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Faster reduction in hyperinflation and improvement in lung ventilation inhomogeneity promoted by aclidinium compared to glycopyrronium in severe stable COPD patients. A randomized crossover study

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ABSTRACT

Standard spyrometric assessment in chronic obstructive pulmonary disease (COPD) only evaluates bronchial obstruction. However, airflow limitation and hyperinflation are the main pathophysiological factors responsible for dyspnoea and reduced exercise tolerance in patients with COPD. This study evaluated the effects of aclidinium bromide 400 μg and glycopyrronium bromide 50 μg on these parameters.

Patients with stable severe/very severe COPD were randomized in this double-blind, double-dummy, crossover, Phase IV study. Patients received single doses of each drug on separate days. Primary endpoints were changes in residual volume (RV) and intra-thoracic gas volume (ITGV), assessed by full-body plethysmography. Other endpoints included changes variations in lung ventilation inhomogeneity (Phase III slope of single-breath nitrogen washout test, SBN2), dyspnoea visual analogue scale, and pulmonary specific total airway resistances. Assessments were performed at baseline and 5, 15, 30, 60, and 180 min post-administration.

Thirty-seven patients were randomized (31 male; mean age 71 years). Aclidinium and glycopyrronium significantly improved ITGV versus baseline at all-time points ($p < 0.05$). Significant improvements in RV were observed after 5 min with aclidinium and after 60 min with glycopyrronium. RV improvements were significantly greater with aclidinium than glycopyrronium from 5 to 60 min post-administration ($p < 0.05$). Both treatments improved dyspnoea versus baseline at all-time points ($p < 0.05$). Aclidinium significantly improved ventilation inhomogeneity versus baseline at all-time points; no significant changes were observed for glycopyrronium.

For the first time two long-acting muscarinic antagonists have been compared in acute conditions with body plethysmography and SBN2 test. We demonstrated that both aclidinium and glycopyrronium significantly reduce hyperinflation and dyspnoea in severe and very severe COPD patients. Aclidinium however promoted a faster reduction in RV and was the only able to reduce lung ventilation inhomogeneity.

Trial Registration numbers available on Clinicaltrials.gov: NCT02181023.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease characterized by partially reversible bronchial obstruction that leads to airflow limitation [1]. The key pathophysiological changes associated with COPD are lung parenchymal changes and

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inflammation with remodeling of the bronchial wall [1]. Both emphysema and small airways disease (≤2 mm internal diameter) result in airflow limitation in COPD. In emphysema, parenchymal destruction reduces the surface area available for gas exchange, reducing elastic recoil, which causes small airway narrowing, airflow limitation, and finally airway closure [2]. The small airways are the most likely anatomical site for airway obstruction in COPD and most other chronic lung diseases [3]. Inflammation with fibrosis, wall thickening, and mucus in small airways are additional causes of airflow limitation in COPD [4]. Even in early stages, the damage to the small airways and the loss of elastic recoil provoke parenchymal disruption that eventually cause air trapping and hyperinflation [5,6]. Severity assessments and management options for COPD are usually established using clinical examination and pulmonary function tests developed to assess the larger airways, such as forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), assessed by spirometry. Hyperinflation and air trapping must be evaluated by body-plethismography, that directly measures the increase in functional residual capacity (FRC) and residual volume (RV). The single-breath nitrogen washout test (SBN2) has been used to assess the premature closure of small airways, the closing volume, and also, by evaluating the Phase III slope, ventilation inhomogeneity [7,8]. Airflow limitation and lung hyperinflation are the physiological factors responsible for dyspnoea and reduced exercise tolerance in patients with COPD [9–11]. Inhaled bronchodilators, such as long-acting muscarinic antagonists (LAMAs) and long acting beta-2 agonists (LABA), represent the cornerstone of long term pharmacological treatment in COPD; because of their ability in increasing inspiratory capacity (IC) and reducing hyperinflation, they have an important role in improving dyspnoea and respiratory symptoms [1,12,13]. LAMAs due their efficacy to the contrasting effect on the dysfunction of autonomic nerve regulation of airway smooth muscle, that contributes to bronchoconstriction and therefore dyspnoea in COPD patients [14] LAMAs are therefore recommended as a first choice therapy either alone or in combination with LABAs or inhaled corticosteroids depending on the severity of disease and history of exacerbation [1]. Aclidinium bromide and glycopyrronium bromide are two recent LAMAs with proven efficacy and safety profile [14–16]. Both drugs significantly reduce hyperinflation and respiratory symptoms in COPD patients and have a faster onset of action when compared to Tiotropium [16–19].

The aim of our study was to evaluate the acute effects of aclidinium bromide and glycopyrronium bromide – on lung hyperinflation, ventilation inhomogeneity, and dyspnoea at rest in patients with severe COPD.

2. Methods

2.1. Patients

Eligible patients were aged 50–80 years with stable COPD, pre-bronchodilator FEV_1 < 50% predicted, and an FEV_1/VC ratio below the 5th percentile of the predicted value [20]. Patients were ex- or current smokers with ≥20 pack-year history and had a residual volume (RV) ≥125% of predicted value. All patients had been diagnosed with COPD for ≥1 year and had been clinically stable for at least 1 month. Patients were excluded if they had experienced an exacerbation of COPD at enrollment, had alpha-1 antitrypsin deficiency, required long-term oxygen therapy >6 L/min, or if they underwent lung volume reduction surgery.

2.2. Study design

This was a prospective, single-center, randomized, double-blind, double-dummy, crossover, Phase IV study conducted in patients with stable severe COPD. The study was registered with Clinicaltrials.gov (NCT02181023), approved by the Fondazione Salvatore Maugeri Central Ethics Committee (approval number 960), and conducted according to Good Clinical Practice guidelines. Written consent was signed by all the patients. Patient data were collected using case report forms. All data were treated anonymously and in accordance with Italian laws on the protection of personal data (DL 196/2003).

The primary objective was to evaluate post-administration reductions in RV and FRC (measured as intra-thoracic gas volume [ITGV]). Other endpoints were to evaluate the effects of study drugs on lung ventilation heterogeneity (SBN2 slope phase III), dyspnoea, inspiratory capacity (IC), vital capacity (VC), FEV_1 and pulmonary specific total airway resistances ($sRaw_{tot}$). Patients received a single dose of aclidinium bromide 400 μg via Genuair™/Pressair®[a] plus placebo via Breezhaler® on one study visit and glycopyrronium bromide 50 μg via Breezhaler plus placebo via Genuair at the other visit. The two drugs were randomly administered by a blinded trained nurse following a randomization list generated using www.graphpad.com and visits were performed on separate days. Before each visit, patients were required to undertake a 72-h washout, during which time no long-acting bronchodilators could be administered. Only short-acting bronchodilators and, for the patients treated with inhaled corticosteroids, prior the study enrollment, an equivalent dose of fluticasone as maintenance ICS were permitted during washout.

2.3. Assessments

Static and dynamic lung volumes, $sRaw_{tot}$ and pulmonary diffusing capacity for carbon monoxide (DLCO) have been assessed by means of a constant-volume body plethysmograph (MasterScreen Body, Erich Jaeger GmbH, Würzburg, Germany), according to current recommendations [21]. Dynamic volumes were obtained during a spirometry test. ITGV was assessed as close as possible to the end-expiratory lung volume with an automatic shutter valve mounted distal to the mouthpiece. As the shutter was closed, patients were instructed to perform gentle efforts against the valve with no change in respiratory rate and no need for panting because of computer-assisted compensation for thermal and humidity effects. After a maximum of 4 s the shutter was opened and patients were requested to exhale to RV and then perform a slow VC maneuver. $sRaw_{tot}$ were obtained during tidal breathing before the ITGV maneuver. DLCO was assessed with the single breath maneuver according to latest guidelines [22]. Lung ventilation heterogeneity was determined using the SBN2 test (VMAX encore, Viasys Health Care, Yorba Linda, CA, USA). and the slope of phase III was taken in account Quality of lung function maneuvers was assessed according to current guidelines [21–23]. For every parameter the mean value of at least three reproducible maneuvers was considered for the analysis [21]. Dyspnoea was evaluated at rest using a visual analogue scale (VAS) to assess the degree of breathlessness at rest, scored from 0 (no breathlessness) to 10 (maximum breathlessness) according to ATS indications [24,25]. All assessments were performed at baseline and 5, 15, 30, 60, and 180 min after drug administration.

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