

A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis

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Intranasal ipratropium bromide has been shown to significantly reduce rhinorrhea. Use of a freon-propelled intranasal preparation has resulted in side effects associated with the drying properties of the propellant. The purpose of the present trial was to study the safety and efficacy of a new isotonic aqueous ipratropium bromide nasal spray pump, specifically in patients with perennial nonallergic rhinitis. Two hundred thirty-three patients participated in an 8-week double-blind parallel comparison of ipratropium bromide nasal spray with its vehicle, a saline solution. Treatment with the ipratropium spray resulted in a 30% reduction in rhinorrhea; this reduction was significantly greater than that seen with the saline vehicle. There was a modest reduction in postnasal drip, sneezing, and congestion with both treatments, which may be attributable to the salutary effects of the saline solution. Patients also perceived a significant reduction in the degree to which rhinorrhea interfered with their daily activities and moods. Treatment was well tolerated, with no drug-related systemic adverse events and no evidence of nasal rebound on discontinuation of treatment. Minor, infrequent episodes of nasal dryness and epistaxis were the only significant adverse events reported; these did not limit treatment. (J ALLERGY CLIN IMMUNOL 1995;95:1117-22.)

Key words: Nonallergic rhinitis, ipratropium, rhinorrhea, nasal spray, safety, efficacy

Despite being one of the most common forms of chronic rhinitis seen in clinical practice,¹ perennial nonallergic rhinitis (PNAR) is often resistant to conventional therapy. By definition PNAR has an obscure etiology and cannot be attributed to allergy, infection, or any obvious cause. The absence of an identifiable etiology makes it difficult to select an appropriate treatment based on pathophysiology, and PNAR therefore does not usually respond to specific therapy or first-line rhinitis medications. Symptoms of PNAR can be caused by many nonspecific stimuli over which there is little, if any, effective environmental control—that is, heat, cold, humidity, and various irritants.

Patients with PNAR generally experience intermittent symptoms for 6 to 9 months of the year. These can include hypersecretion, nasal stuffiness,

Abbreviation used

PNAR: Perennial nonallergic rhinitis

sneezing episodes, and postnasal drip. The nasal hypersecretion (rhinorrhea) associated with PNAR can cause significant discomfort and interference with daily activities.² Nasal secretions originate from serous and seromucous glands innervated by the parasympathetic nervous system. Anticholinergic medications would seem to be a possible choice for reducing and controlling such secretions. In Europe and Canada, a fluorocarbon anticholinergic metered-dose inhaler (Rhinatec; ipratropium bromide) has been approved specifically for vasomotor rhinitis, which is sometimes defined as a subset of PNAR. Although it is effective in reducing rhinorrhea, this formulation causes bothersome side effects associated with the drying properties of the freon propellant: nasal

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TABLE I. Sex, race, age, and weight of patients who entered the treatment period

Treatment group	No. of patients	Sex		Race			Mean age (yr) $\pm$ SD	Mean weight (lb) $\pm$ SD
		M	F	White	Black	Other		
Vehicle	116	38	78	106	1	9	44.4 $\pm$ 14.2	160.3 $\pm$ 40.8
Ipratropium bromide (42 μ g)	117	33	84	113	0	4	42.6 $\pm$ 13.9	154.3 $\pm$ 34.5

SD, Standard deviation.

TABLE II. Summary of the four major parts of the trial

	Part I	Part II	Part III	Part IV
Purpose	Screening	Baseline	Treatment comparisons	Follow-up
Treatment	None	Vehicle	Ipratropium bromide, 42 μ g, or vehicle	None
Blind	None	Single-blind	Double-blind	None
Duration	1 wk	1 wk	8 wk	1 wk

TABLE III. Degree of rhinorrhea at baseline

	Vehicle $\pm$ SD	Ipratropium bromide (42 μ g) $\pm$ SD
Patients with symptoms	(n = 89)	(n = 99)
Rhinorrhea severity*	3.08 $\pm$ 0.57	2.92 $\pm$ 0.60
Rhinorrhea duration (hr)	6.45 $\pm$ 2.91	5.84 $\pm$ 2.79
All analyzable patients	(n = 111)	(n = 113)
Rhinorrhea severity*	2.78 $\pm$ 0.88	2.76 $\pm$ 0.76
Rhinorrhea duration (hr)	5.60 $\pm$ 3.25	5.40 $\pm$ 2.92

SD, Standard deviation.

*Five-point scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, 5 = very severe.

dryness, crusting, epistaxis, and nasal irritation. These effects have limited the dosage and frequency of use, two significant drawbacks in the treatment of perennial disease.

The freon-related side effects of the aerosol intranasal formulation have led to the development of an isotonic aqueous ipratropium bromide nasal spray. Several studies have shown that the new spray effectively controls rhinorrhea without causing significant nasal side effects, especially mucosal drying.³⁻⁶ Because most published studies of the new spray have included patients with allergic perennial rhinitis, the purpose of the present study was to determine the safety and efficacy of the spray especially in patients with PNAR.

MATERIAL AND METHODS

This trial compared the efficacy and safety of ipratropium bromide (Atrovent) nasal spray 0.03% with placebo during a treatment period of 8 weeks in 224 patients with PNAR. The patients used two sprays per nostril three times a day, corresponding to 42 μ g of active drug or placebo saline vehicle. Because this solution has been adjusted to the pH of the nasal mucosa and seems to have a salutary effect of its own beyond the "placebo effect," it will be henceforth referred to as "vehicle." This was a double-blind, multicenter, randomized, parallel-group study involving adult patients aged 18 to 75 years who exhibited clinically significant rhinorrhea as a major component of perennial nonallergic rhinitis. Patient demographics are summarized in Table I. Clinically significant anterior nasal rhinorrhea was defined as the following: (1) presence of rhinorrhea for more than 1 hour daily at least 4 days per week in the month prior to the trial; (2) presence of rhinorrhea for 2 to 3 weeks per month for 6 months of the previous year; and (3) a minimum severity of "mild" nasal secretions. This last parameter was scored by patients on the following six-point symptoms scale: 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe. A nonallergic etiology was established by reviewing each patient's history and by performing allergy skin tests for the allergens prevalent in the indoor and outdoor environment at the time of study participation. Patients had to have nasal blockage and/or repetitive sneezing attacks to be included in the trial.

The trial had four parts: screening, placebo run-in, double-blind treatment comparisons, and drug-free follow-up (Table II). The primary efficacy measures as recorded by patients in diaries during the 8-week treatment period were the average duration, average severity,

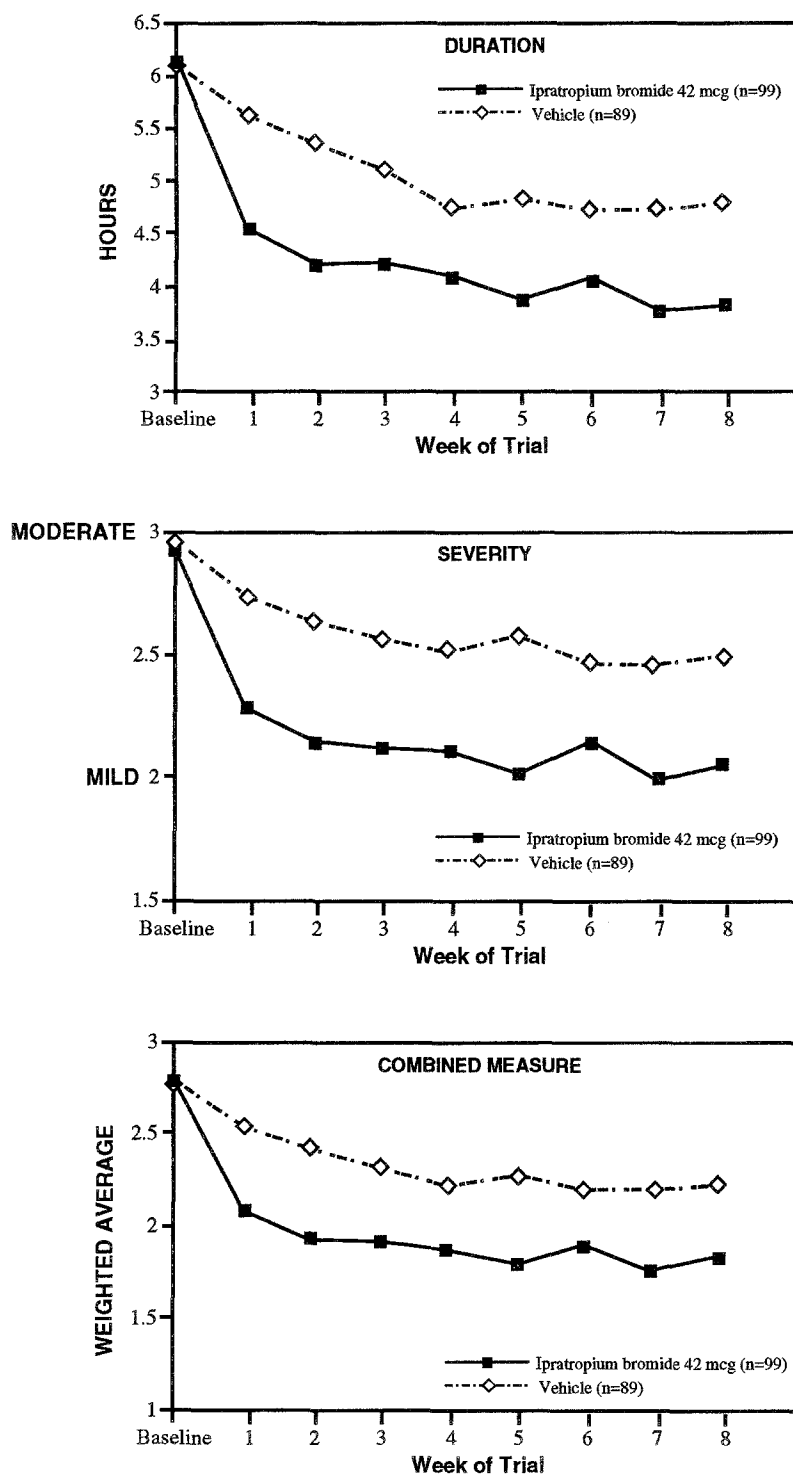


FIG. 1. Adjusted mean change in rhinorrhea during 8 weeks of treatment. The combined measure was a weighted average of duration and severity.

and average combined duration and severity of rhinorrhea. The trial also assessed the effects of ipratropium bromide nasal spray on postnasal drip, nasal congestion, and sneezing associated with PNAR.

Safety was evaluated primarily from reports of adverse

events and laboratory results. Nasal rebound was assessed during a 1-week period in which patients were treated with no nasal medications following the 8-week treatment period. Nasal examinations and nasal cytology were used to assess the effects of ipratropium use on the

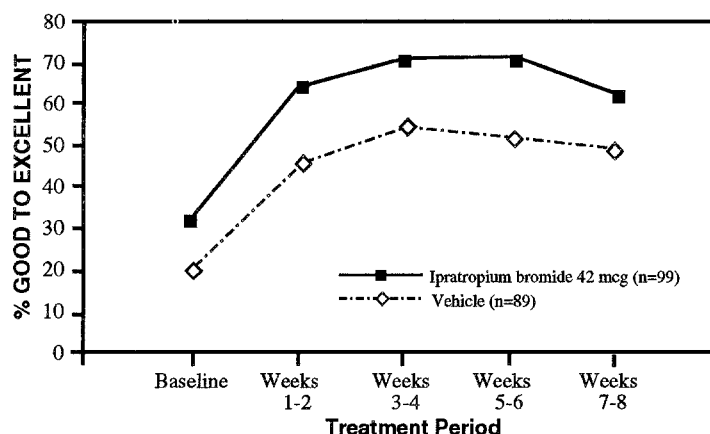


FIG. 2. Proportion of patients with symptoms who believed the trial medication provided either "good" or "excellent" control of rhinorrhea.

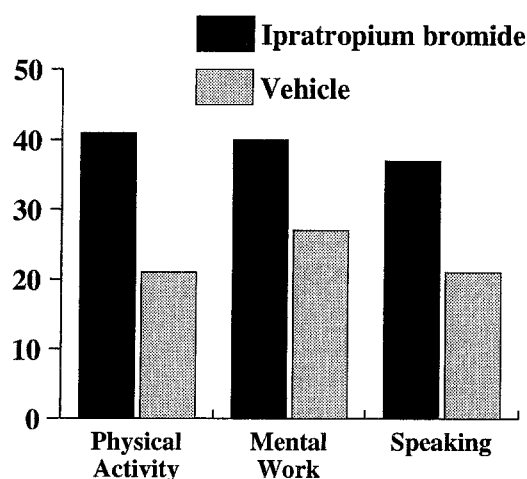


FIG. 3. Reduction in the degree to which rhinorrhea interfered with daily activities and moods: percentage of patients experiencing a significant improvement in quality of life (i.e., interference none or little of the time).

nasal mucosa. Clinical laboratory tests and physical examinations were also performed to evaluate potential systemic effects.

Prior to screening, patients refrained from the use of rhinitis and anticholinergic medications for 1 to 4 weeks. These medications included antihistamines, decongestants, cromolyn, topical and systemic steroids, and tranquilizers with anticholinergic effects. During the 1-week screening period, patient evaluations included a complete blood cell count, chemistry screen, urinalysis, determination of IgE levels, Waters' view x-ray, pregnancy test (where applicable), nasal cytology via rhinoprobe sampling, and recording of vital signs. Skin testing was performed with Multi-test with appropriate regional and environmental allergens.

After qualifying, patients entered a single-blind baseline phase during which they were treated with

TABLE IV. Mean percentage decrease from baseline during the 8 weeks of treatment

	Placebo (n = 89)	Ipratropium bromide (42 µg)/nostril (n = 99)
Combined measure (%)	17	32
Duration (%)	19	34
Severity (%)	15	30

the vehicle spray. All patients who completed this period were entered into the 8-week treatment period. Those who responded significantly to the vehicle alone, that is, those whose rhinorrhea dropped below the level of "mild," were entered into the double-blind phase of the study but were used to evaluate safety only. Those whose rhinorrhea was still "mild" or worse after treatment with the vehicle (approximately 80% of patients) were used for both safety and efficacy analysis. In addition to the daily diaries, the effects of treatment were evaluated weekly during the 8-week period by physical examination. Adverse events were recorded at each visit. Laboratory studies (not including sinus x-rays and determination of IgE levels) were repeated at the end of the 8-week treatment comparison period.

Statistical methods

As in previous studies, significance levels were derived from normal-theory analysis of covariance. Terms included in the statistical model were treatments, centers, treatment-center interaction, and baseline as the covariate. Because sample size was similar in each center, SAS type III analysis (SAS Institute Inc., Cary, N.C.) was used. Symptom averages from the vehicle-treatment run-in week were used as baseline. Symptom averages

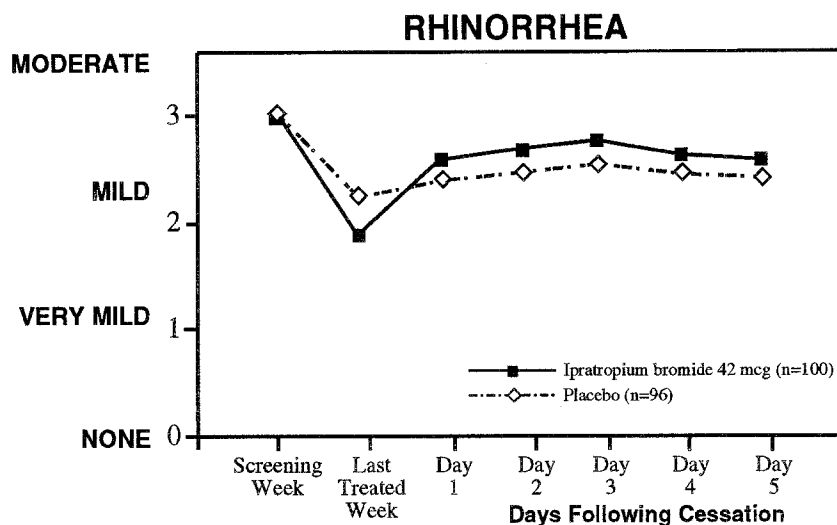


FIG. 4. Absence of nasal rebound on cessation of treatment with ipratropium bromide nasal spray.

from the screening week were used as the covariate for assessment of rebound.

RESULTS

A total of 233 patients were randomly assigned to ipratropium bromide nasal spray 0.03% or vehicle (Table I); analyzable data were obtained for 224 patients. The primary efficacy analysis included 188 patients who did not respond to the vehicle alone. The degree of rhinorrhea at baseline is shown in Table III. Based on patient diaries, those treated with the ipratropium spray experienced rhinorrhea of significantly less severity and shorter duration than those treated with the vehicle spray ($p < 0.05$). The difference between treatments was apparent during the first week and remained stable for the duration of the treatment period. Both groups continued to improve during this period. These results are depicted in Fig. 1.

The mean percentage decrease from baseline with the ipratropium spray was almost double that of the vehicle spray. Both severity and duration of rhinorrhea decreased by at least 30% with ipratropium (Table IV). Global evaluations by patients and physicians were consistent with the results from the patient diaries. The ipratropium spray was judged by 60% to 70% of patients and physicians to have had either an "excellent" or "good" effect on rhinorrhea, compared with 45% to 50% with the vehicle spray (Fig. 2). Although a slight change in postnasal drip, sneezing, and nasal congestion was noted during the 8-week treatment period, there was no significant difference

between the effects of ipratropium and vehicle on these symptoms.

Quality of life evaluations were made prior to and at the end of the trial. Patients rated the degree to which rhinorrhea interfered with their daily activities and affected them emotionally, using a four-point scale: 1 = none of the time, 2 = a little of the time, 3 = some of the time, and 4 = all of the time. At the beginning of the trial, more than 90% believed that rhinorrhea interfered with their daily activities and more than 75% believed that rhinorrhea affected them emotionally. Quality of life subsequently improved with both treatments during the trial. Patients given ipratropium bromide experienced a substantially greater improvement in physical activities and moods than those given the vehicle ($p < 0.05$) (see Fig. 3).

Use of ipratropium bromide nasal spray in this trial was associated with a low incidence of adverse events. There were no serious drug-related adverse events and no nasal rebound after cessation of treatment (Fig. 4). No systemic anticholinergic effects were noted. Nasal adverse events in general were intermittent and of short duration; none required medical intervention or medication except in one patient, who was using the vehicle spray. Epistaxis was seen in 11 patients (9.4%) who were given ipratropium as opposed to three patients (2.6%) who were given the vehicle. Epistaxis was predominantly reported as "mild" (55% with ipratropium and 66% with vehicle) and lasted 12.2 and 7.3 days with the two treatments, respectively. It was not serious enough to disrupt treatment.

TABLE V. Summary of nasal adverse events

Nasal adverse events	No. of patients (%)			
	Vehicle (n = 116)		Ipratropium bromide (42 µg) (n = 117)	
	Total	related*	Total	related*
Epistaxis	2 (1.7)	2 (1.7)	10 (8.5)	8 (6.8)
Blood-tinged mucus	1 (0.9)	1 (0.9)	1 (0.9)	1 (0.9)
Rhinitis	0	0	1 (0.9)	0
Nose congestion	1 (0.9)	0	1 (0.9)	1 (0.9)
Nose dryness	1 (0.9)	1 (0.9)	6 (5.1)	6 (5.1)
Nasal irritation	2 (1.7)	1 (0.9)	1 (0.9)	1 (0.9)
Postnasal drip	1 (0.9)	0	0	0
Rhinorrhea	1 (0.9)	0	2 (1.7)	1 (0.9)
Sneezing	1 (0.9)	0	1 (0.9)	1 (0.9)

*Drug relationship was based on Karch-Lasagna criteria.

Nasal dryness occurred in six patients (5%) who were given ipratropium and one patient (1%) who was given the vehicle. Nasal examinations and assessment of nasal cytology demonstrated that intranasal use of ipratropium bromide had no deleterious effect on the nasal mucosa (see Table V for a summary of adverse events).

DISCUSSION

The rhinorrhea associated with PNAR can be quite annoying and is often resistant to conventional treatments and strategies. Studies involving patients with perennial allergic rhinitis have shown that ipratropium bromide nasal spray 0.03% is safe and effective when administered three times a day;⁴ one study of the drug taken twice a day by patients with PNAR had similar results.³ No previous study has evaluated the administration of the ipratropium spray three times a day in patients with PNAR.

In the present study, treatment with this new aqueous ipratropium bromide spray formulation

resulted in a significantly greater reduction in both the severity and duration of rhinorrhea than treatment with the vehicle spray. The clinical significance of this reduction in rhinorrhea was evident by several measures: patient diary records, global assessment of treatment by both patients and physicians, and improvement in the patients' sense of well-being as demonstrated by a quality of life assessment. A modest improvement in sneezing, congestion, and postnasal drip, although not clinically significant, occurred with both treatments and suggests some benefit to use of the saline vehicle.

There were no systemic anticholinergic or drug-related adverse effects noted with the ipratropium spray compared with its vehicle. Local nasal symptoms were infrequent, mild, and did not limit treatment.

These results indicate that ipratropium nasal spray 0.03% delivered three times a day is effective in reducing rhinorrhea, does not cause significant adverse effects locally or systemically, and can contribute to an improved quality of life for patients with PNAR.

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