Tiotropium administered by a pressurized metered dose inhaler (pMDI) and spacer produces a similar bronchodilator response as that administered by a Rotahaler® in adult subjects with stable moderate-to-severe COPD


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Summary

Background: Tiotropium is a new long-acting anticholinergic bronchodilator, which is recommended as first-line therapy in the management of chronic obstructive pulmonary disease (COPD). It is currently available in the form of a dry powder inhaler worldwide. Some COPD patients find it difficult to generate inspiratory flow rates of up to 40 l/min, which is required for the drug to reach the airways. To overcome this, a new pMDI form has been developed for administration of tiotropium in patients with COPD. The clinical efficacy of this mode of tiotropium delivery has, so far, not been compared with the currently available dry powder inhaler (DPI) devices.

Aims and objectives: To compare the bronchodilator effects of a single dose of 18 mcg of tiotropium administered via a pressurized meter dose inhaler (pMDI) and spacer with the currently available DPI form through Rotahaler®.

Study design: A randomized, double-blind, double-dummy, three-period, placebo-controlled, crossover, single-center study was conducted in 19 patients with stable COPD. Single doses of tiotropium (18 mcg) or placebo were administered on three separate study days (4–7 days apart) through a Rotahaler® and pMDI with a non-static spacer (Zerostat, Cipla Ltd.). During each study visit forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were measured over a period of 24 h at 11 different time points (0, 15, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h), using a bellows spirometer (Vitalograph®, 2160, UK) while static parameters like inspiratory capacity (IC), residual volume (RV), intrathoracic
Background

The cholinergic nervous system plays an important role in the pathophysiology of chronic obstructive pulmonary disease (COPD). Anticholinergic drugs are effective not only in relieving symptoms but also improve lung functions and exercise tolerance. They are therefore recommended as the bronchodilators of choice in COPD patients. Tiotropium is a newly introduced inhaled long-acting muscarinic subtype M1 and M3 receptor antagonist, which when administered once daily produces marked beneficial effects on several parameters such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), inspiratory capacity (IC), respiratory symptoms, exercise endurance and quality of life. Currently, tiotropium is available for inhalation only via dry powder inhaler (DPI) in many countries. Although most COPD patients are comfortable with this device, one of the drawbacks of using a DPI device is that it requires generation of sufficient inspiratory flow rates (at least 30–60 l/min) for adequate deposition of the drug into the airways. Many COPD patients, particularly those who have moderate-to-severe disease may find it difficult to generate these inspiratory pressures and therefore find it difficult to use the DPI device. In vitro deposition studies have suggested that care should be taken when shifting from one inhaler device to another because this may affect the actual dose delivered to the lung and therefore comparison between the efficacy of different inhaler devices is necessary to ensure appropriate therapeutic effect. We have currently developed a tiotropium formulation to be administered via a pMDI. The aim of this study was to compare the therapeutic efficacy of tiotropium delivered by a pMDI and spacer versus that administered by a DPI.

Materials and method

Subjects

Twenty-four stable moderate-to-severe COPD male and females subjects aged 40–70 years were recruited into this study. COPD was defined according to the Global Initiative of Obstructive Lung Disease (GOLD) criteria viz. current or ex-smokers with smoking history of at least 10 pack years or significant occupational exposure symptoms of chronic cough, sputum production, and breathlessness that is progressive and persistent in nature, and a post-bronchodilator FEV1/FVC ratio <0.7. Only subjects having an FEV1 of <65% predicted and a bronchodilator reversibility of at least 12% in FEV1, 30–45 min after 40 µg of ipratropium bromide were recruited in to the study. None of the subjects had received oral corticosteroids or had history suggestive of acute exacerbation for COPD for at least 4 weeks prior to the start of the study. Pregnant and lactating women and subjects with concomitant asthma, heart failure, cardiac arrhythmia, ischemic heart disease and liver disease were excluded from the study. Peripheral venous blood was analyzed for routine hemogram and biochemistry during the screening visit to rule out other associated disorders. Chest X-ray was obtained to rule out any active pulmonary disease or other concomitant diseases likely to affect the study, e.g. lung carcinoma, bronchiectasis and pneumonia. Intra-ocular pressure was measured in all subjects with a tonometer (Schioetz tonometer, Biso, Germany) to rule out associated glaucoma, and those having raised intra-ocular pressure were excluded from the study. The study was approved by the independent local ethics committee and a written informed consent was obtained from all study subjects prior to the start of the study. The study was conducted according to ICH-GCP guidelines.

Study design

Single doses of 18 mcg tiotropium [via pMDI plus spacer (Zerostat™ spacer, Cipla Ltd., India) and DPI (Rotahaler™, Cipla Ltd.), India] and placebo were administered on three separate days, at least 4 days apart, in this single-center study, in a randomized, double-blind, double-dummy, crossover manner. Care was taken to ensure that the subjects had avoided ipratropium for 12 h, short-acting β2 agonist for 6 h,
short-acting oral xanthines for 24 h and, long-acting \( \beta_2 \) agonist, long-acting oral xanthenes and oral leukotrienes for at least 72 h prior to each study visit. During the study visits, after determination of the baseline lung functions, the subjects received study medication in a random order, using a double-dummy technique. The medication was administered between 7.30 and 9.00 a.m. during all study visits. Subjects were asked to inhale tiotropium/placebo either through the DPI or pMDI according to the standard methods (one actuation of pMDI released 9 μg of tiotropium, therefore two inhalations were required). The pMDI was primed with two actuations before every inhalation. The subjects were trained for the proper inhalation technique and the study team monitored the study drug administration.

FEV\(_1\) and FVC were measured before and 15, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h after the study drug was administered using bellows spirometer (Vitalograph\textsuperscript{®} 2160, UK), while IC residual volume (RV), intrathoracic gas volume (ITGV) and total lung capacity (TLC) were measured using a bodyplethysmograph (Jaeger Master Screen, Germany) before and 3, 8 and 24 h (trough values) after administration of study medications (Figure 1). Repeatability and acceptability standards of lung functions were maintained according to American Thoracic Society (ATS) criteria by a trained lung function technician.

The primary efficacy variables used for analysis were mean maximum difference in FEV\(_1\) and FVC from baseline and FEV\(_1\) and FVC area under response curve over a period of 24 h. On the other hand, the secondary efficacy variables were the mean maximum difference in the IC from the baseline, mean maximum difference in the RV from the baseline, mean difference in ITGV from the baseline, mean difference in TLC from the baseline, time to onset of bronchodilator response and time to maximum bronchodilator response.

### Statistical analysis

Sample size estimation for this study was made using a PS (Power and Sample size) software version 2.1.31 (Vanderbilt, Canada). To achieve a power of 80% and show equivalence at the significance level of 5% with a clinically significant difference in FEV\(_1\) of 100 ml and a standard deviation of 150 ml, a sample size of 18 subjects was estimated. We enrolled 24 subjects into the study to cover for the dropouts.

Mean maximum change in FEV\(_1\) and FVC, the mean change from the baseline in IC and the mean change from the baseline in RV between the two formulations of tiotropium, were analyzed using paired t-test. Area under curve (AUC) was calculated for the absolute change in FEV\(_1\) and FVC from the baseline over the 24 h study period using the trapezoidal rule. The AUC was measured for each patient on each treatment regime. The AUCs between the two active medication periods were compared using analysis of variance (ANOVA). The confidence interval (CI) obtained from this was used for the Schuirmann’s two–one-sided test (TOST) of equivalence between the two active treatments. An improvement of more than 100 ml in FEV\(_1\) and 150 ml in FVC, IC, RV, ITGV and TLC were considered clinically significant as efficacy endpoints.

Time to onset of response was defined as the first time point after drug administration when a 100 ml increase in FEV\(_1\) and a 150 ml increase in FVC were achieved. The time point at which maximum response was observed during the 24 h study period was considered for time to maximum response.

### Results

Of the 24 subjects screened, 20 were randomized (4 subjects could not be randomized due to ischemic heart disease or refusal to follow up), and 19 subjects completed all the three study visits. One subject discontinued the study due to noncompliance. Of the 19 subjects who completed the study, 15 were chronic ex-smokers (mean smoking pack years of 17.6 years), 2 (both females) had a history of exposure to biomass fuel for 25–30 years and 2 had history of occupational exposures (both were working in road construction). The mean baseline FEV\(_1\) values were 0.769 ± 0.29 l. All of the subjects were on oral medications (salbutamol and theophylline) before the enrollment; none of them had used inhalation therapies before. The characteristics of study subjects are summarized in Table 1.

Single doses of 18 mcg tiotropium administered via pMDI with spacer and 18 mcg of tiotropium administered via DPI produced a significantly better time-dependent bronchodilator response as measured by AUC percentage change for FEV\(_1\) and FVC from the baseline when compared to placebo (p-values <0.01 for FEV\(_1\) and p-values <0.01 for FVC) (Figures 2 and 3). The mean difference of AUC for percent change in FEV\(_1\) and FVC between tiotropium delivered through pMDI plus spacer and DPI from baseline to 24 h were not significant [[(FEV\(_1\) AUC\(_{0-24h}\): 997 versus 1589 for pMDI plus spacer and DPI, respectively; p>0.05) (FVC AUC\(_{0-24h}\): 526 versus 421 for pMDI and DPI, respectively; p>0.05)] (Figures 2 and 3 showing AUC FEV\(_1\) % change and FVC % change, respectively), suggesting that 18 mcg of tiotropium delivered through pMDI plus spacer and 18 mcg of tiotropium delivered through DPI produced similar bronchodilator responses when measured over 24 h.

The mean maximum change from the baseline for FEV\(_1\) was 384.2 ml with pMDI plus spacer and 342.1 ml with DPI (Figure 4), while the mean maximum change from the baseline for FVC was 564.2 and 573.2 ml, respectively.

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**Figure 1** Study design.
These differences were not statistically significant, suggesting that 18 mcg of tiotropium delivered through pMDI and 18 mcg of tiotropium delivered through DPI produced an equivalent mean maximum increase in FEV₁ and FVC from the baseline values.

Tiotropium administered by pMDI plus spacer and DPI both produced a significant increase in the IC at the 3rd and the 8th hour, post-administration, when compared with placebo (pMDI plus spacer–placebo, 3rd hour \( p = 0.01 \) and 8th hour \( p = 0.049 \); DPI–placebo, 3rd hour \( p = 0.006 \) and 8th hour \( p = 0.03 \)) (Figure 6). On the other hand, RV (Table 2), ITGV and TLC did not show any significant reduction with tiotropium administered via pMDI plus spacer and DPI versus placebo, at any time point.

Tiotropium delivered by pMDI took 5.58 and 5.52 h to reach maximum FEV₁ and FVC response, while tiotropium delivered through DPI took 6.42 and 5.34 h, respectively. These differences were not statistically significant when compared to each other (\( p = 0.61 \)). The time to onset of bronchodilator response (increase of at least 100 ml FEV₁ from the baseline) for pMDI was 28.21 min, while that of DPI was 15.98 min and the differences between the two were not significant.

**Table 1** Demographic details of study subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>17/2</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>59.15 (7.98)</td>
</tr>
<tr>
<td>Smoking history (pack years)</td>
<td>17.61 (4.02)</td>
</tr>
<tr>
<td>Mean FEV₁ (l)</td>
<td>0.77 (0.29)</td>
</tr>
<tr>
<td>Mean % predicted FEV₁</td>
<td>33.80 (11.36)</td>
</tr>
<tr>
<td>Mean FEV₁ reversibility* (%)</td>
<td>25.52 (8.99)</td>
</tr>
<tr>
<td>Mean FVC (l)</td>
<td>1.60 (0.43)</td>
</tr>
<tr>
<td>Mean % predicted FVC</td>
<td>57.70 (15.07)</td>
</tr>
<tr>
<td>Mean FVC reversibility* (%)</td>
<td>2.22 (13.23)</td>
</tr>
<tr>
<td>Mean IC (l)</td>
<td>1.28 (0.38)</td>
</tr>
<tr>
<td>Mean % predicted IC</td>
<td>52.50 (17.36)</td>
</tr>
<tr>
<td>Mean RV (l)</td>
<td>4.53 (2.02)</td>
</tr>
<tr>
<td>Mean % predicted RV</td>
<td>222.9 (110.78)</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume after 1 s; FVC: forced vital capacity; IC: Inspiratory capacity; RV: residual volume; S.D.: standard deviation.

*Change 30–45 min after inhalation 40 μg of ipratropium bromide.

**Discussion**

In this randomized, double-blind, double-dummy, placebo-controlled crossover study, we have demonstrated for the first time that a single dose of 18 mcg tiotropium administered via pMDI inhaler plus spacer produced a similar time-dependent bronchodilator response as 18 mcg tiotropium delivered through a DPI. Similarly, time to onset and time to reach maximum FEV₁ and FVC, were similar between the two study devices. These results indicate that tiotropium administered by a pMDI plus spacer produces an equivalent bronchodilator therapeutic response as that administered by a DPI.

Tiotropium is a new long-acting inhaled anticholinergic. Clinical studies with single doses of inhaled tiotropium confirm that it is a potent and long-lasting bronchodilator. Furthermore, it protects against cholinergic bronchoconstriction for more than 24 h and has been shown to improve quality of life in patients with COPD; this has led it to be the bronchodilator of choice in the management of COPD. Tiotropium is usually available in a dry powder form all over the world. Although in vivo data have not been conclusive, most in vitro studies have implicated a need of high inspiratory flow rates for the better drug delivery with the dry powder inhaler devices. The pMDI with a spacer is an...
ideal alternative in subjects who are unable to generate an adequate inspiratory flow rate. Moreover, pMDI offers a combination of reliability, accurate dosing and low cost, which makes it the more popular and a preferred form of delivery in the treatment of COPD.

The pulmonary component of COPD is usually characterized by a progressive airflow limitation, which contributes to respiratory symptoms and in order to reduce these symptoms, it is necessary to effectively reduce this air flow limitation by dilating the airways. The spirometric parameters like FEV₁, FVC values and FEV₁/FVC ratio are the best standardized, most reproducible and the most reliable objective parameters available to measure airflow limitation. These indices are the gold standard for diagnosing the disease, staging the disease and for evaluating the response to treatment. Our study demonstrated that 18 mcg of tiotropium administered via a pMDI formulation is as effective as 18 mcg dry powder tiotropium formulation, when measured by percentage changes in FEV₁ and FVC area under curve from baseline to 24 h, trough FEV₁ and FVC, and mean maximum change in FEV₁ and FVC. In addition, the mean maximum improvement in FEV₁ was 384.2 ml with pMDI plus spacer and 342.1 ml with DPI, which was achieved in 5.58 and 5.52 h, respectively. We believe this to be a

Figure 3  Mean percentage change in FVC over a period of 24 h following a single-dose administration of tiotropium by pMDI plus spacer, DPI and placebo.

Figure 4  Change in mean maximum FEV₁ from the baseline for pMDI plus spacer, DPI and placebo.

Figure 5  Change in mean maximum FVC from the baseline for pMDI plus spacer, DPI and placebo.
clinically significant bronchodilator response in subjects with moderate-to-severe COPD, who use either a DPI or a pMDI with spacer further reinforcing the importance of tiotropium in COPD subjects.

The amount of bronchodilator response seen in our subjects with COPD after the administration of tiotropium was higher than what we had anticipated and raises a possible doubt of whether these subjects had concomitant asthma. However, we feel confident that these subjects had only underlying COPD based on their clinical presentation and history. Calverley et al.\textsuperscript{11} and Donohue and co-workers\textsuperscript{12} earlier argued that nearly 50\textendash{}70\% COPD patients can show significant bronchodilator reversibility with bronchodilators. Our study adds to the growing body of evidence that COPD is not necessarily an irreversible disease especially with the advent of highly effective anticholinergic bronchodilator drugs like tiotropium.

It has been suggested that severe COPD subjects may not be able to generate adequate flow rates for attaining good therapeutic response with DPI, we did not find any difference in the bronchodilator response between the tiotropium delivered through DPI and pMDI with the spacer in different severities of COPDs. These observations were in accordance with the observations made by Cuvelier et al.,\textsuperscript{13} who had shown that ipratropium dry powdered form produced an equivalent therapeutic response as pMDI formulation in moderate-to-severe COPDs. Sarinas et al.\textsuperscript{14} have shown that the subjects with stable COPD of varying severity could comfortably generate necessary flow rates to operate new and currently available DPIs over wide range of inspiratory flow rates.

Although, the degree of airflow limitation as measured with spirometric indices like FEV\textsubscript{1} still remains the defining characteristic of COPD, it does not evaluate the full impact of COPD in the patient’s life. This is because the pathology of COPD is not only characterized by a progressive airflow obstruction, but also a progressive destruction of supporting tissues and elastin fibers of the lungs.\textsuperscript{15,16} As a result, during exhalation the unsupported bronchioles collapse before the full air is exhaled out, which leads to progressive air trapping distally with increase in RV, ITGV, TLC and decrease in the IC. The lung hyperinflation contributes to the development of breathlessness and physical limitations.\textsuperscript{16\textendash{}19} Hyperinflation increases the elastic load in the lungs and diaphragm, which in turn increases the work of breathing, disrupts the neuroventilatory coupling and finally leads to increased perception of dyspnea.\textsuperscript{15,16} Amongst the static lung volumes which a bodyplethysmograph can measure...
(RV, IC, ITGV, TLC, etc.) IC has the highest correlation with respiratory symptoms like dyspnea in the COPD subjects. Therefore, we measured resting IC at three different time points post drug administration (3, 8 and 24 h) after tiotropium administration. An equivalent improvement in IC was noted particularly in the 3rd and 8th hour, with mean maximum improvements of 350 and 379 ml after administration of tiotropium by pMDI plus spacer and DPI. This was both statistically and clinically superior to that of placebo suggesting that single doses of tiotropium reduce lung hyperinflation markedly and that this effect starts within 3 h of administration, and with a single dose lasts for at least up to 8 h. The amount of improvement seen in IC in our study is similar to that noted in an earlier study. An improvement of over 350 ml in IC in subjects with COPD translates into significant improvements in clinical symptoms. An earlier study which administered tiotropium daily for a period of 4 weeks, reported that the lung deflation even persists after 24 h. It is likely that because ours was a single-dose study, we did not observe significant improvements in IC values at 24 h post-administration.

We also measured RV, ITGV and TLC at baseline and at three different time points as parameters to assess the extent of lung deflation after tiotropium administration. However, we did not find any significant reductions in RV, ITGV and TLC after administration of single doses of tiotropium through either of devices. Possible explanations for these are: firstly, we had large standard deviation values for RV, TLC and ITGV in our study subjects because we had recruited subjects with varying severity of COPD. Probably, this itself could possibly explain the lack of significant effects on these values at different time points, following administration of single dose of tiotropium. Secondly, our COPD subjects had never received inhaled bronchodilators before and were receiving only oral medications (salbutamol and theophylline). Thirdly, it is likely that RV, TLC and ITGV are less sensitive parameters than FEV1 and IC, and may likely start showing significant improvements only after few days of tiotropium administration particularly in the severe COPD subjects. Santus et al. have earlier reported a significant improvement in ITGV within 24 h following a single dose of tiotropium administration. This is in contrast to our observations, and clearly more studies are required to evaluate the effects of single doses of tiotropium on RV, TLC and ITGV in subjects with COPD.

In summary, a single dose of tiotropium administered via pMDI formulation with a spacer produced an equivalent time-dependent bronchodilator response, as measured by changes in FEV1 and FVC, over 24 h as tiotropium administered via a DPI formulation through a Rotahaler. In addition, a single dose of tiotropium administered via both the devices reduced lung hyperinflation (as measured by IC) markedly, an effect which started within 3 h of administration. The amount of improvement in FEV1 and FVC noted in our study with single doses of tiotropium administered via both the devices adds to the body of evidence that COPD is not necessarily a reversible airways disease. Thus, tiotropium in pMDI formulation may be used routinely in patients with COPD. Further studies involving larger number of patients and for longer duration are required to determine long-term safety, efficacy and effect on quality of life of tiotropium administered via a pMDI.

Conflict of interest

Ms. Purnima Mahadik, Dr. Parth Gokhale and Dr. Jaideep Gogtay work for Cipla Ltd., a pharmaceutical company, which is manufacturing the medication described in the study (Tiotropium pMDI), while the other authors do not have any conflict of interest in the research paper. This study was conducted at Chest research Foundation, which is an independent institute.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rmed.2007.07.006.

References


