

Ten Days' Use of Oxymetazoline Nasal Spray With or Without Benzalkonium Chloride in Patients With Vasomotor Rhinitis

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Context: In most countries, the use of topical nasal decongestants is limited to a maximum of 10 days because of the risk of developing rebound mucosal swelling and rhinitis medicamentosa.

Objective: To determine whether topical nasal decongestants can be safely used for 10 days in patients with chronic inflammation of the nasal mucosa.

Design: Double-blind, randomized, controlled, parallel study.

Patients: Thirty-five patients with vasomotor rhinitis selected from our outpatient department.

Intervention: Eighteen patients received oxymetazoline hydrochloride (0.5 mg/mL) nasal spray containing the preservative benzalkonium chloride (0.1 mg/mL), and the other 17 were treated with oxymetazoline nasal spray without benzalkonium chloride. Before and after the treatment, recordings of the nasal mucosa and minimal cross-

sectional area were made with rhinostereometry and acoustic rhinometry, followed by histamine hydrochloride challenge tests. Symptoms of nasal stuffiness were estimated on visual analog scales (0-100) in the morning and the evening, just before the nasal spray was used.

Results: No rebound swelling was found after the 10-day treatment in the 2 groups with either of the methods or as estimated by symptom scores. In the group receiving oxymetazoline containing benzalkonium chloride, but not in the other group, the histamine sensitivity was significantly reduced after treatment ($P < .001$).

Conclusions: It is safe to use topical nasal oxymetazoline with or without benzalkonium chloride for 10 days in patients with vasomotor rhinitis. However, this study indicates that benzalkonium chloride in nasal decongestant sprays affects the nasal mucosa also after short-term use.

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THE PRONOUNCED nasal vasoconstriction induced by topical nasal decongestants may be followed by rebound vasodilatation and stuffiness. This is especially likely after long-term use of these drugs. The patient may then become uncertain as to whether congestion is still being caused by the nasal disease or by rebound congestion. The stuffiness is relieved by additional doses of the vasoconstrictor eventually in larger doses, ie, tolerance. Thus, the patient becomes increasingly dependent on the topical decongestant and a vicious circle is established with long-term daily overuse. This phenomenon is called *rhinitis medicamentosa* (RM), a term coined as far back as 1946¹ when the topical decongestants contained ephedrine hydrochloride and RM was a common problem. With modern vasoconstrictors, such as oxymetazoline hydrochloride and xylometazoline hydrochloride, the risk of developing RM and

tolerance has been considered to be much smaller or even nonexistent.² However, recent studies have shown that overuse of these drugs also results in rebound congestion^{3,4} and histological changes in the nasal mucosa.⁵

Most nasal drops and sprays are multidose preparations that contain a preservative to prevent the growth of microorganisms. The preservative benzalkonium chloride, a quaternary ammonium compound, has a bactericidal effect, since it damages the cell wall of the microorganisms.⁶ The use of benzalkonium chloride has been questioned because it is toxic to the cilia in the nose.^{7,8} We have shown that daily use of benzalkonium chloride in oxymetazoline nasal spray for 30 days induces a more pronounced rebound swelling in healthy volunteers than does oxymetazoline nasal spray used alone for 30 days, indicating that benzalkonium chloride plays an important role in the development of RM.⁹

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PATIENTS AND METHODS

STUDY DESIGN

The study was designed as a parallel, randomized, double-blind trial. Thirty-five patients with vasomotor rhinitis (**Table**) were randomized for treatment with oxymetazoline nasal spray either with (18 patients) or without (17 patients) benzalkonium chloride in the morning and in the evening for 10 days. Nasal mucosal swelling and nasal reactivity, as estimated by histamine challenge, were studied with rhinostereometry and acoustic rhinometry before and after treatment, and symptom scores of nasal stuffiness were estimated throughout the treatment.

At noon, after an acclimatization period of 30 minutes, the position of the nasal mucosa of the inferior concha in both nasal cavities was recorded repeatedly with rhinostereometry, to establish the baseline mucosal position. In the same sitting position, the minimal cross-sectional area (MCA 2) was then recorded with acoustic rhinometry. Next, the nasal mucosa was challenged with histamine hydrochloride, 1, 2, and 4 mg/mL, where 0.14 mL of the solution was syringed over the inferior concha in 1 side of the nose. The positions of the mucosal surface and MCA 2 were determined 5 minutes after each histamine provocation. The subjects then used their nasal spray. After 10 days of treatment with the drug, the patients discontinued the spray in the morning. At noon, 14 to 17 hours after the last dose on the night before, the mucosal baseline positions and MCA 2 were recorded. Then a histamine provocation test was done as before.

Throughout the 10 days of medication, each subject filled in a diary card in the morning and the evening, just before using the nasal spray. Nasal stuffiness was estimated on a visual analog scale (0-100). The scale ranged from 0 (nose completely clear) to 100 (nose completely blocked). Informed consent was obtained before any procedure was performed. The study was approved by the local ethics committee and the medical product agency.

PATIENTS

Thirty-five patients with vasomotor rhinitis, 26 women and 9 men (mean age, 38 years), entered the trial. Most of them had nasal blockage as their main symptom, but, in some patients, secretions and/or sneezing was the dominating symptom (**Table**). Eighteen patients had used nasal corticosteroids before entering the trial, but no one was allowed to use any medication for nasal symptoms for 1 month before entering the study. On rhinoscopy, no signs of a structural basis for the nasal symptoms were noted. A skin test (Soluprick; ALK, Hørsholm, Denmark) performed on all patients confirmed that no one was allergic. The skin test contained the following allergens: birch, hazel, timothy, mold (*Alternaria*, *Cladosporium*), house dust mite (*Dermatophagoides pteronyss*, *Dermatophagoides farinae*), cat, dog, horse, rabbit, and guinea pig. All patients were selected from

the outpatient department of the ear, nose, and throat clinic at Huddinge University Hospital or Södersjukhuset, Stockholm, Sweden.

MEASURING METHODS

The nasal mucosal swelling was recorded with rhinostereometry and acoustic rhinometry. Rhinostereometry is an optical, direct, noninvasive method for measuring nasal mucosal swelling with a high degree of accuracy. A surgical microscope is placed on a micrometer table fixed to a frame. The microscope is movable in 3 angular directions, establishing a 3-dimensional coordinate system. The subject is fixed to the apparatus by a plastic, individually made tooth splint. The eyepiece has a horizontal millimeter scale. The nasal cavity is viewed through the eyepiece. 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 concha are registered in the plane of focus along the millimeter scale. The accuracy of the method is 0.2 mm.¹³

Acoustic rhinometry produces an acoustic pulse that enters the nose via a tube equipped with a nose adapter tightly placed in the nostril. Changes in the cross-sectional area are digitized by a computer, and numerical values of the cross-sectional area are recorded. The minimal cross-sectional area, MCA 2, is the cross-sectional area between the anterior portions of the inferior concha and the septum. This method has been described elsewhere,¹⁴ and in previous studies it seems to have been accurate.¹⁵ The apparatus used in this study was a RHIN 2100 (SR Electronics APS, Lyngø, Denmark).

STUDY DRUGS

Both groups sprayed 0.1 mL of the substances into each nostril 3 times daily. One group was randomized to treatment with oxymetazoline hydrochloride (Nezeril) (0.5 mg/mL) nasal spray without benzalkonium chloride, and the other group received oxymetazoline hydrochloride (Nezeril) (0.5 mg/mL) nasal spray with benzalkonium chloride (0.1 mg/mL) (Draco Läkemedel AB, Lund, Sweden). The study drugs were all in a new type of nasal spray bottle shown to withstand bacterial contamination.

STATISTICAL ANALYSES

Trends and spread were analyzed with the use of the means and SDs. For further statistical analyses, analysis of variance and paired and unpaired *t* tests were used. In calculating the mucosal swelling, the baseline position recorded on the first day was considered as the reference position and set at 0. The changes in the mucosal positions in each side of the nose, after 10 days of treatment with the nasal sprays, were added. 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 the reference values.

Opinions vary as to how long topical decongestants can safely be used without risking the development of RM. Some authors claim that the risk of developing RM with oxymetazoline and xylometazoline is very small and recommend regular use for at least 2 or 3 weeks, without risking adverse effects.¹⁰ Other authors recom-

mend that present products be used only for "emergency situations" and for not more than 3 consecutive days.^{11,12} No other drugs are more effective than topical nasal α_2 -agonists for relieving nasal stuffiness. Oxymetazoline and xylometazoline produce immediate, powerful, long-lasting decongestion, and therefore it is clini-

Patient Characteristics*

Patient No./ Sex/Age, y	Nasal Symptoms†			Previous Use of Topical Corticosteroid
	Running	Blockage	Sneezing	
Oxymetazoline Hydrochloride With Benzalkonium Chloride				
1/F/69	+++	-	-	No
2/F/43	++	+++	-	Fluticasone propionate
3/F/42	+++	++	+++	No
4/F/48	+	+	+++	Budesonide
5/F/22	++	+	++	No
6/F/29	-	+++	-	Budesonide
7/F/37	+	++	-	No
8/F/19	+++	+	-	No
9/F/51	-	+	+	No
10/F/35	+	++	-	No
11/M/44	-	+++	-	No
12/M/41	-	+++	-	Fluticasone propionate
13/F/41	-	++	-	Budesonide
14/M/76	++	++	++	Mometasone furoate
15/F/51	++	+++	+	Budesonide
16/F/76	+	++	-	Budesonide
17/F/44	-	+++	-	No
18/M/25	+	++	-	No
Oxymetazoline Hydrochloride Without Benzalkonium Chloride				
1/M/32	+	++	-	No
2/F/30	-	+++	-	Budesonide
3/M/35	++	+++	-	Budesonide
4/F/32	++	++	-	No
5/M/34	+	+++	+	No
6/F/22	+	+++	-	Budesonide
7/F/18	-	++	-	Budesonide
8/F/18	-	+++	-	No
9/F/54	+++	+	-	No
10/M/32	+	+++	-	Budesonide
11/M/26	++	+	+	No
12/F/25	+	+++	-	Budesonide
13/F/32	++	++	-	Budesonide
14/F/26	-	++	-	Budesonide
15/F/26	-	+++	-	Budesonide
16/F/65	++	+++	-	No
17/F/15	++	++	++	Mometasone furoate

*Allergy test results were negative in all patients.
†+ indicates mild; ++, moderate; +++, severe; and -, no symptoms.

cally important to establish for how long these drugs may safely be used without risking the development of RM. We have previously shown that it is safe to use oxymetazoline containing benzalkonium chloride in healthy subjects 3 times daily for 10 days.⁴ However, Åkerlund and Bende³ report that 3 weeks' regular use of xylo-metazoline containing benzalkonium chloride induces rebound swelling in patients with vasomotor rhinitis, but not in healthy subjects. They conclude that predisposed persons with an underlying inflammatory nasal disease are more prone to develop RM than healthy subjects with a normal nasal mucosa. In the present study, we therefore used patients with chronic untreated rhinitis.

In most countries, the use of topical nasal decongestants is limited to a maximum of 10 days because of the risk of developing rebound mucosal swelling and RM. The aim of this study was to determine whether 10 days'

regular spraying with oxymetazoline with or without benzalkonium chloride in patients with chronic inflammation in their nasal mucosa is safe in this respect.

RESULTS

All patients completed the study. However, because of technical difficulties, the rhinostereometric baseline values are missing in 4 subjects and the corresponding measurements with acoustic rhinometry are missing in 5 other subjects. Since all subjects had complete measurements with at least 1 of the objective methods, no patient was excluded.

**OXYMETAZOLINE WITH
BENZALKONIUM CHLORIDE**

Rhinostereometric Measurements

In the group receiving oxymetazoline with benzalkonium chloride, the mean mucosal swelling after histamine hydrochloride challenge before treatment was 1.4 mm with a dose of 1 mg/mL, 1.8 mm with 2 mg/mL, and 2.2 mm with 4 mg/mL. After 10 days of treatment, the corresponding values for mucosal swelling were 0.5, 0.8, and 1.1 mm (**Figure 1**). The reduction in mucosal swelling after histamine challenge was significant at all 3 histamine provocation levels (analysis of variance, $P < .001$). The mean mucosal swelling after 10 days was 0.21 mm, compared with the reference value before starting the medication (**Figure 2**).

Acoustic Rhinometric Measurements

The mean MCA 2 after histamine hydrochloride challenge before treatment was -0.09 cm^2 with a dose of 1 mg/mL, -0.12 cm^2 with 2 mg/mL, and -0.20 cm^2 with 4 mg/mL. After 10 days of treatment, the corresponding MCA 2 values were -0.03 , -0.08 , and -0.15 cm^2 (**Figure 3**). The increase in MCA 2 was significant after histamine hydrochloride challenge with 1 mg/mL (analysis of variance, $P = .02$), but not after challenge with 2 and 4 mg/mL. The mean MCA 2 when both nasal cavities were added before treatment was 0.7 cm^2 , and the corresponding MCA 2 after 10 days' treatment was 0.63 cm^2 (paired t test, $P = .38$) (**Figure 4**).

**OXYMETAZOLINE WITHOUT
BENZALKONIUM CHLORIDE**

Rhinostereometric Measurements

In the group receiving oxymetazoline without benzalkonium chloride, the mean mucosal swelling after histamine hydrochloride challenge before treatment was 0.6 mm with a dose of 1 mg/mL, 0.9 mm with 2 mg/mL, and 1.0 mm with 4 mg/mL. After 10 days of treatment, the corresponding values for mucosal swelling were 0.7, 0.9, and 1.1 mm (Figure 1). The increase in mucosal swelling was not significant at any histamine provocation level (by analysis of variance). The mean mucosal swelling after 10 days was 0.17 mm, compared with the reference value before the medication was started (Figure 2).

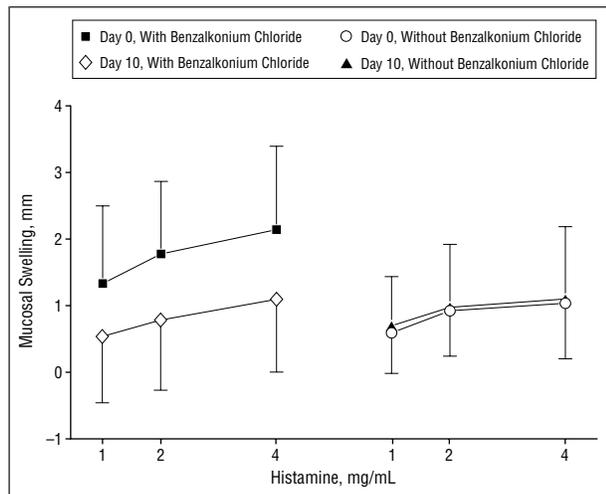


Figure 1. Mean (\pm SD) mucosal swelling after histamine hydrochloride challenge of the nasal mucosa before and after 10 days' treatment with oxymetazoline hydrochloride nasal spray with or without benzalkonium chloride as measured with rhinostereometry. The nasal mucosa was challenged with histamine hydrochloride, 1, 2, and 4 mg/mL, applied to 1 side of the nose. Recordings were made before and 5 minutes after each challenge.

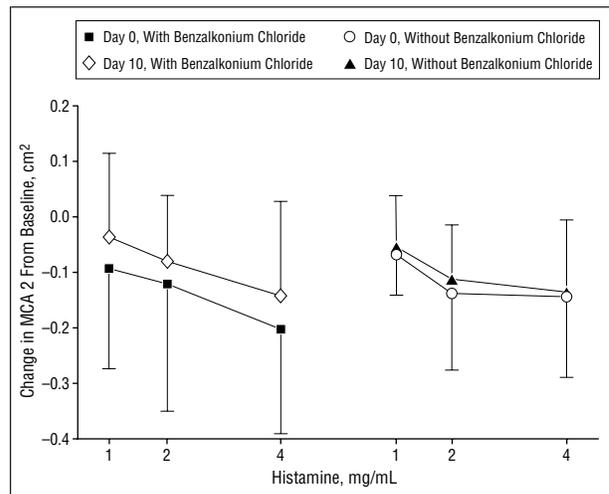


Figure 3. Mean (\pm SD) change in minimal cross-sectional area (MCA 2) from baseline after histamine hydrochloride challenge of the nasal mucosa before and after 10 days' treatment with oxymetazoline hydrochloride nasal spray with and without benzalkonium chloride, as measured with acoustic rhinometry. The nasal mucosa was challenged with histamine hydrochloride, 1, 2, and 4 mg/mL, applied to 1 side of the nose. Recordings were made before and 5 minutes after each challenge.

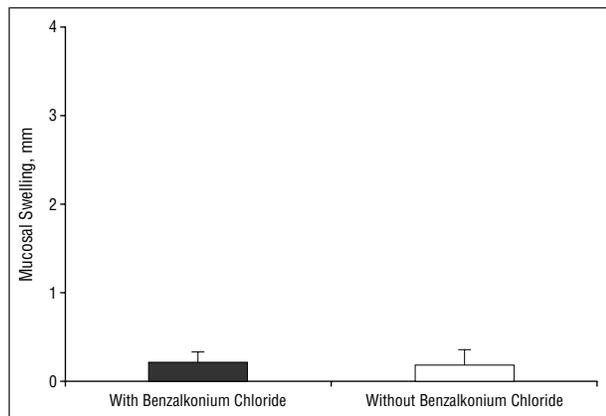


Figure 2. Mean (\pm SD) nasal mucosal swelling 10 days after treatment with oxymetazoline hydrochloride nasal spray with or without benzalkonium chloride as measured with rhinostereometry. Baseline values were set at 0 before drug treatment.

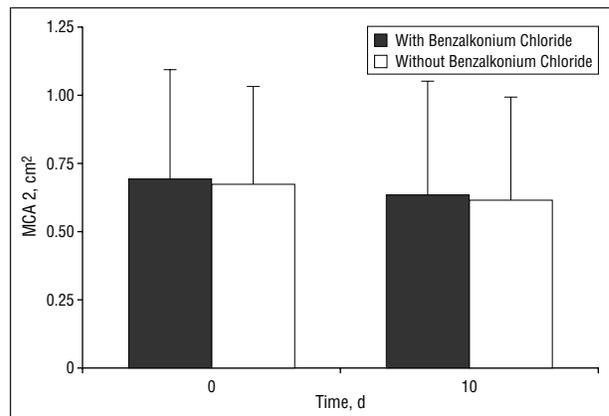


Figure 4. Mean (\pm SD) minimal cross-sectional area (MCA 2) before and after treatment with oxymetazoline hydrochloride nasal spray with or without benzalkonium chloride, as measured with acoustic rhinometry.

Acoustic Rhinometric Measurements

The mean MCA 2 after histamine hydrochloride challenge before treatment was -0.07 cm^2 with a dose of 1 mg/mL, -0.14 cm^2 with 2 mg/mL, and -0.15 cm^2 with 4 mg/mL. After 10 days of treatment, the corresponding MCA 2 values were -0.06 , -0.11 , and -0.13 cm^2 (Figure 3). There were no significant differences in MCA 2 at any histamine provocation level.

The mean MCA 2 when values from both nasal cavities were added before treatment was 0.67 cm^2 , and the corresponding MCA 2 after 10 days of treatment was 0.61 cm^2 (paired t test, $P = .34$) (Figure 4).

COMPARISONS BETWEEN GROUPS

The mean mucosal swelling as measured with rhinostereometry after 10 days' treatment with oxymetazoline with benzalkonium chloride was 0.21 mm, compared with the

reference value before the medication was started. The corresponding mucosal swelling in the group receiving oxymetazoline without benzalkonium chloride was 0.17 mm (unpaired t test, $P = .99$). The corresponding MCA 2 figures for both groups also show no significant difference between the groups (unpaired t test).

In the group receiving oxymetazoline with benzalkonium chloride, the mean symptom score for nasal stuffiness was 50 before and 49 after the treatment. The corresponding figures in the group receiving oxymetazoline without benzalkonium chloride were 48 and 51.

COMMENT

This study shows that rebound swelling does not follow 10 days' use of oxymetazoline with or without benzalkonium chloride 3 times daily in patients with vasomotor rhinitis. This is clinically important, since the rec-

ommendation of a 10-day limitation of topical nasal decongestants seems adequate. However, our study indicates that oxymetazoline containing benzalkonium chloride, unlike the vasoconstrictor without benzalkonium chloride, reduces histamine sensitivity already after 10 days' use in patients with vasomotor rhinitis.

Rhinostereometry and the estimates of symptom scores proved to be useful tools for detecting rebound swelling in our previous studies.^{9,16,17} However, in this study we found no rebound mucosal swelling with either of the objective rhinometric methods or in symptom scores in any of the investigated groups. The histamine sensitivity in the group that received oxymetazoline containing benzalkonium chloride was higher than in the other group before receiving the study drugs. Despite this difference between the groups, the reduction in histamine sensitivity is probably caused by benzalkonium chloride, since we previously showed that the use of oxymetazoline nasal spray alone increases histamine sensitivity.¹⁷

We previously reported that the long-term use of benzalkonium chloride in oxymetazoline nasal spray worsens RM in healthy volunteers.⁹ Moreover, a nasal decongestant spray composed of a combination of vasoactive substance and benzalkonium chloride has a long-term adverse effect on the nasal mucosa, unlike the vasoactive substance without benzalkonium chloride.¹⁶ The nose has a reflex pathway, consisting of afferent unmyelinated C fibers and efferent parasympathetic nerves,^{18,19} and activation of nonmyelinated C fibers induces nasal blockage.²⁰ Long-term exposure to irritants may cause alterations in vasomotor tone, with increased parasympathetic activity, which results in vascular dilatation, increased permeability, edema, and nasal blockage.²¹ Benzalkonium chloride may be such an irritant, since it has been shown to induce mucosal swelling after 30 days' use of benzalkonium chloride nasal spray alone in healthy subjects.¹⁷ This study shows that short-term use of oxymetazoline containing benzalkonium chloride also affects the nasal mucosa of patients with vasomotor rhinitis by reducing nasal reactivity. Patients with vasomotor rhinitis have an increased sensitivity to histamine compared with healthy subjects,²² and 14 days' treatment with topical nasal corticosteroids reduces nasal reactivity and symptoms.²³ Likewise, Stjärne and co-workers²⁴ treated therapy-resistant patients with vasomotor rhinitis with capsaicin, a substance known to activate unmyelinated C fibers, with a depletion of vasoactive substances. These patients reported a positive effect on nasal symptoms for up to 6 months before nasal symptoms recurred. It is possible that benzalkonium chloride may affect the nasal mucosa in a similar way to capsaicin.

This study supports the current recommendation in Sweden that oxymetazoline and xylometazoline nasal spray with or without benzalkonium chloride may safely be used for 10 days in patients with chronic untreated vasomotor rhinitis. There is no evidence indicating that this recommendation should not include other types of rhinitis, such as the common cold. However, for safety reasons, patients should be instructed to use topical decongestants only as long as the common cold produces nasal stuffiness, which usually lasts not more than 3 to 5 days. Clinical practice and some studies²⁵ show that certain patients may develop rebound swelling and RM after only a few

days' use of these drugs. Therefore, all patients must be warned about the risk of developing rebound swelling and RM after the use of topical nasal decongestants.

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