Respiratory Medicine (2013) 107, 848–853

Available online at www.sciencedirect.com

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Chronic treatment with indacaterol and airway response to salbutamol in stable COPD

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Received 29 October 2012; accepted 11 February 2013
Available online 11 March 2013

KEYWORDS
COPD;
Indacaterol;
Formoterol;
Salbutamol;
Tolerance

Summary
Tolerance to both the bronchoprotective effect, and, to a lesser extent, the bronchodilator activity, occurs with all inhaled β_2-agonists. Assumed the importance of this topic and the lack of a clinical evaluation specifically designed to assess the impact of chronic administration of indacaterol on the response to salbutamol, we sought to compare the effect of 4-week treatment with indacaterol 150 μg once-daily versus formoterol 12 μg twice-daily on the dose-response curve to inhaled salbutamol (total cumulative dose of 800 μg) in a non-double-blinded, crossover, randomised, and controlled pilot trial that enrolled 20 outpatients with moderate to severe COPD. At the end of 4-week treatments, there was not a statistically significant difference between the two trough FEV_1 ($p = 0.16$), and both indacaterol and formoterol were able to produce a significant ($p < 0.001$) increase in FEV_1 mean differences (L) = indacaterol 0.15 (95% confidence interval (CI) 0.12–0.18); formoterol 0.10, (95% CI 0.08–0.12) 2 h after their inhalation. Salbutamol elicited an evident dose-dependent increase in FEV_1 and this occurred also after regular treatment with indacaterol and formoterol with a further mean maximum increase of 0.10L (95% CI 0.05–0.14) and 0.05L (95% CI 0.02–0.08), respectively. The differences between indacaterol and formoterol in FEV_1 increases after salbutamol were never statistically significant. The results of

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http://dx.doi.org/10.1016/j.rmed.2013.02.008

this study support the use of salbutamol as rescue medication for rapid relief of bronchospasm in patients suffering from COPD, even when they are under regular treatment with indacaterol.

Introduction

Tolerance to both the bronchoprotective effect, and, to a lesser extent, the bronchodilator activity, occurs with all β_2-agonists.[1] Bronchodilator tolerance develops rapidly, with a reduced response to salbutamol after a single dose of formoterol and reaches a plateau after 1 week of regular therapy.[2] Apparently, the degree of β_2-agonist tolerance increases with the degree of bronchoconstriction.[3]

Clinically relevant tolerance to rescue β_2-agonist treatment is likely to occur in asthmatic patients treated with LABAs.[4] Tolerance to the bronchodilator effects of LABAs may occur with their prolonged use also in COPD.[5] However in COPD, a pre-treatment with a conventional dose of formoterol or salmeterol does not prevent the possibility of inducing a further bronchodilation with salbutamol.[6] Moreover, the results of another study suggest that during chronic therapy with conventional doses of formoterol in moderate-to-severe COPD, the add on use of salbutamol does not improve peak expiratory flow and FEV_1 markedly, but is still effective in reducing air trapping, as shown by the increase in FVC and possibly dynamic pulmonary hyperinflation in the presence of tidal expiratory flow limitation at rest.[7]

The lack of induction of tolerance is an occurrence extremely useful because the usual approach in a COPD patient who complains of worsening dyspnoea and in which the physician suspects an increase of bronchial obstruction is to use salbutamol as rescue medication to produce rapid relief of bronchospasm.

Nonetheless, there are some differences between LABAs that could cause difference in airway response to salbutamol. Thus, high-efficacy agonists may cause a greater loss of receptors,[8] and it has also been suggested that relevant tolerance to rescue salbutamol treatment could be more likely with β_2-agonists that are able of a really long residency at the β_2-adrenoceptor.[9] This is because of prolonged, 24-h receptor occupancy and the associated propensity for agonist-promoted reduction in the number and coupling efficiency of β_2-adrenoceptors on airway smooth muscle and inflammatory cells, where such receptors are expressed.[9]

However, Battram et al.[10] evaluated the ability of indacaterol, which is the first LABA able to induce 24-h bronchodilation, formoterol and salmeterol to induce tachyphylaxis in guinea pigs. None of the compounds was subject to desensitization at any of the doses tested. Indeed, for indacaterol and formoterol, the inhibitory effect of each dose after 5-day treatment compared with that of a single treatment was enhanced and reached significance for the indacaterol dose of 0.006 and 0.6 μg/kg and for the formoterol dose of 0.0006 μg/kg. Such a phenomenon was not observed for salmeterol.

Assumed the importance of this topic and the lack of a clinical evaluation specifically designed to assess the impact of chronic administration of indacaterol on the response to salbutamol, we assessed whether a regular treatment with this once-daily LABA might modify the dose-response curve to inhaled salbutamol in patients with stable COPD.

Patients and methods

We studied 20 outpatients with moderate to severe COPD, They were ≥60 years of age, current or former smokers (>10 pack-years), reporting chronic cough with or without sputum production and/or dyspnoea when walking quietly on level ground. In addition, all patients had FEV_1 ≤70% of predicted normal, and a best post-bronchodilator (salbutamol 200 μg) FEV_1/FVC of less than 0.7. Table 1 describes the baseline characteristics of the randomised patients.

Patients had experienced no change in symptom severity or treatment in the preceding 2 months, had shown no signs of a respiratory tract infection in the month preceding or during the trial, and had not taken oral corticosteroids, other inhaled or oral bronchodilators, leukotriene modifiers or β_2-blockers for at least 2 months. Patients were allowed to continue taking inhaled corticosteroids, provided a regimen of regular use had been stable for at least 1 month previously. Patients with a history of allergic diseases such as allergic rhinitis, asthma and atopic dermatitis (eczema), and positive skin test or with a total blood eosinophil count >400 mm^{-3} were excluded. Patients were also excluded if they had any coexisting cardiovascular or lung disorder, a resting PaO_2 of less than 60 mm Hg, or use of long-term oxygen therapy (Fig. 1). Patients were asked to refrain from consumption of cola drinks, coffee, tea, and from smoking, in the 12 h before and also during the investigation.

The study was conducted according to the rules of the declaration of Helsinki and each patient gave written informed consent to all procedures.

This was a non-double-blinded, crossover, randomised, and controlled pilot trial. The total study duration was 10 weeks. It had three parts. Part 1 was the run-in period of 1-week duration that followed screening visit 1. During this period, patients received inhaled salbutamol for relief therapy and they were asked to withhold rescue salbutamol for 8 h prior to come to our outpatient office for the next visit at the end of the run-in period when baseline measurements (FEV_1 and FVC) were performed, and the eligibility of screened patients to participate in the randomized treatment periods was assessed. In addition to the qualifying spirometric tests, each patient was subjected to the evaluation of the response of his/her airways to increasing