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Effect of tiotropium bromide on the cardiovascular response to exercise in COPD

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Dyspnea;
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Summary
Introduction: Exercise limitation and exertional dyspnea are important symptoms of chronic obstructive pulmonary disease (COPD), which may be partially relieved by tiotropium. Although the mechanism of relief is multifactorial, improved dynamic ventilatory mechanics appear to be important. It is not however known whether tiotropium may also act by improving cardiovascular function during exercise.
Methods: We conducted a randomized, placebo-controlled crossover study in 18 COPD subjects with a FEV_1 40 $\pm$ 3% predicted (mean $\pm$ SEM). Subjects inhaled either tiotropium 18 μg or placebo once daily for 7–10 days then the other intervention for a further 7–10 days after a 35-day washout period. Subjects performed constant work rate cycle exercise at 75% of maximum after each treatment period. Heart rate, blood pressure, oxygen uptake, operating lung volumes and breathing pattern were measured.
Results: Heart rate was 7 beats/min lower at rest and throughout exercise with tiotropium compared to placebo ($p = 0.001$). Oxygen uptake was unchanged throughout exercise. Oxygen pulse on exercise was greater by 7.4% ($p < 0.01$) and systolic blood pressure was lower by 7 mmHg ($p = 0.03$). The cardiac rate pressure product was reduced by 7.6% ($p < 0.01$) with tiotropium. Exercise endurance tended to be greater with tiotropium. Reduction in heart rate on exercise correlated with an increase in inspiratory reserve volume ($r = -0.50$, $p = 0.04$).
Conclusion: Tiotropium may improve cardiac as well as pulmonary function during exercise in COPD. We suggest that this effect may be due, in part, to improved cardiopulmonary interaction as a result of mechanical unloading of the ventilatory muscles however further study is required. ClinicalTrials.gov Identifier: NCT00274027.

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Introduction

Exercise limitation and exertional dyspnea are often the most important symptoms experienced by individuals with chronic obstructive pulmonary disease (COPD). The cause of exercise limitation is multifactorial. Dynamic pulmonary hyperinflation during exercise with resulting neuromechanical dissociation is likely to be important in individuals with moderate to severe COPD.[1] Abnormalities of cardiovascular function, pulmonary gas exchange, peripheral muscle function, and perception of symptoms may also contribute.[2–4]

Tiotropium bromide is a long acting anticholinergic agent that has demonstrated efficacy as inhaled therapy for COPD in improving exertional dyspnea, health status, spirometry, exercise tolerance and exacerbation frequency.[5–7] It is as effective or more effective than the short acting anticholinergic agent ipratropium and the long-acting β-adrenoreceptor agonist salmeterol.[8,9] Tiotropium therapy produces a reduction in dynamic hyperinflation and neuromechanical dissociation during exercise in COPD patients,[10] a potential explanation for the improvements in exertional dyspnea and exercise capacity.

What is not known is whether the beneficial effect of tiotropium on exercise capacity may be due in part to improvements in the cardiovascular response to exercise. No study to date has examined the cardiovascular effects of tiotropium during exercise. Tiotropium could affect the cardiovascular system either directly or through its pulmonary effects via a cardiopulmonary interaction. A direct cardiac action is plausible as other anticholinergic agents are known to exert direct effects on the cardiovascular system. Atropine is a nonselective anticholinergic that increases heart rate and myocardial work at rest and during exercise.[11] In contrast, when the anticholinergic agents ipratropium and oxitropium are inhaled, resting heart rate may be slightly reduced.[12,13] Oxitropium has also been shown to slightly attenuate the exercise-induced rise in pulmonary artery pressure in COPD patients.[13] Like ipratropium and oxitropium, tiotropium has not been associated with classic anticholinergic effects such as tachycardia and may also slightly reduce resting heart rate.[14] Tiotropium however differs from traditional anticholinergic agents in its relative kinetic selectivity for M1 and M3 airway muscarinic receptor subtypes over the M2 cardiac muscarinic receptor subtype[15] and its direct cardiac effects during exercise are unknown.

Another possibility is that tiotropium may affect the cardiovascular response to exercise by improving expiratory airflow and pulmonary mechanics via a cardiopulmonary interaction. Tiotropium improves dynamic hyperinflation during exercise.[7,16] This allows tidal breathing to occur on the more favorable, linear portion of the respiratory pressure–volume curve and allows tidal breaths to be generated using less negative inspiratory pleural pressures.[10] Negative pleural pressures increase cardiac afterload as the ventricles must overcome the transmural pressure, the difference between thoracic and ventricular pressure, in addition to arterial pressure.[17,18] This cardiopulmonary interaction may be a limiting factor for exercise in individuals with severe COPD[19] and other cardiopulmonary interactions may also be relevant.

We recently conducted a controlled clinical study designed to assess the effect of tiotropium on the sensory and pulmonary responses to exercise in COPD patients.[10] In the current study, we assessed cardiovascular data obtained at the time of this study to determine the effect of tiotropium on the cardiovascular response to exercise in COPD.

Methods

Subjects

Subjects were eligible for inclusion if they had COPD,[20] were clinically stable, had a $\geqslant$20 pack-year cigarette smoke exposure, a forced expiratory volume in 1 s (FEV_1) $\leqslant$65% predicted, a functional residual capacity (FRC) $\geqslant$120% predicted and a modified baseline dyspnea index score $\leqslant$6.[21] Subjects were excluded if they had comorbid disease that could contribute to dyspnea and exercise limitation, a contraindication to exercise testing,[22] daytime oxygen use or had participated in a pulmonary rehabilitation program in the 6 weeks prior to the study.

Study design

The study incorporated a randomized, double-blind, placebo-controlled crossover design. Approval was obtained from the local hospital and university research ethics board. After giving written informed consent, subjects completed a screening assessment to determine eligibility where medical history, physical examination, chronic dyspnea evaluation, pulmonary function testing and a symptom-limited incremental cycle exercise test were performed. Eligible subjects entered a baseline period during which further pulmonary function tests and a constant load exercise test were performed to familiarize subjects with testing procedures in order to avoid possible learning effects. These tests were performed again both prior to and at the end of each of two 7–10 day treatment periods separated by a 35 day washout period. During each treatment period, subjects inhaled visually identical study medication, either tiotropium 18 μg or placebo, once daily in addition to other regular medication. Subjects were randomized in blocks of four using commercial software (ClinPro/LBL Version 5.2, Clinical Systems Inc.) to have an equal chance of being allocated to receive tiotropium during the first treatment period followed by placebo during the second treatment period or placebo during the first treatment period followed by tiotropium during the second treatment period. Subjects completed a follow up visit 1 week after completion of the second treatment period consisting of a physical examination and pulmonary function tests.

Subjects avoided oral and long-acting β-agonists for 1 week before the screening visit and throughout the study and short-acting anticholinergics for 1 day before and throughout the study. Tiotropium or other long-acting anticholinergics were avoided apart from the study medication. Salbutamol was provided as an aerosol inhaler as rescue medication during the study. Concomitant regular corticosteroids and theophylline were permitted throughout the study except that before each study visit, short-acting