

Ipratropium in the Treatment of Patients with Perennial Rhinitis

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Rhinorrhea is due to increased parasympathetic activity. This study was undertaken in order to study the applicability and efficacy of ipratropium, an anticholinergic drug, in patients with perennial rhinitis seen in an allergy clinic. Thirteen patients were included in the double-blind, cross-over study following screening with methacholine test. The number of paper tissues used during the period with active drug decreased significantly. Other variables did not change significantly. Eight patients preferred the active drug. The findings of this study suggest that ipratropium bromide is a valuable addition in the treatment of patients with perennial rhinitis with rhinorrhea.

Key words: ipratropium; methacholine test; perennial rhinitis.

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In patients with perennial rhinitis, where no allergy can be demonstrated, either nasal congestion or rhinorrhea can be the dominating symptom. When congestion dominates, topical corticosteroid treatment may be helpful, but in rhinorrhea this type of drug is usually of little help. Antihistamines may be tried, but the problem of sedation limits their use.

Rhinorrhea is considered to be due to increased activity of the parasympathetic innervation of the submucosal glands of the nasal mucosa (5). Treatment with anticholinergic drugs is therefore logical. Borum (1, 2) has shown that ipratropium applied locally in the nose is effective in perennial rhinitis with rhinorrhea.

This investigation was undertaken in order to study the applicability and efficacy of the drug in patients with perennial rhinitis seen at an allergy clinic. An effort was also made to individualise the dose.

PATIENTS

Thirteen patients referred to the Allergy Clinic of the Department of Thoracic Medicine,

Karolinska Hospital, who had perennial rhinitis with dominating rhinorrhea and in whom no atopic disease could be demonstrated, were included in the study: five men and eight women, aged between 21 and 61 years.

Screening included history, prick test with 15 standard allergens, determination of the total IgE-level, total blood eosinophil count and the radio-allergo-sorbent test (RAST) for suspected allergens. In cases with doubtful results, provocation tests were used. Further investigations were rhinoscopy, X-ray of the nose and paranasal sinuses and a methacholine test in the nose. Patients with nasal polyposis or congestion were excluded. No patient was pregnant.

Most of the patients had stated that their attacks of rhinorrhea lasted for at least 1 h and those with shorter attacks had repeated attacks throughout the day. They had attacks of sneezing, mostly 1-5 sneezes in a row.

All drugs that might influence the nasal mucosa, such as antihistamines, steroids, anticholinergics, antidepressants and neuroleptics, were withdrawn during the whole study, from 3 days before the first methacholine test until the

completion of the second 3-week period of the study.

METHODS

The methacholine test

Methacholine bromide was dissolved and diluted in sterile water in the following concentrations: 7.5 mg/ml, 15.0 mg/ml, 30 mg/ml, 60 mg/ml and 120 mg/ml. Methacholine dilutions were freshly prepared by the hospital pharmacy and were not used if they were older than 1 week. 0.4 ml of each concentration was given during a few seconds, half in each nostril, initially with a De Vilbiss No. 15 insufflator, later with a plastic cannister identical to those used for Lomudal Nasal spray®. Immediately after the insufflation, the patient kept his head bent forward for 15 min. The number of sneezes and the volume of nasal secretion collected via a small funnel into a syringe during these 15 min were recorded. The volume of secretion was considered to fall within normal limits if it was less than the amount of secretion $\pm$ SEM found by Borum (1) in 20 normal subjects.

Patients falling within the normal limits were considered unsuitable for the study and patients whose secretion exceeded the upper limit were subjected to repeat methacholine tests after pretreatment with ipratropium (Atrovent®) in order to establish the optimum individual dose of the active substance. The doses of ipratropium used were 20 µg in each nostril, 40 µg in each nostril and 60 µg in each nostril. The pretreatment dose that blocked the nasal secretion so that it was within the normal limits found by Borum, was considered to be the optimum dose of the active substance for that patient.

Symptom recording

The patient recorded the following symptoms at the end of every day on a record sheet: the number of hours of running of the nose, the number of sneezes, the number of paper tissues used, the degree of congestion rated on a scale 0–3. The patients were instructed to use

each tissue once only. Used tissues were to be collected and brought back to the clinic at the end of the first, fourth and seventh week together with the completed record sheets.

Double-blind cross-over study

The study was designed as a double-blind cross-over study. During the first week, no intra-nasal aerosol was given (control period). Placebo and ipratropium aerosols were randomly allocated to each patient, to be used during the first or the second 3-week period. The aerosols were delivered coded by Boehringer Ingelheim. A nasal adaptor was supplied separately.

After completing the seventh week the patient was interviewed about which period he had preferred.

Evaluation

The paper tissues returned to the clinic were counted for the first four patients and found to agree extremely well with the numbers recorded by the patients. The counting was therefore omitted during the rest of the study. All records were collected until the end of the study, when the code was broken and the statistical evaluation was done. Wilcoxon's signed rank test was used for evaluation of differences.

RESULTS

Routine tests

The mean total blood eosinophil count was $186 \times 10^6/l$ (range 30–330). The mean total IgE-level was 62 (kU/l) (range 5.9–230 kU/l). The RAST-test was negative in all cases. Single positive reactions equivalent to that to histamine were seen in the prick tests in two patients. Nasal provocation tests with the corresponding allergens were negative. The history was negative in both cases, and thus no atopy could be demonstrated. The prick tests were negative in the other patients. In one patient with a significantly raised IgE-level the standard allergens all gave negative results in the prick tests as well as

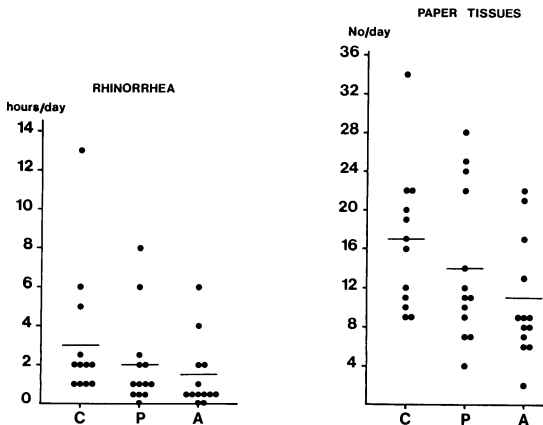


Fig. 1. Number of hours/day of rhinorrhea (left) and of paper tissues/day (right) during the control (C), placebo (P) and ipratropium (A) periods.

in the RAST. The history did not give any clue as to a specific allergen, although the patient had eczema and swellings around her eyes as well.

Methacholine nasal test

The amount of secretion collected after methacholine challenge was above normal limits in all 13 patients. In four patients 20 µg of ipratropium in each nostril was sufficient to block the methacholine-induced rhinorrhea, two needed 60 µg and in the remaining seven a dose of 40 µg in each nostril was sufficient. All the challenges were performed by a trained technician (Mrs Margit Östlund).

Double-blind cross-over study

Rhinorrhea. During the control week the mean period of rhinorrhea recorded was 3 h/day, during the placebo period 2 h/day, and during the ipratropium period 1.5 h/day. The differences are not statistically significant (Fig. 1).

Number of paper tissues. Since each paper tissue was to be used only once, the number of paper tissues indicates how many times the patient felt the need to wipe his or her nose. During the control period a mean of 17 paper tissues/day were used, during the placebo period 14 and during the ipratropium period 11. The differences between the control period and ipra-

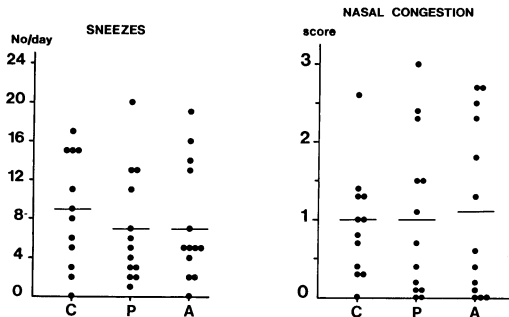


Fig. 2. Mean number of sneezes/day (left) and mean daily score of nasal congestion (right) during the control (C), placebo (P) and ipratropium (A) periods.

tropium as well as between placebo and ipratropium are significant ($P < 0.01$) (Fig. 1).

Sneezing. A mean of 9 sneezes per day was recorded during the control week, 7 sneezes per day during the placebo period and 7 sneezes per day during the ipratropium period. The differences are not statistically significant (Fig. 2).

Nasal congestion. The mean congestion score was 1.0 during the control week, 1.1 during the placebo period and 1.1 during the ipratropium period. The differences are not statistically significant (Fig. 2).

Preference. Eight patients preferred the ipratropium period, one preferred the placebo period, three thought both periods were equal and one patient's preference is not known.

Side effects. Five patients complained of nasal irritation and three patients of excessive drying of the nasal mucosa during the Atrovent treat-

ment. The corresponding figures for the placebo treatment were three and none respectively.

DISCUSSION

Patients with perennial rhinitis in whom no atopy can be demonstrated often have a clearly hyperreactive nasal mucosa. The patients in this study complained of symptoms induced by exposure to fresh newspapers, tobacco smoke, cold air and strong perfumes – all indicating a nasal hyperreactivity.

Borum (2) showed that nasal methacholine challenge produced a much more pronounced secretory response in patients with perennial rhinitis than in controls. We used the normal limits found by Borum in 20 normal subjects in order to establish whether a patient had significant rhinorrhea. We found, however, that we had difficulty in getting a defined dose when we used the De Vilbiss No. 15 atomizer. In order for the atomizer to deliver the appropriate dose, the container had to be filled with more than the dose to be applied. Large quan-

tities of the methacholine dilutions were therefore wasted. Later we started using the empty plastic cannisters used for application of Lomudal Nasal spray® in our nasal challenge tests and decided to try them in the methacholine challenge test. We found that it was easier to apply the defined dose with this type of atomizer, and that the amount of methacholine dilution that had to be prepared before each challenge could be reduced considerably.

The number of patients in this study is small. Far-reaching statistical conclusions may therefore not be drawn. One reason for the small differences between the periods may be that the dose of ipratropium used, although sufficient to inhibit methacholine-induced rhinorrhea, was not enough to prevent reflex-induced rhinorrhea, as indicated by findings in the bronchi (4).

The patients' preference and the number of used paper tissues favours the ipratropium treatment. The paper tissues were to be used only once, and therefore probably give a very good indication of the severity of the symptoms in each patient during each period. It is probably more difficult for a patient to make up his mind at the end of the day how many hours his nose has actually been running that day. The number of paper tissues used gives a more objective measure.

Compared to Borum's patients (5) our patients probably had less severe disease. This is illustrated by the number of hours of rhinorrhea during the control and placebo periods, the mean being 3 and 2.5 h/day, whereas Borum's patients had a mean symptom duration of 6 h/day.

One patient, whose rhinorrhea increased during the active drug period, had withdrawn from neuroleptic drugs on account of the study. She also had the highest IgE-level, but no demonstrable atopy. If she is excluded, there is a significant decrease in rhinorrhea (5% level) between the control and the ipratropium period.

The side effects noted during the study were not severe. The drug was well tolerated, and five patients wished to continue the treatment with ipratropium. A few patients, whose symptoms were not continuous, preferred antihistamines even after the study. The most difficult part of the study was the period of 1 + 3 weeks without active treatment. During this period three patients, who had taken antihistamines regularly, experienced increased symptoms from other organs, such as the eyes and the gastro-intestinal tract.

CONCLUSION

Ipratropium bromide is a valuable addition to the therapeutical arsenal for treatment of patients with perennial rhinitis with rhinorrhea as the dominating symptom. In this study, the patients' preference and the symptom intensity, measured as the number of paper tissues used, indicate that the ipratropium treatment was of benefit. Side effects were mostly mild.

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