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Intranasal ipratropium: inhibition of methacholine induced hypersecretion

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SUMMARY

The submucous glands of the nose have an abundant innervation from the parasympathetic nervous system, and rhinorrhea, a symptom of perennial rhinitis, is in all probability caused by an increased activity in these nerves. Pharmacological blockade with atropine-like compounds will therefore be a logical method of treatment.

Rhinorrhoea was brought about in the laboratory in 15 healthy experimental subjects by the intranasal application of methacholine. The experimental subjects were pretreated with Ipratropium (Atrovent®, Boehringer-Ingelheim) or placebo in a double-blind trial and it was found that Atrovent® could effectively inhibit the methacholine induced hypersecretion for up to 6 hours, without local or systemic side-effects. The methacholine induced hypersecretion could also be effectively blocked in 10 patients with perennial rhinitis, and an open clinical study demonstrated that Atrovent® had an effect on the spontaneous rhinorrhoea of these patients.

INTRODUCTION

Colourless rhinorrhoea is a characteristic symptom of perennial rhinitis, the former often being quite annoying for the patient. Nasal hypersecretion is induced directly via autonomic efferent nerve endings of the nasal glands (Eccles and Wilson, 1973; Golding-Wood, 1973) in one type of perennial rhinitis, where hypersecretion is a dominant symptom; in this condition the etiological factor is presumed to be an autonomic imbalance with parasympathetic dominance (Fowler, 1943; Golding-Wood, 1961; Krajina, 1970). The symptoms of the allergic type of perennial rhinitis are due to mast cell release of biochemical mediators, particularly histamine. However, there is evidence suggesting that airway glands possess few or no receptors for histamine; therefore it would appear likely that the histamine induced nasal hypersecretion in this disease occurs via epithelial irritant receptors and reflex activity in the nervous system (Okuda, 1977).

It has been demonstrated that nasal glands have an abundant innervation from the parasympathetic nervous system (Cauna, Cauna and Hinderer, 1972; Aenggard, 1974), but few or no efferent sympathetic nerves (Nomura and Matsuura, 1972). Therefore it would appear logical to treat nasal hypersecretion in both allergic and non-allergic perennial rhinitis with a specific antagonist of the transmitter substance, acetylcholine; the latter being the transmitter between the efferent parasympathetic nerve terminals and the glands.

Ipratropium (Atrovent®, Boehringer-Ingelheim) is a parasympatholytic, with topical activity. The drug was introduced as a broncho-dilatator for the treatment of broncho-constrictive diseases (Poppius and Salorinni, 1973; Spector and Ball, 1975). This compound has no systemic activity when inhaled in therapeutic doses (Wieser and Koeningshofer, 1975).

We have therefore considered it of interest to determine whether this compound has a therapeutical effect on perennial rhinitis.

Intranasal methacholine challenge and measurement of nasal hypersecretion have been used as a test of nasal reactivity (Borum, 1979).

As Ipratropium is a specific antagonist of methacholine, the methacholine test has been used in the present investigation to answer the following questions: (1) Can Ipratropium, when applied intranasally reach the acetylcholine receptors of the glands? (2) What is a suitable dosage? (3) How long is the drug effective?

The present study has demonstrated that intranasal Ipratropium can inhibit methacholine induced hypersecretion. Further, it has shown that it may be possible to obtain a prolonged local effect in the treatment of perennial rhinitis, without the risk of adverse systemic effects.

MATERIAL AND METHODS

Subjects: Fifteen healthy medical students volunteered to take part in the study. They had no history of atopic disease or of chronic rhinitis, and their nasal mucosa had a normal appearance. Nine were females and six males. Their mean age was 25.5 years (range: 24–27 years). Ten patients suffering from perennial rhinitis were also included in the investigation. The definition of perennial rhinitis, as employed in this investigation, is a disease which produces at least two of the following symptoms almost every day for a period of more than one hour: Attacks of sneezing, colourless rhinorrhoea, nasal blockage due to swelling of the mucous membrane. Rhinorrhoea was the main symptom in all of the patients.

Methacholine challenge: Four-tenths of a ml of a methacholine aerosol was delivered from a DeVilbiss No. 15 atomizer for the nasal application. A titration series was produced from methacholine bromide powder (Meco-Benzon, Copenhagen) using 3, 6, 12, 24 and 48 milligrams dissolved in 0.4 ml of destilled

water. Serial challenges in normal subjects were carried out at 30 minute intervals by the application of methacholine in dosages from 3 to 48 mg. The lowest dosage producing at least 0.15 ml of secretion was employed for the subsequent Ipratropium experiments. Whereas a standard dosage of 6 mg was used for the challenge in the patients suffering from perennial rhinitis.
Immediately after the methacholine challenge the subject bent his head forward and remained in this position for a period of 15 minutes, without touching or blowing the nose, or sniffing. The secretion was collected in a funnel attached to a syringe, in order that the volume could be measured directly. Details of the methacholine test will be described elsewhere (Borum, 1979).

Nasal airway resistance (NAR): This was measured with a rhinomanometer (Mercury Electronics, Glasgow) equipped for posterior rhinomanometry. The mean of five readings before and five after each challenge were noted.

Ipratropium: The pressurized cannister for inhalation, equipped with a nasal adaptor (Atrovent®, Boehringer-Ingelheim) was used for delivery of this compound. Each puff gave 20 micrograms of Ipratropium. The subject slowly inhaled through the nose during use of the aerosol cannister; the latter was held as nearly as possible in the sagittal plane.

Experiment 1: A double-blind cross-over trial. Two puffs of Ipratropium (40 micrograms) were given in each nostril from the aerosol cannister 30 minutes before a methacholine test. One puff was given in the upper part of the nose and one puff in the lower part in order to ensure optimal distribution of the drug on the mucous membrane. A randomized application of placebo and active drug was employed, and at least one day passed between each test (medication + challenge). Fifteen healthy medical students took part in the experiment.

Experiment 2: To compare the effect of 80 and 40 micrograms. One puff (20 micrograms) was given in the upper part of the nose in each nostril 30 minutes before a methacholine test. The same 15 students were used for this open study.

Experiment 3: A study of the dose-time-response relationship. Six normal control subjects were employed. Each received 40 micrograms into each nostril 5 and 30 minutes, 1, 2, 4, 6, 8, 12 and 18 hours before a methacholine test. At least one day elapsed between each test.

Experiment 4: To establish whether the effect was comparable in patients and normal subjects. A methacholine test was performed one day before and 30 minutes after the intranasal application of 80 micrograms of Ipratropium to 10 patients with perennial rhinitis. The blood pressure and pulse rate were measured before and after each methacholine challenge and Ipratropium administration.

Statistical calculations: Probit analysis and variance analysis were carried out for each methacholine concentration used for stimulation of the normal subjects to ensure approximation to a normal distribution. Statistical analysis was performed using the two-tailed paired *t*-test.

RESULTS

Methacholine test: It was possible to collect at least 0.15 ml of secretion in all the normal subjects within 15 minutes of the intranasal application of methacholine. Registration of the blood pressure and pulse rate showed no systemic effects of the methacholine or Ipratropium.

Experiment 1: As seen from Figure 1, the mean volume of secretion, following methacholine challenge was significantly lower when the subjects were pretreated with 80 micrograms of Ipratropium (0.04 ml secretion), than when pretreated with placebo (0.21 ml secretion, $P < 0.001$). Pre-treatment with 80 micrograms of Ipratropium showed a parallel displacement of the log-dosage-reponse relationship, indicating a competitive inhibition of the muscarin receptors (Figure 2).

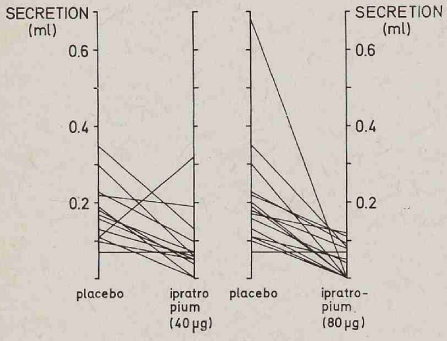

Figure 1. Inhibition of methacholine induced nasal secretion by Ipratropium in 15 healthy subjects. *Left figure:* One puff (20 micrograms) of Ipratropium in each nostril before methacholine challenge reduced the secretion significantly ($P < 0.001$). *Right figure:* Two puffs (40 micrograms) in each nostril had an even greater effect, but the difference between the two dosages was not significant ($P > 0.20$).

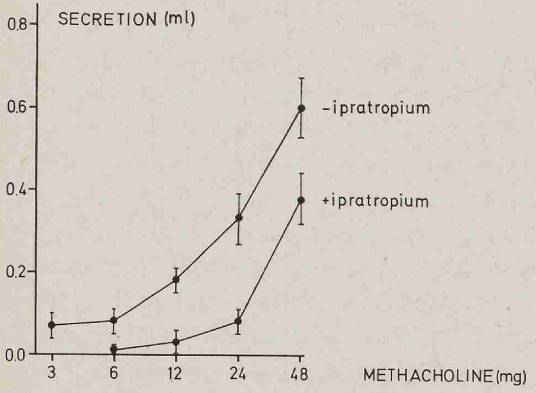

Figure 2. The dose-response relationship between intranasal nebulized methacholine and the resulting amount of secretion (mean +/− SEM) in 15 healthy subjects, with and without pre-treatment with 80 micrograms of Ipratropium. The drug caused a significant reduction in the secretion ($P < 0.001$) and a parallel displacement of the dose-response figure. Note the logaritmic abscissa.

Experiment 2: In this open experiment, 40 micrograms of Ipratropium had a significant inhibiting effect on the methacholine induced hypersecretion, as compared to placebo (Figure 1). Although the mean secretion (0.09 ml) was higher than that obtained following pre-treatment with 80 micrograms of Ipratropium (0.04 ml), the difference between these two dosages was not significantly significant ($P > 0.20$).

Experiment 3: The nasal response to methacholine challenge was diminished to about 30% of the pre-treated volume already 5 minutes after the administration of Ipratropium (Figure 3). The drug had its maximum effect from 1 to 4 hours after the application. After this the effect diminished slowly, but owing to the considerable scatter of the values it is impossible to state exactly the duration of action.

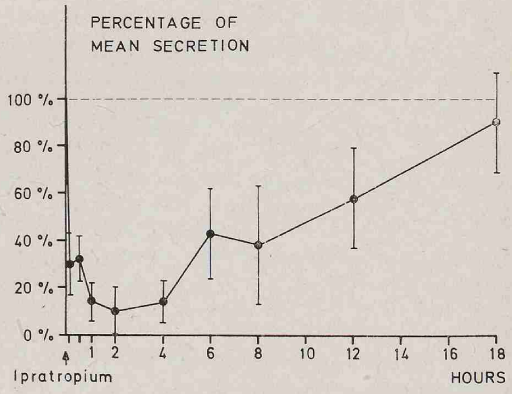

Figure 3. The nasal secretory response to methacholine at varying time intervals after intranasal application of two puffs (40 micrograms) of Ipratropium into each nostril in 6 healthy subjects. *Mean and Standard error of the mean is indicated.* The secretory response was diminished to about 30% of the individual mean secretion already after 5 minutes *and to about 15% after one to two hours.*

Experiment 4: As can be seen from Figure 4, pre-treatment with Ipratropium was able to reduce the methacholine response in the patients to a level comparable to that obtained in the normal controls; this means that the percentual reduction was even larger in the patients than in the controls.

Nasal airway resistance: The changes in NAR measured before and 15 minutes after methacholine challenge were not statistically significant after placebo or Ipratropium (Figure 5).

Statistical calculations: Probit analysis showed that approximation to the normal distribution was permissible, thus allowing the use of parametric statistics.

DISCUSSION

It is important in the development of new drugs that the pharmacological efficacy and the dose-response relationship can be estimated before a controlled clinical trial is carried out. Allergen induced asthma and rhinitis were found to be of value in the development of sodium chromoglycate-like drugs (Taylor

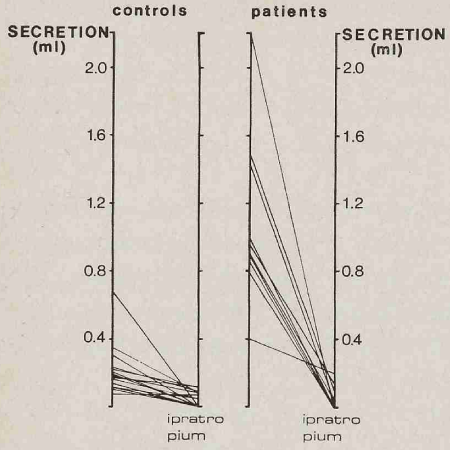

Figure 4. Inhibition of methacholine induced nasal secretion by 80 micrograms of Ipratropium in 15 healthy subjects and 10 patients with perennial rhinitis. The patients produced much more secretion on the same dosage of methacholine (6 mg) ($P<0.001$). Two puffs of Ipratropium into each nostril reduced the secretory response significantly ($P<0.001$), not only in the healthy subjects, but also in the patients.

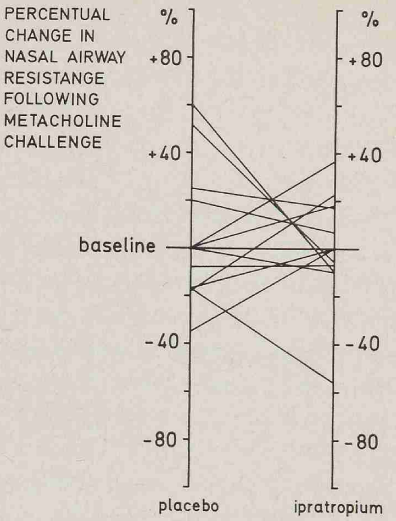

Figure 5. Percentual changes in nasal airway resistance (NAR) following intranasal methacholine challenge after pre-treatment with placebo or two puffs (40 micrograms) of Ipratropium into each nostril 30 minutes before the challenge. The changes in NAR were small and insignificant ($P>0.30$).

and Shivalkar, 1970). The present study indicates that nasal methacholine challenge of normal controls and patients will be helpful in the early evaluation of parasympatholytic compounds.

The marked inhibition by Ipratropium of the methacholine induced nasal hypersecretion could not be predicted directly from the use of the drug in bronchial disease. Although it relaxes the smooth bronchial muscles, it has no demonstrable effect on secretory activity in the bronchi (Krieger and Reitberger, 1975). The different dosage applied per square centimeter to the nose and bronchi would appear to be the most likely explanation of this, but differences in the anatomy and nervous regulation are also of possible importance. While there is an abundance of publications on bronchial treatment with atropine and Ipratropium (Postgraduate Medical Journal, 1975), there are, as far as is known to the present authors, no trials on atropine-like drugs used for the treatment of perennial rhinitis. However, the efficacy of antihistaminics (Goodman and Gilman, 1975) and tricyclic antidepressants (Foxen, 1972) in the treatment of rhinorrhoea is certainly due to some extent to their parasympatholytic activity.

Airway secretion is produced by the submucosal glands, as well as, by the

epithelial goblet cells. The glands are mainly regulated through the parasympathetic nervous system (Nomura and Matsuura, 1972), but there is no evidence to indicate that this regulation also applies to the goblet cells. Consequently, a drug such as Ipratropium would not be expected to have any effect on goblet cell secretory activity. However, secretion from goblet cells in the surface epithelium probably only constitutes a few per cent of the total airway secretion (Reid 1960).

It was found, in a more detailed examination of the nasal methacholine test (Borum, 1979), that there was a transient drop in nasal patency following the challenge, and that most of this was due to the secretion in the nasal cavity. This is in accordance with experimental data from animal studies (Eccles and Wilson, 1973; Malm, 1973), and from histochemical examination of human nasal mucosa (Nomura and Matsuura, 1972), which showed that while the parasympathetic nervous system controls the glands, the sympathetic nervous system is most important with regard to the regulation of the capacitance vessels of the nose and thereby the patency. Therefore, Ipratropium would be expected to be effective in the treatment of rhinorrhoea, but not in the treatment of nasal blockage.

The study performed here of the dose-response relationship showed that Ipratropium, in dosage well tolerated locally and without adverse systemic effects, was effective for a minimum of 4 hours and in most cases for 6 to 8 hours. This would indicate that the aerosoled drug is suitable for use in therapeutic trials.

An open trial on 10 patients with perennial rhinitis and hypersecretion, as the major complaint, has recently shown an effect on the spontaneous hypersecretion in more than half of the patients. We have therefore planned a doubleblind controlled study (in preparation).

Normal olfactory function depends to a great extent on the sensory epithelium being constantly moist. As we have no knowledge as to whether atropine or Ipratropium have any effect on the Bowmann glands in the olfactory region, the sense of smell should be checked when repeated doses of Ipratropium are used in the nose.

ZUSAMMENFASSUNG

Die submukösen Drüsen der Nase sind vom parasympathischen Nervensystem reichlich versorgt. Die Rhinorrhoea bei der nicht saisonbedingten Rhinitis hängt warscheinlich mit einer vergrösserten Aktivität dieser Nerven zusammen. Eine Blockade mit atropin-ähnlichen Mitteln würde deshalb eine logische Behandlung sein.

Bei 15 gesunden Versuchspersonen wurde im Laboratorium durch intranasale Applikation von Metacholin eine Rhinorrhoea hervorgerufen. Die Versuchs-

personen wurden im voraus mit Atrovent (Boehringer-Ingelheim) oder mit Plazebo behandelt. Der Versuch wurde doppelblindt ausgeführt. Es stellte sich heraus, dass Atrovent die metacholininduzierte Hypersekretion bis 6 Stunden hindurch effektiv blockieren konnte. Lokale oder systematische Nebenwirkungen wurden nicht gesehen. Auch bei 10 Patienten mit nicht saisonbedingter Rhinitis konnte die metacholininduzierte Hypersekretion effektiv blockiert werden. Bei Patienten mit spontaner Rhinorrhoea zeigte sich Atrovent gleichfalls effektiv.

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