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Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD

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Abstract

Background: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends long-acting bronchodilators as first-line maintenance treatment for patients with chronic obstructive pulmonary disease (COPD). A study was conducted comparing the long-acting anticholinergic tiotropium with the long-acting beta-agonist salmeterol to confirm the significant improvements in daytime bronchodilator efficacy seen with tiotropium in previous studies.

Methods: Randomized, double-blind, double-dummy, parallel-group study, comparing daytime bronchodilator efficacy of tiotropium 18 mcg once daily with salmeterol 50 mcg twice daily in patients with COPD. Serial spirometry was performed over 12 h after 12 weeks of treatment. Co-primary endpoints were average (over 12 h) and peak FEV_1 at 12 weeks.

Results: 653 patients were randomized (328 tiotropium, 325 salmeterol): mean age 64 years; 66% male; mean baseline FEV_1 1.05 l (37.7% predicted). After 12 weeks, the average post-dose FEV_1 over 12 h was significantly higher with tiotropium compared with salmeterol (167 vs. 130 mL, respectively, $p=0.03$), as was peak FEV_1 (262 vs. 216 ml, respectively, $p=0.01$). The average FEV_1 responses from 0–6 h and 6–12 h were higher in the tiotropium group compared with salmeterol ($p<0.05$). Peak and average FVC were significantly higher with tiotropium compared with salmeterol ($p<0.01$). Morning pre-dose FEV_1 responses were not significantly different; however, tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol ($p<0.05$).

Conclusion: Tiotropium demonstrated significantly greater post-dose improvements in spirometric parameters compared with salmeterol. These improvements were sustained over 12 h.

Keywords: COPD; Tiotropium; Salmeterol; Bronchodilator

1. Introduction

Bronchodilator medications are central to the long-term management of stable COPD patients. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, regular treatment with long-acting bronchodilators is more convenient and effective than treatment with short-acting bronchodilators [1]. Therefore, long-acting bronchodilators are currently recommended as maintenance therapy for patients with moderate to severe COPD [1]. Similarly, ATS/ERS guidelines recommend bronchodilators for persistent symptoms [2]. Two classes of long-acting, inhaled bronchodilators are currently available: anticholinergics and beta-adrenergic agonists. The guidelines do not currently recommend one class over the other, and the decision to use agents from one class of long-acting bronchodilator over another is based on efficacy, onset of action, side effect profile, and dosing frequency. Efficacy during daytime hours is particularly important when selecting a maintenance bronchodilator for patients with COPD, as this is the period of time during which patients would be expected to be most active and to be performing their usual daytime activities.

Tiotropium is a new, once-daily, inhaled anticholinergic that provides sustained bronchodilation through prolonged

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M_3 receptor blockade [3]. In previous controlled clinical trials, tiotropium was shown to improve lung function, dyspnea and health-related quality-of-life in patients with COPD when compared with placebo or the short-acting anticholinergic bronchodilator, ipratropium [4,5]. Two previous controlled clinical trials compared the efficacy and safety of tiotropium with the long-acting beta-agonist, salmeterol, over 6 months. The analysis of the combined trials indicated that both active treatment groups have superior bronchodilator efficacy over placebo for all spirometric endpoints with tiotropium exhibiting significantly higher post-dose FEV_1 and FVC responses compared with salmeterol [6]. One of the two trials measured spirometric responses over 12 h while the other included spirometry over 3 h [6,7].

The purpose of the present study (Boehringer Ingelheim Study 205.264) was to confirm the greater bronchodilator efficacy of tiotropium compared with that of salmeterol during daytime hours. The primary outcome measures after 12 weeks of treatment were average post-dose FEV_1 over a 12 h period and peak FEV_1 responses. Secondary outcome measures included the additional spirometric endpoints of morning pre-dose FEV_1, FEV_1 at each timepoint during the 12 h observation period, as well as parallel assessments of the same FVC parameters. Use of rescue medication and COPD exacerbations were also compared for the two treatment groups.

2. Methods

2.1. Study design

This was a 12-week, randomized, double-blind, double-dummy, parallel-group study comparing the daytime bronchodilator efficacy of tiotropium 18 mcg once daily with salmeterol 50 mcg twice daily in patients with COPD. The study was conducted in 50 centers located in 8 countries, including Finland, Greece, Italy, Portugal, Sweden, Turkey, the United Kingdom, and the United States. The protocol was approved by ethics committees and/or institutional review boards for all participating centers. All patients signed written informed consent before any study procedures were performed.

2.2. Patients

Patients who were 40 years of age or older, with a cigarette smoking history of 10 pack years or more, and a clinical diagnosis of COPD, were eligible for inclusion in the study if they had a forced expiratory volume in 1 s (FEV_1) $\leq$60% of predicted normal [8] and $\leq$70% of the forced vital capacity (FVC). Patients with a history of asthma, allergic rhinitis, atopy, or a total (absolute) blood eosinophil count $\geq 600\ mm^3$ were excluded from the study, as were those with a history of moderate to severe renal impairment, moderate to severe symptomatic prostatic hypertrophy or bladder-neck obstruction, narrow-angle glaucoma, inability to give informed consent, or any significant medical condition that could preclude participation for the full duration of the trial or interfere with the interpretation of the study results. Patients were also excluded from the study if they took systemic corticosteroids at unstable doses or in daily doses of $\geq$10 mg (or its equivalent), if they were using beta-blockers, cromones, or anti-leukotrienes prior to enrollment in the trial, or if they had experienced a respiratory tract infection or a COPD exacerbation within 30 days of randomization. Patients using oxygen for more than 1 h per day and who were unable to refrain from its use during pulmonary function testing were also excluded. Additionally, patients were excluded who were actively participating in a rehabilitation program or had completed such a program during the previous 30 days.

2.3. Procedures

After patients signed written informed consent, baseline data concerning COPD and other relevant medical history were obtained. Patients then entered a 2-week screening period during which baseline use of rescue salbutamol (albuterol) use was recorded on a diary card. During the screening period, patients who were taking fixed combination respiratory medications (i.e. combinations of inhaled corticosteroids plus long-acting beta-agonists, or anticholinergics plus short-acting beta-agonists) prior to study enrollment were switched to the component monoproducts. Patients taking long-acting beta-agonists were required to stop this medication 24 h prior to randomization. At the end of the screening period, patients meeting all inclusion and exclusion criteria were randomly assigned (1:1) to receive either tiotropium (18 mcg once daily via the HandiHaler® device (Boehringer Ingelheim GmbH and Co. KG, Ingelheim, Germany)) or salmeterol (2 actuations of 25 mcg each, twice daily via a metered dose inhaler). Study medications were provided in a double-blind, double-dummy manner as indicated in Table 1.

Table 1
Treatment schedule

Treatment group	Dosing time	
	AM	PM
Tiotropium	Tiotropium 18 mcg: 1 inhalation via HandiHaler® [9]	
	Placebo: 2 inhalations via MDI	Placebo: 2 inhalations via MDI
Salmeterol	Placebo: 1 inhalation via HandiHaler® [9]	
	Salmeterol 25 mcg: 2 inhalations via MDI	Salmeterol 25 mcg: 2 inhalations via MDI

MDI, metered dose inhaler.

Patients were not permitted to take anticholinergic agents or long-acting beta-agonists other than study medication during the treatment period. Patients otherwise received usual medical care, and were permitted to use rescue salbutamol, which was provided during the study, as well as previously prescribed theophylline compounds, inhaled steroids, and modest doses of oral steroids. Patients were asked to record the number of occasions of rescue salbutamol use during daytime and nighttime, as well as to record each administration of study medication, on a diary card throughout the study.

Baseline spirometry was conducted prior to the first dose of study medication at the randomization visit. Medication washout requirements prior to spirometric testing are provided in Table 2. Two study visits were scheduled during the treatment period, at 6 and 12 weeks after randomization. At Week 6, spirometry was performed prior to administration of study medication. The primary outcome measurements were determined by serial spirometry performed after 12 weeks of treatment. At Week 12, pulmonary function testing was conducted 10 min pre-dose, and at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h after taking the study medication. Patients were asked to refrain from strenuous activity for at least 12 h prior to pulmonary function testing and throughout the testing period on each study day. Smoking was discouraged throughout the study day and was not permitted within 30 min of spirometry. Patients were also asked to avoid cold temperatures, environmental smoke, dust, or areas with strong odors (e.g. perfumes) prior to and during the testing period. Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages were not allowed the morning of, or during the pulmonary function testing. At Week 12, patients were required to remain in the study center for the full 12-hour testing period. All open-label bronchodilators, inhaled steroids, and study drug were withheld prior to spirometry. If patients required rescue medication during spirometry or at any time during the 12-h testing period at Week 12, pulmonary function testing was discontinued. Study sites performed spirometry using a common predictive nomogram and with equipment and methods that conformed to American Thoracic Society recommendations [10].

Data on COPD exacerbations were collected throughout the trial. COPD exacerbations were defined as at least two new or increased respiratory symptoms (cough, wheeze, dyspnea, chest congestion, shortness of breath, chest tightness, or sputum production) occurring for at least 3 days and reported as an adverse event.

Safety data was collected through adverse event reporting, which began immediately after each patient signed informed consent, and continued until 30 days after the last dose of study medication. Serious adverse events were defined as those events which resulted in hospitalization or prolonged a hospitalization, were immediately life threatening or fatal, resulted in serious or prolonged disability, were new occurrences of cancer, or were determined by the investigator to be of significant hazard to warrant being categorized as serious.

2.4. Statistical analyses

Patients were included in the efficacy analyses if they were randomized, took at least one dose of study medication, and completed baseline and at least one set of post-dose spirometric tests. Results are presented as means (SE) with statistical significance considered at $p < 0.05$.

The co-primary efficacy outcomes were average post-dose FEV_1 over 12 h and peak FEV_1 after 12 weeks of treatment. Average FEV_1 was estimated from the area under the curve from 0 to 12 h (AUC_{0-12}) calculated by the trapezoidal rule and normalized by dividing by 12. Analysis of covariance with baseline as a covariate and terms for treatment and center was used to evaluate these primary outcomes as well as secondary spirometric outcomes including morning pre-dose FEV_1, FEV_1 at each time point over 12 h, and corresponding FVC parameters. Missing values due to worsening of the disease were imputed by patient's least favorable observation while missing values due to other reasons were imputed by the last observation carried forward method.

Analyses of differences in the incidence and frequency of COPD exacerbations between the two treatment groups were performed as secondary outcome measures. However, the study lacked sufficient power to detect a difference in

Table 2
Medication restrictions for pulmonary function testing

Medication	Withheld at Visit 2	Withheld at Visits 3 and 4
Long-acting beta-agonists[a]	24 h prior to visit and during treatment period	N/A
Short-acting anticholinergics[a]	8 h prior to visit and during treatment period	N/A
Short-acting beat-agonists[a]	8 h prior to visit	8 h prior to visit
Theophylline compounds[b] (short and intermediate-acting)	24 h prior to visit	24 h prior to visit
Inhaled corticosteroids	AM dose on day of visit	AM dose on day of visit
Study medication	N/A	AM dose on day of visit

N/A, not applicable.

[a] Fixed combinations were switched to monocomponents at Visit 1.

[b] Long-acting theophylline preparations were not permitted, and were switched to short or intermediate-acting agents at Visit 1.

exacerbations, and hence the analyses were conducted largely for descriptive purposes. Fisher's Exact test was used to compare the number or percentage of patients with at least one COPD exacerbation. Times to first exacerbation were compared using the log-rank test. The number of exacerbations, as well as exacerbation days, were compared using the Wilcoxon–Mann–Whitney test. Ratio estimates were provided to describe the number of exacerbations and exacerbation days.

Rescue medication use was also analyzed as a secondary efficacy endpoint. Rescue salbutamol use was compared between the two treatment groups by determining the average number of daily occasions of rescue medication use each week. Analysis of covariance with terms for treatment and center and the average weekly use in the screening period as a covariate was used to compare the differences between the two groups over the 12 week treatment period.

A post-hoc analyses of differences in the incidence of serious adverse events and COPD exacerbations reported as serious were conducted using Fisher's Exact test with mid-p correction.

3. Results

3.1. Study population

A total of 831 patients signed written informed consent and were screened for participation in the study. Six-hundred and fifty-three of these potential study subjects met all eligibility criteria and were randomized, 328 to salmeterol and 325 to tiotropium.

The two treatment groups were well matched for demographic and disease-specific characteristics (Table 3). The study population was approximately 66% male and had a mean age of approximately 64 years. The mean baseline FEV_1 was 1.04 l (37.7% predicted). Baseline use of respiratory medications prior to entry into the trial was also similar in both treatment groups (Table 4). A high percentage of patients in both groups reported taking at least one respiratory medication at baseline (87.8 and 87.1% in the tiotropium and salmeterol groups, respectively). A higher percentage of patients randomized to tiotropium reported taking inhaled corticosteroids at baseline compared with the salmeterol group.

Table 3
Baseline characteristics of patients in the tiotropium and salmeterol groups

Characteristic	Tiotropium ($n=328$)	Salmeterol ($n=325$)
Male (%)	65	68
Age (years)[a]	64.2±8.6	64.6±7.8
Smoking status		
Current smoker (%)	34.5	36.6
Smoking history (pack-years)[a]	55.6±29.6	56.1±27.9
Duration of COPD (years)[a]	9.4±6.5	9.4±6.8
Baseline spirometry[a]		
FEV_1 (L)	1.04±0.37	1.05±0.39
FEV_1 (% predicted)	37.7±11.9	37.7±12.2
FVC (L)	2.40±0.71	2.46±0.81
FEV_1/FVC (%)	43.7±10.0	43.0±9.7

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.
[a] Mean±SD.

Table 4
Baseline use of respiratory medications in the tiotropium and salmeterol groups (% of patients)

Medication	Tiotropium ($n=328$)	Salmeterol ($n=325$)
Any respiratory medication	87.8	87.1
Anticholinergics	57.0	53.8
Short-acting beta-agonists	58.8	57.2
Long-acting beta-agonists	49.4	45.5
Any inhaled corticosteroid	54.3	46.8
Fixed combinations of inhaled corticosteroids/long-acting beta-agonists	13.4	12.3
Theophylline compounds	11.0	12.6
Oral steroids	1.8	2.8
Oxygen	2.1	3.7

Of the randomized patients, 29 (8.8%) of the tiotropium group and 41 (12.6%) of the salmeterol group prematurely discontinued study medication. The most commonly cited reason was worsening of COPD. Fewer patients in the tiotropium group compared with the salmeterol group prematurely discontinued from the study due to worsening of COPD (9 patients (2.7%) vs. 20 patients (6.2%), respectively). Approximately 89% of the randomized patients completed all study visits.

3.2. Spirometric outcomes

Treatment with tiotropium resulted in significantly greater bronchodilation compared with salmeterol, as measured by the co-primary endpoints of average FEV_1 over 12 h and peak FEV_1 at the end of the 12-week treatment period (Table 5). The mean average FEV_1 response over 12 h was significantly higher with tiotropium than with salmeterol (167 vs. 130 ml, respectively, $p=0.03$), as was the peak FEV_1 response (262 vs. 216 ml, respectively, $p=0.01$). This difference was maintained over the full 12-h testing period, as demonstrated by a significantly higher average FEV_1 response with tiotropium over the first 6 h of testing and a similar response difference over the second half of the 12-h testing period ($p<0.05$). The mean FEV_1 values observed at all time points during the 12-h testing interval were higher in the tiotropium group compared with the salmeterol group, with the difference achieving statistical significance ($p<0.05$) at the 2, 3, 8, 10, and 12 hour timepoints (Fig. 1). The morning pre-dose FEV_1 response was numerically higher but not statistically

Table 5
Mean (SE) FEV_1 response (mL) after 12 weeks of treatment

FEV_1 Response	Tiotropium ($n=308$)	Salmeterol ($n=300$)	Difference	p-value	95% C.I.
Average (0–12)	167 (12)	130 (12)	37 (17)	0.03	(4, 69)
Average (0–6)	189 (10)	155 (10)	34 (20)	0.04	(1, 67)
Average (6–12)	144 (10)	104 (10)	40 (20)	0.02	(6, 73)
Peak	262 (13)	216 (13)	46 (18)	0.01	(11, 81)
Trough	88 (10)	71 (11)	18 (15)	0.24	(−12, 47)

significantly different with tiotropium compared with salmeterol.

Tiotropium demonstrated significantly greater post-dose average FVC response compared with salmeterol (Fig. 2), which was maintained over the full 12-h testing period (Table 6, $p<0.01$). The peak FVC response was significantly greater with tiotropium than with salmeterol, as were mean FVC measurements at all timepoints throughout the 12-h testing period ($p<0.05$). Morning pre-dose FVC was also significantly higher with tiotropium compared with salmeterol ($p<0.05$).

3.3. Rescue medication use

Rescue salbutamol use was low at baseline and decreased after the first week of treatment in both groups. Patients in the tiotropium group used rescue medication on average, approximately 0.01–0.51 more occasions per day compared with the salmeterol group. This difference became statistically significant after Week 3. This pattern was also observed in daytime salbutamol use (1.56–1.75 vs. 1.33–1.57 mean occasions per day, tiotropium vs. salbutamol, respectively). Nighttime use of rescue salbutamol use was considerably lower and was similar in both groups. The use of other concomitant respiratory medications was similar in both groups.

3.4. COPD exacerbations

The overall incidence of COPD exacerbations was low. The percentage of patients with at least one exacerbation during the 12-week period was numerically lower in the tiotropium group compared with salmeterol (9 vs. 11%, respectively, $p=0.37$). The frequency of exacerbations, exacerbation days and time to first exacerbation were similar between treatment groups. Fewer patients in the tiotropium group compared with the salmeterol group experienced a COPD exacerbation requiring hospitalization (4 vs. 9, respectively, $p=0.16$).

3.5. Adverse events

The overall incidence of adverse events was comparable in both treatment groups; 41.5% of patients in the tiotropium group and 40.6% in the salmeterol group experienced an adverse event. As might be expected in this patient population, disorders of the lower respiratory tract were the most commonly reported adverse events. Fewer patients treated with tiotropium compared with salmeterol experienced these events (12.5 vs. 17.5% of patients, respectively). The most common adverse event related to tiotropium was dry mouth, which occurred in a higher percentage of patients in the tiotropium group compared with salmeterol (4.9 vs. 1.2% of patients, respectively).

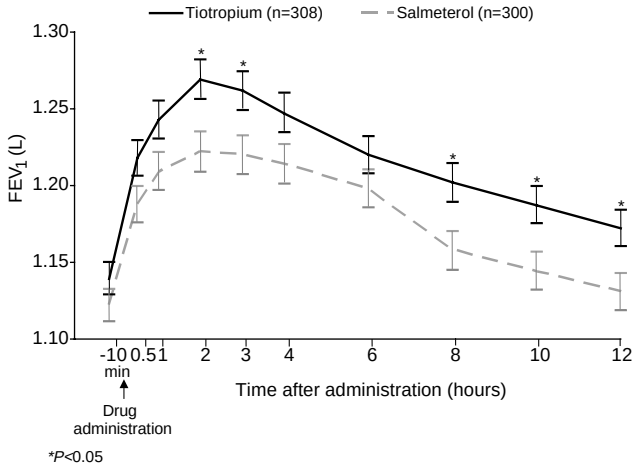

Fig. 1. Mean (SE) FEV_1 (L) over the 12-h testing interval after 12 weeks of treatment in the tiotropium and salmeterol groups. Means are adjusted for baseline FEV_1, treatment and center.

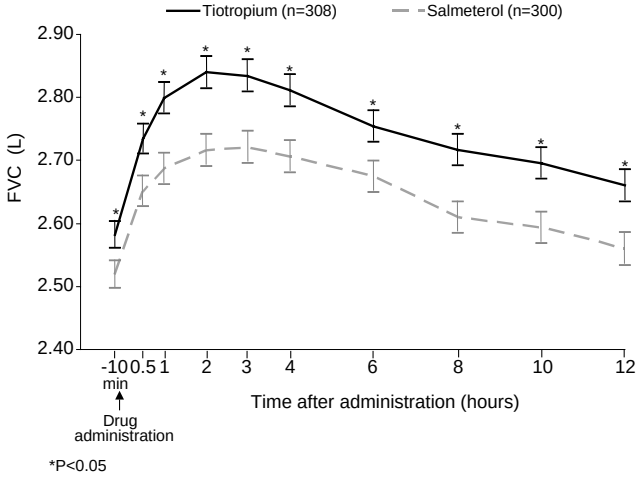

Fig. 2. Mean (SE) FVC (L) over the 12-h testing interval after 12 weeks of treatment in the tiotropium and salmeterol groups. Means are adjusted for baseline FVC, treatment and center.

Table 6
Mean FVC responses (mL) after 12 weeks of treatment

FVC Response	Tiotropium ($n=308$)	Salmeterol ($n=300$)	Difference	p-value	95% C.I.
Average (0–12)	315 (23)	214 (24)	101 (34)	<0.01	(35, 167)
Average (0–6)	355 (20)	254 (20)	102 (30)	<0.01	(36, 168)
Average (6–12)	273 (20)	173 (20)	100 (30)	<0.01	(32, 168)
Peak	493 (25)	374 (25)	120 (36)	<0.01	(49, 190)
Trough	149 (21)	85 (22)	64 (31)	0.04	(4, 124)

Only 26 patients (4%) experienced a serious adverse event during the 12-week treatment period. Significantly, fewer patients experienced serious adverse events in the tiotropium-treated group (2.4 vs. 5.5%, respectively, $p=0.04$) predominantly due to fewer serious lower respiratory tract events. Of note, the percentage of patients with a COPD exacerbation which met serious adverse criteria (i.e. resulting in or prolonging a hospitalization, immediately life-threatening or resulting in serious or prolonged disability, as determined by the investigator) was significantly lower in the tiotropium group compared with the salmeterol group (0.9 vs. 3.1%, respectively, $p=0.04$). During the trial, one death occurred as a result of newly diagnosed adenocarcinoma of the liver in a patient in the tiotropium group.

4. Discussion

This large, multicenter, multinational trial provides further evidence that treatment with tiotropium results in significantly greater bronchodilation compared with salmeterol, and that this enhanced bronchodilation is maintained throughout the day. Patients in the tiotropium-treated group demonstrated significantly higher mean peak and average FEV_1 and FVC responses than those in the salmeterol group. In addition, treatment with tiotropium resulted in significantly higher average FEV_1 and FVC responses than with salmeterol treatment over the entire 12 h observation period. Of note, the average FEV_1 and FVC responses to tiotropium over both the first and second half of the observation period were significantly higher than for salmeterol, indicating consistency throughout the day.

Bronchodilators are central to the management of COPD and current guidelines recommend long-acting bronchodilators as first-line therapy for patients requiring long-term maintenance treatment [1,2]. Long-acting inhaled bronchodilators include two classes of medication, long-acting beta-adrenergic agonists and the long-acting anticholinergic, tiotropium. Guidelines do not specifically recommend one class of long-acting inhaled bronchodilator over the other, and clinicians must take several factors into account when deciding which agent to prescribe to a patient. While individual patient response certainly plays a role in clinical decision making, bronchodilator efficacy, onset of action, safety and convenience of dosing are key factors in determining which agent to prescribe. Spirometric comparisons provide a means of directly measuring relative efficacy, although the specific spirometric outcome of most value (i.e. peak post-dose, end of dosing, average over a pre-specified time period) is debatable. Efficacy during daytime hours may be a particularly important factor when selecting a maintenance bronchodilator for patients with COPD, as this is the period of time during which patients would be expected to be most active. Consistently, effective bronchodilation throughout the day may reduce symptoms, which could result in improved functional capacity.

In this study, daytime bronchodilation was assessed by serial spirometric measurements over a 12-h period. This enabled evaluation of the consistency of the post-dose response during daytime, waking hours. Tiotropium manifested consistently higher FEV_1 responses than did salmeterol throughout the 12-h observation period. Peak FEV_1 was specifically evaluated to enable comparison of the two agents independent of the influence of the pharmacodynamic properties of each agent. In a recent publication by Calverley et al. comparing daytime and nighttime dosing of tiotropium with placebo, serial spirometry was performed in COPD patients over a 24-h period [11]. Circadian variability in pulmonary function was clearly demonstrated, with the highest FEV_1 measurements occurring during the daytime post-dose period in all treatment arms including placebo. These data support the concept that the daytime peak FEV_1 reflects the highest attainable post-bronchodilator FEV_1 in a given 24 h period, regardless of whether the agent is administered once daily, as with tiotropium, or twice daily, as with long-acting beta-agonists. Given the findings of the Calverley study, the 'second peak' after the evening dose of long-acting beta-agonist would be expected to be lower than the daytime peak and thus, comparing daytime peaks of FEV_1 and FVC serves as a reasonable comparative measure of maximal bronchodilation over a 24-h period.

Considering the severity of COPD in the study population, rescue salbutamol use at entry into the study was relatively low in both treatment groups. Not unexpectedly, there was an initial reduction in salbutamol use after the first week of treatment which was sustained throughout the treatment period in both treatment groups. However, the tiotropium-treated patients used salbutamol an average 0.01 to 0.51 more occasions per day compared with the salmeterol-treated patients. This difference became statistically significant after Week 3. Decreased rather than increased rescue medication use is generally expected in

the setting of greater bronchodilation. Therefore, these results are somewhat paradoxical and the reasons are unclear. Furthermore, the clinical relevance of an average increase in use of rescue medication of less than one occasion per day is unknown.

Mechanistically, several factors may help explain the greater degree of bronchodilation attained with tiotropium compared with salmeterol. Airflow limitation in COPD is the functional consequence of 3 major processes: airway smooth muscle constriction, inflammation and remodeling of the airways, and destruction of lung parenchyma [12,13]. COPD has both a reversible and irreversible component. Smooth muscle contraction represents the major reversible cause of airflow limitation in COPD and is mediated primarily by cholinergic tone [12,14–16]. In the lungs, acetylcholine released by postganglionic nerve endings stimulates airway smooth muscle contraction [15]. Tiotropium is a long-acting, inhaled, anticholinergic agent with affinity for the three types of cholinergic receptors (muscarinic receptors: M_1, M_2, and M_3) found in the human lung. Stimulation of M_3 receptors on airway smooth muscle by acetylcholine results in bronchoconstriction. The excitatory M_1-receptors are responsible for reflex bronchoconstriction. M_2-receptors have an inhibitory effect on acetylcholine release [16]. Tiotropium exhibits its pharmacologic effects through prolonged inhibition of M_3-receptors at the smooth muscle, leading to bronchodilation [3]. Cholinergic tone, mediated by basal activity of the autonomic nervous system via the vagal nerve, is present in both the COPD and the normal airway [16]. Cholinergic tone is of particular importance in COPD, where airways have pre-existing narrowing by largely irreversible factors such as airway remodeling and parenchymal destruction [15,16]. In contrast to the direct inhibition of cholinergic tone with tiotropium, beta-agonists such as salmeterol work as functional antagonists by inhibiting the bronchoconstricting effects of a variety of mediators, such as histamines, leukotrienes, and kinins [17].

Several clinical trials have compared the relative bronchodilator effect of anticholinergic agents and beta-agonists in patients with COPD. Initial evidence is derived from an early study comparing the bronchodilator efficacy of the short-acting anticholinergic, ipratropium, with the short-acting beta-agonist, metaproteranol, in 261 patients with mild to moderate COPD [18]. Ipratropium demonstrated significantly higher average FEV_1 and FVC responses than metaproteronol over a 6-h, post-dose testing period [18]. Mahler and colleagues compared the efficacy of the short-acting anticholinergic, ipratropium (36 mcg twice daily) with the long-acting beta-agonist, salmeterol (42 mcg twice daily) in a 12-week, randomized, placebo-controlled study that included 411 patients with symptomatic COPD [19]. Both active treatment groups demonstrated significant improvements in FEV_1 as evidenced by serial spirometric measurements over 12 h [19]. Although at Weeks 4 and 8 salmeterol demonstrated greater improvements in FEV_1 area under the curve over 12 h ($AUC_{0–12}$) compared with ipratropium, this difference was not detectable at 12 weeks [19]. Salmeterol displayed significantly higher FEV_1 responses than ipratropium during the first half of the testing period at the 0, 4, and 6 h timepoints. However, both agents displayed similar FEV_1 responses during the second half of the testing period (over hours 6–12) [19]. This finding is consistent with the recommended dosing intervals of the two agents. Both agents demonstrated similar statistically significant improvements in dyspnea at Weeks 2, 4, 8, and 10 compared with placebo; ipratropium also showed statistically significant improvements compared with placebo at Weeks 6 and 12 [19]. More recently, in two 6-month placebo-controlled trials comparing the efficacy of tiotropium and salmeterol in 1207 patients with COPD, tiotropium displayed significantly greater post-dose bronchodilator responses than salmeterol [5,6].

In summary, tiotropium and salmeterol are both effective bronchodilators in COPD and can be considered as first line maintenance treatment options. The present findings are consistent with the results of previously reported clinical trials [6,7] and confirm the greater degree of bronchodilation achieved with tiotropium compared with salmeterol during daytime hours. Future studies are needed to investigate the magnitude of improvement that could be achieved by combining long-acting inhaled bronchodilators with different mechanisms of actions in COPD, and to determine when and which combination medications should be introduced.

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