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


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Received 9 January 2007; accepted 16 March 2007

Available online 1 May 2007

KEYWORDS
Dyspnea;
Placebo;
Heart rate;
Blood pressure

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 FEV1 ≤ 73% predicted (mean ± 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. Abnormalities of cardiovascular function, pulmonary gas exchange, peripheral muscle function, and perception of symptoms may also contribute.

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. It is as effective or more effective than the short acting anticholinergic agent ipratropium and the long-acting β-adrenoceptor agonist salmeterol. Tiotropium therapy produces a reduction in dynamic hyperinflation and neuromechanical dissociation during exercise in COPD patients, 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. In contrast, when the anticholinergic agents ipratropium and oxitropium are inhaled, resting heart rate may be slightly reduced. Oxitropium has also been shown to slightly attenuate the exercise-induced rise in pulmonary artery pressure in COPD patients. Like ipratropium and oxitropium, tiotropium has not been associated with classic anticholinergic effects such as tachycardia and may also slightly reduce resting heart rate. 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 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. 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. 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. This cardiopulmonary interaction may be a limiting factor for exercise in individuals with severe COPD 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. 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, were clinically stable, had a forced expiratory volume in 1 s (FEV1) ≥ 65% predicted, a functional residual capacity (FRC) ≥ 120% predicted and a modified baseline dyspnea index score ≤ 6. Subjects were excluded if they had comorbid disease that could contribute to dyspnea and exercise limitation, a contraindication to exercise testing, 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...
theophylline and long-acting theophylline were withheld for at least 24 and 48 h, respectively. Subjects avoided β-agonist use, caffeine, alcohol, heavy meals and major physical exertion before study visits which were all held in the morning. Post treatment assessments were performed 80–120 min after the last study medication dose.

Procedures

Pulmonary function measurements were collected according to recommended standards23–25 by use of automated equipment (Vmax 229d with Autobox 6200 DL, SensorMedics, Yorba Linda, CA) and expressed as percentages of predicted normal values as previously described.10 Predicted inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted FRC. Symptom-limited exercise tests were conducted on an electronically braked cycle ergometer (Ergometrics800S, SensorMedics) by use of a cardiopulmonary exercise testing system (Vmax 229d, SensorMedics) as previously described.7,26–28 Incremental exercise testing was performed using 1 min increments of 10W each following a 1 min warm up of unloaded pedaling. Constant-load tests were performed at 75% of the maximal incremental work rate for each subject. Endurance time was defined as the duration of loaded pedaling.

Measurements were collected while subjects breathed through a mouthpiece with a low-resistance flow transducer while nose clips were worn. Standard cardiopulmonary exercise test parameters29 were collected on a breath-by-breath basis. Intensity of dyspnea and leg discomfort was recorded using the 10-point Borg scale30 at rest, during the last 30 s period of every 1 min interval during exercise and at end exercise. Operating lung volumes were derived from IC manoeuvres31–33 performed at rest, within the last 30 s period of every 2 min interval during exercise and at end exercise. Blood pressure was measured by auscultation of the right brachial artery, using a sphygmomanometer with an arm cuff, at rest, within the first 30 s period of every 2 min interval, at end exercise and every 5 min during recovery until blood pressure measurements returned to near baseline. Oxyhemoglobin saturation was recorded continuously via a pulse oximeter.

Analysis of exercise endpoints

All breath-by-breath measurements were averaged in 30 s intervals throughout each test stage, rest, exercise and recovery. To avoid contamination of breath-by-breath data by the artifact of the IC maneuver, symptom ratings and IC measurements collected in a 30 s period that included an IC maneuver were linked to breath-by-breath data collected in the previous 30 s period. Systolic and diastolic blood pressure measurements were linearly extrapolated where necessary to give an estimated blood pressure that was linked to breath-by-breath data and symptom ratings obtained in between blood pressure measurements. Pre-exercise rest was defined as the steady-state period after at least 3 min of quiet breathing on the mouthpiece while seated at rest before exercise. Cardiopulmonary parameters were averaged over the last 30 s of this period and IC measurements at rest were collected while breathing on the same system immediately after completion of the quiet breathing period. A standardized time near end exercise (isotime) was defined as the highest common exercise time achieved during post treatment constant-load tests performed by a given subject, rounded down to the nearest whole minute. Peak exercise was defined as the last 30 s of loaded pedaling, cardiopulmonary parameters were averaged over this period, symptom ratings and IC measurements were collected immediately at the end of this period. The rate pressure product, a noninvasive marker of myocardial oxygen consumption31 was calculated as heart rate multiplied by systolic blood pressure.

Statistical analysis

The sample size was chosen to have adequate power to detect a 300 ml difference in IC at isotime, \( p < 0.05 \) significance level was used for all analyses. Treatment responses were compared by two-tailed paired t-tests. Pearson correlations were used to establish associations between cardiopulmonary variables. Data are shown as mean plus or minus the standard error of the mean.

Results

Eighteen subjects completed the study (Table 1). No subject experienced oxyhemoglobin desaturation below 88% or a significant elevation of end-tidal carbon dioxide tension during incremental exercise. No sequence or carryover effects were found with respect to cardiorespiratory variables, pulmonary variables or symptoms. The work rate for constant load exercise was 50 ± 5 W.

Effect of tiotropium at rest

Heart rate was lower at rest following tiotropium treatment compared to placebo by 6.7 ± 1.8 beats/min (95% confidence interval 3.2–10.1, \( p = 0.001 \)). Diastolic blood pressure and the rate pressure product were also lower by 4.0 ± 1.5 mmHg (95% confidence interval 1.0–7.0, \( p = 0.014 \)) and 900 ± 200 mmHg beats/min (95% confidence interval 400–1300, \( p = 0.001 \)), respectively (Table 2). Other cardiovascular variables were not significantly changed. FEV1 and FVC increased at rest following tiotropium treatment compared to placebo (Table 2). There was no significant change in the FEV1/FVC ratio. Lung hyperinflation and airway resistance decreased and airway conductance increased with tiotropium. Breathing pattern during preexercise rest was unchanged except that the ratio of inspiratory time to total breath time increased with tiotropium (\( p = 0.003 \)).

Effect of tiotropium on the response to exercise

Post-treatment exercise endurance time was greater by \( 0.9 ± 0.8 \) min or 14% after tiotropium compared to placebo, not a statistically significant difference. Selected mean cardiovascular and pulmonary responses to exercise are shown in Fig. 1. Heart rate was significantly lower with tiotropium throughout exercise. Oxygen uptake (\( \text{VO}_2 \)) was
Correlates of reduced heart rate on exercise

The difference in heart rate at isotime with tiotropium compared to placebo correlated with the difference in end-inspiratory lung volume (EIL V) as a percent of TLC (partial multiple $r = 0.53$, $p = 0.02$) and the difference in IRV (partial multiple $r = -0.50$, $p = 0.04$) more strongly than with any other measured cardiopulmonary variables.
Discussion

The novel finding of this study is a consistent, statistically significant and potentially clinically important effect of tiotropium on the cardiovascular response to exercise in subjects with COPD. Heart rate was lower with tiotropium at rest and throughout exercise by 7 beats/min with a corresponding increase in oxygen pulse, a surrogate measure of cardiac stroke volume, and a reduction in the rate pressure product, a surrogate measure of myocardial work at isotime during exercise. The reduction in heart rate at isotime during exercise correlated best with indices of dynamic hyperinflation, suggesting an association between the cardiac effects of tiotropium and improved pulmonary mechanics. These results suggest that either tiotropium exerts a direct effect on the cardiovascular system or that...
longer. Although systemically available, the current results by intravenous administration and persisting in plasma for plasma concentrations approximately 60% of that achieved that reaches the lung has a high bioavailability giving peak meta-analysis suggests that there is an increased rate of clinically significant effects. A recent pulmonary arterial pressure.

Tiotropium antagonism of the M3 receptors of the pulmonary vasculature may result in both inhibition of vasoconstriction and inhibition of endothelial-dependent vasodilatation. It is possible that the net effect of these actions may reduce resting or exercise-induced pulmonary vascular tone and possible that the net effect of these actions may reduce inhibition of endothelial-dependent vasodilatation. It is lawful may result in both inhibition of vasoconstriction and inhibition of endothelial-dependent vasodilatation. It is possible that the net effect of these actions may reduce resting or exercise-induced pulmonary vascular tone and possible that the net effect of these actions may reduce inhibition of endothelial-dependent vasodilatation. It is possible that the net effect of these actions may reduce restoration of exercise-induced pulmonary vascular tone and pulmonary arterial pressure.

Studies of the cardiovascular effects of tiotropium at rest have reported few clinically significant effects. A recent meta-analysis suggests that there is an increased rate of cardiac arrhythmias, primarily atrial fibrillation, with tiotropium although this increase was statistically significant only after one study responsible for significant heterogeneity was excluded. An increased rate of cardiac death with ipratropium was noted in the Lung Health study but this finding was not replicated in other studies and has not been reported with tiotropium.

Potential cardiopulmonary interactions

Tiotropium significantly improved measures of dynamic hyperinflation during exercise, confirming the findings of other studies. As described above, this effect could result in reduced cardiac afterload which may explain the observed improvement in cardiac function. The association of improvement in EILV and IRV, both measures of dynamic hyperinflation, with improvement in heart rate is consistent with this hypothesis but the association does not imply causation. Other potential interactions mediating the effect of tiotropium include improved pulmonary blood flow associated with reduced air trapping, reduction in heart rate due to reduced discharge from slowly adapting pulmonary stretch receptors, reduction in left ventricular compression from right ventricular overfilling and reduction in positive pleural pressure during expiration.

Relation to other research

We are not aware of any other study that has examined the effect of tiotropium on the cardiovascular response to exercise. The reduction in heart rate during exercise that we observed with tiotropium was not seen with either the short-acting anticholinergic oxitropium or the short-acting β-agonist fenoterol in a study of exercise hemodynamics. A study of the effects of the long-acting β-agonist salmeterol during exercise also showed no reduction in heart rate despite a similar degree of improvement in dynamic hyperinflation to that observed with tiotropium. The apparent difference between tiotropium and salmeterol is suggestive of a direct cardiovascular effect of tiotropium. The alternative explanation is that both agents act to reduce heart rate during exercise via improved cardiopulmonary interactions but in the case of salmeterol the effect is obscured by the tachycardia resulting from systemic β-adrenergic stimulation.

Clinically and statistically significant differences in exercise endurance time with tiotropium have been previously reported in large trials. As described above, this effect could result in reduced cardiac afterload which may explain the observed improvement in cardiac function. The association of improvement in EILV and IRV, both measures of dynamic hyperinflation, with improvement in heart rate is consistent with this hypothesis but the association does not imply causation. Other potential interactions mediating the effect of tiotropium include improved pulmonary blood flow associated with reduced air trapping, reduction in heart rate due to reduced discharge from slowly adapting pulmonary stretch receptors, reduction in left ventricular compression from right ventricular overfilling and reduction in positive pleural pressure during expiration.

Limitations of this study

The data presented here were derived from a study primarily designed to assess the pulmonary and symptomatic response to exercise in COPD so a full range of hemodynamic measurements was not undertaken. Oxygen pulse and rate pressure product are only surrogate measures of stroke volume and myocardial work, respectively. We have no reason to suspect that the changes in these measures observed with tiotropium do not reflect similar changes in the bronchodilating and lung deflating actions of tiotropium result in improved cardiac function via a cardiopulmonary interaction.

Potential direct cardiovascular effects of tiotropium

Tiotropium administered by inhalation is mostly swallowed, very little of which is absorbed systemically. The fraction that reaches the lung has a high bioavailability giving peak plasma concentrations approximately 60% of that achieved by intravenous administration and persisting in plasma for longer. Although systemically available, the current results cannot be explained by tiotropium antagonism at cardiac M2 muscarinic receptors as this effect would produce an increase rather than a decrease in heart rate. Tiotropium agonism of the M3 receptors of the pulmonary vasculature may result in both inhibition of vasoconstriction and inhibition of endothelial-dependent vasodilatation. It is possible that the net effect of these actions may reduce resting or exercise-induced pulmonary vascular tone and pulmonary arterial pressure.

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Values are means ± SE. *p < 0.05 tiotropium versus placebo. VO₂, oxygen uptake. Vₑ, minute ventilation. VCO₂, carbon dioxide production. V₅, tidal volume. IC, inspiratory capacity. IRV, inspiratory reserve volume. EILV, end-inspiratory lung volume. TLC, total lung capacity.
stroke volume and myocardial work, but further study utilizing invasive hemodynamic measurement is required to conclusively determine this. Likewise, we were not able to directly measure cardiac output, ejection fraction or pulmonary artery pressure to help explain the mechanism or mechanisms by which tiotropium affects the cardiac response to exercise and determine whether the effect of tiotropium on the cardiovascular system is physiologically beneficial or not. From our data, we observed that exercise endurance was at least as good with tiotropium while measures of myocardial work were reduced suggesting that the effect of tiotropium is more likely to be beneficial than not. As the current analysis was performed post hoc, the chance that the results presented here represent a type I error is increased. The consistency of the effect throughout exercise suggests that the effect is real however prospective validation is required.

Conclusion

Tiotropium may improve cardiac as well as pulmonary function during exercise in COPD. We hypothesize that this is due to a reduction in negative inspiratory pressure brought about by alleviation of dynamic hyperinflation through bronchodilation rather than a direct effect of tiotropium on the heart. Further study is required to determine the mechanism of this effect.

Conflict of interest statement

This research was supported by the Ontario Ministry of Health, Boehringer Ingelheim (Canada) and Pfizer Canada. Steven Kesten is an employee of Boehringer Ingelheim Pharmaceuticals, Inc.

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