

Efficacy of adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered-dose inhaler with a spacer device in adults with acute severe asthma

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Background: The efficacy of combination therapy adding multiple doses of anticholinergics to β_2 -agonists to improve outcome has not been established in adults with acute severe asthma.

Objective: This study was undertaken to compare the outcome of adults with acute severe asthma treated with 4 puffs of salbutamol (100 μ g/actuation) every 20 minutes for 3 doses plus 4 puffs of oxitropium bromide (100 μ g/actuation) with each of the 3 salbutamol doses versus salbutamol alone administered by means of a metered-dose inhaler with a spacer device.

Methods: A randomized, single-blind, placebo-controlled study was performed in 74 patients between 18 and 55 years old presenting to the emergency department (ED) for treatment of acute asthma with a peak expiratory flow (PEF) of 50% or less than the normal predicted value. The primary endpoint was improvement in PEF over the course. The secondary endpoint was the need for additional ED treatment at 120 minutes.

Results: The increase in PEF over the course was significantly greater in the oxitropium plus salbutamol treatment group ($P < .0001$). The mean absolute difference in PEF at 120 minutes for combination therapy compared with salbutamol alone was 37.8 L/min ($P = .001$). In addition, the proportion of need for additional ED treatment was less in the combination group than the group receiving salbutamol alone (odds ratio, 0.32; 95% confidence interval, 0.11-0.90).

Conclusion: Adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered-dose inhaler with a spacer device for acute severe asthma produces a significant improvement in lung function and reduces the need for additional ED treatment. (*J Allergy Clin Immunol* 2000;106:472-8.)

Key words: Asthma, oxitropium bromide, salbutamol, metered-dose inhaler, bronchodilator treatment

The pharmacologic treatment of acute severe asthma includes high-dose inhaled bronchodilators and the early

Abbreviations used

CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
ED:	Emergency department
MDI:	Metered-dose inhaler
OR:	Odds ratio
PEF:	Peak expiratory flow

administration of oral or intravenous corticosteroids.¹ β_2 -Agonists are accepted as first-line bronchodilators because of their rapid onset of action and the extent of achieved bronchodilation.¹ Anticholinergic agents, such as ipratropium bromide and oxitropium bromide, have a slower onset of action and weaker bronchodilating effect than β_2 -agonists, but these protect against various bronchoconstrictors and may decrease mucosal edema and secretions.^{2,3} Thus the combination of inhaled anticholinergics with β_2 -agonists may enhance bronchodilation. Randomized controlled trials of the addition of anticholinergic agents to β_2 -agonists for acute asthma in adults have shown statistically significant benefit about as often as they have failed to do so.⁴⁻¹⁰ A recent meta-analysis indicates that adding ipratropium bromide to standard β_2 -agonists produces a modest statistical improvement in lung function and reduces the need for hospitalization.^{11,12} Additionally, a systematic review by the Cochrane Airways Group showed that adding multiple doses of anticholinergics to β_2 -agonists is a safe and effective strategy for improving lung function and avoiding hospital admission for school-aged children and adolescents with acute severe asthma.¹³ The Expert Panel Report 2 of the National Asthma Education and Prevention Program recommended combination therapy of multiple doses of β_2 -agonists and anticholinergics by using a wet nebulizer or metered-dose inhaler (MDI) with a spacer device in the emergency department (ED) for moderate-to-severe acute asthma.¹ The trend toward use of an MDI in the ED suggests that an MDI preparation of anticholinergic agents combined with β_2 -agonists should be investigated. We conducted a prospective, randomized, single-blind, placebo-controlled study to determine whether administration of multiple doses of oxitropium bromide, an anticholinergic agent, plus salbutamol deliv-

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ered by means of an MDI with a spacer device provides an additional benefit to adults with acute severe asthma compared with salbutamol alone.

METHODS

Eighty consecutive patients with acute exacerbation of asthma treated at Hamamatsu Rosai Hospital, a 400-bed urban medical center, between August 1998 and July 1999 were enrolled in the trial. All patients met the criteria for asthma proposed by the American Thoracic Society.¹⁴ The inclusion criteria were as follows: (1) age between 18 and 55 years; (2) ability to perform an adequate forced expiratory maneuver; (3) peak expiratory flow (PEF) of 50% or less than the normal predicted value; and (4) smoking history less than 10 pack-years.

Patients were excluded from the study if they (1) had chronic obstructive pulmonary disease (COPD), pneumonia, pneumothorax, acute myocardial infarction, or congestive heart failure; (2) had a history of glaucoma, urinary retention, or prostatic hypertrophy; (3) needed immediate resuscitation or airway intervention; (4) had been treated with anticholinergic medication within 6 hours before visiting to the ED; or (5) were pregnant. To exclude patients with COPD, patients older than 55 years, at which time the incidence of COPD is high; those with a history of heavy smoking (≥ 10 pack-years); and those with a history suggesting the presence of chronic bronchitis were excluded. All subjects were followed up for 4 weeks after presenting to the ED. The FEV₁/forced vital capacity after this follow-up period was 70% or more in all subjects, confirming the exclusion of patients with COPD. Patients were not excluded if they had received β_2 -agonists delivered by means of a wet nebulizer or MDI in the 6 hours before presentation. Before enrollment, informed consent was obtained from all patients.

Patients who agreed to participate in the study were randomly assigned to one of two treatments by means of sealed envelopes. Subjects were treated with either 4 puffs of salbutamol (Sultanol, 100 μ g/actuation; GlaxoWellcome K.K., Tokyo, Japan) every 20 minutes for 3 doses (total, 1200 μ g) plus 4 puffs of oxitropium bromide (Tersigan, 100 μ g/actuation; Nippon Boehringer Ingelheim Co, Ltd, Hyogo, Japan) with each of the 3 salbutamol doses (total, 1200 μ g) or salbutamol plus placebo (propellant gas only, 4 puffs in the same manner) administered through an MDI with a spacer device (InspirEase; Schering-Plough K.K., Osaka, Japan). We prepared MDI canisters containing oxitropium and those containing only propellant gas that are indistinguishable from the former by external appearance. A single dose of 8 mg of betamethasone (Rinderon, Shionogi Co., Ltd, Osaka, Japan) was administered intravenously to all patients with the first dose of salbutamol.

Demographic data collected on entry into the study were age, sex, and height. Clinical data, including respiratory rate, heart rate, accessory muscle use, dyspnea, wheezing, smoking history, asthma history, usual medications, and medications taken within 6 hours before presentation, were recorded. Dyspnea was defined as the patient's own assessment of breathlessness. Wheezing was defined as musical breath sounds heard with a stethoscope. Both dyspnea and wheezing were graded on a scale from 0 to 3 (0, absent; 1, mild; 2, moderate; and 3, severe). Blood samples were drawn for baseline serum theophylline concentration. PEF was measured at baseline and at 20, 40, 60, and 120 minutes. PEF was measured with a mini-Wright peak flow meter (Clement Clarke Inc, Harlow, Great Britain). Trained nurses unaware of the group assignments measured the PEF. The highest of 3 values was recorded. Predicted values for PEF were obtained from the data of Tsukioka.¹⁵ Pulse oximetry (Pulsox-M2; Minolta Inc, Osaka, Japan) was recorded on room air, and oxygen was given as required. Side effects of treatment were recorded.

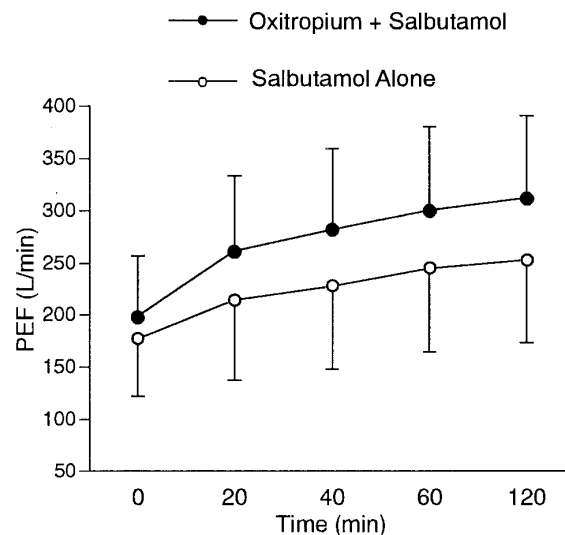


FIG 1. Changes in PEF from baseline. There was a significantly different PEF response over time between the two treatment groups (ANOVA, $P < .0001$). Values are means $\pm$ SD.

After 120 minutes, patients were considered ready to be sent home if they (1) were asymptomatic and free of accessory muscle use, (2) had absent or diminished wheezing, and (3) had a PEF value of 55% or greater than the predicted value.¹⁶ Patients not meeting these indications were given further treatment for an additional 2 hours with intravenous aminophylline, inhaled bronchodilators, or both and were reassessed. If they still did not meet the discharge requirements, they were admitted to the hospital. The study was approved by the institutional review board.

The primary outcome measures were improvements in PEF and in percentage predicted PEF over the course of treatment. Secondary measures were proportion of additional ED treatments, hospital admission rates, and adverse effects. Further analyses were then undertaken to assess the effects of (1) a PEF of less than 200 L/min and a PEF of 200 L/min or greater at baseline and (2) inhaled β_2 -agonist use in the previous 6 hours before presentation on the differential effect of combination therapy and salbutamol alone on an absolute improvement in PEF at 120 minutes.

Statistical analysis

Mean values $\pm$ SD were calculated for all continuous variables. Data were examined for statistical significance by the two-tailed Student *t* test for continuous variables and the Fisher exact test for categorical variables. The effects of improvements in PEF and in percent predicted PEF values over the course of two different treatments was assessed by using ANOVA for repeated measures. The Fisher exact test was used to analyze the proportion of need for additional ED treatment and hospital admission rate, with odds ratios (ORs) used as summary statistics. For all the analyses, a two-tailed *P* value of less than .05 indicated statistical significance. Statistical analysis was done with the StatView Statistical Package 5.0 (SAS Institute, Cary, NC).

RESULTS

Of the 80 patients who were enrolled and randomized, 6 patients (2 receiving combination therapy and 4 receiving salbutamol alone) requested early withdrawal and were excluded. The remaining 74 patients were analyzed;

TABLE I. Baseline characteristics

	Combination therapy (n = 38)	Salbutamol alone (n = 36)	P value
Age (y)	43 ± 10	41 ± 11	.35
Female (%)	47	61	.25
Duration of asthma (y)	14 ± 12	15 ± 15	.78
ED visits in past year (%)	40	28	.33
Asthma hospitalizations in past year (%)	21	14	.54
Duration of acute symptoms (h)	12 ± 10	12 ± 11	.98
Asthma medication within 6 h			
β ₂ -Agonists (%)	47	44	.82
Theophylline (%)	61	58	.99
Inhaled steroids (%)	63	67	.81
Symptoms			
Wheeze*	2.6 ± 0.5	2.5 ± 0.5	.51
Dyspnea*	2.0 ± 0.4	2.0 ± 0.4	.78
Accessory muscle use (%)	45	48	.67
Heart rate	90 ± 17	94 ± 14	.37
Respiratory rate	19 ± 3	19 ± 4	.58
Pulse oximetry (%)	95 ± 3	95 ± 2	.27
PEF (L/min)	198 ± 58	177 ± 55	.13
PEF % predicted	39 ± 10	37 ± 10	.55

Values are given as means ± SD where shown.

*Scale of 0 to 3.

38 patients received combination therapy, and 36 patients received salbutamol alone. The mean age ± SD for all patients was 41.9 ± 10.3 years. Fifty-four percent of patients were women. The mean initial PEF was 188 ± 58 L/min (range, 60-310 L/min; 38.1% ± 10.3% of predicted value). Baseline characteristics are summarized in Table I. The groups did not differ significantly in age, sex, duration of asthma, number of previous ED visits or hospitalizations, or time from onset of asthma exacerbation to ED visit. In addition, there was no difference between the groups in asthma medication use within 6 hours before the ED visit, symptoms, pulse oximetry, baseline PEF, or percentage of predicted PEF at entry into the study.

Improvement in PEF

Among all subjects, the mean PEF increased from 188 ± 58 L/min at baseline to 284 ± 84 L/min at the end of treatment (improvement from baseline, 96 ± 51 L/min). There was a highly significant difference in PEF response over time between the two treatment groups (ANOVA, $P < .0001$; Fig 1). When the percent predicted PEF value was used as a dependent variable, a similar level of significance was observed in favor of the combination therapy group (ANOVA, $P = .0001$). At the first 120 minutes, subjects receiving combination therapy had a 113.9 ± 45.4 L/min improvement from baseline, whereas salbutamol alone yielded a 76.1 ± 49.2 L/min improvement from baseline. The mean absolute difference in PEF at 120 minutes for combination therapy compared with salbutamol alone was 37.8 L/min (95% confidence interval [CI], 15.9-59.8 L/min; $P = .001$). Similarly, subjects with combination therapy showed an overall 15.9% (95% CI, 1.4%-30.3%; $P = .0307$) greater improvement in PEF compared with control subjects.

Predictors of response to combination therapy

Baseline PEF was then treated categorically in the manner used by Lin et al⁷ (PEF <200 L/min [38 patients; 45% combination therapy, 58% salbutamol alone] or PEF ≥200 L/min [36 patients; 55% combination therapy, 42% salbutamol alone]). At 120 minutes, patients with a PEF of less than 200 L/min at baseline showed significant increment in improvement in PEF from combination therapy (110 ± 55 L/min) compared with salbutamol alone (67 ± 44 L/min; difference = 44 L/min, $P = .00106$), whereas patients with a PEF of 200 L/min or greater at baseline showed a small increment in improvement in PEF from combination therapy (116 ± 37 L/min) compared with salbutamol alone (88 ± 54 L/min; difference = 28 L/min, $P = .0714$; Fig 2).

Among patients using inhaled β₂-agonists within 6 hours of presenting at the ED, the increment in improvement in PEF at 120 minutes (difference = 42 L/min, $P = .0317$) was similar to the increment in improvement among patients who did not use β₂-agonists in the past 6 hours (difference = 33 L/min, $P = .0129$; Fig 3).

Need for additional ED treatment

The proportion of additional ED treatment was less in the combination group (7/38) than in the group receiving salbutamol alone (15/36). The OR for additional ED treatment was 0.32 (95% CI, 0.11-0.90).

Hospital admissions

Five (13.2%) patients who received combination therapy and 10 (27.8%) who received salbutamol alone were admitted to the hospital. The OR for hospital admission

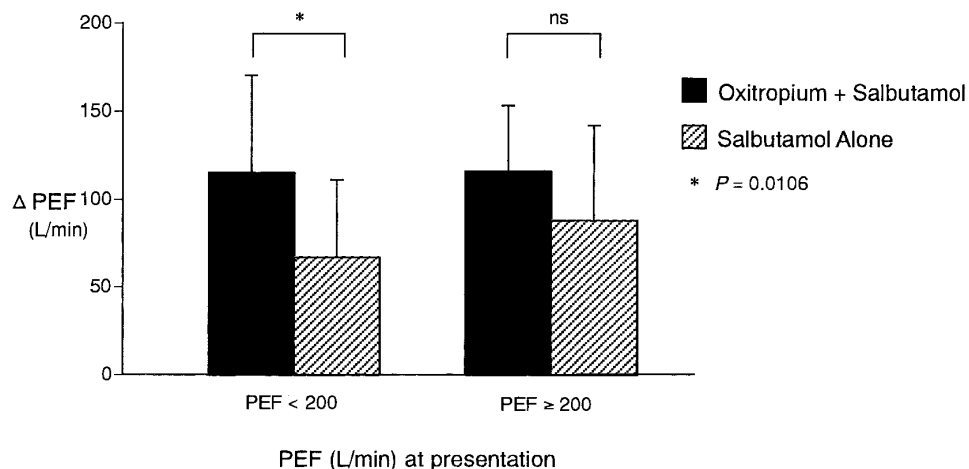


FIG 2. Effect of baseline PEF response to combination therapy compared with salbutamol alone at 120 minutes. Values are means $\pm$ SD.

was 0.39 (95% CI, 0.12-1.27), but this difference did not reach statistical significance.

Complication

No patients required intubation. There was no statistically significant difference in incidence of tremor, palpitation, cough, dry mouth, or bad taste between the groups.

DISCUSSION

The purpose of this study was to determine whether administration of multiple doses of oxitropium bromide and salbutamol by MDI with a spacer device would provide an additional benefit to adults with acute severe asthma compared with salbutamol alone. Our data show that the addition of oxitropium bromide to salbutamol and corticosteroids improved lung function and reduced the need for additional ED treatment. Patients who received combination therapy had an absolute 37.8 L/min greater improvement in PEF compared with control subjects. This difference is even greater than the 31.5 L/min estimated in a recent review.¹¹ In addition, we found that patients with more severe asthma (baseline PEF <200 L/min) benefited from the addition of oxitropium to salbutamol. However, the hospital admission rate was not statistically different in the two treatment groups. This study differed from previous studies in the following ways. First, we examined whether adding multiple doses of oxitropium bromide combined with salbutamol gave an additional bronchodilation above that achievable with salbutamol alone. Second, bronchodilators were administered by means of an MDI with a spacer device. Finally, the study measured the effect of combination therapy on the need for additional ED treatment.

Several randomized controlled trials have examined the efficacy of the addition of anticholinergic agents to β_2 -agonists for treating acute asthma in adults.⁴⁻¹⁰ Conflicting results from these trials were attributed to differ-

ences in the severity of asthma, the number of doses of anticholinergic treatment, and study power. A recent meta-analysis of the treatment of adult acute asthma indicates that adding ipratropium bromide to standard salbutamol therapy produces a modest statistical improvement in lung function and reduces the need for hospitalization.^{11,12} Plotnick and Ducharme¹⁷ reported that ipratropium administered in multiple doses in combination with β_2 -agonists and corticosteroids reduces hospital admissions and improves lung function in children and adolescents presenting to the ED with acute asthma. Similarly, a recent study of children who had an acute exacerbation of asthma found a significant decrease in the rate of hospitalization in patients treated with ipratropium using a multiple-dose protocol.¹⁸ However, the efficacy of combination therapy adding multiple doses of anticholinergics to β_2 -agonists to improve outcome has not been established in adults with acute severe asthma. A reason why previous studies may not have shown a benefit is the fact that only a single dose of bronchodilator was used, whereas current recommendations suggest that multiple doses are appropriate.¹ We used a protocol that incorporated the consensus guidelines with regard to choice for bronchodilators, use of corticosteroids, and length of treatment. Our study protocol of bronchodilator delivery is now recommended by the Expert Panel Report 2 for patients with a PEF of less than 50% of the predicted value.¹ Our study patients had the typical features of acute severe asthma when they presented to the ED: a mean age of 40 years, a baseline PEF of 38% of the predicted value, and a female/male ratio of greater than 50%.^{11,12}

Further analyses were conducted to determine whether we could identify subgroups that reacted differently to the treatments. A meta-analysis indicated that patients with more severe airflow obstruction showed greater benefits of combination therapy.^{11,12} In our study patients with baseline PEF values of less than 200 L/min show a greater increment in improvement of combination

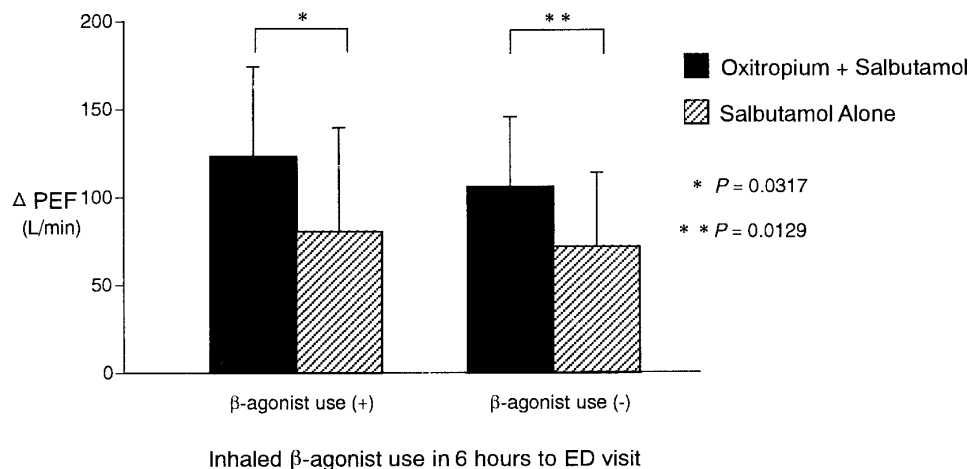


FIG 3. Effect of inhaled β -agonist in the previous 6 hours on response to combination therapy compared with salbutamol alone at 120 minutes. Values are means $\pm$ SD.

therapy than those with PEF values of 200 L/min or greater at baseline. Garrett et al⁶ suggested that subjects responded better to combination therapy if they had used less β_2 -agonists before presentation at the ED. We did not find this result in our study. The benefit of combination therapy was equally evident independent of prior use of β_2 -agonists. This independent benefit of oxitropium is consistent with the proposal that muscarinic receptors are described in the large airways, and β_2 -receptors are mainly in the small airways.¹⁹

Delivery methods of bronchodilators include MDI with or without a spacer device, a wet nebulizer powered by air or oxygen, and dry powder inhalers. Costs for nebulized therapy are necessarily higher than for MDI therapy because a trained nurse must supervise the administration of nebulized therapy, and the tubing and mask must be discarded after each treatment. It has been shown that routine substitution of MDI with a spacer device saves hospital resources.²⁰ The study of bronchodilation with β_2 -agonists by Colacone et al²¹ showed a relative potency of 6:1 in favor of an MDI with a spacer device compared with a wet nebulizer. The total dose of 1200 μ g of salbutamol in our study patients was relatively small compared with the optimal dose (2400-3600 μ g of salbutamol) estimated by Rodrigo and Rodrigo.²² They found that 53% of patients treated for acute asthma in the ED would have met discharge requirements after receiving 1200 μ g of salbutamol delivered by means of an MDI with a spacer device. The dose of 4 puffs of salbutamol every 20 minutes for 3 doses may produce less than the maximal bronchodilation achievable with salbutamol alone. In the recent meta-analysis of the role of anticholinergics in the ED treatment of acute adult asthma, there was no relation between effect size and the dosage of β_2 -agonist.¹¹ Further examination should be made to determine whether anticholinergics confer additional benefit in acute asthma when larger doses of β_2 -agonists are administered.

Oxitropium bromide is a quaternary anticholinergic compound based on scopolamine instead of atropine. It appears to be more potent and to have a longer duration of action than ipratropium bromide, with bronchodilator activity up to 8 hours after administration. The peak bronchodilator effect after administration of oxitropium occurs within 1 to 2 hours.²³⁻²⁵ It was reasonable to expect significant improvement at this time in our study. However, there were no published studies of optimal doses of inhaled oxitropium bromide in combination with β_2 -agonists in patients with acute asthma. Peel et al²⁶ gave 20 asthmatic subjects either 80 μ g (4 puffs) of ipratropium or 200 μ g (2 puffs) of oxitropium administered by means of an MDI. Both drugs showed a beneficial and equal effect on bronchodilation up to 10 hours after administration. Their study showed a relative potency of 2:1 in favor of one puff of oxitropium bromide compared with one puff of ipratropium bromide to achieve equivalent bronchodilation. The Expert Panel Report 2 recommended adding 4 to 8 puffs of ipratropium bromide to β_2 -agonists delivered by means of an MDI with a spacer device repeatedly for the patients with moderate-to-severe acute asthma.¹ We chose to administer 4 puffs (400 μ g) of oxitropium bromide delivered by means of an MDI with a spacer device every 20 minutes because 4 puffs of oxitropium bromide was estimated to be equivalent to 8 puffs of ipratropium bromide. The use of oxitropium bromide instead of ipratropium bromide reduces the number of inhalations in patients who are exhausted by acute severe asthma.

There was no statistically significant difference between treatments in the incidence of adverse effects in our study. Oxitropium bromide is poorly lipophilic and not absorbed substantially from the respiratory or gastrointestinal tracts. This lack of severe adverse effects in patients who received combination therapy suggests that repeated oxitropium bromide plus salbutamol administered by means of an MDI with a spacer device at this dose is safe and well tolerated.

We chose 120 minutes as the cutoff point for defining the additional ED treatment. Stein and Cole²⁷ studied 194 consecutive patients who presented to the ED for acute asthma. They demonstrated that the change in PEF after 2 hours of bronchodilator treatment predicted the need for hospital admission. In our study the proportion of additional ED treatment at the initial 120 minutes was statistically less in the combination group than in the group receiving salbutamol alone. The extent of improvement in lung function is clinically meaningful because it was associated with a substantial reduction in the need for additional ED treatment. Reduction in additional treatment in turn may reduce the overall ED costs. The results of Lord et al²⁸ demonstrate that adding multiple doses of anticholinergic agents to inhaled β_2 -agonists in children and adolescents with severe asthma results in savings in health service resources. Further analysis is needed to determine whether combination therapy in adults with acute asthma reduces ED costs.

We did not demonstrate a significant reduction in hospitalization in this study. However, the trend toward a reduction of hospitalization among patients receiving combination therapy was consistent with that found in previous trials.⁷ Recent reviews have reported the relative risks of hospitalization of subjects receiving ipratropium and β_2 -agonists to be 0.62 and 0.73, respectively.^{11,12} This outcome is difficult to assess in an asthma trial because it requires very large sample sizes to demonstrate statistical significance. Additionally, the decision to admit patients is based on many factors, including past asthma history, ability of patients to manage their disease, and severity of airflow obstruction, as well as the patient's own assessment.

There are several limitations to our study. Because the study was conducted at a single institution, generalizability of our findings to other settings may be limited. The decisions concerning additional treatment and when to admit or discharge patients were made subjectively by the clinicians involved and may vary in other settings or populations. Second, we chose to administer oxitropium bromide instead of ipratropium bromide because the former is a more potent bronchodilator. In Japan, oxitropium bromide is first-line therapy for patients with chronic pulmonary disease.²⁹ Third, our study was conducted in a single-blind fashion. Because it was not evaluated whether repeated oxitropium bromide plus salbutamol administration by means of an MDI with a spacer device at this dose is safe and well tolerated, we conducted a single-blind trial. However, trained nurses who were unaware of the group assignments measured the PEF for a fair and objective evaluation. Finally, because the sample size of our study was small, we could not draw firm conclusion about the effects of oxitropium on these outcomes.

Overall, our data suggest that oxitropium should be combined with salbutamol delivered through an MDI with a spacer device in the treatment of acute severe asthma in adults. Future trials are needed to reproduce these results in other large settings and to determine

whether combination therapy with anticholinergic agents reduces the need for hospitalization. Additional studies should compare the efficacy of ipratropium bromide with oxitropium bromide and of a wet nebulizer with an MDI. An attempt also should be made to titrate the number of inhalations to a patient's response and assess the cost-effectiveness of this medication.

REFERENCES

1. National Asthma Education, and Prevention Program Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. Bethesda, MD: US Department of Health and Human Services; 1997. National Institutes of Health publication No. 97-405.
2. Gross NJ. Ipratropium bromide. *N Engl J Med* 1988;319:486-94.
3. Douglas EB. The use of anticholinergics in asthma. *J Asthma* 1997;34:357-68.
4. Rebuck AS, Chapman KR, Abboud R, Kreisman H, Wolkove N, Vikerson F. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987;82:59-64.
5. O'Driscoll BR, Taylor RJ, Horsley NG, Chambers D, Bernstein A. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet* 1989;24:1418-20.
6. Garrett JE, Town I, Rodwell P, Kelly AM. Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma. *J Allergy Clin Immunol* 1997;100:165-70.
7. Lin RY, Pesola G, Bakalchuk L, Morgan JP, Heyl G, Freyberg CW, et al. Superiority of ipratropium plus albuterol over albuterol alone in the emergency department management of adult asthma: a randomized clinical trial. *Ann Emerg Med* 1998;31:208-13.
8. McFadden ER Jr, ElSanadi N, Strauss L, Galan G, Dixon L, McFadden CB, et al. The influence of parasympatholytics on the resolution of acute attacks of asthma. *Am J Med* 1997;102:7-13.
9. FitzGerald JM, Grunfeld A, Pare P, Levy R, Newhouse MT, Hodder R, et al. The clinical efficacy of combination nebulized anticholinergic and adrenergic bronchodilators vs nebulized adrenergic bronchodilator alone in acute asthma. *Chest* 1997;111:311-5.
10. Karpel JP, Schacter EN, Fanta C, Levey D, Spiro P, Aldrich T, et al. A comparison of ipratropium and albuterol vs albuterol alone for the treatment of acute asthma. *Chest* 1996;110:611-6.
11. Stoodley RG, Aaron S, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. *Ann Emerg Med* 1999;34:8-18.
12. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999;107:363-70.
13. Plotnick LH, Ducharme FH. Efficacy and safety of combined inhaled anticholinergics and beta-2-agonists in the initial management of acute pediatric asthma [Cochrane Review]. *Cochrane Library* 1999 (issue 1). Oxford, United Kingdom: Update Software; 1997.
14. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
15. Tsukioka K. Standard range of peak expiratory flow in normal, healthy Japanese subjects. *Arerugi* 1996;45:4442-50.
16. Rodrigo G, Rodrigo C. A new index for early prediction of hospitalization in patients with asthma. *Am J Emerg Med* 1997;15:8-13.
17. Plotnick LH, Ducharme FM. Should inhaled anticholinergics be added to β_2 agonists for treating acute childhood and adolescent asthma? A systematic review. *BMJ* 1998;317:971-7.
18. Qureshi F, Pestian J, Davis P, Zavistky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med* 1998;339:1030-5.
19. Barnes PJ, Basbaum C, Nadel J. Autoradiographic localization of autonomic receptors in airway smooth muscle. Marked differences between large and small airway. *Am Rev Respir Dis* 1983;127:758-62.
20. Bowton DL, Goldsmith WM, Haponic EF. Substitution of metered dose inhalers for hand held nebulizers: success and cost savings in a large acute care hospital. *Chest* 1992;101:305-8.

21. Colacone A, Afilalo M, Wolkove N, Kreisman H. A comparison of albuterol administered by meter dose inhaler (and holding chamber) or wet nebulizer in acute asthma. *Chest* 1993;104:835-41.
22. Rodrigo C, Rodrigo G. The response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest* 1998;113:593-8.
23. Dharma AP. Oxitropium bromide. *Drugs of the Future* 1979;4:117-21.
24. Minette A, Marcq M. Oxitropium bromide (Ba 253), an advance in the field of anticholinergic bronchodilating treatments: preliminary results. *Rev Inst Hyg Mines* 1979;34:115-23.
25. Lulling J, Delwiche JP, Prignot J. Early bronchodilating effect of oxitropium bromide in comparison with ipratropium bromide. *Respiration* 1981;42:188-92.
26. Peel ET, Cheong AB, Broderick N. A comparison of oxitropium bromide and ipratropium bromide in asthma. *Eur Respir Dis* 1984;65:106-8.
27. Stein LM, Cole RP. Early administration of corticosteroids in emergency room treatment of acute asthma. *Ann Intern Med* 1990;112:822-7.
28. Lord J, Ducharme F, Stamp RJ, Littlejohns P, Churchill R. Cost effectiveness analysis of inhaled anticholinergics for acute childhood and adolescent asthma. *BMJ* 1999;319:1470-1.
29. Teramoto S, Ouchi Y. Inhaled oxitropium bromide is currently used as first-line therapy of patients with chronic pulmonary disease in Japan. *Eur Respir J* 1999;13:473-5.

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