Respiratory Medicine (2007) **101**, 1218–1228

ELSEVIER

respiratoryMEDICINE

# A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma

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Received 25 August 2006; accepted 2 November 2006
Available online 18 December 2006

**KEYWORDS**
Anti-cholinergic;
Bronchodilation;
Body plethysmography

**Summary**
We conducted a double blind, randomised, placebo-controlled, crossover study evaluating the effects of halving inhaled steroid dosage plus salmeterol, or salmeterol and tiotropium. Eighteen life-long non-smoking severe asthmatics [mean $FEV_1$ 1.49 l (51%)] were run-in for 4 weeks on HFA-fluticasone propionate 1000 μg daily, and were subsequently randomised to 4 weeks of either (a) HFA-fluticasone propionate 500 μg BD/salmeterol 100 μg BD/HFA-tiotropium bromide18 μg od; or (b) fluticasone propionate 500 μg BD/salmeterol 100 μg BD matched placebo. Measurements of spirometry and body plethysmography were made. Adding salmeterol to half the dose of fluticasone led to a mean improvement (95% CI) vs. baseline in morning PEF of 41.5 (14.0–69.0) l/min [$p<0.05$]; and RAW of 0.98 (0.14–1.8) cm $H_2O$/l/s [$p<0.05$]. Adding salmeterol/tiotropium produced similar improvements in PEF and RAW, but also improved $FEV_1$ by 0.17 (0.01–0.32) l [$p<0.05$]; FVC 0.24 (0.05–0.43) l [$p<0.05$] and reduced exhaled NO by 2.86 (0.12–5.6) ppb [$p<0.05$]. RV and TLC were not altered by either treatment; there were no significant changes in symptoms or quality of life compared with baseline. Addition of salmeterol/tiotropium to half the dose of fluticasone afforded small, but significant improvements in pulmonary function. These effects were not associated with commensurate changes in subjective symptoms or quality of life.


## Introduction

Asthma is an inflammatory disorder of the airways and the spectrum of disease is wide, ranging from intermittent mild disease, to severe disease.[1,2] These severe, difficult to manage patients present with poorly controlled asthma; often despite high doses of inhaled corticosteroids. True

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doi:10.1016/j.rmed.2006.11.001

steroid resistant asthma is rare, with an incidence of 1 in 1000 to 1 in 10,000 asthmatic patients,[3,4] however a cohort of severe asthmatics do demonstrate minimal therapeutic benefit from the highest doses of inhaled and oral, corticosteroids. The mechanisms of this relative steroid resistance are not fully understood, however it may be due to the severity of the disease itself (via inactivation of glucocorticoid receptors by IL-1$\alpha$ and TNF-$\delta$[5,6]), or by high doses of $\beta_2$ agonists (due to inactivation of glucocorticoid receptors by $\beta_2$ agonist activated cyclic adenosine monophosphate response binding element[7,8]).

Progressive airflow obstruction occurs in severe asthmatic patients,[9,10] the exact mechanism of this deterioration is not known, however it may be due to airway remodelling secondary to uncontrolled chronic airway inflammation.[11] The fibrotic changes seen in remodelled airways are unresponsive to ICS therapy, and as such ever-increasing high doses of steroid at this stage can be ineffective. The systemic burden of inhaled corticosteroid should not be underestimated, with even clinically moderate doses of modern ICS leading to significant hypothalamic–pituitary–adrenal axis suppression,[12] and bone demineralization.[13] The latest asthma guidelines suggest ''Stepping-down'' the dose of prescribed ICS to the minimum dose that gives adequate control. In the severe patient group, this is a difficult clinical problem, as many patients will not achieve ''adequate control'' without, or despite a high dose of ICS. The use of second line therapies has been proposed as a method to not only improve asthma control, but also give a steroid sparing effect, allowing step down of ICS.

Treatment options for severe asthma with airway remodelling are, therefore, limited, and, in reality, most patients are prescribed a combination of ICS and various bronchodilators such as $\beta_2$ agonists, anticholinergics and theophyllines. The use of second line agents may facilitate step down of inhaled corticosteroid dosage, without deterioration in pulmonary function of quality of life.

To our knowledge, there have been no studies that investigate the potential benefit of the addition of long acting bronchodilators to facilitate step down of ICS in the severe cohort of patients. The present study aims to demonstrate that inhaled corticosteroids may be stepped down safely with adjuvant therapy of long acting $\beta_2$ agonists with or without tiotropium; we measure the benefits in terms of effort dependent pulmonary function testing, body plethysmography and quality of life scoring.

## Methods

### Patients

Twenty-six patients were initially enrolled into the randomised, placebo-controlled, crossover study. We identified patients from our database of volunteers, who were lifelong non-smokers with severe persistent asthma, evidence of airway remodelling; that is, severe volume-dependent airway closure on an expiratory flow volume loop and a reduced FVC% predicted.

### Screening visit

Patients attended an initial visit to assess eligibility and perform measurements. All routine first and second line treatment was stopped. Patients were then prescribed HFA-fluticasone 1000 μg pMDI (as 2 puffs bd of Flixotide 250 μg per actuation, Flixotide Evohaler, GlaxoSmithKline, Uxbridge, UK) for a run-in period of 4 weeks.

### Study visits

They returned for visit one (baseline) for spirometry measurements and reversibility testing. Reversibility was assessed on 2 separate days in random order with either salbutamol 400 μg, as 2 puffs of Ventolin Accuhaler 200 μg per actuation (GlaxoSmithKline, Uxbridge, UK), followed by ipratropium bromide 80 μg, as 2 puffs of Atrovent Aerocaps 40 μg per actuation (Boerhinger Ingelheim, Bracknell, UK) or the reverse order. $FEV_1$ and FVC were recorded 30 min after the administration of salbutamol or ipratropium. The second drug in sequence was given 30 min after the first drug.

Following run-in, the dose of HFA-fluticasone was halved to 500 μg daily. To facilitate step down patients received either fluticasone and salmeterol, as Seretide Evohaler 125/25 μg per actuation, 2 puffs BD (GlaxoSmithKline, Uxbridge, UK), and tiotropium, CFC formulation 9 μg per actuation, two puffs OD, 18 μg OD (Cipla Ltd, Mumbai, India) or fluticasone, salmeterol and matched placebo.

Patients were randomised to the study tiotropium or placebo groups in a crossover fashion, with measurements made after 4 weeks of each treatment (Fig. 1).

Comparisons were made with reference to the baseline values after fluticasone propionate 1000 μg daily, in order to evaluate the effects of halving the fluticasone dose with the addition of either salmeterol alone or salmeterol and tiotropium.

### Inclusion criteria

Inclusion criteria were; forced expiratory volume in 1 s ($FEV_1$) $\leqslant$ 65% predicted, FVC $<$ 80% predicted, $FEF_{25-75}$ $<$ 50% predicted at visit one, males or females over 18 years of age, a positive reversibility (at least 15% improvement) to ipratropium bromide and salbutamol, and no evidence of an upper respiratory tract infection or the use of oral corticosteroids in the 3 months preceding screening day. All patients gave informed written consent, and the study was approved by the Tayside Committee for Medical Research Ethics.

### Laboratory testing

At each visit blood was taken for estimation of eosinophil catatonic protein (ECP) using a UniCAP100 (Pharmacia, UK).

### Body plethysmography

Body plethysmography was performed using an Autolink Whole Body Plethysmograph (PK Morgan, Kent, UK). Two repeatable tests performed were airway resistance and