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Research Paper

Responsiveness to Ipratropium Bromide in Male and Female Patients with Mild to Moderate Chronic Obstructive Pulmonary Disease

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ABSTRACT

Introduction: Although the prevalence of chronic obstructive pulmonary disease (COPD) is similar between men and women, current evidence used to support bronchodilator therapy has been generated in therapeutic trials that have predominately enrolled male patients. Here, we determined whether there is any significant sex-related differences in FEV_1 responses to ipratropium bromide.
Methods: Data from the Lung Health Study (n = 5887; 37% females) were used to determine changes in FEV_1 with ipratropium or placebo in male and female subjects with mild to moderate COPD over 5 years. Lung Expression Quantitative Trait Loci (eQTL) dataset was used to determine whether there were any sex-related differences in gene expression for muscarinic (M2 and M3) receptors in lungs of male and female patients.
Results: After 4 months, ipratropium therapy increased FEV_1 by 6.0% in female and 2.9% in male subjects from baseline values ($p = 2.42 \times 10^{-16}$). This effect was modified by body mass index (BMI) such that the biggest improvements in FEV_1 with ipratropium were observed in thin female subjects (p for BMI * sex interaction = 0.044). The sex-related changes in FEV_1 related to ipratropium persisted for 2 years ($p = 0.0134$). Female compared with male lungs had greater gene expression for M3 relative to M2 receptors ($p = 6.86 \times 10^{-8}$).
Conclusion: Ipratropium induces a larger bronchodilator response in female than in male patients and the benefits are particularly notable in non-obese females. Female lungs have greater gene expression for the M3 muscarinic receptor relative to M2 receptors than male lungs. Female patients are thus more likely to benefit from ipratropium than male COPD patients.

1. Introduction

Traditionally, owing to greater cigarette smoking in men, chronic obstructive pulmonary disease (COPD) has been considered a "male disease". However, with the marked rise in the smoking rates in women since the 1960's, there has been a sharp increase in the burden of COPD among women throughout much of the Western world. Today, in the United States (US), there are 7 million more women than men with COPD and 10,000 more women than men die from COPD each year. Currently, the mortality rate is nearly 10 fold higher in women than in men (3.7%/year in females and 0.4%/year in males) (Ma et al., 2015). Despite this, ironically, the current management strategies for COPD (in both men and women) are largely based on therapeutic clinical trials that have recruited mostly male patients. In most therapeutic trials (even contemporary ones), female patients make up only 20%–25% of the total cohort (Calverley et al., 2007; Magnussen et al., 2014).

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There are some compelling biological reasons why there may be significant sex-related differences in the therapeutic responsiveness of inhaled drugs in COPD. Firstly, there are emerging data that indicate for the same severity of COPD, as measured by lung function, female patients have less emphysema and more small airways disease (Dransfield et al., 2007; Cazzola et al., 2011). Secondly, female patients with COPD demonstrate greater levels of bronchial reactivity to non-specific stimuli such as methacholine compared with male patients for the same degree of airflow limitation (Tashkin et al., 1992). Thirdly, women may have heightened xenobiotic metabolism of chemicals including those related to cigarette smoke and medications, as well different gene or protein expression (compared to men) of known drug targets and transporters which may modify the effectiveness of therapeutic drugs (Benowitz et al., 2006). Despite these considerations, it is not known whether there is any significant sexual dimorphism in the way in which men and women respond to commonly inhaled drugs in COPD (Statista, n.d.; FirstWord Pharma, 2013). The principal aim of the present study was to determine whether there are any sex-related differences in bronchodilation related to the use of inhaled ipratropium, one of the most commonly prescribed muscarinic receptor antagonist in the world, in patients with COPD (Statista, n.d.; FirstWord Pharma, 2013).

2. Methods

2.1. Data Source

To address the primary aim of the current study, we used data from the Lung Health Study (LHS). The details of LHS have been reported previously (Anthonisen et al., 1994). Briefly, LHS was originally designed to determine the effects of ipratropium and smoking cessation programs on the rate of decline in lung function over 5 years. At the time of recruitment all subjects were active smokers between the ages of 35 and 60 years (with a mean age of 48 years) who had smoked at least 10 cigarettes a day within the 30 days prior to initial screening and who demonstrated mild to moderate COPD on spirometry defined by forced expiratory volume in 1 s (FEV_1) of 55% to 90% of predicted, in the presence of FEV_1/forced vital capacity (FVC) ratio of <0.70 after bronchodilation (mean FEV_1 of the cohort was 75% predicted and the mean FEV_1/FVC was 63% post-bronchodilator).

After enrollment, these patients were randomly assigned to one of 3 groups: 1) usual care (UC), who received no intervention, n = 1964; 2) an intense anti-smoking (special) intervention and ipratropium bromide (Atrovent®, Boehringer Ingelheim Pharmaceuticals) n = 1961 (SIA); or 3) an intense anti-smoking (special) intervention and an inhaled placebo, n = 1962 (SIP). Subjects were excluded if they had serious co-morbidities that could have interfered with follow-up or impacted lung function (e.g. overt heart failure, ischemic heart disease, or malignancy other than skin cancer). Ten centres participated in the original study and together they recruited 5887 patients (of whom 37% were females). Those who were in the SIP or SIA groups received a program that consisted of: 1) a strong recommendation by attending physician for smoking cessation in an one-to-one encounter; 2) a group program led by a health educator that met 12 times over 10 weeks, which taught behaviour modification techniques; and 3) a nicotine replacement therapy with nicotine gum (Nicorette Gum, Marion Merrell Dow Inc), which was provided at no cost to patients. Those who successfully quit smoking were enrolled in a maintenance program to prevent relapses.

2.2. Spirometry and Follow-up

At the baseline visit, a detailed history of respiratory symptoms and smoking status was obtained. These included years of smoking, number of pack-years of smoking, current number of cigarettes smoked per day and the age of initiation. Additionally, all subjects underwent spirometry, which was performed according to the standards of the American Thoracic Society. Bronchodilator response was measured after 2 inhalations of isoproterenol (200 μg total dose).

2.3. Interventions

Patients who were assigned to ipratropium or inhaled placebo were instructed on the use of metered dose inhalers by a physician and were asked to use 2 puffs (36 μg) of the inhaler 3 times a day. All subjects were brought back 4 months following randomization to encourage inhaler compliance and to determine smoking status. Smoking status was ascertained by detailed self-report that included the number of cigarettes smoked per day and exposure to any other forms of nicotine and objectively validated by measuring exhaled carbon monoxide (at every visit) and salivary cotinine (at annual visits) using well-validated immunoassays. The cutoff of exhaled carbon monoxide was 10 parts per million (ppm) to denote active smoking and that for salivary cotinine was 20 ng/ml. All subjects who exceeded any of these thresholds were classified as smokers. These objective measures of smoking status were blinded to patients. Non-smoking was defined at each annual visit by abstinence from all smoked tobacco products, validated by salivary cotinine and exhaled carbon monoxide. Sustained quitters were defined as non-smoking at all annual visits from year 1 through year 5. Continuous smokers were defined as smokers at all annual visits and intermittent quitters were defined as those who were nonsmokers in at least one annual follow-up visit (Anthonisen et al., 1994). At annual visits, in addition to the above, spirometry was performed before and after 2 puffs of isoproterenol. Compliance with inhalers was assessed by self-report and by weighing the canister. Follow-up was successful in 90% of patients over these 5 years.

2.4. Gene expression for M2 and M3 Muscarinic Receptor Subtypes in Lungs

One important factor that may determine responsiveness to inhaled therapeutic drugs is the receptor expression for the ligand in lung tissue. As the LHS did not obtain lung tissue, we used data from the Lung Expression Quantitative Trait Loci (eQTL) study (Hao et al., 2012) to determine whether there was a sex-related difference in the gene expression for M3 (CHRM3) and M2 (CHRM2) muscarinic receptor in lungs of individuals, who underwent lung resection surgery. The M3 receptor is the primary muscarinic receptor subtype that induces bronchial smooth muscle contraction; whereas presynaptic M2's are autoreceptors that prevent the release of acetylcholine from preganglionic and parasympathetic nerve fibres and thus negatively regulate the M3 receptor pathway (Karakiulakis and Roth, 2012). Post-synaptic M2 receptors, which are also expressed in airway smooth muscle cells, attenuate adenylyl cyclase activity and thus promote smooth muscle relaxation (Montuschi and Ciabattoni, 2015). Since ipratropium is a non-selective anti-muscarinic agent, we used the ratio of M3/M2 (CHRM3/CHRM2) receptor gene expression in lungs to estimate the potential responsiveness to ipratropium. The details of the eQTL study have been previously published (Hao et al., 2012). Briefly, gene expression profiles were obtained, using a custom Affymetrix array, which contained 51,627 non-control probesets, on 1111 lung tissue samples from individuals, who underwent lung resection surgery for a variety of different clinical indications, at 3 centres (Laval University, University of British Columbia [UBC] and University of Groningen). After quality control, the data were filtered and normalized. Samples that did not pass quality control were discarded. The final dataset contained 964 samples (n = 441 females; 46% of cohort). On the Affymetrix array, the CHRM3 and CHRM2 genes were represented by 100154030_TGI_at and 100310990_TGI_at probesets, respectively. The lung tissue expression data are available at NCBI Gene Expression Omnibus repository (GEO, http://www.ncbi.nlm.nih.gov/geo) through accession number GSE23546.

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