

Benzalkonium chloride in a decongestant nasal spray aggravates rhinitis medicamentosa in healthy volunteers

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Summary

A randomized double-blind parallel study with 20 healthy volunteers was performed to research the effect of a preservative in a decongestant nasal spray on the development of rhinitis medicamentosa. Ten subjects received oxymetazoline nasal spray with benzalkonium chloride and the others used oxymetazoline nasal spray without the preservative three times daily for 30 days. 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) in the morning and the evening just before using the nasal spray. After 30 days, rebound swelling and nasal stuffiness were found in both groups. In the group receiving oxymetazoline nasal spray with benzalkonium chloride the mean rebound swelling was 1.1 mm and the estimated mean evening symptom score for nasal stuffiness was 43. In the group without benzalkonium chloride the corresponding variables were significantly less marked, with a mean rebound swelling of 0.5 mm ($P < 0.05$) and a mean evening symptom score of 25 ($P < 0.05$). The increase in histamine sensitivity in both groups was interpreted as a sign of nasal hyperreactivity. A new type of nasal spray bottle was used that has been shown to prevent bacterial contamination. In conclusion, the long-term use of benzalkonium chloride in oxymetazoline nasal spray accentuates the severity of rhinitis medicamentosa in healthy volunteers.

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Introduction

Therapy-resistant nasal blockage due to overmedication with nasal decongestants, a well-known entity from the beginning of this century [1], is referred to as rhinitis medicamentosa. With modern decongestants, such as oxymetazoline, the risk of rhinitis medicamentosa has been considered to be much smaller or even non-existent [2]. However, in a recent study, we found that healthy volunteers who were given oxymetazoline nasal spray with benzalkonium chloride (BC) for 30 days developed rebound swelling and increased histamine sensitivity as a sign of rhinitis medicamentosa [3,4]. Since 1981, it has been possible to purchase single-dose preparations of oxymetazoline nasal drops over the counter in Sweden. This has increased the sales, particularly after 1989 when

multi-dose preparations of oxymetazoline and xylometazoline nasal sprays also became available [5]. Unlike single-dose preparations all multi-dose preparations of nasal decongestants on the Swedish market contain BC. In the last few years the number of reports of patients suffering from rhinitis medicamentosa has increased [6] and the roles of vasoconstrictors and preservatives in this regard have therefore been discussed.

The preservative BC is a quaternary ammonium compound which acts by damaging the cell wall of the micro-organisms [7]. Because of its marked bacteriocidal effect, BC is used in many multi-dose preparations, such as nasal drops and sprays, eye and ear drops and in nebulizer solutions for the lungs. The use of BC has been questioned, because of its reported bronchoconstrictive effect [8,9] and its ciliary toxicity, as shown in many *in vitro* studies [10–12]. It has also been found that BC damages the corneal epithelium by cellular destruction

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[13] and BC-induced contact allergy has been reported in patients with chronic external otitis [14]. Moreover, BC applied to the serosal surface of the intestine of the rat has been shown to injure intramural nerve elements selectively, thereby causing aganglionosis [15]. Regarding the compounds in nasal decongestant preparations, such as oxymetazoline, xylometazoline and BC, deleterious effects of granulocyte chemotaxis and phagocytosis [16,17] and other important functions of defence by the neutrophils [18] have been reported *in vitro*. The effects of such compounds on the mucociliary transport rate *in vivo* are not clear, since conflicting results have been noted [19–21] and it is difficult to evaluate the significance of these findings clinically. Therefore, *in vivo* studies are needed to evaluate the effects of the overuse of decongestive nasal sprays with and without BC.

The aim of the present study was to investigate whether the use of BC in oxymetazoline nasal spray had any effect on the development of rhinitis medicamentosa. A further aim was to determine whether the previously-found rhinitis medicamentosa was reproducible in another group of subjects.

Materials and methods

Twenty volunteers, 16 women and four men, 22–41-years-old, entered the trial, which was performed during the autumn of 1993. All of them were healthy and not on drugs. They had no history of allergy or other rhinological diseases. On rhinoscopy, no signs of mucosal inflammation were noted. They were students or staff members of the Department. The study was designed as a parallel randomized, double-blind trial, with 10 volunteers in each group.

The subjects were divided into two groups that were randomly selected for treatment with Nezeril® oxymetazoline (0.5 mg/ml) nasal spray, 0.1 ml in each nostril three times daily for 30 days, with or without 0.1 mg/ml BC. The study drugs, all in a new type of nasal spray bottle shown to withstand bacterial contamination, were supplied by Draco Läkemedel AB, Lund, Sweden. The swelling of the nasal mucosa was recorded with rhinostereometry. This technique first described in 1982 [22] is an optical, direct, non-invasive method designed to measure nasal mucosal swelling with a high degree of accuracy. The aim of the method is to allow topographic measurements within the nose without manipulation of the nasal structures. Topographical measurements require a defined fixed point to which the position of any object studied can be related. In rhinostereometry, the origin of a three-dimensional coordinate system is used as the fixed point. The apparatus consists of a surgical microscope placed on a micrometer table fixed

to a frame. The microscope can be moved in three angular directions establishing the coordinate system. To permit measurements, the nasal cavity must be placed in the coordinate system in such a way that it resumes the same position with a high degree of precision upon repeated measurements. This is achieved by immobilizing the subject's head and attaching it to the frame by an individually made tooth-splint. The objective and eyepiece of the microscope are chosen to give the microscope a short depth of focus. The eyepiece is equipped with a horizontal mm-scale which is used to measure the position of the nasal mucosa, i.e. mucosal swelling. Since the microscope has a short depth of focus, the mucosal surface position can be recorded in the plane of focus along the mm-scale. Thus, the mucosal area studied during the measurements is restricted to almost a line. With this method, the observed area of measurement can be re-identified with a high degree of accuracy in the same individual at times with the subject as his own control. In registrations of positional changes, the accuracy of the method is 0.2 mm. With respect to the systematic error, the true variation of the mucosal surface is 97–102% of the measured variation.

When the study began and before the treatment with the nasal spray, the baseline position of the nasal mucosa was determined. This was done by making repeated recordings of the inferior concha in both nasal cavities at noon, after an acclimatization period of 30 min. The nasal mucosa was then 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 this solution was deposited on the mucosa of the medial wall of the interior concha on one side of the nose during visual inspection with 5 min between doses. Just before increasing the dose on the challenged side, the position of the surface was determined, i.e. 5 min after each provocation.

The subjects then began to use their nasal spray three times daily. After 30 days on the drug, the morning spray was discontinued. At noon, 14–17 h after the last dose the night before, the mucosal baseline positions were recorded first and then a histamine provocation was performed, as before. When the study was performed, the new type of nasal spray bottle used in the study had not yet been approved by the Medical Products Agency in Sweden. Therefore, we were obliged to send all of them to a laboratory for bacteriological analyses. Throughout the month of treatment, all subjects filled in a diary card in the morning and the evening, just before using the nasal spray. Nasal stuffiness was estimated on a visual analogue scale (0–100 symptom scores). Each day they noted whether they had a dry nose, a runny nose, irritation, nasal bleeding or a cold.

Trends were analysed using means and, for further

statistical analyses, paired and unpaired *t*-tests were employed. When the mucosal swelling due to the nasal spray was calculated, the mean value of the mucosal baseline position on each side of the nose before the course of treatment was started served as the reference position. The degree of mucosal swelling following the histamine challenges was assessed from the data in only the challenged nasal cavity, baseline values on days 0 and 30 being used as references. The daily symptom score during each week was added and the mean value for the week was calculated for every subject. The mean nasal stuffiness in the group was then calculated for each week. The study was approved by the local Ethics Committee.

Results

All subjects completed the study. In the group receiving oxymetazoline nasal spray with BC, the mucosal surface position increased in nine subjects and ranged from 0.8 to 2.1 mm after 30 days on the drug. In the remaining subject, the surface position showed a decrease of 0.65 mm. The mean increase in mucosal swelling (1.14 mm) was significant ($P < 0.01$) (Fig. 1). The mean estimated nasal stuffiness in the morning was a symptom score of 3 in the first week, 9 in the second, 18 in the third and 29 in the fourth week (Fig. 2). The corresponding symptom scores for stuffiness in the evening were 5, 18, 31 and 43 (Fig. 3). The increases in morning and evening

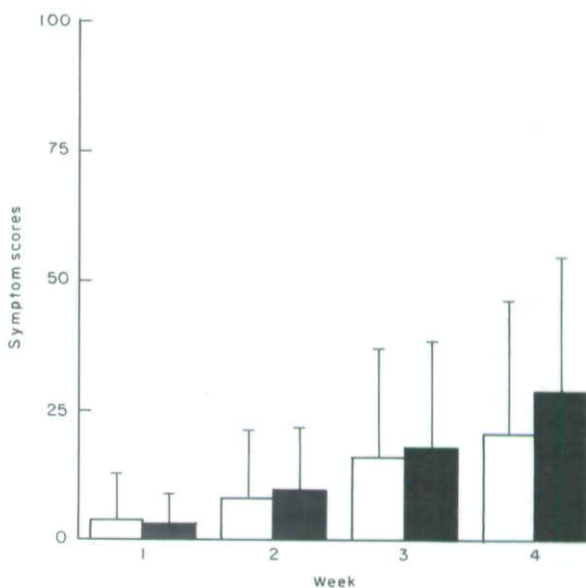


Fig. 2. Morning nasal stuffiness during 4 weeks' treatment with oxymetazoline nasal spray with and without BC, respectively (mean $\pm$ SD). ■. With BC. □. Without BC.

nasal stuffiness were significant from the second week of drug treatment ($P < 0.05$). All subjects had a mucosal swelling below 0.5 mm after challenge with 1.0 mg/ml and 2.0 mg/ml of histamine before starting the course of treatment. After 30 days on the drug, six subjects had a mucosal swelling above 0.5 mm after challenge with

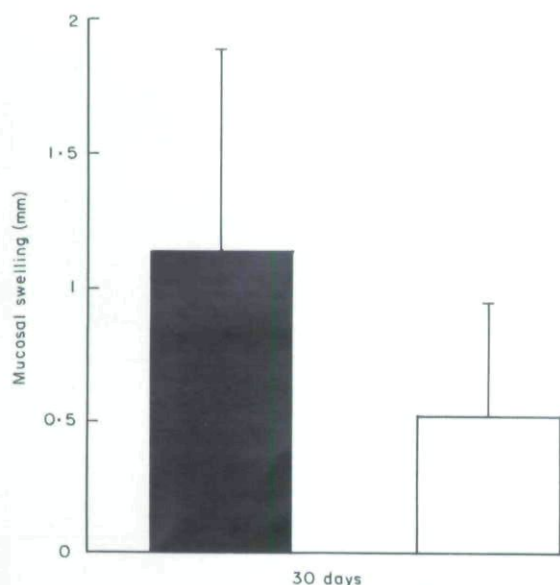


Fig. 1. Mucosal swelling of both inferior conchae after 30 days on oxymetazoline nasal spray with and without BC, respectively (mean $\pm$ SD). Baseline values were set at zero before starting the course of treatment. ■. With BC. □. Without BC.

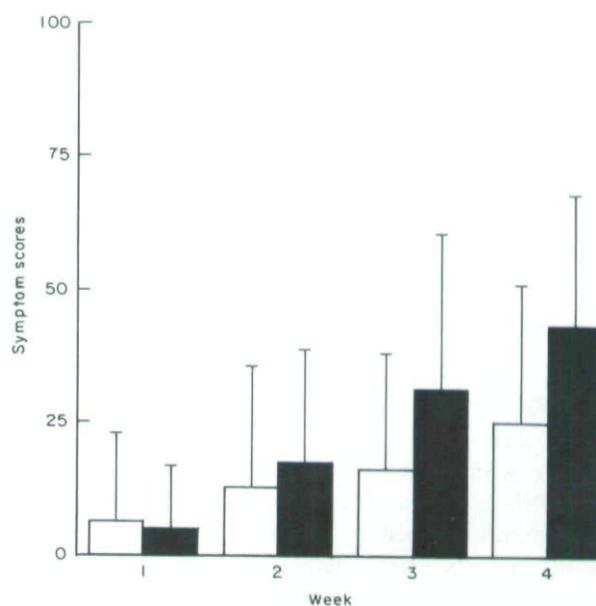


Fig. 3. Evening nasal stuffiness during 4 weeks' treatment with oxymetazoline nasal spray with and without BC, respectively (mean $\pm$ SD). ■. With BC. □. Without BC.

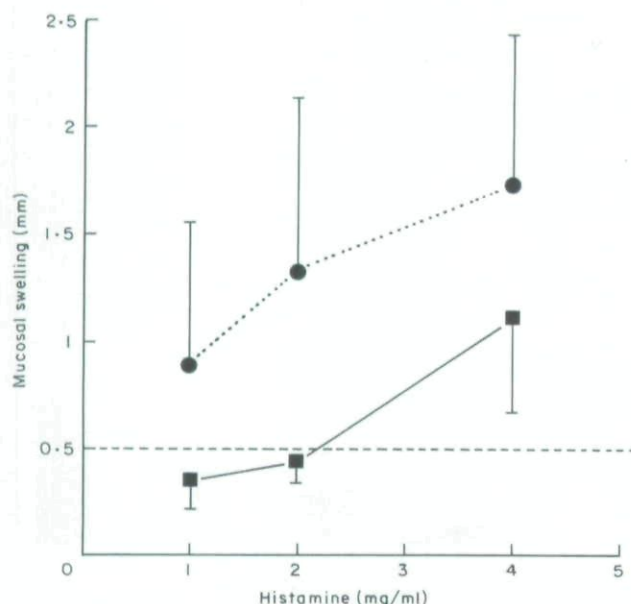


Fig. 4. Mucosal swelling 5 min after histamine challenges before and after 30 days on the drug in the group receiving oxymetazoline nasal spray with BC. Baseline values were set at zero on day 0 (—■—) and day 30 (···●···), respectively (mean $\pm$ SD).

1.0 mg/ml and nine subjects after 2.0 mg/ml. With all three histamine provocation doses, the mean mucosal swelling in the group was greater than that at the start of the medication (1.0 mg/ml $P < 0.05$, 2.0 mg/ml $P < 0.01$, 4.0 mg/ml $P < 0.05$) (Fig. 4).

In the group receiving oxymetazoline nasal spray without BC, the position of the mucosal surface had increased from 0.15 to 1.3 mm in nine subjects and decreased to 0.2 mm in one subject after 30 days on the drug. The mean increase in mucosal swelling was significant (0.52 mm) ($P < 0.01$) (Fig. 1). The mean estimated symptom score for nasal stuffiness in the morning were 4 in the first week, 8 in the second, 16 in the third and 20 in the fourth week (Fig. 2). The corresponding symptom scores for nasal stuffiness in the evening were 7, 13, 16 and 25 (Fig. 3). The increases in morning and evening nasal stuffiness were significant from the second week of drug treatment onwards ($P < 0.05$). Before starting the course of treatment, all subjects had a mucosal swelling below 0.5 mm after challenge with 1.0 mg/ml and 2.0 mg/ml of histamine. After 30 days on the drug, six subjects had a mucosal responsiveness exceeding 0.5 mm following 1.0 mg/ml and 10 subjects after challenge with 2.0 mg/ml. The mean mucosal swelling in the group was greater than before the start of the drug treatment with all three histamine provocation doses (1.0 mg/ml $P < 0.01$, 2.0 mg/ml $P < 0.01$, 4.0 mg/ml $P < 0.05$) (Fig. 5).

Unpaired *t*-tests were employed to compare the results in the two groups. After 30 days of drug treatment, a more pronounced mucosal swelling was found in the group receiving oxymetazoline with BC ($P < 0.05$). In this group, the mean estimated stuffiness was greater in the evenings during the fourth week of drug treatment ($P < 0.05$). There was no difference in mucosal swelling between the two groups at any histamine provocation level before and after drug treatment. Six subjects reported a dry nose, four a runny nose, two had a common cold and two subjects had nasal bleeding during their month on medication. Regarding these symptoms, no differences were found between the two groups. There was no growth of gram-negative bacteria either in the bottles or the nasal adapters, but low amounts of cocci were found in the nasal adapters. These findings were in accordance with the results of another clinical study designed to evaluate microbial contamination of the new product after conventional usage. The latter study was included in the documentation of the product approved by the Medical Products Agency in Sweden.

Discussion

There is an evident risk that certain types of gram-negative bacteria will grow in nasal spray solutions without BC. Therefore, when evaluating the results of this study it was important to ensure that none of the

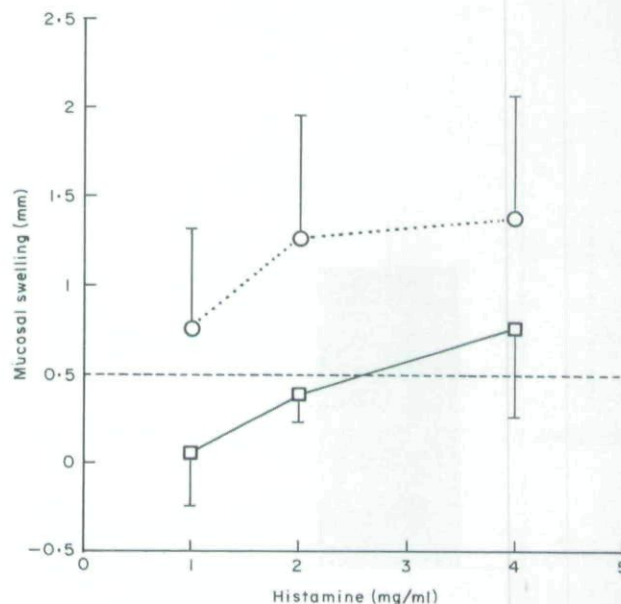


Fig. 5. Mucosal swelling 5 min after histamine challenges before and after 30 days on the drug in the group receiving oxymetazoline nasal spray without BC. Baseline values were set at zero on day 0 (—□—) and day 30 (···○···), respectively (mean $\pm$ SD).

volunteers had been exposed to a microbiologically-contaminated nasal spray during the study. Moreover, the nasal spray solution without BC could have been damaged if it had not been protected by the construction of the bottle, since a large variety of micro-organisms have been found in the nasal mucosa of healthy volunteers [23]. In a study aiming to investigate whether mucosal swelling can be found after the prolonged use of a vasoconstrictor, one must use a reproducible technique to measure this swelling and obtain a reliable, individual value before drug treatment. To determine the amount of mucosal swelling, the mean changes in the mucosal positions of both nasal cavities was used. This was done to take into account the occurrence of reciprocal swelling in the nose [24]. The measurements were made only once before the drug treatment started, since healthy subjects show no significant day-to-day variations [3].

This study confirmed our previous results concerning rebound swelling after treatment with the combination of oxymetazoline and BC for 30 days. However, rebound swelling was also found in the group receiving oxymetazoline alone. The mucosal swelling and nasal stuffiness were significantly less marked in the group receiving oxymetazoline alone than in the group receiving oxymetazoline and BC. In the latter group, the nasal stuffiness was greater, especially in the evening, throughout the month of medication. This is of clinical importance because nasal stuffiness at night interferes with sleep.

The pathophysiology of the mucosal swelling in rhinitis medicamentosa is not understood. The rebound swelling could be due either to vasodilation or interstitial oedema. In a study of patients with vasomotor rhinitis, increased nasal airway resistance was found after a 3-week use of xylometazoline nasal spray with BC. Moreover, the decongestive effect of the drug was incomplete. Since interstitial oedema does not respond to treatment with alpha agonists, it was suggested that rhinitis medicamentosa may be due to oedema [25]. In another investigation, patients were studied during and after an overuse of nasal decongestants 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 vasodilation [26]. Furthermore, rebound swelling was found in healthy subjects who received oxymetazoline nasal spray for 30 days. Since the decongestive effect was unchanged throughout the month of medication, the swelling was ascribed to vasodilation rather than to oedema [3].

Hitherto, it has always been assumed that the vasoconstrictor alone is responsible for the development of rhinitis medicamentosa. The results of this study show

that BC potentiates the effect of oxymetazoline. The design of this study does not answer the question whether BC alone causes rebound swelling.

In lung medicine, BC is added to nebulizer solutions and in asthmatic patients it acts as a potent bronchoconstrictor. It has been suggested that the bronchoconstriction results from vagal reflex mechanisms by a direct action of BC on receptors of myelinated nerves and nerve endings on non-myelinated C-fibres as well as by a release of mediators from mast cells [8,9,27,28].

Regarding the nose, it has been proposed that non-myelinated C-fibre afferents containing vasoactive peptides may be involved in the pathophysiology of non-allergic nasal hyperreactivity [29] and that activation of non-myelinated C-fibres induces nasal blockage [30]. If BC has the same effects on the nasal mucosa as in the bronchus, the rebound swelling seen in this trial can be explained. Long-term exposure to irritants may induce alteration of the vasomotor tone with increased parasympathetic activity, which results in vascular dilatation, increased permeability, oedema formation and nasal blockage [31]. BC may be such an irritant, either alone or with oxymetazoline.

The increase in the number of patients with rhinitis medicamentosa in Sweden may be due to the increase in the total use of decongestants. However, in accordance with the results of this study, it may also be due to the switch from the use of preservative-free to BC-preserved solutions.

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