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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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 $\mu$g daily, and were subsequently randomised to 4 weeks of either (a) HFA-fluticasone propionate 500 $\mu$g BD/salmeterol 100 $\mu$g BD/HFA-tiotropium bromide $18 \mu$g od; or (b) fluticasone propionate 500 $\mu$g BD/salmeterol 100 $\mu$g 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$_2$O/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.

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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...
steroid resistant asthma is rare, with an incidence of 1 in 1000 to 1 in 10,000 asthmatic patients, 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-1x and TNF-α), or by high doses of β2 agonists (due to inactivation of glucocorticoid receptors by β2 agonist activated cyclic adenosine monophosphate response binding element).

Progressive airflow obstruction occurs in severe asthmatic patients, the exact mechanism of this deterioration is not known, however it may be due to airway remodelling secondary to uncontrolled chronic airway inflammation. 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, and bone demineralization. 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 β2 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 β2 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 (Boehringer Ingelheim, Bracknell, UK) or the reverse order. FEV1 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 (FEV1) < 65% predicted, FVC < 80% predicted, FEF25-75 < 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
SVG/TLC using the panting method with cheek support and tidal breathing. Patients were trained in the technique prior to measurements.

Exhaled NO

Patients underwent exhaled nitric oxide (NO) measurement using an integrated LR2000 clinical real-time NO gas analyser under standardised conditions.\(^\text{14}\) The normal cut off value for patients in our laboratory is < 6 parts per billion.

Pulmonary function

Spirometry was performed according to American Thoracic Society criteria\(^\text{15}\) using a Micro Medical SuperSpiro (Micro Medical Ltd, Rochester, UK). FEV\(_1\) was measured in triplicate, the highest being used.

Mini juniper quality of life questionnaires (Mini-AQLQ)

At each visit a Mini AQLQ\(^\text{16}\) was given out to be self-administered by the patient to assess their quality of life scores during the study.

Domiciliary diaries

Domiciliary PEF was measured twice daily throughout the study using a Mini-Wright peak flow meter (Clement Clarke, Essex, UK); the best of 3 measurements was recorded. Diurnal reliever use and symptom scores on a 0–3 scale, ranging from 0 meaning no symptoms to 3 meaning severe symptoms, were recorded.

Statistical analysis

A total 16 completed patients were required to achieve 80% power to detect a 15% difference in FEV\(_1\) between treatments in this cross-over study. Absolute values were compared by multifactorial analysis of variance over all three treatments: (a) fluticasone 1000 \(\mu\)g daily alone (FP1000); (b) fluticasone 500 \(\mu\)g/salmeterol 100 \(\mu\)g daily/placebo (FP/SM/PL); and (c) fluticasone 500 \(\mu\)g daily/salmeterol 100 \(\mu\)g daily/tiotropium18 \(\mu\)g OD (FP/SM/TIO).

Where an overall significant difference was found, pair-wise comparisons were carried out, with Bonferroni correction for multiple range testing. Thus, pair-wise comparisons are quoted as being either significant (\(p < 0.05\), two tailed) or not. Statistical analysis was performed using SPSS\(^\text{c}\) version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Twenty-six patients were initially enrolled into the study of which 18 (11 males) completed (mean age 54, SEM 2.44). Demographic data for all patients are given in Table 1. Pulmonary function results following all treatments are shown in Fig. 2 and Table 2. Adequate treatment periods prior to assessment lead to no carry over effects for any outcome measure.

 Screening visit and baseline

The conversion of patients from their regular ICS dosing (mean 782 \(\mu\)g/day, SEM 96) to fluticasone propionate 1000 \(\mu\)g daily did not significantly improve any outcome measure.

Reversibility

Acute responses (Fig. 3)

The sequence of salbutamol then ipratropium gave 8.6 (0.45–16.76)% (\(p < 0.05\)) more improvement in FEV\(_1\) than the opposite sequence.

The FEV\(_1\) response to salbutamol alone [i.e., given first in sequence] was 22.6 (4.1) as % change, while the FEV\(_1\) response to ipratropium alone [i.e., given first in sequence] was 17.6 (3.7) as % change, with no significant difference between sequences. Corresponding data for FVC showed a...
### Table 1 Demographics.

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Figure 2 Pulmonary function results as FEV\(_1\)% predicted for all treatments. FP 1000—fluticasone 1000\(\mu\)g daily; FP 500/SM/PL—fluticasone 500\(\mu\)g daily, salmeterol 50\(\mu\)g BD and placebo BD; FP 500/SM/TIO—fluticasone 500\(\mu\)g daily, salmeterol 50\(\mu\)g BD and tiotropium 18\(\mu\)g OD. *Denotes a difference of \(p < 0.05\).
significant difference ($p<0.05$) between the first and second drug irrespective of sequence.

The addition of salbutamol to ipratropium conferred a 7.47 (1.89–13.05)\% ($p<0.05$) improvement in FEV$_1$. The addition of ipratropium to salbutamol conferred a 7.24 (3.46–11.02)\% ($p<0.05$) improvement in FEV$_1$.

**Acute vs. chronic response**
The acute response in FEV$_1$ of a single dose of salbutamol was compared to the chronic response to fluticasone propionate 500 $\mu$g daily and salmeterol (Fig. 4). The mean (95\% CI) difference in acute vs. chronic response was 9 (1.5–16.6)\% predicted ($p<0.05$) in favour of the response to salbutamol. The mean difference in FVC was 10.4 (1.66–19.1)\% predicted ($p<0.05$) in favour of the response to salbutamol.

Similarly, the acute response in FEV$_1$ to salbutamol and ipratropium given to patients receiving fluticasone propionate 1000 $\mu$g daily was compared with the chronic response to fluticasone propionate 500 $\mu$g daily plus salmeterol and tiotropium (Fig. 4). The mean (95\% CI) difference in response was 13.7 (0.6–28.0)\% predicted ($p<0.05$) in favour of the response to salbutamol and ipratropium. The mean difference in FVC was 11.4 (2.8–20.0)\% predicted ($p<0.05$) in favour of the response to salbutamol and ipratropium. Individual data are shown in Fig. 5.

**Chronic dosing effects on spirometry and peak flow**
In comparison with baseline measurements after fluticasone 1000 $\mu$g daily, halving the dose of fluticasone to 500 $\mu$g daily in conjunction with salmeterol 100 $\mu$g daily and placebo or fluticasone 500 $\mu$g daily plus salmeterol 100 $\mu$g daily plus tiotropium 18 $\mu$g daily, resulted in significant improvements in morning and evening domiciliary peak expiratory flow (PEF) (Fig. 6). The mean (95\% CI) improvement in morning PEF was 41.5 (14.4–68.6) l/min ($p<0.01$) and 55.3 (31.97–78.7) l/min ($p<0.01$) (FP/SM/PL and FP/SM/TIO, respectively). The mean (95\% CI) improvement in evening PEF was 37 (12–63) l/min and 44 (26–62) l/min ($p<0.01$) (FP/SM/PL and FP/SM/TIO, respectively).

The triple combination of FP/SM/TIO resulted in mean (95\% CI) improvements FEV$_1$ of 0.17 (0.03–0.31) l ($p<0.05$), 6.8 (0.8–12.8)\% predicted ($p<0.05$); and FVC of 0.24 (0.06–0.42) l ($p<0.05$), 7.4 (1.87–13.02)\% predicted ($p<0.05$) compared with fluticasone 1000 $\mu$g daily (Fig. 2). There were no significant differences between the double and triple therapy combinations for any outcome measures.

**Effects on body plethysmography outcomes**
Data for 17 patients were analysed, due to malfunction of the body plethysmograph for patient 19 at visit 1. Body
plethysmography results are shown in Table 3. There was a significant reduction in RAW% predicted after FP/SM/PL: 32.87% (CI 2.4–63.4) (p < 0.05) and after FP/SM/TIO: 34% (CI 6.7–61.3) (p < 0.05) when compared with FP 1000 daily. There were no significant differences in RV or TLC for the same comparisons.

Exhaled NO, ECP and Mini AQLQ

There was a significant reduction in exhaled NO values following treatment with FP/SM/TIO compared with FP 1000 of 2.86 ppb (CI 0.12–5.6) (p < 0.05). There was no significant difference in ECP values, or in any of the domains for the Mini-AQLQ with any treatment (Table 4).

Discussion

The present study shows that the concept of safe step down of inhaled corticosteroids with the addition of long acting bronchodilators can be supported in this severe cohort of patients: the addition of salmeterol alone to half the dose of fluticasone afforded small, but significant improvements in PEF and RAW, however the addition of salmeterol and tiotropium to half the dose of fluticasone also afforded further significant improvements in FEV1, FVC and eNO. These improvements were not associated with commensurate improvements in quality-of-life scores.

The initial run-in for the present study involved optimisation of anti-inflammatory treatment by the administration of 1000 µg daily of fluticasone propionate. At screening, the mean dose of inhaled corticosteroid was 782 µg daily of CFC-BDP equivalent, yet despite increasing this dose to an equivalent daily dose of 2000 µg CFC-BDP (i.e., fluticasone 1000 µg daily) during the run in, there were no significant improvements in any pulmonary function, body plethysmography or quality-of-life measures when comparing values pre- vs. post-fluticasone run in. It is likely, therefore, that this group of patients did demonstrate a significant degree of relative steroid resistance, particularly as they were shown to have significant improvements in FEV1 and FVC when maximally bronchodilated. Current guidelines advocate that optimising steroid therapy is important in this severe cohort of patients; however, our findings suggest that there is little benefit in using a 1000 µg daily dose of fluticasone propionate in severe asthmatics, but it is known that there are significant effects on the hypothalamic–pituitary–adrenal axis at this dose.12

It is clear that the use of long-acting bronchodilating therapies gives symptomatic improvement at all severities of asthma. Lemanske et al.17 showed that adding salmeterol during ICS step down improves lung function, but had no effect on exacerbations in patients with moderate to severe asthma, and Van Noord et al.18 showed that adding salmeterol to fluticasone propionate was as effective as doubling the dose of fluticasone, in terms of pulmonary function and exacerbations, in moderate to severe asthmatic patients. However, Currie et al showed that adding salmeterol to fluticasone propionate is inferior to doubling the dose of fluticasone propionate, in terms of inflammatory markers.19 In the present study, PEF was improved by stepping down ICS dose with salmeterol, and there was no deterioration in inflammatory

Figure 4  Acute vs. chronic dosing as % change in FEV1 from fluticasone propionate 1000 µg daily, FP 1000/Salb—fluticasone 1000 µg daily plus 400 µg salbutamol; FP 500/SM/PL—fluticasone 500 µg daily, salmeterol 50 µg BD and placebo BD; FP 1000/Salb/Ipr—fluticasone 1000 g daily plus 400 µg salbutamol and 80 µg ipratropium bromide; FP 500/SM/TIO—fluticasone 500 µg daily, salmeterol 50 µg BD and tiotropium 18 µg OD. *Denotes a difference of p < 0.05.
surrogates (ECP and eNO), indeed there was a non-significant trend towards improvement in eNO in the salmeterol alone arm.

The addition of long-acting $\beta_2$-agonists to corticosteroid treatment has been shown to improve measures of pulmonary function.\textsuperscript{20-24} In these studies, the selected patients had marked salbutamol reversibility, which is similar to the present study (22% salbutamol reversibility). We, too, have shown a 12% improvement in FEV\textsubscript{1} after the addition of salmeterol to fluticasone propionate 500 $\mu$g daily, compared with the post run in baseline value of fluticasone propionate 1000 $\mu$g daily, however the patients' % predicted FEV\textsubscript{1} in the present study was lower than other previous studies. Despite this, the lack of concomitant improvement in quality-of-life

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\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Individual data for comparison of acute and chronic bronchodilator effects. FP1000/Salb—fluticasone 1000 $\mu$g daily and salbutamol 400 $\mu$g; FP500/SM/PL—fluticasone 500 $\mu$g daily, salmeterol 50 $\mu$g BD and placebo BD. FP1000/Salb/Ipr—fluticasone 1000 $\mu$g daily, salbutamol 400 $\mu$g and ipratropium 80 $\mu$g; FP 500/SM/Tio—fluticasone 500 $\mu$g daily, salmeterol 50 $\mu$g BD and tiotropium 18 $\mu$g OD.}
\end{figure}
improvements in our patients, perhaps suggests that there is little clinical benefit to be had from maximally bronchodilating patients with severely impaired lung function, although much larger studies would be required to confirm our preliminary findings.

Although there is speculation over the anti-inflammatory effects of long acting beta agonists\(^8,25,26\) there is conflicting data, showing that surrogates of inflammation are not improved by the addition of salmeterol. There is, indeed, evidence to show that halving the dose of fluticasone in

![Figure 6](image)

**Figure 6** Mean Peak Flow Rates following 4 weeks of treatment. FP 1000—fluticasone 1000μg daily; FP 500/SM/PL—fluticasone 500μg daily, salmeterol 50μg BD and placebo BD; FP 500/SM/TIO—fluticasone 500μg daily, salmeterol 50μg BD and tiotropium 18μg OD. *Denotes a difference of p<0.05.

### Table 3
Mean (SEM) body plethysmography values for airway resistance (RAW), residual volume (RV), and total lung capacity (TLC).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FP 1000</th>
<th>FP500/SM/PL</th>
<th>FP500/SM/TIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAW (cm H(_2)O l/s)</td>
<td>3.88 (0.34)</td>
<td>2.96* (0.27)</td>
<td>2.97* (0.10)</td>
</tr>
<tr>
<td>RAW (%)</td>
<td>149.3 (12.2)</td>
<td>116.67* (12.5)</td>
<td>115.3* (15.9)</td>
</tr>
<tr>
<td>RV (L)</td>
<td>4.44 (0.31)</td>
<td>4.38 (0.41)</td>
<td>3.87 (0.23)</td>
</tr>
<tr>
<td>RV (%)</td>
<td>235.4 (16.1)</td>
<td>231.8 (21.8)</td>
<td>205.8 (13.2)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>7.46 (0.38)</td>
<td>7.84 (0.3)</td>
<td>7.2 (0.28)</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>136.8 (5.5)</td>
<td>145.2 (6.2)</td>
<td>133.2 (5.2)</td>
</tr>
</tbody>
</table>

*Denotes a difference from FP1000 of p<0.05. FP—fluticasone propionate (doses in μg daily); SM—salmeterol (50μg BD); PL—placebo; TIO—tiotropium (18μg OD).

### Table 4
Mean (SEM) quality-of-life scores for each domain and for overall score.

<table>
<thead>
<tr>
<th></th>
<th>FP1000</th>
<th>FP500/SM/PL</th>
<th>FP500/SM/TIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.0 (0.32)</td>
<td>5.3 (0.35)</td>
<td>5.3 (0.35)</td>
</tr>
<tr>
<td>Activity</td>
<td>5.4 (0.45)</td>
<td>5.6 (0.4)</td>
<td>5.6 (0.4)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>5.0 (0.37)</td>
<td>5.4 (0.3)</td>
<td>5.4 (0.31)</td>
</tr>
<tr>
<td>Emotions</td>
<td>4.6 (0.36)</td>
<td>5.0 (0.49)</td>
<td>5.1 (0.44)</td>
</tr>
<tr>
<td>Environment</td>
<td>4.6 (0.36)</td>
<td>5.0 (0.4)</td>
<td>5.0 (0.4)</td>
</tr>
</tbody>
</table>

*Denotes a difference from FP1000 of p<0.05. FP—fluticasone propionate (doses in μg daily); SM—salmeterol (50μg BD); PL—placebo; TIO—tiotropium (18μg OD).
combination with salmeterol leads to a significant deterioration in inflammation, despite maximising pulmonary function. In the present study, there was a significant difference between exhaled nitric oxide levels (eNO) in the FP/SM/TIO limb of the study compared to baseline of FP1000 μg daily, which is interesting considering the dose of ICS was halved. It has been shown that the dose response of eNO to inhaled corticosteroid reaches plateau at 800 μg CFC-BDP equivalent (400 μg daily FP); which may explain the effective suppression of eNO. There was also a non-significant trend towards suppression of eNO in the FP/SM limb of the study. Perhaps this is further evidence that the bronchodilating drugs may have an anti-inflammatory action in asthmatic patients. We analysed exhaled nitric oxide, however recent evidence advocates the use of alveolar NO as a better assessment of inflammatory status in asthma.

The parasympathetic nervous system is dominant in control of airway smooth muscle tone, and despite the abundance of β2 adrenoceptors within the smooth muscle, no sympathetic nervous system innervation of the airway smooth muscle cells has been proven. As such there is a role for anticholinergic drugs in the management of chronic airway constriction. Anticholinergic therapy has been utilised in the management of chronic obstructive pulmonary disease (COPD) in the form of short- and long-acting moieties. Recently developed long-acting anticholinergic tiotropium bromide has been shown to confer positive effects of pulmonary function and quality of life in patients with COPD. Although there is little evidence, and no license, for pulmonary function and quality of life in patients with COPD, it has been shown to confer positive effects of pulmonary function and quality of life in patients with COPD. COPD and severe asthma with airway remodelling have similar pathophysiological features, and may have a common predisposition—the use of additional bronchodilation in severe asthma may give rise to similar improvements in pulmonary function and quality of life. We chose to evaluate tiotropium as add on to fluticasone and salmeterol, rather than fluticasone alone, as current guidelines advocate the use of the ICS and LABA combination for the sever cohort of patients. The rationale for use of tiotropium was to produce additive effect, rather than to replace the use of LABA in this group.

We did not show any effect of sequence on the response to randomised treatments, in terms of whether Tiotropium was given prior to or after placebo. This is to be expected given that the half life of tiotropium is 24 h, with five half lives being required to washout the drug, as compared to the 4 weeks period for each randomised treatment.

To assess the potential benefit of adding a long acting β2 agonist and anticholinergics to ICS we assessed the effect of short acting variants. Treatment with salbutamol led to an improvement in FEV1 of 22 %, however further treatment with ipratropium led to a further, significant increase in FEV1, and FVC. Thus, the ceiling for bronchodilation is not reached by salbutamol alone, giving room for further therapeutic benefit on an individual patient basis. Despite the significant additive acute effect of ipratropium to salbutamol, this was not reflected by any significant improvement in any outcome measure when tiotropium was added to salmeterol during chronic dosing, in patients receiving fluticasone propionate 500 μg daily. Moreover, the acute response to salbutamol alone or salbutamol plus ipratropium in patients taking fluticasone propionate 1000 μg daily was found to be significantly greater than the chronic response to salmeterol alone or salmeterol plus tiotropium in patients taking salmeterol plus ipratropium 300 μg daily. This in turn suggests that acute reversibility testing with short acting bronchodilators may not predict the magnitude of chronic dosing response to long acting bronchodilators. Salbutamol has a relative intrinsic efficacy of 0.8 with respect to isoprenaline at the β2 receptor, whereas salmeterol has a relative intrinsic efficacy of 0.4, explaining why there may be larger response to salbutamol over salmeterol. Tiotropium is a selective anti-cholinergic treatment, more selective for M1 and M3 receptors than ipratropium, and dissociates more rapidly from the M2 receptor, thus releasing the “Brake” on adrenergic smooth muscle relaxation that can occur with non-selective anti-cholinergic blockers. Thus, one might expect that the tiotropium response would if anything be greater than the ipratropium response. In this respect Van Noord found tiotropium OD to be more effective than ipratropium QDS, in terms of FEV1 in COPD, however this has not been shown to be the case in asthma, and our data refutes this assertion.

It is interesting that during the acute reversibility testing, there was a larger response to the bronchodilator given first, regardless of drug. It is known that there are pre-junctional β2 receptors on cholinergic nerves that act to attenuate airway cholinergic tone. Thus, β2 agonists have a dual mechanism—by direct stimulation of β2 receptors on bronchial smooth muscle cells and indirectly by down-regulating cholinergic tone. If salbutamol is given first, the subsequent ipratropium has less effect due to the partial blockade of cholinergic transmission by prior salbutamol. However, if ipratropium is given first, cholinergic transmission is completely blocked, thus the subsequent salbutamol dose has only a single effect, directly on smooth muscle β2 receptors. Also the blockade of M3 receptors caused by ipratropium effectively “brakes” the effect of adrenergic agonism.

The results from acute reversibility testing with short acting β2 agonists and short acting anti-cholinergics did not predict which patients would have a similar response to either salmeterol or tiotropium, therefore we do not recommend withholding either medication due to lack of response to the short-acting moieties.

One could postulate that, in patients with severe asthma, the magnitude of the bronchodilator signal from effort independent tests of pulmonary function may be greater than those which are effort dependent, as effort dependent closure of small airways may significantly alter results in forced expiratory manoeuvres. This may be seen on the expiratory flow volume loops of our patients, who all had severe volume dependent airway closure with a mean FEF25–75 of 30 % predicted. In the present study, the use of body plethysmography provided no additional benefits over conventional effort-dependent forced expiratory manoeuvres in terms of detecting a signal from additional bronchodilator therapy. In both treatment limbs within the study there was improvement in RAW, however this was matched by similar improvements PEF and, for salmeterol and tiotropium, FEV1 and FVC were also significantly improved. Body plethysmography requires expensive equipment, expertise in its use and is time consuming. If it does not appear to add to simple measures of pulmonary function, its use in routine clinical practice is cast into doubt.
Our patient cohort had severe asthma with markedly impaired airway calibre (FEV1 = 51% predicted, FVC = 65% predicted, FEF25–75 = 30% predicted, PEF = 63% predicted). There have been few studies examining the effects of long-acting bronchodilators in this cohort of patients. It is known that severe asthmatic patients develop irreversible airway obstruction as a consequence of long-standing active inflammation. The airways of these patients progress to obstruction as a consequence of long-standing active inflammation. There have been few studies examining the effects of long-acting bronchodilators in this cohort of patients. It is known that severe asthmatic patients develop irreversible airway obstruction as a consequence of long-standing active inflammation. The airways of these patients progress to obstruction as a consequence of long-standing active inflammation.  

Although there was no demonstrable change in quality of life endpoints during the study, the numbers of subjects were small, as the study was not powered on these outcomes. The severe asthmatic population have significant co-morbidity, and it is possible that improvements in asthma-related quality of life may be masked by overall ill health and poor quality of life. A longer, larger study would be indicated to demonstrate any improvement in subjective quality of life. During the study, 8 patients dropped out due to exacerbations of asthma. This is clearly a major problem in the severe cohort of patients. A longer term study, powered on exacerbation rate, may elucidate further benefits of triple therapy for asthma which this study could not.

In conclusion, the addition of salmeterol and tiotropium in association with halving the dose of fluticasone propionate in severe asthmatics leads to small improvements in effort dependent and independent pulmonary function outcomes, but not quality-of-life scores. There may be a role for tiotropium in the management of severe asthmatics, and may facilitate the reduction of inhaled corticosteroid doses, reducing side effects. The magnitude of improvements in pulmonary function provided by salmeterol and tiotropium were not predicted by the acute reversibility to salbutamol and ipratropium.

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References


