Use of Ipratropium Bromide in Asthma

Results of a Multi-Clinic Study

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A multi-center, double-blind, 90-day study compared an ipratropium bromide metered-dose inhaler (40 μg four times a day) with a metaproterenol metered-dose inhaler (1,500 μg four times a day) in 164 patients with asthma; of the 144 patients who completed the study, 71 received ipratropium and 73 received metaproterenol. Our results suggest that both drugs were equally effective bronchodilators. Although the shape of the pulmonary function response curves suggested that ipratropium has different bronchodilator kinetics than metaproterenol (in that it has a slower onset of action and a more prolonged duration), comparison of the areas under the curves for the two drugs showed that there was no statistical difference between ipratropium or metaproterenol. The only significant side effects noted with ipratropium were cough and exacerbation of symptoms; no anticholinergic side effects were noted.

Although anticholinergic drugs have not previously been approved for use in the treatment of asthma in the United States, many physicians use aerosolized atropine, delivered by a compressor-nebulizer, for the treatment of bronchospasm [1]. Ipratropium bromide, a quaternary derivative of atropine, was developed to provide bronchodilation without anticholinergic side effects, such as dry mouth and tachycardia. The current study was conducted to evaluate the efficacy and safety of ipratropium bromide, delivered by a metered-dose inhaler, in the treatment of patients with asthma over a 90-day period.

PATIENTS AND METHODS

This double-blind, randomized, parallel, multi-center trial was conducted at five sites in the United States: Colorado Springs, Colorado; Madison, Wisconsin; Denver, Colorado; Portland, Oregon; and Ann Arbor, Michigan. The study objective was to compare the safety and efficacy of ipratropium bromide with those of a standard beta-adrenergic bronchodilator, metaproterenol sulfate. Both drugs were delivered by metered-dose inhalers. All patients who entered the study met the American Thoracic Society criteria for bronchial asthma. Patients ranged in age from 13 to 50 years, with an average age of 31.0 years. There were 82 male and 82 female patients enrolled. Each patient had a forced expiratory volume in one second (FEV_1) of less than 75 percent of predicted normal, and a ratio of FEV_1 to forced vital capacity of less than 70 percent. In addition, reversibility of airways obstruction was required, as evidenced by a 15 percent or greater improvement of FEV_1 within 30 minutes after inhalation of two puffs (0.15 mg) of isoproterenol from a standard metered-dose inhaler. Patients with any significant medical diseases, prostate disease, bladder neck obstruction, narrow-angle glaucoma, or a clinical diagnosis of chronic bronchitis were excluded from the study. Also excluded were patients who were hypersensitive to sympathomimetic or anticholinergic

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TABLE I Patient Characteristics by Group and Overall*

	Ipratropium	Metaproterenol	Overall
Sex:			
Female	42	40	82
Male	39	43	82
Asthma history			
Diagnosis			
Intrinsic	16	20	36
Extrinsic	41	43	84
Both	24	18	42
Not reported	0	2	2
Severity			
Mild	10	18	28
Moderate	58	55	113
Severe	13	8	21
Not reported	0	2	2

*For original cohort of 164 patients.

agents; patients who were or expected to become pregnant; patients who smoked regularly during the previous year or who had a smoking history of more than 10 pack-years; and patients with chronic sputum production. Before the start of the study, electrocardiograms, complete blood cell counts, biochemical surveys, and urinalyses were obtained for all patients; patients with clinically significant abnormalities on these tests were excluded. Prior to entry in the study, all patients gave written informed consent, according to the guidelines of each investigator's local committee for the protection of human rights.

After the screening visit, patients entered a two-week washout period during which all oral and inhaled beta-adrenergic bronchodilators and all anticholinergic drugs were excluded. They then entered the 90-day period of the study in which they were randomly assigned to one of two treatment groups: ipratropium, two puffs (40 μg) four times a day, or metaproterenol, two puffs (1,500 μg) four times a day. Patients were instructed as to the proper use of a metered-dose inhaler.

Concomitant medications that were allowed during the 90-day period were oral theophylline products, inhaled steroids, inhaled cromolyn sodium, and antibiotics; doses of these agents (except for the antibiotics) had to be stable throughout the study. Oral corticosteroids were only allowed if the dosage was stable and was equal to or less than 20 mg of prednisone (or its equivalent) every other day. Any patient who required an increased dose of steroids during the study was allowed to continue in the study only if the increased dose did not last more than five days and if there were no more than two of these increased dosage periods. No inhaled bronchodilators, other than the study drugs, were allowed. For the treatment of an acute asthmatic episode during the study period, parenteral epinephrine, parenteral terbutaline, or intravenous aminophylline were the only drugs permitted.

The first day of the 90-day treatment period began with a clinic visit at which pulmonary function tests monitored over six hours were given. In preparation for this and the other pulmonary function test days, patients discontinued all medication the evening before the visit. Spirometry (FEV_1, forced vital capacity, forced expiratory flow between 25 and 75 percent of forced vital capacity, and peak expiratory flow rate) was performed at baseline, at five, 15, and 30 minutes, and at one, two, three, four, five, and six hours after drug administration. Each patient was given the blinded metered-dose inhaler, which was then used on a daily basis at home for the next 90 days. Each patient was instructed and observed during the administration of the medication for proper inhalation technique. Pulse and blood pressure were recorded at the same time points as the pulmonary function tests were done. No caffeinated beverages were allowed at any time during this six-hour pulmonary function test day. Identical procedures for pulmonary function testing were followed on days 45 and 90.

Bronchodilator efficacy was evaluated on the basis of the FEV_1 response to drug treatment. The primary measure of FEV_1 efficacy that was used for the statistical analysis was the area under the FEV_1 curve (calculated using the trapezoidal rule). Treatment comparisons were made using an analysis of covariance. The statistical model also included terms for treatment and clinics. Median durations of action among patients who showed a response were compared using the median test.

RESULTS

Originally, 164 patients were entered into the study, but only 144 completed the full 90-day period and were available for the statistical analysis of pulmonary function. Nine patients in the ipratropium group dropped out: three who were lost to follow-up and six because of lack of efficacy. From the metaproterenol group, seven patients dropped out: three because of side effects; two who were lost to follow-up; one because of lack of efficacy; and one for protocol violation. Seventy-one of the 144 patients received ipratropium, and 73 received metaproterenol.

All 164 patients were included in the summary of patient characteristics. The two treatment groups were compared as to age, sex, height, weight, asthma history, and other parameters. There were no significant differences between the treatment groups; they were comparable in median age, median age of asthma onset, and median height and weight. **Table I** summarizes important parameters for the two groups. Baseline values for FEV_1 on day 1 prior to drug administration were not significantly different (ipratropium 2.44 liters, metaproterenol 2.32 liters).

The prior use of asthma medications by each of the two treatment groups was recorded. More patients in the ipratropium group (43) had a past history of steroid use than in the metaproterenol group (27), but this was not statistically significant. During the study, steroid use was comparable between the two groups. In addition, both groups used equivalent amounts of medications. Nearly all of the patients required theophylline, and approximately 25 percent of the patients in each group received inhaled steroids.

The mean FEV_1 (adjusted for baseline differences) val-

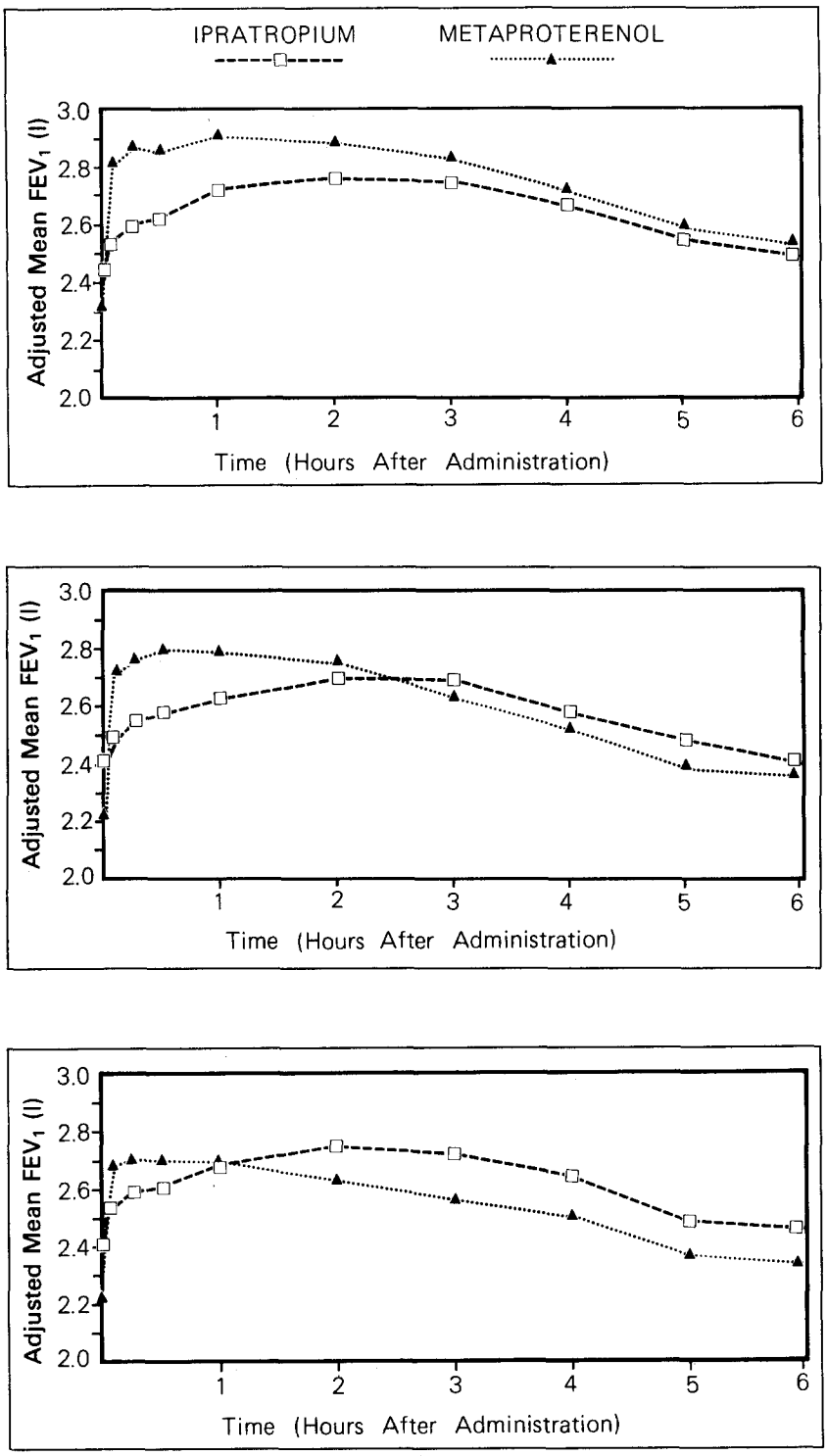

Figure 1. *Changes in FEV_1 for all patients on days 1 (**top**), 45 (**middle**), and 90 (**bottom**).*

ues at each time after drug administration on study days 1, 45, and 90 are shown in **Figure 1**. On day 1, the area under the curve for metaproterenol was slightly larger than for ipratropium, but this was not statistically significant ($p = 0.15$). On day 45, the areas under both curves were almost identical, and on day 90, the area for ipratropium was larger than that for metaproterenol. The differences in areas under the curves were not statistically significant.

When the pulmonary function responses were examined closely, it became apparent that a number of patients in each treatment group had no bronchodilator response

TABLE II Bronchodilator Efficacy in Responders

FEV_1 (liters)	Ipratropium			Metaproterenol		
	Day 1	Day 45	Day 90	Day 1	Day 45	Day 90
Onset of 15 percent or greater increase in a majority of patients (minutes)	≤15	≤15	≤15	≤5	≤5	≤5
Median duration of 15 percent or greater increase (hours)	5.5	3.0	5.0*	4.0	3.0	2.0
Median time to peak effect (hours)	2.0	2.0	1.5	1.0	0.5	0.25

*Significant difference in favor of ipratropium.

TABLE III Number of Patients with Adverse Experiences Following Treatment with Ipratropium or Metaproterenol*

	Ipratropium (81 patients treated)		Metaproterenol (83 patients treated)	
	Number	Percent	Number	Percent
Cardiovascular				
Tachycardia	0	0	1	1.2
Palpitations	0	0	3	3.6
Central nervous system				
Dizziness	3	3.7	3	3.6
Nervousness	5	6.2	14	16.9
Headache	4	4.9	2	2.4
Insomnia	1	1.2	1	1.2
Weakness	0	0	1	1.2
Drowsiness	0	0	1	1.2
Dermatologic				
Rash	1	1.2	1	1.2
Hives	0	0	1	1.2
Oro-otolaryngeal				
Dry mouth	1	1.2	0	0
Musculoskeletal				
Tremor	0	0	2	2.4
Respiratory				
Exacerbation of symptoms	6	7.4	1	1.2
Cough	8	9.9	2	2.4

*For original cohort of 164 patients.

and that this obscured the interpretation of the response characteristics such as onset, duration, and time to peak effect. Patients were therefore classified as responders or non-responders based on whether or not they achieved at least a 15 percent increase over baseline FEV_1 values within two hours following the test dose on day 1. Forty of 78 (51 percent) of the patients receiving ipratropium and 56 of 77 (73 percent) of the patients receiving metaproterenol were defined as responders by this definition. In responders, the onset of bronchodilation was slower and the time to peak effect and duration of action longer with ipratropium than with metaproterenol (**Table II**). A statistical search technique [2] did not reveal any physical or clinical characteristics that might be predictive of response to ipratropium.

Global evaluations of asthma symptoms performed by physicians at two-week intervals showed that both treatment groups had almost identical scores. No differences whatsoever were noted in the severity of day-to-day asthma in either treatment group.

Pulse rates and blood pressure determinations were recorded during the pulmonary function testing days. On each test day, mean pulse decreased about two to five beats per minute with both ipratropium and metaproterenol. These decreases reached statistical significance with respect to baseline, but not between the drugs. After treatment with both drugs, the mean systolic and diastolic blood pressure readings declined 0 to 4 mm Hg from the baseline measurements on each of the pulmonary function test days. None of the changes in either pulse rate or blood pressure was clinically significant. The laboratory analyses before and after the 90-day treatment period, including complete blood cell counts, biochemical surveys, electrocardiograms, and urinalyses, did not reveal any abnormalities that were deemed to have any clinical significance by the investigators. There were no statistically significant differences in the mean laboratory values compared with baseline values in either treatment group during the 90 days of study.

Table III shows adverse experiences associated with the drugs. The most common adverse experiences noted in the ipratropium group were cough and exacerbations of symptoms. Side effects attributed to metaproterenol in a total of three patients were shakiness (two patients), headache and dizziness (one patient), and nervousness, face and body rash, and mouth irritation (one patient). Tachycardia, palpitations, and tremor were not observed with ipratropium, but occurred in 4.8 percent of the patients who received metaproterenol.

COMMENTS

Anticholinergic drugs have not previously been approved in the United States for the treatment of asthma, and their use has been restricted to the aerosol solution form of atropine, delivered by a compressor nebulizer system [3]. In addition, aerosolized atropine is absorbed and may produce systemic anticholinergic side effects, which further limits its use. Therefore, ipratropium bromide, a quaternary ammonium anticholinergic that is notably free of atropine-like side effects, has generated considerable interest for use in asthma therapy.

Since ipratropium has not previously been used in the United States, it is difficult to identify completely its place in the armamentarium of drugs that are available for asthma. Previous studies have shown that ipratropium is an effective bronchodilator, but one that has notable differences from the beta-adrenergic agonists [4,5]. Al-

lergen-induced bronchospasm is only partially prevented by pretreatment with ipratropium [6]. In that model, ipratropium is not as effective as a beta agonist. The use of ipratropium in combination with theophylline, a beta agonist, and an oral steroid has been evaluated [7]. Ipratropium gives an additive bronchodilator effect when used with these drugs. Since ipratropium has different pharmacologic effects than those of the beta-adrenergic agonists, its role in the treatment of patients with asthma is not established, although it is likely to be used as a second-line, or adjunctive, form of therapy.

Other studies have suggested that there may be specific indications for ipratropium in certain asthmatic patients, such as those whose asthma is brought on by psychogenic factors [8,9], cigarette smoke [10], or beta-blocking drugs [11]. Thus, there may be certain specific triggering factors that would produce an indication for the use of ipratropium in a given patient with asthma.

Although our study indicates that there is a subset of patients with asthma who show a better response to ipratropium than to beta-adrenergic agonists, we were unable to characterize these patients; therefore, one cannot predict the effectiveness of this treatment without a therapeutic trial.

One major strength of ipratropium is its safety. The current study found no significant adverse reactions caused by use of ipratropium for 90 days. Similar results were found in other studies [12,13]. This safety profile makes ipratropium quite appealing, especially since it may be used with other anti-asthmatic drugs, such as beta-adrenergic agonists or theophyllines [7]. Since beta agonists or theophyllines have sometimes been used to the extent that side effects occur, the addition of ipratropium to the treatment program of a given patient may allow for increased bronchodilation while permitting the individual asthmatic patient to reduce the dosage of the beta-adrenergic agonist or theophylline. In addition, patients with coronary heart disease, who might be at risk of cardiac arrhythmias from beta agonists or theophyllines, may benefit from the use of ipratropium because of its lack of cardiac side effects. Similarly, patients receiving multiple drugs for hypertension and cardiac problems, including arrhythmias, might be better served with ipratropium, since many of the beta-adrenergic agonists and theophylline compounds may have effects on blood pressure as well as on cardiac rhythm.

Thus, although bronchodilation with ipratropium is not as rapid in onset as that with the beta-adrenergic agonists, it has a very wide margin of safety and a tendency for a longer duration of bronchodilation. Therefore, it should be very useful as an adjunct in our current therapeutic program for asthma.

SUMMARY

This 90-day, double-blind, parallel, randomized study compared the efficacy and safety of a metered-dose inhaler containing ipratropium bromide with those of a similar inhaler containing metaproterenol sulfate in 164 patients with asthma. Both drugs showed equal bronchodilator efficacy on all pulmonary function study days, as measured by the area under the FEV_1 curve. In patients who showed a response to the drugs, the onset of a 15 percent increase in FEV_1 was slower and the duration more prolonged with ipratropium than with metaproterenol, although these differences were not statistically significant.

The symptomatic improvement in asthma reported by both the ipratropium and the metaproterenol groups was equivalent. The only significant side effects noted with the use of ipratropium during the 90-day study were cough and exacerbation of symptoms; no anticholinergic side effects were noted.

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Discussion

Dr. Edward Bergofsky: This study indicates a decreasing response to metaproterenol over the 90-day period. I wonder whether this response demonstrates tachyphylaxis or just a worsening of asthma in the metaproterenol group. Could you comment on that?

Dr. William Storms: The attenuation of response to metaproterenol suggests that tachyphylaxis is not observed with ipratropium. The study was not designed specifically to evaluate tachyphylaxis or tolerance, and I therefore cannot make any conclusions on this point. The results do tend to suggest, however, a lack of tachyphylaxis with ipratropium.

Dr. Roberta Goldring: It has been suggested that the study design would tend to bias the results in favor of a beta agonist rather than an anticholinergic, because one of the entry criteria was a significant response to a beta agonist. Despite this criterion, a large number of patients did not show a response to metaproterenol during the course of the 90-day trial. Can you explain this?

Dr. Storms: Patients had to show a response to isoproterenol before entering the study. Once the study began, 30 percent of patients in the metaproterenol group did not show a response to the first dose, and when that subgroup was examined more closely, we discovered that a number of these non-responding patients had a FEV_1 value greater than 75 percent of predicted; they actually had too good a level of bronchodilation on the first study day for their FEV_1 value to improve by 15 percent. When these patients were excluded, more than 90 percent of the metaproterenol group did show a response. So some of our finding of non-responsiveness to metaproterenol was due to a difference in the patients' baseline pulmonary function on day 1 as compared with their previous qualification test.

Dr. Nicholas Gross: This brings up something I am concerned about. Classifying asthma patients as responders or non-responders is quite bothersome to me, because, as was just shown, baseline values have a lot to do with how much of a response will be observed. If the baseline is high, and a 15 percent FEV_1 response is required, that response may be too great for these patients to achieve. I would therefore suggest that we calculate the response in terms of the *achievable* response. That would eliminate arbitrariness. For instance, if a patient has a baseline FEV_1 of 75 percent of predicted, response could be calculated by comparing that 75 percent to the highest values obtained in the patient.

Dr. John O'Hollaren: I would like to add a point about study follow-up. One thing we should emphasize in this study was the need for concomitant medication in those patients who showed a response to ipratropium. It is my impression, however, that responders have reduced needs for concomitant therapy compared with non-responders. Three patients in this study who had been steroid-dependent are now taking only ipratropium four times a day, and there are no signs of tachyphylaxis.