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

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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 (FEV_1) 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 FEV_1 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 FEV_1 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.

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Although the bronchodilating effects of inhaled $beta_2$ adrenergic and anticholinergic drugs have been widely studied in patients with asthma and chronic bronchitis, few studies have compared the FEV_1 response to the two drugs in the same patients.[1–3] The three studies that have done so looked at a small number of patients referred for specialist treatment so it is difficult to known 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 FEV_1 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.[4] One hundred and eighty eight patients of 30 years and over with mild to moderate airflow obstruction were recruited from 29 general practices. FEV_1 had to be two standard deviations below their FEV_1% predicted value[5] 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.[6] 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 (FEV_1 $\leqslant$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 (FEV_1 increase $\geqslant$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 FEV_1 (PC_{20}) $\leqslant$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

	Chronic bronchitis	Asthma	Total
Number	113	75	188
Age (mean (SD) y)	53 (13)	51 (13)	52 (13)
Sex (% male)	62*	47	56
Smokers (%)	88**	71	81
Pack years (mean No)	19**	13	16
Allergic (%)	18**	35	24
Symptom score (mean (SD))	4·9 (1·8)	5·1 (1·7)	5·0 (1·8)
Exacerbations (mean (SD) No)	1·1 (2·1)*	1·6 (2·5)	1·3 (2·2)
Lung function (mean (SD))			
FEV_1 (l)	2·39 (0·79)*	2·13 (0·73)	2·29 (0·77)
FEV_1 % pred[5]	76 (18)	71 (21)	74 (19)
FEV_1/IVC (%)	68 (10)**	63 (11)	66 (11)
FEV_1/IVC % pred[5]	84 (12)**	76 (12)	81 (12)
Geometric mean PC_{20} (mg/ml)	20***	5	14

*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 order of the two days was randomised. The drugs were administered at about 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*[7]). 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 × 400 μg/day salbutamol by dry powder inhaler (n = 49); 4 × 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

FEV_1, 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 FEV_1 (out of three measurements). All bronchodilator medication was discontinued eight hours before the start of the test. FEV_1 and FVC were measured by three doctors and two laboratory workers trained in using the Microspiro spirometer HI-298 (Chest Corporation, Tokyo). This spirometer measures instantaneous flow, which is electronically integrated to give volume.[8] IVC was measured with a wet spirometer (Gould, Bilthoven, The Netherlands).

Bronchial reactivity (PC_{20}) was tested by means of a histamine challenge test as described by Cockcroft *et al*.[9] Symptoms were assessed by the MRC-ECCS questionnaire (Dutch version)[10] and quantified by addition to provide a score of 0–8.[4] 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*) (Pharmacia AB, Uppsala, Sweden). Patients were considered to be allergic if at least one RAST response was positive. The allergy response was measured semi-quantitatively 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.[11]

ANALYSES

Change in FEV_1 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.[3] 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 FEV_1, and geometric mean PC_{20} during the 12 preceding months. PC_{20} values were logarithmically transformed before analysis. The distribution of the nominal variables was tested by the χ^2 test and of the remaining variables by the Kruskal-Wallis test.

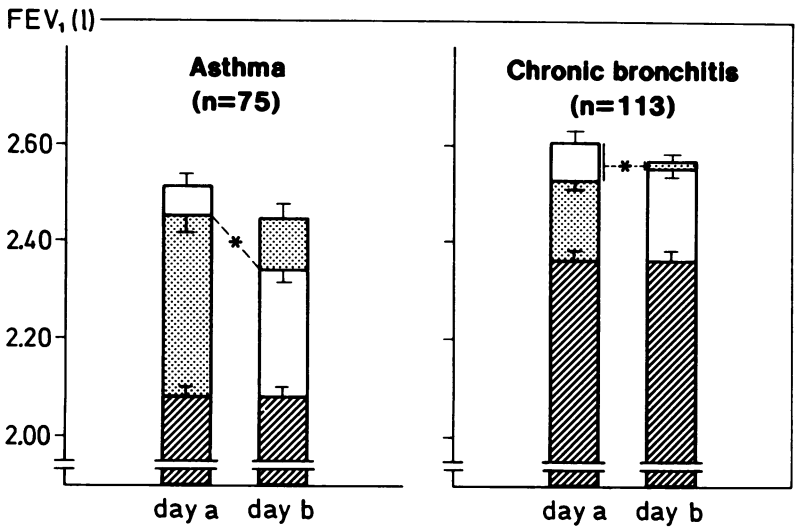

*Figure 1 Mean (SEM) baseline FEV_1 (▨) and increases after salbutamol 400 μg (▤) and after ipratropium bromide 80 μg (□) for patients with asthma and chronic bronchitis. *p < 0·05.*

The possibility of tolerance to ipratropium bromide or salbutamol after the 12 month intervention study was investigated in two ways. Firstly, the increases in FEV_1 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 FEV_1 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 FEV_1 (on the first day of the current crossover study) was incorporated as a covariate in this multivariate model.

Table 2 Relation between the response patterns to salbutamol 400 μg and to ipratropium bromide 80 μg and the clinical characteristics of the patients

Response class:*		*1*	*2*	*3*	*4*	*5*
Number		11	35	74	47	7
% Asthmatic patients	†	64	57	41	30	0
Age (years)		50	53	54	49	60
Sex (% male)		55	49	57	55	71
Smokers (%)		91	69	80	87	86
Pack years (number)		16	13	16	17	21
Allergic (%)	†	45	41	22	11	14
Symptom score		5·2	5·1	4·8	5·2	4·4
Exacerbations (number)		1·8	1·5	1·1	1·3	0·8
FEV_1 (l)		2·37	2·07	2·25	2·40	2·26
FEV_1 % pred		73	68	74	76	76
FEV_1/IVC (%)		64	63	66	68	68
FEV_1/IVC pred[5]		78	76	81	83	85
Geometric mean PC_{20} (mg/ml)		7	12	15	14	20

*Response pattern on a scale beginning with response class 1 (salbutamol 400 μg gives a better response—>75% of total) and going up to response class 5 (ipratropium bromide 80 μg gives a better response). Distributions of variables are compared by the χ^2 and Kruskal-Wallis tests.
†The distribution of the variable is different from what was expected (p < 0·005).
FEV_1—forced expiratory volume in one second; IVC—inspiratory vital capacity; PC_{20}—provocative concentration of histamine causing a 20% fall in FEV_1.

Results

CHANGE IN FEV_1 AFTER SALBUTAMOL AND IPRATROPIUM BROMIDE

Baseline values of FEV_1 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 FEV_1 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 FEV_1 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 FEV_1 in patients with asthma was 0·37 l (18% of the prebronchodilator FEV_1) 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 FEV_1 after salbutamol (0·16 l; 7%) and after ipratropium bromide (0·19 l; 8%) given as first drug. The additional increase in FEV_1 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 FEV_1 (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 FEV_1 after salbutamol 400 μg or ipratropium bromide 80 μg showed a linear relation to age (fig 2*a–c*). The regression coefficient for the effect of ipratropium bromide in asthmatic patients did not deviate significantly from zero. In general (fig 2*c*), patients under the age of 60 appeared to show a greater increase in FEV_1 with sal-

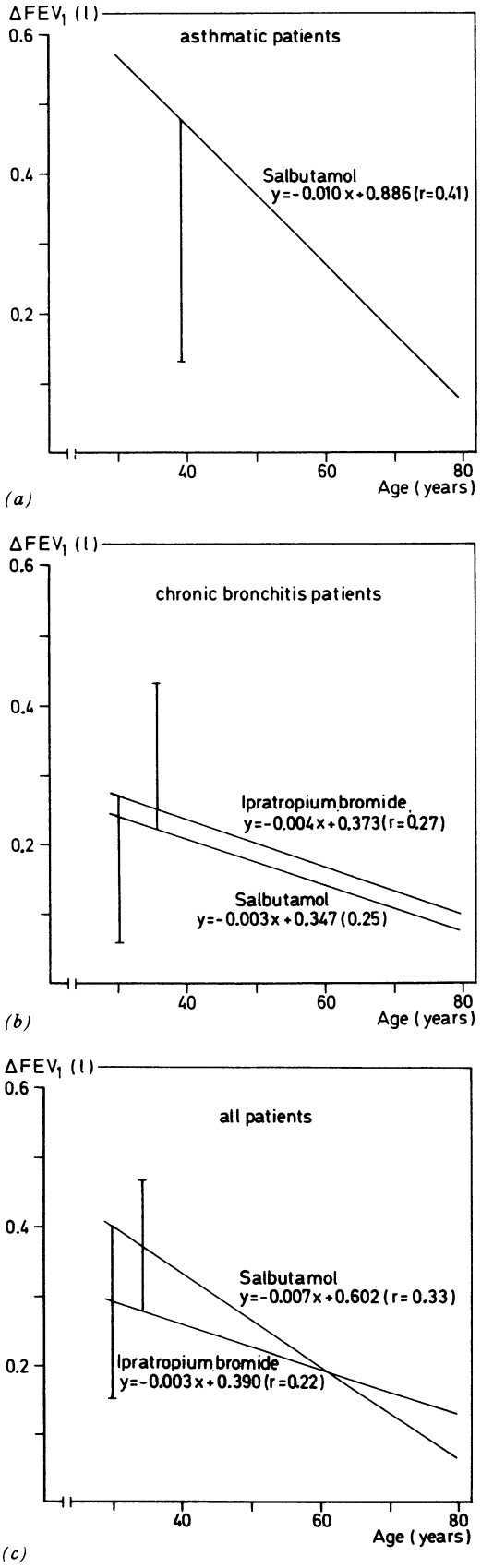

Figure 2 Increase in FEV_1 after salbutamol 400 μg and ipratropium bromide 80 μg related to age for (a) asthmatic patients, (b) patients with chronic bronchitis, and (c) all patients, with 95% confidence limits for the regression lines (all p values <0·005).

butamol, whereas patients aged 60 and over benefited more from ipratropium bromide ($p < 0·005$).

TOLERANCE TO SALBUTAMOL AND IPRATROPIUM BROMIDE

There was no difference in the increase in FEV_1 in response to salbutamol or ipratropium bromide between patients who had used one of these drugs in the preceding year and those who had not (table 3). Neither the drug (salbutamol versus ipratropium) nor the treatment regimen (continuous versus symptomatic) had a significant influence on the increase in FEV_1 to salbutamol or to ipratropium bromide.

Discussion

Most studies have agreed that $beta_2$ adrenergic drugs are more efficacious in asthma than anticholinergic drugs when given in conventional clinical doses.[3 12 13] 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 $beta_2$ adrenergic drugs.[2 14 15] Other studies report more improvement after anticholinergic drugs.[16 17] 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 FEV_1 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,[4] suggesting that no bias had been introduced in the selection procedure.[18]

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.[19] The dose-response relationships of $beta_2$ 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.[20] 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.[6] 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 PC_{20} of

Table 3 Increase in FEV_1 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 FEV_1)

Medication preceding year	n	Increase in FEV_1 (%) after salbutamol	Increase in FEV_1 (%) after ipratropium
ASTHMA			
Ipratropium 4 × 40 μg/day	17	21·5 (6·0)	19·4 (3·0)
Salbutamol 4 × 400 μg/day	21	24·0 (3·3)	17·1 (3·6)
Ipratropium symptomatically	19	14·3 (3·0)	12·2 (2·3)
Salbutamol symptomatically	18	19·8 (3·9)	10·3 (2·9)
CHRONIC BRONCHITIS			
Ipratropium 4 × 40 μg/day	26	8·0 (1·6)	11·2 (1·7)
Salbutamol 4 × 400 μg/day	28	10·7 (2·0)	9·6 (1·3)
Ipratropium symptomatically	25	7·5 (1·8)	10·3 (1·7)
Salbutamol symptomatically	34	7·2 (1·5)	5·9 (1·4)

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 clearance[21] 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 degranulation of the mast cell.[1] 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.

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