Acute effect of pretreatment with single conventional dose of salmeterol on dose-response curve to oxitropium bromide in chronic obstructive pulmonary disease

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Abstract

***Background*—An earlier study documented that, in patients with chronic obstructive pulmonary disease (COPD), addition of ipratropium bromide at the clinically recommended dose (40 µg) does not produce any further bronchodilation than that achieved with salmeterol 50 µg alone. However, the dose of ipratropium bromide needed to produce near maximal bronchodilation is several times higher than the customary dosage. The full therapeutic potential of combined salmeterol plus an anticholinergic drug can therefore only be established using doses higher than those currently recommended in the marketing of these agents. A study was undertaken to examine the possible acute effects of higher than conventional doses of an anticholinergic agent on the single dose salmeterol induced bronchodilation in patients with stable and partially reversible COPD.**

***Methods*—Thirty two outpatients received 50 µg salmeterol or placebo. Two hours after inhalation a dose-response curve to inhaled oxitropium bromide (100 µg/puff) or placebo was constructed using one puff, one puff, two puffs, and two puffs—that is, a total cumulative dose of 600 µg oxitropium bromide. Dose increments were given at 20 minute intervals with measurements being made 15 minutes after each dose. On four separate days all patients received one of the following: (1) 50 µg salmeterol + 600 µg oxitropium bromide; (2) 50 µg salmeterol + placebo; (3) placebo + 600 µg oxitropium bromide; (4) placebo + placebo.**

***Results*—Salmeterol induced a good bronchodilation (mean increase 0.272 l; 95% CI 0.207 to 0.337) two hours after its inhalation. Oxitropium bromide elicited an evident dose-dependent increase in forced expiratory volume in one second (FEV_1) and this occurred also after pretreatment with salmeterol with a further mean maximum increase of 0.152 l (95% CI of differences 0.124 to 0.180).**

***Conclusions*—This study shows that acute pretreatment with 50 µg salmeterol does not block the possibility of inducing more bronchodilation with an anticholinergic agent when a higher than normal dosage of the muscarinic antagonist is used.**

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Recent British Thoracic Society guidelines for the management of stable chronic obstructive pulmonary disease (COPD) state that bronchodilators are the cornerstone of symptomatic treatment for the reversible component of airways obstruction.[1] Short acting β_2 agonists used as required should be tried first in view of their more rapid relief of symptoms. If these do not control symptoms adequately or if regular maintenance therapy is desired, an anticholinergic agent can be added. This recommendation is based on the fact that anticholinergic and β adrenergic agents, which are distinct classes of drugs with different mechanisms of action, are additive when used together.[2 3]

Long acting β agonist bronchodilators such as formoterol and salmeterol are a new interesting therapeutic option for COPD.[4–6] However, their impact on combinations is still unclear.

A combination of ipratropium with salmeterol[7] or formoterol[8] in their normal dosages does not appear to improve pulmonary function, but this lack of improvement with the combination should not in itself prevent implementation of further therapeutic steps in patients responsive to ipratropium and/or salmeterol or formoterol administered singly.

In the present study we have investigated the possible acute effects of higher than normal doses of an anticholinergic agent on the single dose salmeterol induced bronchodilation in patients with stable and partially reversible COPD.

Methods

Thirty two outpatients with moderate to severe COPD but in a stable phase of the disease and with partially reversible airway obstruction were assessed. They gave their informed consent to participate in the study. All fulfilled the criteria proposed by the American Thoracic Society[9]—that is, they were >50 years of age, current or former smokers (>10 pack years) without a history of asthmatic attacks, reporting chronic cough with or without sputum production and/or dyspnoea when walking quietly on level ground, or both; they had had no change in symptom severity or treatment in the preceding four weeks, had shown no signs of a respiratory tract infection

Table 1 Anthropometric data and pulmonary function of patients

Patient	Sex	Age (years)	FEV_1 (% predicted)	FVC (% predicted)	Reversibility 15 min after 200 µg salbutamol (% increase in FEV_1 from baseline)
1	F	62	48	51	15
2	M	66	30	45	18
3	M	73	36	39	17
4	M	55	48	55	18
5	M	61	29	34	31
6	M	58	36	48	21
7	M	71	19	24	18
8	F	70	55	69	17
9	M	65	42	60	25
10	M	57	37	44	21
11	M	68	58	65	15
12	F	62	20	27	24
13	M	68	33	36	15
14	M	69	44	54	23
15	M	58	29	36	19
16	M	61	47	61	16
17	F	73	43	44	17
18	M	67	40	58	15
19	M	64	38	53	27
20	M	65	25	32	28
21	F	71	50	61	26
22	M	55	33	39	24
23	M	63	47	60	19
24	M	68	55	56	16
25	F	74	45	51	18
26	M	72	43	49	20
27	M	68	18	29	18
28	M	64	22	25	15
29	F	62	33	35	19
30	F	58	49	55	17
31	M	65	21	28	19
32	M	64	41	57	28

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

in the month preceding or during the trial, had not been taking oral or inhaled corticosteroids for at least three months, and had a forced expiratory volume in one second (FEV_1) of <65% of predicted normal and a forced vital capacity (FVC) of <70% after bronchodilators had been withheld for 24 hours and a best post-bronchodilator FEV_1/FVC of less than 0.7. Patients with allergic rhinitis, atopy, positive skin test, or with a total blood eosinophil count over 400 mm^{-3} were excluded. Patients were also excluded if they had any co-existing cardiovascular or lung disorder. At an initial screening visit patients were required to demonstrate an increase in FEV_1 of at least 15% from baseline to inhaled 200 µg salbutamol. Table 1 outlines the baseline characteristics of the population studied.

No oral bronchodilators were permitted for one week before and during the study while inhaled short acting bronchodilator drugs and inhaled long acting bronchodilator agents were not permitted for at least 12 hours and 24 hours, respectively, before each test. Patients were also asked to refrain from consumption of cola drinks, coffee, tea, and smoking in the 12 hours before and during the investigation.

The study, which was conducted according to the rules of the declaration of Helsinki, was performed using a randomised, double blind, crossover design. Patients received two puffs of salmeterol (25 µg/puff) or placebo inhaled from matched metered dose inhalers (MDI) and a holding chamber (AeroChamber) with a mouthpiece. Although oxitropium bromide and placebo could have been given by nebuliser, we chose MDI dosing for this study because salmeterol is not available as a solution and a double blind study would otherwise have not been possible.

Spirometric testing was performed according to the procedures described in the American Thoracic Society's 1987 update.[10] Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for FVC and FEV_1. The higher of the two FEV_1 results was kept for analysis. Measurements were performed immediately before inhalation of treatment and after two hours.

Two hours after the inhalation of salmeterol or placebo spirometric tests were performed in each patient, after which a dose-response curve to inhaled oxitropium (100 µg/puff) or placebo was constructed using one puff, one puff, two puffs, and two puffs—that is, a total cumulative dose of 600 µg oxitropium. Oxitropium or placebo were administered from an MDI and holding chamber (AeroChamber) with a mouthpiece. Dose increments were given at 20 minute intervals with measurements being made 15 minutes after each dose. On four non-consecutive days all patients received one of the following: (1) 50 µg salmeterol + 600 µg oxitropium bromide, (2) 50 µg salmeterol + placebo, (3) placebo + 600 µg oxitropium bromide, or (4) placebo + placebo.

The increases in the functional indices from baseline after salmeterol or placebo were assessed. The FEV_1 value induced by 600 µg oxitropium bromide or placebo (six puffs) was chosen as the primary outcome variable. With an estimation of the within subject variability (residual standard deviation) of 0.10 l, this crossover study with 32 patients had 80% power to detect a difference of at least 0.08 l between treatments.

Analysis of spirometric data for each treatment was performed using the Student's *t* test for paired variables. Mean responses were also compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between all four treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence

Table 2 Mean (95% CI) baseline values and changes in FEV_1 and FVC two hours after placebo (P) or 50 µg salmeterol (S), and changes from values at 2 hours after 6 puffs of oxitropium bromide (OB) or placebo (P). Values are mean (95% CI)

	P + P	P + OB	S + P	S + OB
FEV_1 (l)				
Baseline	1.16 (1.02 to 1.30)	1.17 (1.02 to 1.32)	1.15 (1.01 to 1.29)	1.14 (1.00 to 1.28)
Mean change from baseline after 2 hours	0.00 (−0.04 to 0.03)	0.00 (−0.08 to 0.07)	0.25 (0.19 to 0.31)	0.27 (0.21 to 0.34)
Mean change from value at 2 hours after 6 puffs of OB or P	0.01 (−0.03 to 0.04)	0.27 (0.21 to 0.33)	0.03 (0.00 to 0.06)	0.15 (0.12 to 0.18)
FVC (l)				
Baseline	2.05 (1.84 to 2.27)	2.02 (1.78 to 2.26)	1.97 (1.75 to 2.19)	1.98 (1.78 to 2.28)
Mean change from baseline after 2 hours	−0.03 (−0.15 to 0.09)	0.01 (−0.06 to 0.08)	0.23 (0.14 to 0.30)	0.18 (0.08 to 0.28)
Mean change from values at 2 hours after 6 puffs of OB or P	0.02 (−0.05 to 0.09)	0.19 (0.05 to 0.33)	0.02 (−0.09 to 0.13)	0.06 (−0.09 to 0.20)

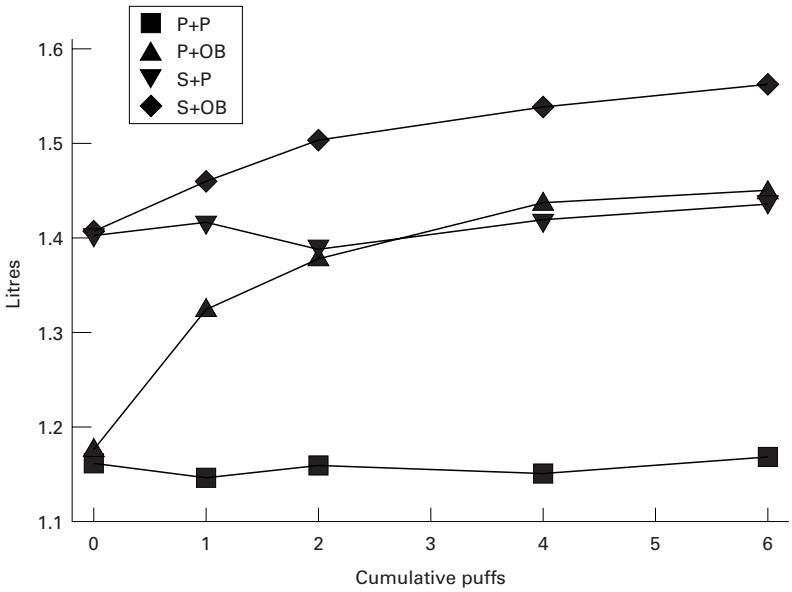

Figure 1 Mean dose-response curves to inhaled oxitropium bromide (OB) or placebo (P) constructed two hours after inhaling placebo or 50 µg salmeterol (S) for FEV_1.

limits was used to identify where differences were significant. A probability level of $p<0.05$ was considered significant for all tests.

Results

All patients completed the four day study. There were no significant differences between the baseline spirometric values of the four treatment groups (FEV_1, $p = 0.411$)

Salmeterol induced a significant bronchodilation two hours after its inhalation (mean increase 0.272 l; 95% CI of differences 0.207 to 0.337) whereas placebo did not modify the baseline values (table 2).

In the dose-response curve (fig 1) oxitropium but not placebo elicited an evident increase in FEV_1. Specifically, the further mean maximum increase induced by 600 µg oxitropium after pretreatment with 50 µg salmeterol was 0.152 l (95% CI of differences 0.124 to 0.180). Maximum values of bronchodilation induced by 600 µg oxitropium after pretreatment with 50 µg salmeterol or placebo were always statistically different ($p<0.0001$) from their baseline and post-inhalational values (table 2).

Analysis of variance of FEV_1 values induced by 600 µg oxitropium bromide or placebo (six puffs) across all four treatments was significant ($p = 0.002$). The comparison between salmeterol + 600 µg oxitropium and salmeterol + placebo (six puffs) showed a mean difference of 0.128 l (95% CI of differences 0.096 to 0.159) that was statistically significant ($p<0.0001$). The mean difference between the highest FEV_1 after salmeterol + 600 µg oxitropium and that after placebo + 600 µg oxitropium was also statistically significant ($p<0.01$). In fact, the increase in FEV_1 induced by 600 µg oxitropium after pretreatment with salmeterol tended to be greater than that after placebo (0.111 l; 95% CI of differences 0.044 to 0.177). It should also be noted that treatment with 200 µg oxitropium after salmeterol was significantly ($p<0.01$) more effective than 200 µg oxitropium after placebo (0.124 l; 95% CI of differences 0.075 to 0.173).

No patient complained of adverse symptoms (palpitations or significant increased heart rate) or reported any difference in the taste of the inhalers.

Discussion

A number of clinical studies have shown the benefit of adding a β agonist to an anticholinergic agent such as ipratropium in COPD.[11] Combination therapy with an inhaled anticholinergic and β agonist may be more effective in bronchodilation than either of the two agents alone.[12] In particular, several studies have reported that standard doses of short acting β_2 agonists do not give optimal results in patients with COPD and that an anticholinergic agent gives additional bronchodilation.[13–15]

The introduction of long acting β agonist bronchodilators gives physicians additional therapeutic options for COPD, but their place in its treatment is currently not known. In any case, both salmeterol and formoterol appear to be more effective than short acting β agonists[16] and in patients with stable COPD salmeterol is more effective than anticholinergic agents.[17 18]

Unfortunately, use of combination therapy of a long acting inhaled β_2 agonist and an anticholinergic agent in COPD has not been sufficiently studied with respect to its effect on pulmonary function. In particular, a trial of an anticholinergic agent in patients with inadequate responsiveness to long acting β_2 agonists, especially in those with severe airflow obstruction, is lacking. To our knowledge there are only two published studies on small numbers of patients which found no substantial additive effect when a long acting β_2 agonist was combined with ipratropium at the clinically recommended dose (40 µg) in patients with COPD. Matera *et al*[7] found that the peak response for 50 µg salmeterol was greater than for 40 µg ipratropium, but equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium. Another study has recently reported that a regimen of 12 µg formoterol plus 40 µg ipratropium was superior to 40 or 80 µg ipratropium, but no statistically significant difference was observed between the combination regimen and 12 or 24 µg formoterol.[8] It is possible that the subjects studied in these two specific clinical situations were at the top of their bronchodilation response curve after inhalation of salmeterol or formoterol. However, it must also be stressed that the dose of ipratropium bromide needed to produce near maximal bronchodilation is several times higher than the normal dosage.[19] Consequently, the full therapeutic potential of combined salmeterol or formoterol plus an anticholinergic drug can only be established using doses higher than those currently recommended in the marketing of antimuscarinic agents.

The results of the present study show that acute pretreatment with 50 µg salmeterol does not block the possibility of inducing further bronchodilation with oxitropium bromide when a higher than normal dosage of the

anticholinergic drug is used. Our data suggest that the inhalation of 600 μg oxitropium may be required to achieve a further bronchodilation when inadequate relief is obtained after 50 μg salmeterol.

In this study we used oxitropium bromide as the anticholinergic agent because it is an effective bronchodilator in COPD,[20 21] exhibits a certain dose response relationship,[22] and, more important, FEV_1 reaches a plateau after administration of a cumulative dose of only six puffs of oxitropium (600 μg) in patients with COPD.[19]

In conclusion, the results of this study suggest that higher than normal doses of an anticholinergic drug must be used for further relief of bronchospasm in patients with COPD when a single conventional inhaled dose of salmeterol is given first. However, we should stress that this study remains an observation of an acute effect and is limited to the effects on airway obstruction. Further larger studies are needed to verify the impact of regularly scheduled salmeterol combined with higher than the conventional dosage of an anticholinergic agent on spirometric values. It will also be interesting to examine the impact of such a combination on dyspnoea, improvement in quality of life, exercise capacity, and activities of daily living.

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