Influence of higher than conventional doses of oxitropium bromide on formoterol-induced bronchodilation in COPD

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We examined the influence of higher than conventional doses of oxitropium bromide on formoterol-induced bronchodilation in patients with partially reversible stable COPD. Twenty outpatients inhaled one or two puffs of formoterol (12 µg puff⁻¹), or placebo. Two hours after inhalation, a dose-response curve to inhaled oxitropium bromide (100 µg puff⁻¹) or placebo was constructed using one puff, one puff, two puffs and two puffs, for a total cumulative dose of 600 µg oxitropium bromide. Doses were given at 20-min intervals and measurements made 15 min after each dose. On six separate days, all patients received one of the following: (1) formoterol 12 µg + oxitropium bromide 600 µg, (2) formoterol 12 µg + placebo, (3) formoterol 24 µg + oxitropium bromide 600 µg, (4) formoterol 24 µg + placebo, (5) placebo + oxitropium bromide 600 µg, or (6) placebo + placebo. Both formoterol 12 µg and 24 µg induced a good bronchodilation (formoterol 12 µg, 0.19-0.20 l; formoterol 24 µg 0.22-0.24 l). The dose-response curve of oxitropium, but not placebo, showed an evident increase in FEV₁, with a further significant increase of respectively 0.087 l and 0.082 l after the formoterol 12 µg and formoterol 24 µg pre-treatment. This study shows that improved pulmonary function in patients with stable COPD may be achieved by adding oxitropium 400-600 µg to formoterol. There is not much difference in bronchodilation between combining oxitropium with formoterol 12 µg or 24 µg. In any case, formoterol 24 µg alone seems sufficient to achieve the same bronchodilation induced by oxitropium 600 µg alone in most patients.

Introduction

The analysis of the literature does not reveal a unequivocal predominance of a class of bronchodilator over others in the treatment of chronic obstructive pulmonary disease (COPD), but it seems to indicate that the combination of different broncholytic agents is currently the only strategy to adopt (1). Nevertheless, we must define the correct dosage of each drug that is currently used in association with other broncholytic agents. In fact, it is still not clear whether higher doses of monotherapy are better than combination therapy with lower doses of bronchodilators. In any case an additive effect may be expected when combining β₂-agonists and anticholinergic agents because they are distinct classes of drugs with different mechanisms of action (1).

Long-acting β₂-agonist bronchodilators (e.g. formoterol, salmeterol) are a new therapeutic option for COPD (1-3). Both formoterol and salmeterol appear to be more effective than short-acting β₂-agonists and anticholinergic agents in patients with stable COPD (4-6). However, the impact of long-acting β₂-agonists on combinations is still unclear.

We have documented that in patients with COPD the addition of ipratropium bromide at clinically recommended dose (40 µg) does not produce any further bronchodilation than that achieved by using a long-acting β₂-agonist (salmeterol 50 µg) alone, although the onset of action after the combination of the two drugs is faster than after salmeterol alone (7). It is possible that the subjects studied in that specific clinical situation were at the top of their bronchodilation response curve after inhalation of salmeterol, but it must also be stressed that the dose of ipratropium bromide needed to produce near maximal bronchodilation is several times higher than the customary dosage (8). Therefore, the full therapeutic potential of a combined long-acting β₂-agonist plus an anticholinergic drug can only be established using doses higher than those currently recommended in the marketing of these agents.

The present study was designed to examine the possible influence of higher than conventional doses of an anticholinergic agent on formoterol-induced bronchodilation in patients with stable and partially reversible COPD.
Patients and methods

The study involved 20 outpatients (19 men and one woman) with co-existing moderate to severe COPD (baseline FEV₁ = 21 ± 63% predicted), but in a stable phase of disease, and with reversible airway obstruction (reversibility 15 min after salbutamol 200 µg = +15–31% from baseline) were enrolled. Other inclusion criteria were: > 50 years of age with a 20 or more-yr smoking history, AFEV₁/predicted FEV₁ < 12%, and post-bronchodilator FEV₁ < 85%. Exclusion criteria were: current evidence of asthma as primary diagnosis, unstable respiratory disease requiring oral/parenteral corticosteroids within the 4 weeks prior to commencing the study, upper or lower respiratory tract infection within the 4 weeks of screening visit, concurrent use of medications that affect COPD and evidence of alcohol abuse. All patients fulfilled the criteria proposed by the American Thoracic Society (9).

The study, which was conducted according to the rules of the declaration of Helsinki, was performed using a randomized, single-blinded, cross-over design.

Spirometric testing was performed immediately before inhalation of treatment and 2 h after inhalation of one or two puffs of formoterol (12 µg puff⁻¹), or placebo, which were inhaled from metered dose inhalers (MDI) and holding chamber (AeroChamber) with mouthpiece.

Soon after the patients had performed the post-treatment spirometries, a dose-response curve to inhaled oxitropium (100 µg puff⁻¹) or placebo was constructed using one puff, one puff, two puffs and two puffs from a MDI with spacer and mouthpiece for a total cumulative dose of 600 µg oxitropium. Doses were given at 20 min intervals and the measurements made 15 min after each dose.

On six separate days, all patients received one of the following treatment combinations: 1. formoterol 12 µg + oxitropium 600 µg, 2. formoterol 12 µg + placebo, 3. formoterol 24 µg + oxitropium 600 µg, 4. formoterol 24 µg + placebo, 5. placebo + oxitropium 600 µg, or 6. placebo + placebo.

The maximum FEV₁ value of the dose-response curves to oxitropium bromide or placebo was chosen as the primary outcome variable. We did not estimate the power of the main analysis because this was a pilot study. The spirometric data for each treatment were analysed using Student’s t-test for paired variables. The mean responses to all of the treatments were also compared by multifactorial analysis of variance (ANOVA) in order to establish any significant overall effect. In the presence of a significant overall ANOVA, Duncan’s multiple range testing with 95% confidence limits was used to identify where the differences were significant. A probability level of P < 0.05 was considered as being of significance for all tests.

Results

All patients completed the 6-day study. There were no significant differences between the baseline spirometric values of the six treatment groups (FEV₁ P = 0.994).

Both doses of formoterol elicited a statistically significant (P < 0.05) increase in FEV₁ 2 h after its inhalation (mean differences (i) = formoterol 12 µg before placebo: 0.20 (95% CI 0.14–0.26); formoterol 12 µg before oxitropium: 0.19 (95% CI 0.09–0.29); formoterol 24 µg before placebo: 0.22 (95% CI 0.11–0.32); formoterol 24 µg before oxitropium: 0.24 (95% CI 0.13–0.33)) whereas placebo did not modify the baseline values (Fig. 1).

The dose-response curve of oxitropium, but not placebo, showed an evident increase in FEV₁, with a further maximum increase of respectively 0.087 l (95% CI 0.033–0.141) and 0.082 l (95% CI 0.037–0.128) after the formoterol 12 µg and formoterol 24 µg pre-treatment (Fig. 2). These maximum FEV₁ values were statistically different (P < 0.05) from both their baseline and post-formoterol levels. The difference between the FEV₁ values 2 h after formoterol 24 µg and oxitropium 600 after placebo (0.001 l; 95% CI −0.069–0.067) was not significant (P = 0.976).

The mean difference between the highest oxitropium FEV₁ and highest placebo FEV₁ after formoterol 12 µg (0.091 l; 95% CI 0.026–0.156) and formoterol 24 µg (0.083 l; 95% CI 0.020–0.146) were statistically significant.
Discussion

Use of combination therapy of a long-acting inhaled $\beta_2$-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 $\beta_2$-agonist, especially in those with severe airflow obstruction, is lacking in literature.

In this study we have examined the bronchodilating impact of oxitropium on two doses of formoterol because it has been shown that, while the majority of 318 adults with reversible obstructive airways disease was adequately treated with formoterol 12 $\mu$g twice daily, a subgroup of patients with more severe airway obstruction required the 24 $\mu$g dose (10). Moreover, we have used oxitropium bromide as the anticholinergic agent because it is an effective bronchodilator in COPD (11,12), exhibits a certain dose response relationship (13) and, more importantly, FEV$_1$ reaches a plateau after administration of a cumulative dose of only six puffs of oxitropium (600 $\mu$g) in patients with COPD (8).

Our results indicate that improved pulmonary function in patients with stable COPD may be achieved by adding oxitropium 400–600 $\mu$g to formoterol. There is not much difference in bronchodilation between combining oxitropium with formoterol 12 $\mu$g or 24 $\mu$g. Formoterol 24 $\mu$g is in any case sufficient to achieve the same bronchodilation induced by oxitropium 600 $\mu$g alone in most patients.

Larger studies are needed to determine whether the bronchodilation gained by using combination therapy may be maintained for a long period (and therefore whether the combination is meaningful as maintenance therapy in COPD), and also to verify the long-term impact of combination therapy on different clinical outcomes.

References