

Rhinitis medicamentosa: aspects of pathophysiology and treatment

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With modern vasoconstrictors, such as oxy- and xylometazoline, the risk of developing rhinitis medicamentosa (RM) has been considered to be small or even nonexistent. However, recent studies have shown that overuse of these drugs may result in rebound congestion, nasal hyperreactivity, tolerance, and histologic changes of the nasal mucosa. Using rhinostereometry, it has also been shown that the long-term use of the preservative benzalkonium chloride (BKC) in oxymetazoline nasal spray accentuates the severity of rhinitis medicamentosa in healthy volunteers. A nasal decongestant spray composed of a combination of vasoactive substances and BKC has a long-term adverse effect on the nasal mucosa. BKC alone induces mucosal swelling after 30 days use of the nasal spray in healthy subjects, unlike placebo. According to the author, rhinitis medicamentosa can be defined as a condition of nasal hyperreactivity, mucosal swelling, and tolerance that is induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative. An adequate treatment of these patients consists of a combination of vasoconstrictor withdrawal and a topical corticosteroid to alleviate the withdrawal process. The underlying nasal disorder must then be treated. Patients with rhinitis medicamentosa who overuse topical decongestants and are able to stop using such drugs should be careful about taking these drugs again, even for a few days. They must be informed about the rapid onset of rebound congestion upon repeated use in order to avoid the return of the vicious circle of nose-drop abuse.

Peter Graf

Department of Otorhinolaryngology,
Södersjukhuset, Karolinska Institute,
Stockholm, Sweden

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Peter Graf MD, PhD, Department of
Otorhinolaryngology, Södersjukhuset,
S-118 83 Stockholm. Tel: +46-8-6163712.
Fax: +46-8-6163685

Introduction

Local decongestants for the nose include all substances that can reduce the thickness of the nasal mucosa. However, in the majority of cases, decongestants are vasoconstrictors that mostly contain oxy- and xylometazoline (29). The first topical vasoconstrictors were based on ephedrine with a brief decongestive effect. Even then, Kully reported that prolonged use of these drugs could result in nasal stuffiness and tolerance (26).

The nasal stuffiness caused by overuse of nasal vasoconstrictors has been ascribed to a rebound phenomenon when the decongestive effect of the drug disappears. The stuffiness is relieved by additional doses of the vasoconstrictor, possibly in larger doses, i.e. tolerance. The patient becomes increasingly dependent on the drug, and a vicious circle is established that may result in drug habituation. This condition is called rhinitis medicamentosa (RM), a term coined as far back as 1946

(28). At that time these drugs were based on ephedrine and RM, i.e. rebound congestion, was a common problem. The term has not been restricted to nasal stuffiness caused by topical vasoconstrictors. It refers also to the side-effects of other drugs, such as oral antidepressants, antipsychotics, oral contraceptives and antihypertensive drugs.

With modern vasoconstrictors, such as oxy- and xylometazoline, the risk of developing RM and tolerance has been considered to be much smaller or even nonexistent (34). However, recent studies have shown that overuse of these drugs also results in rebound congestion and histologic changes of the nasal mucosa (39, 44).

Since 1981, it has been possible to purchase nose drops 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 nose drops in single-

dose pipettes, most nasal decongestant sprays on the Swedish market contain the preservative benzalkonium chloride (BKC). Since 1989, the sales of these drugs have increased tremendously in Sweden, and the number of patients with RM has also increased. Therefore, the role of the BKC will be discussed in the development of RM.

Topical vasoconstrictors

The two main groups of topical vasoconstrictive drugs are sympathomimetic amines (ephedrine, phenylpropanolamine (PPA)) and imidazoline derivatives (oxy- and xylometazoline), which are α -adrenoreceptor agonists. The sympathomimetic amines act mainly on the α -receptors in the nasal mucosa and the imidazoles are more selective α_2 -agonists. These vasoconstrictors act either by directly stimulating the α -receptors, due to their resemblance to noradrenaline (imidazoles), or by indirectly stimulating the α -receptors via release of noradrenaline presynaptically (PPA).

The amines and the imidazoles are powerful decongestants, and the capacitance vessels responsible for mucosal congestion are regulated by α_1 - and α_2 -receptors. The subdivision of the α -receptors is important regarding the action of topical decongestive drugs. It has been shown that oxymetazoline, but not phenylephrine, an α_1 -selective sympathomimetic amine, constricts nasal resistance vessels. This results in a reduction in mucosal blood flow, which is more pronounced in patients with acute rhinitis than in healthy subjects (4).

Pathophysiology of rhinitis medicamentosa

The pathophysiology of the rebound swelling in RM is not known. However, several theories have been postulated, some of which are more plausible than others. According to Baldwin (2), secondary vasodilatation may develop because all sympathomimetic amines have both α - and β -receptor activity. The β effect, although not so pronounced, outlasts the α effect and causes rebound swelling. Beside α - and β -receptor activity, ephedrine has an indirect action by releasing noradrenaline from nerve terminals.

The development of tolerance has been explained as exhaustion of the vasopressor mechanism due to overuse of ephedrine because less noradrenaline is released from nerve terminals. However, oxy- and xylometazoline act selectively on the α -receptors, but the long-term use of these drugs also induces rebound swelling.

It has further been suggested that the rebound swelling occurs because of tissue hypoxia, resulting in reactive hyperaemia, which is manifested as

vasodilatation (2, 8). This is improbable because the resistance vessels regulating mucosal blood flow are affected mainly by α_2 -adrenoreceptor agonists (1). Unlike the imidazoles, the α_1 -selective sympathomimetic amines cause decongestion without reducing nasal mucosal blood flow (1). However, the sympathomimetic amines also induce rebound swelling after long-term use.

The rebound swelling has also been attributed to long-term use of α_2 -receptor agonists that may stimulate the negative feedback mechanism presynaptically, resulting in reduction of endogenous noradrenaline (27). The α -adrenergic tone would then persist only so long as the topical α_2 -receptor agonist is used. When the action of the drug disappears, rebound swelling follows (30). This theory is supported by evidence that, in the dog, nasal mucosa pretreatment with an α_2 -receptor agonist reduces the response to sympathetic nerve activation (5). However, vasoconstrictors without α_2 -receptor action also induce rebound swelling.

Finally, the rebound phenomenon has been ascribed to alteration in the vasomotor tone with increased parasympathetic activity, vascular permeability, and oedema formation. This hypothesis accords with a study in guinea pigs, which received naphazoline for 4 months (9). An increased activity of the choline esterase enzyme in the cholinergic nerves around the blood vessels was found, and this was interpreted as parasympathetic hyperactivity. Marked vascular dilatation and oedema were also present, indicating an increased vascular permeability. Similar results have been reported by Talaat and co-workers (40), whereas no such histologic changes were found in studies performed by others (34, 36).

Benzalkonium chloride as a preservative

Most nasal drops and sprays are multi-dose preparations that contain a preservative to prevent the growth of microorganisms. The preservative BKC, a quaternary ammonium compound, has a bactericidal effect, because it damages the cell wall of the microorganisms (35). It can also be toxic to human cells, and an *in vitro* experiment has shown that BKC (0.2 mM) induces irreversible depolarization of the cell membrane of the frog skeletal muscle after a few minutes, which injures the muscle cells (7).

As an added preservative, BCK has been used in the eye, the ear, the nose, and for inhalation. The addition of BCK to nebulizer solutions for inhalation has now largely been abandoned because of the bronchoconstrictive effects BCK (31, 32). It has also been shown that exposure to 0.01% BKC for 2 minutes damages the corneal

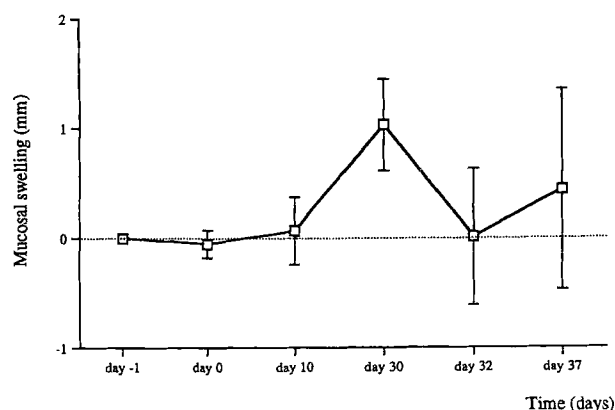


Fig. 1. The nasal mucosa swelling of both inferior turbinates as measured with rhinostereometry in healthy subjects before, during and after 30 days' use of decongestant nasal sprays, and after stopping the medication (mean $\pm$ S.D.). The swelling on day -1 served as the reference position. The recordings day 10 and 30 were made 14–17 hours after drug administration. From (18, 19).

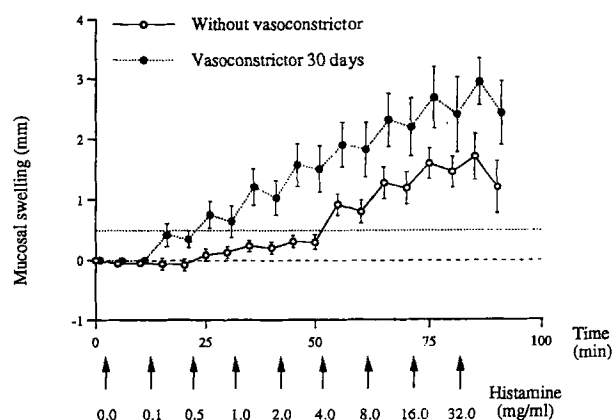


Fig. 2. Mucosal swelling in one side of the nose (mean $\pm$ S.D.) in healthy subjects as measured with rhinostereometry after application of histamine solutions in rising concentrations every 10 minutes (arrows). Filled circles indicate the time of the provocation after use of the decongestant nasal sprays in each nostril, three times daily for 30 days. Open circles indicate the time of the provocation before the medication with the vasoconstrictor started. From (18, 19).

epithelium by cellular destruction (41) and BKC-induced contact allergy has been reported in patients with chronic external otitis (10).

When used in the concentrations ordinarily used in nasal sprays and drops, i.e. 100–200 mg/l, *in vitro* studies, it has been shown that BKC is toxic to the nasal cilia (3, 24, 42, 43). Moreover, it has been reported that nasal decongestants containing BKC can have deleterious effects on granulocyte chemotaxis and phagocytosis (22) and other important defence functions of the neutrophils *in vitro* (6). The effects of such compounds on the mucociliary transport rate are not yet clear, because conflicting results have been reported (34, 37, 38).

Rhinostereometry

This is an optical, direct, noninvasive method designed to measure nasal mucosal swelling with a high degree of accuracy. It was first described in 1982 (25). The aim of this method is to allow topographic measurements in the nose without manipulation of the nasal structures. Such measurements require a definite fixed point to which the position of any object studied can be related. In rhinostereometry, the origin of a three-dimensional co-ordinate system is used as the fixed point.

The apparatus consists of a surgical microscope placed on a micrometre table fixed to a frame. The microscope can be moved in three angular directions, thus establishing the co-ordinate system. To permit measurements, the nasal cavity must be placed in the co-ordinate system in such a way that it resumes the same position with a high degree of precision in repeated measurements. This is achieved by fixing the skull of the subject to be examined immobile and exactly to the frame by an individually-formed tooth splint.

The nasal cavity is viewed through the eyepiece of the microscope. Because the microscope has a small depth of focus, a sharply delineated area of the surface is viewed in the plane of focus. Because the ocular is equipped with a horizontal millimetre scale, the sharply delineated area, vertically directed, crosses the millimetre scale and its position can be recorded.

With this method, the area of measurement can be re-identified with a high degree of accuracy in the same individual in different observations over time, with the subject as his or her own control. The accuracy of the method is 0.2 mm.

Induction of rhinitis medicamentosa in healthy subjects

Clinically, one cannot distinguish between vasomotor rhinitis (perennial non-allergic rhinitis) and RM, because the medical history of patients with RM resembles that of patients having vasomotor rhinitis with blockage as the main symptom. It is therefore important to ask all patients with nasal obstruction about their use of topical decongestants.

Using rhinostereometry to record the nasal mucosal reaction in terms of congestion, a histamine provocation model has recently been presented, standardizing the nasal mucosal reactivity. With the histamine challenge test, it is possible to distinguish between healthy subjects and patients with vasomotor rhinitis (20), who have an increased sensitivity to histamine.

We have shown that healthy subjects who use

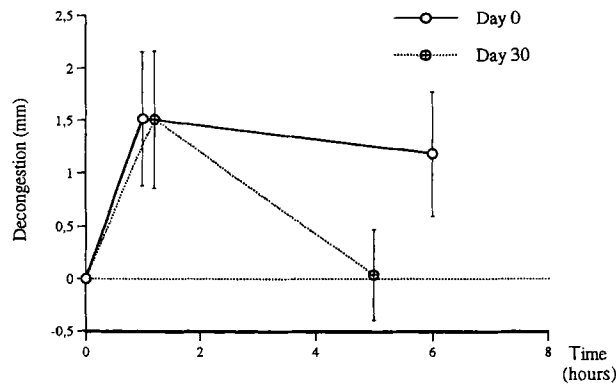


Fig. 3. Decongestion of both inferior turbinates as measured with rhinostereometry in healthy subjects who used decongestant nasal sprays for 30 days (mean $\pm$ S.D.). Open circles represent the mean decongestion 1 and 6 hours after administration of the sprays before starting the medication. Partly filled circles indicate the corresponding decongestion 1 and 5 hours after 30 days on the nasal sprays. From (17).

oxymetazoline nasal spray for 30 days develop rebound swelling, increased histamine sensitivity indicating nasal hyperreactivity (18, 19) (Figs. 1 and 2), and a reduction in the duration of the decongestive response indicating development of tolerance (17) (Fig. 3). Two days after stopping the medication, the rebound swelling disappears, but in some subjects, the increased histamine sensitivity persisted for more than 1 month (11).

Moreover, healthy volunteers develop rhinitis medicamentosa also when they use oxymetazoline nasal spray with BKC only once daily at night for 30 days (15). Symptom scores show that, regardless of the frequency of administration of the spray, the subjects are particularly bothered by nasal obstruction in the evenings.

Role of benzalkonium chloride in the development of rhinitis medicamentosa

We have also studied the effect of BKC in a decongestant nasal spray in the development of RM. Twenty healthy volunteers entered a trial that was double-blind, randomized and parallel. Ten subjects received oxymetazoline nasal spray with BKC three times daily for 30 days, and the others used oxymetazoline nasal spray without the preservative. Before and after drug treatment, the mucosal surface positions were recorded with rhinostereometry, followed by a histamine challenge test. Symptoms of nasal stuffiness were estimated twice daily on visual analogue scales.

After 30 days, rebound swelling and nasal stuffiness were found in both groups. However, in the group receiving oxymetazoline nasal spray without BKC, both variables were significantly less marked (14) (Figs. 4 and 5).

Three months after the 30-day treatment, the subjects who had been treated with oxymetazoline nasal spray with BKC were again treated with the same combination of substances as before, and the subjects who had been treated with oxymetazoline nasal spray alone were also treated with oxymetazoline nasal spray alone, but on this occasion only for 10 days. It was found that only the subjects who were treated with the combination of oxymet-

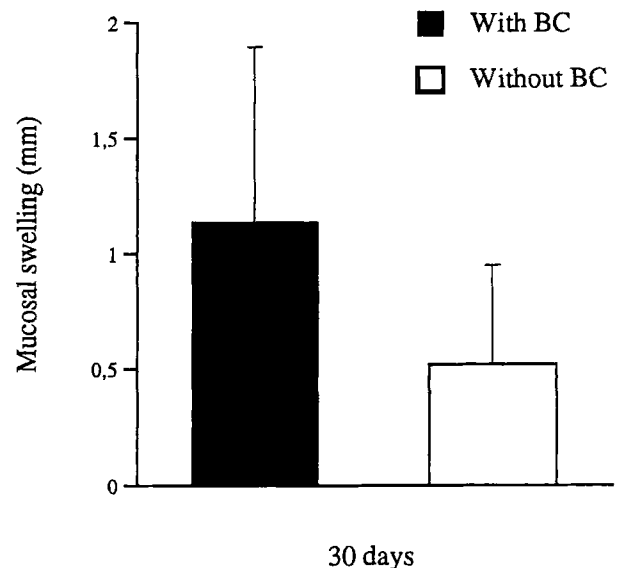


Fig. 4. Mucosal swelling of both inferior turbinates after 30 days on oxymetazoline nasal spray with and without benzalkonium chloride (BC), respectively (mean $\pm$ S.D.). Baseline values were set at zero before starting the course of treatment. From (14).

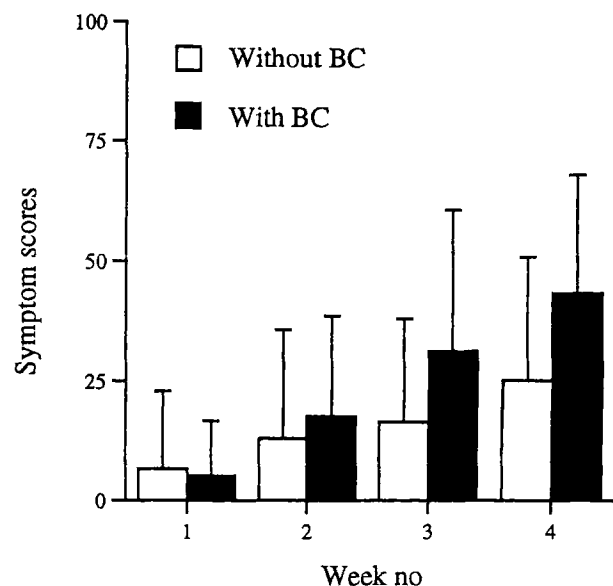


Fig. 5. Evening nasal stuffiness during 4 weeks' treatment with oxymetazoline nasal spray with and without benzalkonium chloride BC, respectively (mean $\pm$ S.D.). From (14).

Table 1. Characteristics and medical history of 10 patients suffering from rhinitis medicamentosa

Age	Allergy	Time of use	Reason for starting	Sprays per day	Duration of each spraying
18	-	1.5 y	common cold	3-8	0.5-4 h
38	+	0.5 y	common cold	2	6 h
41	-	6 y	sinusitis	2-5	3-4 h
29	-	0.5 y	common cold	6-8	0.5-2 h
31	-	4.5 y	common cold	4-5	3-4 h
28	-	1.5 y	sinusitis	5-8	2-3 h
25	-	3 y	common cold	4-7	2-3 h
36	-	6 y	common cold	4	4-5 h
23	+	1.5 y	unknown	4-5	4-5 h
31	-	4 m	pregnancy	8-10	1.5-2 h

azoline and BKC had increased nasal stuffiness, estimated by symptom scores and measurements of nasal mucosal swelling after 10 days of treatment (21). Thus, the long-term use of BKC in oxymetazoline nasal spray accentuates the severity of RM in healthy volunteers. Moreover, a nasal decongestant spray composed of a combination of vasoactive substance and BKC has a long-term adverse effect on the nasal mucosa.

In another double-blind placebo-controlled study, we have shown that BKC alone induces mucosal swelling after 30 days' use of the nasal spray in healthy subjects, unlike placebo (12). Oxymetazoline nasal spray induces a pronounced nasal hyperreactivity. Regular spraying with placebo three times a day induces an increase in nasal reactivity, but not to the same extent as oxymetazoline nasal spray. The long-term use of oxymetazoline results in a sensation of nasal stuffiness, which can be ascribed to unconscious exaggeration of nasal stuffiness, induced nasal hyperreactivity, or a combination of both. These factors are probably the main reasons for the prolonged use of nasal decongestive sprays and the development of rhinitis medicamentosa. BKC induces mucosal swelling, and this explains why BKC in a decongestant spray aggravates RM.

Treatment of rhinitis medicamentosa

The various treatments for RM have the same goals. 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. An abrupt cessation induces marked nasal blockage, and the patient then needs other medical treatment to alleviate the withdrawal process. Some authors have suggested treatment with systemic decongestants and/or antihistamines. Others recommend

nocturnal sedation, corticosteroid injections into the inferior turbinate and surgery. The most effective treatment is probably a combination of a topical and an oral corticosteroid.

The pronounced nasal obstruction is hard to endure, and therefore patients often start using the decongestants again after only a few days of withdrawal. This is why treatment of RM often fails. The first few days are crucial, and it is the authors' impression that patients, despite years of vasoconstrictor overuse, when they are given topical corticosteroids note a rapid reduction of the worst symptoms of nasal stuffiness, i.e. within 3-7 days. However, this is only the case if the decongestants are withdrawn. Corticosteroid treatment during sustained use of the decongestants will not cure RM. It is of great importance for successful treatment and compliance to inform patients about the rapid recovery.

An objective systematic follow-up of patients with RM after vasoconstrictor withdrawal has hitherto been lacking. With this in mind, we selected 10 patients with RM who had used topical vasoconstrictors daily for at least 4 months and promptly discontinued them (16) (Table 1). The thickness of the nasal mucosa, the decongestive effect of oxymetazoline, and the histamine sensitivity were measured with rhinostereometry for one year after vasoconstrictor withdrawal. Symptom scores were also estimated.

During the withdrawal of the vasoconstrictors, the patients' nasal obstruction was alleviated by the administration of budesonide nasal spray, 400

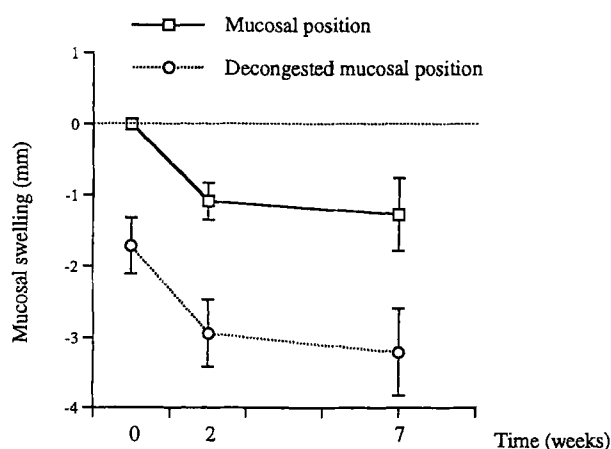


Fig. 6. Mucosal surface position in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor overuse on the night before the first recording, which represents the reference position set at zero (mean $\pm$ S.D.). The patients then started to use budesonide nasal spray, 400 μ g/day, for 6 weeks. Recordings were also made after 2 and 7 weeks. After each recording, the nasal mucosa was decongested with oxymetazoline and the mean decongested mucosal position was recorded 30 minutes later. From (16).

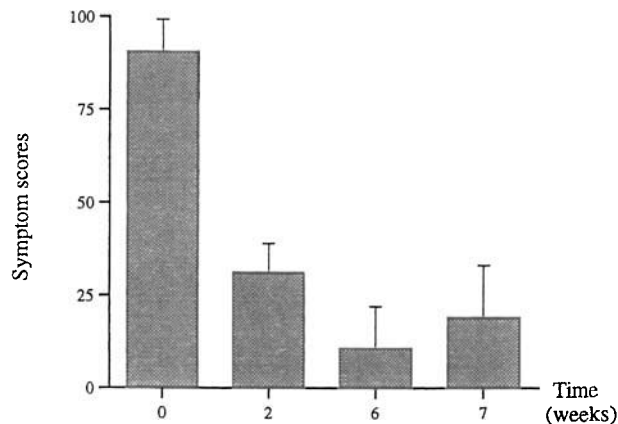


Fig. 7. Nasal symptom scores (mean $\pm$ S.D.) in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor overuse on the night before the first estimate (day 0). The other estimates were made 2, 6, and 7 weeks later. After day 0, the patients were treated with budesonide nasal spray, 400 μ g/day, for 6 weeks. From (16).

μ g/day, for 6 weeks. The symptom scores of nasal stuffiness and the thickness of the nasal mucosa were reduced considerably 14 days after vasoconstrictor withdrawal (Figs. 6 and 7). 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, as oedema cannot be treated with an α -agonist.

Before and 7 weeks after the withdrawal of vasoconstrictors, the patients had an increased histamine sensitivity reflecting nasal hyperreactivity. The increased histamine sensitivity was still present after 6 months, but not after 12 months. 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. The fact that the decongestive effect of oxymetazoline increased after 6 months shows that the drug tolerance has been reversed, also indicating that the oedema 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. This is clinically important, because it is not the intention to turn an overuse of nasal vasoconstrictors into a chronic use of topical corticosteroids unless the reason for the vasoconstrictor overuse was a steroid-responsive rhinitis.

It is important to investigate whether patients with RM who stopped using the topical vasoconstrictors may use these drugs again. For this purpose, eight of the previously treated patients

received oxymetazoline nasal spray containing BKC three times daily for 7 days, 13–19 months after they had stopped using nasal decongestant sprays (13). Before starting the course of treatment and after its conclusion, recordings of the mucosal surface positions were made with rhinostereometry, followed by histamine challenge tests. Symptoms of nasal stuffiness were estimated on visual analogue scales (0–100).

After 7 days, nasal stuffiness, estimated by symptom scores and measurements of nasal mucosa swelling, was found, as well as an increased histamine sensitivity, reflecting nasal hyperreactivity. Thus, patients with RM who overuse topical decongestants and are able to stop using such drugs should be careful about taking these drugs again, even for a few days. They must be informed about the rapid onset of rebound congestion upon repeated use in order to avoid the return of the vicious circle of nose-drop abuse.

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