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A time-dose study of the effect of topical ipratropium bromide on methacholine-induced rhinorrhoea in patients with perennial non-allergic rhinitis

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A time-dose study of the effect of topical ipratropium bromide on methacholine-induced rhinorrhoea in patients with perennial non-allergic rhinitis

Intranasal application of the anticholinergic drug, ipratropium bromide, is used for the treatment of watery rhinorrhoea. We have performed a time-dose study of ipratropium bromide in patients with perennial non-allergic rhinitis, using rhinorrhoea, induced by nasal methacholine challenge, as a laboratory model. Two doses of ipratropium bromide, 40 μg and 80 μg, delivered from a pressurized aerosol, were both very effective, reducing the volume of methacholine-induced secretion by 85 to 95%. The maximum effect lasted for at least 4 h and then slowly diminished. A significant effect was demonstrable for 12 h with 40 μg and for 18 h with 80 μg ipratropium bromide. These results from a laboratory challenge study indicate that the presently used frequency of ipratropium bromide, namely four times daily, may not be necessary in many patients. Perhaps once in the morning, followed by an as-needed medication, will be a better way to use intranasal ipratropium bromide in perennial non-allergic rhinitis.

Keywords *ipratropium bromide anticholinergic medication rhinitis rhinorrhoea*

Ipratropium bromide is an anticholinergic agent with topical activity in the respiratory tract. It was first used as a bronchodilator, and was later introduced for the treatment of watery rhinorrhoea in perennial non-allergic rhinitis, and in the common cold.[1,2,3]

It is possible, in the laboratory, to study the duration of the anti-rhinorrhoea effect of ipratropium bromide, when methacholine-induced rhinorrhoea is used as the effect parameter. A study of normal volunteers showed that pretreatment with ipratropium bromide markedly inhibits the response to methacholine and that the effect lasts for at least 6 to 8 h.[4]

Clinical trials in patients with perennial rhinitis were therefore performed with medication four times daily. Clinical experience, however, has now indicated that such frequent medication may not be necessary in many patients and that unnecessary medication can induce an unpleasant sensation of nasal dryness.[5,6,7]

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As time-effect studies of ipratropium bromide have only been performed in normal subjects we have now undertaken a laboratory study in patients with perennial non-allergic rhinitis, using methacholine-induced rhinorrhoea as the effect parameter, in order to estimate whether it may be possible to reduce the dose-frequency of ipratropium bromide. We studied the duration of the effect of two dosages of ipratropium bromide in the patients using the same design as originally used in the study of normal volunteers.[1]

Patients and methods

PATIENTS

Seven patients (three women and four men) volunteered to take part in the study, but one woman dropped out due to severe rhinitis symptoms. Their mean age was 42.9 yr (range 24–53). All volunteers had a more than 1 yr history of perennial rhinitis with watery nasal discharge, lasting for more than 1 h per day, as the predominant symptom. They were not on any other medication. Skin tests to ordinary inhaled

allergens were negative, and rhinoscopy did not reveal major abnormalities. All volunteers gave informed consent to the study protocol which was approved by the Ethical Committee of Copenhagen County.

METHACHOLINE CHALLENGE

A solution of methacholine bromide in distilled water was made (concentration 60 mg/ml) every week. It was delivered from a metered-dose pump spray, two puffs of 0.1 ml into each nostril (a total of 24 mg methacholine). The resulting nasal secretions were collected over a 15-min period in a funnel connected to a syringe, as described previously.[1]

TEST MEDICATION

The commercially available freon-propelled ipratropium bromide micronized powder was used, delivering 20 μg per actuation from a pressurized canister (Atrovent Nasal®). The aerosols were delivered coded by Boehringer Ingelheim, Ingelheim, Germany. The patients used two puffs into each nostril, of either placebo/placebo (placebo), placebo/active (40 μg ipratropium bromide) or active/active (80 μg ipratropium bromide).

STUDY DESIGN

In a double-blind, placebo-controlled and randomized design trial each patient pretreated herself/himself with either placebo, 40 μg ipratropium bromide or 80 μg ipratropium bromide, each used 340 min, 1, 2, 4, 8, 12 or 18 h before methacholine challenge. The individual placebo mean value, ranging from 0.40 to 1.29 ml, was used as a 100% reference point for the presentation of the results (see Fig. 1). All volunteers were studied on 19 occasions, with at least one day in between each medication/challenge. By mistake, only ipratropium bromide, 40 μg, was given at the 12-h time-point before challenge.

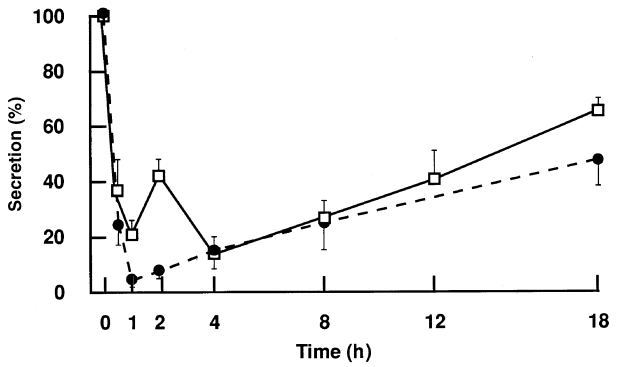

Figure 1. Nasal secretory response to methacholine challenge after pretreatment with ipratropium bromide 40 μg (□) and 80 μg (●), administered at various time-intervals before challenge (mean ± SEM).

STATISTICS

The statistical analyses were performed using the SPSS/PC System installed in an IBM PS-2/50 computer. The difference between secretion volumes on two test days or between two test doses was calculated as a paired *t*-test. To test the hypothesis that several population means were equal (the secretion volumes at different time intervals after medication) analysis of variance (ANOVA) was performed. Scheffe's multiple comparison test was performed in order to identify the differences.

Results

Ipratropium bromide, in both doses, caused a marked, 85–95%, reduction of the secretory response to methacholine (Fig. 1). The maximum effect lasted for about 4 h and thereafter it diminished very slowly. With ipratropium bromide, 40 μg, the effect was significant at 12 h and with 80 μg it was still significant at 18 h after medication. The total secretory response to methacholine, estimated as the area-under-the-curve, was 39% lower following pretreatment with ipratropium bromide 80 μg compared with ipratropium bromide 40 μg ($P > 0.05$).

The repeated methacholine challenges allowed an analysis of the data showing that the nasal responsiveness to challenge with methacholine and to treatment with ipratropium bromide did not change significantly during the entire trial period (data and analyses not presented).

Discussion

The results of ipratropium bromide pretreatment and methacholine challenge of patients with perennial rhinitis, presented in this paper, are similar to the results earlier obtained in normal volunteers.[1] Indeed, the effect of ipratropium bromide in inhibiting methacholine-induced rhinorrhoea seems to be even more long lasting in the patients with rhinitis than in the normal volunteers. An earlier study has shown that ipratropium bromide pretreatment reduces the volume of secretion, produced by methacholine challenge, to the same level in patients and in normal controls. This means that the percentage symptom reduction is larger in the patients than in the normal controls, because the patients produce more secretion in response to methacholine challenge.[4]

The design used in the present study, with only one methacholine challenge and time-interval after medication per day, is very time-consuming and only a few patients can accept this study protocol which necessitates 19 visits. Only six patients were therefore examined, but we feel confident that the results presented in this paper are reliable and reproducible.

Earlier challenge studies of normal volunteers, as well as clinical experience in the treatment of patients, have indicated that the duration of effect of ipratropium bromide pressurized

aerosol is very long, lasting for at least 8 h. However, it was unexpected that, in the present study, an effect of the drug could still be identified 18 h after medication. It is difficult to say whether the marked diurnal variation in rhinitis symptoms can have had any influence on these results and neither can we be certain that the medication in all instances has been taken at the correct point of time, because patients, for practical reasons, had to administer the aerosol at home. Nevertheless we find that our results showing a very long-lasting effect of ipratropium bromide as a pressurized aerosol are reliable and that this information may be useful in future recommendations of a less frequent dosing of patients with perennial non-allergic rhinitis.

The results in the studies mentioned above were all obtained with ipratropium bromide administered as a pressurized aerosol. An aqueous solution of ipratropium bromide is now marketed in the USA and there are a number of observations which all indicate that there are differences between these two formulations with regard to potency, duration of action, and perhaps adverse effects. In the only direct comparison[8] we have recently found a significantly more pronounced and longer-lasting action of the pressurized aerosol than of the aqueous spray in inhibiting methacholine-induced rhinorrhoea in normal volunteers. Using a similar study design, Wagenman *et al*.[9] found the aqueous spray to have a relatively short time-period of efficacy as compared to our results with the pressurized aerosol.

The main message of the present study is that the very long duration of action of ipratropium bromide on methacholine-induced rhinorrhoea, earlier found in normal volunteers, also applies to patients with rhinitis. Our results, therefore, question the necessity of using ipratropium bromide four times daily as a routine. Clinical experience has suggested that this practice results in local adverse effects which may be diminished if the dose and frequency of medication are adjusted to the individual need and the marked diurnal variation of rhinorrhoea.[10] We hypothesize that the best way to use ipratropium bromide is to give a high dose early in the morning and thereafter only to use the medication on an as-needed basis, especially before exposure to known trigger factors.

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