The effect of oral corticosteroids on bronchodilator responses in COPD

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There have been suggestions that corticosteroid treatment might improve bronchodilator responses in chronic obstructive pulmonary disease (COPD). We have studied bronchodilator responses to salbutamol and to oxitropium bromide in 20 patients with stable moderate to severe COPD. Dose responses to the two bronchodilators were tested before and after 3 week courses of placebo and 30 mg prednisolone. Thirteen patients were taking inhaled corticosteroids. There were no significant changes in numbers of responses or maximum bronchodilator effects from either bronchodilator, although there was a trend towards higher maximum levels after 3 weeks of prednisolone. Spirometry measured at home each morning before and after oxitropium bromide showed no difference between prednisolone and placebo periods. This study provides no evidence for a significant effect on bronchodilator responses to β-agonists or anticholinergic agents from 3 weeks of oral prednisolone in moderately severe COPD.

Introduction

Oral corticosteroids are used widely in the treatment of chronic airflow obstruction. They have an established place in the treatment of acute exacerbations of asthma and in chronic severe asthma (1). In patients with stable chronic obstructive pulmonary disease (COPD) 2-3 week courses of steroids produce a clinically significant increase in forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) in a minority of patients (2). Corticosteroids are often used in acute exacerbations of COPD (3,4).

It has been suggested that oral corticosteroids might improve bronchodilator responses in airflow obstruction. In vitro β-receptor numbers are increased by corticosteroid treatment (5,6). They have been shown to increase the effects of β-adrenergic agonists in animal models and in human tissue in vitro (7,8). Treatment with corticosteroids can prevent or reverse decline in β-receptor density and the development of tolerance (9-11).

A study in ten patients with COPD found a trend towards an increase in the bronchodilator response to ipratropium bromide after an 8 day course of oral corticosteroids (12). Inhaled steroids for 3 months failed to change bronchodilator responses in smokers with mild airflow obstruction (13). We have explored this area further with a longer course of oral prednisolone in a larger group of patients with more severe COPD. The laboratory measurements of bronchodilator responses were complemented by daily home spirometry measurements of responses to an anticholinergic agent.

Methods

Twenty subjects with COPD entered the study. Two patients dropped out during the first phase and 18 completed the cross-over study. The study was approved by the local Research Ethics Committee.

All patients were aged over 40 years with FEV₁ less than 70% predicted and FEV₁/FVC ratio less than 60%. All were smokers or ex-smokers and had a clinical diagnosis of COPD. Exclusion criteria were diabetes mellitus, left-heart failure, active peptic ulceration, clinical diagnosis of asthma or positive skin tests for common allergens. Patients who had a previous documented response to oral steroids or who had been on oral steroids in the past 3 months were excluded.

All patients were receiving treatment with inhaled β-adrenergic agonists and some were taking inhaled anticholinergic drugs. These were continued as needed through the study except that inhaled bronchodilators were stopped for at least 8 h and oral bronchodilators and long-acting inhaled bronchodilators for at least 24 h before measuring bronchodilator responses. Thirteen of the 18 patients were taking inhaled corticosteroids, either beclomethasone dipropionate or budesonide. The median dose of inhaled steroid was 800 μg daily (range 0–2000 μg daily). These were continued throughout the study.

Bronchodilator responses to salbutamol and oxitropium bromide were carried out on two consecutive days at the same time of day. Over the next 3 weeks subjects received prednisolone 30 mg daily orally or matching placebo.
Bronchodilator responses were repeated in the same order and at the same time over 2 days at the end of this 3 weeks. Then subjects crossed over to receive 3 weeks of the second oral medication followed by a repeat of their bronchodilator responses. The order of treatment and of dose–response curves were randomized. Patients were blind to the bronchodilator medication. Patients and technicians were blind to the order of prednisolone and placebo.

Compliance was assessed by tablet counting. Mean compliance was 96% (range 78–102%). Bronchodilators were given by supervised inhalation and the final dose by nebulizer. Doses of salbutamol were 100, 100, 200 and 5000 μg. Doses of oxitropium bromide were 100, 100, 200 and 1000 μg.

Measurements of FEV₁ and FVC were made on a dry bellows spirometer (Vitalograph). The best of three reproducible traces was used in the analysis.

At home over the 6 weeks of the study each subject took their usual inhaled medication. In addition they were asked to take 200 μg oxitropium bromide each morning and to measure their FEV₁ and FVC on a portable turbine spirometer (Micromedical) before and 45 min after. The best FEV₁ and FVC from these three recordings were used. The mean oxitropium responses over the last 7 days of prednisolone and placebo treatment were compared by paired t test.

Bronchodilator responses were analysed as absolute change from baseline value and as absolute level of FEV₁ to allow for baseline shifts from steroid therapy. Results after prednisolone and placebo were compared by paired t tests for salbutamol and oxitropium bromide.

Responders were defined as those who achieved an FEV₁ response of at least 15% and 200 ml change from baseline or a vital capacity response of 15% and 350 ml. The numbers of responders were compared for the different periods.

Results

The mean age (range) of the patients was 69.9 years (56–81 years); 16 of the 18 patients were men. Mean baseline FEV₁ was 0.86 l.

There was a tendency for baseline spirometry values to increase after prednisolone (Figs 1 and 2). The only significant change was an increase in FVC after prednisolone compared with initial values (salbutamol day, 0.331 95% CI 0.06–0.60 l, P=0.02; oxitropium day, 0.261 95% CI 0.03 to +0.55 l, P=0.07). Only one patient had an FEV₁ increase of 200 ml and 15% baseline with prednisolone.

Overall there were 'responses' to salbutamol or oxitropium bromide on 63% of the days using the criteria of >15% and 200 ml change from baseline or a vital capacity response of 15% and 350 ml. The numbers of responders were compared for the different periods.

Mean absolute levels of FEV₁ and FVC in response to salbutamol and oxitropium bromide are shown in Figs 1 and 2. Absolute levels of FEV₁ and FVC during the dose–response curves showed no significant differences between placebo and prednisolone periods. The maximal levels reached after prednisolone and placebo are not significantly different although in three of the four measurements the highest values occurred on prednisolone. At the maximum doses of oxitropium bromide differences between prednisolone and placebo periods were 0.00 l for FEV₁ (95% CI −0.07 to +0.08 l) and 0.13 l for FVC (95% CI 0.10 to +0.35 l). With salbutamol equivalent differences were 0.04 l for FEV₁ (95% CI −0.05 to +0.13 l) and 0.18 l for FVC (95% CI −0.07 to +0.43 l).

Sixteen of the 18 subjects produced adequate home recordings of spirometry throughout the 6 weeks of the study. There were no significant differences between the mean absolute FEV₁ or FVC responses to oxitropium bromide during the last week of placebo and prednisolone treatment. The FEV₁ increase after oxitropium was 0.12 l on prednisolone and 0.14 l on placebo (t=0.62, P=0.51; 95% CI of difference −0.14 to +0.10 l). The FVC increase with oxitropium was 0.24 l on prednisolone and 0.28 l on placebo (t=0.17, P=0.26; 95% CI of difference −0.20 to +0.12 l).
FIG. 2. Absolute values of FVC during dose-response curves to (a) salbutamol and (b) oxitropium bromide at the start of the study and after 3 weeks of prednisolone and placebo in 18 patients with COPD. ●, initial; ○, placebo; ▲, prednisolone.

The results in the five patients who were not taking inhaled corticosteroids were no different from those of the whole group.

Discussion

In this group of 18 patients with moderate to severe COPD there was a trend to an increase in baseline levels of FEV₁ and FVC after 3 weeks of oral prednisolone, as expected. Most studies show that around 10–20% of such patients will achieve a significant improvement in a formal trial of steroids (2) but in this study those shown previously to respond to steroids were excluded. The only significant change in baseline levels with 3 weeks prednisolone was an increase in baseline levels of FVC. Only one individual showed a significant change in FEV₁.

There were no significant differences in bronchodilator responses expressed as changes from baseline during the prednisolone and placebo periods. The most significant change in bronchodilator response for patients with moderately severe COPD might be considered to be an increase in the maximal levels reached with bronchodilators on top of any corticosteroid response. For the absolute levels of FEV₁ and FVC there was a trend towards higher values on prednisolone than placebo but none of these changes was statistically significant. The 95% confidence intervals for differences between prednisolone and placebo did not cover a possible clinically significant effect on FEV₁. The upper limit of the 95% confidence intervals for FVC change did not exclude an effect up to 0.43 l. We cannot rule out the possibility of an FVC change of marginal clinical significance in a larger study.

All the patients in this study had been taking inhaled bronchodilators. Anticholinergic agents do not lose their effect with repeated use (14) but small changes may occur with β-agonists (15). Reversal of any reduced effectiveness might result in an increased bronchodilator response after corticosteroids but such changes were not seen in this study. Thirteen patients were taking inhaled steroids. A previous study has shown that there is no effect on bronchodilator responses from 3 months of inhaled steroids at a dose of 600 µg budesonide twice daily (13). This is greater than the median dose of inhaled steroids in the 13 users in this study. Our results show that additional use of oral steroids does not have a significant effect on bronchodilator responses.

Responders to bronchodilators are sometimes taken to be those who show a change outside the 95% confidence intervals of the test. For FEV₁ this requires a change approaching 200 ml and for FVC around 350 ml (16,17). Overall 63% of challenges produced a response on this basis and numbers of responders to β-agonist and anticholinergic drugs were similar. With these criteria the number of responders was not significantly changed by 3 weeks of treatment with prednisolone.

Bronchodilator responses are known to vary between assessments (18,19). We used home measurements to look at the consistency of responses in the usual clinical situation. Sixteen patients were able to produce reproducible home recordings of FEV₁ and FVC with their responses to

**TABLE 1. Numbers of 'responders' to oxitropium bromide and salbutamol after placebo and prednisolone periods**

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<td>Oxitropium</td>
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<td>Salbutamol</td>
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inhaled oxitropium bromide. The last week of the 3 weeks of recordings was used to avoid any carry-over effect from the previous treatment period. These results confirmed the laboratory measurements showing no difference between prednisolone and placebo weeks. The size of the changes was a little smaller on home recordings than in the respiratory function laboratory. Probably this reflects a different degree of effort for home and technician-supervised recordings. However, it was encouraging that the majority of this selected group of patients were able to produce adequate recordings at home with simple portable equipment.

Spirometry is likely to be more useful than the simpler peak expiratory flow in the monitoring of patients with COPD, in contrast to asthma.

The findings in this study provide no evidence for a clinically important increase in bronchodilator responses to either β-adrenergic or anticholinergic agents with a 3 week course of 30 mg oral prednisolone in moderate to severe COPD.

Acknowledgement

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References