Ipratropium Bromide Added to Asthma Treatment in the Pediatric Emergency Department

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ABSTRACT. *Objective.* **To determine if the addition of ipratropium bromide to the emergency department (ED) treatment of childhood asthma reduces time to discharge, number of nebulizer treatments before discharge, and the rate of hospitalization.**

Methods. **Patients >12 months of age were eligible if they were to be treated according to a standardized ED protocol for acute asthma with nebulized albuterol (2.5 mg/dose if weight <30 kg, otherwise 5 mg/dose) and oral prednisone or prednisolone (2 mg/kg up to 80 mg). Subjects were randomized to receive either ipratropium (250 μg/dose) or normal saline (1 mL/dose) with each of the first three nebulized albuterol doses. Further treatment after the first hour was determined by physicians blinded to subject group assignment. Records were reviewed to determine the length of time to discharge home from the ED, number of doses of albuterol given before discharge, and the number of patients admitted to the hospital.**

Results. **Four hundred twenty-seven patients were randomized to ipratropium or control groups; these groups were similar in all baseline measures. Among patients discharged from the ED, ipratropium group subjects had 13% shorter treatment time (mean, 185 minutes, vs control, 213 minutes) and fewer total albuterol doses (median, three, vs control, four). Admission rates did not differ significantly (18%, vs control, 22%).**

Conclusions. **The addition of three doses of ipratropium to an ED treatment protocol for acute asthma was associated with reductions in duration and amount of treatment before discharge.** *Pediatrics* **1999;103:748–752;** ***asthma, ipratropium, albuterol, randomized controlled trial, emergencies, child, adolescence, critical pathway, practice guidelines.***

ABBREVIATION. ED, emergency department.

Treatment of childhood asthma has received increasing attention in recent decades because of the rising morbidity of the disease. Asthma prevalence, hospitalizations, and deaths have all increased according to epidemiologic studies from the 1970s and 1980s.[1–3] In 1991, an expert committee convened by the National Heart, Lung and Blood Institute of the National Institutes of Health published guidelines for asthma management that summarized findings of clinical research with recommendations for standard therapy.[4] Based on data from randomized trials, the guidelines recommended high-dose inhaled β-agonists and systemic corticosteroids for moderate to severe asthma exacerbations.

Inhaled anticholinergic agents such as atropine have long been known to be effective for acute asthma, but until recently their use has been limited because of systemic side effects.[5] Ipratropium bromide is a synthetic derivative of atropine that was designed to act locally in the lung with minimal systemic absorption. Studies of efficacy and safety of ipratropium have been conducted predominantly in adults.[6–10] Used alone, ipratropium has been shown to reduce bronchospasm with minimal cardiovascular or other systemic effects.[6,11–13] In combination with high-dose β-agonists, ipratropium improves pulmonary function above that seen with β-agonists alone.[14]

Information on the role of ipratropium in pediatric asthma therapy is limited. Several studies of children with severe asthma exacerbations have found improvement in pulmonary function when ipratropium was added to high-dose β-agonists.[15–19] A recent trial in an emergency department (ED) found additional improvement when repeated doses of ipratropium were used.[18] With limited sample size, none of these studies demonstrated significant overall reductions in clinical outcomes such as the amount of ED treatment or hospitalizations; one study did demonstrate reduced hospitalizations in a subgroup of the most severe children.[18] The benefits of ipratropium have yet to be assessed for moderate asthma exacerbations and among young children unable to perform pulmonary tests. The goal of this study was to measure the effect of adding ipratropium to standard asthma therapy in a pediatric ED asthma population.

METHODS

Design The study was designed as a double-blind, randomized, controlled trial of ipratropium added to a standard asthma treatment protocol (Critical Pathway), which had been previously established in the pediatric ED at the Johns Hopkins Hospital.

Subjects

Patients >12 months of age presenting to the ED with wheezing were eligible for enrollment if they were to be treated on the Critical Pathway after an initial assessment by the ED attending or fellow (enrolling physician). Patients were excluded from enrollment if they showed signs of respiratory failure or required initial

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therapy in addition to the Critical Pathway (eg, continuous albuterol, or subcutaneous epinephrine or terbutaline) in the judgment of the enrolling physician. Other exclusion criteria included a history of pretreatment with corticosteroids (within 3 days) or ipratropium (within 24 hours) or a history of glaucoma, cystic fibrosis, or sickle cell disease. All ED attending physicians and fellows received study enrollment training to allow for enrollment during day and night shifts. Patients were allowed to enroll in the study on more than one occasion. For all study patients, assent and written consent of a guardian were obtained according to a process approved by the Institutional Review Board. An audit of all ED charts was performed during the study period to collect data on patients who were treated for asthma-related diagnoses (asthma, status asthmaticus, reactive airway disease, wheezing, and bronchiolitis with a previous history of wheezing) but who were not enrolled in the study.

Baseline Assessment

As part of the Critical Pathway, nursing staff measured initial pulse oximetry in all patients and peak expiratory flow in children >5 years of age who were able to cooperate with testing. For study patients, the enrolling physician assigned baseline clinical severity scores for accessory muscle use, wheeze, and dyspnea (see Table 1).[18] Before the study, interrater reliability of the baseline clinical scoring was assessed by comparing the ratings of the principal investigator with those of five ED attendings on 32 asthmatic patients. Individual severity scores were summed and divided into three severity groups, ie, mild (1–3) moderate (4–6) or severe (7–9). Interrater reliability was measured (75% agreement, κ = 0.6), using these severity subgroups.

Study Interventions

After consent was obtained, each patient was assigned a study vial that had been prepared in advance by the pharmacy. Each numbered amber vial contained either normal saline or a solution of ipratropium bromide in a concentration of 250 μg/mL normal saline. Both solutions are clear, odorless, and indistinguishable in the liquid and nebulized states. Before the study, vials were block randomized in groups of eight by a standard computerized method in the Investigational Pharmacy. Investigators, physicians, nurses, and patients were blind to the randomization code.

As per the Critical Pathway, all patients enrolled in the study received three doses of nebulized albuterol (2.5 mg in 3 mL saline or 5.0 mg in 6 mL based on weight < or ≥ 30 kg) every 20 minutes and one dose of oral prednisone or prednisolone (2 mg/kg to a maximum of 80 mg) during the first hour of treatment. Nebulizer treatments were administered by face mask (Hudson RCI, Temecula, CA) with oxygen at a flow rate of 5 to 6 L/min. One milliliter from each study vial was added to each of the first three albuterol treatments. After the first hour of therapy, further treatment was left to the discretion of the treating physician. Patients who vomited or were unable to take oral medications were given parenteral methylprednisolone at the discretion of the treating physician. Physicians were asked not to administer ipratropium outside of the study unless a patient was clinically worsening and the decision had been made to admit the patient to the hospital.

Outcomes

The outcomes of interest were disposition (discharge home, admission to the ward, or admission to the intensive care unit) and, for discharged patients, the time and number of nebulizer treatments before discharge. Time to discharge was calculated from the beginning of the initial aerosol to the time when either nurse or physician gave discharge instructions. If nursing and physician discharge times varied, the earlier of the two times was used. Return visits to the Johns Hopkins ED within 72 hours of discharge were determined by reviewing an administrative database of all ED visits. Hospital charges for discharged patients were compared in a secondary analysis; these charges are separate from physician charges and are based on a level of severity (1–5) assigned by the patient's nurse at the time of the visit. An additional incremental charge is assigned per hour of observation beyond the initial 2 hours.

Statistical Analysis

Initial sample size was calculated at 900 patients to detect a 25% decrease in the admission rate (predicted to be 35% among controls, based on pilot data) with a power of 80% and $\alpha_2 = 0.05$. An interim analysis with predetermined stopping rules was planned after the enrollment of 250 patients. At this interim point, sample size was recalculated based on the actual control admission rate (22%), showing that >1600 patients would be required to detect a significant reduction in the admission rate. As study enrollment would be inadequate to reach this sample size, it was decided to discontinue enrollment after 1 year. At this point, adequate power had been reached to detect clinically significant reductions in the other two study outcomes (30 minutes in time to discharge and 0.3 albuterol doses per subject).

Group differences were assessed by using standard bivariate tests. Student's t test for continuous variables (time to discharge), Mann-Whitney U test for non-normally distributed numerical variables (number of albuterol doses before discharge), and χ^2 comparison for categorical variables (percentage admitted to hospital). Unless otherwise specified in tables, data are expressed as mean ± SD values.

RESULTS

A total of 2151 visits for asthma and related diagnoses were made by patients >12 months of age during a 1-year period beginning in July 1997. Based on chart review, patients were eligible for study enrollment on 1215 of these visits. Reasons for exclusion were as follows: mild illness or decision not to treat on the Critical Pathway (383 patients), severe presentation requiring additional therapy (78 patients), pretreatment with corticosteroids (432 patients) or ipratropium (3 patients), a history of glaucoma, cystic fibrosis, or sickle cell disease (9 patients), and no guardian available for consent (31 patients). Enrolling physicians approached 488 patients for study enrollment, and 88% of these gave consent for a total of 427 visits made by 365 individuals. Study participants and eligible nonparticipants did not differ significantly by age, history of previous asthma admission, initial respiratory rate, pulse oximetry, or frequency of hospitalization after the ED visit (all $P > .10$). The proportion of male patients was greater among participants than among eligible nonparticipants (70% vs 63%, $P = .02$). The mean age of study participants was 7.6 (SD, ±5.0) years; 11% were <2 years old and 17% were >12.

Records for all study participants were reviewed

TABLE 1. Baseline Clinical Asthma Score*

Score	Accessory Muscle Score	Wheeze Score	Dyspnea Score
0	No retractions	No wheeze and well	Absent dyspnea
1	Intercostal retractions	End-expiratory wheezes	Normal activity and speech; minimal dyspnea
2	Intercostal and suprasternal retractions	Panexpiratory ± inspiratory wheeze	Decreased activity; 5–8 word sentence; moderate dyspnea
3	Nasal flaring	Wheeze audible without stethoscope	Concentrates on breathing; <5 word sentences; severe dyspnea

* From Schuh et al.[18]

to determine adherence to the experimental design. Adherence to the study protocol was documented for all but 20 visits. Five enrolled patients did not meet eligibility criteria; ie, 1 was <12 months of age and 4 had been pretreated with corticosteroids during the preceding 72 hours. Two patients were assigned mistakenly to the same study vial. Eleven patients were treated with ipratropium outside of the study protocol after the initial hour and subsequently discharged from the ED, 3 in the ipratropium group and 8 controls. Two patients were withdrawn before completion of the study protocol, 1 because the parent felt the child was not tolerating nebulizer treatments and the second for unstated reasons. In accordance with an intention to treat strategy, all patients who were randomized in the study were included in the data analysis.

Adherence to the Critical Pathway was also assessed. The mean time to administration of corticosteroids was 7 ± 14 minutes, and the mean time to initiation of the third albuterol nebulizer dose was 49 ± 13 minutes. Pulse oximetry was measured in all study patients. Peak expiratory flow was measured successfully in 32% of patients 6 to 10 years old and 58% of older patients.

Of the 427 participants, 211 were randomized to the ipratropium group and 216 to the control group. The groups did not differ significantly in terms of demographic, historical, or baseline clinical measurements (Table 2, all $P > .05$). Initial respiratory rate was slightly higher in the control group, and this difference approached statistical significance ($P = .06$).

Study outcomes are presented in Table 3 and graphically represented in Fig 1. In the ipratropium group, 18% of patients were admitted compared with 22% of control patients ($P = .3$). One percent of patients in each group was admitted to the intensive care unit. Mean time to discharge was 28 minutes shorter in the ipratropium group compared with controls ($P = .001$). Fewer albuterol nebulizer treatments were ordered before discharge for patients in the ipratropium group compared with controls ($P < .01$). There was no difference in the proportion of cases with a return visit to the ED within 72 hours.

Results for subgroups by severity and age are presented in Table 4. Initial severity score was incomplete or missing for 14% of study subjects; scored and nonscored subjects did not differ significantly in any of the other dependent variables listed in Fig 1. Hospitalizations were not significantly reduced in any severity subgroup. When moderate and severe patients were combined, the admission rate was 8% lower in the ipratropium group, corresponding to an odds ratio for admission of 0.64 (95% confidence interval = 0.36,1.15). Time to discharge was reduced significantly in mild and moderate patients. The number of albuterol doses before discharge was reduced significantly in mild and severe patients ($P < .05$; not shown in Table 4). Average time to discharge was reduced by 42 minutes or 19% among children <5 years.

To assess whether the reduction in time to discharge had an effect on hospital charges, we obtained billing information for the first 250 patients enrolled in the study. Among patients discharged from the ED, ipratropium-treated patients were significantly more likely to be assigned to a lower level of care than controls ($P < .05$), corresponding to a difference in mean hospital charges of $36 per patient.

TABLE 2. Baseline Comparison by Study Group

	Control ($n = 216$)	Ipratropium ($n = 211$)	P
Age in years	7.7 ± 5.0	7.4 ± 5.0	.23
Male, %	69	70	.96
African-American, %	95	95	.96
Previous asthma hospitalization, %	59	54	.26
Respiratory rate per minute	36 ± 12	34 ± 10	.06
Room air pulse oximetry, %	95 ± 3	95 ± 3	.56
Severity score (range 0–9)	4.6 ± 1.8	4.4 ± 1.7	.37

TABLE 3. ED Disposition by Study Group

	Control	Ipratropium	P
All subjects	($n = 216$)	($n = 211$)	
Admitted to hospital from ED, %	22	18	.33
Admitted to intensive care, %	1	1	.6
Discharged home from ED	($n = 169$)	($n = 173$)	
Time to discharge (minutes)	213 ± 82	185 ± 69	.001
Median number of albuterol doses	4	3	<.01
Initial three doses only, %	49	64	
Four doses, %	31	25	
Five doses, %	16	9	
Six or more doses, %	4	2	
Returned to ED within 72 hours, %	2	4	.38

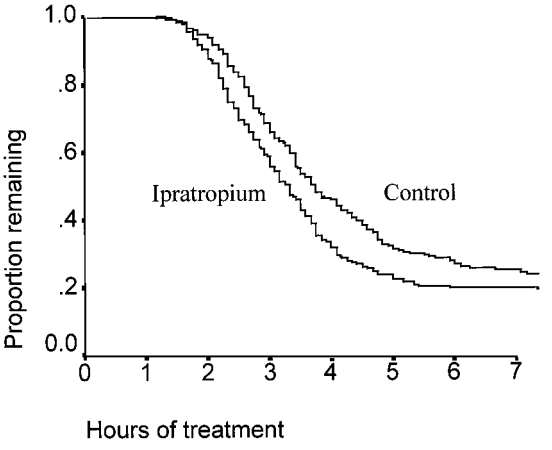

Fig 1. Proportion of patients remaining in the hospital (in the ED and admitted to the ward) over time by study group. Curves are significantly different by log-rank test ($P < .05$).

DISCUSSION

This study evaluated the addition of repeated doses of ipratropium to the treatment of acute asthma in a pediatric ED. The addition of ipratropium to albuterol and corticosteroids was associated with reduced treatment time and number of albuterol doses before discharge. Although fewer patients were admitted to the hospital in the ipratropium group, this difference did not reach statistical significance with this sample size. This study differed from previous trials in the following several ways: First, all study patients were being treated on a Critical Pathway that standardized initial asthma

TABLE 4. ED Disposition by Subgroup

	n	% Admitted			Minutes to ED Discharge		
		Control	IB	*P*	Control	IB	*P*
Initial severity score							
Mild (1–3)	118	7	10	.55	193 ± 75	164 ± 56	.03
Moderate (4–6)	195	26	18	.21	227 ± 78	201 ± 76	.04
Severe (7–9)	52	40	32	.55	224 ± 86	188 ± 81	.22
Moderate or severe	247	29	21	.13	226 ± 80	199 ± 76	.02
Age							
Less than 5 years	165	19	17	.71	217 ± 96	175 ± 54	.002
Five years or older	262	23	19	.35	210 ± 72	192 ± 77	.09

Abbreviation: IB, ipratropium bromide.

care within the ED. Second, a broad sample of ED asthma patients was enrolled in the study, including milder patients and young children excluded from previous trials. Third, the study measured the effect of ipratropium on further treatment and time to discharge, which were not reported in previous trials.

Critical Pathways (also referred to as Clinical Pathways) define multidisciplinary care for a specific medical condition.[20] Diagnostic tests, monitoring, evaluation, and therapies are planned according to a time schedule for expected performance. Critical Pathways may be derived from published guidelines or other evidence that define a specific plan of care. The Critical Pathway used in this study was adapted from the NHLBI Asthma Guidelines[4] and includes peak flow measurement, pulse oximetry, and standardized medication doses. The decision to initiate treatment by using the Pathway is left to the judgment of the physician after clinical assessment of the patient. Previous studies of Critical Pathways have demonstrated reductions in length of stay and charges when they were implemented in clinical settings.[21,22] Our study demonstrates another potential benefit of a Pathway by using it as the basis for a trial of a new intervention, in this case the addition of ipratropium to asthma therapy.

Previous studies of ipratropium have focused on children with severe asthma exacerbations as defined by pulmonary function testing. Five well-designed pediatric trials reported significant improvement in FEV_1 (forced expiratory volume in 1 second) when ipratropium was added to high-dose β-agonist therapy for severe asthma.[15–19] One of these studies, by Schuh et al,[18] found a dose-response relationship when three doses of ipratropium were compared with 0 or 1 dose. The clinical applicability of these studies is complicated by the definition of severity. Measurement of FEV_1 is not generally available in the ED, and other tests such as peak expiratory flow may be difficult to obtain acutely in young children who make up a large proportion of the pediatric asthma population.[23] Application of the previous literature is also affected by a recent change in asthma therapy; only one of the studies used corticosteroids as part of routine management. We chose to study a representative sample of children being treated with high-dose albuterol and corticosteroids after a routine assessment under usual clinical conditions.

The dependent variables measured in this study also differed from previous trials. Previous studies have found improvement in pulmonary function and severity scores with ipratropium but have been unable to demonstrate improved clinical outcomes as measured by the hospitalization rate. This outcome is difficult to use in an asthma trial because it requires very large sample size to demonstrate statistical significance. We chose to measure time and number of nebulizer treatments before discharge as objective measures, which would be of clinical importance to physicians and patients.

The clinical significance of our findings can be assessed from several viewpoints. For an individual patient, the average reduction in treatment before discharge associated with ipratropium was modest, 28 minutes and less than one albuterol dose. The subjective value of this reduction to the patient would require further study. From the standpoint of an ED director, 13% reduction in time to discharge for asthmatic patients might reduce overall ED costs by decreasing demands on staff, space, and other resources. This possibility is reflected in calculation of patient charges, which includes time in the ED at this and other institutions. We reviewed outpatient bills in a subset of our study population and found that patient charges were reduced significantly in the ipratropium group. A full assessment of this benefit would require a formal cost-effectiveness analysis with conversion of charges to costs so that they could be compared with the cost of the medication to the hospital (less than $5 per patient in our institution).

Although we did not demonstrate a significant reduction in asthma hospitalizations in this study, the trend toward a reduction among higher severity patients was consistent with previous research. The admission rate for patients scored as moderate and severe was 8% lower in the ipratropium group compared with controls, corresponding to an odds ratio of 0.64 for admission. Previous studies of patients with $FEV_1 < 50\%$ have reported reductions in admission rate of 19%[18] and 11%.[16] Direct comparison of our results is not possible because of the lack of an accepted severity score for pediatric asthma that has been well validated against pulmonary function. Future comparison may be possible because we chose the same severity score that was used in a previous ipratropium study.[18] Final resolution of whether ipratropium reduces hospitalizations will await a larger trial or a meta-analysis of all available data.

The subgroup analysis presented in Table 4 sug-

gests several new areas for further study. Time to discharge was reduced significantly in mild as well as moderate to severe patients who were treated with ipratropium. This finding suggests a potential role for the medication beyond that previously described in severe asthmatics. The reduction in time to discharge was highly significant among children <5 years old; ipratropium has not been studied previously in this age group.

There are several limitations to our study. A few patients in the control group received ipratropium outside of the study protocol after the initial hour of treatment. This could have reduced the size of the observed treatment effect, although only 8 of these patients were discharged and therefore included in the outcomes showing significant benefit. The reliability of the baseline severity score was not high ($\kappa = 0.6$); this may have resulted in some overlap between the severity subgroups. Because patients were allowed to enroll in the study more than once, the population was biased toward frequent ED visitors. We felt that this was appropriate because we were attempting to assess the benefit of ipratropium in usual clinical practice; the proportion of repeat visits in the study sample resembled that in the total ED asthma population. The overall results did not change when repeat visitors and those with protocol violations were excluded from the analyses.

Because this study was conducted at a single institution, generalizability of our findings to other settings may be limited. The decision of when to admit or discharge patients was made subjectively by the clinicians involved and may vary in other settings or populations. The presence of resident physicians and students might also have affected the length of treatment and observation. Follow-up of patients after discharge was not attempted in this study. Although return ED visits to our institution within 72 hours did not differ between ipratropium and control groups, we cannot exclude the possibility that such visits were made to other facilities.

Overall, our study demonstrated a benefit of adding ipratropium to ED treatment for childhood asthma. Time to discharge and number of nebulizer treatments were reduced in the overall study group, and benefits were identified in all severity subgroups including the mildest subgroup. Future research is needed to reproduce these results in other settings, measure the effect of ipratropium on asthma hospitalizations, and assess the cost-effectiveness of the medication.

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