Effects of formoterol, salmeterol or oxitropium bromide on airway responses to salbutamol in COPD


ABSTRACT: We examined whether a pretreatment with formoterol, oxitropium bromide, or salmeterol might modify the dose-response curves to inhaled salbutamol in patients with stable and partially reversible chronic obstructive pulmonary disease (COPD).

Sixteen outpatients with partially reversible, stable COPD received 24 µg formoterol, 50 µg salmeterol, 200 µg oxitropium bromide, or placebo on four non-consecutive days. Spirometric testing was performed immediately before inhalation of treatment and after 2 h. A dose-response curve to inhaled salbutamol was then constructed using doses of 100, 100, 200 µg and 400 µg - that is, a total cumulative dose of 800 µg. Dose increments were given at 20 min intervals with measurements being made 15 min after each dose.

Formoterol, salmeterol, or oxitropium bromide elicited a significant increase in forced expiratory volume in one second (FEV1) compared with placebo (mean differences (L) = placebo 0.05; formoterol 0.34; salmeterol 0.27; oxitropium bromide 0.23). Dose-dependent increases in FEV1 were seen (mean values (L) before salbutamol and after a cumulative dose of 100, 200, 400, and 800 µg = placebo: 1.06, 1.28, 1.35, 1.39, 1.41; formoterol: 1.33, 1.37, 1.41, 1.44, 1.44; salmeterol: 1.30, 1.33, 1.36, 1.39, 1.42; oxitropium bromide: 1.27, 1.34, 1.37, 1.41, 1.40). Statistical analysis revealed no significant differences in FEV1 and forced vital capacity (FVC) responses to salbutamol after therapy with formoterol, salmeterol, or oxitropium bromide compared with placebo.

This study clearly shows that a pretreatment with a conventional dose of formoterol, salmeterol, or oxitropium bromide does not preclude the possibility of inducing a further bronchodilation with salbutamol in patients suffering from partially reversible chronic obstructive pulmonary disease.


Although there are several doubts on effect of bronchodilators in the treatment of chronic obstructive pulmonary disease (COPD) because in this pathological disease the bronchial obstruction is very often "irreversible", many clinicians think that it is necessary to treat patients suffering from COPD with bronchodilator drugs [1, 2]. The consensus guidelines of a Canadian Thoracic Society Workshop group [3] and the most recent guidelines from the American Thoracic Society [4] suggest the inhaled administration of an anticholinergic agent as first-line therapy in stable COPD; however, the introduction of long acting β2-adrenoceptor agonists (e.g., salmeterol and formoterol) gives physicians additional therapeutic options. In fact, formoterol induced an improvement in airflow limitation in chronic obstructive airway disease [5], and salmeterol resulted in a definite reduction in the bronchial obstruction after 1 yr of treatment [6].

Worsening of the underlying bronchospasm may be associated with acute exacerbations of COPD. As the airway obstruction becomes more severe, the therapeutic option is to add a short acting inhaled β2-agonist, such as salbutamol, as rescue medication to cause rapid relief of bronchospasm. Unfortunately, the recommended dosage may increase during acute exacerbations [7]; it is usually greater than the conventional dosage via a metered-dose inhaler (MDI) [8]. However, a pretreatment with formoterol and salmeterol could reduce the airway's responses to repeated doses of a short acting inhaled β2-agonist. In fact, formoterol and salmeterol are partial β2-receptor agonists and in the presence of a full β2-agonist they may act as a β2-antagonist [9]. In fact, a partial β-adrenoceptor agonist exhibits opposite agonist and antagonist activity depending on the prevailing degree of adrenergic tone or the presence of a β2-adrenoceptor agonist with higher intrinsic activity.

Against this background, we felt it useful to examine if a pretreatment by formoterol or salmeterol might modify the dose-response curves to inhaled salbutamol in patients with stable and partially reversible COPD. Moreover, we have also investigated the effect of a pretreatment by oxitropium bromide on these dose-response curves since oxitropium and salbutamol are distinct classes of drugs by differing mechanisms of action and, therefore, it seems reasonable to expect that they might have additive, complementary effects when combined.
Patients and methods

We assessed 16 outpatients with coexisting moderate to severe COPD, but in a stable phase of disease, and with reversible airway obstruction, who gave their informed consent. All fulfilled the criteria proposed by the American Thoracic Society [4]: i.e. they were >40 yrs of age, current or former smokers (>10 pack-yrs) without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both, had had no change in symptom severity or treatment in the preceding 4 weeks, had shown no signs of a respiratory tract infection in the month preceding or during the trial, were not taking oral or inhaled corticosteroids for at least 3 months prior and had a forced expiratory volume in one second (FEV1) <65% of predicted normal and a forced vital capacity (FVC) <70% after bronchodilators had been withheld for 24 h and a best post-bronchodilator FEV1/FVC of less than 0.7. Patients with allergic rhinitis, atopy, skin-test positivity or with a total blood eosinophil count >400 cells·mm⁻³ were excluded. Patients were excluded also if they had any coexisting cardiovascular or lung disorder. At an initial screening visit, patients were required to demonstrate an increase of FEV1 of at least 15% in response to inhaled 200 µg salbutamol.

No oral bronchodilators were permitted for one week before and during the study, whereas inhaled short acting bronchodilator drugs and inhaled long acting bronchodilator agents were not permitted for at least 12 h prior to each test, respectively. Consumption of cola drinks, coffee, tea, and smoking in the hours before and during the investigation was also avoided.

The study, which was conducted according to the rules of the declaration of Helsinki, was performed using a double-blind, crossover, randomized design. Patients received two puffs of salmeterol (50 µg), formoterol (24 µg), oxitropium bromide (200 µg), or placebo, which were all inhaled from matched MDI and holding chamber (AeroChamber Trudell Medical, London, Ontario, Canada) with mouthpiece, on four non-consecutive days. 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 FEV1. The highest FEV1, obtained from one or the other of the reproducible curves, was kept for analysis. Measurements were performed immediately before inhalation of treatment and two hours post inhalation.

Two hours after the inhalation of each treatment, following planned spirometries, a dose-response curve to inhaled salbutamol was constructed using a dose of 100, 100, 200 and 400 µg - that is a total cumulative dose of 800 µg. Salbutamol was also administered from a MDI and holding chamber (AeroChamber Trudell Medical, London, Ontario, Canada) with mouthpiece. Dose increments were given at 20 min intervals with measurements being made 15 min after each dose.

A standard lead II electrocardiogram was monitored and recorded with paper speed set at 25 mm·s⁻¹. Heart rate was calculated from the mean of five consecutive R-R intervals.

The functional indices’ increases from baseline after formoterol, salmeterol, oxitropium bromide, and placebo were assessed. The maximum FEV1 value during the dose-response curve to salbutamol was chosen as the primary outcome variable to compare the four treatments. Analysis of spirometric data and those of pulse rate for each treatment were 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 limits was used to identify where differences were significant. A probability level of p<0.05 was considered as being of significance for all tests.

Results

All patients completed the four-day study. There were no significant differences between the baseline spirometric values and heart rates of the four treatment groups (FEV1 values; p=0.46) (table 1).

Table 1. – Baseline values and changes in FEV1, FVC and HR 2 h after placebo, formoterol, salmeterol or oxitropium and maximum change after cumulative doses of salbutamol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Formoterol (24 µg)</th>
<th>Salmeterol (50 µg)</th>
<th>Oxitropium (200 µg)</th>
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</thead>
<tbody>
<tr>
<td>FEV1 L</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.01 (0.79–1.21)</td>
<td>0.99 (0.77–1.21)</td>
<td>1.03 (0.80–1.26)</td>
<td>1.04 (0.81–1.17)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.05 (0.01–0.09)</td>
<td>0.34 (0.24–0.43)</td>
<td>0.27 (0.19–0.34)</td>
<td>0.23 (0.15–0.30)</td>
</tr>
<tr>
<td>Maximum change from baseline after salbutamol</td>
<td>0.42 (0.32–0.52)</td>
<td>0.48 (0.37–0.59)</td>
<td>0.39 (0.28–0.40)</td>
<td>0.41 (0.33–0.49)</td>
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<tr>
<td>FVC L</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1.82 (1.43–2.21)</td>
<td>1.81 (1.41–2.21)</td>
<td>1.84 (1.45–2.23)</td>
<td>1.81 (1.41–2.21)</td>
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<tr>
<td>Change from baseline</td>
<td>0.03 (0–0.06)</td>
<td>0.39 (0.30–0.48)</td>
<td>0.31 (0.25–0.38)</td>
<td>0.35 (0.29–0.41)</td>
</tr>
<tr>
<td>Maximum change from baseline after salbutamol</td>
<td>0.52 (0.39–0.65)</td>
<td>0.55 (0.40–0.70)</td>
<td>0.52 (0.35–0.69)</td>
<td>0.59 (0.44–0.74)</td>
</tr>
<tr>
<td>HR beats·min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80.7 (76.3–85.1)</td>
<td>80.0 (75.5–84.5)</td>
<td>77.9 (73.1–82.4)</td>
<td>77.7 (72.7–82.7)</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>2.1 (-2.1–6.3)</td>
<td>1.3 (-2.7–5.3)</td>
<td>4.4 (0.5–8.3)</td>
<td>4.0 (5.7–8.5)</td>
</tr>
<tr>
<td>Maximum change from baseline after salbutamol</td>
<td>4.2 (-0.2–8.6)</td>
<td>7.5 (1.4–13.6)</td>
<td>11.2 (5.1–17.3)</td>
<td>8.2 (2.4–14.0)</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval (CI)). FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HR: heart rate.
Formoterol, salmeterol and oxitropium bromide elicited an increase in FEV1 (mean differences (L) = formoterol 0.34 (95% confidence interval (CI) 0.24–0.43); salmeterol 0.27 (95% CI 0.19–0.34); oxitropium bromide 0.23 (95% CI 0.15–0.30)) and in FVC (mean differences (L) = formoterol 0.39 (95% CI 0.30–0.48); salmeterol 0.31 (95% CI 0.25–0.37); oxitropium bromide 0.35 (95% CI 0.29 to 0.41)) which was significant (p<0.05) when compared with placebo (table 1). There were no significant differences between the bronchodilator responses to formoterol, salmeterol, and oxitropium (FEV1 values; p=0.29).

Salbutamol induced a large dose-dependent increase in FEV1 (fig. 1) and FVC after placebo and a further increase after formoterol, salmeterol, or oxitropium. However, 800 µg salbutamol did not induce further benefit when compared with 400 µg salbutamol. Maximum values of bronchodilation of all the four treatments were statistically different (p<0.05) from their postinhalational baseline levels. In the main analysis (based on the maximum FEV1 obtained during the dose-response curve to salbutamol) the within-subject variability was 0.1037 L. Therefore, this 4x4 crossover study with 16 patients had an 80% power of detecting a difference in FEV1 of at least 0.11 L between treatments. Statistical analysis showed no significant differences (p=0.61) between the four treatments.

We were unable to find statistically significant differences (p>0.05) in maximum heart responses to salbutamol after treatment with the three bronchodilators when compared with placebo (table 1; fig. 2).

**Discussion**

This study shows that an acute pretreatment with a long acting β2-agonist or an anticholinergic drug does not reduce the possibility of inducing a further bronchodilation with a short acting β2-agonist in patients who are suffering from COPD and present a partially reversible bronchospasm. It is difficult to draw certain conclusions regarding the synergistic, additive or antagonistic actions of salbutamol following long acting β2-agonists or oxitropium unless compared with formoterol, salmeterol and oxitropium limbs alone. Such a design would be interesting, but it is complex to perform. Nevertheless, we underline that our study had an 80% power of detecting a difference in FEV1 of at least 0.11 L between treatments. The absolute increase in FEV1 necessary to distinguish, with 95% confidence, between natural variability and a response to bronchodilator in patients with COPD is 0.16 L [11].

Salbutamol was chosen to construct the dose-response curves although it has been shown that this short acting β2-agonist acts as a partial β2-agonist/antagonist and inhibits the effects of endogenous adrenaline at extrapulmonary β2-receptors in normal subjects [12]; moreover, a subsensitivity to salbutamol has been demonstrated after chronic dosing with salmeterol [13]. However, our choice was suggested by the evidence that salbutamol exhibits in vitro partial β2-agonist activity at cardiac β2-adrenoceptors and full agonist activity at airway β2-adrenoceptors [14], produces more relaxant effect than salmeterol at very high level of precontraction in the guinea-pig isolated trachea [15], and, finally, acts in vivo as a partial agonist only in a state of high adrenergic tone [13], but this is not the case of patients with stable COPD. In any case, our data are in agreement with those of Smyth et al. [16], who found a good rise in FEV1 after addition of increasing doses of salbutamol in asthmatic patients pretreated with salmeterol 50 µg (but this rise became progressively smaller after salmeterol 100 and 200 µg).

The evidence that prior treatment with formoterol and salmeterol does not alter bronchodilator response to repeated doses of a short acting β2-agonist conflicts with data of several in vitro researches. In fact, Dougall et al. [17], using adrenaline and isoprenaline as agonists, noted significantly less steep concentration-effect curves in the presence of salmeterol as compared to control curves. More, recently, Naude et al. [18] showed that when isolated human bronchi were incubated in the presence of formoterol, a significant (1 log unit) displacement of the concentration-response curves to adrenaline was observed with long acting β2-agonist at a concentration giving a maximal effect. With salmeterol, the concentration-response curves were displaced by 0.6 log units at a concentration producing 17–26% of relaxant effect, and by 1.7 log units at a concentration producing 60% of the relaxant effect. In particular, Källström et al. [19] reported that in guinea-pig, salbutamol and several other β2-agonists show-ed concen-
tration-effect curves that tended to be less steep in the presence of salmeterol.

It is interesting to highlight that Grove and Lipworth [20] have documented high doses of formoterol (72 µg) and salmeterol (300 µg) which, in the presence of endogenous adrenaline or exogenous fenoterol, act as β2-receptor antagonists in terms of antagonising the extrapulmonary responses to fenoterol, as evidenced by the potentiation of exercise-induced hyperkalaemia and the attenuation of hypokalaemic, tremor, and heart rate responses in normal subjects. However, in a second study which included 10 patients with stable asthma, the same researchers observed that prior treatment with low doses of salmeterol (25 µg) and formoterol (12 µg) had no significant effects on the bronchodilator or systemic β2-receptor-mediated responses to fenoterol [21].

In contrast to the study of Grove and Lipworth [21], we have used the recommended doses of salmeterol (50 µg) and formoterol (24 µg). These doses were chosen as we were expecting that formoterol and salmeterol did not induce the maximum bronchodilation. In fact, we have previously examined the dose-response effect curves to formoterol and salmeterol in a population of patients with partially reversible severe COPD [22]. Both drugs induced a functional improvement lasting 12 h, but formoterol (12–36 µg) caused a dose-dependent increase in FVC, FEV1 and forced mid-expiratory flow (FEF25–75%), whereas salmeterol (75 µg) did not elicit a further increase in bronchodilation than salmeterol (50 µg). Moreover, at the recommended dose (50 µg), salmeterol was more active than formoterol (12 and 24 µg), but less effective than formoterol (36 µg). These findings clearly indicated that further bronchodilation was still possible.

A number of clinical studies have shown a benefit of combining a short acting β2-agonist with anticholinergic agents such as ipratropium and oxtropium in COPD [23]. In fact, since β2-agonists and anticholinergic agents are distinct classes of drugs with different mechanisms of action, an additive effect may be expected [24–26]. Prior attenuation of vagal tone by anticholinergic drug permits optimal achievable dilatation to be attained by subsequent inhalation of a short acting β2-agonist. Furthermore, there are prejunctional inhibitory β2 receptors on cholinergic fibres which might conceivably result in attenuation of resting vagal tone, in addition to direct β2-mediated smooth muscle relaxation [27]. Nevertheless, it seems that there is no significant benefit of adding a β-agronist when the antimuscarinic agent has been given previously [28]. Our data showed that adding salbutamol to oxtropium induced further bronchodilation and the peak values obtained during the dose-responses curves following treatment with oxtropium were not significantly different from those obtained after salmeterol or formoterol. However, we observed an absence of difference between oxtropium + salbutamol versus placebo + salbutamol. Evidence is mounting to support the clinical practice of combining an anticholinergic bronchodilator with a β2-agonist only in patients with COPD who exhibit suboptimal response to first-line therapy [29]. It is conceivable that the subjects studied in this specific clinical situation reached the top of their bronchodilation response curve after inhalation of salbutamol. A positive correlation between maximum bronchodilator response and the dose of β2-adrenoceptor agonist used is not always observed. However, a 50% increase in FEV1 is obtained with 400 µg salbutamol and an increase in the dose of this agent may produce further increases in FEV1 [30]. In any case, the results of this study apparently refute the assertion that airway obstruction secondary to increased vagal tone, and is the only dominant reversible element in patients suffering from COPD.

In conclusion, the results of this study support the use of salbutamol as rescue medication for rapid relief of bronchospasm in patients suffering from partially reversible chronic obstructive pulmonary disease, even after conventional inhaled doses of long acting β2-adrenoceptor agonists or anticholinergic drugs. Obviously, we have yet to establish whether the long-term treatment with these long acting bronchodilating agents may have a different impact on the dose-response to a short acting β2-agonist.

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References


