ORIGINAL CONTRIBUTION
β-agonists;
chronic obstructive pulmonary disease;
ipratropium bromide

Decreased Duration of Emergency Department Treatment of Chronic Obstructive Pulmonary Disease Exacerbations With the Addition of Ipratropium Bromide to β-Agonist Therapy

Study objectives: *To determine the benefit of the addition of ipratropium bromide to β-agonist therapy of acute exacerbations of chronic obstructive pulmonary disease.*

Design: *The trial was randomized and double blinded.*

Setting: *The study was conducted in the emergency department of Parkland Memorial Hospital, a busy, inner-city, county hospital.*

Interventions: *Patients were treated in the medicine emergency department with either the standard regimen of nebulized isoetharine, 0.5 mL of a 1% solution (5.0 mg) diluted to 2.0 mL with normal saline every hour (control group) or with the same regimen plus ipratropium bromide, 54 μg (three puffs) after the first isoetharine treatment and 36 μg (two puffs) after the second and fourth (experimental group). A placebo metered-dose inhaler used in the same manner as the ipratropium blinded the study to both the patients and medical personnel.*

Measurements and main results: *The group treated with the addition of ipratropium (30) was discharged from the ED an average of 91 minutes ($P < .05$) sooner than the control group (25) and required on the average one less isoetharine treatment ($P < .05$). The pulmonary functions tested, forced expiratory volume in the first second, and the forced vital capacity were the same in the two groups initially and on discharge, as identical discharge criteria were used in each group.*

Conclusion: *The addition of ipratropium to standard β-agonist treatment of chronic obstructive pulmonary disease exacerbations shortens the duration of treatment required in the ED. [Shrestha M, O'Brien T, Haddox R, Gourlay HS, Reed G: Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to β-agonist therapy. Ann Emerg Med November 1991;20:1206-1209.]*

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INTRODUCTION

Atropine is a bronchodilator through its inhibition of muscarinic cholinergic receptors in the airways.[1,2] Ipratropium bromide is a quaternary methyl isopropyl derivative of atropine that is not absorbed systemically except in minute quantities when delivered by aerosol.[3] It thus retains bronchodilator properties without the systemic anticholinergic side effects of atropine. Ipratropium has been studied extensively in the treatment of asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. Most of the studies have been on stable outpatients. In asthma, they show that the bronchodilator effect is smaller than that seen with β-agonists,[4] but combination treatment may be beneficial if the patient is resistant to the effects of the β-agonist,[5] or if the β-agonist dose must be decreased because of side effects.[1,6] Ipratropium results in a similar magnitude of bronchodilatation in COPD patients. Because COPD tends to respond poorly to β-agonists, the bronchodilatation from ipratropium is nearly equal or greater in magnitude to the bronchodilatation seen with β-agonists, making it a possible first-line drug for these patients.[1,7]

There are very few studies of ipratropium in acute exacerbations of COPD. A recent multicenter study showed that asthmatics who present to the emergency department responded best to a combination of fenoterol (a

β-agonist) and nebulized ipratropium. The patients with COPD, on the other hand, had only small improvements in spirometry after treatment with a single dose of fenoterol, ipratropium, or the combination.[8] The differences between these treatment groups were not significant. In this study, we show the effects of adding ipratropium to repeated doses of inhaled, nebulized β-agonist during ED visits for patients with COPD exacerbation.

MATERIALS AND METHODS

The subject population included any adult over the age of 40 who presented to the ED of Parkland Memorial Hospital, an inner-city, county hospital, between April 1, 1988, and September 30, 1988, with a clinical diagnosis of COPD exacerbation.[9] Patients were required to be moderately to severely dyspneic as determined by a forced expiratory volume in the first second (FEV_1) of 40% or less of predicted. All spirometry was performed on a portable Spiroflow® volume displacement dry rolling seal spirometer (PK Morgan Instruments Inc, Andover, Massachusetts), analyzed by computer. The readings were performed and recorded by one of the respiratory therapists on duty in the ED.

Upon presentation the patients were immediately evaluated by the supervising physician. If resuscitation or intubation was not required, a respiratory therapist measured initial FEV_1 and forced vital capacity (FVC) and administered isoetharine (0.5 mL of a 1% solution, 5.0 mg, diluted to 2.0 mL, in normal saline, the manufacturer's suggested dose) by nebulized inhalation. Isoetharine was given every hour as strictly as possible given the confines of a busy ED. FEV_1 and FVC were measured after each inhalation treatment.

As soon as possible during or after the first isoetharine treatment, an investigator explained the purpose of the study and obtained an informed consent. Within five to ten minutes of the first isoetharine dose, three puffs of blinded ipratropium (54 μg total) or placebo were given by metered-dose inhaler under supervision of the respiratory therapist. All patients entered in the study had experience with metered-dose inhalers. The ipratropium canisters were indistinguishable from the placebo canisters.

TABLE 1. *Patient characteristics*

	Control Patients (25)	Experimental Patients (30)	P
Median age (yr ± SD)	63 ± 8.0	62 ± 9.3	NS†
Gender (%)			
Male	16 (64)	19 (63)	NS*
Female	9 (36)	11 (37)	NS*
Race (%)			
Black	15 (60)	18 (60)	NS*
White	7 (28)	9 (30)	NS*
Latin American	3 (12)	3 (10)	NS*
Nonipratropium treatments (%)			
Isoetharine	25 (100)	30 (100)	NS*
Aminophylline	15 (60)	11 (37)	NS*
Methylprednisolone	17 (68)	20 (67)	NS*
Blood pressure			
Systolic (± SD)	148 ± 24	146 ± 17.0	NS†
Diastolic (± SD)	93 ± 17.5	92 ± 15.3	NS†
Heart rate (± SD)	100 ± 19	103 ± 17.0	NS†
Initial spirometry			
FEV_1 (± SD)	0.69 ± 0.25	0.68 ± 0.27	NS†
FVC (± SD)	1.08 ± 0.35	1.15 ± 0.49	NS†

*Statistical comparisons of proportions were done using the χ^2 test.
†Statistical comparisons of means were done using the Mann-Whitney *U* test.
$P < .05$ was considered significant.

Randomization was accomplished by blindly drawing pieces of paper that indicated to which group the patient would belong. The key to the code stating which inhalers contained ipratropium and which contained placebo was kept by an administrative assistant and was not available to any of the people treating the patient. A second dose of ipratropium (36 μg or two puffs) versus placebo was given at one hour, just after the second nebulized isoetharine treatment. If the patient had not been discharged from the ED by the fourth isoetharine treatment, another dose (36 μg, two puffs) of ipratropium or placebo was given again.

IV aminophylline was given if the patient did not already have an adequate serum theophylline level. If there was no contraindication and if the physician thought that the patient would benefit from corticosteroid treatment, 125 mg IV methylprednisolone was administered. There was continual clinical assessment by the emergency physician, who discharged patients from the ED as they improved both subjectively and objectively, as seen in improvement in spirometry. The same criteria were used in making the decision to discharge the patients of either group, as the physician had no way of knowing who received ipratropium and who received placebo.

If the patients failed to show improvement in six hours, they were admitted. The number of patients admitted to the inpatient medical service in each group was recorded. Because the time to discharge, number of β-agonist treatments, and final FEV_1 were not applicable to admitted patients, they were not used in the statistical comparisons of these variables.

The Mann-Whitney *U* statistical test was used in comparison of treatment times and spirometry as this nonparametric test does not make any assumptions of normalcy of frequency distributions in the samples being compared. The χ^2 test was used in comparisons of proportions. Follow-up of patients was attempted by chart review.

RESULTS

Seventy-six ED visits for COPD exacerbations were randomized either to the standard treatment regimen (control group) or the group also receiving ipratropium bromide by metered-dose inhaler (experimental group). Of the 37 patients random-

TABLE 2. *Results*

	Control Patients (25)	Experimental Patients (30)	P
Duration of therapy (min ± SD)			
Mean	317 ± 135	226 ± 102	< .05
Minimum	95	80	
Maximum	530	435	
Number of β-agonist treatments (± SD)	4.8 ± 1.73	3.7 ± 1.26	< .05
FEV_1s			
Initial (± SD)	.69 ± .25	.68 ± .27	NS
After first treatment (± SD)	.88 ± .25	.92 ± .33	NS
At discharge (± SD)	1.36 ± .61	1.13 ± .50	NS
Number admitted*	3 (12%)	2 (6.6%)	
Number intubated*	0	0	

*Too few for meaningful statistical comparisons.
Statistical comparisons were made using the nonparametric Mann-Whitney *U* test. $P < .05$ was considered significant.

ized to the control group, four were repeat visits (less than three days apart), three were admitted to the inpatient medical wards, no data could be located for two, protocol was not adhered to in two, and one had an FEV_1 of more than 40%, leaving 25 patients for statistical comparison. Of the 39 patients randomized to the experimental group, four were repeat visits (less than three days apart), two were admitted to the inpatient medical wards, two left the ED against medical advice, and no data could be located for one, leaving 30 patients in this group for comparison with the 25 patients in the control group, a total of 55 patients.

Patient characteristics are summarized (Table 1). Most were in their early 60s. Two thirds were male, and the majority were black. Demographically, the control and experimental groups were very similar. Blood pressure and heart rate were borderline elevated, indicating a stressed physiological state, equally so in both groups. Approximately the same proportion of patients in each group received methylprednisolone. A greater proportion of patients in the control group, 60%, versus 30% in the experimental group, received aminophylline, used to increase the blood theophylline level into the therapeutic range. The initial spirometries, which consisted of FEV_1 and FVC, were nearly identical, indicating that severity of disease was very similar in the two groups.

The significant result of the study is that patients in the group given ipratropium were discharged 91 minutes sooner than the patients in the control group. This corresponded to approximately one less nebulized isoetharine treatment. Most of the patients who received ipratropium (22 of 30, 70%, all in the experimental group) received two ipratropium treatments, a total of five puffs. The other eight received three ipratropium treatments, a total of seven puffs. The shortest and longest stays in the ED for each study group were similar. As expected, the final FEV_1s and FVCs were not statistically different between groups because improvement in these were part of the criteria for discharge (Table 2).

The number of patients admitted to the inpatient medical services was too small for meaningful statistical comparisons. No patient required intubation. Specific adverse effects of the treatments were not sought, and there were none reported in either study group.

We reviewed charts to study the effect of the experimental therapy on relapse rates. We were able to find charts on 19 patients in the experimental group (63%) and on 16 patients in the control group (64%). One patient in each group was taking ipratropium routinely. No one in the experimental group was discharged with the addition of ipratropium to the COPD medication regimen, while two in the control group had ipratropium added (physician's choice, not part of protocol). Within three days, one patient in the experimental group (5%) and two patients in the control group (13%) required ED treatment. Within two weeks, five patients in the experimental group (26%) and five in the control group (31%) required repeat ED treatment.

The patients in this study were of a population that required ED treatment frequently throughout the course of the year. The average number of yearly visits was 27 for the experimental group and 21 for the control group. Thus, it is not surprising that nearly one third of the patients in either group returned to the ED within two weeks. The differences in relapse rates between the two groups were not statistically significant.

DISCUSSION

The data obtained show that, in a population of patients with COPD in an urban, county hospital ED, the addition of ipratropium bromide to the standard hourly nebulized β-agonist inhalation treatment significantly accelerates the improvement of COPD exacerbations. The patients treated with the addition of ipratropium to the standard regimen of hourly isoetharine became well enough to leave the ED on average 91 minutes sooner than their counterparts given only the standard regimen. This corresponds to 29% less time in the ED. ED treatment time was 5 hours, 17 minutes for those not given ipratropium and 3 hours, 46 minutes for those given ipratropium.

In this analysis we decided not to use relapsed patients (those with visits less than three days apart) as these may represent a subset of COPD patients that would not respond well to any medication. There were four of these patients in each group, and thus the comparisons would not have been altered had they been included.

As the criteria for discharge included pulmonary function test results, the final FEV_1s and FVCs of patients in each group were not significantly different from each other at the .05 level. The final FEV_1 in the group given ipratropium (1.13 L) was actually worse than that of the control group (1.36, $P = .14$). If there was a difference in final spirometry, we had too few patients to detect it. If the true population difference in means of the final FEV_1s was .23, as it was in our samples, our study had only a 33% chance (power) of recognizing this difference. It is tempting to speculate that the group given ipratropium felt less dyspnea for a given FEV_1 and FVC. There is some

evidence that cholinergic pathways are important in the afferent signals from various types of lung receptors that mediate dyspnea.[2] If ipratropium were to block these pathways, then the patient would experience less dyspnea. Further studies are needed to evaluate this possibility.

A potentially confounding variable in the study was the administration of aminophylline. Sixty percent of the patients in the control group received aminophylline, compared with only 37% in the experimental group. The difference was not statistically significant, and the chance of finding such a difference statistically significant, given the number of patients enrolled, is 39% (power). It is doubtful that this possible difference in the administration of aminophylline is responsible for the difference between the two study groups, as the aminophylline was given more than two hours into the course of treatment. The delays were logistic, common to those in most busy public hospitals. In addition, comparison of patients receiving aminophylline with those not receiving it showed no difference in duration of treatment or in final spirometry: 272 minutes versus 264 minutes ($P > .8$) and 1.28 L versus 1.25 L ($P > .8$), respectively.

In the study of Rebuck et al, pulmonary function (FEV_1, FVC, and peak expiratory flow rate) was measured 45 and 90 minutes after a single-dose bronchodilator inhalation, which was either 1.25 mg fenoterol, 500 μg nebulized ipratropium, or both in combination.[8] For the COPD patients tested, there was no difference in the pulmonary functions tested among the three single-dose treatments. The absolute increase in FEV_1, about 0.2 L after 45 minutes, agrees with that of our study after one treatment of 0.19 L for the control group and 0.24 L for the experimental group. Similar results were found in a recent study done in the United Kingdom.[10]

The difference between the current study and the two previous ones mentioned is that in the current study, inhalation therapy was sequential and repetitive. Pathophysiologically, repeated treatments may dilate progressively more distal airways. The first bronchodilator works on proximal airways and dilates them, allowing the subsequent treatments to be delivered more distally. The site of action of ipratropium is still controversial, with some investigators claiming it has its predominant action on proximal large airways and others arguing that it acts distally.[11] Perhaps the one-time treatment of COPD patients is inadequate to deliver the ipratropium fully to all its site(s) of action.

Easters et al, in a small study of stable COPD outpatients, has shown that when what was called a maximum dose of either albuterol (400 μg followed 15 minutes later by 200 μg, followed 15 minutes later by another 200 μg, all by metered-dose inhaler) or ipratropium (80 μg followed 30 minutes later by 40 μg) was administered, the addition of the other bronchodilator 90 minutes later did not alter pulmonary function tests significantly.[12]

This study was done on stable COPD patients and thus is not generalizable to ED patients. However, it does raise the possibility that hourly isoetharine is not a maximal dose and that addition of ipratropium to a maximum dose of β-agonist may not result in any additional benefit. We are currently pursuing studies with more frequent treatment with β-agonists to clarify this issue.

CONCLUSION

We added ipratropium bromide delivered by hand-held inhaler to our current ED treatment of COPD exacerbation, which consists of nebulized isoetharine every hour with or without parenteral corticosteroids and aminophylline. This simple addition significantly shortens the treatment time required for these patients in the ED.

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