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Bronchodilator efficacy of the fixed combination of ipratropium and albuterol compared to albuterol alone in moderate-to-severe persistent asthma

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Abstract

Background: The potential of anticholinergics to provide bronchodilatory benefits over short-acting β_2-agonists (SABA) alone in patients with moderate-to-severe persistent asthma has not been well defined.
Methods: An outpatient, randomized, double-blind, single-dose, crossover study in adult asthmatics with moderate-to-severe obstruction despite treatment with inhaled corticosteroids (ICS) was conducted comparing the fixed combination of ipratropium and albuterol (IB + ALB) to albuterol alone (ALB). Serial spirometry was performed over 6 h. SABA were withheld for 8 h, ICS and LABA for 24 h.
Results: A total of 113 patients were randomized, 106 completed the study (males $n = 47$; mean ± SD age = 51 ± 13 years). Mean ± SD baseline $FEV_1 = 1.4 \pm 0.5$ L (49 ± 12% predicted). IB + ALB resulted in significantly greater improvements over ALB in the average improvement over baseline in FEV_1 as approximated from the area under the curve from 0 to 6 h after drug administration (72 ml, $p < 0.01$) and mean peak FEV_1 response (55 ml, $p < 0.01$) as well as higher FEV_1 responses at individual time points from 0.5 to 6 h postdose ($p < 0.01$ for all). Time to onset of response was similar between groups but time to peak and duration of response were longer with IB + ALB versus ALB (120 versus 60 min and 245 versus 106 min, respectively).
Conclusion: IB + ALB resulted in significantly greater improvement in FEV_1 and longer duration of response compared to ALB alone in patients with moderate-to-severe persistent asthma (Trial number: 1012.50; ClinicalTrial.gov NCT00096616).
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1. Introduction

While short-acting β_2-agonists (SABA) are recommended as first-line rescue medication in asthma, inhaled corticosteroids (ICS) are the mainstay of controller therapy for mild persistent asthma, with higher doses recommended for increasing severity [1,2]. Additionally, long-acting β_2-agonists (LABA), and if needed, leukotriene modifiers, theophylline, and oral corticosteroids are recommended as controller medication in combination with ICS in symptomatic patients with moderate-to-severe persistent asthma [1,2]. However, in moderate-to-severe persistent asthma, the bronchodilator effectiveness of SABA has been shown to become blunted with concurrent LABA use following induced bronchoconstriction challenge with methacholine and exercise [3–5]. However, while inhaled anticholinergics

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have also been recommended in acute asthma treatment, their therapeutic benefit has not been clearly demonstrated [1,2–9]. In the present study, we hypothesized that single-dose fixed combination of ipratropium and albuterol (IB + ALB) would provide greater bronchodilation than single-dose albuterol (ALB) alone in adult patients with moderate-to-severe persistent asthma [1,2] who have persistent symptoms despite treatment with ICS monotherapy or combined ICS and LABA. This cohort of treated asthmatics has not been previously evaluated with respect to single-dose add-on ALB versus IB + ALB.

2. Methods

2.1. Study design

This study was a *randomized*, *double-blind*, *crossover comparison* of treatment with a *single dose* of IB + ALB versus a single dose of ALB in symptomatic adult patients with moderate-to-severe persistent asthma [1,2] despite treatment with ICS. Coprimary efficacy endpoints were: (1) average improvement over baseline in the forced expiratory volume in one second (FEV_1) as approximated from the area under the curve from 0 to 6 h after drug administration ($AUC_{0–6}$) and (2) peak FEV_1 response. Secondary efficacy outcomes included forced vital capacity (FVC) peak response, FVC $AUC_{0–6}$ response, and FEV_1 and FVC at each time point. Percentage of responders, as well as onset, duration, and time to peak therapeutic response were also evaluated.

2.2. Participants

Participants were outpatients with a diagnosis of asthma, ⩾18 years of age, current non-smokers (⩾1 year) with a smoking history ⩽10 pack-years, and persistent symptoms (shortness of breath, wheezing, cough, and nocturnal awakenings), despite using SABA and ICS with or without LABA or other controller medication. Participants had baseline $FEV_1 \leqslant 70\%$ predicted [10] and FEV_1/FVC ratio $< 75\%$, and $FEV_1 < 80\%$ predicted [10] after administration of albuterol 240 mcg (Ventolin® HFA, GlaxoSmithKline, Research Triangle Park, NC) via a metered-dose inhaler (MDI). Reversibility (⩾12% and 200 mL improvement over baseline FEV_1 postalbuterol) had to have been documented either upon enrollment or within ⩽5 years. At entry, patients were required to have been treated with ICS for ⩾1 year at one of the following doses: beclomethasone dipropionate ⩾504 mcg/day; budesonide ⩾400 mcg/day; fluticasone propionate ⩾440 mcg/day; flunisolide ⩾1000 mcg/day; triamcinolone acetonide 1000 mcg/day. Patients were also required to be currently using albuterol as rescue therapy at a dose of 6–56 puffs per week as determined from patient daily records from the 2-week screening period.

Asthmatics were excluded if they had been intubated within ⩽5 years, if they had myocardial infarction or unstable or life-threatening cardiac arrhythmias (⩽1 year), hospitalization for heart failure (⩽3 years), moderate-to-severe renal insufficiency, or any respiratory tract infection or acute asthma exacerbation within 6 weeks prior to screening. Patients were also excluded if they were taking systemic corticosteroids at unstable doses or more than 10 mg/d prednisone (or its equivalent), beta-blockers, open-label anticholinergic bronchodilators, or domiciliary oxygen.

During the trial, respiratory medications including ICS, SABA, LABA, fixed combinations of LABA and ICS, and leukotriene modifiers were permitted.

The study was conducted at 23 investigational sites. The protocol was approved by institutional review boards and written informed consent was obtained from all subjects.

2.3. Treatments

Patients received either IB + ALB (fixed combination of ipratropium bromide 18 mcg and albuterol 103 mcg (Combivent® Inhalation Aerosol, Boehringer Ingelheim GmbH, Ingelheim, Germany) via a CFC MDI) or ALB (albuterol 120 mcg via an HFA MDI). Each dose of IB + ALB or ALB consisted of 2 puffs from the MDI each test day. Consistent with a single-dose, crossover design, patients received one treatment at Visit 3 and the other at Visit 4. The washout period between visits was approximately 5 days. Since the half-life of the active treatments is less than 3 h, no residual effect was expected. Furthermore, both inhalers were fitted into blinding devices which were indistinguishable.

2.4. Procedures

Demographic and asthma background characteristics were collected at the screening visit (Visit 1). Symptom frequency in the 2 weeks prior to Visit 1 was collected using a questionnaire.

At Visit 2 (baseline), spirometry was performed prior to and 30 min following inhalation of 2 puffs of albuterol HFA and qualified patients were randomized. At Visits 3 and 4, spirometry was performed prior to and at 0.25, 0.5, 1, 2, 3, 4, and 6 h following administration of study drug (IB + ALB or ALB). To ensure patient stability, predose spirometry at Visits 3 and 4 had to be within 15% of predose spirometry from the previous visit. Spirometry was performed in triplicate with the patient in a seated position. The best of three spirometric efforts (defined as highest FEV_1 or highest FVC obtained) was reported in accordance with American Thoracic Society recommendations [11]. Inhaled LABA and ICS were withheld for 24 h and SABA were withheld for at least 8 h prior to Visits 2–4. If asthmatics were clinically unstable during Visits 3 and 4 such that additional SABA was required, that study was voided.

Rescue albuterol use was monitored during the study to assess patient stability. Patients recorded the number of

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