Effects of replacing oxitropium with tiotropium on pulmonary function in patients with COPD: A randomized study

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Summary

Background: Inhaled bronchodilators are first line drugs in the treatment of chronic obstructive pulmonary disease (COPD). Tiotropium bromide is a recently introduced long-acting anticholinergic agent able to reduce dyspnoea and COPD exacerbations and to improve pulmonary function and quality of life. We designed a study to compare the short-term efficacy of tiotropium bromide with that of oxitropium bromide in improving pulmonary function in patients with COPD.

Methods: Eighty patients were randomized either to continue oxitropium 800 mcg/day or to receive tiotropium 18 mcg/day. Seventy-six (39 in the tiotropium and 37 in the oxitropium group) completed the study. Plethysmography was performed at baseline and after 72 h in all patients. The changes in functional parameters in the two groups were compared by the Mann–Whitney U-test.

Results: There were no differences between the two groups regarding age (72.5 vs. 74.2 years), male/female ratio (25/14 vs. 23/14) and pulmonary function at baseline. The changes in spirometric parameters were significantly greater in tiotropium- than in oxitropium-treated patients: mean forced expiratory volume in 1 s (FEV₁) increased significantly by 15% vs. 3% (P = 0.017), mean FVC by 10.5% vs. 2.2% (P = 0.044), and FEF 25, 50, and 75 by 34% vs. 14% (P < 0.05), 33% vs. 7% (P < 0.05), and 50% vs. 6% (P < 0.0001), respectively; mean FRC and RV decreased nonsignificantly by 7.5% and 4% in tiotropium vs. 4.3% and 6.5% with oxitropium, respectively.

Conclusion: The replacement of oxitropium with tiotropium significantly increases pulmonary function in patients with COPD. The improvement involves also small airways that have not been investigated thus far.

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Introduction

Inhaled bronchodilators, namely β2-agonists and anticholinergic agents, are the mainstay of treatment for chronic obstructive pulmonary disease (COPD). They are able to improve symptoms and exercise capacity, and to decrease the frequency of COPD exacerbations.

Tiotropium bromide is a second-generation anticholinergic agent that is structurally related to ipratropium bromide. Its main distinguishing characteristic is slow dissociation from Hm1 and Hm3 muscarinic receptors, which results in sufficiently prolonged pharmacological activity to allow once daily administration. After the first dose, mean time to onset of its bronchodilating effect is 30 min and mean time to peak effect is about 3 h. Subsequent doses increase efficacy even further until maximum bronchodilating activity is achieved after 1 week.

A number of clinical studies have demonstrated the efficacy of tiotropium in reducing dyspnoea and COPD exacerbations and in improving quality of life. Moreover, significant effects on pulmonary function have been reported, namely increase in forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), and decrease in functional residual capacity (FRC), which indicates that the drug reduces lung hyperinflation.

The objective of this study was to assess short-term changes in pulmonary function, including small airways variables, in patients with COPD on treatment with another anticholinergic agent, oxicthropium bromide, during either continuation of treatment with oxicthropium bromide or replacement treatment with tiotropium bromide.

Materials and methods

Patients

Eighty patients referred to the Unit of Pulmonary Rehabilitation of the ICP Hospital in Milan were included in the study. To be included, patients had to be in stable conditions, with no exacerbations for at least 2 months, in GOLD stage 2–4 according to FEV1 values, and on treatment with only oxicthropium bromide as bronchodilator. Treatment with other bronchodilators or inhaled corticosteroids was an exclusion criterion. The patients were randomized either to continuation of treatment with oxicthropium (800 mcg daily) or to replacement of oxicthropium with tiotropium (18 mcg daily). In patients maintained on treatment with oxicthropium, the inhalation technique was optimized by using spacer devices, if they had not been already introduced. The need to inhale the drug every 6 h was stressed. Patients initiating treatment with tiotropium were instructed to use the dry powder inhaler device.

Methods

Pulmonary function

The FEV1, the FVC, the expiratory flows at low volumes (FEF 25, 50, and 75), the FRC, and the residual volume (RV) were measured by an automated pulmonary function testing center (6200 Autobox DL, Sensor Medics, Yorba Linda, CA, USA) in accordance with recognized standards. Variables were measured at inclusion and after 72 h: this interval was chosen to avoid confounding by pulmonary rehabilitation procedures. The last dose before repeat measurement was given 3 h before for oxicthropium and 1 h before for tiotropium.

Statistical analysis

The differences in the absolute changes of respiratory parameters between post- and pre-intervention in tiotropium- and oxicthropium-treated patients were analysed by the Mann–Whitney U-test, setting a P value lower than 0.05 as significant.

Results

Of the 80 patients included, four did not perform the second plethysmography, three (two in the oxicthropium and one in the tiotropium group) because they withdrew the informed consent and one (in the oxicthropium group) because family problems made compliance with the rehabilitation program difficult. Thus, 76 patients (39 in the tiotropium and 37 in the oxicthropium group) were evaluated for the study. Thirteen patients of the oxicthropium group did not use any spacer device and were instructed to use it. The baseline characteristics of the two treatment groups are shown in Table 1: the two groups were well matched.

The changes in each parameter vs. baseline are reported in Table 2. The increases in mean FEV1, FVC, and FEF 25, 50, and 75 were significantly higher in patients treated with tiotropium than in those treated with oxicthropium, whereas the decrease in mean FRC and RV was larger in tiotropium treated patients but did not reach statistical significance. This is depicted in Fig. 1.

Discussion

A considerable body of evidence collected following the introduction of tiotropium bromide into clinical practice makes it a first-line drug for the treatment of COPD. A recent meta-analysis of nine randomized controlled studies has clearly shown that the drug ameliorates...
symptoms and related quality of life, reduces the incidence of disease exacerbations and improves pulmonary function, as well as increasing exercise capacity.\textsuperscript{17} The improvement in spirometric parameters achieved with tiotropium was apparent not only as compared to placebo-treated patients,\textsuperscript{13,14} but also in subjects treated

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oxitropium</th>
<th>Tiotropium</th>
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<tr>
<td>Baseline</td>
<td>Post-treatment</td>
<td>% difference</td>
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<tr>
<td>FEV\textsubscript{1}</td>
<td>949 ± 301</td>
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<td>FVC</td>
<td>1917 ± 604</td>
<td>1980 ± 706</td>
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<td>FRC</td>
<td>4308 ± 1706</td>
<td>4577 ± 1648</td>
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<tr>
<td>RV</td>
<td>3689 ± 1444</td>
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<td>FEF\textsubscript{25}</td>
<td>1262 ± 905</td>
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<td>FEF\textsubscript{50}</td>
<td>541 ± 355</td>
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<tr>
<td>FEF\textsubscript{75}</td>
<td>178 ± 81</td>
<td>149 ± 110</td>
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**Table 2** Changes in mean values of functional parameters in patients treated with oxtropium and tiotropium.

**Figure 1** Changes in mean values of FEV\textsubscript{1}, FVC, FRC, and RV (A) and of FEF\textsubscript{25}, 50, and 75 (B) in patients treated with oxtropium and tiotropium.
with other bronchodilators. For example, the early increase in mean FEV₁ in patients treated with tiotropium was significantly higher compared to those treated with the long-acting β₂-agonist salmeterol and an improvement in FEV₁ value was observed even in patients regularly treated with the other β₂-agonist formoterol. The superiority in respect of the first-generation anticholinergic ipratropium is made unmistakable by the meta-analysis, while to our knowledge no comparison with oxitropium is available. In respect to ipratropium, oxitropium has a longer pharmacological action which enables twice a-day dosing and is as effective as ipratropium in terms of the bronchodilating activity.

In the present study we compared the short-term effects on pulmonary function parameters of the introduction of tiotropium in patients with COPD, randomizing the subjects either to continue treatment with oxitropium—after optimizing the dosage and the inhaling technique—or to replace it with tiotropium. In oxitropium-treated subjects small increases in FEV₁, FVC, and FEF 25, 50, and 75 were found, as well as small decreases in FRC and RV, which were likely to be due to the optimization of treatment. The changes were greater in tiotropium-treated patients: mean FEV₁ increased significantly by 15% vs. 3% in oxitropium-treated patients, mean FVC by 10.5% vs. 2.2%, FEF 25 by 34% vs. 14%, FEF 50 by 33% vs. 7%, and FEF 75 by 50% vs. 6%. By contrast, mean FRC decreased nonsignificantly by 7.5% with tiotropium vs. 4.3% with oxitropium, and RV decreased nonsignificantly by 10% vs. 6.5%.

This degree of improvement is not unexpected, because even higher values were reported in placebo-controlled studies. For example, the first dose of tiotropium increased mean FEV₁ by 16% and mean FVC by 17% in patients with stable COPD. In a long-term study the addition of tiotropium to other standard drug treatments was able to increase mean FEV₁ up to 22% and mean FVC up to 12%. In our study, also the difference in FEF 25, 50, and 75 between tiotropium- and oxitropium-treated patients was significant: tiotropium produced larger increase in these parameters, as measured by FRC and RV, and did not achieve statistical significance; this may have been due to the short period of observation—3 days. This short period was planned to avoid confounding effects by the pulmonary rehabilitation protocol, but may have been not long enough to reach maximum improvement, which was achieved with tiotropium in other studies after 42 days and 28 days. A recent study showed that also shorter durations of treatment with tiotropium, starting from 1 week, are sufficient to significantly improve IC but not RV, and this offers support to our findings.

In conclusion, the results of our study confirm the greater efficacy of tiotropium in respect of previous generation anticholinergic agents in the treatment of COPD, and suggest that the drug possesses a significant effect on small airways thus far not investigated.

References


