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Bronchodilating effect of combined therapy with ipratropium bromide and ondansetron in patients with COPD

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Abstract

The objectives of this study were to determine the effect of single and repeat dosing with oral ondansetron, a 5-HT3-specific receptor blocker, on the degree and duration of bronchodilation induced by inhaled ipratropium bromide in patients with COPD. Five clinics and university medical centers in four countries participated in the study; 47 patients with COPD were randomized to treatment; 44 completed all treatments. Patients had a baseline (pre-bronchodilator) FEV1 > 1 L and post-bronchodilator (200 mcg salbutamol) FEV1 < 90% of predicted, with FEV1 reversibility (to 80 mcg inhaled ipratropium bromide and 400 mcg salbutamol) of at least 12% or 200 mL over baseline. The study was divided into two parts. In Part A, each patient received in a random order, four-way crossover manner, single doses of ondansetron placebo (oral) plus ipratropium bromide placebo (inhaled), ondansetron placebo plus ipratropium bromide 40 mcg inhaled via MDI, ondansetron 24 mg oral plus ipratropium bromide placebo and ondansetron 24 mg plus ipratropium bromide 40 mcg. In Part B, each patient received in a random order, two-way crossover manner, ipratropium bromide 40 mcg tid via MDI plus ondansetron 8 mg oral, qid, for 2 days; on day 3 patients received a single dose of ipratropium bromide 40 mcg plus 8 mg oral ondansetron. Alternatively, patients received ipratropium bromide via MDI and oral ondansetron placebo, as described above. Statistically significant differences in weighted mean FEV1 (0–6 h), peak FEV1 and FEV1 determined 6 h post-dose were noted comparing ipratropium bromide to placebo. Similar positive results were observed for sGaw and FVC. Addition of ondansetron to ipratropium bromide did not significantly modify values obtained with ipratropium alone. Ipratropium bromide induced a marked bronchodilation, compared to placebo. Addition of ondansetron (single or repeated doses) did not significantly increase the degree or duration of bronchodilation induced by ipratropium alone. sGaw was consistently more sensitive than FEV1 in measuring extent and duration of bronchodilation.

Keywords: Drug combination; Combination bronchodilator; COPD; Bronchodilation; Ondansetron; 5-HT3; Ipratropium bromide

1. Introduction

Chronic obstructive pulmonary disease (COPD) has been recognized as a major health problem for about 50 years [1]. In contrast with other leading chronic diseases, its prevalence and disease-related morbidity and mortality are increasing [2–6]. Bronchodilators are typically prescribed for maintenance therapy of the reversible obstructive component of the disease. In patients with minimally reversible or irreversible obstruction, symptom improvement observed following bronchodilator therapy may be related to the degree of reduction in gas trapping and dynamic hyperinflation, which, in turn, may result in reduction in the overall work of breathing [7,8]. The bronchodilators most commonly used are inhaled beta2-adrenoceptor agonists and inhaled anticholinergics [2–5,9]; current international guidelines recommend combination

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therapy for patients not well controlled by monotherapy [2–6], since anticholinergics and beta2-adrenoceptor antagonists achieve their bronchodilating effects via different mechanisms [9]. A number of studies have indeed demonstrated that, in patients with stable COPD, the combination is more effective than either agent alone [9–13].

Dominant autonomic control of the airways is provided by the parasympathetic nerves, which control a variety of airway functions [14,15]. Acetylcholine, released from the parasympathetic nerves, stimulates muscarinic receptors, causing bronchoconstriction and mucus secretion. The effect of acetylcholine in the airways is mediated mainly through three muscarinic receptor subtypes, designated M1, M2 and M3 [16]. M1 receptors facilitate neurotransmission through the cholinergic ganglia; M2 receptors are found on pre- and post-ganglionic parasympathetic nerves and inhibit release of acetylcholine, while M3 receptors are present in airway smooth muscle (ASM) and submucosal glands and are responsible for mediating bronchoconstriction and mucus secretion [16,17]. Inhibition of acetylcholine release by M2 receptors may be decreased or lost due to M2 receptor dysfunction in asthma and in COPD [18,19], resulting in unopposed activity at the M3 receptors. This excessive M3 receptor stimulation may contribute to the bronchoconstriction and mucus hypersecretion observed in inflammatory airways diseases.

Serotonin (5-HT) has also been reported to have effects on ASM contraction through interactions with multiple receptor subtypes. Most data has been generated in in vitro experiments. In isolated rat bronchi 5-HT induced contraction of ASM directly, by activating ASM 5-HT2 receptors, and indirectly, by activating 5-HT2 receptors on parasympathetic nerve endings, leading to release of acetylcholine [20,21].

Studies in human airways have shown that cholinergic contraction induced in vitro following electrical stimulation was increased by the presence of 5-HT; this facilitation of cholinergic contraction could be blocked completely by tropisetron, a 5-HT3 and 5-HT4 receptor blocker, and partially by ondansetron, a 5-HT3 receptor blocker [22]. In subjects with asthma, plasma levels of 5-HT are elevated and correlate with clinical severity rating and FEV1 [23]. One possible source of 5-HT are the endocrine cells of the lung [24]; an increase in the number of endocrine cells (and presumably 5-HT) has been described in bronchiectatic lungs, lung containing neoplasms and lungs of subjects exposed to hypoxia [25]. In a small group of subjects with COPD reversible to albuterol, administration of inhaled or of intravenous ketanserin, a 5-HT2 antagonist, induced a small degree of bronchodilation that was statistically significantly different from placebo, 30 min following administration of the drug [26]. Combination therapy has become standard in the treatment of airway disease; this allows the targeting of diverse mechanisms that participate in the disease process. Identification and characterization of these mechanisms utilizing specific inhibitors may improve our understanding of the disease and could help in the development of optimal treatment. The objective of this study was to determine the short-term effect of single and repeat dosing with ondansetron, a 5-HT3-specific receptor blocker, on the degree of bronchodilation induced by inhaled ipratropium bromide in patients with stable COPD. Three endpoints were evaluated in the determination of bronchodilation: FEV1 and FVC, measured by spirometry, and sGaw, determined by plethysmography.

2. Materials and methods

2.1. Study design

This was a double-blind, randomized, placebo-controlled, crossover, two-part study comparing the effect on pulmonary function of inhaled ipratropium bromide (Atrovent®, Boehringer Ingelheim, Ref. [27]), 40 mcg (single dose or tid), given by metered-dose inhaler, ondansetron (Zofran®, GlaxoSmithKline, Ref. [28]), 24 mg single dose or 8 mg tid, given orally, and their combination.

The study was carried out in five centers in four countries (two centers in the US, one center each in Belgium, The Netherlands and Germany). The study was approved by the appropriate Ethics Committee/Institutional Review Board at each site and was conducted according to the principles of good clinical practice.

The study was divided into two parts and a screening visit. At screening, baseline measurements were performed and the eligibility of patients to participate in the study was determined. Part A of the study (four-way crossover) was conducted within 2 weeks of the screening visit; patients were randomized to receive, in a crossover manner, single doses of ondansetron placebo plus ipratropium bromide placebo, ondansetron placebo plus ipratropium bromide 40 mcg via MDI, ondansetron 24 mg oral plus ipratropium placebo, and ondansetron 24 mg oral plus ipratropium bromide 40 mcg via MDI. Patients received single doses of each study medication in the clinic; spirometry and plethysmography were performed 30 min before and 0.5, 1, 2, 3, 5 and 6 h following administration of study medication. Dosing days were separated from each other by at least 48 h.

Part B of the study was conducted at least 48 h following the last administration of study medication in Part A. Part B was a randomized, double-blind, placebo controlled, two-period crossover study. Patients were randomized to receive ipratropium bromide 40 mcg tid via MDI plus ondansetron placebo qid for 2 days; on day 3, patients received a single dose of ipratropium bromide 40 mcg via MDI plus ondansetron placebo. Alternatively, patients received ipratropium bromide 40 mcg tid via MDI plus ondansetron 8 mg qid orally, for 2 days; on day 3 patients received a single dose of ipratropium bromide 40 mcg via MDI plus ondansetron 8 mg orally. The two study periods were separated from each other by at least 48 h. Patients remained in the clinic for about 7 h following administration of study medication on day 3 of each