.

The decongestive effect of a single dose of oxymetazoline was significantly less in the patient group before treatment than in the controls. This shows that tolerance develops after prolonged use of topical vasoconstrictors in the sense that the decongestive effect is decreased. Tolerance can also be expressed as a decreased duration of the effect of a drug after the prolonged use of vasoconstrictors. It has been reported that the decongestive effect of oxy- or xylometazoline lasts for approximately 7 or 9 hours, respectively.[14] In this study, seven of 10 patients estimated the duration of a single dose of the vasoconstrictor at 4 hours or less, which is approximately half the expected duration of the effects of oxy- or xylometazoline. This may explain why most patients used the drug oftener than two or three times a day, the dose recommended by the manufacturers (Table 1).

Although the duration of the effect of the vasoconstrictor was not objectively recorded, it is fair to say that tolerance was seen in this trial as a reduction both of the decongestive effect and of the duration of the effect of the vasoconstrictor.

Histamine sensitivity

Healthy volunteers have been reported to have a mucosal responsiveness below 0.5 mm, with histamine provocations up to 2.0 mg/ml.[15] In a recent study, healthy volunteers were given oxymetazoline nasal spray for 30 days to study the possible development of rhinitis medicamentosa. At the end of the month, rebound swelling [5] and increased histamine sensitivity [16] were present and were diagnosed as signs of rhinitis medicamentosa and nasal hyperreactivity, respectively. The degree of increased histamine sensitivity was comparable to that seen in patients with vasomotor rhinitis.[17]

It has been suggested that the severity of rhinitis medicamentosa is proportional to the period during which the drug is used, to the frequency of its use and to the amount of drug administered.[7,18] Most patients in this trial had used the nosedrops for a very long period (Table 1) and some had allergy and vasomotor rhinitis as their underlying nasal disease (Table 2). It was therefore expected that histamine sensitivity would be greater at the start of this trial. In the study of healthy volunteers, the increased histamine sensitivity found after 4 weeks on oxymetazoline had disappeared in most subjects 14 days after vasoconstrictor withdrawal without corticosteroid treatment. Moreover, it has been shown that budesonide treatment for 14 days significantly reduces the histamine sensitivity in patients with vasomotor rhinitis.[19] It was therefore assumed that budesonide, treatment together with the withdrawal of the vasoconstrictors, would reduce or normalize histamine sensitivity at the end of this trial. Instead, seven weeks after the withdrawal of the vasoconstrictor, histamine sensitivity had increased slightly more, which also supports the theory that rhinitis medicamentosa is partly due to interstitial oedema. On the first day of vasoconstrictor withdrawal, the inferior concha was congested and oedematous, with a limited capacity to decongest or expand. Seven weeks later, when the oedema was reduced, the increased histamine sensitivity reflected the persistence of nasal hyperreactivity.

Aspects of treatment

Most authors agree that vasoconstrictors should be discontinued immediately and completely.[7] An abrupt cessation induces marked nasal blockage and various types of therapy are used to facilitate the withdrawal process in clinical practice. It has been proposed that the most effective treatment is to combine topical and oral corticosteroids.[8] Other authors recommend systemic decongestants and/or antihistamines.[2] Nocturnal sedation, corticosteroid injection into the inferior turbinate and surgery have also been suggested.[20] However, no controlled studies have been performed to evaluate these

treatments objectively, but the success rate on the short-term follow-ups regarding the patients´ ability to stop using the vasoconstrictors ranges between 72-100%.[7]

Since many patients with rhinitis medicamentosa do not know that their nasal stuffiness is mainly caused by the overuse of vasoconstrictors, it is important to ask all patients with nasal stuffiness about their use of topical decongestants. In our opinion, the main aim of treatment is to convince patients that the long-term use of vasoconstrictors is responsible for the stuffiness and that overuse is harmful, regardless of the underlying nasal disease. Some patients have already unsuccessfully tried the therapy recommended by the physician during the withdrawal period and, in these cases, it is particularly important not to compromise. It takes time and patience to explain the mechanisms of rhinitis medicamentosa, but an explanation is essential for the treatment to be successful.

In this trial, the symptom scores decreased significantly between the second and sixth weeks after vasoconstrictor withdrawal. However, increased sensitivity to histamine was still present one week later, suggesting that these patients had non-allergic nasal hyperreactivity as their underlying nasal disorder, without knowing it (VIII, Table 2). Although a careful medical history was taken at the first visit, it was difficult or impossible for the patients to recall the nasal problems they had months or years earlier. In fact, two patients who had nasal allergy were unaware of it and, although at least three patients probably had vasomotor rhinitis, only one of them reported nasal symptoms prior to the overuse of topical decongestants.

Conclusion

All patients were able immediately to stop using the vasoconstrictors and they all denied using any topical vasoconstrictor during the study period. The symptom scores and the thickness of the nasal mucosa were reduced considerably 14 days after vasoconstrictor withdrawal. 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. The results support the theory that the rebound swelling found in this group of patients is partly due to interstitial oedema. Moreover, we noted the presence of tolerance, as reflected by a reduction in both the decongestive effect of oxymetazoline and a reduction in drug duration.

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