EFFECT OF NEBULIZED IPRATROPIUM ON THE HOSPITALIZATION RATES OF CHILDREN WITH ASTHMA

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ABSTRACT

Background Anticholinergic medications such as ipratropium improve the pulmonary function of patients with acute exacerbations of asthma, but their effect on hospitalization rates is uncertain.

Methods We conducted a randomized, double-blind, placebo-controlled study of 434 children (2 to 18 years old) who had acute exacerbations of moderate or severe asthma treated in the emergency department. All the children received a nebulized solution of albuterol (2.5 or 5 mg per dose, depending on body weight) every 20 minutes for three doses and then as needed. A corticosteroid (2 mg of prednisone or prednisolone per kilogram of body weight) was given orally with the second dose of albuterol. Children in the treatment group received 500 μg (2.5 ml) of ipratropium bromide with the second and third doses of albuterol; children in the control group received 2.5 ml of normal saline at these times.

Results Overall, the rate of hospitalization was lower in the ipratropium group (59 of 215 children [27.4 percent]) than in the control group (80 of 219 [36.5 percent], P=0.05). For patients with moderate asthma (indicated by a peak expiratory flow rate of 50 to 70 percent of the predicted value or an asthma score of 8 to 11 on a 15-point scale), hospitalization rates were similar in the two groups (ipratropium: 8 of 79 children [10.1 percent]; control: 9 of 84 [10.7 percent]). For patients with severe asthma (defined as a peak expiratory flow rate of <50 percent of the predicted value or an asthma score of 12 to 15), the addition of ipratropium significantly reduced the need for hospitalization (51 of 136 children [37.5 percent], as compared with 71 of 135 [52.6 percent] in the control group; P=0.02).

Conclusions Among children with a severe exacerbation of asthma, the addition of ipratropium bromide to albuterol and corticosteroid therapy significantly decreases the hospitalization rate. (N Engl J Med 1998;339:1030-5.)

STANDARD therapy for acute exacerbations of asthma in children consists of inhaled β_2-adrenergic–receptor agonists and oral or parenteral corticosteroids.[1] Even with optimal use of these agents, many children continue to have considerable residual airway obstruction, necessitating hospital admission for ongoing therapy. Several studies, including one conducted in our emergency department,[2] demonstrated that the addition of ipratropium bromide, an anticholinergic drug, to standard albuterol therapy significantly improves pulmonary function as compared with albuterol alone.[2-8] In a previous study,[2] we noted that 31 percent of children given albuterol alone, as compared with 20 percent of children given the combined treatment, were hospitalized. Because the sample was small (90 subjects), statistically relevant inferences could not be drawn from this observation.

Other studies concluded that the addition of ipratropium did not improve rates[4-6] or durations[9,10] of hospitalization. These studies, however, enrolled few patients and often used a relatively small (250 μg), single dose of ipratropium. We therefore designed a larger, double-blind, randomized, prospective study to determine whether the addition of ipratropium bromide to standard emergency department therapy for asthma in children would reduce hospitalization rates.

METHODS

Subjects

The subjects were children 2 to 18 years old who had a known history of asthma and who presented to the pediatric emergency department with an acute exacerbation of asthma. Eligible children were enrolled if personnel were available to collect study data. An acute exacerbation of asthma was defined as wheezing and worsening of asthmatic symptoms or increased difficulty in breathing, with deterioration of the peak expiratory flow rate. Children less than two years old were not enrolled, because in this age group, wheezing may be due to bronchiolitis.

The initial severity of the episode of asthma was expressed either as a percentage of the predicted peak expiratory flow rate or as an "asthma score." Our asthma-scoring system, a modification of one published by the National Institutes of Health,[11] rates the severity of an episode according to signs and symptoms (Table 1). It was developed as part of our asthma-treatment protocol and has been used extensively in both the emergency department and the inpatient units to evaluate the degree of respiratory distress in patients unwilling or too young to perform reliable pulmonary-function tests. Before performing this study, we confirmed that the interrater reliability of the scoring system, tested in 98 children in the emergency department, was good (Pearson correlation statistic, 0.92). Each patient's asthma was classified as mild (peak expiratory flow rate, >70 percent of the predicted value, or an asthma score of 5 to 7), moderate (peak expiratory flow rate, 50 to 70 percent of the predicted value, or an asthma score of 8 to 11), or severe (peak expiratory flow rate, <50 percent of the predicted value, or an asthma score of 12 to 15). If the child's effort during measurement of the peak expiratory flow rate was

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TABLE 1. METHODS OF CALCULATING THE ASTHMA SCORE AND THE SEVERITY OF ASTHMA.*

VARIABLE	ASTHMA SCORING		
	1 POINT	2 POINTS	3 POINTS
Respiratory rate (breaths/min)			
2–3 yr	≤34	35–39	≥40
4–5 yr	≤30	31–35	≥36
6–12 yr	≤26	27–30	≥31
>12 yr	≤23	24–27	≥28
Oxygen saturation (%)	>95 with room air	90–95 with room air	<90 with room air or supplemental oxygen
Auscultation	Normal breathing or end-expiratory wheezing	Expiratory wheezing	Inspiratory and expiratory wheezing, diminished breath sounds, or both
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts

	SEVERITY OF ASTHMA		
	MILD	MODERATE	SEVERE
Peak expiratory flow rate (% of predicted value)†	>70	50–70	<50
Asthma score	5–7	8–11	12–15

*The overall asthma score (range, 5 to 15 points) was calculated by adding the scores for each of five variables: respiratory rate, oxygen saturation, auscultation, retractions, and dyspnea. The overall asthma score was then used to stratify children according to the severity of disease.

†When the peak expiratory flow rate was known and reliable, it, rather than the asthma score, was used to stratify the children according to severity.

judged to be poor, the asthma score was used to classify the severity of asthma; otherwise, the measurement of flow rate was used. Only children with moderate or severe exacerbation of asthma were considered for enrollment.

Children were excluded from participation for any of the following reasons: treatment with ipratropium within six hours before the visit to the emergency department, a disease known to have a chronic effect on respiratory function (e.g., cystic fibrosis or cardiac disease), concurrent stridor, possible presence of an intrathoracic foreign body, a medical condition that would contraindicate the use of β_2-adrenergic or anticholinergic medications, or the need for immediate resuscitation or airway intervention. Before enrollment, informed consent was obtained from a parent or legal guardian and from the patient if he or she was competent to give it.

Study Design

We used a randomized, double-blind, placebo-controlled experimental design approved by the institutional review board of Eastern Virginia Medical School. The study took place between November 1996 and June 1997 at a 168-bed, tertiary care, urban medical center.

Pharmacy staff used a table of random numbers to assign children by block randomization to treatment and control groups. They also provided numbered plastic bags, each containing either two single-dose vials (500 μg per dose) of ipratropium bromide (Atrovent, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Conn.) or two vials of preservative-free normal saline, which served as a placebo. The contents of the two types of vials were identical in appearance and aroma. Both the investigators and the patients were unaware of the group assignments and vial contents. A supply of the vials was maintained in the emergency department to avoid delays in treatment.

All the children were treated with nebulized 0.5 percent albuterol solution at a dose of 2.5 mg (for children weighing <20 kg) or 5 mg (for children weighing ≥20 kg) every 20 minutes for three doses. A corticosteroid (2 mg of prednisone or prednisolone per kilogram of body weight, to a maximal dose of 60 mg) was given orally with the second dose of nebulized albuterol. Children in the treatment group received 500 μg (2.5 ml) of ipratropium bromide with the second dose and again with the third dose of albuterol; children in the control group received albuterol with 2.5 ml of normal saline.

Only the data from children who received both doses of ipratropium were included in the final analysis. Data from children who had a response to the first or second dose of albuterol, suggesting that they had milder disease and therefore were less likely to be hospitalized, were eliminated. After the first 60 minutes of treatment, albuterol was given at the physician's discretion until a decision was made to admit or discharge the patient. Medications were administered with the use of a nebulizer and a well-fitting face mask, at an oxygen flow rate of 6 liters per minute. Oxygen was administered if the patient's oxygen saturation (as measured by pulse oximetry) was 94 percent or less. The predicted peak expiratory flow rate was determined from normative data for patients of the same height, sex, and race.[12] For each child, the percentage of the predicted peak expiratory flow rate was calculated from the measured peak expiratory flow rate and was used in subsequent analyses.

The peak expiratory flow rate, asthma score, pulse rate, respiratory rate, and oxygen saturation were determined before the first nebulizer treatment and then after each treatment. The time of each nebulizer treatment, the total number of treatments, the time of disposition, the time of discharge from the emergency department, and the disposition were recorded. A decision to admit or discharge the child was made by the attending physician according to objective changes in the measurements of clinical and pulmonary function and according to the oxygen saturation (<94 percent or ≥94 percent in room air). A research assistant contacted the patient's family three to five days after discharge from the emergency department to determine whether any subsequent visits had been made to a medical facility.

Statistical Analysis

Judging from our previous observation,[2] we expected a 31 percent rate of hospitalization among patients treated with standard therapy and an absolute difference of 11 percent in the rate of hospitalization between the two groups. According to this assumption, a two-tailed power estimate (power, 0.80; alpha level, 0.05) required a minimum of 211 children per group.

The principal outcome measure was the rate of hospitalization, for each of the two treatment groups overall and for children in each treatment group according to the initial severity of the asthma. Hospitalization was defined as admission to the short-stay (23-hour) unit, a general pediatric ward, the intermediate care unit, or the intensive care unit. The secondary outcome measures were the number of nebulizer treatments until disposition, the time to disposition, the need for any visits to a medical facility within 72 hours after discharge, and any changes in peak expiratory flow rate, asthma score, heart rate, respiratory rate, or oxygen saturation from entry into the study until disposition. Fisher's exact test or analysis of variance[13] was used, as appropriate, to test for statistical differences between the groups. For all the analyses, a two-tailed P value of less than 0.05 was considered to indicate statistical significance. The 95 percent confidence intervals, absolute risk reductions, relative risk reductions, and number needed to treat were calculated with standard formulas.[14]

RESULTS

A total of 480 children were enrolled and randomly assigned to treatment groups after 17 children, whose parents declined to give permission for participation, had been excluded. In 46 children, wheezing resolved before the second dose of the study medication had been given. Of these 46, 18 (all of whom had an exacerbation of asthma initially described as moderate) received a single albuterol treatment. Of the remaining 28 children, 15 (1 with a severe exacerbation) received saline and 13 (1 with a severe exacerbation) received ipratropium. A total of 434 children (215 in the treatment group and 219 in the control group) completed the study. Table 2 shows the demographic and base-line clinical characteristics of the two groups. There was a greater proportion of girls in the ipratropium group than in the control group (P=0.04). Otherwise, there were no significant differences between the groups as a whole or between groups stratified according to the severity of asthma.

Figure 1 shows the rates of hospitalization in the ipratropium and control groups. The overall rate of hospitalization was lower in the ipratropium group (27.4 percent [59 of 215 children], as compared with 36.5 percent [80 of 219] in the control group; P=0.05). There was no significant difference in the rates of hospitalization (10.1 percent [8 of 79] in the ipratropium group and 10.7 percent [9 of 84] in the control group) for patients with moderate asthma. For patients with severe asthma, however, the addition of ipratropium significantly reduced the hos-

TABLE 2. BASE-LINE CHARACTERISTICS OF THE 434 CHILDREN WHO COMPLETED THE STUDY.*

CHARACTERISTIC	CONTROL GROUP (N=219)	IPRATROPIUM GROUP (N=215)
Sex (no.)		
Male	136	112
Female	83	103†
Race (no.)		
White	34	35
Black	184	172
Other	1	8
Age (yr)	8.3±4.0	8.4±4.1
Asthma score		
Median	11	11
Range	6–15	8–15
Peak expiratory flow rate (% of predicted value)	39.3±8.2	40.0±7.5
Severity of asthma (no.)		
Moderate	84	79
Severe	135	136

*Plus–minus values are means ±SD.

†P=0.04 for the comparison with the control group.

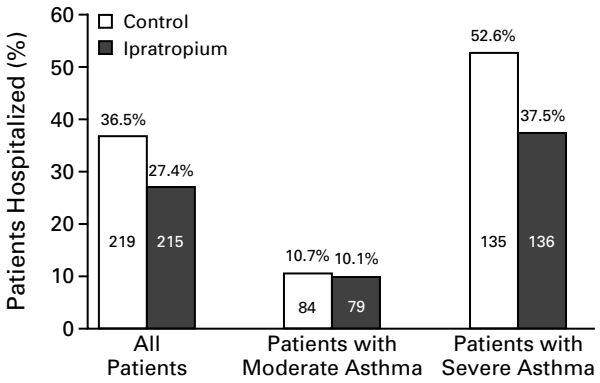

Figure 1. Rates of Hospitalization in the Control and Ipratropium Groups.

When the 434 patients who completed the study were stratified according to the severity of the exacerbation of asthma at presentation, 163 were classified as having moderate asthma and 271 as having severe asthma. The number of children who received saline or ipratropium in each group is shown within the bars. The overall rate of hospitalization was lower in the ipratropium group (P=0.05). In children with severe asthma, the rate of hospitalization was significantly lower in those receiving ipratropium than in those receiving saline (P=0.02).

TABLE 3. SECONDARY OUTCOMES.*

OUTCOME	CONTROL GROUP		IPRATROPIUM GROUP	
	MODERATE ASTHMA (N=84)	SEVERE ASTHMA (N=135)	MODERATE ASTHMA (N=79)	SEVERE ASTHMA (N=136)
Time to disposition (hr:min)	2:23±0:44	2:44±1:20	2:22±0:60	3:03±1:05
No. of nebulizer treatments before disposition	3±1	4±1	3±1	4±1
Peak expiratory flow rate†				
Initial (% of predicted value)	54.9±6.7	33±8.6	57.3±6.8	34.1±8.1
Change (%)	29±12	31±17	26±12	32±15
Oxygen saturation (%)				
Initial	96.1±2.6	93.8±3.8	95.5±2.4	94.2±3.3
At disposition	97.3±1.8	95.7±3.2	97.4±1.8	96.5±2.7‡
No. of patients seeking medical care within 72 hr after discharge	2	4	1	7
Disposition location (no. of patients)				
Home	75	64	71	85
Short-stay unit	6	14	5	9
General pediatric ward	3	21	2	13
Intermediate care unit	0	29	1	23
Pediatric intensive care unit	0	7	0	6
Change in severity according to asthma score (no. of patients)§				
Moderate→mild	76		75	
Severe→moderate¶	60		43	
Severe→mild¶	56		77	
Moderate→moderate	8		4	
Severe→severe¶	19		16	

*Data are stratified according to treatment group and initial asthma-severity score. Plus–minus values are means ±SD.

†The peak expiratory flow rate was used to determine the severity of asthma in 25 children with moderate asthma and 62 with severe asthma in the control group and in 22 children with moderate asthma and 65 with severe asthma in the ipratropium group.

‡P=0.02 for the comparison with the children with severe asthma in the control group.

§The change was from the initial asthma score to the score at disposition. When all the children were compared, the asthma score improved to a greater extent in the treatment group (P=0.05).

¶In the children with severe asthma on presentation, the asthma score improved to a greater extent in the treatment group (P=0.01).

pitalization rate, to 37.5 percent (51 of 136) as compared with 52.6 percent (71 of 135) (P=0.02). Of the 46 children whose condition improved before completion of the study, only 2 presented with severe asthma; therefore, an intention-to-treat analysis had similar results (admission rate, 52.2 percent with saline vs. 37.2 percent with ipratropium).

In children with severe asthma who received both doses of the study medication, the absolute reduction in the rate of hospitalization between the treatment and control groups was 15.1 percent (95 percent confidence interval, 3.4 to 26.8 percent); the relative reduction in the rate of hospitalization was 28.7 percent. The number of children with severe asthma who would need to be treated with ipratropium to prevent one hospitalization was 6.6 (95 percent confidence interval, 3.7 to 29.4).

When the patients were stratified according to the initial severity of asthma, there were no significant differences between groups in measures of secondary outcome, except for the asthma score and the change in oxygen saturation in children with severe asthma (Table 3). The heart rate increased and the respiratory rate decreased after treatment, but the differences between groups were not significant. Overall, the asthma score improved more often in children treated with ipratropium than in those treated with saline (P=0.05); in children with severe asthma, the effect of ipratropium on the improvement in the asthma score was greater (P=0.01). The mean improvement in oxygen saturation in the treatment group was significantly greater than that in the control group (2.3 percent vs. 1.9 percent among children with severe asthma, P=0.02), but this improvement was not clinically significant. In none of the children was there a deterioration of respiratory function, an increase in heart rate, or other adverse effects requiring interruption of the study protocol.

DISCUSSION

We found that adding ipratropium bromide to standard therapy consisting of albuterol and a corticosteroid for acute exacerbations of asthma in children significantly decreased the hospitalization rate for those with severe asthma (peak expiratory flow rate, <50 percent of the predicted value or an asthma score of 12 to 15). We found no similar reduction in hospitalization rates for children with moderate asthma. On the basis of our data, approximately seven children with severe acute asthma would need to be treated with ipratropium to prevent one hospitalization. This represents a substantial reduction in cost, since the average per-child cost of hospitalization for asthma at our institution is $3,267. In contrast, because ipratropium is administered with albuterol, the incremental cost is related solely to the cost of the drug ($3 per 500-$\mu$g dose).

Ipratropium bromide is an effective bronchodilator for patients with acute asthma.[15,16] Studies of the effectiveness of a combination of ipratropium bromide and a β_2-adrenergic agonist in adults with an acute exacerbation of asthma have produced conflicting results.[7,8,17,18] In contrast, most[2-6,19] but not all[9,10,16] studies in children have shown that the addition of ipratropium to a nebulized β_2-adrenergic agonist has an additive effect in improving pulmonary function. A meta-analysis[20] concluded that in children receiving ipratropium bromide and a β_2-adrenergic agonist, the percentage of the predicted forced expiratory volume in one second improved significantly (a change of 12.5 percent; 95 percent confidence interval, 6.6 to 18.4 percent) as compared with that in children receiving the β_2-adrenergic agonist alone. However, none of the studies in the meta-analysis found a significant difference between the treatment and control groups with respect to vital signs, the clinical asthma score, the number of nebulizer treatments, the hospitalization rate, the duration of hospitalization, or side effects. Reasons for this apparent lack of improvement in outcome measures may include one or more of the following: the relatively small number of patients enrolled, the use of a single dose or a smaller dose of ipratropium (250 μg), lack of a consistent treatment protocol, and a short duration of observation.

In a study of 125 children with severe asthma, Schuh and coworkers[3] found that the forced expiratory volume in one second improved to a greater extent in children receiving combined albuterol and ipratropium than in those receiving albuterol and placebo, but there was no effect on overall rates of hospitalization. In a subgroup analysis of children in whom the forced expiratory volume in one second was less than 30 percent of the predicted value, the hospitalization rate among those receiving the combination therapy was significantly lower than the rate with albuterol alone; however, the small number of patients in this subgroup limited the extent to which these observations could be generalized.

Comparison of the treatment and control groups in our study showed that the addition of ipratropium had a significant effect on improvement of the asthma score, but there were no significant differences in improvement of the peak expiratory flow rate. This rate was recorded only in the 40 percent of children who made an acceptable effort during testing. Because measurement of the peak expiratory flow rate was not the focus of our study, we relied more on the asthma score to assess the degree of respiratory distress. Furthermore, our experience suggests that measurements of the peak expiratory flow rate may not be reliable unless the child is coached to make a consistent, maximal effort.

Besides showing good interobserver agreement, our study provides additional support for the validity of our asthma-scoring system, since the rate of hospitalization in children with moderate asthma was significantly lower than that in the group with severe disease. Furthermore, the asthma score improved to a greater extent in children receiving ipratropium than in those receiving albuterol alone, especially in the children with severe asthma.

There were significantly more girls in the ipratropium group than in the control group. We considered the possibility that the girls weighed less than the boys and therefore received a larger dose of albuterol on a milligram-per-kilogram basis. However, analysis failed to show that sex or body weight had any relation to the risk of hospitalization.

In our emergency department, the treatment of children with asthma is carried out according to an "asthma clinical pathway," which includes administration of three doses of nebulized albuterol within the first 60 minutes of treatment. Corticosteroids are administered with the second dose of albuterol. Adherence to this protocol reduces variation in treatment, thereby increasing the likelihood that the reduction in hospitalization rates observed in this study was due to the addition of ipratropium. In addition, physicians are encouraged to reach a disposition decision within two to three hours. This may explain why there was no significant difference in our study between the treatment and control groups in the number of nebulized treatments given or the time until disposition. We chose not to study the time spent in the emergency department, because this interval depends on many factors that are independent of drug therapy, such as the availability of beds in the hospital, the time needed to obtain discharge medications and to provide good patient education, and the ability of the family to arrange transportation.

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