Should Ipratropium Bromide be Added to Beta-Agonists in Treatment of Acute Severe Asthma?*

R. M. Higgins, M.A.; J. R. Stradling, M.D.; and D. J. Lane, D.M.

In a double-blind randomized trial, 40 patients with acute severe asthma were given either nebulized salbutamol, 5 mg, or salbutamol, 5 mg mixed with ipratropium bromide 500 μg, on admission to hospital and again two hours later. There was no significant difference between the mean peak flows of the two treatment groups at any time. However, two hours after each treatment, there were fewer subjects in the ipratropium and salbutamol group whose peak flow rates had fallen back toward baseline levels than in the salbutamol only treatment group. Thus, although ipratropium did not improve the overall maximal bronchodilator response, it may have prolonged the duration of the response, which would be a clinically useful effect. (Chest 1988; 94:718-22)

Ipratropium bromide is a synthetic cholinergic antagonist with an atropine-like effect on bronchial smooth muscle. Given alone in chronic stable asthma, it is an effective bronchodilator and may have an additional effect when given in combination with a beta-adrenoceptor agonist.1,2 However, it is not clear whether there is an additive effect when ipratropium is used in combination with a nebulized beta-adrenoceptor agonist in the emergency treatment of acute severe asthma. It certainly has a bronchodilator effect given on its own, which may be comparable with that of salbutamol.3,4 Two other published studies have examined the effects of ipratropium combined with a beta-agonist in acute asthma, and have reported that treatment with two drugs produced an additive effect.4,5 Unfortunately, these studies have possible drawbacks, so we performed a further study, which was also designed so that the duration of bronchodilation could be assessed.

METHODS

Forty subjects admitted to the hospital with acute severe asthma were studied in double-blind fashion. Asthma was defined as at least 20 percent variability in peak expiratory flow rate (PEFR) within six months of entry into the trial, with a best PEFR of at least 50 percent of predicted value. Subjects were eligible for the study if the PEFR on admission to the hospital (before administration of bronchodilator) was less than 35 percent predicted value.

After informed consent had been obtained, subjects received either salbutamol, 5 mg with 2 ml 0.9 percent NaCl, or salbutamol, 5 mg mixed with ipratropium bromide 500 μg. This was delivered through an Acorn nebulizer driven with oxygen at a rate of 8 L/min. The same treatment was given two hours later. The randomization procedure was stratified so that there were separate but balanced randomization schedules for four groups of patients: men aged under 35 years; men aged 35 years or older; women aged 35 years; and women aged 35 years or older. Measurements of PEFR were made using a Wright peak flow meter, readings being recorded before the first nebulizer (time 0), one-half hour later, one hour later, two hours later (just before the second nebulizer was given), 2½ hours later, three hours later, and four hours later. The best of three measurements of PEFR was recorded. Pulse and respiratory rate was measured at times zero and four hours. Blood was taken at time zero for measurement of arterial oxygen and carbon dioxide tensions. All patients were given hydrocortisone, 200 mg intravenously, on admission. Treatment with intravenous aminophylline was not used. After the first four hours in the hospital, the patients were treated according to the physicians discretion. The study was approved by the Central Oxford Research Ethics Committee.

Statistical analysis was made using chi-square tests, Student's t-tests, Pearson's correlation coefficient, and analysis of variance.6 Calculation of confidence intervals was performed as previously described6 and calculation of power according to the nomogram by Altman.7

RESULTS

Details of the subjects are shown in Table 1; there were no significant differences between the two groups in PEFR, age, sex distribution, pulse, respiratory rate, or blood gas levels at the start of the study. Bronchodilator response was not related either to the age or sex of subjects, or to their smoking history (eight subjects in the salbutamol group and 12 in the salbutamol and ipratropium group were current smokers or ex-smokers).

The mean absolute PEFR values for the two treatment groups are shown in Figure 1. The rise in PEFR after the first nebulizer was significant in each group

<table>
<thead>
<tr>
<th>Table 1—Baseline Characteristics of Subjects*</th>
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<tbody>
<tr>
<td>Number</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Peak flow L/min</td>
</tr>
<tr>
<td>Pulse</td>
</tr>
<tr>
<td>Respiratory rate</td>
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<tr>
<td>Arterial O2 kPa</td>
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<tr>
<td>Arterial CO2 kPa</td>
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</tbody>
</table>

*Baseline characteristics of subjects, mean values (SEM).

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*From the Osler Chest Unit, Churchill Hospital, Oxford, England. Manuscript received July 23, 1987; revision accepted March 15. Reprint requests: Dr. Higgins, Nuffield Department of Surgery, John Radcliffe Hospital, Oxford, England OX3 9DU.
There were no statistically significant differences in PEFR between the two groups at any time.

The mean percentage changes in PEFR over the initial PEFR are shown in Figure 2. Again, there was no significant difference between the two groups at any time. In addition, there were no significant differences between the treatment groups when analysis was performed in three further ways as follow: (a) according to the absolute changes in PEFR; (b) by the changes expressed as a percentage of the predicted PEFR; (c) and when changes in PEFR were related to each subject's best PEFR recorded within six months of entry into the study (data not shown).

Figure 3 shows the percentage changes in PEFR for individual subjects in each treatment group at 30 minutes and two hours after each treatment. The figure shows that at two hours after each treatment, the percentage improvement in PEFR had declined in some patients. If improvements of less than 10 percent two hours after the first treatment and less than 20 percent two hours after the second treatment are taken as arbitrary levels which might be of clinical relevance, the salbutamol and ipratropium group had fewer patients who have failed to improve than the salbutamol only group (p<0.05 after first treatment).

**Table 2—Duration of Bronchodilation**

<table>
<thead>
<tr>
<th></th>
<th>Salbutamol Only</th>
<th>Salbutamol and Ipratropium</th>
</tr>
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<tbody>
<tr>
<td>PEFR Rising</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>PEFR Not Rising</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*The numbers of patients whose PEFR was rising or not rising (falling or the same) at two hours after each treatment, compared to the peak response at one-half or one hour after the same treatment.
nebulized ipratropium was added to salbutamol in the emergency treatment of acute severe asthma. However, the addition of ipratropium may have resulted in a greater duration of bronchodilator effect than when salbutamol was given alone. This prolongation of effect may be of clinical relevance in patients who are acutely ill, requiring frequent administration of bronchodilators.

Our study did show, one-half hour after the first nebulizer, an advantage with combined treatment which was not statistically significant (37.0, SEM 7.0) percent improvement after salbutamol, 47.8 (SEM 8.3) percent after salbutamol and ipratropium, a difference of 10.8 percent (p = NS). However, our study did not have sufficient power to be sure of demonstrating or excluding a difference of this magnitude, as it had been designed to detect larger differences between treatments (thus, we excluded a 25 percent difference between treatments at one-half hour after the second nebulizer with greater than 92 percent confidence). In order to determine whether smaller differences in bronchodilation are significant, it is necessary to pool data with the other two similar clinical trials that have been performed. This shows 12.5 percent extra bronchodilation with ipratropium (Fig 4, p<0.05). The confidence intervals even with the pooled data are still wide (1.2 to 23.8 percent), and do not exclude an advantage of about 20 percent with combined treatment. Another study, with similar design and variability in the data to our own, would require about 140 subjects to demonstrate or to exclude with confidence a 20 percent advantage with combined treatment.

Although the pooled data do appear to confirm a small advantage with combined treatment, the data in Figure 4 refer only to maximal bronchodilation after the first dose of ipratropium, so a sustained advantage with combination treatment cannot be inferred. Further studies would be necessary to investigate this.

Our data suggest that combination treatment may have prolonged the duration of effective bronchodila-

Table 3—Change in Peak Flow According to Admission Value*

<table>
<thead>
<tr>
<th>Initial PEFR</th>
<th>Change in PEFR</th>
<th>Change in PEFR</th>
</tr>
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<tbody>
<tr>
<td>No. of Subjects</td>
<td>Initial PEFR</td>
<td>Initial PEFR</td>
</tr>
<tr>
<td>&lt;100</td>
<td>27</td>
<td>74.9 (2.4)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>37</td>
<td>131.6 (4.5)</td>
</tr>
<tr>
<td>p (Student's t-test)</td>
<td>0.028</td>
<td>0.979</td>
</tr>
</tbody>
</table>

*Mean changes in PEFR (absolute change and percentage change over baseline) in subjects with initial PEFR of above or below 100 L/min. Total 64 subjects. Mean values (SEM).

Discussion

This study did not show any significant advantage in the overall maximum bronchodilator response when...
dilation in our subjects, but the study was not large enough to demonstrate this with statistical confidence. Figure 3 shows that if improvements of less than 10 percent at two hours and less than 20 percent at hour hours are taken as levels which may be of clinical significance, then significantly fewer patients receiving combined treatment than salbutamol only had PEFR fall below this level (p<0.05 at two hours, p<0.02 at four hours). However, interpretation of this analysis depends on whether the 10 and 20 percent levels chosen have physiologic relevance. It has been shown that the change in peak flow during the first few hours of treatment of acute asthma is a major determinant of outcome,10-12 and that modification of this early change by treatment may also improve the long-term response.13 The magnitude of any clinically relevant change in lung function has only been demonstrated clearly in three studies, in which subjects with less than 25 to 30 percent improvement at six hours after admission appeared to have a less favorable outcome than those with greater than 30 percent improvement.14-16 Thus, there may be some physiologic justification for using levels of less than 10 percent improvement at two hours, and 20 percent at four hours in our study. Analysis of the direction of change in peak flow at two and four hours after admission suggests that ipratropium may have improved the duration of bronchodilation (Table 2), but the numbers in our study are not large enough to reach statistical significance. However, it has been shown clearly in the past that ipratropium prolongs the duration of bronchodilation in patients with chronic airways obstruction,17 so it is likely that ipratropium will have a similar effect in acute severe asthma. Future studies using combination treatment in acute severe asthma should be designed to test our results suggesting that duration of bronchodilation is improved with combined treatment.

There were no adverse effects observed in the salbutamol only group, but a fall in PEFR was recorded 30 minutes after each treatment in one subject in the ipratropium group, with subsequent improvement before the next nebulizer was given. This fall in PEFR was not associated with any apparent deterioration in the subject's clinical state (although PEFR fell from 105 to 80 L/min after the first treatment, and from 120 to 110 L/min after the second), but may represent "paradoxical" bronchoconstriction after nebulized ipratropium, an effect which may be due to preservatives in the nebulizer solution.18 It is likely that any such adverse effects will not be seen if ipratropium nebulizer solution is marketed in single dose vial form without any preservative. Subjects given ipratropium bromide should be monitored closely in case of any such fall in PEFR after treatment.

Our study used separate but balanced schedules to randomize subjects according to age and sex, so that the composition of the treatment groups was balanced physiologically. However, although previous studies have suggested that age and sex influence bronchodilator responsiveness,14-15,18 analysis of our data (Table 3) and other work10-12 suggests that bronchodilator responsiveness is related most strongly to initial PEFR. It may be that future trials in acute severe asthma should balance treatment groups physiologically by randomizing subjects with PEFR above or below 100 L/min separately. Subsequent analysis of data according to percentage change rather than absolute change may then further reduce the impact of any differences between the treatment groups. We feel that some previous work may be criticized because of substantial differences between treatment groups on entry, which may have influenced interpretation of the results.20

In conclusion, the addition of ipratropium to salbutamol in our subjects may have prolonged the duration of bronchodilator effect. Although our study was able confidently to exclude a large benefit from ipratropium treatment (of greater than 25 percent extra bronchodilation), there was a 10.8 percent advantage which was not statistically significant. If data from all the trials examining beta-agonist only with beta-agonist plus ipratropium are pooled, there is a significant advantage with combined treatment of 12.5 percent (95 percent confidence intervals +1.2 to +23.8 percent, p<0.05).

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Ipratropium and Beta-Agonists in Acute Severe Asthma (Higgins, Stradling, Lane)