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Respiratory Medicine (2013) **107**, 107–111

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Effect of an additional dose of indacaterol in COPD patients under regular treatment with indacaterol

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Received 31 December 2011; accepted 12 September 2012
Available online 18 October 2012

KEYWORDS
COPD;
Indacaterol;
Dose escalation;
Lung function;
Side effects

Summary
Aim: In this randomized, double-blind, crossover study, we explored the acute effects on respiratory function and safety of an additional dose of indacaterol 150 μg in stable COPD patients regularly treated with a conventional dose of indacaterol 150 μg.
Methods: On two non-consecutive days, patients inhaled indacaterol 150 μg. After 180 min, they inhaled an additional dose of indacaterol 150 μg or placebo. Lung function, oxygen saturation by pulse oximetry (SpO_2) and heart rate were measured before the first drug administration and up to 360 min thereafter.
Results: In both treatment groups, indacaterol induced a significant ($P < 0.05$) bronchodilation during all the study time. The difference between the FEV_1 $AUCs_{0-180\ min}$ was not statistically significant ($P = 0.971$). On the contrary, the difference between the FEV_1 $AUCs_{180-360\ min}$ was significant ($P < 0.0001$). However, only 8 out of 20 patients showed a further increase of at least 100 ml from the peak obtained after the first administration of indacaterol 150 μg with the second dose of 150 μg. Indacaterol 150 μg induced a modest but significant decrease in SpO_2 up to 60 min and a second dose of indacaterol 150 μg significantly decreased the SpO_2 mean value up to 360 min.
Conclusion: This study suggests that it is reasonable and safe to increase the dose of indacaterol in those stable COPD patients who are under regular therapy with indacaterol 150 μg from which they do not draw the maximum benefit because they are unable to perceive bronchodilation. However, only a minority of patients seem to benefit from this dose escalation, at least in terms of spirometric improvement.
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http://dx.doi.org/10.1016/j.rmed.2012.09.022

Introduction

Indacaterol is a novel once-daily ultra-long-acting β_2-adrenoceptor agonist bronchodilator now approved in many Countries for maintenance bronchodilator treatment of airflow obstruction in adult patients with COPD, to be administered as 150 or 300 μg once-daily dose by means of a single-dose dry powder inhaler. These two doses were selected by an independent data monitoring committee using pre-set efficacy criteria for trough (24-h post-dose) and early (1−4 h post-dose) bronchodilator effect after 14 days, and all safety data.[1] More specifically, the recommended and usual dosage of indacaterol is the inhalation of 150 μg capsule once a day, using the Breezhaler® (Novartis) inhaler. Once a day inhalation of indacaterol 300 μg has been shown to provide additional clinical benefit to some patients,[2,3] but the dosage should only be increased on medical advice.

Usually, physicians recommend to increase the dose when patients report the persistence of symptoms despite they are under regular therapy with indacaterol 150 μg. However, no studies have evaluated the risks and benefits of this increase.

In the present pilot study, we explored the acute effects on respiratory function of a further dose of indacaterol 150 μg in stable COPD patients regularly treated with the conventional dose of indacaterol 150 μg. Moreover, we also investigated whether this added dose was safe.

Methods

We assessed 20 outpatients with moderate to severe COPD, who were in a stable phase of the disease and were under regular therapy with indacaterol 150 μg once a day from at least 2 months. All patients reported a good compliance with indacaterol before the study. They were ≥60 years of age, current or former smokers (>10 pack-years) without a history of asthmatic attacks, reporting chronic cough with or without sputum production and/or dyspnea when walking quietly on level ground. In addition, all patients had FEV_1 ≤70% of predicted normal, and a best post-bronchodilator FEV_1/FVC of less than 0.7. Patients' characteristics and lung function data are given in Table 1.

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 or inhaled corticosteroids, other inhaled or oral bronchodilators, leukotriene modifiers or β_2-adrenoceptor blockers for at least 2 months. Patients with allergic rhinitis, atopy, 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 mmHg, or use of long-term oxygen therapy. 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, which was approved by the local Ethics Committee, was conducted according to the rules of the declaration of Helsinki and each patient gave informed consent to all procedures.

A randomized, double-blind crossover design was used. On two non-consecutive days, all patients, who continued regular therapy with indacaterol 150 μg once a day, inhaled their usual dose of indacaterol 150 μg Breezhaler®. After 180 min they inhaled additional indacaterol 150 μg Breezhaler® (indacaterol arm) or placebo Breezhaler® (placebo arm). Lung function was controlled before the first drug administration and 30, 60, 180, 210, 240, and 360 min thereafter. At the same times, we also measured oxygen saturation by pulse oximetry (SpO_2) and heart rate. All experiments began at 8 a.m. to avoid well-known interference of the circadian rhythm on bronchomotor tone.

As an expression of the total effect of each treatment, the areas under the FEV_1 response−time curves (FEV_1 AUC) were calculated for each patient.

Spirometric data for each treatment were analyzed using the Student's *t*-test for paired variables. Mean responses were also compared by multifactorial analysis of variance (ANOVA) to establish any significant overall effect between the two treatments. In the presence of a significant overall ANOVA, Duncan's multiple range testing with 95% confidence limits was used to identify where differences were significant. A probability level of $P < 0.05$ was considered as significant for all tests. The areas under the FEV_1 response/time curves were analyzed by the trapezoidal rule.

The study had a power of 80% to detect a difference in FEV_1 of at least 110 ml between treatments. A joint European Respiratory Society/American Thoracic Society statement concluded that the minimal important difference for FEV_1 lies within a range of 100−140 ml.[4] For comparison purposes, a difference of 100 ml has been reported as the threshold at which a COPD patient can perceive an effect.[5]

Results

All patients completed the 2-day study. There was no significant difference between the baseline FEV_1 values of the two treatment groups ($P > 0.05$).

Changes in FEV_1 and FVC values are shown in Figs. 1 and 2, respectively. In both treatment groups, indacaterol induced a significant ($P < 0.05$) bronchodilation during all the study time. The mean peak of the change in FEV_1 from baseline was observed after 180 min in the indacaterol 150 μg + placebo arm, although it ranged from 30 min to 240 min. In the indacaterol 150 μg + indacaterol 150 μg arm, the mean peak of the change in FEV_1 from baseline

Table 1 Demographics of the population studied.

Sex (no.)	18 M − 2 F
Age (years)	71.0 ± 1.5
FEV_1 (% predicted)	48.8 ± 2.3
FVC (% predicted)	80.7 ± 3.5
Reversibility (% from baseline)	9.3 ± 1.2
Basal SpO_2 (%)	95.8 ± 0.4

Data are presented as mean ± SE unless otherwise indicated. M, male; F, female.

was observed after 360 min and it ranged from 30 min to 360 min.

The mean increases in FEV_1 $AUC_{0-360\ min}$ for all patients were 0.58 (95% CI: 0.40—0.77) L when indacaterol was added and 0.47 (95% CI: 0.28—0.66) L when placebo was inhaled. The difference between the two arms was not significant ($P = 0.073$). Also the difference between the FEV_1 $AUCs_{0-180\ min}$ (0.22 L, 95% CI: 0.15—0.29; and 0.22 L, 95% CI: 0.14—0.30, respectively) was not statistically significant ($P = 0.971$). On the contrary, the difference between the FEV_1 $AUCs_{180-360\ min}$ (0.15, 95% CI: 0.11—0.19; and −0.05, 95% CI: −0.09 to 0.00, respectively) was significant ($P < 0.0001$).

Apparently, the baseline (predose) FEV_1 value did not influence the possibility of a further increase in FEV_1 of at least 100 ml after the extra dose of indacaterol. However, only 8 out of 20 patients showed a further increase of at least 100 ml from the peak obtained after the first administration of indacaterol 150 μg with the extra dose of indacaterol 150 μg (Fig. 3).

The inhalation of indacaterol 150 μg did not significantly increase the heart rate, but the addition of an extra dose of indacaterol 150 μg induced a significant ($P = 0.035$) increase in heart rate at 360 min (Fig. 4). On the contrary, the inhalation of indacaterol 150 μg induced a modest but significant decrease in SpO_2 up to 60 min and a second dose of indacaterol 150 μg significantly decreased the SpO_2 mean value up to 360 min (Fig. 5). In any case, SpO_2 never decreased to less than 92%.

Discussion

The results of our study suggest that the acute increase in the dose of indacaterol with an additional dose of indacaterol 150 μg administered to patients with stable COPD who are under regular treatment with indacaterol 150 μg once daily, can give room for further increase in peak FEV_1 in some of them. This finding is not unexpected considering that Rennard and co-workers[6] showed that indacaterol (50, 100, 200 or 400 μg) caused a clear dose-dependent increase in FEV_1.

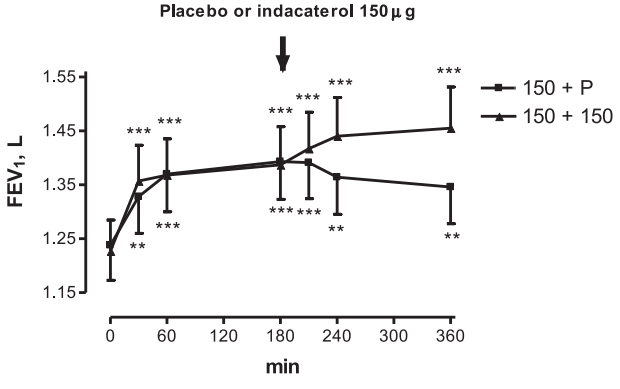

Figure 1 Mean changes (±SE) in FEV_1 (L) from pre-dosing value at different times after the inhalation of indacaterol 150 μg. At 180 min, patients inhaled placebo or an additional dose of indacaterol 150 μg. $^{**}P < 0.01$; and $^{***}P < 0.001$ vs. pre-dosing value.

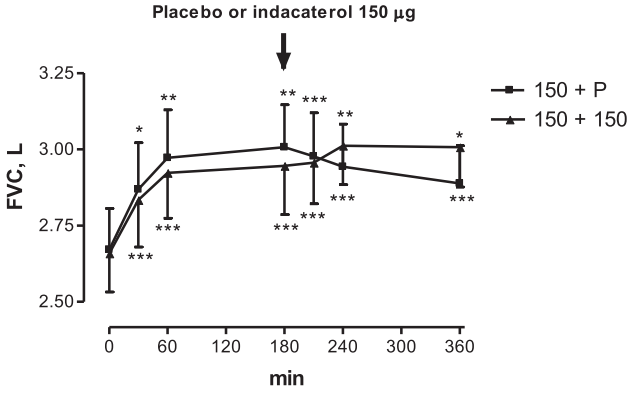

Figure 2 Mean changes (±SE) in FVC (L) from pre-dosing value at different times after the inhalation of indacaterol 150 μg. At 180 min, patients inhaled placebo or an additional dose of indacaterol 150 μg. $^{*}P < 0.05$; $^{**}P < 0.01$; and $^{***}P < 0.001$ vs. pre-dosing value.

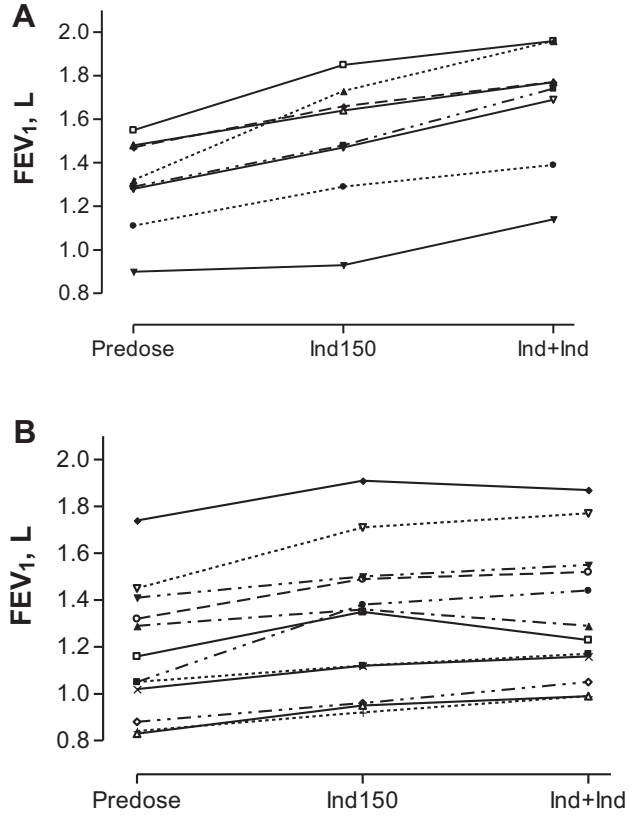

Figure 3 Individual changes in FEV_1 (L) from pre-dosing value (predose) after the inhalation of indacaterol 150 μg (Ind150) and that of an additional dose of indacaterol 150 μg (Ind + Ind). A: patients that showed a further increase of at least 100 ml from the peak obtained after the first administration of indacaterol 150 μg with the additional dose of indacaterol 150 μg; B: patients that did not show a further increase of at least 100 ml from the peak obtained after the first administration of indacaterol 150 μg with the additional dose of indacaterol 150 μg.

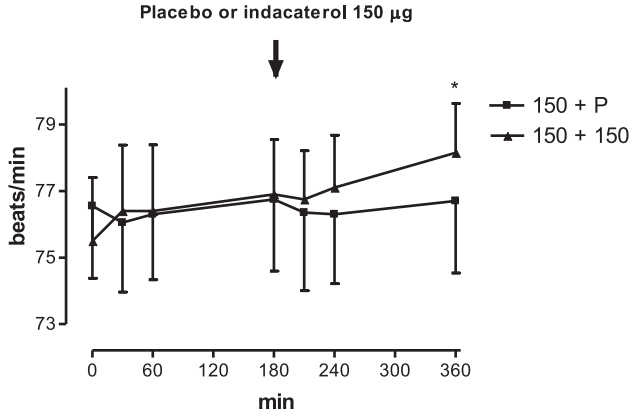

Figure 4 Mean changes (±SE) in heart rate (beats/min) from pre-dosing value at different times after the inhalation of indacaterol 150 μg. At 180 min, patients inhaled placebo or an additional dose of indacaterol 150 μg. *$P < 0.05$ vs. pre-dosing value.

As already mentioned, indacaterol has been approved in many Countries (including throughout the European Union) for use in COPD at the dose of 150 μg once daily, dose that can be increased on medical advice to a maximum of 300 μg once daily, although in Phase II dose-ranging studies in COPD, indacaterol consistently demonstrated bronchodilator efficacy that was superior to placebo, regardless of the dose tested.[6,7] In effect, a comprehensive assessment of the bronchodilatory dose response of indacaterol in COPD patients has provided a robust confirmation that 75 μg is the minimum effective dose, and that 150 and 300 μg are expected to provide optimal bronchodilation, mainly in COPD patients with baseline FEV_1 less than 1 L.[8]

Our data indicate that patients suffering from COPD, who are taking indacaterol 150 μg as regular maintenance therapy, may increase the dose of indacaterol if it is needed, although only a proportion of patients with COPD seem to require a dose escalation, while in many patients this increase does not induce any substantial improvement in lung function. This finding can probably be attributed to the high FEV_1 values that we have observed 3 h after the inhalation of the first dose of indacaterol, which left relatively little room for bronchodilator improvement in response to an additional dose of indacaterol. In effect, each patient with COPD has his/her own optimal function that is regarded to be the best lung function that patients can achieve either spontaneously or as a result of the treatment.[9] It is conceivable that many of our patients, who were in stable clinical condition and under regular therapy with indacaterol 150 μg, were near the top of their bronchodilation response after inhalation of the first dose of indacaterol 150 μg also because under regular therapy with this bronchodilator. Alternatively, we could postulate that, since our patients were under chronic administration of indacaterol, a subsequent reduced sensitivity of β_2-adrenoceptors was a possibility in some patients. However, no tachyphylaxis has been demonstrated for indacaterol, at least in guinea pig.[10] Moreover, tachyphylaxis and tolerance have not been observed with long-term indacaterol administration.[11–13]

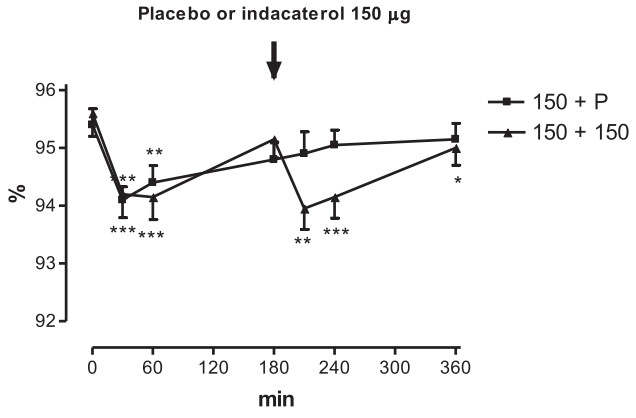

Figure 5 Mean changes (±SE) in pulse oximetry (SpO_2) (%) from pre-dosing value at different times after the inhalation of indacaterol 150 μg. At 180 min, patients inhaled placebo or an additional dose of indacaterol 150 μg. *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$ vs. pre-dosing value.

Our data also suggest that only a proportion of patients with COPD require such additional dose while in many patients an additional dose does not induce any substantial improvement in lung function. In any case, it must be highlighted that the population in our study was small and the results were measured only once. We do not know whether the findings of our study were reproducible in the same subjects or they were random noise. In effect, poor responders could have been good responders on a second day. This is a possibility that we have not tested because we aimed to understand what happens soon after our decision to increase the dose of indacaterol. In real life, the bronchodilator response that we record can influence our choice of continuing with a higher dose and/or the compliance of our patient to the increased dose.

In any case, apparently, the baseline FEV_1 value does not seem to influence the possibility of a further increase in FEV_1 of at least 100 ml after an additional dose of indacaterol 150 μg. This finding is in contrast with what reported by Renard and co-workers.[8]

The lack of effects on heart rate that we have recorded in this study even when the dose of indacaterol has been increased, confirms cardiac safety of this β-adrenoceptor agent. It is important to highlight that Holter monitoring in some clinical trials in some clinical trials proved that mean heart rate does not differ in a statistically significant manner among the treatments (indacaterol 150 and 300 μg, and placebo).[14]

In our study, indacaterol induced small but statistically significant modifications in SpO_2. Because of the lack of sensitivity of the technique, we cannot exclude that these small variations in SpO_2, could result in mild hypoxemia.[15] It is well known that the administration of β-adrenoceptor agents to patients with airway obstruction often results in a transient decrease in oxygen partial pressure (PaO_2) despite concomitant bronchodilation.[16] However, we must mention that all our patients had a resting PaO_2 higher than 60 mm Hg and SpO_2 never decreased to less than 92% after indacaterol, even when we increased the dose. It is likely that the small modifications in SpO_2 that we have recorded had no real clinical impact. Nonetheless, we believe that a study focused on the impact of different doses of indacaterol on blood gases is now mandatory.

In conclusion, this study suggests that it is reasonable and safe to increase the dose of indacaterol in those COPD patients who are under regular therapy with indacaterol 150 μg from which they do not draw the maximum benefit because they are unable to perceive bronchodilation. However, only a minority of patients seem to benefit from this dose escalation, at least in terms of spirometric improvement. A study designed to assess the long-term effects of the indacaterol dose escalation in COPD patients already receiving regular therapy with 150 μg indacaterol is imperative in order to understand who can benefit from this increase. For this purpose, the study will not only focus on respiratory function but will explore patient-reported outcomes.[4]

Conflict of interest statement

We declare that we have no conflict of interest with this study that has not been sponsored by any Drug Company.

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