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Lack of protective effect of tiotropium vs induced dynamic hyperinflation in moderate COPD

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Summary
Study objective: Novel evaluation of protective effect of tiotropium against induced dynamic hyperinflation (DH) during metronome paced hyperventilation (MPH) in moderate COPD.
Methods: Prospective, randomized, double-blind, placebo control, crossover study. Lung function measured pre/post MPH at 30 breaths/min for 20 s in 29 (18M) COPD patients (GOLD Stage 2) age 70 ± 9 yr (mean ± SD) before and after 30 days of 18 μg tiotropium bromide vs placebo. Lung CT scored for emphysema (ES).
Results: At baseline post 180 μg aerosolized albuterol sulfate, FEV_1: 1.8 ± 0.6 L (69 ± 6%pred) and ≥60% predicted in all, and 14 of 29 had FEV_1 (L) ≥70% predicted with FEV_1/FVC 58 ± 8%. After 29 days + 23 h post tiotropium (trough) there was significant decrease only in FRC/TLC% ($p = 0.04$); after 30 days + 2 h post tiotropium (peak) significant increase only in FEV_1 (L) ($p = 0.03$) compared to placebo. Results post MPH induced DH at baseline and after 30 days and 2 h post placebo or tiotropium were similar with decrease in IC 0.44 ± 0.06 L ($p < 0.001$). Correlation between ES and increased FEV_1 (L) at peak tiotropium: $r = 0.19$, $p = 0.96$ and decreased FRC/TLC% at trough tiotropium: $r = -0.26$, $p = 0.36$.
Conclusion: In moderate COPD, tiotropium did not reduce MPH induced DH and reduction in IC. However, at peak tiotropium, there was significant bronchodilation in FEV_1 (L) and at trough a decrease in FRC/TLC% compared to placebo despite varying emphysema.

Abbreviations: IC, inspiratory capacity; MPH, metronome paced hyperventilation; DH, dynamic hyperinflation; FEV_1, forced expiratory volume (L) in 1 s; FRC, functional residual capacity (L); TLC, total lung capacity (L).

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Introduction

In moderate-to-severe COPD, FEV_1 (L) % predicted correlated poorly with clinical symptoms, exercise endurance and response to bronchodilators. Alternatively, exercise testing using constant or incremental cycle ergometry with repeated measurements of inspiratory capacity (IC) has been used to detect dynamic hyperinflation and evaluate the response to bronchodilators.[1]

O'Donnell et al.[2] have reported that Borg dyspneic ratings and inspiratory capacity (IC) and endurance time during submaximal cycle exercise testing were highly reproducible and responsive to intervention in moderate-to-severe COPD. Repeated measurements of IC during exercise reflect changes in end-expiratory lung volume[3–5] since total lung capacity remains constant after acute bronchodilation and during exercise.[6,7] Additionally, peak values of inspiratory esophageal pressures used as a surrogate to estimate effort, are relatively constant and correlated with breathing frequency at a given tidal volume during multiple measurements of exercise IC.[8,9]

Reduction in IC during exercise, reflects dynamic hyperinflation (DH), and correlates with decreased exercise endurance, and increased exertional dyspnea as well as breathing frequency in COPD patients.[5] We previously reported the reduction in IC with metronome paced hyperventilation (MPH), a relatively simple procedure, was similar to decrease in IC following incremental symptom-limited cycle ergometry in moderate-to-severe COPD.[1] We also noted 54 μg of inhaled ipratropium bromide (IB) failed to blunt the decrease in IC.[1] Previously, O'Donnell et al.[2] noted greater bronchodilation with much larger doses of nebulized IB (500 μg) when compared to usual doses of inhaled albuterol sulfate in patients with COPD. Subsequently, using constant cycle ergometry, O'Donnell et al.[10] reported 18 μg tiotropium in patients with moderate-to-severe COPD improved IC, exercise endurance and exertional dyspnea.

We previously reported in moderate-to-severe COPD patients, tiotropium did not reduce DH induced by MPH.[11] However, tiotropium induced bronchodilation with increase in IC and decrease in end-expiratory lung volume was in part compensatory and helped blunt dynamic hyperinflation.[11] Moreover, tiotropium induced bronchodilation was independent of the extent of lung CT scored emphysema in moderate-to-severe COPD[12] (GOLD Stage 2 and 3).[13]

The primary co-end points of the current novel study were to evaluate: (1) trough and peak bronchodilator role of tiotropium and (2) its ability to blunt MPH induced DH in moderate GOLD Stage 2 COPD patients.[13] The secondary endpoints were to correlate primary physiologic responses with varying extent of lung CT scored emphysema.[14]

Methods

We recruited 30 patients with smoking history >20 pack yr with documented GOLD Stage 2 moderate COPD[13] who were clinically stable for at least 6 weeks prior to the present study and were not on oxygen or oral corticosteroid. This was a prospective, randomized, double-blind, placebo control, tiotropium crossover pilot study. History of wheezing and/or responsiveness to aerosolized albuterol were not specific inclusion or exclusion criteria. Quality of life was graded using established SGRQ criteria.[15] Patients were instructed to continue all their usual medications, but to withhold short-acting aerosolized $beta_2$-agonists and/or ipratropium bromide for 6 h and long-acting inhaled $beta_2$-agonists (salmeterol or formoterol in all patients) for 48 h prior to initial baseline testing. Volunteer patients for this study were required to be off tiotropium for at least 4 weeks or be tiotropium naïve prior to initiating the study. During the study only short-acting aerosolized $beta_2$-agonist was permitted.

Informed patient consent and approval from the University of Toronto Medical Center, Ontario, Canada and Western Institutional Review Board, Olympia, Washington was obtained and this study was registered with NCT: 00569270. Patients underwent lung function studies before and after 180 μg of aerosolized albuterol sulfate via MDI using techniques and predictive values previously described in detail.[1,11,12] We used a spirometer (Model Vmax29), and pressure-compensated flow plethysmograph (Model 6200), both from SensorMedics, CareFusion, Yorba Linda, California.

Subsequently, on separate days, MPH was obtained (Vmax29) using previously described methods[1,11,12] in 30 COPD patients. The goal was to achieve respiratory rate twice baseline rate for 20 s, which was immediately followed by sequential measurement of inspiratory capacity, expiratory spirometry, and within 30 s plethysmographic measurement of functional residual capacity. While no attempt was made to control end tidal carbon dioxide, patients were coached to maintain a respiratory rate synchronous with the metronome. Near-constant dynamic tidal volume during MPH was achieved by having patients observe a graphic display of their breathing pattern, however no attempt was made to blunt any increase in ventilation synchronous with the metronome. Patients were studied at baseline and subsequently randomized to either 30 days of 18 μg tiotropium or 30 days of placebo and then intervention crossed. Technicians who performed these studies were blinded as were treating physicians and patients to their medication. The technique for measuring inspiratory capacity has been previously described.[1,2,4]

High-resolution thin-section CT of lung

High-resolution, thin-section scans of the lung were obtained using a helical 64 slice multi detector-row CT (Siemens Model Sensation 64, Malverne, PA) were obtained in a subset of 19 patients. Images were obtained at 5 mm collimation at intervals of 6 mm using 120 kVp and varying mA dependent upon patient size. Reconstructured 1 mm slices were obtained every 9 mm using window width of 850 HU and level of −600 HU with edge enhancing algorithm. Images were scored by a radiologist (Mark J. Schein MD, Department of Radiology, Lakewood Regional Medical Center, Lakewood, California) 0 to 100, none to worst emphysema, using picture templates, we previously validated using inflated whole lung specimens.[14]

Statistical analysis

Statistical analyses was performed by Fernando Camacho (Damos Inc., Toronto, Ontario, Canada.) Since a crossover design was used, the *p*-value for a given variable was