Effects of allergy and age on responses to salbutamol and ipratropium bromide in moderate asthma and chronic bronchitis

C P van Schaeyck, H Folgering, H Harbers, K L Maas, C van Weel

Abstract
The bronchodilating responses to 400 μg salbutamol and 80 μg ipratropium bromide were studied in 188 patients with chronic bronchitis (n = 113) or asthma (n = 75) and mild to moderate airflow obstruction (forced expiratory volume in one second (FEV₁) above 50% but below 2 SD of predicted value) in a crossover study on two days a week apart. Both the patients with asthma and the patients with chronic bronchitis varied considerably in their responses to the salbutamol and the ipratropium bromide. The mean increase in FEV₁ in the subjects with asthma was higher after salbutamol (0·37 l or 18% of the prebronchodilator value) than after ipratropium bromide (0·26 l or 13%). In chronic bronchitis there was no difference between the increase in FEV₁ after salbutamol (0·16 l or 7%) and after ipratropium bromide (0·19 l or 8%). When patients were categorised into those with a better response to salbutamol 400 μg and those with a better response to ipratropium bromide 80 μg, patients with chronic bronchitis responded better in general to ipratropium bromide whereas asthmatic patients responded better to salbutamol. The response pattern was also related to allergy and age, allergic patients and patients under 60 being more likely to respond better to salbutamol 400 μg than non-allergic patients and older patients, who benefited more from ipratropium bromide 80 μg. The response pattern was not related to sex, smoking habits, lung function, bronchial reactivity, respiratory symptoms, or number of exacerbations during the preceding year.

Although the bronchodilating effects of inhaled β₂ adrenergic and anticholinergic drugs have been widely studied in patients with asthma and chronic bronchitis, few studies have compared the FEV₁ response to the two drugs in the same patients. The three studies that have done so looked at a small number of patients referred for specialist treatment so it is difficult to know how generally applicable the findings are. The small numbers also make it difficult to relate the bronchodilator responses to the clinical characteristics of the patients. The current study assessed the bronchodilator response to salbutamol 400 μg and ipratropium bromide 80 μg in 188 patients with mild to moderate airflow obstruction selected from general practice. The aim of the study was to investigate the FEV₁ response to these doses of salbutamol and ipratropium bromide in patients with asthma or chronic bronchitis and to relate the response to the clinical characteristics of the patients.

Methods
The current study was part of an intervention study, designed to assess the long term effects of bronchodilator treatment in patients with asthma and chronic bronchitis. One hundred and eighty eight patients of 30 years and over with mild to moderate airflow obstruction were recruited from 29 general practices. FEV₁ had to be two standard deviations below their FEV₁%, predicted value but above 50%.

All subjects had participated in the intervention study for 12 months before the current study was carried out.

PATIENTS
One hundred and thirteen patients with chronic bronchitis and 75 patients with asthma were included in the study (table 1). The criteria for the diagnosis of chronic bronchitis and asthma were based on those of the American Thoracic Society. Patients were diagnosed by assessing symptoms (Medical Research Council (MRC)-European Community for Coal and Steel (ECCS) questionnaire), lung function (before and 60 minutes after 400 μg salbutamol and 80 μg ipratropium bromide), and bronchial reactivity one week and six and 12 months before the start of the current crossover study. Chronic bronchitis was defined as persistent bronchial obstruction (FEV₁ ≤ 85% of the predicted value for all measurements) combined with chronic cough or chronic sputum production during at least three months for at least two consecutive years. Asthma was defined as reversible airway obstruction (FEV₁ increase ≥ 15% 60 minutes after inhalation of 400 μg salbutamol plus 80 μg ipratropium bromide on every occasion) and bronchial hyperreactivity (concentration of histamine causing 20% fall in FEV₁ (PC₂₀) ≤ 8 mg/ml on every occasion) combined with dyspnoea, wheezing, or allergy. Only patients with mild to moderate airflow obstruction were included, as these patients may be treated with a bronchodilator alone.

All patients gave informed consent and the study was approved by the university ethics committee.
Table 1 Clinical characteristics of the patients with chronic bronchitis and asthma

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% pred FEV₁</th>
<th>% pred IVC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>113</td>
<td>75</td>
<td>188</td>
</tr>
<tr>
<td>Age (mean SD) y)</td>
<td>53 (13)</td>
<td>51 (13)</td>
<td>52 (13)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>62*</td>
<td>47</td>
<td>56</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>88**</td>
<td>71</td>
<td>81</td>
</tr>
<tr>
<td>Pack years (mean No)</td>
<td>19**</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Allergic (%)</td>
<td>18**</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Symptom score (mean SD)</td>
<td>4 ± 1 (8)</td>
<td>5 ± 1 (7)</td>
<td>5 ± 1 (8)</td>
</tr>
<tr>
<td>Exacerbations (mean SD No)</td>
<td>1 ± 2 (1)*</td>
<td>1 ± 2 (5)</td>
<td>1 ± 2 (2)</td>
</tr>
<tr>
<td>Lung function (mean SD)</td>
<td>2 ± 0.79</td>
<td>1 ± 0.73</td>
<td>2 ± 0.77</td>
</tr>
<tr>
<td>FEV₁,(l)</td>
<td>76 (18)</td>
<td>71 (21)</td>
<td>74 (19)</td>
</tr>
<tr>
<td>FEV₁,% pred</td>
<td>68 (10)**</td>
<td>63 (11)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>84 (12)**</td>
<td>76 (12)</td>
<td>81 (12)</td>
</tr>
<tr>
<td>Geometric mean PC₂₀ (mg/ml)</td>
<td>20**</td>
<td>5</td>
<td>14</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.005 (differences between asthma and chronic bronchitis compared by the non-paired Student's t test).

Study design

The experiment had a single blind crossover design (blind observer). The bronchodilator responses to salbutamol 400 µg and to ipratropium bromide 80 µg were assessed on two days: on one day salbutamol was given first and ipratropium bromide second and on the other day the drugs were given in reverse order. The sequence of the two drugs was randomised. The drugs were administered at almost the same time of day during two consecutive weeks in an exacerbation free period.

During the 12 month intervention study the number of exacerbations was assessed by the general practitioner. An exacerbation was defined according to Fletcher (modification by Boman et al.)*. Lung function and bronchial reactivity were assessed during an exacerbation free period one week and six and 12 months before the start of the study.

Medication during the intervention study

No corticosteroids or bronchodilators other than salbutamol or ipratropium bromide were permitted in the 12 month study. At the start of the intervention study patients were randomly assigned to one of four parallel treatment groups: continuous medication with 4 x 400 µg/day salbutamol by dry powder inhaler (n = 49); 4 x 40 µg/day ipratropium bromide by dry powder inhaler (n = 43) or symptomatic medication with dry powder inhalations of salbutamol (n = 52) or ipratropium bromide (n = 44) during exacerbations or periods of dyspnoea. The patients were asked to report the medication used each week. During the study year the symptomatically treated patients used the same number of dry powder inhalations of salbutamol as of ipratropium—a mean of 0-6 (SD 0-8) a day. The medication the patients had used in the preceding year was known, and used to determine whether there was evidence of tolerance to ipratropium bromide or salbutamol.

Measurements

FEV₁, forced vital capacity (FVC), and inspiratory vital capacity (IVC) were assessed before and 15 minutes after inhalation of 400 µg salbutamol and before and 45 minutes after 80 µg ipratropium bromide, both given by metered dose inhaler. Data were derived from the curve with the largest sum of FVC and FEV₁ (out of three measurements). All bronchodilator medication was discontinued eight hours before the start of the test. FEV₁ and FVC were measured by three doctors and two laboratory workers trained in using the Microspirometrie HI-298 (Chest Corporation, Tokyo). This spirometer measures instantaneous flow, which is electronically integrated to give volume. IVC was measured with a wet spirometer (Gould, Bilthoven, The Netherlands).

Bronchial reactivity (PC₂₀) was tested by means of a histamine challenge test as described by Cockcroft et al. Symptons were assessed by the MRC-ECCS questionnaire (Dutch version) and quantified by addition to provide a score of 0–8. Smoking history was assessed in pack years (number of packets of cigarettes smoked daily * years of smoking). Allergy was tested with seven radioallergosorbent tests (RAST) (pollen: wild flowers, grasses, trees; animals: cats and dogs; house dust mite; Aspergillus fumigatus) (Pharmonica AB, Uppsalta, Sweden). Patients were considered to be allergic if at least one RAST response was positive.

The allergen response was measured semiquantitatively on a scale ranging from 0 (no response) to 4 (strong response). The scores for all seven tests were added to provide an allergy score.

Analyses

Change in FEV₁, in response to 400 µg salbutamol and 80 µg ipratropium bromide was related to the clinical characteristics of the patients by means of pattern recognition. With this method the total bronchodilator response after both drugs is 100% and the response is classified as follows.

Response class 1 More than 75% of the total response after salbutamol, whatever the order of drug administration.

Response class 2 More than 75% of the total response when salbutamol was given first, 25–75% when it was given second.

Response class 3 From 25% to 75% of the total response caused by either salbutamol or ipratropium bromide, whatever the order; or more than 75% of total response caused by either salbutamol or ipratropium bromide, whichever was given first.

Response class 4 More than 75% of total response when ipratropium bromide was given first, 25–75% when it was given second.

Response class 5 More than 75% of total response caused by ipratropium bromide, whatever the order.

Response patterns were correlated with pulmonary disease (chronic bronchitis or asthma), age, sex, allergy, number of exacerbations, smoking or non-smoking, pack years, symptoms, mean baseline of FEV₁, and geometric mean PC₂₀ during the 12 preceding months. PC₂₀ values were logarithmically transformed before analysis. The distribution of the nominal variables was tested by the χ² test and of the remaining variables by the Kruskal-Wallis test.
The possibility of tolerance to ipratropium bromide or salbutamol after the 12 month intervention study was investigated in two ways. Firstly, the increases in FEV₁ to salbutamol and to ipratropium bromide (given as first drug) in patients who had used these drugs continuously were compared; then the responses in patients who had used one of the drugs symptomatically were compared with the responses in patients who had used the same drug continuously. These differences were tested by means of the non-paired Student's t test. Secondly, a MANOVA procedure was carried out, in which the drug used in the preceding year was the independent variable and the increase in FEV₁ to salbutamol or to ipratropium bromide the dependent variable. Asthma versus chronic bronchitis and continuous versus symptomatic treatment were defined as two binary grouping factors. The initial FEV₁ (on the first day of the current crossover study) was incorporated as a covariate in this multivariate model.

Results

CHANGE IN FEV₁ AFTER SALBUTAMOL AND IPRATROPIUM BROMIDE

Baseline values of FEV₁ on day a and b differed by less than 3% (not significant), so a mean baseline value for the two days was calculated. The mean (SD) baseline FEV₁ was 2.08 (0.13) l for the asthmatic patients and 2.36 (0.10) l for the patients with chronic bronchitis. The mean increases in FEV₁, after salbutamol 400 μg followed by ipratropium bromide 80 μg (day a) and after ipratropium bromide 80 μg followed by salbutamol 400 μg (day b) are shown in figure 1.

The increase in FEV₁ in patients with asthma was 0.37 l (18% of the prebronchodilator FEV₁) after salbutamol and 0.26 l (13%) after ipratropium bromide given as a first drug (p < 0.05). In patients with chronic bronchitis no significant difference was observed between the increases in FEV₁, after salbutamol (0.16 l; 7%) and after ipratropium bromide (0.19 l; 8%) given as first drug. The additional increase in FEV₁ after salbutamol and ipratropium given as the second drug was different in chronic bronchitis (0.01 and 0.08 l respectively, p < 0.05), but not in asthma (0.11 and 0.06 l).

RESPONSE PATTERNS IN PATIENTS WITH ASTHMA AND CHRONIC BRONCHITIS

The response patterns to salbutamol 400 μg and ipratropium bromide 80 μg differed in asthma and chronic bronchitis (p < 0.005; table 2). Asthmatic patients were more likely to respond better to salbutamol than to ipratropium bromide (response classes 1 and 2) and patients with chronic bronchitis were more likely to respond better to ipratropium bromide than to salbutamol (response classes 4 and 5). Seventy-four patients (30 asthma, 44 chronic bronchitis) had a roughly equal response to the two drugs (response class 3). Fourteen patients had no response to either drug and could not be classified; all had chronic bronchitis.

RESPONSE PATTERNS RELATED TO THE CLINICAL CHARACTERISTICS

The presence of allergy correlated with the response patterns (p < 0.005). Patients with a greater response to salbutamol 400 μg were more likely to be allergic than patients showing a greater response to ipratropium bromide (table 2). The allergy score also showed a positive linear relation to the response to salbutamol in asthmatic patients (y = 0.032a + 0.314, r = 0.34; y = increase in FEV₁, litres, a = allergy score).

Apart from allergy, only age was slightly (but not significantly) correlated with the response patterns (p < 0.1). The increase in FEV₁ after salbutamol 400 μg or ipratropium bromide 80 μg showed a linear relation to age (fig 2c). The regression coefficient for the effect of ipratropium bromide in asthmatic patients did not deviate significantly from zero. In general (fig 2c), patients under the age of 60 appeared to show a greater increase in FEV₁ with sal-

![Figure 1](image-url)
Figure 2 Increase in FEV₁ after salbutamol 400 µg and ipratropium bromide 80 µg related to age for (a) asthmatic patients, (b) patients with chronic bronchitis, and (c) all patients, with 95% confidence limits for the regression lines (all p values <0.005).

Discussion
Most studies have agreed that beta₂ adrenergic drugs are more efficacious in asthma than anticholinergic drugs when given in conventional clinical doses. There is disagreement, however, about the efficacy of both drugs in chronic bronchitis. Several studies have shown that anticholinergic drugs cause the same degree of bronchodilatation as beta₂ adrenergic drugs. Other studies report more improvement after anticholinergic drugs. Most of these studies concern small, selected groups of patients referred for specialist treatment. In the present study 188 patients from 29 general practices participated. Only patients with moderate airflow obstruction were selected (the mean FEV₁ was 74% predicted) as these patients may be adequately treated with a bronchodilator only. When a 20% random sample of patients who refused to take part or who were excluded from the initial study was carried out they were found not to differ from the study group with respect to age, sex, smoking behaviour, symptoms, and reversibility of obstruction, suggesting that no bias had been introduced in the selection procedure.

The present study confirmed that, in general, patients with asthma of moderate severity benefited more from 400 µg salbutamol than from 80 µg ipratropium bromide, and that patients with chronic bronchitis responded better to 80 µg ipratropium bromide than to 400 µg salbutamol. In this study we compared conventional clinical doses of ipratropium bromide 80 µg and salbutamol 400 µg. Different doses of salbutamol or ipratropium bromide would have given different results. A recent study in patients with mild asthma showed maximum effects of both salbutamol and ipratropium bromide at doses of 1000 µg, and equipotency of the two drugs at lower doses. The dose-response relationships of beta₂ adrenergic and anticholinergic drugs appear not to have been compared previously in patients with chronic bronchitis.

As the criteria for the diagnosis of asthma and chronic bronchitis vary widely in different countries, it is important to know the criteria used in studies such as ours. The diagnosis in this study was based on the combination of several "typical features" of chronic bronchitis and asthma, as indicated by the American Thoracic Society. Patients had to have all the features listed for chronic bronchitis or asthma. If they had one or more features of the other condition in addition they remained in the study, but not if they had all features of both conditions. For examples, 42% of the patients with a label of chronic bronchitis had a PC20 of
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Table 3 Increase in FEV₁, after salbutamol 400 µg or ipratropium bromide 80 µg in relation to treatment in the preceding year (percentages of the mean (SEM) increase compared with initial FEV₁)

<table>
<thead>
<tr>
<th>Medication preceding year</th>
<th>n</th>
<th>Increase in FEV₁ (%)</th>
<th>salbutamol</th>
<th>ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASTHMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium 4 × 40 µg/day</td>
<td>17</td>
<td>21-5 (6-0)</td>
<td>19-4 (3-0)</td>
<td></td>
</tr>
<tr>
<td>Salbutamol 4 × 400 µg/day</td>
<td>21</td>
<td>24-0 (3-3)</td>
<td>17-1 (3-6)</td>
<td></td>
</tr>
<tr>
<td>Ipratropium symptomatically</td>
<td>19</td>
<td>14-9 (3-0)</td>
<td>12-2 (2-3)</td>
<td></td>
</tr>
<tr>
<td>Salbutamol symptomatically</td>
<td>18</td>
<td>19-8 (3-9)</td>
<td>10-3 (2-9)</td>
<td></td>
</tr>
<tr>
<td><strong>CHRONIC BRONCHITIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium 4 × 40 µg/day</td>
<td>26</td>
<td>8-0 (1-6)</td>
<td>11-2 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Salbutamol 4 × 400 µg/day</td>
<td>28</td>
<td>10-7 (2-0)</td>
<td>9-6 (1-3)</td>
<td></td>
</tr>
<tr>
<td>Ipratropium symptomatically</td>
<td>25</td>
<td>7-5 (1-8)</td>
<td>10-3 (1-7)</td>
<td></td>
</tr>
<tr>
<td>Salbutamol symptomatically</td>
<td>34</td>
<td>7-2 (1-5)</td>
<td>9-9 (1-4)</td>
<td></td>
</tr>
</tbody>
</table>

less than 8 mg histamine/ml and 18% were allergic. Among the asthmatic patients 19% had chronic cough, sputum production, or persistent airways obstruction.

The greater response to ipratropium bromide 80 µg than to salbutamol 400 µg in the patients with chronic bronchitis might be due to increased parasympathetic tone in the airways. Other factors, such as increased mucociliary clearance3 and decreased bronchial secretions, may also play a part.

The greater response of asthmatic patients to salbutamol 400 µg may be due to the additional effect of this adrenergic drug on degradation of the mast cell. Allergy was one of the discriminating factors in the response to salbutamol versus ipratropium bromide, the response to salbutamol even being related to the allergy score. The large variance in response to salbutamol and ipratropium bromide was partly explained by allergy and partly by age. More than 70% of the variance, however, remained unexplained. Other factors, such as vagal tone or mucociliary clearance, may be important.

We conclude that patients with mild to moderate airway obstruction vary considerably in their bronchodilating response to salbutamol and ipratropium bromide. In general, salbutamol 400 µg gives a better bronchodilating response in asthma, whereas ipratropium bromide 80 µg gives a better bronchodilating response in chronic bronchitis. Allergic patients and those under the age of 60 are more likely to benefit from salbutamol; non-allergic patients and patients aged 60 and over are more likely to respond better to ipratropium bromide.

We wish to thank the Dutch Asthma Foundation and Boehringer Ingelheim Netherlands for their financial support to this study. We are greatly indebted to Mrs L Bierman, Mrs A Rayment, and Dr M Peerdens for their cooperation in measuring the lung function and bronchoscopic reactions of these patients. We would also like to thank Mr HJ M van den Hoogen for his statistical advice and Mr H Bor for his computer assistance.

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