

Long-term treatment of perennial allergic rhinitis with ipratropium bromide nasal spray 0.06%

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The purpose of this study was to assess the safety and efficacy of ipratropium bromide nasal spray 0.06% (aqueous solution), 84 µg per nostril three times a day, in reducing nasal hypersecretion in the long-term treatment of patients with perennial allergic rhinitis (PAR). This was an open-label 1-year trial. In the first 6 months all patients were treated with two puffs ipratropium bromide nasal spray 0.06%, 84 µg per nostril three times per day, unless they were unable to tolerate the dose. In the last 6 months the dose could be reduced to the lowest amount required to control rhinorrhea. Ninety-six patients entered the trial, and 47 completed it. Sixty-three patients completed more than 6 months of treatment. Patient and physician global evaluation suggested that ipratropium bromide nasal spray 0.06% is effective in controlling rhinorrhea associated with PAR and can contribute to control of congestion, postnasal drip, and sneezing. There was also a trend toward reduction of mucosal edema and improvement in quality of life. The most common drug-related adverse events were nasal dryness, epistaxis/nose bleed, and increased rhinitis. Most adverse events were mild and resulted in drug discontinuation in less than 10% of patients. Ipratropium bromide nasal spray was well tolerated and not associated with serious drug-related adverse events or clinically significant anticholinergic side effects. Use of ipratropium bromide nasal spray alone or with other standard medications should be considered in treating patients with PAR. (J ALLERGY CLIN IMMUNOL 1995;95:1128-32.)

Key words: Perennial allergic rhinitis, ipratropium bromide, nasal spray, rhinorrhea, long-term

Allergic rhinitis affects more than 15% of the population.¹ The major symptoms are nasal congestion, rhinorrhea, and itching of the eyes, ears, nose, and throat. Symptoms occur seasonally in many individuals and perennially especially in those individuals who are sensitive to dust mites or multiple allergens present throughout the year. Treatment of allergic rhinitis includes avoidance of allergens when possible, medications when necessary, and immunotherapy when appropriate.

Nasal discharge (rhinorrhea) involves secretions

Abbreviations used

IB: Ipratropium bromide
PAR: Perennial allergic rhinitis
PNAR: Perennial nonallergic rhinitis

from about 200 anterior serous glands and 12,000 small seromucus glands. These seromucus glands have parasympathetic innervation, which is important for regulation of nasal secretions and the nasal environment.^{2,3}

Ipratropium bromide (IB) (Atrovent, Boehringer Ingelheim Corp., Ridgefield, Conn.) is an anticholinergic compound that is related to atropine. IB has good topical activity and works by selective binding of muscarinic receptor sites. It is poorly absorbed, and systemic cholinergic side effects such as dry mouth, urinary retention, vision problems, tachycardia, and the like are rare. IB is available for intranasal admin-

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TABLE I. Open-label patient dose status

	No. patients			
	3 mo	6 mo	9 mo	12 mo
Total treated with IB (0.06% dose)*	82	63	51	49
2 sprays tid	74	51	44	43
1 spray tid	7	9	6	5
2 sprays bid	1	3	1	1
1 spray bid	0	0	0	0
2 sprays qd	0	0	0	0
1 spray qd	0	0	0	0

Data from Case Report Form Tabulations.

tid, Three times a day; *bid*, twice a day; *qd*, every day.

*Fourteen patients left the study before completing 3 months of open-label treatment.

istration or as a metered dose inhaler and as an aqueous nasal spray.

The mechanism of action of IB in the control of rhinorrhea is well established.⁴ Nasal secretions are under the control of the parasympathetic nervous system, which innervates the serous and seromucus glands of the nose. When these parasympathetic pathways are stimulated, acetylcholine is released and interacts with muscarinic receptors on the nasal glands, inducing secretions. IB, a cholinergic receptor antagonist, blocks the interaction of acetylcholine with these muscarinic receptors, thereby inhibiting nasal secretion. Patients with either perennial allergic rhinitis (PAR) or perennial nonallergic rhinitis (PNAR) have cholinergic hyperactivity.^{5,6} From a pathophysiologic viewpoint, this indicates that rhinorrhea in PAR is derived from cholinergic stimulation of nasal glands and from transudation of histamine-induced extravascular fluid.

In previous clinical studies in Canada and Europe, intranasal IB administered by metered dose inhaler has been shown to significantly decrease rhinorrhea in patients with PNAR and also in normal subjects after intranasal methacholine challenge.⁷⁻¹² In more recent United States studies using the new aqueous nasal spray pump, IB administered in a dose of 42 µg per nostril three times a day for 4 weeks and 42 µg per nostril and 84 µg per nostril for 8 weeks significantly decreased rhinorrhea in patients with PAR¹³ (Kaiser HB, Findlay SR, Georgitis JW, et al. Unpublished data). A recent nasal methacholine nasal provocation study showed that both patients with PAR and patients with PNAR demonstrated a dose-dependent increase

TABLE II. Baseline demographics and site of nasal discharge

No. patients entered	96
Sex	
M	32 (33%)
F	64 (67%)
Age (yr)	
Range	18-75
Mean	38.4 ± 13.7
Race	
White	88 (92%)
Black	3 (3%)
Other	5 (5%)
Weight (mean)(lb)	162.2 ± 44.1
Site of nasal discharge	
Anterior	(45%)
Posterior	(4%)
Anterior/posterior	(51%)

TABLE III. Patient disposition summary

	No. patients (%)
Received treatment	96
Treated ≥3 mo	82 (85.4)
Treated ≥6 mo	63 (65.6)
Treated ≥9 mo	51 (53.1)
Treated ≥12 mo	49 (51.0)
Completed trial	47 (49.0)
Discontinued trial	49 (51.0)
Reasons for discontinuation	
Adverse event	16 (16.7)
Protocol violation	6 (6.3)
Administrative reasons	22 (23)
Treatment failures	5 (5)

in methacholine-induced rhinorrhea that is inhibited by prior treatment with IB.¹⁴

The purpose of this study was to determine the long-term safety and efficacy of the new 0.06% IB nasal spray formulation, 84 µg per nostril three times a day, in reducing nasal hypersecretions in patients with PAR. Another purpose was to assess any changes in quality of life as measured by^a reduction of the degree of interference with daily activities and mood.

MATERIAL AND METHODS

This was a 1-year, open-label multicenter trial. Patients selected had (1) a clinically significant history of PAR, (2) a positive skin test to perennial allergens

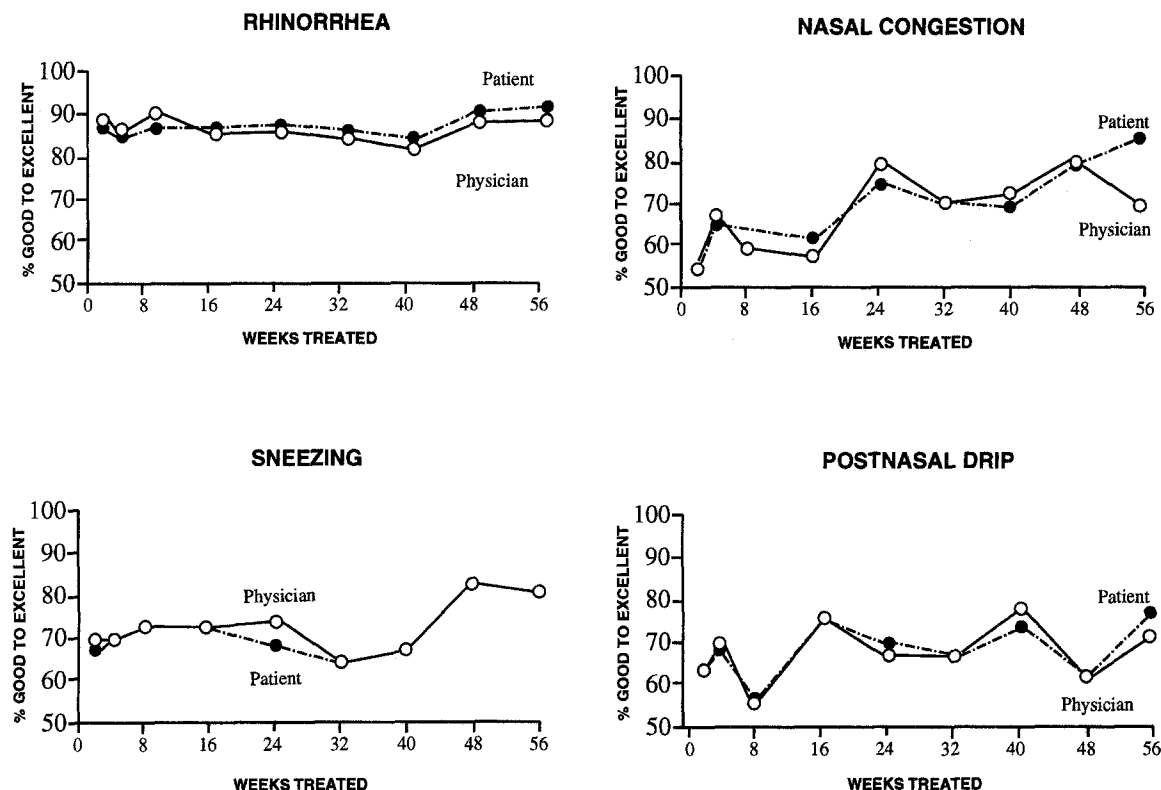


FIG. 1. Patient and physician assessments of the long-term efficacy of IB in treating PAR.

TABLE IV. Changes in nasal examination after 1 year of treatment with IB nasal spray 0.06%

Characteristic	Baseline (%)	End of long-term (%)
Degree of mucosal edema		
None/mild	41 (43)	71 (75)
Moderate/severe	54 (57)	14 (25)
Color of nasal mucosa		
Normal	16 (17)	35 (37)
Red	35 (37)	39 (41)
Pale	40 (42)	21 (22)
White/blue	4 (4.0)	0 (0)
Quantity of rhinorrhea		
None/scanty	41 (43)	87 (92)
Some/profuse	54 (57)	8 (8)
Postnasal drip		
Not present	68 (72)	84 (88)
Present	27 (28)	11 (12)

present in the environment, and (3) a definite causative association between the patient's symptoms and exposure to these allergens.

To obtain safety data at the highest dose permitted,

TABLE V. Use of standard concomitant perennial rhinitis medications by 96 patients with PAR

	Baseline	During long-term
Any use	46 (48%)	26 (27%)
Chronic use (>3 mo)	32 (33%)	12 (13%)

patients received ipratropium bromide nasal spray 0.06%, 84 µg per nostril, for the first 6 months. Dose reduction was allowed for intolerable adverse events. During the second 6-month period, dosage was titrated down to the lowest amount required to control rhinorrhea (Table I). Patients were allowed concomitant medications including antihistamines, decongestants, and steroids as required. Safety was evaluated from adverse event reports and from nasal examinations. Efficacy was evaluated through patient and physician global evaluations of treatment, the need for extra medications, and incidence of treatment failures. A quality of life questionnaire was also administered.

Demographics

Patients with PAR who had completed a 10-week double-blind trial of IB nasal spray 0.03%, 42 µg per nostril three times a day, 0.06% IB nasal spray, 84 µg per

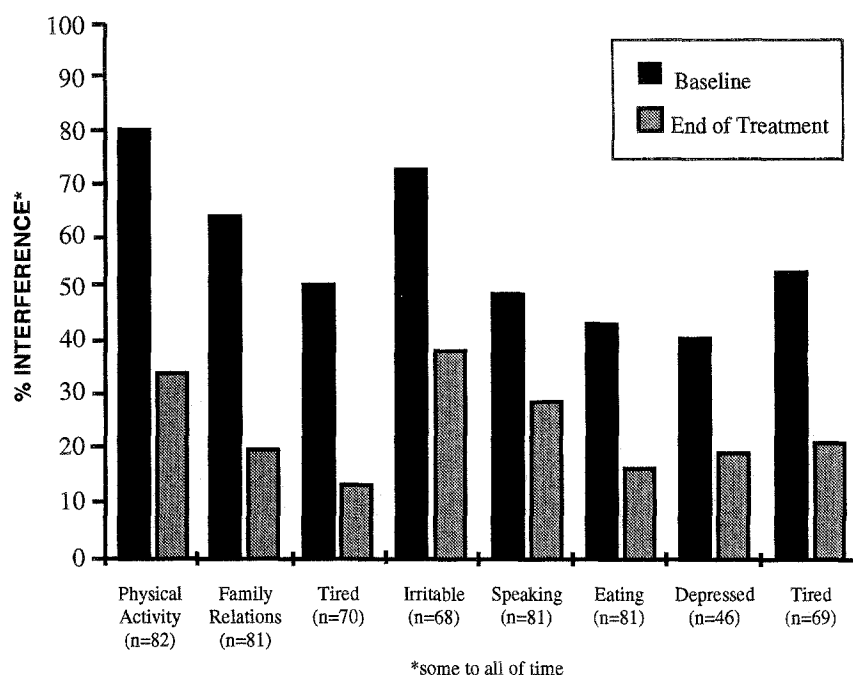


FIG. 2. Quality of life assessment after 1 year of therapy with IB for PAR.

nostril three times a day, or placebo were given the option of enrolling in the 52-week open-label trial of IB nasal spray, 0.06%, 84 µg per nostril three times a day. Ninety-six patients enrolled, and 47 (49%) completed the study. Patients were 18 to 75 years old (mean age, 38.4 years) (see Table II).

RESULTS

Ninety-six patients enrolled and 47 (49%) completed the trial. Sixty-three patients (66%) completed more than 6 months of treatment. Sixteen patients (17%) were discontinued because of adverse events, and 14 patients (15%) required dose reduction of their study medication because of adverse events. Six patients (6%) were discontinued due to protocol violations, and 27 (28%) for administrative reasons. A majority of patients (82 of 96) continued treatment at the higher dose (84 µg per nostril three times a day) throughout the trial (see Table III).

EFFICACY

Patient and physician global assessment indicated that IB nasal spray 0.06% was effective in controlling rhinorrhea in patients with PAR and contributed to control of congestion, postnasal drip, and sneezing (Fig. 1). Approximately 80% to 90% of patients and physicians rated control of rhinorrhea as good to excellent. Patients and physicians also perceived benefit in control of conges-

TABLE VI. Selected adverse events in long-term trial of IB nasal spray

	No. patients (%)	
	First 6 mo	Second 6 mo
Nonnasal adverse events		
URTI	20 (20.8)	13 (20.6)
Sinusitis	6	7 (11.1)
Headache	6 (6.3)	1 (1.6)
Pharyngitis	10 (10.4)	3 (4.8)
Nasal adverse events		
Epistaxis	9 (9.4)	1 (1.6)
Nasal dryness	21 (21.9)	4 (6.3)
Nasal irritation	6 (6.3)	2 (3.2)
Increased rhinitis	5 (5.2)	5 (7.9)
Nasal congestion	3 (3.1)	1 (1.6)
Potential systemic anticholinergic adverse events		
Mouth dry/throat dry	2 (2.1)	0
Supraventricular tachycardia	1 (1.0)	0

URTI, Upper respiratory tract illness.

tion (60% to 70%), sneezing (70% to 80%), and postnasal drip (60% to 70%).

There was also a trend toward reduction of mucosal edema, as well as a reduction in degree of inflammation, rhinorrhea, and postnasal drip as observed objectively by anterior rhinoscopy (Table IV).

The need for concomitant PAR medications

(antihistamines, decongestants, and topical steroids) was markedly reduced from baseline (Table V).

Long-term treatment with IB nasal spray resulted in improvement of patient quality of life as shown by a reduction in the degree of interference with daily activities and in improvement in mood (Fig. 2).

ADVERSE EVENTS

There were no deaths and no serious drug-related adverse events. The most common drug-related adverse events were nasal dryness, epistaxis/nosebleed, and increased rhinitis (Table VI). Most events were simple episodes of mild to moderate intensity and resulted in patient discontinuation in less than 10% of patients. All patients with nasal adverse events that required dose reduction recovered from these events. In 75% of these cases, resolution of the adverse event occurred during the trial with continued control of nasal symptoms. Sixteen patients (17%) were discontinued from the trial because of adverse events. All 16 patients recovered. Nine of the 16 events were possibly drug related. Discontinuation specifically because of nasal dryness and epistaxis was very infrequent (2%).

CONCLUSIONS

IB nasal spray, 0.06%, 84 µg per nostril three times a day, was well tolerated in a 1-year open-label trial. It was not associated with serious drug-related adverse side effects or clinically significant anticholinergic systemic effects. It caused no deleterious changes in nasal mucosa, and patient and physician assessments indicate effectiveness in controlling rhinorrhea in patients with PAR and suggest that long-term treatment can contribute to control of congestion, postnasal drip, and sneezing.

There was an improvement in patients' quality of life as measured by a questionnaire during the course of the study. Recent reports have supported the validity of these quality of life assessments and confirmed that treatment of perennial rhinitis symptoms with other nasal sprays improves patients' ability to perform day-to-day activities.^{15, 16}

IB nasal spray alone or with other standard medications should be considered in treating patients with PAR.

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