

Benzalkonium chloride in nasal decongestive sprays has a long-lasting adverse effect on the nasal mucosa of healthy volunteers

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Summary

Twenty healthy volunteers participated in the present study on the long-term effects of a nasal decongestive spray composed of either a combination of oxymetazoline nasal spray and benzalkonium chloride or of oxymetazoline nasal spray alone. Three months before the present study the participants had undergone treatment with nasal decongestants for 4 weeks. Ten of the subjects had been treated with oxymetazoline nasal spray without benzalkonium chloride and 10 of them had been treated with oxymetazoline nasal spray with benzalkonium chloride. In a double-blind study the subjects who had been treated with oxymetazoline nasal spray and benzalkonium chloride 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 again with oxymetazoline nasal spray alone, but on this occasion only for 10 days. Three variables were studied before and after the 10 days of treatment, i.e. nasal mucosa congestion, nasal reactivity and symptom scores. It was found that only the subjects who were treated with the combination of oxymetazoline nasal spray and benzalkonium chloride had increased nasal stuffiness, estimated by symptom scores and measurements of nasal mucosa swelling after 10 days of treatment. It is concluded that a nasal decongestant spray composed of a combination of vasoactive substance and benzalkonium chloride has a long-term adverse effect on the nasal mucosa.

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Introduction

A stuffy nose is a common problem among patients. However, it is a symptom that may be caused by various disorders, such as infectious rhinitis, allergic rhinitis, vasomotor rhinitis, nasal septal deviation, anti-hypertensive medication, pregnancy, narrow isthmus of the nose, nasal polyps, etc. When topical vasoconstrictors, sympathomimetic amines and imidazole derivatives are purchased over the counter without requiring an examination by a physician, the patients may use these vasoconstrictors to treat all of these conditions. Vasoconstrictors temporarily induce vasoconstriction and subsequent decongestion of the nasal mucosa via

α -receptors in the nasal erectile tissues [1,2]. Thus, the use of vasoconstrictors will afford only temporary symptomatic relief, without any therapeutic value. When the vasoconstrictive action disappears, there is a compensatory vasodilatation with subsequent swelling of the nasal mucosa [2]. Together these factors involve a great risk with prolonged use of the vasoconstrictors and rebound nasal congestion. The term mostly used for this condition is rhinitis medicamentosa [2–5].

Topical vasoconstrictors mostly contain both an active vasoconstrictor and preservatives, often benzalkonium chloride. Previous *in vivo* studies of rhinitis medicamentosa do not, however, distinguish between the effects of the vasoconstrictor and of the preservative. *In vitro* studies of the effects of preservatives in nasal drops [6–9] suggest that they affect the mucociliary clearance and phagocytosis. Furthermore, benzalkonium chloride

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appears to cause increased permeability of rabbit corneal epithelium [10] and bronchoconstriction in patients with mild asthma [11]. In a recent double-blind investigation we evaluated the effects of oxymetazoline with and without benzalkonium chloride during 4 weeks of treatment [12]. It was found that the group treated with oxymetazoline nasal spray with benzalkonium chloride developed greater rebound swelling than did the group treated with oxymetazoline nasal spray without benzalkonium chloride. In view of the results of that study, we decided to determine whether the effects of the long-term treatment with nasal decongestive sprays persisted. In Sweden it is currently recommended that nasal decongestants should not be used for more than 10 days. The present study was designed to assess the effects of treatment with nasal decongestants during 10 days, 3 months after the previous treatment for 4 weeks.

The aim of the study was to determine if there were any long-term effects of the use of nasal decongestive sprays over such a long period and, if so, if there were any differences between subjects who had been treated with nasal decongestive spray containing benzalkonium chloride and those who had been treated with nasal decongestant spray without benzalkonium chloride.

Materials and methods

Twenty healthy volunteers entered the trial. They had used a nasal spray three times a day during 4 weeks. Ten of them had used a nasal spray composed of oxymetazoline 0.5 mg/ml and benzalkonium chloride 0.1 mg/ml (Nezeril®) and the remaining 10 used a oxymetazoline nasal spray 0.5 mg/ml alone.

The present trial was performed 3 months after using a spray for 4 weeks. In each group the subjects were treated with the same substance as in the previous study, i.e. oxymetazoline nasal spray with benzalkonium chloride or oxymetazoline nasal spray alone was given to the subjects who had received this before, one dose in each nostril, three times a day for 10 days. The study was parallel and double-blind. It was possible to ensure that the study was still blind by having one author perform all the analysis in the first, 4 week study, and the other author could perform all the measurements and the analysis in the present study, without knowing which of the substances were used by the different volunteers. Furthermore, after the first study, the subjects were not told which of the substances they had taken. None of the subjects had used nasal decongestants during the 3 months preceding this study. They were all clinically healthy, with no history of atopy and had had no common colds for at least 2 months. None of the subjects were on any other medication during the study.

The following variables were studied: symptom scores, nasal mucosa swelling and nasal mucosa reactivity. The symptom scores were noted on a card with a visual analogue scale, which the subjects used to estimate the degree of nasal stuffiness every morning and evening before using the nasal sprays. The subjects also recorded whether they had a nasal discharge, a dry nose or a common cold. The nasal mucosa swelling was determined between 10.00 h and 14.00 h, with rhinostereometry before and after the 10 day period of treatment. The swelling before medication was considered as the zero level. The subjects took no morning dose on the day when the measurements were made. To avoid the influence of the nasal cycle, the congestion on both sides of the nose was measured. The recordings from each side were added and the sum was divided by two. The nasal mucosa reactivity was estimated by employing the histamine provocation model [13]. With this model the nasal mucosa response to increasing concentrations of histamine is recorded with rhinostereometry. Three concentrations were used: 1, 2 and 4 mg histamine/ml. The solutions (0.14 ml) were applied with a syringe to the nasal mucosa over the medial surface of the inferior turbinate under visual control. Recordings were made 5 min after challenge.

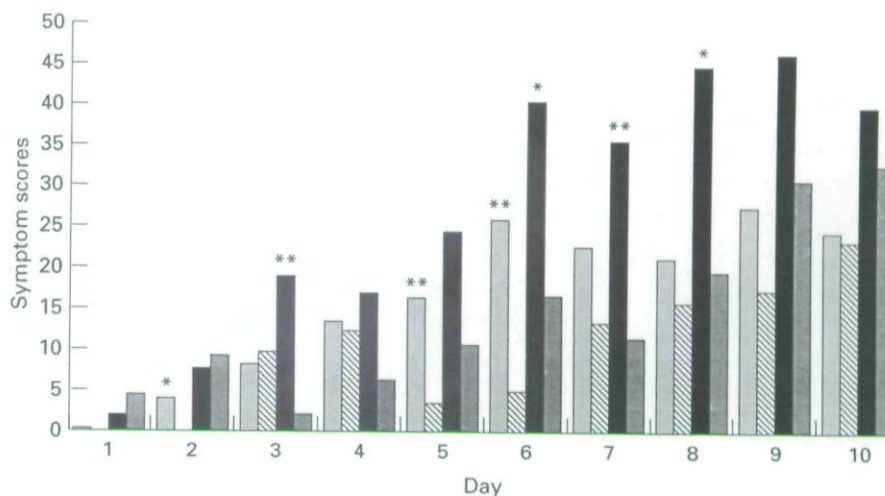
Rhinostereometry is an optical method for measuring congestional changes in the nasal mucosa with high accuracy [14,15]. A microscope is placed on a frame, movable in three angular directions, thus defining a three-dimensional coordinate system, in which the nasal mucosa is placed when the subject to be examined bites down on an individually made tooth splint fixed to the frame. Congestional changes are recorded on a horizontal mm scale in the eyepiece.

Results

Nineteen of the subjects completed the study since one of them had to go on a trip during the trial. Ten subjects were treated with oxymetazoline nasal spray without benzalkonium chloride and nine subjects were treated with oxymetazoline nasal spray with benzalkonium chloride. None of them complained of nasal secretions, dry nose or a common cold.

From the third day of medication the mean symptom scores were higher in the group treated with oxymetazoline containing benzalkonium chloride, in the morning and the evening. The differences on some days were small. However, when employing the unpaired *t*-test to analyse the differences between the symptom scores in the two groups, we found significant differences on most of the following days, when the morning and evening symptoms were compared separately (Fig. 1). The mean

Fig. 1. Mean symptom scores estimated on a visual analogue scale by healthy volunteers treated with a nasal decongestive spray. One group received oxymetazoline nasal spray with benzalkonium chloride (BC) and one group received oxymetazoline nasal spray without benzalkonium chloride. Symptom scores were estimated in the morning and in the evening just before the nasal spray was administered. (* $P < 0.05$, ** $P < 0.01$). ▨. Morning with BC. ▩. Morning without BC. ■. Evening with BC. □. Evening without BC.



congestion after 10 days of medication was 0.733 mm in the group treated with oxymetazoline nasal spray with benzalkonium chloride. Comparison before and after treatment, showed a significant increase in swelling after treatment, as evaluated with the paired *t*-test ($P < 0.001$). In the group treated with oxymetazoline nasal spray alone, the mean congestion after 10 days' treatment was only 0.205 mm, which was not significant ($P > 0.05$) (Fig. 2). Further comparison of the two groups showed significantly greater degree of swelling in the group treated with the oxymetazoline nasal spray

with benzalkonium chloride, using the unpaired *t*-test ($P < 0.05$). Comparison of the reactivities before and after treatment between the two groups at each challenge level showed no significant differences, using the unpaired *t*-test. There were no differences between the reactivities in the two groups when they were compared before and after treatment with the paired *t*-test. (Fig. 3a & b).

Discussion

The nasal mucosa surface position before this 10 day trial was back to the baseline position recorded before the 4 week study, which accords to the results from a previous study [16], where the nasal mucosa positions were back to baseline position 2 weeks after a long-term treatment with nasal decongestant spray.

In the present study it was found that the group treated with oxymetazoline nasal spray containing benzalkonium chloride developed nasal mucosa swelling during the period of 10 days, both when estimated with symptom scores and when measured with rhinostereometry. The group treated with oxymetazoline nasal spray alone developed no significant nasal mucosa swelling, and there was a significant difference between the two groups both in the estimated symptom scores for mucosa congestion and in measurements with rhinostereometry. However, there was no increase in reactivity in either group and no difference between the two groups. The results concerning reactivity accord with the diary cards on which the subjects reported no nasal discharge, as an indication of the absence of an influence on reactivity. In the 4 week study performed 3 months before this study, increased reactivity was noted in both of the groups. Since there were no differences in the reactivity between the two groups, this would suggest that the increased reactivity was caused by oxymetazoline and not by benzalkonium chloride. The results of this study

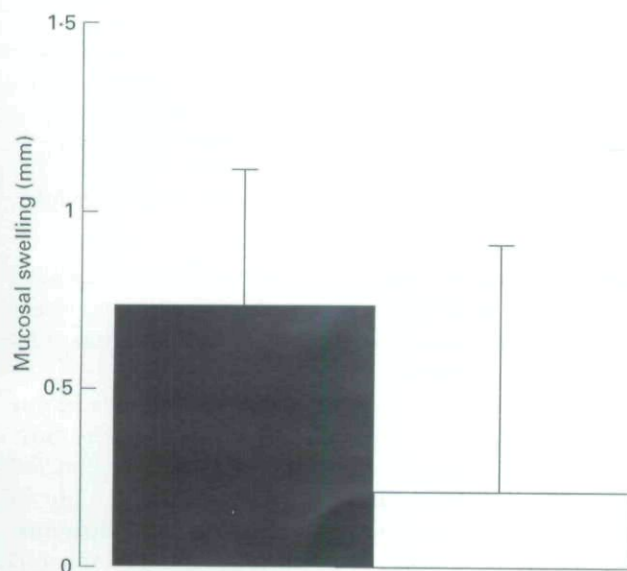


Fig. 2. Mean mucosal swelling $\pm$ SD, as measured with rhinostereometry, after 10 days of treatment with nasal decongestive spray. One group was treated with oxymetazoline nasal spray with benzalkonium chloride (BC) and one group treated with oxymetazoline nasal spray without benzalkonium chloride. ■. With BC. □. Without BC.

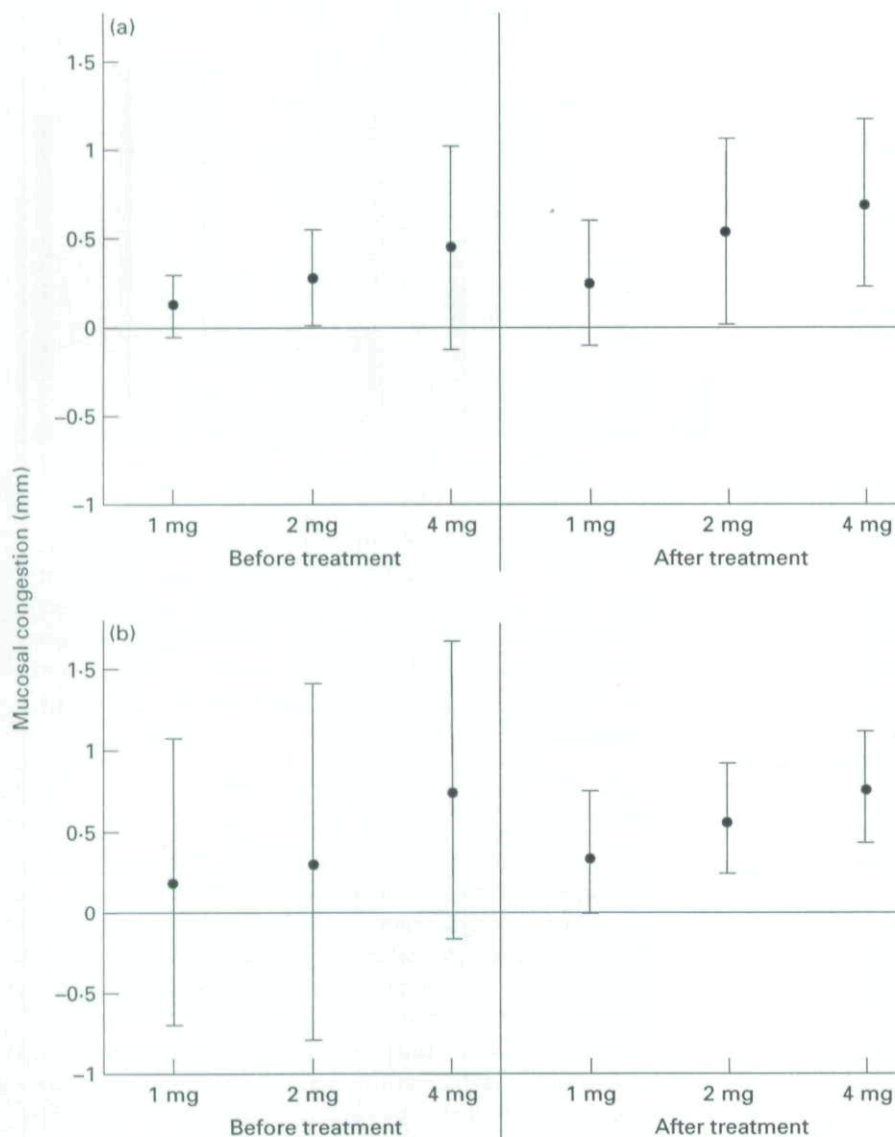


Fig. 3. (a) Mean response $\pm$ SD of the nasal mucosa as measured with rhinostereometry, 5 min after challenge with histamine chloride, 1 mg/ml, 2 mg/ml and 4 mg/ml, before and after treatment with oxymetazoline nasal spray without benzalkonium chloride during 10 days. (b) Mean response $\pm$ SD of the nasal mucosa, as measured with rhinostereometry, 5 min after challenge with histamine chloride, 1 mg/ml, 2 mg/ml and 4 mg/ml, before and after treatment with a combination of oxymetazoline nasal spray with benzalkonium chloride during 10 days.

indicate that the oxymetazoline effect is not, however, long-lasting.

In a previous study [16] of healthy volunteers who used nasal spray containing both oxymetazoline and benzalkonium chloride during 1 month, the nasal mucosa swelling was measured by rhinostereometry and the stuffiness was estimated after 10 and 30 days. The recordings after 10 days showed no significant nasal mucosa swelling nor did the patient's estimate show nasal stuffiness. The main difference between that study and the present one is, that the latter study was performed 3 months after a 4 weeks treatment. In the present study, it is only the group treated with oxymetazoline nasal spray with benzalkonium chloride that developed more nasal stuffiness, as estimated by symptom scores as well as increased nasal mucosa swelling, when measured with

rhinostereometry. The latter finding is highly suggestive of a long-term effect on the nasal mucosa of treatment with oxymetazoline nasal spray in combination with benzalkonium chloride.

The development of nasal mucosa swelling may be due to vasodilatation or to interstitial oedema. The nose has a reflex pathway consisting of afferent unmyelinated c-fibres and efferent parasympathetic nerves [17,18]. In the cat parasympathetic activation results in atropine-resistant vasodilatation in the nasal mucosa [19] suggesting that VIP (vasoactive peptide) may be a mediator. A report concerning patients with mild asthma who were studied during provocation with benzalkonium chloride suggested that benzalkonium chloride might cause bronchoconstriction via adapted nerve endings of unmyelinated c-fibres [11]. Our study indicates that this

may also be a possible explanation of the effects of benzalkonium chloride in the nose, and would suggest the occurrence of vasodilatation. The effects of benzalkonium chloride on the permeability of the rabbit cornea have been studied [10]. They reported lysis of the cell membranes with subsequent leakage of a tracer into and underneath the superficial cells, after treatment with benzalkonium chloride. Furthermore, the degree of cellular destruction depended upon the exposure-time. If benzalkonium chloride acts thus on the capillary endothelia in the nose, oedema may develop. The design and the results of our study do not show whether the congestion developed is due to oedema or to vasodilatation. However, previous studies reported that the decongestive capability of causing maximum nasal mucosa decongestion did not change in healthy volunteers, after long-term treatment with nasal decongestants [5,16,20] and according to these studies, it is probable that vasodilatation is responsible for the increase in nasal mucosa congestion found in the present study.

In conclusion, benzalkonium chloride in nasal decongestive sprays seems to have a long-term effect on the nasal mucosa, at least for three months, and long-term treatment with nasal decongestive sprays, especially when they contain benzalkonium chloride, should be avoided. Furthermore, it seems very important that patients who once have overused nasal decongestive sprays should be very careful about using them again, and according to our results, they should not be used for more than 3 days. Our results call into question whether long-term studies on the effects of nasal decongestants composed of a combination of vasoactive drug and benzalkonium chloride are ethically acceptable.

Acknowledgements

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