

A dose-response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold

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Rhinorrhea is an annoying symptom of the common cold for which effective therapy is not currently available. Ipratropium bromide (IB) is an anticholinergic drug that has been shown to decrease glandular secretion when applied topically to the nasal mucosa. The purpose of this study was to compare the efficacy and safety of three doses of IB nasal spray versus either vehicle or no treatment in relieving rhinorrhea in patients with naturally acquired colds. Rhinorrhea severity was measured objectively by determining nasal discharge weights and subjectively by means of visual analog scale scores. Compared with either vehicle or no treatment, IB nasal spray produced a significant decrease in the severity of rhinorrhea. A dose of 84 µg (two sprays of a 0.06% solution in buffered saline solution) in each nostril was more efficacious than a 42 µg per nostril dose and only marginally less efficacious than a 168 µg per nostril dose. The 84 µg per nostril dose also was associated with fewer adverse events than was the higher dose. None of the adverse events related to intranasal IB therapy was of a serious nature. The use of IB nasal spray appears to be a rational and safe approach to relieving rhinorrhea associated with the common cold. (J ALLERGY CLIN IMMUNOL 1995;95:1139-46.)

Key words: Common cold, ipratropium, nasal spray, rhinorrhea, administration

The common cold is the most frequently occurring acute illness in the industrialized world. Although it is a benign, self-limited condition, the common cold is recurrent and results in a substantial amount of time lost from work and school. Rhinoviruses are the etiologic agents most clearly associated with the common cold; however, the pathophysiology of rhinovirus infection is not completely understood. The primary site of infection is the nasal epithelium, and the constellation of symptoms attending rhinovirus infection appears to emanate from the inflammatory response mounted by the body's immune system rather than from direct cellular necrosis or mucosal

Abbreviations used

IB: Ipratropium bromide
VAS: Visual analog scale

damage. The inflammatory response is characterized in part by the release of chemical mediators from inflammatory cells. These mediators (e.g., bradykinin and substance P) are capable of causing vascular engorgement and increased vascular permeability, which leads to nasal congestion and rhinorrhea, two familiar and unpleasant symptoms of the common cold.

Because there is no cure for the common cold, treatment is directed toward the alleviation of symptoms. Decongestant drugs such as oral and topical sympathomimetic agents can relieve nasal congestion by constricting the nasal microvasculature, but they have little or no effect on rhinorrhea. Because the parasympathetic nervous system regulates the mucous and seromucous glands in the

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nasal mucosa that are responsible for the production of rhinorrhea, this system is a logical target for drug therapy. Indeed, the competitive muscarinic receptor blocking agent, atropine methonitrate, has been shown by Gaffey et al.¹ to reduce nasal mucus production when administered intranasally to subjects with experimentally induced viral rhinitis. However, in this study the dose of atropine methonitrate required to suppress rhinorrhea also produced systemic anticholinergic side effects.

Ipratropium bromide (IB) is a quaternary ammonium derivative of atropine that is minimally absorbed across biologic membranes. This characteristic of IB limits its systemic anticholinergic side effect liability after topical application to the nasal mucosa and makes the drug an ideal candidate for alleviating mucus hypersecretion in the early stages of a common cold. The present study was undertaken to assess the efficacy and safety of three different concentrations of IB nasal spray versus vehicle in relieving rhinorrhea symptoms in patients with naturally acquired common colds. For comparative purposes a no treatment group also was included in the study design.

MATERIAL AND METHODS

Study design

The study was conducted at six geographically diverse sites in the United States between October 30, 1990, and March 29, 1991. The date for the end of the study was selected to avoid the onset of the allergy season. A parallel as opposed to a crossover design was used in light of the relatively brief duration of rhinorrhea symptoms associated with the common cold. Two control groups were included in the trial; one group received a buffered saline solution nasal spray (the vehicle for IB), and the other group received no treatment and was included to allow evaluation of the relative contribution of the vehicle to the therapeutic effects of IB nasal spray. The study was double-blind with respect to IB and vehicle.

Study participants

A total of 955 patients (492 male subjects and 463 female subjects) between the ages of 12 and 70 years (mean age, 27.5 years) participated in the study. The patients were recruited from the general population, primarily through advertising. Upon arrival at the study site, each patient was screened to ensure the presence of the following three specific enrollment requirements: (1) swollen, erythematous nasal mucosal membranes on visual examination; (2) subjective reporting of a moderate or greater degree of rhinorrhea present for no more than 36 hours; and (3) production of 1.5 gm or more of

nasal discharge during a 1-hour baseline measurement period.

Patients were excluded from the study if they had significant cardiovascular, renal, hepatic, endocrine, metabolic, neurologic, pulmonary or other systemic disease or if they had a history of asthma or other chronic respiratory disease, perennial rhinitis, nasal polyps, glaucoma, or unresolved prostatic hypertrophy. Patients with allergic rhinitis were excluded if their allergen was in season or ubiquitous in their environment (e.g., animal dander). In addition, subjects were not admitted to the study if they had a positive *Streptococcus* culture, the presence of rales or rhonchi indicative of a lower respiratory tract infection, an oral temperature of higher than 102° F, or a history of frequent complications such as sinusitis or bronchitis arising from an upper respiratory tract infection. Also excluded were lactating women, women with positive results of a pregnancy test, women of childbearing potential who were not using a medically approved method of contraception, persons judged incapable of accurately maintaining a symptom record form, and individuals who could not tolerate anticholinergic drugs or who were sensitive to the preservative present in the IB nasal spray vehicle, benzalkonium chloride.

At each study site, the trial was approved by the appropriate institutional review board. Subjects who presented at a study site, whether admitted to the trial or not, signed an informed consent form. A legal guardian signed on behalf of subjects less than 18 years of age.

Drug administration

Patients were randomly assigned to receive either no treatment, vehicle treatment, or treatment with IB nasal spray. The duration of each treatment was 4 days. Before beginning the drug administration phase of the study, patients were instructed in the proper use of the nasal spray dosage form, which delivered 0.07 ml per actuation. Three concentrations of IB nasal spray were used: 0.03%, 0.06%, and 0.12%. The dose of each concentration was two sprays (yielding 42, 84, or 168 µg) in each nostril three times daily at roughly equal time intervals during the waking hours. The distribution of patients among the five groups was approximately equal.

Concomitant medications

The concomitant use of over-the-counter analgesics such as aspirin, acetaminophen, and ibuprofen was allowed during the trial. Use of either Robitussin or Robitussin-DM (A.H. Robins Company, Inc., Richmond, Va.) also was permitted during the trial. For 24 hours before being entered into the trial and throughout the duration of the trial, patients were not allowed to take any other medications, over-the-counter or prescription, for relief of their cold symptoms. Drugs with anticholinergic properties, such as antihistamines and antidepressants, also were prohibited during this period.

Data collection

On the first day of the study, before being randomly assigned to a no treatment, vehicle, or IB nasal spray treatment group, patients underwent a nasal and general physical examination and completed a baseline subjective self-assessment of the severity of their nasal symptoms (rhinorrhea, sneezing, and nasal congestion) using a modified visual analog scale (VAS). The modified VAS consisted of a horizontal line with a 0- to 10-point scale below it. Patients were asked to rate the severity of their symptoms by inscribing a vertical line on the VAS. A score of 0 indicated an absence of a given symptom, and a score of 10 represented an unbearable level of discomfort necessitating additional treatment and withdrawal from the trial. Intermediate degrees of discomfort were defined as very mild (doubtful, trivial, or just noticeable), mild (present but not uncomfortable), moderate (present and somewhat uncomfortable or annoying), and severe (present and definitely uncomfortable or annoying).

Before randomization on day 1, patients also were required to collect their nasal secretions during a 1-hour baseline period. This was accomplished by giving each patient a preweighed, sealed plastic bag containing a packet of paper tissues. Patients were instructed to use the tissues to clear their nose whenever necessary and to keep the tissues in the sealed plastic bag to minimize evaporation. The weight of nasal secretions produced during the baseline period was determined as the difference between the final and starting weights of the tissues and the plastic bag. Immediately after the baseline measurement, the first dose of IB nasal spray or vehicle was administered.

Objective measurements (nasal discharge weights) and subjective assessments (VAS scores) of the severity of rhinorrhea were repeated hourly on day 1 for 6 hours after treatment or no treatment and hourly for 3 hours on day 2 after treatment or no treatment. At the time patients left the study site on day 1, they were given symptom record forms to be completed daily in the evening for 4 consecutive days. The forms used VAS scores to assess the nasal symptoms of rhinorrhea, sneezing, and nasal congestion experienced by the patients during the course of the entire day. Patients in the no treatment group were not required to complete symptom record forms; these patients completed their study participation at the end of day 2. Five to 7 days after randomization, patients in the four treatment groups returned to the study site for a final nasal and physical examination. At this time, the patients also returned their daily symptom record forms and trial medication containers.

Adverse events were monitored throughout the trial by questioning patients about the development of problems since their previous visit. Adverse events were recorded along with the date of onset, duration and intensity, relationship to the investigational drug, action taken with respect to the investigational drug, treatment required, and event outcome.

Data analysis

One of the major objectives of this trial was to determine whether rhinorrhea was diminished in patients who received three different doses of IB nasal spray compared with those who were treated with vehicle alone or who received no specific therapy at all. Two primary efficacy endpoints were selected to detect changes in rhinorrhea: nasal discharge weights and in-clinic VAS scores. Weights of nasal discharge for each of the 6 hours after the dose was taken on day 1 and for each of the 3 hours after the dose was taken on day 2 were averaged to obtain mean hourly discharge weights for days 1 and 2, respectively. Furthermore, weights of nasal discharge for the first 3 hours on day 1 and the first 3 hours on day 2 were averaged to obtain a mean for the 2 test days combined. VAS scores were averaged in the same manner as nasal discharge weights, except that baseline scores were first subtracted from scores after the dose was taken to assess degrees of improvement in this subjective index of rhinorrhea. Secondary efficacy endpoints also were included in the data analysis; these endpoints were the daily at-home VAS scores for rhinorrhea, sneezing, and nasal congestion.

For the two primary endpoints the following hypotheses were tested: (1) there is no difference between the no treatment and treatment groups, and (2) there is no difference between the vehicle group and the IB nasal spray groups. For the secondary endpoints, only the second hypothesis was tested because no data were obtained for the no treatment group. The statistical model used to test the hypotheses included fixed terms for center, treatment, and treatment by center interaction. In addition, baseline was used as a covariate in all analyses except for those performed on the secondary endpoints of daily sneezing and nasal congestion. Adjusted means are SAS LSMEANS resulting from the specified model.

RESULTS

Efficacy

Overall, this trial demonstrated that IB nasal spray produced a significant reduction in rhinorrhea in patients with the common cold as measured objectively by nasal discharge weights and subjectively by in-clinic VAS scores. Mean hourly nasal discharge weights plotted as a function of time are shown in Fig. 1, and mean nasal discharge weights for hours 1, 2, and 3 after the dose was administered on days 1 and 2 are displayed in Table I. All five groups exhibited decreases in nasal discharge weight over time on both days 1 and 2 (Fig. 1). However, the decreases were greater for the IB nasal spray and vehicle-treated groups than for the no treatment group. Furthermore, within the IB treatment groups, a dose-related increase in efficacy was evident between the 0.03% and 0.06% treatment groups but not between the 0.06% and 0.12% treatment groups (Table I).

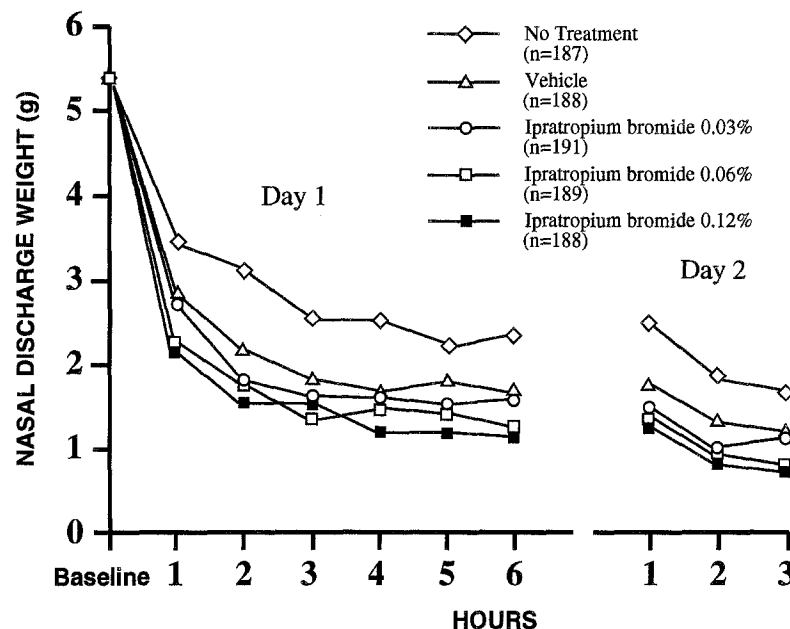


FIG. 1. Mean hourly nasal discharge weights for day 1 of trial.

TABLE I. Adjusted mean hourly nasal discharge weight (μ g) averaged over days 1 and 2*

	Baseline	After administration	Difference from no treatment (%)	Difference from vehicle (%)
No treatment	5.41	2.55		
Vehicle	5.17	1.86†	0.69 (27)	
Ipratropium bromide 0.03%	5.71	1.62†	0.93 (36)	0.24 (13)
Ipratropium bromide 0.06%	5.64	1.36†‡	1.19 (47)	0.50 (27)
Ipratropium bromide 0.12%	5.21	1.36†‡	1.19 (47)	0.50 (27)

*Adjusted for center, treatment-by-center interaction, and baseline.

† $p < 0.01$ versus no treatment.‡ $p < 0.02$ versus vehicle.

Comparison of data from the no treatment group with data from the four treatment groups revealed consistent, statistically significant ($p < 0.001$) mean decreases in hourly nasal discharge weight for all four treatment groups on both day 1 and day 2. The combined day 1 and day 2 means listed in Table I show that the vehicle group had 27% less discharge, the 0.03% IB group had 36% less discharge, and the 0.06% and 0.12% IB groups each had 47% less discharge than the no treatment group. These results clearly indicate that although untreated patients show a decrease in nasal discharge weight over time, treatment with either buffered saline solution vehicle or IB nasal spray produces a still further decrease.

An analysis of nasal discharge weight data was undertaken to evaluate possible differences between vehicle and IB treatment groups. The mean

hourly nasal discharge weights associated with the two higher doses of IB were found to be significantly lower ($p < 0.02$) than the corresponding mean of the vehicle group. The lowest dose of IB nasal spray did not produce an effect significantly superior to that produced by vehicle when mean nasal discharge weights were compared for day 1 alone, day 2 alone, or for days 1 and 2 combined.

The results of the patients' in-clinic self-evaluation of the severity of their rhinorrhea paralleled the results of the nasal discharge weight assessments. Mean VAS scores as a function of time for days 1 and 2 are shown in Fig. 2. All five groups demonstrated an improvement from baseline over time that persisted for the entire 6-hour postdose observation period on day 1 and the entire 3-hour postdose period on day 2. On each day, the improvement in the mean hourly

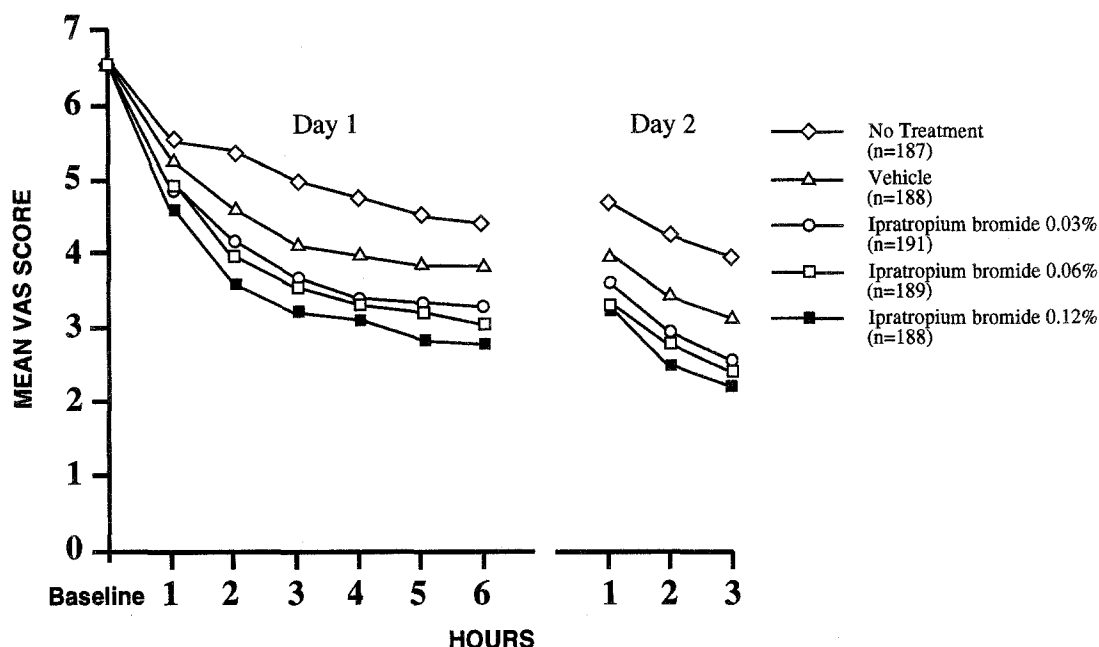


FIG. 2. Mean VAS assessment of severity of rhinorrhea for days 1 and 2.

VAS scores was significantly greater ($p < 0.001$) for the four treatment groups than for the no treatment group. Groups receiving IB nasal spray had an improvement in mean hourly VAS scores that exceeded those of the vehicle treated group, and within the IB-treated groups the magnitude of improvement in VAS scores was dose related.

Comparison of change from baseline VAS scores for the no treatment group with corresponding VAS scores for the four treatment groups (using combined data from hours 1 through 3 after administration of the dose on days 1 and 2) revealed highly significant ($p < 0.001$) improvements for all treatment groups. Compared with the no treatment group, mean VAS score improvement was 40% greater for the vehicle treated group, 65% greater for the 0.03% IB group, 73% greater for the 0.06% IB group and 89% greater for the 0.12% IB group (Table II). Similarly, comparison of change from baseline VAS scores for the vehicle-treated group with the three IB-treated groups revealed highly significant ($p < 0.004$) improvements for each of the IB groups. Compared with the vehicle-treated group, mean VAS score improvement was 18% greater for the 0.03% IB group, 24% greater for the 0.06% IB group, and 35% greater for the 0.12% IB group (Table II).

TABLE II. Adjusted mean improvement in severity of rhinorrhea (VAS)*

	Mean improvement†	% Difference no treatment	% Difference vehicle
No treatment	1.77		
Vehicle	2.48‡	40	
Ipratropium bromide 0.03%	2.92‡§	65	18
Ipratropium bromide 0.06%	3.07‡§	73	24
Ipratropium bromide 0.12%	3.35‡§	89	35

*Adjusted for center, treatment-by-center interaction, and baseline.

†Change from baseline.

‡ $p < 0.001$ versus no treatment.

§ $p < 0.004$ versus vehicle.

To assess the clinical benefit of rhinorrhea reduction, the percentage of patients in each treatment group reaching a severity level low enough to represent a clinically significant improvement was calculated. At entry, all patients rated the severity of their rhinorrhea symptoms as moderate or

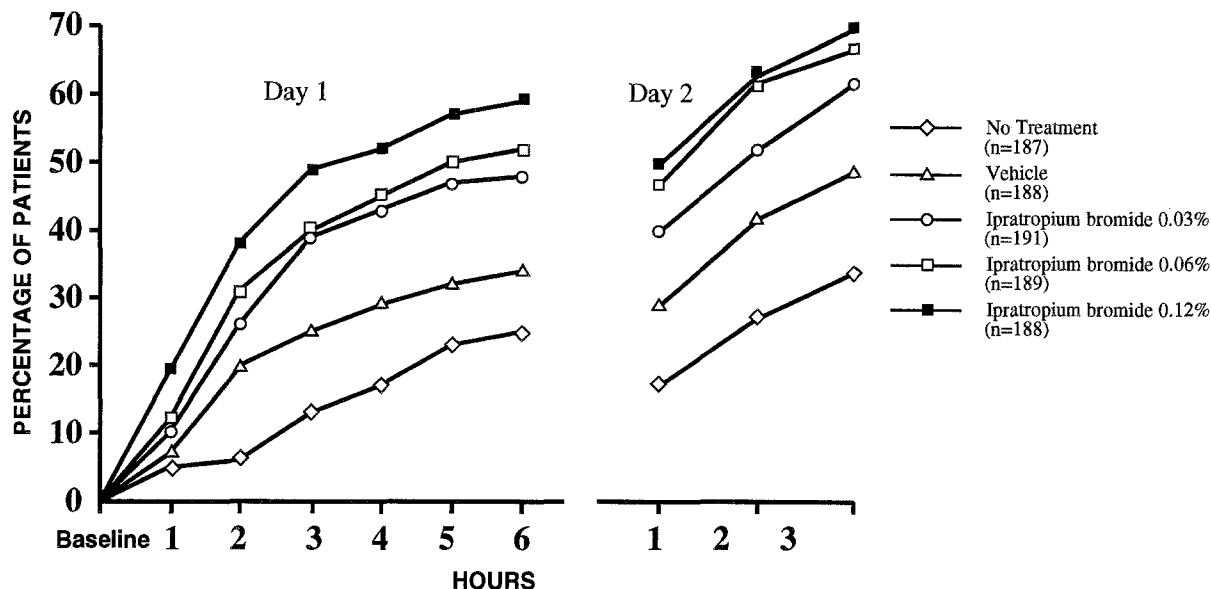


FIG. 3. Percentage of patients whose rhinorrhea symptoms improved to "very mild" or "none" on days 1 and 2.

worse. The percentage of patients improving to a severity level of very mild or none was considered a measure of the clinical benefit of treatment. The percentage of patients in each group who reached these low levels of rhinorrhea severity at each hourly measurement interval on days 1 and 2 is displayed in Fig. 3. All treatment groups demonstrated some improvement during the 6-hour observation period on day 1 and the 3-hour observation period on day 2, but the IB groups showed substantially greater improvements than the no treatment or vehicle treatment groups. In addition, the improvements noted in the IB groups were dose related. These results demonstrate the value of IB treatment using a clinically meaningful endpoint.

Daily at-home VAS scores rating the severity of patients' nasal symptoms were used as secondary efficacy endpoints. Analyses of these data showed that all three doses of IB nasal spray were superior to vehicle in improving the severity of rhinorrhea during the entire 4-day trial period. IB nasal spray had no clearly detectable effect on patients' self-evaluation of the severity of nasal congestion or sneezing.

Safety

The safety component of this trial included nasal and physical examinations conducted before and at the conclusion of each patient's participation and

the recording of adverse events as they occurred during the course of the investigation. There were no consistent, clinically significant changes noted on final nasal or physical examination. Likewise, there were no serious adverse events or deaths reported during or after conclusion of the trial. The incidence of adverse events was highest in the IB treatment groups (31%, 23%, and 22% for the 0.12%, 0.06%, and 0.03% IB groups, respectively) and lowest in the vehicle and no treatment groups (12% and 3%, respectively).

Headache was the most frequently reported nonnasal adverse event. This event was reported with similar frequency among all treatment groups (5.3% to 8.7% incidence). The most commonly reported nasal adverse events were nasal dryness (incidence of 3%, 6%, 5%, and 10% respectively in vehicle, 0.03%, 0.06%, and 0.12% IB treatment groups); blood-tinged nasal mucus (incidence of 1%, 7%, 9%, and 10%, respectively, in the aforementioned treatment groups); and epistaxis (incidence of 0%, 5%, 6%, and 7%, respectively, in the aforementioned treatment groups). None of the nasal bleeding events was of sufficient severity to require patient discontinuance from the trial.

Eleven patients in the IB treatment groups reported adverse events that could be classified as anticholinergic in nature. There were nine reports of dry mouth, one report of blurred vision, and one report of tachycardia. Most of the anticholinergic

adverse events were reported by patients in the high-dose (0.12%) IB treatment group.

DISCUSSION

The efficacy of various formulations and dosages of IB nasal spray in relieving the rhinorrhea that typically attends the common cold has been studied previously by three different groups of investigators. Borum et al.² examined the efficacy of an inhalation aerosol formulation of IB administered intranasally at a dose of 40 µg per nostril four times a day to patients with spontaneously occurring colds. These investigators found that, compared with placebo, IB significantly reduced rhinorrhea. The effect was most prominent during the first 3 days of a 7-day treatment period. However, the index used to assess efficacy in this study (number of paper tissues used per day) was somewhat crude, and the interpretation of the study results was complicated by the fact that all patients received pretreatment with a vasoconstrictor nasal spray.

Gaffey et al.³ used an induced-cold model to evaluate the efficacy of IB in relieving rhinorrhea. These investigators also used an inhalation aerosol formulation of IB and administered the drug intranasally three times a day at a dose of 40 µg per nostril beginning 24 hours after the instillation of rhinovirus into the nasal cavity. The primary efficacy endpoint was nasal discharge weight measured over the course of 5 days. No significant difference in total nasal discharge was noted between the IB treated group and a control, placebo treated group. However, there was a trend toward less nasal discharge in the IB treatment group and, compared with the individuals in the placebo group, the individuals in the IB group perceived their rhinorrhea to be less severe during the last 4 days of treatment. The induced colds in this study were quite mild, and the number of patients per treatment group was relatively small. One or both of these factors may have been responsible in part for the failure of IB to produce a conclusive effect on rhinorrhea.

Most recently, Dockhorn et al.⁴ evaluated the efficacy of IB nasal spray and vehicle in patients with naturally occurring colds. The protocol for this study was essentially the same as that used in the current study, with the following notable exceptions: in the previous study only one dose (84 µg per nostril) of IB was used; the dosage regimen was four times a day rather than three times a day; no minimum amount of nasal discharge weight was required for enrollment; and a no treatment group

was not included in the trial. The results of the study showed that IB treatment reduced nasal discharge weight an average of 18% beyond that which occurred after vehicle treatment. In addition, the VAS scores of the group treated with IB were on average 22% better than the VAS scores of the vehicle-treated group. Both results were statistically significant.

In the present study, IB in a saline solution-buffered vehicle was administered as a nasal spray to patients with naturally acquired colds at three dose levels three times a day for 4 days. To qualify for the study, patients had to have at least a moderate level of rhinorrhea with an onset of 36 hours or less. By selecting patients whose colds were in the early and particularly annoying secretory phase, and by confirming this through measurements of nasal discharge weight and patient self-assessment, a study population was assembled in which topical intranasal anticholinergic therapy was most likely to be beneficial. This proved to be the case. Patients treated with IB nasal spray at any of three different dosage levels experienced a reduction in rhinorrhea severity that significantly exceeded the reduction noted in a no treatment group or in a buffered saline solution vehicle treated group. By comparing differences in efficacy between the three doses of IB nasal spray and contrasting this information with reported incidences of adverse events, a dose of two sprays of a 0.06% solution of IB in each nostril was determined to be the safest and most effective dose for alleviating the symptom of rhinorrhea in patients with colds.

Two clinically important aspects of IB nasal spray therapy were not specifically addressed in the present study, that is, onset and duration of action. Borum⁵ has shown that intranasal IB is capable of inhibiting nasal hypersecretion induced by methacholine within minutes. And in the current study, significant effects on nasal discharge weights and VAS scores were noted within 1 hour. It is therefore likely that patients with colds who are seeking relief of rhinorrhea will experience a rapid beneficial effect from IB nasal spray. The duration of rhinorrhea relief provided by IB nasal spray has not been documented in patients with colds, but it is clearly in excess of 3 hours. This conclusion is based on the observation that on both days 1 and 2 of the present study, significant relief of rhinorrhea was noted at the end of a 3-hour observation period. It is not possible to state how much longer than 3 hours IB remained effective, because the protocol for the study did not stipulate a specific

administration interval; therefore, on day 1, when measurements were carried out for 6 hours, some patients received a second dose of drug between hours 3 and 6. Interestingly, Borum's study of inhibition of methacholine-induced nasal hypersecretion showed that IB was effective for at least 8 hours.⁵

There is need for a safe, rapid, and long-acting therapeutic agent to treat rhinorrhea associated with the common cold. In light of the results of this and earlier studies, IB in the form of a 0.06% nasal spray appears to be such an agent. As such, it is deserving of careful consideration by those responsible for prescribing symptomatic therapy for patients suffering from the common cold.

CONCLUSION

IB nasal spray was found to be effective in reducing the specific symptom of rhinorrhea in patients with the common cold. A dose of 84 μ g (two sprays of a 0.06% solution in buffered saline solution) in each nostril produced demonstrable relief of rhinorrhea within 1 hour. This dose of IB was more efficacious than a 42 μ g per nostril dose and only marginally less efficacious than a 168 μ g per nostril dose. Furthermore, the 84 μ g per nostril

dose was associated with fewer adverse events compared with the higher dose. None of the adverse events related to intranasal IB therapy was of a serious nature. The use of IB nasal spray appears to be a rational and safe approach to relieving the rhinorrhea that typically attends the common cold.

REFERENCES

1. Gaffey MJ, Gwaltney JM Jr, Dressler WE, Sorrentino JV, Hayden FG. Intranasally administered atropine methonitrate treatment of experimental rhinovirus colds. *Am Rev Respir Dis* 1987;135:241-4.
2. Borum P, Olsen L, Winther B, Mygind N. Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold. *Am Rev Respir Dis* 1981;123:418-20.
3. Gaffey MJ, Hayden FG, Boyd JC, Gwaltney JM Jr. Ipratropium bromide treatment of experimental rhinovirus infection. *Antimicrob Agents Chemother* 1988;32:1644-7.
4. Dockhorn R, Grossman J, Posner M, Zinny M, Tinkelman D. A double-blind, placebo-controlled study of the safety and efficacy of ipratropium bromide nasal spray versus placebo in patients with the common cold. *J ALLERGY CLIN IMMUNOL* 1992;90(suppl):1076-82.
5. Borum P. Intranasal ipratropium: inhibition of methacholine induced hypersecretion. *Rhinology* 1978;16:225-33.