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Efficacy of Ipratropium Bromide Aqueous Nasal Spray in the Prevention of Nasal Secretion Induced by Inhaled Methacholine

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Abstract

Objective: The present study was conducted to assess if a new formulation of ipratropium bromide nasal spray could prevent the nasal hypersecretion induced by a whole nasal challenge with increasing doses of methacholine.

Patients and methods: Twenty adult outpatients with ongoing hypersecretive rhinitis were selected and, after a preliminary session without any pretreatment, randomised to receive a single dose of nasal aqueous ipratropium bromide 80μg and matched placebo administered via a metered pump 60 minutes before methacholine challenge on two consecutive days. In each session, methacholine was inhaled into the nostrils at four increasing concentrations of 1, 4, 16 and 64 mg/ml, at 20-minute intervals. The induced secretion was evaluated by weighing a cotton tampon placed in each nostril for 30 seconds following the methacholine stimulation; weights were adjusted for spontaneous secretion. In addition, an acoustic rhinometer was used to measure the change in resistance and volume of each nasal cavity.

Results: The nasal discharge (adjusted for pretreatment values) was significantly reduced after pretreatment with ipratropium bromide, both in the cumulative weight ($p < 0.01$) and at each methacholine concentration ($p < 0.05$ after 1 and 4 mg/ml, $p < 0.01$ after 16 and 64 mg/ml). No relevant changes in nasal patency were observed during the test without pretreatment, nor during the two treatment sessions; similarly, no significant differences were observed in the comparison between active drug and placebo for both resistance and volume.

Conclusions: The results of the present study demonstrate that an intranasal aqueous solution of ipratropium bromide reduces the nasal discharge induced by locally applied methacholine. No effects were seen in the parameters used to measure nasal congestion.

Rhinorrhoea is a symptom common to both primary chronic rhinitis (i.e. vasomotor rhinitis or nonallergic rhinitis) and secondary chronic rhinitis (i.e. allergic rhinitis), as well as to the common cold.

The submucosal nasal glands and the goblet cells of the nasal mucosa are the main sources of nasal secretion.[1] These glands have an abundant innervation that stems from the cholinergic nervous system.[2] In fact, a profuse hyper-reactiv-

ity of the nasal mucosa is caused when surgical operation on the vidian nerve is followed by the administration of methacholine (a cholinergic agonist).[3] Nasal provocation with methacholine, which binds reversibly to the muscarinic receptors on the seromucous glands, is the standard model used in the induction of secretion, and allows a local triggering without any systemic effect.[4] Anticholinergic drugs are therefore useful in treating excessive rhinorrhoea in patients with rhinitis. Ipratropium bromide, a derivative of scopolamine with a quaternary ammonium structure, is an anticholinergic drug and was the first muscarinic receptor blocker to achieve wide therapeutic use in pressurised aerosol form. The efficacy and tolerability profiles were demonstrated in clinical trials, both in long-term treatment[5,6] and in the prevention of rhinorrhoea induced by methacholine.[7-9] In addition, intranasal ipratropium bromide provides effective relief and control of rhinorrhoea in the common cold.[10,11]

Recently, a new formulation of ipratropium bromide nasal spray, an aqueous solution delivered via a metered pump, has been developed without using potentially ozone-depleting propellants. The aim of the present study was to assess whether pretreatment with intranasal ipratropium bromide aqueous spray could prevent the nasal secretion induced by increasing doses of methacholine inhaled in both nostrils during a whole nasal challenge, in comparison with matched placebo. A secondary objective was to investigate if local stimulation with methacholine could induce nasal congestion, by measuring the size and resistance of the nasal cavity via acoustic rhinometry, and to verify if ipratropium bromide could prevent such an event.

Patients and Methods

Study Population

Adult outpatients with allergic and nonallergic hypersecretive rhinitis were recruited on the basis of evidence of rhinorrhoea in the month before starting the trial for at least 1 hour a day and at least 4 days a week, or for 2 to 3 weeks per month in the previous 6 months. The study was conducted outside of seasonal sensitising periods and patients were to stay in the same geographic area for the total study duration.

Patients were excluded from taking part in the study if they had evidence of nasal polyps and/or an abnormal nasal septum, airways infection in the previous 2 weeks, asthma and acute or chronic sinusitis, history of abnormal laboratory tests, history of clinically significant concomitant diseases, pregnancy or risk of pregnancy, hypersensitivity to parasympathetic agonists and/or anticholinergic drugs, and exposure to potential allergens for the total study period. In addition, they had to abstain from the use of anticholinergic and short-acting antihistamines in the previous week, use of nasal decongestants and nonsteroidal anti-inflammatory drugs in the previous 2 weeks, use of corticosteroids, sodium cromoglycate and nedocromil in the previous 4 weeks, and use of long-acting antihistamines in the previous 6 weeks. Patients were also admitted to the treatment phase if the cumulative weight of nasal secretion was at least 50mg in a preliminary test done without any preventive treatment.

Patients gave their written informed consent before any study-related procedure was started. The study protocol was approved by the Ethics Committee of the 'Dipartimento di Scienze Motorie e Riabilitative', University of Genoa, Italy.

Study Design and Protocol

This was a randomised, double-blind, placebo-controlled, crossover design trial. Eligible patients entered a 3- to 5-day run-in period and were then randomised to receive a single dose of 80μg ipratropium bromide nasal spray in an aqueous solution (Rinoatem Aqua®, Chiesi Farmaceutici SpA, Parma, Italy) administered via a metered pump and matched placebo on two consecutive days, with a 3- to 5-day washout between the two tests. After a screening visit, when patients were checked against the inclusion/exclusion criteria, they were submitted to a methacholine challenge test without

any pretreatment prior to being assigned to the two treatment days with ipratropium bromide and placebo. Patients were allocated to one of the two sequences (ipratropium bromide-placebo or vice-versa) following a four-block design (i.e. two sequences in each four-patient group). In the two treatment sessions the challenge test was done 60 minutes after the intake of the assigned drug.

Methacholine chloride (Lofarma, Milan, Italy) in powder form was dissolved in saline solution to obtain concentrations of 1, 4, 16 and 64 mg/ml in a 10µl volume. Increasing methacholine concentrations were delivered via bilateral intranasal aerosolisation with a French-Rosenthal dosimeter (Sensor Medics Srl, Milan, Italy). The four administrations of methacholine were separated by 20-minute intervals. In each application, 20 nasal inhalations were performed. The device was set to deliver the methacholine aerosol during the last 0.4 seconds of each inspiration to minimise deposition in the intrathoracic airways. This was obtained by introducing a 0.6-second delay between the triggering of the valve opener by the inspiratory flow and the opening of the valve. To evaluate the spontaneous secretion, a cotton tampon (Dental rolls, Roeko, Italy) was applied in each nostril (for 30 seconds) before the procedure was started and it was weighed using an electronic balance (PB 153, Mettler Toledo) sensitive to 0.01mg. Likewise, the secretion induced by methacholine was measured after 30 seconds, as previously described, and the net secretion weight was calculated using the following formula: post-stimulation tampon weight minus tampon weight minus spontaneous secretion weight.

In addition, the patency of nasal airways was measured at the start of each session and 5 minutes after removal of the cotton tampon at each step of methacholine challenge using an acoustic rhinometer EccoVision® (Sensor Medics, Italy). An analysis was carried out on a segment of 6cm taken from the nose tip, and the resistance (Req, cm H_2O/L/min) and volume of the analysed segment (Vol, cm^3) were calculated in both sides. Values of the left and right sides were then averaged. Vital signs (pulse and blood pressure) were measured at the start of each session and 10 minutes after removal of the cotton tampon at each methacholine stimulation. Adverse events were recorded each session day.

Statistics

The sample size was based on an hypothesis of superiority between the active drug and placebo. The cumulative weight of net secretion after the four challenges was considered as the primary variable. Estimating a mean value of 90mg in the placebo group (30mg as standard deviation) and an expected difference between treatments of 30mg, at an α level of 0.05 and a power of 90%, 20 evaluable patients were required to demonstrate that the active drug was more effective than placebo in the prevention of the cumulative secretion after the four stimulations.

An ANOVA model for the crossover design was used in the analysis of the secretion weight and of airway patency parameters.

SAS® software version 6.12 was used for data management and analysis. Values were reported as means and standard deviation or standard error, when appropriate.

Results

The study population was made up of 20 patients in total, six males and 14 females, with a mean age of 36.7 ± 17.0 years. The mean duration of the disease was 8.1 ± 6.4 years: 10 patients had allergic seasonal rhinitis and the other 10 had vasomotor rhinitis. The individual demographic characteristics of the patient population are presented in table I.

Figure 1 shows the results of the nasal secretion weight in the basal test without any pretreatment and in the two pretreatment sessions, including the values measured at each methacholine challenge test after the intake of ipratropium bromide or placebo. The mean cumulative weights of nasal secretion were 115.4mg (SE 11.0) in the preliminary session without pretreatment, 69.1mg (SE 11.3) after treatment with ipratropium bromide and

Table I. Demographic details of the patient population

Patient no.	Age (years)	Gender	Height (cm)	Weight (kg)	Duration of illness (years)	Diagnosis
1	34	M	188	79	10	AR
2	26	F	160	60	3	VR
3	51	F	164	73	3	VR
4	19	F	175	60	19	AR
5	20	F	160	52	20	VR
6	50	F	156	48	3	AR
7	51	F	160	54	3	AR
8	57	M	175	80	5	VR
9	67	F	163	60	18	VR
10	18	F	170	55	6	VR
11	25	F	164	46	7	AR
12	67	F	170	55	10	AR
13	42	F	163	52	2	VR
14	36	M	175	70	18	AR
15	22	M	178	70	3	VR
16	57	F	162	67	1	VR
17	25	F	164	52	5	AR
18	19	M	180	71	2	AR
19	19	M	189	93	10	AR
20	29	F	161	52	14	VR
Mean ± SD	**36.7 ± 17.04**		**168.85 ± 9.58**	**62.45 ± 12.46**	**8.1 ± 6.41**	
Total		**6 M; 14 F**				**10 AR; 10 VR**

AR = allergic rhinitis; **VR** = vasomotor rhinitis.

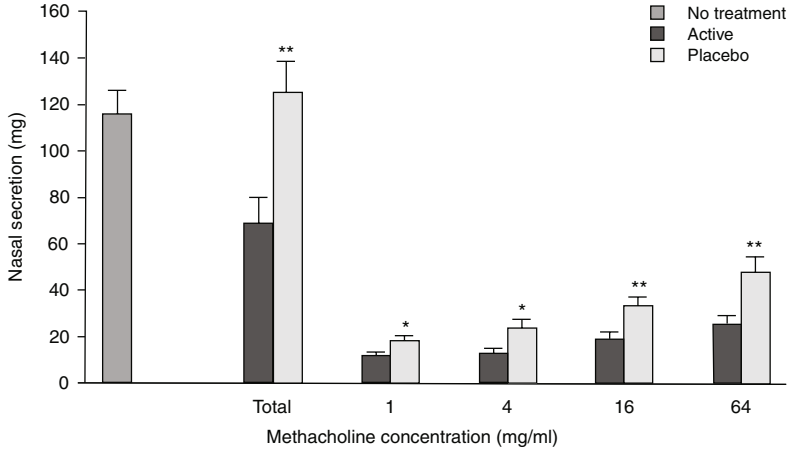

Fig. 1. Weight of nasal secretions with and without pretreatment with ipratropium bromide or placebo (showing SE bars).
* $p < 0.05$; ** $p < 0.01$.

Table II. Acoustic rhinometry: calculated resistance (cm H_2O/L/min)[a]

	No treatment (mean ± SE)	Ipratropium bromide (mean ± SE)	Placebo (mean ± SE)
Pretreatment		4.13 ± 0.78	3.98 ± 0.66
Prestimulation	5.06 ± 1.59	4.77 ± 1.11	4.57 ± 0.93
First methacholine stimulation (1 mg/ml)	5.24 ± 1.61	6.53 ± 3.09	4.10 ± 0.86
Second methacholine stimulation (4 mg/ml)	4.99 ± 1.51	4.73 ± 1.74	4.46 ± 1.28
Third methacholine stimulation (16 mg/ml)	5.33 ± 1.52	5.35 ± 1.98	4.10 ± 0.83
Fourth methacholine stimulation (64 mg/ml)	5.87 ± 1.69	5.46 ± 1.68	5.14 ± 1.37

a Nonsignificant differences between and within groups.

Table III. Acoustic rhinometry: volume of the analysis segment (cm^3)[a]

	No treatment (mean ± SE)	Ipratropium bromide (mean ± SE)	Placebo (mean ± SE)
Pretreatment		7.06 ± 0.81	6.97 ± 0.59
Prestimulation	7.77 ± 0.76	6.73 ± 0.54	6.70 ± 0.65
First methacholine stimulation (1 mg/ml)	7.00 ± 0.60	6.73 ± 0.66	6.57 ± 0.56
Second methacholine stimulation (4 mg/ml)	7.35 ± 0.77	6.59 ± 0.54	6.43 ± 0.51
Third methacholine stimulation (16 mg/ml)	7.42 ± 0.71	6.41 ± 0.50	6.35 ± 0.54
Fourth methacholine stimulation (64 mg/ml)	7.44 ± 0.82	6.28 ± 0.54	6.11 ± 0.47

a Nonsignificant differences between and within groups.

124.6mg (SE 14.1) after treatment with matched placebo. The comparison between treatments for the total weight of nasal secretion (adjusted for pretreatment values) showed a statistically significant difference ($p < 0.01$) in favour of the active drug. Furthermore, there was a significant difference between ipratropium bromide and placebo when the secretion weights were compared at each methacholine concentration ($p < 0.05$ after 1 and 4 mg/ml, $p < 0.01$ after 16 and 64 mg/ml). A dose-linearity in response after prestimulation with the four scalar doses of methacholine was evident after treatment with both ipratropium bromide and placebo.

The results of the acoustic rhinometry tests, done before treatment, before the start of the first stimulation, and after each methacholine stimulation, are reported in table II (calculated resistance) and in table III (volume of the analysis segment). No relevant changes were observed in either parameter during the basal test without any pretreatment, or in the two pretreatment sessions. The analysis of the results did not show any significant change over the pretreatment value (or prestimulation value in the basal test) on any of the three test days. Similarly, no differences between groups were observed in the comparison between ipratropium bromide and placebo for either variable.

No clinically significant changes were reported for pulse and blood pressure. No adverse events occurred during the total study period.

Discussion

The results of the present study demonstrate that an aqueous solution of ipratropium bromide, given intranasally in a single dose of 80μg via metered pump, is effective in the prevention of nasal hypersecretion induced by local applications of methacholine. In addition to total weight of nasal secretions, significant differences between the active drug and placebo have been shown at each methacholine stimulation, given at increasing concentrations of 1, 4, 16 and 64 mg/ml. Taking into account that the weight of active drug and placebo in each delivered dose is around 90mg, which may contribute to the weight of nasal secretion measured after the stimulation tests, the estimated net difference between the two treatments is

even higher. The weight-per-shot can also explain why the cumulative nasal secretion measured in the test day without any pretreatment tended to be lower than that measured in the sessions with placebo, thereby suggesting the lack of any apparent placebo effect.

The methods used in the present study for the assessment of nasal secretion and nasal congestion include a whole nasal challenge, a dose response curve, the recovery of nasal secretions by means of a weighed cotton tampon, and the subtraction of the spontaneous secretions. Unpublished data collected in our centre showed good reproducibility of the method, with a 10% coefficient of variation between two repeated challenges in eight patients. Previous dose-response trials used single side nasal challenge with local paper filter application,[8,9] collection of the secretions via a microtube, and the measurement of runny nose and congestion via rating scales. In our study an acoustic rhinometer, a validated method to show changes of the nasal cavity before and after a given treatment,[12] was used.

In accordance with previous findings,[13] the results of the present study seem to confirm that methacholine acts directly on nasal glands even at minimal doses and with dose-dependent effects on nasal secretions. In contrast, results obtained in the test without any pretreatment have confirmed the lack of effects of methacholine on nasal patency and congestion, which are regulated by blood vessels controlled by sympathetic rather than parasympathetic nerves.[14] As a consequence, preventive treatment with ipratropium bromide was not expected to affect these parameters. The effects of ipratropium bromide on nasal secretions were obtained regardless of the type of rhinitis, i.e. allergic or vasomotor, which were equally distributed among the patient population (10 patients each). This evidence confirms that the action of methacholine and preventive drugs is not related to the underlying mechanism of nasal hypersecretion.

Conclusion

It can be concluded that intranasal ipratropium bromide provides efficient prevention of nasal hypersecretion induced by locally applied methacholine, as studied in a validated and reliable experimental model.

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