

## Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma

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**Objective:** The objective of this trial was to determine the efficacy of frequent nebulized ipratropium added to high-dose albuterol therapy in children with severe asthma.

**Methods:** One hundred twenty children (5 to 17 years of age) with severe acute asthma (forced expiratory volume in 1 second (FEV<sub>1</sub>), <50% of the predicted value) were enrolled into a randomized double-blind three-arm placebo-controlled trial comparing three groups: group 1, three doses of nebulized ipratropium bromide within 60 minutes (250 µg/dose); group 2, one dose of ipratropium; group 3, no ipratropium. All patients were also treated with three doses of nebulized albuterol within 60 minutes (0.15 mg/kg per dose). Pulmonary function and clinical measures were assessed every 20 minutes for up to 120 minutes.

**Results:** The groups were comparable at baseline. At 120 minutes, the mean percentage of predicted FEV<sub>1</sub> improved from 33.4% to 56.7% in group 1, from 34.2% to 52.3% in group 2, and from 35.4% to 48.4% in group 3 ( $p = 0.0001$ ). The differences between groups were larger in those children with a baseline FEV<sub>1</sub>  $\leq 30\%$  of the predicted value: FEV<sub>1</sub> increased from 24.5% to 50.9% in group 1, from 25.0% to 39.8% in group 2, and from 25.9% to 36.5% in group 3 ( $p = 0.0001$ ). In group 1, 38% of the patients were hospitalized after the study, 44% in group 2, and 46% in group 3 ( $p$  value not significant). However, in patients with FEV<sub>1</sub>  $\leq 30\%$ , the hospitalization rates were 27% in group 1, 56% in group 2, and 83% in group 3 ( $p = 0.027$ ). There were no toxic effects attributable to ipratropium.

**Conclusion:** The addition of repeated doses of nebulized ipratropium to frequent high-dose albuterol therapy in patients with acute severe asthma is both safe and more effective than albuterol alone; its use in patients with very severe asthma may reduce hospitalizations. (J PEDIATR 1995;126:639-45)

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Frequent administration of nebulized  $\beta_2$  agonists and of corticosteroids at the time of onset has been shown to be more effective than less aggressive therapy for acute exacerbations of asthma.<sup>1-5</sup> However, many children do not respond adequately to this regimen and require prolonged treatment and hospitalization. Nebulized ipratropium bromide, an acetylcholine antagonist, has been used as an adjunct to therapy for asthma in Europe and in Canada for almost a decade. Well-executed studies have demonstrated,

ANOVA	Analysis of variance
ED	Emergency department
FEV <sub>1</sub>	Forced expiratory volume in 1 second

in both adults and children, that the combination of ipratropium and a  $\beta_2$  agonist is superior to the use of a  $\beta_2$  agent alone.<sup>6-12</sup> However, all these studies have used either low-dose or infrequent albuterol therapy, potentially resulting in a submaximal response to this drug. Because of the current widespread use of frequent, high-dose  $\beta_2$  agonist therapy in severe asthma, we thought it important to establish whether the addition of ipratropium bromide to this already aggressive treatment provides additional benefit. Further, the relative efficacy of administering a single dose versus multiple doses of nebulized ipratropium has not been established.

The objective of this trial was to study the efficacy and safety of the addition of three doses versus one dose of nebulized ipratropium bromide to frequent administration of albuterol, in comparison with albuterol alone in the emergency department treatment of severe childhood asthma.

## METHODS

The study design was a double-blind, randomized, placebo-controlled trial with three study groups: all patients received three nebulizations of albuterol in combination with either no ipratropium, one dose of ipratropium, or three doses of ipratropium. The study took place in the emergency department of the Hospital for Sick Children, Toronto, between October 1991 and December 1993. Included in the study were children with an acute asthma attack who were 5 through 17 years of age and were able to perform the pulmonary function testing reliably; baseline forced expiratory volume in 1 second was less than 50% of the predicted value. Excluded were children who had had their first wheezing episode only, those who had used ipratropium within 4 hours of this ED visit, those with a previous admission to the intensive care unit, children with concurrent cardiopulmonary disease, those near death and therefore requiring immediate intervention, and patients with known or suspected hypersensitivity to the study drugs. Informed consent was obtained for all the patients, and the study was approved by the ethics committee of this hospital. An experienced research nurse (S.C.) enrolled all patients and performed all observations. The randomization code was generated by the hospital pharmacy department from a standard table of random numbers in blocks, so that after each nine patients there would be three subjects allocated to each group. A log of all patients screened for this trial listed reasons for those excluded.

After arrival of the patient in the ED and initial assess-

ment by the ED staff, the research nurse evaluated each child for study eligibility, and obtained written consent. She also completed a questionnaire detailing demographics, history of present condition, and current medications. The pharmacy department provided three vials that contained either ipratropium or placebo (0.9% saline solution) labeled Nos. 1, 2, and 3. Albuterol-ipratropium and albuterol-saline mixtures are indistinguishable in both the liquid and the nebulized states. The patient, the research nurse, and the investigator were masked to the group assignment.

All patients received three standard doses of nebulized albuterol (Allen & Hanbury Canada), 0.15 mg/kg per dose, 20 minutes apart. Those in group 1 also got three doses of ipratropium bromide (Boehringer Ingelheim), 250  $\mu$ g/dose (1 ml = 1 dose) mixed with the albuterol; those in group 2 received only one dose of ipratropium, and those in group 3 received no ipratropium. The nurse thus mixed the weight-appropriate albuterol dose from the ED stock with 1 ml of the content of vials marked Nos. 1, 2, and 3 (ipratropium or placebo). The inhalations were given by nebulizer (Whisper Jet; Intec Medical, Inc. [Marquest Medical Products, Inc.], Englewood, Colo.) with 2 ml of 0.9% saline solution at an O<sub>2</sub> flow of 6 to 7 L/min. A tight-fitting plastic face mask was used, and each inhalation lasted about 15 minutes. To avoid a potential confounder, we administered neither corticosteroids nor other bronchodilators during the study.

The primary outcome measure was the difference (between groups) in the change of the percentage of predicted FEV<sub>1</sub>. The FEV<sub>1</sub> was measured by a portable, battery-operated hand spirometer (P. K. Morgan Ltd., Kent, United Kingdom). After the initial demonstration and teaching, the pulmonary function tests were performed in sets of six (to ensure maximal effort and to allow for a learning curve) and expressed as a percentage of that predicted for height and sex.<sup>13</sup> The highest FEV<sub>1</sub> from each set was used in the analysis.<sup>14, 15</sup> Secondary outcomes included the changes in the accessory muscle score, wheeze score, dyspnea score, overall score (Table I), respiratory rate, heart rate, and oxygen saturation (Nellcor Inc., Hayward, Calif.).

All outcome measures were taken at baseline (time 0), at 20, 40, and 60 minutes (i.e., after each treatment), and at 80 and 120 minutes. Side effects (as reported by the patient or observed by the research nurse) were monitored. Disposition and additional therapy (after the study) in the ED were also noted. Children with respiratory distress at the end of the study were admitted. The decision to hospitalize the patients was made by the ED staff pediatrician not involved in the trial and unaware of the outcome measure changes (except for the oxygen saturation). The research nurse also followed all patients (by telephone) 72 hours af-

Table I. Clinical scores

Severity	Accessory muscle score	Wheeze score	Dyspnea score
0	No retractions	No wheeze and well	Absent dyspnea
1	Intercostal retractions	End-expiratory wheeze	Normal activity and speech; minimal dyspnea
2	Intercostal and suprasternal retractions	Pan-expiratory $\pm$ inspiratory wheeze	Decreased activity; 5- to 8-word sentences; moderate dyspnea
3	Nasal flaring	Wheeze audible without stethoscope	Concentrates on breathing; <5-word sentences; severe dyspnea

Table II. Baseline characteristics of study groups: Clinical demographics

	Group 1 (n = 40)	Group 2 (n = 39)	Group 3 (n = 41)
Age (yr)*	9.2 $\pm$ 2	9.3 $\pm$ 3	9.4 $\pm$ 3
Duration of symptoms (hr)*	22 $\pm$ 21	31 $\pm$ 24	30 $\pm$ 18
ED visits for asthma (total within past 2 years—as reported by the parents)	86	67	61
URI (within past 7 days)	34	28	29
Fever (within 48 hr)	2	3	5
Atopy (personal and/or family history): asthma, eczema, hay fever	38	35	39
FEV <sub>1</sub> (% predicted)*	33.4 $\pm$ 7	34.2 $\pm$ 9	35.4 $\pm$ 8
Respiratory rate (breaths/min)*	30.6 $\pm$ 7	30.8 $\pm$ 8	28.3 $\pm$ 7
Heart rate (beats/min)*	120.4 $\pm$ 19	123.6 $\pm$ 19	121.0 $\pm$ 19
Oxygen saturation % (room air)*	94.4 $\pm$ 3	94.2 $\pm$ 3	93.2 $\pm$ 8
Accessory muscle score	2.3	2.4	2.1
Wheeze score	2.2	2.5	2.1
Dyspnea score	1.8	2.1	1.7

URI, Upper respiratory tract infection.

\*Values are expressed as mean  $\pm$  SD.

ter discharge regarding repeated visits to the ED or hospitalizations for asthma at this or other institutions.

Before the study, we estimated that the minimal requirement for a "positive" result was the difference between groups in the mean improvement of the percentage of predicted FEV<sub>1</sub> of at least 8. In addition, each patient was defined as an "excellent responder" if the percentage of predicted FEV<sub>1</sub> improved by  $\geq 30$  from baseline to 120 minutes (e.g., from 30% to 60% of the predicted value) and as a "poor responder" if it improved by <5. It was also decided to stop the study if the patient had (1) cardiac tachyarrhythmia (except sinus tachycardia), (2) severe clinical deterioration (as judged by the nonstudy ED supervisor) requiring immediate additional intervention or precluding reliable pulmonary function measurement, and (3) severe eye pain or visual acuity changes.

During the 3 weeks before the start of the study, the research nurse was trained to measure pulmonary function and the various scoring measurements by the principal investigator and the chief technician of the pulmonary function laboratory. Furthermore, a videotape of 23 children of various ages and with asthma of varying severity was pro-

duced during this period, to obtain interobserver reliability ratings on the accessory muscle and the dyspnea scores between the research nurse and the principal investigator for the quality assurance measurement.

The primary analysis was the repeated measures analysis of variance on the difference between groups in the changes in the percentage of predicted FEV<sub>1</sub> with time. Several secondary analyses were also performed, including ANOVA on the differences in the respiratory rate, heart rate, and O<sub>2</sub> saturation. The changes in the various scores were analyzed by repeated measures ANOVA. The score differences between baseline and 120 minutes among the three groups were compared by using the Kruskal-Wallis test (nonparametric equivalent of ANOVA). The proportions of excellent and poor responders and the hospitalization rates were examined by the chi-square and the Fisher Exact tests. The required number of subjects was calculated according to the following: clinically significant difference in improvement between groups in the percentage of predicted FEV<sub>1</sub>  $\geq 8$ , standard deviation in the control group of 13.7<sup>1</sup> ( $\alpha = 0.05$ ;  $\beta = 0.01$ ). The appropriate formula yields the total number of 120.<sup>16</sup>

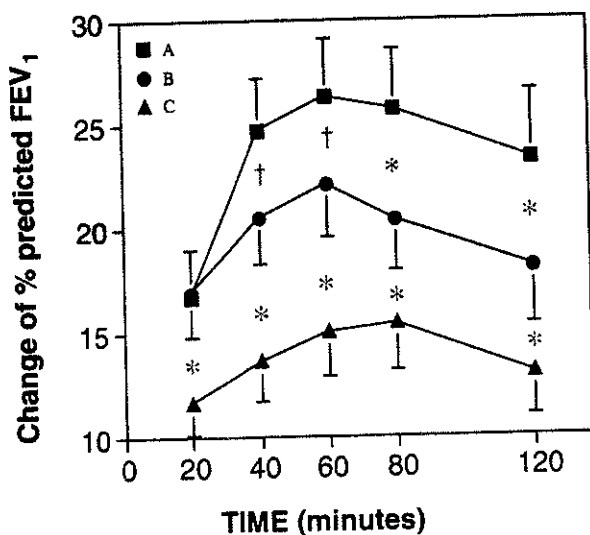


Fig. 1. Mean difference ( $\pm$ SEM) from baseline of percentage of predicted FEV<sub>1</sub> with time in group 1 (three ipratropium doses), group 2 (one ipratropium dose), and group 3 (no ipratropium). Repeated measures ANOVA:  $p = 0.0001$ . \* $p < 0.01$ . † $p < 0.05$ .

## RESULTS

During the study period (Oct. 15, 1991, to Dec. 12, 1993) 1586 children more than 5 years of age with asthma were seen in our ED; 435 of these arrived while the nurse was on duty (usually between 2 and 10 PM). The exclusions comprised 204 patients with baseline FEV<sub>1</sub> 50% of the predicted value or greater, 33 patients previously enrolled in this study, 21 with coexistent medical problems, 32 children who did not perform the pulmonary function test satisfactorily, 15 whose condition was unstable and required immediate intervention, 11 who had no history of wheezing or asthma or of bronchodilator therapy, 6 who had received ipratropium within 4 hours of arrival, and 2 who arrived without a parent. One patient was 19 years of age and thus went to another institution, and 16 patients were missed. Eight families refused to participate.

A total of 121 children were originally enrolled (64 boys), but one parent changed his mind and demanded withdrawal before the start of the experimental therapy. This left 120 patients for analysis. Group 1 consisted of 40 patients, group 2 of 39, and group 3 of 41. Randomization produced equivalent groups with respect to contributory variables such as demographics, duration of present illness, baseline severity measures, and medications before arrival (Table II).

Repeated measures ANOVA showed significant differences in improvement among the three groups ( $p = 0.0001$ ) (Fig. 1) and even larger differences in patients with FEV<sub>1</sub> less than 30% of the predicted value ( $p = 0.0001$ ) (Fig. 2).

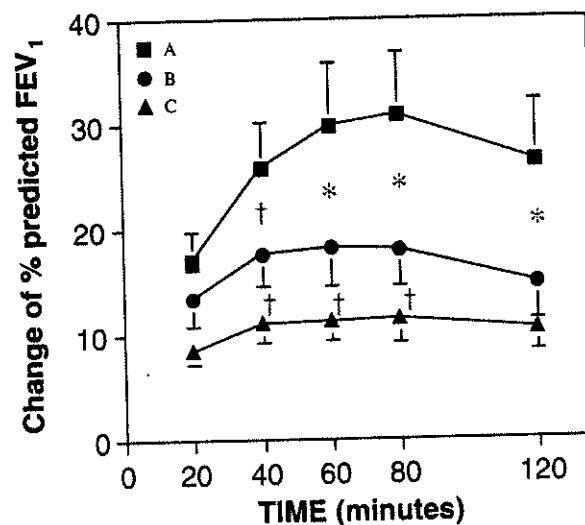


Fig. 2. Mean difference ( $\pm$ SEM) from baseline of the percentage of the predicted FEV<sub>1</sub> with time in groups 1 (three ipratropium doses), 2 (one ipratropium dose), and 3 (no ipratropium); very severe group). Repeated measures ANOVA,  $p = 0.0001$ . \* $p < 0.01$ . † $p < 0.05$ .

Seven patients had to stop the trial prematurely at either 60 or 80 minutes; three children (one each in groups 1, 2, and 3) stopped cooperating before the 120-minute measurement, and three children in group 2 and one child in group 3 were too ill to continue. Two patients had missing data at 80 minutes (because of vomiting), but both had recovered by 120 minutes. Separate analyses—with and without the nine subjects with missing data—were carried out. In this former analysis the missing data were substituted by the data from the preceding observation (Fig. 1). These nine patients were omitted in the latter analysis, with similar results (ANOVA:  $F = 3.31$ ,  $p = 0.0003$ ). Post hoc analysis showed that most of the differences between improvements in group 1 versus group 2 and improvements in group 2 versus group 3 were statistically significant (Figs. 1 and 2). To compare the mean changes with time in the secondary variables, we used the repeated measures ANOVA (Table III). The differences between groups in the dyspnea score were also significant when the Kruskal-Wallis test was performed ( $p = 0.014$ ). The differences for the other scores were not significant by this test.

There were 23 "excellent" responders in the trial (% FEV<sub>1</sub>  $\uparrow \geq 30$  at 120 minutes): 10 of 40 children in group 1, 11 of 39 in group 2, and 2 of 41 in group 3 (Fisher Exact Test,  $p = 0.009$ ). A total of 22 children responded "poorly" (% FEV<sub>1</sub>  $\uparrow < 5$  at 120 minutes): 4 of 40 children in group 1, 8 of 39 in group 2, and 10 of 41 in group 3 (Fisher Exact Test,  $p = 0.225$ ).

Fifteen patients (38%) in group 1 were hospitalized after the study, 17 (44%) in group 2, and 19 (46%) in group 3 ( $p$  value not significant). However, when the severe cases were examined (baseline FEV<sub>1</sub>  $\leq$ 30%), the differences were larger: 27% were hospitalized in group 1, 56% in group 2, and 83% in group 3 (chi-square test,  $p = 0.027$ ). According to the telephone follow-up, four children had to come back to the ED for further treatment within 72 hours after discharge home (1 in group 1, 3 in group 3), of whom 1 had to be hospitalized (group 3). After the study was completed, 21 (53%) of 40 children in group 1 needed further inhaled bronchodilators in the ED before disposition, 31 (79%) of 39 needed them in group 2, and 30 (73%) of 41 in group 3 ( $p = 0.029$ ). Of the patients with severe symptoms, 27% needed further inhaled bronchodilator therapy after the study in group 1, 75% in group 2, and 100% in group 3 ( $p = 0.00045$ ). Before disposition, the patients received oral or intravenous corticosteroid therapy.

Side effects were not significantly different in the three groups. None caused termination or significant delay in the experimental therapy, and all had resolved by the end of the trial despite continued treatment. One child (group 1) had red and slightly painful conjunctivitis 3 to 5 minutes after the start of the first treatment; both the visual acuity and the pupillary size were normal. The conjunctivitis abated about 40 minutes later and did not recur despite continued experimental treatment. One child (group 3) had a sudden decrease of O<sub>2</sub> saturation into the 60% range while having a coughing spasm followed by a 10-second syncope. He subsequently coughed up large amounts of mucus, after which the O<sub>2</sub> saturation rose to a nearly normal level.

During the training period there was a 100% interobserver agreement in the dyspnea score between the nurse (S.C.) and the principal investigator, and a 91.5% interobserver agreement in the accessory muscle score (a difference of 1 point in two patients).

## DISCUSSION

Our study shows a significant benefit of the addition of repeated doses of nebulized ipratropium to frequent high-dose albuterol therapy in children with severe acute asthma. This benefit seems especially marked in children with very severe baseline status, in whom this regimen also resulted in lower hospitalization rates.

Ipratropium is an acetylcholine antagonist. Although parasympathetic fibers occur primarily in the larger airways,<sup>17</sup> ipratropium may have a generalized action throughout the lung.<sup>18</sup> In contrast,  $\beta$ -adrenergic receptors are more peripherally distributed.<sup>19</sup> This property of differential action, as well as the different pharmacologic mechanisms,

**Table III.** Secondary outcome measures: Mean changes from baseline to 120 minutes

	Group 1	Group 2	Group 3	$p^*$
Accessory muscle score	-1.4	-1.2	-0.9	0.014
Wheeze score	-1.4	-1.6	-1.0	0.011
Dyspnea score	-1.1	-1.3	-0.8	0.018
Respiratory rate (breaths/min)	-3.0	-5.0	-3.1	NS
Heart rate (beats/min)	+15.3	+9.9	+15.1	NS
O <sub>2</sub> saturation (%)	+1.3	+1.4	+0.1	NS

NS, Not significant.

\*By ANOVA.

provides a rationale for using these drugs together. Several studies of adults have demonstrated their synergy.<sup>6-9</sup> Several pediatric studies also show the benefit of this combination, albeit not all. Both Beck et al.<sup>10</sup> and Reisman and Galdes-Sebalt<sup>11</sup> showed differences in pulmonary function improvement in children with acute asthma who were receiving the ipratropium-albuterol mixture, in comparison with albuterol alone. Watson et al.<sup>12</sup> found the ipratropium-fenoterol combination to be beneficial, although the statistical difference from fenoterol alone was marginal (possibly because of small patient numbers). Several other studies showed no added benefit from the anticholinergic drugs,<sup>20-22</sup> but these projects had methodologic problems, such as non-uniform frequency of administration of the study drugs,<sup>20</sup> enrollment of subjects with mild disease,<sup>21</sup> or lack of objective measurement of pulmonary function in many subjects.<sup>22</sup> To date, all the authors dealing with the subject have used submaximal  $\beta$ -agonist therapy—that is, either low or infrequent doses. Given the efficacy of frequent high doses of albuterol,<sup>2</sup> any further benefit of the addition of anticholinergics was in question before this trial.

The ideal dosage and the ideal dosing frequency of ipratropium are unknown. Davis et al.<sup>23</sup> found the optimal dose to be between 75 and 250  $\mu$ g in stable patients with non-acute disease—a scenario not fully comparable to severe, acute disease. The present recommendation in Canada is to use this drug at 4- to 6-hour intervals.<sup>5</sup> Reisman et al.<sup>11</sup> showed that the additional benefit of ipratropium can be maintained by further doses at 40 and 80 minutes, with no toxic effects. Our trial demonstrates that the addition of one ipratropium dose to frequent high-dose albuterol therapy results in a small clinical benefit and that frequent administration is necessary to produce a clinically significant difference from albuterol alone. This benefit was most obvious in the sickest children. A significant vagal component to

bronchospasm must be present in many of these children with asthma, a view previously expressed by others.<sup>10,11</sup>

This benefit is further supported by the differences in the various scores. These scores have been partially validated and have been shown to correlate with the objective "gold standard" measurement of the FEV<sub>1</sub>.<sup>24</sup> These scores are much more crude measures than the FEV<sub>1</sub> and thus do not identify changes in group 1 versus group 2. The credibility of the various measurements is markedly enhanced by the single-observer design of this trial, which eliminated the interobserver reliability issue. Lack of changes in the respiratory rate and the oxygen saturation likely represents poor responsiveness of these outcome measures to therapy in the older children. The relative insensitivity of oxygen saturation is due in part to the curvilinear oxygen-hemoglobin dissociation curve, which accounts for minimal saturation changes when the oxygen tension is greater than 60 mm Hg.

Ipratropium is of low lipid solubility, and thus is poorly absorbed systemically.<sup>25</sup> Toxic effects of this drug are therefore negligible, even at very high doses.<sup>6</sup> Both transient anisocoria and angle-closure glaucoma have been reported in adults.<sup>26,27</sup> Our trial did not show any atropine-attributable side effects, nor any differences in toxic effects between the groups. Paradoxical bronchoconstriction had been reported in infants treated with isoosmolar, preservative-free ipratropium solution.<sup>28</sup> However, the lack of masking and randomization casts some doubt on the validity of the data of that study.

Acute asthma exacerbations often result from suboptimal initial therapy. Only three children had had corticosteroids prescribed before the study. This undertreatment had probably contributed to the severity of the disease in many patients.

This study has some limitations. Systemic corticosteroids were not administered during the study. This design eliminates their possible confounding effect, but current management of severe asthma calls for early steroid therapy. However, it is very likely that the responses would have been similar because the study was of only 2 hours' duration (insufficient time for steroids to act). Although our trial shows a benefit of repeated doses of ipratropium in children with a baseline FEV<sub>1</sub> 17% to 49% of the predicted value and even greater improvement in more severe cases, it was not the goal of this experiment to find the FEV<sub>1</sub> above which this regimen ceases to have significant benefit. Infrequent doses of ipratropium may be sufficient in many children with a baseline FEV<sub>1</sub> greater than 30% of the predicted value. The results of this study are not generalizable to patients with milder asthma, who usually respond readily to albuterol alone.

We conclude that this trial demonstrates the benefit and

safety of the addition of frequent nebulized doses of ipratropium to frequent albuterol therapy in severe childhood asthma, with a decrease in hospitalizations in the very severe cases.

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