Improvements in Symptom-Limited Exercise Performance Over 8 h With Once-Daily Tiotropium in Patients With COPD

François Maltais, Alan Hamilton, Darcy Marciniuk, Paul Hernandez, Frank C. Sciurba, Kai Richter, Steven Kesten and Denis O’Donnell

Chest 2005;128;1168-1178
DOI 10.1378/chest.128.3.1168

The online version of this article, along with updated information and services can be found online on the World Wide Web at: http://chestjournals.org/cgi/content/abstract/128/3/1168
Improvements in Symptom-Limited Exercise Performance Over 8 h With Once-Daily Tiotropium in Patients With COPD*

François Maltais, MD; Alan Hamilton, PhD; Darcy Marciniuk, MD, FCCP; Paul Hernandez, MD, MDCM; Frank C. Sciurba, MD, FCCP; Kai Richter, MD; Steven Kesten, MD, FCCP; and Denis O’Donnell, MD†

Study objectives: We have previously shown that tiotropium at 18 μg reduces lung hyperinflation and dyspnea during exercise and improves exercise tolerance in patients with COPD. The present study was designed to gain further insight into the duration of improvements.

Design, patients, and interventions: A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 261 COPD patients (mean age, 62.5 ± 7.4 years [± SD]; 189 men and 72 women; mean FEV1, 1.2 ± 0.4 L [43 ± 12.7% predicted]). On day 0 (first dose), day 21, and day 42 of treatment, pulmonary function tests were performed before and 1 h after dosing, followed by a constant work rate cycle ergometry test (75% maximum work capacity) to symptom limitation at 2.25 h after dosing. On day 42, an additional constant work rate cycle ergometry test was performed at 8 h after dosing.

Results: Adjusted mean (± SE) endurance time (ET) on day 42 was 803 ± 40 s (tiotropium), vs 568 ± 42 s (placebo) at 2.25 h after dosing (primary end point; treatment difference, 236 ± 58 s; *p* 0.0001) and 665 ± 40 s (tiotropium) vs 494 ± 42 s (placebo) at 8 h after dosing (treatment difference, 171 ± 58 s; *p* = 0.0035). Adjusted mean dyspnea intensity at isotime on day 42 was 4.60 ± 0.16 Borg units (tiotropium), vs 5.65 ± 0.16 Borg units (placebo) at 2.25 h after dosing (*p* < 0.001), and 5.54 ± 0.17 Borg units (tiotropium) vs 6.51 ± 0.18 Borg units (placebo) at 8 h after dosing (*p* < 0.001). Adjusted mean pre-exercise inspiratory capacity (IC) on day 42 was 2.41 ± 0.03 L (tiotropium) vs 2.19 ± 0.03 L (placebo) at 2.25 h after dosing (*p* < 0.001), and 2.31 ± 0.03 L (tiotropium) vs 2.16 ± 0.03 L (placebo) at 8 h after dosing (*p* < 0.001). The significant increase in IC with tiotropium compared with placebo was maintained throughout exercise.

Conclusions: The present study confirms that tiotropium reduces lung hyperinflation at rest and during exercise, reduces exertional dyspnea, and improves symptom-limited exercise tolerance in COPD patients. Furthermore, this study shows that this improvement is present at 2.25 h and at 8 h after dosing after 6 weeks of treatment. (CHEST 2005; 128:1168–1178)

Key words: bronchodilator agents; COPD; dyspnea; exercise tolerance; inspiratory capacity; tiotropium

Abbreviations: CI = confidence interval; DLCO = diffusing capacity of the lung for carbon monoxide; ET = endurance time; FRC = functional residual capacity; IC = inspiratory capacity; IRV = inspiratory reserve volume; RV = residual volume; TLC = total lung capacity; VT = tidal volume; Wmax = maximal work capacity

Management guidelines1–3 for COPD highlight the significant disability experienced by many patients with COPD as a consequence of impairments in pulmonary function. Using the framework established by the World Health Organization for the classification of impairment, disability, and handicap relating to the consequences of disease,4 these COPD management guidelines advocate that therapeutic interventions for COPD should be assessed not only within the domain of impairment (ie, reduced lung function), as has traditionally been the case, but also within the domains of disability and handicap.3 In this regard, an American Thoracic Society/American College of Chest Physicians statement5 has emphasized the utility of clinical exercise testing in the assessment of disability in patients with COPD, specifically noting its advantages in terms of standardizing the measurement of both exertional dyspnea and exercise intolerance, two hallmarks of disability in patients with COPD. Other studies6–11 have shown that the measurement of operating lung volumes during clinical exercise testing comple-
ments the measurements of dyspnea and endurance time (ET) and allows for a more complete characterization of the efficacy of COPD treatments at the impairment/disability interface.

A review of the effects of bronchodilators on exercise capacity in COPD concluded that it would be of clinical and pathophysiologic interest to perform larger-scale studies with ET during cycle ergometry as the primary outcome. We have recently reported results of the first ever, large-scale, multicenter, multinational clinical trial using a submaximal endurance exercise test to symptom limitation in COPD patients as the primary measure of efficacy; 6 weeks of treatment with tiotropium 18 μg qd resulted in increases in inspiratory capacity (IC), reductions in dyspnea, and a 105 ± 40-s improvement in ET during constant work rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wmax), performed 2.25 h after dosing. While these results were encouraging, guidance documents from the US Food and Drug Administration and the Global Initiative for Chronic Obstructive Lung Disease advocate replication of experimental results in order to provide a sufficiently robust degree of evidence in support of the clinical efficacy of treatments. Therefore, the primary goals of the present study were to provide independent substantiation of the effect of tiotropium on exercise tolerance in patients with COPD, and to obtain further evidence in support of the feasibility of exercise testing in a multicenter, multinational setting.

Since tiotropium is a long-acting, once-daily medication, the present study was also designed to address whether administration of tiotropium in the early morning will provide sustained improvements in exercise tolerance throughout the period of the day when the patient is most likely to perform activities of everyday life (8 AM to 5 PM). We therefore evaluated the duration of effect of tiotropium on exercise tolerance by including an additional exercise test at 8 h after dosing after 6 weeks of treatment. Finally, we have also examined whether tiotropium-induced reductions in exertional dyspnea are sufficient to modify the relative contribution of leg discomfort and breathing discomfort to symptom limitation during constant work rate cycle ergometry.

Materials and Methods

Study Subjects

Patients with a clinical diagnosis of COPD based on American Thoracic Society criteria were eligible for the trial (Boehringer Ingelheim 205.223) if they fulfilled the following criteria: age 40 to 75 years, cigarette smoking > 10 pack-years, FEV₁ ≤ 65% predicted, and functional residual capacity (FRC) measured by body plethysmography ≥ 120% predicted. Patients with a history of asthma, allergic rhinitis, or atopy were not eligible for the trial. Also, patients with any recognized contraindication to clinical exercise testing, patients who had participated in a rehabilitation program for COPD within 6 weeks prior to the screening visit, and patients who had participated in the previous study 13 evaluating the effects of tiotropium during constant work rate cycle ergometry were not eligible for the trial.

The concomitant regular use of oral (≤ 10 mg/d of prednisone or equivalent) and inhaled corticosteroids, short-acting theophylline preparations, and mucolytic agents not containing bronchodilators was permitted during the study if the medication was stabilized for at least 6 weeks prior to the screening visit. Patients were not permitted to use oral or long-acting β₂-agonists for at least 1 week prior to the screening visit and throughout the study. Patients were not permitted to use anticholinergics for at least 1 day prior to the screening visit and throughout the study. Open-label albuterol (metered-dose inhaler, 100 μg per actuation) was provided during the study for as-needed symptom relief; patients were required to withhold the use of albuterol for at least 6 h prior to each visit.

Study Design

During an initial screening visit, patients performed pulmonary function tests (body plethysmography, spirometry, single-breath diffusing capacity of the lung for carbon monoxide [DlCO]) to measure baseline characteristics and to determine the patient’s eligibility for the study. Patients also performed incremental cycle ergometry to symptom limitation at this screening visit to determine Wmax. Patients completed two further visits during a 2- to 3-week pretreatment “run-in” phase. At each visit, pulmonary function tests were performed followed by a constant work rate cycle ergometry testing to symptom limitation at 75% Wmax. The constant work rate exercise test performed at the first run-in visit was intended to familiarize the patient with the exercise protocol, while the constant work rate exercise test performed at...
the second run-in visit (day -5) was a priori defined as the pretreatment baseline. In order to avoid unduly long exercise tests, patients who cycled for > 25 min at either of the pretreatment constant work rate exercise tests were not eligible for randomization. After completion of the run-in phase, patients returned to the clinic (day 0) and were randomized to either 18 μg tiotropium or placebo via a dry powder inhaler device. Throughout the 42-day treatment period, trial medication was self-administered by the patient once daily between 8 AM and 9 AM; on test days, administration of trial medication was performed under supervision of research staff. Compliance was monitored by counting of unused medication at each clinic visit. On days 0, 21, and 42 of the treatment period, pulmonary function tests were performed before dosing and 1 h 20 min after dosing, and constant work rate cycle ergometry was performed 2.25 h after dosing. On day 42, an additional constant work rate exercise test was performed 8 h after dosing. Throughout each study visit, patients were discouraged from smoking and from eating or drinking caffeine- or alcohol-containing products. In addition, patients were required to refrain from eating for 2 h prior to each exercise test. The study was approved by local ethics committees, and all patients signed informed consent prior to participation.

Pulmonary Function Testing

On day 0 and day 42 during the treatment period, pulmonary testing included spirometry and body plethysmography. On day 21 during the treatment period, pulmonary function testing only included spirometry. Both spirometry and body plethysmography were performed using standard methodology.17,18 Predose pulmonary function tests on day 0, immediately prior to the first dose of trial medication, were a priori defined as the pretreatment baseline values.

Exercise Testing

The specific details of both the symptom-limited incremental cycle ergometry and the symptom-limited constant work rate cycle ergometry have been described previously.7,8,16 For the incremental exercise test, after subjects performed 3 min of unloaded pedaling, the work rate was increased in a stepwise manner in increments of 10 W/min starting at 10 W; subjects were encouraged to cycle to the point of symptom limitation (ie, patients were instructed “to cycle for as long as you can”). Wmax was defined as the highest work rate that the subject was able to maintain for at least 30 s. For the constant work rate exercise tests, after subjects performed 1 min of unloaded pedaling the work rate was increased to 75% Wmax; subjects were encouraged to cycle to the point of symptom limitation. For all exercise tests, patients were instructed to self-select a comfortable pedaling rate from 50 to 70 revolutions per minute and then to maintain that self-selected pedaling rate throughout exercise. All exercise tests were performed between 10 AM and 11 AM, except for the 8 h postdose test on day 42, which was performed between 4 PM and 5 PM. ET was recorded as the time from the increase in work rate to the point of symptom limitation.

Ventilatory and metabolic parameters were collected breath-by-breath during exercise using commercially available cardio-pulmonary exercise testing equipment. During each constant work rate exercise test, pre-exercise (resting) values were recorded as the average over the last 30 s of the resting period, values during exercise were recorded during the third 30-s period of each 2-min interval during exercise, and end-exercise values were recorded as the average over the last 30 s of exercise. At rest, during each 2-min interval during exercise and at the end of exercise, subjects rated the intensity of breathing discomfort and leg discomfort using the modified Borg scale15 and then performed an IC maneuver. Subjects also rated the intensity of breathing discomfort and leg discomfort and performed an IC maneuver at the end of each minute during the first 5 min of recovery. Immediately after completing exercise, subjects were asked to identify the primary reason for stopping exercise using a questionnaire that has been described previously.20

For dyspnea and leg discomfort, dyspnea-time and leg discomfort-time slopes were determined, since the intensity of dyspnea and leg discomfort increased in an approximately linear manner during exercise. Slopes for other exercise parameters were not determined due to the steady-state conditions associated with the constant work rate exercise protocol. For each individual subject, isotime was defined as the minimum ET among all the constant work rate exercise tests (ie, pretreatment baseline, day 0, day 21, day 42 [2.25 h after dosing], day 42 [8 h after dosing]). Isovalue was defined as the value of a specific parameter at isotime. This isovalue was the observed end-of-exercise value for the exercise test with the minimum ET. For all other exercise tests, which were by definition of longer duration, the isovalue was determined by interpolation between the values at the two time points immediately above and below the isotime.

Analysis

Descriptive data are reported as means ± SD or percentages where appropriate. All other results are reported as adjusted means ± SE (ie, mean adjusted for baseline covariate); for ET results, 95% confidence intervals (CIs) are also provided. The primary end point was a priori defined as the ET on day 42, 2.25 h after dosing. The primary analysis was based on the full analysis data set, which included all patients who completed at least 3 weeks of treatment. Treatment differences between tiotropium and placebo for both primary and secondary end points (except locus of symptom limitation) were compared using analysis of covariance with treatment and center specified as main effects; for all exercise end points, the pretreatment exercise baseline parameters (day -5) were prespecified as covariates; and for all pulmonary function end points, the predose pulmonary function parameters on day 0 were prespecified as covariates. The Fisher Exact Test and x2 test were used to evaluate the effects of treatment with tiotropium compared with placebo on the perceived locus of symptom limitation. For the primary analysis, missing ETs for patients who withdrew due to worsening of study disease were imputed using the last favorable value of all ETs, while ETs that were missing for other reasons were imputed using the last observation carried forward principle. Statistical significance was accepted as p < 0.05 for all analyses. The required sample size of 130 patients per treatment arm was based on an assumption of a true treatment difference in the primary end point, ET on day 42, of 105 ± 258 s using a two-tailed t-test (α = 0.05, β = 0.10). The assumed true treatment difference of 105 ± 258 s was based on the results of the previous study, which provided the best available estimate of the true treatment difference.

Results

Subjects

A total of 261 patients were randomized to treatment (131 tiotropium, 130 placebo); 241 patients (92%) [130 tiotropium, 111 placebo] completed the trial according to the protocol. Of the 20 subjects (1
tiotropium, 19 placebo) who did not complete the trial according to the protocol, the most frequent reason for discontinuation was worsening of disease under study (12 subjects, all in the placebo group). A total of 248 patients (131 tiotropium, 117 placebo) completed at least 3 weeks of treatment and were included in the full analysis data set.

At study entry, groups were well matched for gender, age, pulmonary function, and exercise capacity (Table 1); incremental Wmax ranged from 10 to 220 W. Prestudy use of respiratory medications was well balanced between groups. During the study, 66 patients (50.4%) in the tiotropium group and 67 patients (51.5%) in the placebo group regularly received inhaled corticosteroids, while 10 patients (7.6%) in the tiotropium group and 11 patients (8.5%) in the placebo group regularly received theophylline preparations. Physiologic parameters measured at the end of exercise for the symptom-limited incremental exercise test and the baseline constant work rate exercise test were comparable across groups (Tables 1, 2).

Effects of Tiotropium on Pulmonary Function (Spirometry and Body Plethysmography)

Treatment with tiotropium resulted in the following: (1) significant increases in predose (day 21 and day 42) and postdose (day 0, day 21, and day 42) FEV1, FVC, and slow vital capacity compared with placebo; (2) significant decreases in predose FRC, residual volume (RV), but not total lung capacity (TLC), and a significant increase in predose IC compared with placebo at day 42; and (3) significant decreases in postdose TLC, FRC, and RV, and significant increases in postdose IC compared with placebo at day 0 and day 42 (Table 3).

### Table 2—Baseline Measurements (day – 5) During Constant Work Rate Exercise at 75% Wmax*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tiotropium (n = 131)</th>
<th>Placebo (n = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance time, s</td>
<td>542.9 ± 341.6</td>
<td>526.0 ± 309.8</td>
</tr>
<tr>
<td>Vr, L/min</td>
<td>13.0 ± 3.1</td>
<td>12.8 ± 3.5</td>
</tr>
<tr>
<td>Isotime</td>
<td>40.2 ± 12.8</td>
<td>40.3 ± 12.0</td>
</tr>
<tr>
<td>Peak</td>
<td>41.3 ± 12.9</td>
<td>42.3 ± 12.7</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>18.5 ± 5.4</td>
<td>18.1 ± 5.0</td>
</tr>
<tr>
<td>Isotime</td>
<td>30.5 ± 7.1</td>
<td>29.7 ± 6.4</td>
</tr>
<tr>
<td>Peak</td>
<td>31.8 ± 7.1</td>
<td>31.5 ± 6.5</td>
</tr>
<tr>
<td>Vr, L</td>
<td>0.78 ± 0.27</td>
<td>0.76 ± 0.25</td>
</tr>
<tr>
<td>Isotime</td>
<td>1.35 ± 0.41</td>
<td>1.40 ± 0.45</td>
</tr>
<tr>
<td>Peak</td>
<td>1.33 ± 0.39</td>
<td>1.39 ± 0.43</td>
</tr>
<tr>
<td>IC, L</td>
<td>2.18 ± 0.63</td>
<td>2.22 ± 0.61</td>
</tr>
<tr>
<td>Isotime</td>
<td>1.78 ± 0.57</td>
<td>1.89 ± 0.63</td>
</tr>
<tr>
<td>Peak</td>
<td>1.77 ± 0.57</td>
<td>1.84 ± 0.50</td>
</tr>
<tr>
<td>IRV, L</td>
<td>1.40 ± 0.52</td>
<td>1.45 ± 0.53</td>
</tr>
<tr>
<td>Isotime</td>
<td>0.43 ± 0.31</td>
<td>0.50 ± 0.37</td>
</tr>
<tr>
<td>Peak</td>
<td>0.45 ± 0.33</td>
<td>0.46 ± 0.33</td>
</tr>
<tr>
<td>Dyspnea, Borg</td>
<td>0.5 ± 0.8</td>
<td>0.4 ± 0.7</td>
</tr>
<tr>
<td>Peak</td>
<td>6.7 ± 2.3</td>
<td>7.3 ± 2.4</td>
</tr>
<tr>
<td>Dyspnea-time slope, Borg U/min</td>
<td>0.9 ± 0.7</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>Leg discomfort, Borg</td>
<td>0.3 ± 0.7</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>Peak</td>
<td>6.2 ± 2.8</td>
<td>6.3 ± 2.8</td>
</tr>
<tr>
<td>Leg discomfort-time slope, Borg U/min</td>
<td>0.8 ± 0.7</td>
<td>0.9 ± 0.7</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 1 for expansion of abbreviation.

### Table 1—Subject Characteristics at Study Entry*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tiotropium (n = 131)</th>
<th>Placebo (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>95/36</td>
<td>94/36</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62.9 ± 7.3</td>
<td>62.0 ± 7.5</td>
</tr>
<tr>
<td>Smoking history, pack-yr</td>
<td>54.0 ± 30.5</td>
<td>52.4 ± 26.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.20 ± 0.41</td>
<td>1.22 ± 0.44</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>43.1 ± 12.8</td>
<td>42.8 ± 12.6</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.75 ± 0.76</td>
<td>2.62 ± 0.90</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>44.4 ± 11.9</td>
<td>43.5 ± 9.8</td>
</tr>
<tr>
<td>FRC, L</td>
<td>5.50 ± 1.26</td>
<td>5.62 ± 1.38</td>
</tr>
<tr>
<td>FRC % predicted</td>
<td>171.7 ± 34.7</td>
<td>175.9 ± 40.9</td>
</tr>
<tr>
<td>TLC, L</td>
<td>7.60 ± 1.54</td>
<td>7.69 ± 1.47</td>
</tr>
<tr>
<td>RV, L</td>
<td>4.60 ± 1.20</td>
<td>4.59 ± 1.32</td>
</tr>
<tr>
<td>DLCO, mL/min/mm Hg</td>
<td>14.95 ± 5.53</td>
<td>14.74 ± 5.57</td>
</tr>
<tr>
<td>DLCO % predicted</td>
<td>57.7 ± 19.4</td>
<td>55.8 ± 18.2</td>
</tr>
</tbody>
</table>

**Incremental cycle ergometry (end exercise)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tiotropium (n = 131)</th>
<th>Placebo (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wmax, W</td>
<td>78 ± 32</td>
<td>78 ± 30</td>
</tr>
<tr>
<td>VO2, L/min</td>
<td>1.14 ± 0.47</td>
<td>1.17 ± 0.41</td>
</tr>
<tr>
<td>VO2, % predicted</td>
<td>67.0 ± 23.0</td>
<td>68.8 ± 22.9</td>
</tr>
<tr>
<td>VO2, mL/kg/min</td>
<td>14.8 ± 5.1</td>
<td>15.3 ± 5.1</td>
</tr>
<tr>
<td>VO2CO2, L/min</td>
<td>1.16 ± 0.51</td>
<td>1.19 ± 0.46</td>
</tr>
<tr>
<td>VO2, L/min</td>
<td>41.4 ± 14.0</td>
<td>42.8 ± 13.4</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. VO2 = oxygen consumption; VO2CO2 = carbon dioxide production; VE = minute ventilation.

†Symptom-limited incremental cycle ergometry at study entry. Measurements are averages of last 30 s of loaded exercise.

22.5 h After Dosing: In the tiotropium group, there was an increase in ET after the first dose of trial medication (day 0), with a further increase after 3 weeks of treatment (day 21) that was maintained after 6 weeks (day 42). In the placebo group, ET increased slightly after the first dose of trial medication but decreased toward baseline values after 3 weeks and 6 weeks of treatment (days 21 and 42). At all time points, ET was significantly increased in the tiotropium group compared with the placebo group (Fig 1, top, A).
For the primary end point (day 42, 2.25 h after dosing), the adjusted mean (SE) ET was 803.2 ± 39.5 s (an adjusted mean increase from baseline of 68.5 ± 11.4%) in the tiotropium group, compared with 567.6 ± 41.8 s (an adjusted mean increase from baseline of 10.3 ± 12.1%) in the placebo group (Fig 1, top, A) [adjusted mean difference between tiotropium and placebo, 235.6 ± 56.7 s, p = 0.0001; 95% CI, 122.0 to 349.3 s]. Median increases in ET at 2.25 h after dosing on day 42 (compared with the baseline ET on day −5) were 110.0 s in the tiotropium group and 10.0 s in the placebo group (p = 0.0003). A sensitivity analysis using only patients who completed 6 weeks of treatment (ie, no imputation for missing data) showed that tiotropium improved ET at 2.25 h after dosing on day 42 by 228.5 ± 59.0 s compared with placebo (p = 0.0001).

Two patients (both in the tiotropium group) had ET values > 3,000 s at 2.25 h after dosing on day 42. After removal from the analysis of these two tiotropium patients, adjusted mean ET values were 740.8 ± 29.7 s (an adjusted mean increase from baseline of 46.0 ± 7.0%) in the tiotropium group and 577.2 ± 31.2 s (an adjusted mean increase from baseline of 13.7 ± 7.3%) in the placebo group (adjusted mean difference between tiotropium and placebo, 163.6 ± 43.3 s, p = 0.0002; 95% CI, 78.2 to 248.9 s).

8 h After Dosing (Day 42): The adjusted mean ET was 664.9 ± 39.7 s in the tiotropium group, compared with 493.7 ± 42.0 s in the placebo group (Fig 1, bottom, B) [adjusted mean difference between tiotropium and placebo of 171.1 ± 57.9 s, p = 0.0035; 95% CI, 57.0 to 285.3 s]. In both the tiotropium and placebo groups, ET at 8 h after dosing was significantly decreased compared with ET at 2.25 h after dosing. To allow an appropriate comparison with ET at 2.25 h after dosing, the mean ET at 8 h after dosing was also determined after removal from the analysis of the two outlying tiotropium patients with ET values > 3,000 s at 2.25 h after dosing on day 42; adjusted mean ET values were 609.9 ± 30.0 s in the tiotropium group and 503.6 ± 31.6 s in the placebo group (adjusted mean difference between tiotropium and placebo, 106.3 ± 43.8 s, p = 0.016; 95% CI, 19.9 to 192.7 s).

Effects of Tiotropium on Exertional Dyspnea

2.25 h After Dosing: Dyspnea intensity at isotime was significantly decreased with tiotropium compared with placebo on all test days (p = 0.002 vs
placebo on day 0; p < 0.001 on days 21 and 42; adjusted mean dyspnea intensity at isotime on day 42 was 4.60 ± 0.16 Borg units in the tiotropium group, compared with 5.65 ± 0.16 Borg units in the placebo group (Fig 2, top, A). Despite the significant increase in ET with tiotropium, there was a significant reduction in the intensity of dyspnea at the point of symptom limitation on all test days (p < 0.01 vs placebo on days 0, 21, and 42). Dyspnea-time slopes were also decreased with tiotropium compared with placebo (p < 0.01 on days 0 and 21; p = 0.055 on day 42).

8 h After Dosing (Day 42): The adjusted mean dyspnea intensity at isotime was 5.54 ± 0.17 Borg units with tiotropium, compared with 6.51 ± 0.18 Borg units with placebo (p < 0.001; Fig 2, bottom, B). Despite a significant increase in ET with tiotropium, there was a reduction in the intensity of dyspnea at the point of symptom limitation compared with placebo (p = 0.052; Fig 2, bottom, B). The dyspnea-time slope tended to decrease with tiotropium compared with placebo (p = 0.083).

Dyspnea Intensity During Recovery: The decrease in dyspnea intensity during the first 5 min of recovery is shown in Figure 2, top, A (2.25 h after dosing, day 42) and Figure 2, bottom, B (8 h after dosing, day 42). At 2.25 h after dosing, dyspnea intensity was significantly decreased in the tiotropium group compared with the placebo group for the first 3 min of recovery (p < 0.01). At 8 h after dosing, dyspnea...
Intensity was significantly decreased in the tiotropium group compared with the placebo group for the first minute of recovery (p < 0.01).

Locus of Symptom Limitation

At baseline, in both the tiotropium group and the placebo group, the intensity of breathing discomfort was greater than the intensity of leg discomfort at the point of symptom limitation (tiotropium: breathing discomfort, 6.7 ± 2.3 Borg units [leg discomfort, 6.2 ± 2.8 Borg units]; placebo: breathing discomfort, 7.3 ± 2.4 Borg units [leg discomfort, 6.3 ± 2.8 Borg units]). For all exercise tests during the treatment period, in the tiotropium group the intensity of breathing discomfort was less than the intensity of leg discomfort at the point of symptom limitation (eg, day 42, 2.25 h after dosing: breathing discomfort, 6.1 ± 2.7 Borg units [leg discomfort, 6.4 ± 2.8 Borg units]), while in the placebo group the intensity of breathing discomfort was greater than the intensity of leg discomfort at the point of symptom limitation (eg, day 42, 2.25 h after dosing: breathing discomfort, 7.2 ± 2.4 Borg units [leg discomfort, 6.6 ± 2.9 Borg units]).

Treatment with tiotropium significantly affected the locus of symptom limitation, with a reduction in the proportion of patients reporting limitation by dyspnea (breathing discomfort) and an increase in the proportion of patients reporting limitation by leg discomfort (p = 0.0072; Table 4). In the tiotropium group, the proportion of patients reporting a contribution of breathing discomfort (ie, alone or in combination with leg discomfort) to perceived limitation was 84% at baseline, 69% at 2.25 h after dosing on day 42, and 67% at 8 h after dosing on day 42. In the placebo group, the proportion of patients reporting a contribution of breathing discomfort to perceived limitation was 84% at baseline, 80% at 2.25 h after dosing on day 42 and 79% at 8 h after dosing on day 42.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tiotropium (n = 131), %</th>
<th>Placebo (n = 117), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 42</td>
</tr>
<tr>
<td>Breathing discomfort</td>
<td>35.1</td>
<td>27.5*a</td>
</tr>
<tr>
<td>Breathing discomfort/leg</td>
<td>48.9</td>
<td>41.2</td>
</tr>
<tr>
<td>discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg discomfort</td>
<td>13.7</td>
<td>29.8*a</td>
</tr>
<tr>
<td>None</td>
<td>2.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

*a p < 0.01 vs placebo, χ² test.

Effects of Tiotropium on Operating Lung Volumes During Exercise

2.25 h After Dosing: Treatment with tiotropium resulted in significant increases in IC and inspiratory reserve volume (IRV) at rest (immediately prior to exercise), and significant increases in IC, IRV and tidal volume (VT) at isotime and at the end of exercise compared with placebo on day 0, day 21, and day 42 (day 42 results are shown in Table 5 and Fig 3, top, A). There were no consistent differences between the tiotropium and placebo groups in respiratory rate prior to, during, and at the end of exercise.

8 h After Dosing: Treatment with tiotropium resulted in significant increases in IC and IRV at rest, and significant increases in IC, IRV, and VT at isotime and at end of exercise compared with placebo (Table 5, Fig 3, bottom, B).

IC During Recovery: IC was significantly increased during the first 5 min of recovery in the tiotropium group compared with the placebo group after each constant work rate exercise test. In both groups, complete recovery of IC to pre-exercise values was not achieved by 5 min after exercise. At the end of exercise, IC was reduced to 80% of the pre-exercise value in the tiotropium group (1.92 ± 0.03 L vs 2.41 ± 0.03 L) and to 81% of the pre-exercise value in the placebo group (1.78 ± 0.03 L vs 2.19 ± 0.03 L); by 5 min after exercise, IC had increased to 94% of the pre-exercise value in the tiotropium group (2.27 ± 0.03 L) and to 95% of the pre-exercise value in the placebo group (2.07 ± 0.03 L).

Adverse Events

The number of patients experiencing an adverse event (tiotropium, 57 patients [43.5%]; placebo, 69 patients [53.1%]) and the number of patients experiencing a serious adverse event according to International Conference on Harmonization criteria21 (tiotropium, 2 patients [1.5%]; placebo, 2 patients [1.5%]) was similar between treatment groups. The most common adverse events seen in patients receiving tiotropium were dry mouth (8 patients [6.1%] receiving tiotropium, 5 patients [3.8%] receiving placebo); headache (8 patients [6.1%] receiving tiotropium, 5 patients [3.8%] receiving placebo); nasopharyngitis (7 patients [5.5%] receiving tiotropium, 10 patients [7.7%] receiving placebo); cough (5 patients [3.8%] receiving tiotropium, 2 patients [1.5%] receiving placebo); upper respiratory tract infection (5 patients [3.8%] receiving tiotropium, 2 patients [1.5%] receiving placebo); dizziness (4 pa-
tients [3.1%] receiving tiotropium, 6 patients [4.6%] receiving placebo); COPD exacerbation (4 patients [3.1%] receiving tiotropium, 7 patients [5.4%] receiving placebo).

A total of 1,735 exercise tests were completed by randomized patients during the trial (917 exercise tests in patients receiving tiotropium, 818 exercise tests in patients receiving placebo). Eleven patients (8.4%) in the tiotropium group and 9 patients (6.9%) in the placebo group experienced an exercise-related adverse event; none of these was a serious adverse event.

#### Discussion

Important goals of COPD management include alleviation of exertional dyspnea and improvement in exercise tolerance. In the present study, 6 weeks of treatment with tiotropium 18 μg/d significantly reduced lung hyperinflation at rest and during exercise, reduced exertional dyspnea, and improved exercise tolerance 2.25 h after dosing in patients with COPD, providing independent substantiation of the results of a previous exercise tolerance study conducted with tiotropium. The study has also provided important new information: (1) the effects of tiotropium on lung hyperinflation, exertional dyspnea, and exercise tolerance are still evident 8 h after dosing, and (2) the tiotropium-associated reductions in exertional dyspnea are sufficient to shift the locus of symptom limitation, with a reduction in the contribution of breathing discomfort and an increase in the contribution of leg discomfort.

The results for endurance time during constant work rate exercise testing performed 2.25 h after dosing were generally consistent with the results of the previous exercise study, both in the direction and magnitude of the change. Although the magnitude of the treatment difference was greater in the present study than in the previous study on all test days (day 0, 71 s vs 40 s; day 21, 228 s vs 67 s; day 42, 236 s vs 105 s, respectively), there was an overlap of the 95% CI at each time point between the two
studies (eg, on day 42, 95% CI, 26 to 185 s in the first study, vs 122 to 349 s in the present study). In both studies, there was an increase in ET after 3 weeks of treatment compared with the first dose, but the previously observed trend for a progressive increase in ET between 3 weeks and 6 weeks of treatment was not confirmed in the present study. It remains to be determined whether increases in activities of daily living following longer treatment with tiotropium can result in a physiologic training effect.

The a priori-defined population for the analysis of the primary end point (ET at 2.25 h after dosing on day 42) included all patients who completed at least 3 weeks of treatment. However, two outliers were identified in the tiotropium group who had ETs > 3,000 s on day 42, 2.25 h after dosing. While the ET in these two patients was prolonged, the improvements were plausible and were associated with marked improvements in static lung volumes. The work rate/ET relationship in COPD patients is hyperbolic, such that at certain points of the curve (ie, the elbow of the curve), small reductions in either work rate or exertional dyspnea will result in substantial increases in ET. Thus, it is conceivable that for these outliers, the improvements in IC, exertional dyspnea, and ET were true effects. Nevertheless, a more conservative summary measure of the treatment effect for ET may be the mean treatment difference after removing the outliers (ie, 164-s improvement compared with placebo) or the median increase in ET from baseline for the full analysis data set (ie, 110-s improvement with tiotropium compared with 10-s improvement with placebo).

The inclusion of an 8-h postdose exercise test on day 42 provided new and important information, with regards to the duration of effect of tiotropium on exercise tolerance, and also with regards to the variability in exercise tolerance at different time points during the day in patients with COPD. Although previous studies have demonstrated significant effects of tiotropium on measures of pulmonary function up to 24 h after dosing (ie, predose, or trough values in the present study), direct measurement of exercise tolerance at later time points after dosing is preferable to inferences from results of pulmonary function. Certain constraints of the study design require comment to ensure appropriate interpretation of the results of the 8-h postdose exercise test. A baseline exercise test for the 8-h postdose time point was not included, and so the present study does not provide information regarding treatment effects relative to baseline at 8 h after dosing. Furthermore, the 8-h postdose exercise tests were performed on the same day as the 2.25-h postdose time point, such that the magnitude of the increase in endurance time compared with placebo at 8 h after dosing should be interpreted in the context of the additional work performed by patients during the first symptom-limited exercise test at 2.25 h after dosing. This may be a reasonable representation of the repetitive type of work performed in everyday life.

The degree of improvement in exercise ET during constant work rate cycle ergometry that is considered to be clinically relevant is yet to be determined. Nevertheless, the results of the present study provide important confirmation that improvements in pulmonary function following treatment with tiotropium are meaningful in terms of associated reductions in the degree of dyspnea experienced during exercise and a consequent improvement in symptom-limited exercise performance throughout the major activity-related period of the day, a potentially clinically relevant finding. Since the cycle ergometry methodology employed in the study necessarily constrains patient behavior (ie, work rate set externally), further work is warranted to determine whether the observed improvements in the “capacity” to perform exercise are translated into increases in the degree of activity performed during everyday life, either spontaneously or in combination with additional initiatives such as patient education programs and exercise training.

A recent study has also used constant work rate cycle ergometry at 75% Wmax to examine the effects of the long-acting β-agonist, salmeterol, on ventilatory responses and exercise tolerance in patients with COPD. However, differences in study characteristics (eg, single-center, cross-over design, ET as secondary end point, placebo ET of 4.5 min) precludes any meaningful comparison with the present study. A direct head-to-head comparison is required to appropriately address the relative effects of tiotropium and long-acting β-agonists on exercise tolerance, preferably using a study design that also allows an evaluation of the additive effects of the combination therapy (ie, tiotropium plus long-acting β-agonist) in comparison to the individual monotherapies.

While the diurnal variation in pulmonary function measures such as FEV1 and FVC over the complete 24-h period has been documented, to our knowledge this issue has not previously been addressed with regards to exercise tolerance. A number of factors may be proposed to explain the 13% reduction in ET in the placebo group at 4 to 5 pm (494 s) compared with 10 to 11 am (568 s): (1) a reduction in exercise tolerance due to reductions in pulmonary function (ie, ventilatory capacity); (2) consequences of the first exercise test, eg, residual fatigue resulting from the exhaustive nature of the exercise test, or decreased motivation to tolerate the discomfort associated with the exercise task for a second time in
the space of a few hours; (3) decreased motivation for reasons other than the conduct of the first test, eg, the requirement to stay in the clinic for the full day could reduce the motivation to tolerate the discomfort, or there may be a reduced motivation during the later hours of the day. In the placebo group between 2.25 h and 8 h after dosing, the dyspnea-time slope increased by 20% (from 1.0 to 1.2 Borg units per minute), while IC only decreased by 1.4% (from 2.19 to 2.16 L). Therefore, the concomitant increase in exertional dyspnea and decrease in ET suggest that the decrease in ET is not simply a consequence of a decreased motivation to continue exercise at the later time point, but is associated with an increase in a stimulus for dyspnea. However, the lack of a concomitant decrease in IC suggests that other factors need to be considered with respect to an explanation of the increased dyspnea intensity at later time points during the day. The recognition of the multifactorial nature of exercise tolerance in patients with COPD has promoted an integrative approach to the evaluation of exercise tolerance.

The important contribution of leg discomfort to symptom limitation during incremental cycle ergometry suggests that a perspective of symptom limitation in patients with COPD that only focuses on dyspnea is overly simplistic. In the present study, we have shown that the contribution of leg discomfort to symptom limitation is also important during constant work rate cycle ergometry. Furthermore, tiotropium-induced reductions in exertional dyspnea were sufficient to shift the locus of perceived symptom limitation, with a reduction in the proportion of patients with breathing discomfort alone as the perceived symptom limitation and an increase in the proportion of patients with leg discomfort alone as the perceived symptom limitation. This shift in the locus of symptom limitation may explain the reduction in the intensity of breathing discomfort at the point of symptom limitation with tiotropium, since a greater proportion of patients stopped exercise due to intolerable leg discomfort before the intensity of breathing discomfort reached an intolerable level. This further emphasizes that the relative contribution of breathing discomfort and leg discomfort to symptom limitation is an important consideration in an integrative approach to clinical exercise testing in patients with COPD.

In conclusion, the present study has provided independent substantiation that tiotropium significantly reduces lung hyperinflation at rest and during exercise, reduces exertional dyspnea and improves exercise tolerance in patients with COPD. We have also demonstrated that the reductions in exertional dyspnea as a consequence of treatment with tiotropium were sufficient to shift the locus of symptom limitation from breathing discomfort toward leg discomfort. Finally, we have shown that the improvements in IC, exertional dyspnea, and exercise tolerance are still present 8 h after dosing. Thus, treatment with tiotropium provides sustained improvement in exercise tolerance over a period of the day when patients are most likely to perform significant daily activities.

ACKNOWLEDGMENT: The authors thank the following investigators and their research staff who participated in this trial. The authors also thank Dr. Shailendra Menjoge (Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT) for assistance with statistical analysis.

APPENDIX

Study Participants

Dr. Raja Abboud (Vancouver Hospital & Health Sciences Centre, Vancouver, BC, Canada); Dr. Tony Babb (Presbyterian Hospital, Dallas, TX); Dr. Jean Bourbeau and Dr. Helene Perrault (Montreal Chest Institute, Montreal, PQ, Canada); Dr. Bartolome Celli (St. Elizabeth’s Medical Center, Boston, MA); Dr. Ulrich Fölsch (Klinikum der Christian-Albrechts-University, Kiel, Germany); Dr. Gordon Ford (Rockyview General Hospital, Calgary, AB, Canada); Dr. Peter Frith (Repatriation General Hospital, Daw Park, SA, Australia); Dr. Roger Goldstein (West Park Hospital, Toronto, ON, Canada); Dr. Alejandro Grassino (Centre Hospital de l’Université de Montreal, Montreal, PQ, Canada); Dr. Ulf Hardest (Praxis Dr. Harneit, München, Germany); Dr. Richard Hodder (Ottawa Hospital, Civic Campus, Ottawa, ON, Canada); Dr. Bruce Johnson (Mayo Clinic, Rochester, MN); Dr. Kieran Killian (McMaster University Medical Centre, Hamilton, ON, Canada); Dr. Andree Koch (Universitätsklinikum, Köln, Germany); Dr. Norbert Krug (Fraunhofer-Institut, Hannover, Germany); Dr. Richard Light (St. Thomas Hospital, Nashville, TN); Dr. Christine McDonald (Austin & Repatriation Medical Centre, Heidelberg, VIC, Australia); Dr. David McKenzie (Prince of Wales Hospital, Sydney, NSW, Australia); Dr. Ann-Marie Southcott (Queen Elizabeth Hospital, Woodville, SA, Australia); Dr. Tobias Welte (Universitätsklinikum Otto-von-Guericke, Magdeburg, Germany); Dr. John Whealeys (Westmead Hospital, Westmead, NSW, Australia); Dr. Eric Wong and Dr. Richard Jones (University of Alberta, Edmonton, AB, Canada); Dr. Noe Zamel (Toronto Hospital, Toronto, ON, Canada).

REFERENCES


5 ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167:211–277
15 American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1995; 152:S77–S120
Improvements in Symptom-Limited Exercise Performance Over 8 h With Once-Daily Tiotropium in Patients With COPD
François Maltais, Alan Hamilton, Darcy Marciniuk, Paul Hernandez, Frank C. Sciurba, Kai Richter, Steven Kesten and Denis O'Donnell
Chest 2005;128;1168-1178
DOI 10.1378/chest.128.3.1168

This information is current as of March 16, 2007

Updated Information & Services
Updated information and services, including high-resolution figures, can be found at:
http://chestjournals.org/cgi/content/full/128/3/1168

References
This article cites 20 articles, 16 of which you can access for free at:
http://chestjournals.org/cgi/content/full/128/3/1168#BIBL

Citations
This article has been cited by 8 HighWire-hosted articles:
http://chestjournals.org/cgi/content/full/128/3/1168

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://chestjournals.org/misc/reprints.shtml

Reprints
Information about ordering reprints can be found online:
http://chestjournals.org/misc/reprints.shtml

Email alerting service
Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.

Images in PowerPoint format
Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.