The pathophysiology and treatment of rhinitis medicamentosa

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To evaluate the treatment of rhinitis medicamentosa, 10 consecutive patients discontinued their use of topical vasoconstrictors and were treated with budesonide nasal spray, 400 μg, daily for 6 weeks. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline and the histamine sensitivity were measured with rhinostereometry. All patients were able to stop using the vasoconstrictors and objective variables showed that they needed treatment for at least 6 weeks. The results strongly support the theory that the rebound swelling is due to interstitial oedema rather than to vasodilatation. The presence of tachyphylaxis reflected by a reduction in both the decongestive effect of oxymetazoline and a reduction of drug duration was seen.

Keywords *rhinitis medicamentosa* *histamine challenge* *rhinostereometry* *budesonide* *vasoconstrictors*

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 referred to as rhinitis medicamentosa. The nasal stuffiness is caused by rebound swelling when the decongestive effect of the drug has disappeared. To alleviate the stuffiness, the patient gradually starts using larger doses of the vasoconstrictor more frequently, i.e. as a result of tachyphylaxis. In many cases, the patient is unaware of the cause of the nasal stuffiness and the vicious circle cannot be broken without professional help.[2]

Knowledge about rhinitis medicamentosa has up to now been based on case reports and a few surveys. *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[3] who investigated 20 patients who had overused nose drops for more than 6 months. They were treated with a combination of topical and oral corticosteroids during withdrawal from the decongestants and had metaplasia of the nasal mucosa during the overuse. Moreover, the nasal conductivity, measured with rhinomanometry improved in all patients 4–6 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 intravascular oedema and conflicting results have been reported.[3–5] Moreover, some authors question whether tachyphylaxis can occur with modern decongestants, such as oxy- and xylometazoline.[4,6] Since it has not been possible to measure the thickness of the nasal mucosa accurately, no investigations have been performed to evaluate the rebound swelling and tachyphylaxis in patients with rhinitis medicamentosa.

Although there are various methods for treating rhinitis medicamentosa, they 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] An abrupt cessation induces marked nasal obstruction and the patient then needs other medical treatment to alleviate the withdrawal process. The aim of the present study was to evaluate the treatment of patients with rhinitis medicamentosa. The thickness of the nasal mucosa, the decongestive effect of oxymetazoline and the sensitivity to histamine were studied before, during and after treatment. Symptom scores were also estimated.

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Materials and methods

Ten consecutive patients, five women and five men, who had overused nose drops daily for at least 3 months, were selected from the out-patient 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 nose drops. They were informed that the vasoconstrictors were mainly responsible for their nasal blockage and they were urged to stop using them without any delay. A detailed medical history was taken, with special emphasis on the use of nose drops (Table 1). All patients were tested for allergy with the skin-prick test Soluprick® (ALK, Denmark) and Phadiatop® (Pharmacia, Uppsala, Sweden). The patients' nasal obstruction during withdrawal of the nose drops was alleviated by the administration of budesonide nasal spray, 400 μg/day.

The control group comprised 10 healthy volunteers, six women and four men (22–42 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 of the Department.

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 co-ordinate 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 nasal 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 turbinate in both nasal cavities at noon, after an acclimatization period of 30 min. The nasal mucosa was then decongested by the instillation of oxymetazoline nasal spray (0.5 mg/ml, 0.1 ml in each nostril). Thirty min 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 side of the inferior turbinate on one side of the nose during visual inspection, with 5 min between doses. On the challenged side, the position of the surface was determined 5 min 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 fifth week, budesonide was discontinued and the third recording was performed in the same way.

Each patient filled in a questionnaire before treatment with budesonide and after 2, 6 and 7 weeks. In the questionnaire, nasal obstruction was estimated on a visual analogue scale (0–100 symptom scores) which showed states ranging from no obstruction to very severe obstruction. The patients also stated 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.

Table 1. Patient characteristics and medical history

Patients Sex	Age (years)	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	0.5–4 h
2 male	38	+	0.5	Common cold	Oxy-/xylometazoline	2	2	6 h
3 female	41	–	6	Sinusitis	Oxy-/xylometazoline	2–5	2	3–4 h
4 female	29	–	0.5	Common cold	Oxymetazoline	6–8	2–3	0.5–2 h
5 male	31	–	4.5	Common cold	Oxymetazoline	4–5	2	3–4 h
6 male	28	–	1.5	Sinusitis	Oxymetazoline	8–5	2–4	2–3 h
7 male	25	–	3	Common cold	Oxymetazoline	4–7	2–4	2–3 h
8 female	36	–	6	Common cold	Oxymetazoline	4	2–3	4–5 h
9 male	23	+	1.5	Unknown	Oxy-/xylometazoline	4–5	2	4–5 h
10 female	31	–	4 months	Pregnancy	Oxymetazoline	10	6–8	1.5–2 h

h, hours; –, no; +, yes.

The unpaired *t*-test was used to compare the decongestive effect of oxymetazoline between the patient group and the controls. 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 served as the reference position and was set at zero. 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

No patient used a 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 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, $P < 0.001$) (Figure 1). Five weeks later, the corresponding mucosal position ranged from -0.2 to -2.3 mm the mean being -1.3 mm ($P < 0.001$) (Figure 1). On the recording on the first day, the decongested mucosal position ranged from -0.9 to -2.5 mm, compared with the reference position (mean = -1.72, $P < 0.001$) (Figure 1). Two weeks later, the decongested mucosal position was still lower compared with the reference position, ranging from -1.9 to -4.0 (mean = -2.9), and it was significantly lower than the decongested mucosal position on the first day ($P < 0.001$) (Figure 1). Five weeks later, the corresponding decongested mucosal position ranged from -2.25 to -4.75 mm (mean = -3.2 mm, $P < 0.001$) (Figure 1).

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

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 (Figure 3). In the patient group, the mean decongestive effect after the instillation of oxymetazoline was -1.7 mm the first day, -1.9 mm 2 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). In the patient group the decongestive effect on the first day was significantly less than in the controls ($P < 0.001$) (Figure 4).

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

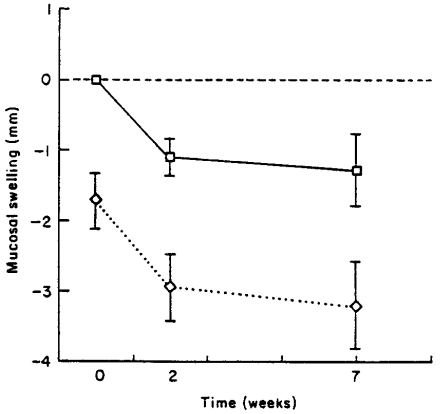

Figure 1. Mean mucosal surface position in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor on the night before the first recording (day 0), which represents the reference position set at zero. The patients then started to use budesonide nasal spray, 400 μg/day, for 6 weeks. Recordings were also taken after 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. —□—, mucosal surface position; --◇--, decongestant mucosal position.

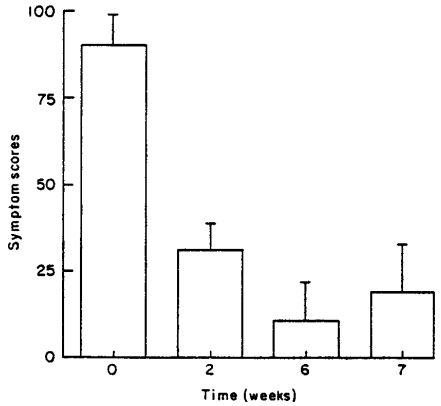

Figure 2. Mean estimated nasal symptom scores in 10 patients with rhinitis medicamentosa after immediate cessation of vasoconstrictor on the night before the first estimate (day 0). The other estimates were made 2, 6 and 7 weeks later during which time the patients had budesonide nasal spray, 400 μg/day,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

Table 2. Symptom scores during the withdrawal period and probable underlying disorder

Patients Sex	Age (years)	Day 1	2 weeks	6 weeks	7 weeks	Underlying disorder
1 female	18	85	45	0	45	Non-allergic nasal hyper-reactivity
2 male	38	90	20	20	20	Allergy
3 female	41	95	30	0	0	Sinusitis
4 female	29	60	50	45	45	Non-allergic nasal hyper-reactivity
5 male	31	100	25	0	0	Common cold
6 male	28	90	40	0	0	Sinusitis
7 male	25	85	15	10	10	Common cold
8 female	36	100	30	0	30	Non-allergic nasal hyper-reactivity
9 male	23	100	30	30	40	Allergy
10 female	31	100	25	0	0	Rhinitis with pregnancy

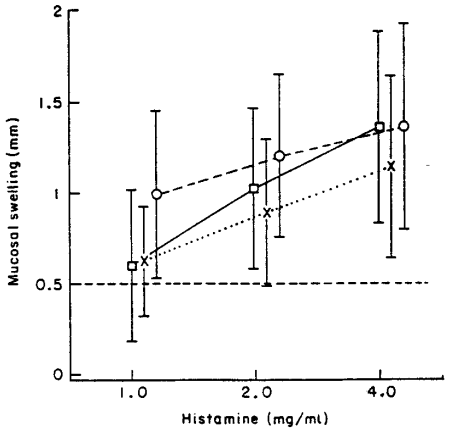

Figure 3. Mean mucosal swelling in 10 patients with rhinitis medicamentosa, after provocation with 1.0 mg ml, 2.0 mg/ml and 4.0 mg/ml of histamine on one side of the nose. 30 min after decongestion with oxymetazoline. The provocation was performed on the first day after discontinuing the vasoconstrictor (—□—) and after 2 (···· × ····) and 7 (– –○– –) weeks. Error bars denote confidence intervals.

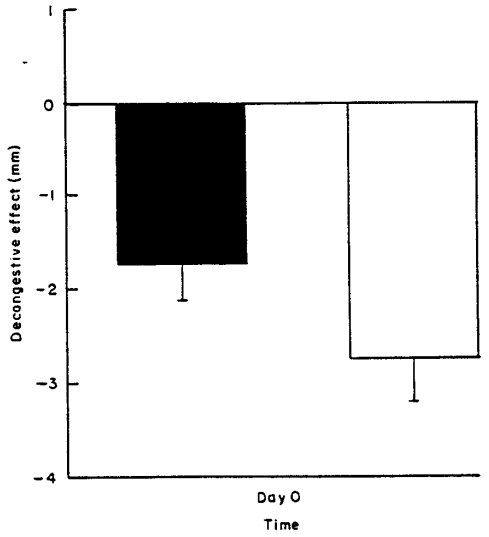

Figure 4. Mean decongestive effect 30 min after oxymetazoline in 10 healthy volunteers (□) and 10 patients with rhinitis medicamentosa (■) after immediate cessation of vasoconstrictor on the night before the recording. Error bars denote 95% confidence intervals.

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. In a study of patients with vasomotor rhinitis, increased nasal airway resistance was found after 3 weeks' use of xylometazoline nasal spray. Moreover, the decongestive effect of the drug was incomplete. Since interstitial oedema does not respond to treatment with alpha agonists, it was suspected that rhinitis medicamentosa might be due to oedema.[3] Rijntjes[2] studied patients with rhinitis medicamentosa during and after they overused nose drops for more than 6 months. 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.

In this study, all patients showed a significant reduction in rebound swelling, i.e. the mucosal baseline position and symptom scores after 14 days on budesonide. All patients also had a significantly lower decongested position than before budesonide treatment. These results strongly suggest that the rebound swelling is mainly due to interstitial oedema. The fact 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 alpha agonists. Moreover, the excellent effect of budesonide treatment on mucosal thickness in all patients also supports the theory that rebound swelling is due to interstitial oedema since it has been reported that budesonide has no vasoconstrictor effect.[11]

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 interstitial 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 patients developed the oedema.

TACHYPHYLAXIS

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,[12] which means that the decongestive effect fades after sustained use of the vasoconstrictor. In the literature on rhinitis medicamentosa, the term tachyphylaxis has been used instead of tolerance. The decongestive effect of a single dose of oxymetazoline was significantly lower in the patient group before treatment than in the controls. This shows that tolerance, or tachyphylaxis in a broader meaning of the term, develops after prolonged use of topical vasoconstrictors in the sense that the decongestive effect is decreased.

However, tachyphylaxis can 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 7 or 9 h respectively.[13] In this study, seven of 10 patients estimated the duration of a single dose of the vasoconstrictor at 4 h or less, which is approximately half the expected duration of the effects of oxy- or xylometazoline. Therefore, most patients used the drug much more often than 2–3 times a day, the dose recommended by the manufacturers (Table 1). Although the duration of the effect of the vasoconstrictor was not objective it is fair to say that tachyphylaxis in a broader meaning of the term 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.[14] 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[15] 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.[16]

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.[7,17] Most patients in this trial had used the nose drops for a very long period (Table 1) and some had allergy and probably 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.[13] 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, histamine sensitivity was increased slightly more 7 weeks after the withdrawal of the vasoconstrictor, which also supports the theory that rhinitis medicamentosa is due to interstitial oedema. On the first day of withdrawal, the inferior turbinate 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, indicating that further budesonide treatment was advisable in some patients.

ASPECTS OF TREATMENT

Most authors agree that the vasoconstrictors should be discontinued immediately and completely.[7,8] There are various ways of facilitating the withdrawal process and making it less onerous. The most effective treatment is to combine topical and oral corticosteroids. Others use systemic decongestants and/or antihistamines. Nocturnal sedation, corticosteroid injection into the inferior turbinate and surgery have also been suggested. It has never been determined how long the medical treatment should continue after withdrawal of the vasoconstrictors, but the success rate in the short-term follow-up ranges between 72 and 100%.[7]

Since most patients with rhinitis medicamentosa do not know that their nasal obstruction is mainly caused by the overuse of vasoconstrictors, it is important to ask all patients with nasal obstruction 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 symptom 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, using only budesonide nasal spray, we achieved a 100% success rate at the 7-week follow-up. This treatment was chosen to show that once the patient understands the origin of the nasal symptoms they can stop using the vasoconstrictors without potent medication, such as sedatives and oral corticosteroids. This knowledge is useful in conditions where oral corticosteroids should be avoided, e.g. diabetes mellitus and pregnancy. Of course, oral corticosteroids may be added to the topical corticosteroid during the first week of withdrawal, when the nasal stuffiness is most troublesome.

After 2–6 weeks on budesonide, the symptom scores decreased significantly. However, increased sensitivity to histamine was still present 1 week later, which suggests that the patients in this study needed at least 6 weeks of corticosteroid medication. By withholding budesonide treatment in the seventh week and by re-evaluating symptom scores after that week, we determined which patients needed further corticosteroid treatment. These patients probably had non-allergic nasal hyper-reactivity as their underlying nasal disorder, without knowing it (Table 2). By using this treatment model we could make a fair estimate of the patient's underlying nasal disorder and determine the need for and the type of medication that might be required subsequently. Although a careful medical history was taken at the first visit, it was difficult or impossible for the patients to recall their nasal problems months or years earlier. In fact, both 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.

Acknowledgements

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