

# Sequential comparison of tiotropium to high-dose ipratropium in patients with chronic obstructive pulmonary disease in a practice setting

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**Objective:** To determine the effect of changing anticholinergic therapy in patients with COPD from ipratropium to tiotropium on pulmonary function.

**Methods:** We examined records of patients prescribed high-dose ipratropium, who were subsequently converted to tiotropium. Spirometric values were obtained within 2 days of the change in medication and after 56 to 224 days of the switch to tiotropium.

**Results:** 15 subjects were documented to have filled a prescription for ipratropium-containing medications the month prior to the change. Medication compliance over the 6 months prior to the switch in these patients was  $72\% \pm 31\%$  (mean  $\pm$  SD) for ipratropium compared to  $87\% \pm 14\%$  for tiotropium over the 6-month period after the switch ( $P = 0.1$ ). FEV<sub>1</sub> improved from  $1.12 \pm 0.39$  L at baseline to  $1.37 \pm 0.49$  L after the change to tiotropium ( $P = 0.01$ ). FVC also improved from  $2.45 \pm 0.73$  L at baseline to  $2.72 \pm 0.69$  L after the change ( $P = 0.04$ ). Maximal voluntary ventilation was also increased from  $39.67 \pm 10.7$  L/min to  $45.13 \pm 15.8$  L/min ( $P = 0.045$ ).

**Conclusions:** We conclude that replacing high-dose ipratropium with tiotropium therapy significantly improves pulmonary function in a clinical setting.

**Keywords:** ipratropium, tiotropium, COPD, pulmonary function, exacerbation rate

## Introduction

To date only smoking cessation or long-term oxygen therapy in patients with chronic obstructive pulmonary disease (COPD) and resting hypoxemia have been shown to impact mortality in this disorder.<sup>1,2</sup> However, some pharmacologic therapies impact a number of clinical parameters in patients with COPD.<sup>2,3</sup> Currently there are 2 available inhaled anticholinergic medications, ipratropium and tiotropium, which improve air flow in patients with COPD. Tiotropium has a prolonged duration of action ( $>24$  hours) compared to ipratropium.<sup>3</sup> A recent study has suggested tiotropium is cost-effective compared to ipratropium.<sup>4</sup> Tiotropium has been shown to improve 1) forced expiratory volume in 1 second (FEV<sub>1</sub>),<sup>3</sup> 2) quality of life, and 3) exercise capacity and dyspnea compared to subjects treated with placebo or ipratropium.<sup>5</sup> Although these premarketing studies suggested an advantage of tiotropium over ipratropium in treatment of COPD patients there has not been any report of the effects of changing from ipratropium to tiotropium therapy in COPD patients followed in a general clinical setting.

## Methods

### Selection of subjects

Clinical records were reviewed of patients followed in a specialized clinic for COPD at the Birmingham VAMC who were previously treated with a regimen that contained

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high-dose ipratropium. This included use of the combination metered dose inhaler containing ipratropium (21 µg per puff), and albuterol (120 µg per puff), 2 puffs 4 times a day followed by ipratropium metered dose inhaler (MDI) (18 µg per puff) 4 inhalations 4 times a day. This resulted in a total of 456 µg of ipratropium inhaled each day. Patients were subsequently changed to tiotropium 18 µg capsule inhaled daily with albuterol MDI when necessary. Records of 24 subjects who had spirometry performed on the day of the change from ipratropium to tiotropium were further examined. Four of these subjects had evidence of a COPD exacerbation on the day of the switch and were not evaluated leaving 20 subjects for further evaluation. When only subjects were included who had refilled the prescription for ipratropium containing medications in the month prior to the switch, to minimize noncompliance as a complicating issue, a total of 15 remained for final evaluation.

### Calculation of medication compliance

The records of prescription refills were examined for each of the 15 subjects and the number of prescription refills of ipratropium over the 6 months prior to, or tiotropium over the 6 months after the switch were determined. The percentage of compliance with the respective medication was calculated by the number of months the medication was refilled in those 6 months. If the subject refilled the medication 6 times (all prescriptions were 1 month supply at a time) compliance was calculated as 100%.

### Pulmonary function testing

Spirometry was performed by American Thoracic Society guidelines.<sup>6</sup>

### Statistical analysis

Differences between means were determined by T test. A *P* value less than 0.05 was considered significant.

## Results

### Subjects and medication compliance

Table 1 shows demographics of the 15 subjects in the study. Of the total number of subjects 15 patients had stage III, 2 subjects had stage IV and 4 subjects had stage II COPD as defined by GOLD.<sup>7</sup> All but 1 of the subjects had quit smoking. The average age for the 14 males and 1 female was 69.53 years. Compliance for anticholinergic use was 72% ± 31% (mean ± SD) for ipratropium 6 months prior to the switch compared to 87% ± 14% for tiotropium over the 6 month period after change in medication (*P* = 0.1). All patients were using the combination salmeterol/fluticasone inhaler Advair<sup>®</sup> during the month prior to the anticholinergic switch and through the entire period of the study.

### Pulmonary function testing

Figure 1 shows individual data for the FEV<sub>1</sub> (A) and FVC (B) determined in the 15 subjects at baseline and after the change to tiotropium. FEV<sub>1</sub> increased by an average of 155 mL (12.8%) (*P* = 0.01). Five of the 15 subjects showed

**Table 1** Characteristics of subjects at baseline

Subject no.	Age	Gender	Smoking status	FEV <sub>1</sub> (%pred)	FVC (%pred)	Comorbidities
1	73	M	Former	1.11 (35)	2 (46)	PUD, GERD, HL
2	81	M	Former	1.41 (50)	1.72 (40)	PUD, A Fib, CAD
3	67	M	Former	0.49 (14)	1.4 (30)	UC, Psoriasis, DM, GERD
4	71	M	Former	1.00 (36)	2.28 (60)	BPH, OSA, CAD
5	76	M	Former	0.87 (30)	2.43 (60)	CAD, Cataracts
6	67	M	Former	0.84 (27)	1.53 (36)	HTN, HL
7	59	M	Former	1.14 (32)	2.43 (52)	HTN, OP, OSA, HT, HL
8	60	F	Current	1.40 (56)	1.74 (58)	Depression, DM, HTN, HL
9	73	M	Former	1.78 (54)	4.06 (88)	DVT, OP, HL, ASCVD
10	77	M	Former	0.98 (32)	2.3 (53)	GERD, HTN, Bladder Ca
11	78	M	Former	1.27 (44)	3.16 (77)	HTN
12	64	M	Former	2.07 (64)	3.1 (71)	CAD, HL, GERD, Psoriasis
13	70	M	Current	1.53 (49)	2.54 (59)	OP, HTN, GERD, CAD
14	63	M	Former	1.03 (31)	2.9 (65)	HTN, BPH, HL
15	64	M	Former	1.26 (39)	3.16 (73)	DM, HTN, HL, GERD

**Abbreviations:** A fib, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BPH, benign prostatic hypertrophy; CAD, coronary artery disease; DM, diabetes mellitus; DVT, deep vein thrombosis; GERD, gastroesophageal reflux disease; HL, hyperlipidemia; HT, hyperthyroidism; HTN, hypertension; OP, osteoporosis; OSA, obstructive sleep apnea; PUD, peptic ulcer disease; UC, ulcerative colitis.

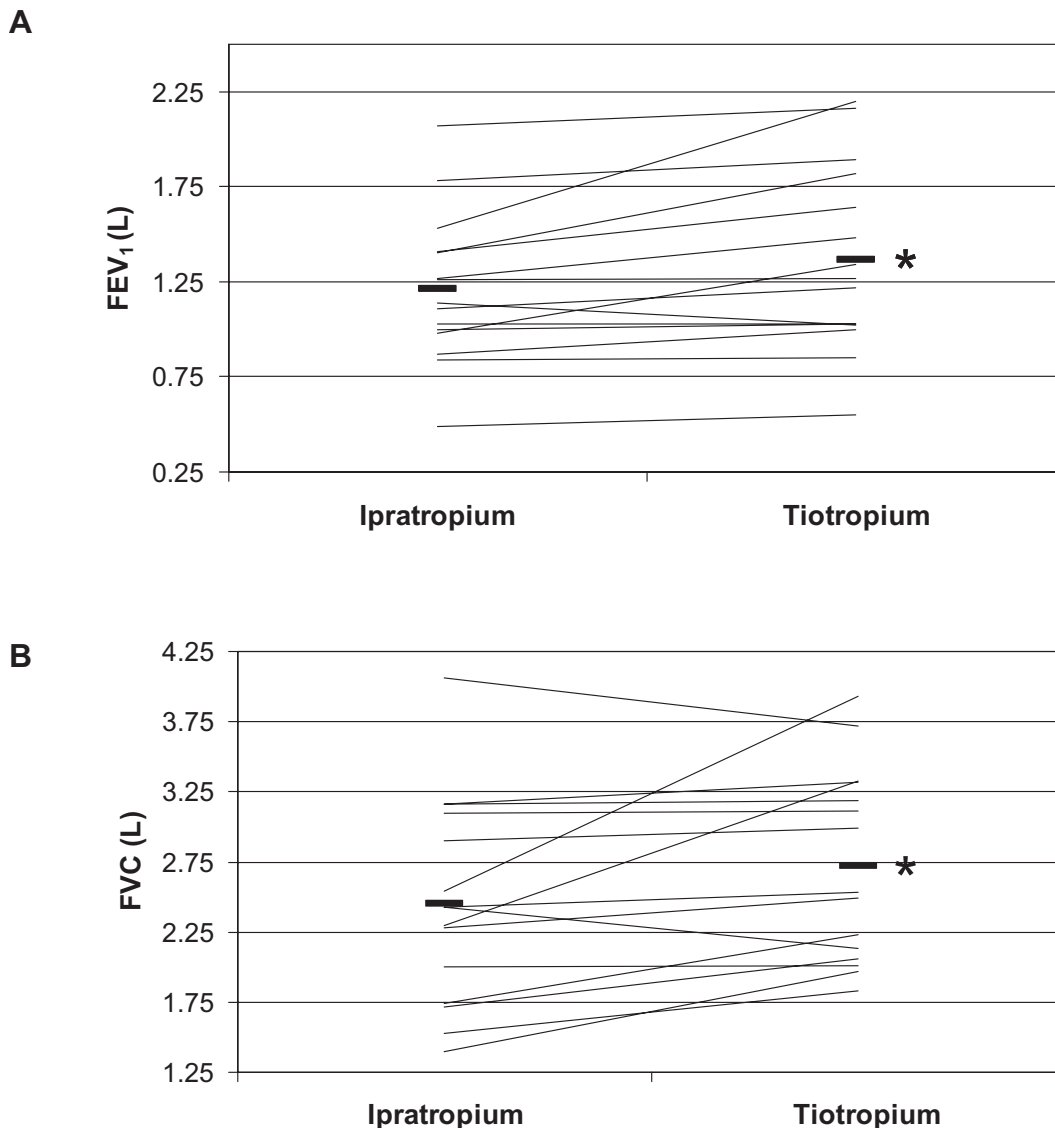
an improvement of over 200 mL in FEV<sub>1</sub>. FVC also improved by an average of 273 mL (11.1%)  $P = 0.04$ . Maximal voluntary ventilation improved 5.46 L/min, an average of 13.8% ( $P = 0.045$ ) (data not shown).

## Discussion

Our study suggests replacing high-dose inhaled ipratropium with tiotropium significantly improves FVC and FEV<sub>1</sub>. The effect on FEV<sub>1</sub> suggests tiotropium has an advantage in improving airflow compared to high-dose ipratropium while effects of the change on FVC may be due to lessened air trapping.

A number of premarketing studies suggested tiotropium provides better bronchodilation compared to ipratropium

administered 4 times a day and salmetrol administered twice a day, as evidenced by peak FEV<sub>1</sub>, trough FEV<sub>1</sub> and area under the curve.<sup>3</sup> However, in all of these studies the comparator group was treated with a lower dose of ipratropium than was employed in the current study. Ikeda et al demonstrated that increasing doses of ipratropium up to 240 µg had progressively beneficial effects on exercise capacity and FEV<sub>1</sub>.<sup>8</sup> The dose of ipratropium used in our study at each single treatment time was 114 µg, less than the optimal dose demonstrated in that study but more than comparator ipratropium arms in premarket studies of tiotropium. However, in clinical practice use of a higher dose of ipratropium to achieve a dose of 160 µg at each dosing time would be problematic because of the large number of



**Figure 1** Effects of the switch from ipratropium anticholinergic therapy to tiotropium on FEV<sub>1</sub> (A) and FVC (B).

**Note:** \* $P < 0.05$  between the two treatments.

inhalations required per day and the cost of the number of inhalers required for that dose. To date, several more studies have demonstrated superior improvements in FEV<sub>1</sub>, FVC and FEV<sub>6</sub> with tiotropium compared to placebo, ipratropium and long-acting  $\beta_2$ -agonists.<sup>9–13</sup> Tiotropium was shown to improve FEV<sub>1</sub> regardless of the presence or absence of short-term improvement in FEV<sub>1</sub>.<sup>14</sup> Moreover, improvements in inspiratory capacity and FEV<sub>1</sub> with tiotropium in patients with hyperinflation are unrelated to small airway heterogeneity.<sup>15</sup> Tiotropium has also been shown to reduce dynamic hyperinflation resulting in improved exercise endurance.<sup>3,16,17</sup>

Tiotropium has an excellent safety profile with dry mouth and urinary retention being the only major adverse events.<sup>3,13,18–20</sup> The incidence of dry mouth was slightly greater than that seen with ipratropium.<sup>3</sup> However, the effect was mild and did not lead to cessation of therapy. Serious adverse events occurred with the same frequency as in the control group.<sup>3</sup> A recently published meta-analysis of 17 randomized controlled trials raised concerns about an increased risk of cardiovascular death, myocardial infarction and stroke among COPD patients with use of inhaled anticholinergics (ipratropium or tiotropium).<sup>21</sup> However, the UPLIFT study did not demonstrate any such risks with long-term use of tiotropium.<sup>22</sup>

Treatment with tiotropium is cost-effective compared to ipratropium.<sup>4,23</sup> In a retrospective pooled analysis of long-acting bronchodilators, treatment with tiotropium was shown to save US\$391 per year while gaining 13 quality-adjusted days compared with ipratropium.<sup>23</sup> Since hospitalizations due to COPD exacerbations account for up to 70% of the medical care costs for COPD patients, reduction in hospitalizations is a major reason for cost-effectiveness of treatment with tiotropium.<sup>24,25</sup>

Our study suggests that tiotropium 18  $\mu$ g in a once-daily regimen improves airway flow rates when compared to a previous regimen of 456  $\mu$ g of ipratropium per day. This, and previous studies, suggest an advantage of long-acting anticholinergic agent over short-acting ipratropium. Larger studies may be needed to determine the “real world” physiologic and economic effect of changing from ipratropium to tiotropium as anticholinergic therapy.

## Disclosures

Dr Cooper has been on the speakers' bureau for Boehringer Ingelheim, Pfizer and Glaxo Smith Kline pharmaceuticals in the past and has also performed clinical trials for each of these companies.

Dr Dransfield has been on the speakers' bureau for Boehringer Ingelheim, Pfizer and Glaxo Smith Kline pharmaceuticals and has performed clinical trials for these companies.

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