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The effect of indacaterol during an acute exacerbation of COPD

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ABSTRACT

Some clinical trials have suggested that the inhaled long-acting β_2-agonists (LABAs) may be effective in the treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Since indacaterol, the first once-daily LABA to be developed for the regular treatment of COPD, exhibits fast onset of action and 24-h duration of bronchodilation, we have investigated its effects in patients with AECOPD managed in the emergency department.

In a randomised controlled pilot trial, we have enrolled 29 consecutive patients with a recent (i.e., within ≤4 d) history of AECOPD and requiring hospitalization. All patients received a standard protocol consisting of ipratropium bromide aerosol 500 μg three times a day, intravenous methylprednisolone 20 mg twice-daily and, if indicated, oral levofloxacin 500 mg once-daily. Moreover, they were randomly allocated to one of the two 5-day treatment groups (indacaterol maleate 300 μg once-daily or salbutamol nebulizer 1250 μg three times a day).

The administration of indacaterol 300 μg to patients admitted to emergency department for an AECOPD resulted in a greater improvement of pulmonary function compared with traditional therapy, without cardiovascular side effects.

Our results suggest that indacaterol could be a useful option in the treatment of AECOPD. However, further larger double-blinded randomized clinical trials are needed to validate the intriguing results obtained in this setting.

1. Introduction

Patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) managed in the emergency department must be treated proactively to prevent rapid respiratory deterioration [1]. All guidelines recommend using bronchodilators because they relieve dyspnoea and airflow obstruction during exacerbations [2,3]. Nebulizers and hand-held inhalers can be used to administer inhaled bronchodilators during AECOPDs and the choice of delivery method should consider the ability of the patient to use the device and the dose of drug required [1–3].

Short-acting inhaled β_2-agonists (SABAs) are usually the preferred bronchodilators for the initial treatment of AECOPD [2,3]. There is a great deal of controversy regarding the timing and optimal dose of inhaled β_2-agonists in the treatment of AECOPD. Regrettably, the duration of the bronchodilator effect of SABAs is decreased in AECOPD [4]. In order to overcome the reduced functional half-life of β_2-agonists, several authors have suggested the use of larger-than-usual doses that are sometimes necessary to relieve airway obstruction, but also to dose more frequently [5,6].

The use of LABAs has been suggested as another potential option to overcome the reduced functional half-life of β_2-agonists in AECOPD [7]. Our group has previously demonstrated that formoterol can be considered an alternative to SABAs in the treatment of AECOPD due to its fast onset of action that further increases by increasing the inhaled dose [8].

Indacaterol is the first once-daily LABA for the regular treatment of COPD [9]. In patients with stable moderate-to-severe COPD, single doses of indacaterol 150 and 300 μg demonstrated a fast onset of action similar to that for salbutamol 200 μg [10].

In consideration of the fast onset of action exhibited by indacaterol and its duration of bronchodilation, we have investigated the effects of this once-daily LABA in patients with AECOPD managed in the emergency department.

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2. Methods

2.1. Patients

Twenty-nine consecutive patients with a recent (i.e., within ≤4 d) history of AECOPD and requiring hospitalization according to their attending physician were enrolled in the study. COPD was diagnosed, and its severity was assessed in accordance with the 2006 guidelines of the Global Initiative for Chronic Obstructive Lung Disease [11]. The study was carried out at the Emergency Department of Santo Spirito Hospital in Rome from September 2011 to April 2012 according to Good Clinical Practice and the Declaration of Helsinki. Each patient gave informed consent for participation.

Patients with cor pulmonale, pneumonia, diabetes mellitus, renal failure, lung cancer, atherosclerotic or congenital cardiac disease, left ventricular failure, need for non invasive mechanical ventilation, or inability to perform spirometry due to poor clinical conditions within 24 h of emergency admission were excluded. Patients were also excluded if they had a personal history of asthma, allergic rhinitis, or atopy.

2.2. Methods

This was a non-blinded, randomised, controlled pilot trial. We must highlight that our study was spontaneous, without any financial and organizational support of Pharma Companies. Therefore, it was impossible for us to prepare treatments to be administered in double-blind, double-dummy fashion. After consenting to participate in the study, consecutive eligible patients were randomly allocated to one of the two treatment groups (group A and B) using the sequential randomization scheme ABA. Group A received inhaled indacaterol maleate 300 μg once a day administered before the spirometry and, in the following days, at 8 AM using Breezhaler device. Group B received salbutamol nebulizer 1250 μg three times a day.

All patients also received therapy with ipratropium bromide aerosol 500 μg three times a day, intravenous methylprednisolone 20 mg twice day and oral levofloxacin 500 mg once a day. These drugs and salbutamol nebulizer 1250 μg three times a day are the usual therapeutic regimen at the Emergency Department of the Santo Spirito Hospital in Rome for treating patients suffering from AECOPD.

All participants underwent clinical and radiological examinations, pulmonary function testing, arterial blood gas analysis, and echocardiographic assessment. Plasma levels of Brain Natriuretic Peptide (BNP), troponin I, creatinine, and C-reactive protein (CRP) were measured. All examinations were carried out at admission (*T*0) and day 5 (*T*5).

At day 5, pulmonary function testing was carried out 24 h or 8 h after the last administration of indacaterol or salbutamol, respectively.

2.3. Statistical analysis

In planning this trial there were a number of uncertainties, mainly the feasibility of the study, the sample size required, and the consent rate. Therefore, we decided to undertake a pilot study to test as many elements of the research proposal as possible. Thus, no formal sample size calculations were done. Statistical analysis was conducted using GraphPad Prism (CA, USA) and SPSS (Chicago, IL, USA) software. The values of the variables were expressed as mean and 95% confidence interval (95% CI) and the difference between *T*0 and *T*5 was considered statistically significant for $P < 0.05$, employing the Student's *t*-test and/or the analysis of variance (ANOVA) associated, when necessary, with the Bonferroni post hoc test.

3. Results

Twenty-nine patients with COPD exacerbation were enrolled, 19 were treated with indacaterol (arm A) and 10 with salbutamol (arm B) (Table 1). The gender distribution was 58.62% (17) males and 41.38% (12) females. There were no statistically significant differences in the study population with respect to age (average 75.9 years, 95% CI 73.2–78.5) and BMI (average 28.2, 95% CI 25.8–30.6).

All patients completed the study. There was not statistically significant difference ($p > 0.05$) between the two treatment arms (salbutamol and indacaterol) at *T*0 (baseline, before treatment) with regard to variables considered in this study but BNP concentration, which was significantly higher in salbutamol arm ($P < 0.001$).

In the salbutamol arm, after 5 days of treatment, respiratory rate significantly improved (Table 3). The changes in all other respiratory variables did not reach statistical significance ($P > 0.05$) (Fig. 1, Table 1).

In the indacaterol arm, after 5 days of treatment (*T*5), lung function improved significantly ($P < 0.05$) from baseline (Fig. 1). Also other variables such as respiratory rate, pO_2 and pO_2/FiO_2 improved in a statistically significant manner (Table 2).

In both groups we observed a reduction of pCO_2 values and an improvement of arterial pH but these changes did not reach statistical significance ($P > 0.05$) (Table 2).

Heart rate was stable during both treatments (Table 3). After 5 days, a reduction of troponin I was reported in both arms, but the change in both arms was not statistically significant ($P > 0.05$) (Table 4). Levels of serum BNP were significantly reduced ($P < 0.001$) in the population B (salbutamol) while there was a not significant reduction in the population A (indacaterol) (Table 4). However, the baseline BNP levels in the salbutamol arm were significantly higher than in the indacaterol arm.

No modification of echocardiographic parameters (Table 3) and/or sings of acute coronary syndrome were recorded during treatment in either treatment arm.

However, in one patient treated with indacaterol, an episode of paroxysmal atrial fibrillation was reported, which regressed spontaneously after 6 h and in conjunction with the improvement of the respiratory condition. The administration of indacaterol was not suspended, as we did not assign any causal relationship between the drug and the onset of the arrhythmia.

4. Discussion

Our study suggests that indacaterol could be a useful option in the treatment of AECOPD. This is a novel finding and, to the best of our knowledge, the present trial is the first that has evaluated the effect of indacaterol in patients suffering from an AECOPD.

In our study, 5-day therapy with indacaterol 300 μg o.d. significantly improved pulmonary function. Furthermore, indacaterol reduced respiratory rate and, more importantly, improved pO_2/FiO_2 ratio, suggesting an amelioration of ventilation-perfusion ratio. It is noteworthy that the improvements in pulmonary function and respiratory exchanges were more marked in the

Table 1
Anthropometric characteristics of the studied patients. Regardless of gender, all values are mean and 95% confidence interval.

	Indacaterol	Salbutamol
Gender	F 10 M 9	F 2 M 8
Age	75.37 (72.59–78.15)	76.80 (71.13–82.47)
Weight	78.37 (69.54–84.19)	73.00 (65.57–80.43)
Height	164.32 (159.90–168.73)	166.40 (162.13–170.67)
BMI	29.18 (25.80–32.56)	26.38 (23.80–28.95)

F, female; M, male; BMI, Body mass index.