Effects of Tiotropium With and Without Formoterol on Airflow Obstruction and Resting Hyperinflation in Patients With COPD*

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Background: The combination of short-acting β2-agonists and anticholinergics in the treatment of COPD has been well documented, but data on combination of long-acting agents are lacking.

Methods: A randomized, open-label, placebo-controlled, three-way crossover study was conducted comparing 2-week treatment periods of tiotropium alone to tiotropium plus formoterol once or twice daily following a 2-week pretreatment period with tiotropium. Lung function (FEV1, FVC, and resting inspiratory capacity [IC]) serially over 24 h was measured in 95 patients with stable COPD at baseline and after 2 weeks of each treatment.

Results: Mean baseline FEV1 was 1.05 L (38% of predicted). There was a circadian variation in FEV1, FVC, and IC at baseline that was maintained during all treatment periods. Average FEV1 (0 to 24 h) improved by 0.08 L with tiotropium, by 0.16 L with tiotropium plus formoterol once daily, and by 0.20 L with tiotropium plus formoterol twice daily (p < 0.01 for all comparisons). Compared with tiotropium alone, add-on formoterol in the morning produced improvement in FEV1, FVC, and IC for > 12 h. The second add-on dose of formoterol in the evening caused further improvement in FEV1 for 12 h, but in FVC and IC for < 12 h. Peak increase in FEV1 was 0.23 L (22% of baseline) with tiotropium and 0.39 L (37% of baseline) with tiotropium plus formoterol (p < 0.0001). Compared with tiotropium alone, add-on formoterol once and twice daily reduced the use of rescue salbutamol during the daytime (p < 0.01) and with add-on formoterol twice daily also during the nighttime (p < 0.05). The combination of tiotropium and formoterol was well tolerated.

Conclusion: In the treatment of COPD, there is benefit from adding formoterol once or twice daily to tiotropium once daily in terms of improvement in airflow obstruction, resting hyperinflation, and the use of rescue salbutamol.

Key words: COPD; formoterol; hyperinflation; long-acting anticholinergic; long-acting β2-agonist; tiotropium

Abbreviations: ATS = American Thoracic Society; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IC = inspiratory capacity; LABA = long-acting β2-agonist; PEFR = peak expiratory flow rate

The management of COPD is largely symptom driven, and bronchodilators are the mainstay in the pharmacotherapy both to prevent and reduce symptoms. In the 2003 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, it is recognized that long-acting inhaled bronchodilators are more effective and convenient than short-acting bronchodilators. It has also been demonstrated that combining bronchodilators improve efficacy without additional side effects, compared to increasing the dose of a single bronchodilator. Presently, two types of inhaled long-acting bronchodilators are available for clinical use: the long-acting β2-agonists (LABAs) formoterol and salmeterol inhaled twice daily, and the new long-acting anticholinergic tiotropium inhaled once daily. The LABAs have a duration of action of 12 h,2,3 Tiotropium has a duration of action of > 24 h, and large studies4,5 lasting 1 year showed sustained improvements in spirometry with no evidence of tolerance.
Tiotropium also leads to reduction in hyperinflation, which is accompanied by improvements in exertional dyspnea and exercise endurance.6

As three large studies7–9 have demonstrated that the combination of the short-acting β2-agonist salbutamol with the short-acting anticholinergic ipratropium is superior to either single agent alone, one can expect that combination therapy with the long-acting drugs may achieve even greater benefit. Limited clinical data on combination therapy of tiotropium and an inhaled LABA in COPD have been published. Using a single-dose study design, Cazolla et al10 found a trend for additive effects of tiotropium and formoterol. We have shown that in patients with COPD, maintenance therapy of combined tiotropium and formoterol, both once daily, provided additive effects on FEV1 throughout the 24-h dosing interval.11 The purpose of the present study was to investigate the effects of formoterol administered once or twice daily in addition to pharmacodynamic steady-state tiotropium on airflow limitation and dynamic hyperinflation at rest over 24 h in patients with moderate-to-severe COPD.

Materials and Methods

Patients

Patients were required to have a clinical diagnosis of COPD according to the American Thoracic Society (ATS) criteria,12 stable airways obstruction with FEV1 ≤ 60% of predicted,13 and an FEV1/FVC ratio < 70%. The patients had to be at least 40 years old, and all had to be current or previous smokers (≥ 10 pack-years).

Patients with any of the following were excluded: history of asthma, allergic rhinitis, atopy or an elevated blood eosinophil count, significant disease other than COPD, or a recent history of myocardial infarction, heart failure, or cardiac arrhythmic requiring drug treatment. In addition, patients were excluded if they were receiving oxygen therapy or had any respiratory infection in the 6 weeks before screening. Patients with a known hypersensitivity to anticholinergic drugs, known symptomatic prostatic hypertrophy, and narrow-angle glaucoma were also excluded.

Study Design

The study was approved by the hospital medical ethics committees, and all patients gave written informed consent before medication washout or any study procedure was undertaken. The study had a three-center, randomized, open-label, placebo-controlled crossover design with 2-week treatment periods (Fig 1). After initial screening (visit 1), patients returned for a second clinic visit (visit 2) and remained in the clinic for 2 nights in order to determine a baseline 24-h profile of FEV1, FVC, and inspiratory capacity (IC). On completion of this 24-h observation period, patients entered a 2-week pretreatment period of tiotropium, 18 μg qd, inhalation powder (HandiHaler; Boehringer Ingelheim; Alkmaar, the Netherlands) in order to achieve a pharmacodynamic steady state of tiotropium.14 Subsequently, treatment with tiotropium once daily was continued and formoterol dry powder inhalation capsule 12 μg qd in the morning (plus tiotropium-matched placebo capsule in the evening), or formoterol dry...
powder inhalation capsule 12 μg bid, or tiotropium-matched placebo capsule twice daily were added in a randomized order for 2-week periods. So, in order to keep the number of inhalations constant and consistent in the three cross-over periods, the patients inhaled two capsules in the morning and one capsule in the evening; however, it was visible if they inhaled additional tiotropium-matched placebo or formoterol in addition to tiotropium. This open design was unavoidable because the placebo-matching formoterol inhalation powder was not available at the time the study was performed. The evening dose was administered approximately 12 h after the morning dose of study medication. On each 24-h pulmonary function test day (visits 3, 4, and 5), the study medication was inhaled in the presence and under the supervision of the trial physician, keeping the pulmonary technician blinded for the inhaled medication. Furthermore, the patients did not communicate to the pulmonary technician which study medication was inhaled.

The patients continued to use the permitted medication for their COPD in stable doses including inhaled steroids, oral steroids up to 10 mg/d of prednisone, and mucolytics. Long-acting inhaled β₂-agonists were not allowed for at least 48 h, and short-acting anticholinergics or β₂-agonists for at least 8 h before the screening visit and the 24-h baseline measurements as well as throughout the three 2-week periods of randomized treatment. Oral β₂-agonists, antihistamines, and theophylline were not allowed for at least 1 month before the screening visit. Tiotropium was not commercially available during the study. Patients were administered open-label salbutamol via metered-dose inhaler as rescue medication as necessary.

Measurements

Before entry and at the completion of the study, patients underwent a medical examination, 12-lead ECG recording, and a laboratory safety screen. At each scheduled visit, details of clinical status and adverse events were recorded.

At the screening visit, bronchodilator responsiveness was tested by measuring FEV₁ 1 h after inhalation of two puffs of 100 μg of salbutamol plus 20 μg of ipratropium bromide by metered-dose inhaler. Bronchodilator responsiveness was not used as an entry criterion.

At baseline (visit 2, previous to the first dose of the tiotropium pretreatment period) and at the end of the three 2-week treatment periods (visits 3, 4, and 5), clinical lung function was assessed over a 24-h period. FEV₁ and FVC measurements were obtained 5 min before inhalation and 30 min and 60 min, and 2, 3, 4, 7, 10, and 12 h after inhalation of the morning dose of study medication and, subsequently, 30 min and 60 min. and 2, 7, 10, 11, and 12 h after inhalation of the evening medication. IC measurements were performed 5 min before inhalation, and 1, 4, 8, and 12 h after inhalation of the morning dose, and 1, 10, and 12 h after inhalation of the evening dose of the study medication.

Testing always started between 7 AM and 9 AM and always within 30 min of the start of the baseline measurements. Rescue salbutamol was withheld at least 8 h before the pulmonary function tests. The measurements were performed with a spirometer meeting ATS criteria. The highest values of FEV₁ and FVC from three technically adequate measurements were retained. IC measurements were performed as described by O’Donnell et al and always before the measurements of FEV₁ and FVC. The quality of a random sample of the lung function measurements was reviewed in a blinded fashion by an external expert and the reviewed maneuvers qualified according to ATS criteria.

Patients completed a daily diary card recording their morning and evening peak expiratory flow rate (PEFR) and the use of daytime and nighttime rescue salbutamol. PEFR was recorded as the best of three efforts using a peak flowmeter (Personal Best; HealthScan Products; Cedar Grove, NJ) immediately on arising and in the evening, always before inhalation of the study medication.

Statistical Analysis

The primary efficacy end points were the average FEV₁ over the full 24-h observation period and over the second half on the last day of each 2-week period of randomized treatment. The average FEV₁ was calculated as the area under the curve from zero time to 24 h or 12 to 24 h, respectively, using the trapezoidal rule divided by the corresponding duration (ie, 12 h or 24 h) to report in liter units. The predose FEV₁ value was assigned to zero time and defined as the measurement before administration of the last morning dose of study drug at the end of each 2-week treatment period. Secondary end points were trough and peak FEV₁, as well as FEV₁ (0 to 12 h) and FEV₁ values at individual time points. Trough is the lung function measurement at 24 h (9 AM). As study medication was inhaled on the previous day in the morning (approximately 9 AM) and in the evening (approximately 9 PM), the 24-h measurement is 12 h after the evening dose on the previous day and 24 h after the morning dose on the previous day. The peak FEV₁ was the highest FEV₁ reading observed within 3 h after inhalation of the morning study medication (peak FEV₁ [0 to 3 h]). Average, trough, and peak responses were defined as the change from the baseline FEV₁ value, which was the first measurement obtained on visit 2 (randomization visit). Analogous definitions were used for FVC- and IC-based parameters. Patient diary-based end points were twice-daily PEFRs (morning and evening) and “as-needed” salbutamol use (daytime and nighttime). The mean of observations obtained during each of the 2-week treatment periods were calculated and used to compare the treatment regimens. Due to the relatively short duration of action of formoterol, only limited and negligible carry-over effects were expected. The run-in period was used for training purposes; diary data recorded in this period were not used for the analysis. The 24-h baseline lung function profile (visit 2) was used to assess the circadian variation and served as reference. Apart from the first measurement, which served as baseline value, these data as well as the diary data recorded during the tiotropium pretreatment period were not used for the efficacy analysis.

The planned sample size was 84 eligible patients. Assuming a SD of 140 mL for paired differences as observed in other trials, this sample size provides a power of 90% to detect a true difference of 50 mL in average FEV₁ over 24 h (type I error rate, 0.05), resulting in an overall power for the two primary comparisons (formoterol once daily vs formoterol twice daily in addition to steady-state tiotropium) of at least 80%.

For all end points, adjusted means for the three treatments were calculated using a fixed-effects analysis of variance model with terms for center, patients within center, treatment, and period as specified in the study protocol. All patients with on-treatment data available were included in the analysis (safety: 95, diary and spirometric end points: 94 and 92, respectively). No period effect could be detected while center and patient were found significant (F test: p < 0.05) for the primary and most of the secondary end points. Sensitivity analysis did not reveal a treatment by center interaction. For the primary end points, treatment means were compared in a prespecified order to control type I error rate (fixed sequence testing). For other end points, no adjustments for multiple comparisons were utilized. Statistical significance was considered at p < 0.05. In order to include the same patients at each time point in the spirometric summaries, missing values were estimated using other values recorded for the patient on that 24-h pulmonary function test day. Randomly missing trough values were estimated by the value
obtained as test day predosing reading and vice versa. Linear interpolation between two adjacent measurements was used to estimate middle missing spirometric measurements, and the last observation carried forward method was applied if no subsequent measurement was available. Values missing for reasons related to the patient’s treatment response, eg, shortness of breath and intake of rescue medication, were estimated using the minimum observed spirometric measurement on a specific test day. For diary end points, similar rules were applied. In order to assess the impact of imputation, data were also analyzed based on patients who completed all 24-h pulmonary function tests. This sensitivity analysis showed that the results were consistent with those obtained after imputation of missing data.

RESULTS

Patients

A total of 100 patients were screened; 95 of them were eligible and entered the study. Of the 95 randomized patients, 91 completed the study and 4 discontinued prematurely. The reasons for withdrawal were as follows: exacerbation of COPD (one patient in the tiotropium pretreatment period and one patient in the tiotropium plus formoterol once-daily period), pneumonia (one patient in the tiotropium period), and not available for follow-up (one patient in the tiotropium plus formoterol twice-daily period).

The demographic and baseline characteristics of the patients are summarized in Table 1. The mean age was 64 years, 72% were men, and mean FEV$_1$ was 1.05 L (38% of predicted). The mean bronchodilator response to 200 μg of salbutamol plus 40 μg of ipratropium bromide was 0.24 L (25% baseline or 9% predicted).

Spirometry

The FEV$_1$ time-response curves measured over 24 h at the end of the 2-week treatment periods are shown in Figure 2. The parameters derived from these curves, ie, trough, average (0 to 12 h, 12 to 24 h, 0 to 24 h), and peak response in FEV$_1$ are given in Table 2. Compared to baseline, 30 min after inhalation, tiotropium achieved a significant bronchodilator response with a peak response between approximately 1 h and 4 h after dosing and sustained improvement during the 24-h observation period (p < 0.001). There was circadian variation with a second rise in FEV$_1$ in the next morning. Add-on therapy with formoterol once daily led to an additional improvement in FEV$_1$ that was sustained for at least 14 h after the morning dose. This is reflected not only in a statistically significant difference of 0.11 L (p < 0.0001) in average FEV$_1$ (0 to 12 h) vs tiotropium but also in average FEV$_1$ (12 to 24 h) [0.05 L; p < 0.001; Table 2]. Compared to the tiotropium response, add-on formoterol in the morning produced an additional increase in peak FEV$_1$ of 0.15 L (p < 0.0001). The combination regimen with formoterol twice daily provided an additional increase in FEV$_1$ after the evening dose that was still evident the next morning. This was reflected in

Table 1—Demographics and Baseline Characteristics of the Study Population (n = 95)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female gender, No.</td>
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<tr>
<td>Age, yr</td>
<td>64 ± 9</td>
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<tr>
<td>Smoking history, pack-yr</td>
<td>36 ± 16</td>
</tr>
<tr>
<td>Duration of disease, yr</td>
<td>10 ± 7</td>
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<td>FEV$_1$, L</td>
<td>1.05 ± 0.31</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
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<tr>
<td>FEV$_1$ reversibility†</td>
<td>0.24 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>% baseline 25 ± 17</td>
</tr>
<tr>
<td></td>
<td>% predicted 9 ± 6</td>
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<tr>
<td>COPD severity according to GOLD¹</td>
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<tr>
<td>Moderate</td>
<td>39 (41)</td>
</tr>
<tr>
<td>Severe</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Very severe</td>
<td>9 (10)</td>
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<tr>
<td>FVC, L</td>
<td>2.59 ± 0.67</td>
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<tr>
<td>FEV$_1$/FVC, %</td>
<td>41 ± 8</td>
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<td>Prestudy medication for COPD</td>
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<td>Anticholinergics (inhaled)</td>
<td>80 (84.2)</td>
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<tr>
<td>α$_2$-Adrenergics (inhaled)</td>
<td>89 (93.7)</td>
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<tr>
<td>Steroid (inhaled)</td>
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<tr>
<td>Steroid (oral)</td>
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</table>

*Values are presented as mean ± SD or No. (%) unless otherwise stated.
†One hour following two puffs of 100 μg of salbutamol plus 20 μg of ipratropium bromide via metered-dose inhaler.

Figure 2. Mean FEV$_1$ before (24-h baseline) and at the end of 2-week treatment periods, adjusted for period, center, and patient within center. *p < 0.05 tiotropium qd plus formoterol bid vs tiotropium qd. #p < 0.05 tiotropium qd plus formoterol qd vs tiotropium qd. †p < 0.05 tiotropium qd plus formoterol bid vs tiotropium qd plus formoterol qd.
significantly greater improvements in average (12 to 24 h) and trough response in FEV₁ compared both with tiotropium alone and tiotropium plus formoterol once daily (p < 0.02).

In general, the pattern of improvement in FVC was similar to that in FEV₁ (Fig 3, Table 2). Compared to add-on formoterol once daily, the improvement in trough FVC with add-on formoterol twice daily did not reach statistical significance.

The mean morning PEFR over 2 weeks with formoterol twice daily was significantly greater than that with formoterol once daily (p < 0.01) and with tiotropium alone (both differences, 9 L/min; p < 0.01). The mean evening PEFR over 2 weeks with formoterol once daily and formoterol twice daily was significant greater (9 L/min; p < 0.01) than with tiotropium alone.

**IC**

The time course over 24 h of the resting IC response at the end of the three treatment periods is shown in Figure 4. Peak, average, and trough response in IC are given in Table 2. Baseline resting IC demonstrated circadian variation with maximum values at approximately noon and minimum values at early morning, the maximum difference being approximately 0.3 L. Treatment with tiotropium resulted in a parallel shift to higher values during the 24-h day, without abolishing circadian variation, with a peak response of 0.39 L and a trough response of

![Figure 3. Mean FVC before (24-h baseline) and at the end of 2-week treatment periods, adjusted for period, center, and patient within center. *p < 0.05 tiotropium qd plus formoterol bid vs tiotropium qd. #p < 0.05 tiotropium qd plus formoterol qd vs tiotropium qd. †p < 0.05 tiotropium qd plus formoterol bid vs tiotropium qd plus formoterol qd.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22041/ on 06/27/2017)
0.17 L. Add-on treatments with formoterol once and twice daily provided an additional increase in IC for 12 h, the difference in average IC (0 to 12 h) being 0.13 L (p < 0.001) and in peak IC (0.14 L) [p < 0.001]. Finally, after formoterol in the evening, a further increase in IC was achieved; however, the duration was < 10 h. There was no significant difference in trough IC response among the three treatments.

**Rescue Medication**

Use of rescue salbutamol during the daytime was four times higher than during the nighttime with all treatments (Fig 5). With combination therapy, the use of daytime salbutamol was significantly lower than with tiotropium alone (p < 0.01). During add-on treatment with formoterol twice daily, the nighttime use of salbutamol was lower than with tiotropium alone but not lower than with add-on formoterol once daily.

**Safety**

There was no evidence for drug-related increase either in frequency or in intensity of adverse events. During the 2-week tiotropium pretreatment period and the three 2-week treatment periods, a comparable number of patients reported adverse events. Exacerbations of COPD and upper respiratory tract infections were the most frequently reported events. Monitoring of safety parameters including BP, pulse rate, ECG, and standard laboratory tests did not reveal any clinically relevant changes.

**DISCUSSION**

The 2003 update of the GOLD management protocol states that long-acting bronchodilators are more effective and convenient than short-acting bronchodilators. This report also emphasizes that combining bronchodilators may improve efficacy without increasing the risk of side effects compared to increasing the dose of a single bronchodilator."
The present study investigates the additional effect of the LABA formoterol, inhaled once or twice daily, on airflow obstruction and resting hyperinflation over 24 h in patients receiving maintenance treatment with the long-acting anticholinergic tiotropium. Our results show a rank order of improvement in FEV₁ and completely in line with the latter, also in FVC and IC. The combination of tiotropium once daily with formoterol twice daily was the most effective, demonstrating the highest value for average FEV₁ (0 to 24 h), one of the primary end points of the study. Second best was combination therapy with formoterol once daily. During this treatment, average FEV₁ (12 to 24 h) was lower than during combination treatment with formoterol twice daily, but higher than with tiotropium alone. There was no difference in average FEV₁ (0 to 12 h) between the addition of formoterol once or twice daily. With both treatments, the mean peak improvement in FEV₁ during pharmacodynamic steady state was similar, amounting approximately 390 mL (14% predicted), and this increase was much greater than the acute bronchodilator response in FEV₁ to salbutamol/ipratropium (9% of predicted), indicating that the effect size of acute bronchodilator response cannot predict the long-term response to long-acting agents. Formoterol has a duration of action of at least 12 h in patients with COPD. Published studies investigating the spirometric effects of formoterol are limited to their daytime dosing interval of 12 h, indicating that the nocturnal effects of LABAs on lung function are unknown in COPD. In the present study, the combination of tiotropium with formoterol once daily in the morning produced superior bronchodilation over tiotropium for > 14 h.

In contrast, the duration of the additional effect of the evening dose of formoterol had disappeared by the next morning. Postma et al pointed out that circadian changes in FEV₁ can be explained by increased sympathetic activity during the day and an increase in parasympathetic activity during the night. In addition, these authors found that in COPD patients, the activity of the adrenergic system was lower and of the vagal system was higher than in normal subjects. This might explain why in our study the add-on effect of formoterol was more pronounced during the daytime than during the nighttime, and suggests that tiotropium is the most relevant factor to maintain bronchodilation during the night.

O’Donnell et al demonstrated in COPD that changes in spirometric measurements are in general poor predictors of symptom relief and improvement in exercise endurance. The authors also showed that changes in IC as an index of resting hyperinflation correlated better than FEV₁ with changes in dyspnea and exercise tolerance. O’Donnell et al have also demonstrated that the reduction in IC from rest to end exercise is similar at baseline condition and during tiotropium treatment, ie, tiotropium causes a downward shift in the IC-time curve. From this follows that both in baseline condition and during treatment with bronchodilators resting IC is a good predictor of dynamic hyperinflation during exercise.

This is the first study to report circadian variation in resting dynamic hyperinflation in patients with stable COPD. IC exhibited maximum values at approximately noon and minimal values in the early morning, irrespective of treatment with tiotropium alone or with add-on formoterol. This implicates that the assessment of bronchodilator therapy on hyperinflation in clinical trials must consider the time of the measurements. The circadian changes in IC were consistent with those in FEV₁ and FVC. Calverley et al reported circadian variation in FEV₁ before and after tiotropium in patients with stable COPD. Similar to FEV₁ in the latter study, treatment with tiotropium in the present study improved IC throughout the 24-h day without abolishing circadian variation. Add-on therapy with formoterol produced further improvements in IC without affecting circadian rhythm. Interestingly, the effect of the second dose of formoterol in the evening was less pronounced and more short lived than that of the morning dose. Peak increase in IC with combination therapy amounted to 550 mL or 25% above baseline. This is much greater than results in this and previous studies with a single bronchodilator. For comparison, Di Marco et al measured IC 30 min after inhalation of a single dose of four different bronchodilators and found a mean increase in IC of 140 mL after oxtropium, 170 mL after salbutamol, 220 mL after salbutamol, and 330 mL after formoterol. Celli et al found a peak improvement in IC of 350 mL following 4 weeks of treatment with tiotropium in patients with COPD.

In COPD, the most disturbing symptom is exertional dyspnea, and this implies that optimal bronchodilation is most critical during activities of daily life. In agreement with previous results, in the present study the use of rescue medication appeared to be substantially higher during the daytime than during the nighttime, irrespective of the type of treatment. Differences in the overall use of salbutamol among the treatment periods were largely due to differences in the daytime use of salbutamol. In both treatment periods with add-on formoterol, the use of salbutamol during the day was significantly lower than that in the tiotropium period, whereas the differences in nighttime use of salbutamol were very
small and probably not clinically relevant. This might indicate that the combination of the add-on evening dose of formoterol to overall symptomatic improvement is rather limited. However, as the treatment period was short, this needs to be confirmed in long-term studies.

The effects of the combination of short-acting β₂-agonist or LABA with short-acting anticholinergics have been well documented. The combination of the short-acting β₂-agonist salbutamol and the anticholinergic ipratropium produced greater and more sustained bronchodilatation over 3 months than each drug alone.⁷ Combination therapy of the LABA salmeterol and the short-acting anticholinergic ipratropium showed added benefit in terms of improvement in airflow obstruction and led to fewer exacerbations.⁸⁻¹⁰ Furthermore, it has been demonstrated in a single-dose study²⁶ that the combination of formoterol and ipratropium produced a greater increase in FEV₁ than double doses of ipratropium. Combining formoterol with ipratropium over a 3-week period in COPD patients produced a greater improvement in FEV₁ and FVC than treatment with the combination of salbutamol and ipratropium.²⁷

In contrast, data on combination treatment of tiotropium with LABAs are largely lacking. We have shown that combination of tiotropium and formoterol once daily provides additive effects throughout the 24-h dosing interval in terms of improvement in FEV₁.¹¹

Cazzola et al.¹⁰ found in a small, single-dose study a trend for additive effects of tiotropium and formoterol. However, it is known that the optimal bronchodilator response to tiotropium is only achieved in pharmacodynamic steady state, i.e., after at least 1 week of treatment.¹² Therefore, in the present study, measurements were performed at the end of 2-week treatment periods in order to measure in steady state and also to rule out any carry-over effects of formoterol.²⁸

In conclusion, while tiotropium is an effective bronchodilator in patients with moderate-to-severe COPD, there is added benefit of combination therapy of tiotropium and formoterol in terms of improvement in airflow obstruction, dynamic hyperinflation, and in reduction of rescue medication. It is likely that in the near future, a combination of tiotropium with formoterol or salmeterol will emerge as the therapy of choice in these patients.²⁹ However, the results of the present study need to be substantiated with long-term studies to establish whether the improvements in lung function translate into improvements in clinical outcomes such as symptom scores, health status, exercise tolerance, and exacerbation rates. Because in monotherapy tiotropium is administered once daily while formoterol is usually required twice daily, it is important to perform further studies to assess the added benefit of the evening dose of formoterol on clinical outcomes. Effective combination therapy of tiotropium with LABAs once daily would enhance compliance with therapy.

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