Pulmonary Pharmacology & Therapeutics 22 (2009) 492–496

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Bronchodilator effects of indacaterol and formoterol in patients with COPD

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ARTICLE INFO

Article history:
Received 2 December 2008
Received in revised form
30 April 2009
Accepted 7 May 2009

Keywords:
Bronchodilation
Chronic obstructive pulmonary disease
Forced expiratory volume in 1 s
Formoterol
Indacaterol
Inspiratory capacity

ABSTRACT

Background: Resting inspiratory capacity (IC) reflects static hyperinflation in chronic obstructive pulmonary disease (COPD). This study compared the effects of formoterol and indacaterol, a novel once-daily ultra-long-acting β_2-agonist (or ultra-LABA), on resting IC and forced expiratory volume in 1 s (FEV_1).

Methods: Thirty patients with COPD (mean FEV_1/FVC 0.49, mean FEV_1 56% predicted) each inhaled three treatments (two in randomized sequence followed by open-label formoterol) on separate study days: a single dose of indacaterol 300 μg, matching placebo, and two doses of formoterol 12 μg 12 h apart.

Results: Indacaterol and formoterol increased FEV_1 and IC at all time points relative to placebo ($p < 0.001$). Peak effects on FEV_1 were similar, while indacaterol had a greater effect on peak IC (31% vs 23% from pre-dose; $p = 0.034$). Indacaterol had a greater effect than formoterol on FEV_1 at 8 h (1.47 vs 1.39 L; $p = 0.014$) and 24 h (1.44 vs 1.35 L; $p = 0.003$), and on IC from 4 to 24 h (differences of 0.13–0.19 L; $p < 0.05$). At 24 h, indacaterol and formoterol increased FEV_1 by 17.7% and 7.5%, respectively, from pre-dose.

Conclusions: This study discriminated between the effects on IC and FEV_1 of once daily indacaterol and twice daily formoterol. The greater effect of indacaterol on IC may translate into improved long-term clinical outcomes.

1. Introduction

Current guidelines emphasize that chronic obstructive pulmonary disease (COPD) is both preventable and treatable, while acknowledging that the condition is characterized by a progressive decline in lung function [1]. Bronchodilators are the cornerstone treatment for all COPD severity stages. In more pronounced stages of airflow obstruction, the regular use of one or more long-acting bronchodilators is recommended. These agents include the twice daily β_2-agonists, formoterol and salmeterol, and the once-daily anticholinergic, tiotropium. Long-acting bronchodilators may improve exercise tolerance [2–4] as a result of bronchodilation and reduction of both static and dynamic hyperinflation.

The diagnosis and severity staging of COPD and measurement of response to therapy are based on objective measures of lung function, i.e. forced expiratory volume in 1 s (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC). However, there is evidence that acute changes in resting FEV_1 do not correlate with improvements in exertional dyspnoea and exercise capacity and vice versa [5,6]. Other spirometric measures such as inspiratory capacity (IC) may correlate better with these measures of clinical response [5]. Resting IC represents the limit for inspiratory volume expansion following exhalation during tidal breathing, and therefore indirectly infers functional residual capacity, i.e. the degree of hyperinflation. Moreover, a decrease in IC during exercise indicates dynamic hyperinflation, assuming that total lung capacity remains constant. Finally, an increased resting IC is a better predictor of exercise tolerance in COPD than other lung function variables, e.g. FEV_1 [5].

Indacaterol is a novel inhaled ultra-long-acting β_2-agonist (ultra-LABA) being investigated for once daily use in subjects with COPD [7,8]. Improved clinical benefits have been demonstrated with the long-acting anticholinergic tiotropium once-daily vs short-acting ipratropium four-times daily [9], and one of the proposed underlying mechanisms for this observation may be a prolonged effect of long-acting bronchodilators on lung emptying, by improving IC and reducing resting hyperinflation. The objective of the present exploratory study was to compare the

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1094-5539/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.pupt.2009.05.001

response in FEV_1 and IC between single doses of indacaterol and matched placebo, with the recommended daily dose of formoterol (12 μg twice daily) as an active control. Safety and tolerability were also assessed.

2. Methods

2.1. Patients (inclusion/exclusion criteria)

The study enrolled males and females aged 40–80 years, with a clinical diagnosis of COPD according to GOLD recommendations [10] and a smoking history of at least 10 pack-years. Spirometric criteria were a post-bronchodilator $FEV_1 \geq 40\%$ predicted at screening and ≥ 1.0 L; FEV_1 reversibility of $\geq 5\%$ to salbutamol 400 μg (after an appropriate bronchodilator washout period: no use of short-acting bronchodilators for 6 h, no long-acting β_2-agonists for 48 h, and no tiotropium for 72 h); and a post-bronchodilator ratio of $FEV_1/FVC < 0.7$.

Patients were allowed to continue taking inhaled corticosteroids, provided a regimen of regular use had been stable for at least 1 month previously. Similarly, patients could continue use of short-acting β_2-agonists, provided the washout period of at least 6 h prior to dosing visits could be adhered to. Apart from inhaled corticosteroids, patients refrained from using concomitant medication on the study dosing day until after assessments had been completed the following day.

The following medications were not allowed throughout the whole study period: tiotropium (a 72 h washout), long-acting β_2-agonists other than study medications (48 h washout), and systemic corticosteroids (1 month washout).

2.2. Study design

The study was a multicentre, placebo-controlled, randomized crossover design comparing indacaterol, matching placebo and formoterol in patients with mild-to-severe COPD. The study was conducted at three sites: insaf Respiratory Research Institute, Wiesbaden, Germany; Chiltern's Clinical Research Unit (CCRU), Slough, UK, and Cyncron (ex-Medicon Clinical Pharmacology) A/S, Copenhagen, Denmark.

Following a maximum 28-day screening period patients were randomly assigned to receive single doses of either indacaterol (300 μg via a single-dose dry powder inhaler [SDDPI]) or matching placebo (SDDPI) in a crossover fashion in the morning under double-blind conditions. Following this, all patients received open-label formoterol 12 μg administered twice, morning and evening, via a single-dose dry powder inhaler device (Aerolizer™, Novartis).

Each treatment period was separated by a 4–7-day washout. Patients could receive allowable COPD medications and prescribed salbutamol (as needed) during washout periods.

All patients received appropriate training in inhaler device use and spirometry manoeuvre techniques prior to receiving treatment.

The study was approved by the internal review board or ethics committee at each centre and the three respective health authorities, and conducted according to the Declaration of Helsinki. Each subject gave written informed consent before randomization.

2.3. Study assessments

Spirometry measures included IC (mean of three reproducible manoeuvres) and FEV_1 (best of three reproducible manoeuvres) that were performed at each visit (pre-dose; and 5 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 23 h 30 min and 24 h post-dose). Spirometry was not assessed between 8 and 23 h post-dose for logistical reasons.

Table 1
Baseline demographic and clinical characteristics at screening.

Variable	Statistic	Total $n = 30$
Age (years)	Mean (SD)	65 (7.5)
	Range	51–78
Sex		
Male	*n* (%)	16 (53)
Female	*n* (%)	14 (47)
Height (cm)	Mean (SD)	171 (6.5)
Weight (kg)	Mean (SD)	77 (15.0)
FEV_1 pre-bronchodilator (L)	Mean (SD)	1.29 (0.317)
	Range	0.80–2.12
FEV_1 post-bronchodilator[a] (L)	Mean (SD)	1.53 (0.348)
	Range	1.19–2.58
FEV_1 reversibility (%)	Mean (SD)	23.0 (12.01)
	Range	(8.1–48.8)
FEV_1 (% predicted) (post-bronchodilator[a] values)	Mean (SD)	56.3 (11.37)
	Range	40.5–84.6
FVC (L) (post-bronchodilator[a])	Mean (SD)	3.20 (0.862)
	Range	1.86–5.82
FEV_1/FVC (post-bronchodilator[a])	Mean (SD)	0.49 (0.099)
	Range	0.31–0.67
IC (L) (pre-bronchodilator)	Mean (SD)	1.87 (0.549)
	Range	1.03–3.68

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; L = litre; SD = standard deviation.
[a] 30 min after inhalation of salbutamol.

Spirometry equipment and performance of spirometric testing was conducted in accordance with American Thoracic Society and European Respiratory Society joint recommendations and standards [11].

The primary efficacy variable in this study was a comparison between FEV_1 and IC in terms of the mean maximal change from baseline following single doses of indacaterol and matched indacaterol placebo with two doses (b.i.d. regimen) of formoterol as an active control. Secondary endpoints were comparisons among indacaterol, formoterol and matched indacaterol placebo of: (1) percent predicted FEV_1 time course change; and (2) mean maximal change in IC time course change. Inspiratory capacity manoeuvres were performed prior to forced measurements to avoid any influence of forced exhalations on resting hyperinflation [11]. Safety assessments included recording of all reported adverse events and serious adverse events.

2.4. Statistical analysis

The efficacy analyses included all randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment of FEV_1. The safety population included all subjects who received at least one dose of study drug.

Exploratory analyses were used to assess the relationship between IC and FEV_1. Comparison of peak and trough FEV_1 and IC between indacaterol and placebo treatments was conducted using a mixed linear model with period, treatment and treatment period effects as fixed effects and subject as a random effect. Comparisons between formoterol vs placebo and formoterol vs indacaterol were conducted using a *t*-test on peak FEV_1.

Data are presented as least square means (LSM) and the significance of between-treatment differences was determined using analysis of covariance (ANCOVA), with baseline (pre-dose values), subject and treatment as factors. For formoterol the baseline value was pre-first dose.

This study was an exploratory study and no sample size computation was performed. A sample size of 30 patients was pre-specified and had at least 80% power to detect a difference of 0.22 L between the mean levels of FEV_1 at 24 h after the morning dose for indacaterol

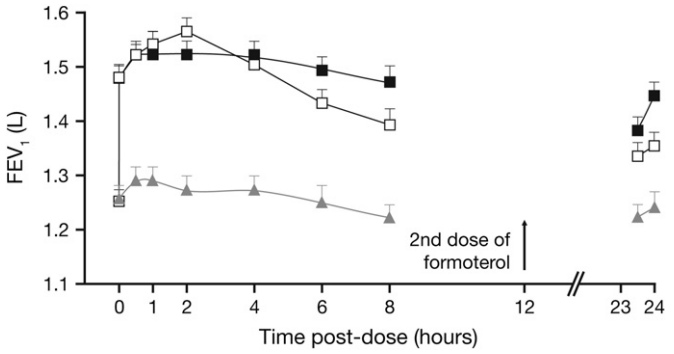

Fig. 1. FEV_1 (adjusted means, ±SE) over 24 h post-dose. $n = 30$ for each treatment. $p < 0.0001$ for indacaterol vs placebo at all time points. $p < 0.0001$ for formoterol vs placebo (5 min–8 h); $p < 0.001$ (23.5 h and 24 h). $p = 0.014$ and $p = 0.003$ for indacaterol vs formoterol at 8 h and 24 h, respectively. ■ = indacaterol; □ = formoterol; ▲ = placebo.

and placebo. This assumes a common within-subject standard deviation of 0.292 L using a paired *t*-test at 5% significance level.

3. Results

3.1. Patients

As planned, 30 subjects were randomized. Demographic and baseline characteristics are shown in Table 1. All subjects were Caucasian. No patient withdrew from the study.

3.2. Efficacy

Spirometry data were available for all 30 subjects on the formoterol treatment day, for all but one subject at the 23.5 and 24 h time points on the indacaterol day, and for all but one subject at 6 and 8 h and two subjects at 23.5 and 24 h on the placebo day, the reasons for missing measurements being administration of rescue medication, or concomitant medication for shortness of breath.

3.2.1. FEV_1, IC and FVC over time

Baseline (pre-dose) mean (SD) FEV_1 values for each treatment were 1.19 (0.328) L for indacaterol, 1.28 (0.319) L for placebo, and 1.29 (0.311) L for formoterol. Respective IC values were 1.89 (0.540) L, 2.00 (0.607) L and 2.01 (0.558) L.

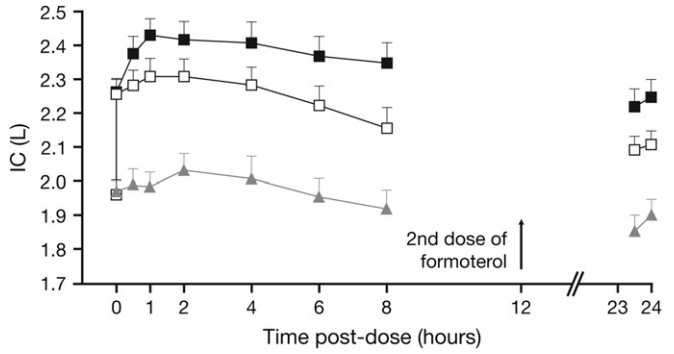

Fig. 2. Inspiratory capacity (least squares means, ±SE) over 24 h post-dose. $n = 30$ for each treatment. $p < 0.0001$ for indacaterol vs placebo at all time points. $p < 0.0001$ for formoterol vs placebo (5 min–6 h); $p < 0.001$ (8 h and 23.5 h); $p < 0.01$ (24 h). $p < 0.05$ for indacaterol vs formoterol (4 h to 24 h). ■ = indacaterol; □ = formoterol; ▲ = placebo.

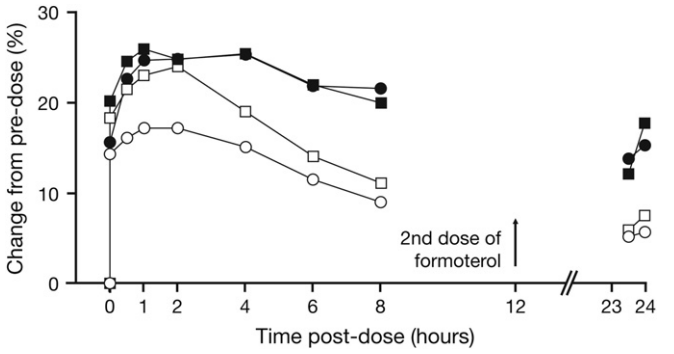

Fig. 3. Comparison of effects of indacaterol and formoterol on FEV_1 and IC as % change in unadjusted mean values from pre-dose. Error bars omitted for clarity. n = 30 for each treatment. ■ = indacaterol (FEV_1); ● = indacaterol (IC); □ = formoterol (FEV_1); ○ = formoterol (IC).

FEV_1 was significantly greater at all assessment time points (5 min–24 h) following treatment with indacaterol ($p < 0.0001$) or formoterol ($p < 0.001$) compared with placebo (Fig. 1). At 5 min post-dose, adjusted mean FEV_1 increased by 0.22 L relative to placebo with both indacaterol and formoterol. Mean FEV_1 for indacaterol was significantly greater than for formoterol at 8 h and 24 h. At 24 h, respective adjusted mean (SE) values were 1.44 (0.029) and 1.35 (0.028) L, a mean (SE) difference of 0.09 (0.029) L ($p = 0.003$). These values reflect unadjusted mean (SD) changes from pre-dose of 17.7 (15.02)% with indacaterol and 7.5 (12.94)% with formoterol at the 24 h time point.

IC was significantly greater at all time points (5 min–24 h) following treatment with indacaterol ($p < 0.0001$) or formoterol ($p < 0.001$) compared with placebo (Fig. 2). Indacaterol had a numerically greater effect than formoterol at all time points, with differences that were significant (at 4 h–24 h; $p < 0.05$) or were close to significance (at 30 min–2 h; $p = 0.059$–0.069). The effects of indacaterol and formoterol on FEV_1 and IC in terms of percentage change from pre-dose values are compared in Fig. 3.

In terms of FVC, for indacaterol and formoterol, respectively, the percent increases from pre-dose were 19.4% and 14.3% at 5 min post-dose, 24.2% and 17.5% at peak effect (1–2 h post-dose), and 16.4% and 6.6% at 24 h post-dose. Analysis of covariance of FVC was not planned or performed.

3.2.2. Peak FEV_1 vs peak IC

Peak effects on FEV_1 and IC as percentages of pre-dose values are shown in Table 2. While the effect of indacaterol and formoterol on peak FEV_1 was of a similar order (32% vs 28% increase from pre-dose, respectively), the two bronchodilators varied in their effect on peak IC and indacaterol had a significantly greater effect (31% increase from pre-dose with indacaterol vs 23% with formoterol, $p = 0.034$).

3.3. Safety

Adverse events according to body system and preferred term are shown in Table 3. Cough was the most common adverse event,

Table 2
Comparison of peak effect on FEV_1 and IC (as % increase from pre-dose value).

		Indacaterol $n = 30$	Placebo $n = 30$	Formoterol $n = 30$
FEV_1, % increase	Mean	32.3[a]	8.0	27.9[a]
	(95% CI)	(26.4, 38.3)	(5.5, 10.4)	(23.6, 32.1)
IC, % increase	Mean	31.2[a,b]	8.8	22.9[a]
	(95% CI)	(23.7, 38.7)	(5.3, 12.3)	(18.2, 27.7)

[a] $p < 0.001$ vs placebo.
[b] $p < 0.05$ vs formoterol.

Table 3
Adverse events, *n* (%).

Body system	Adverse event	Indacaterol n = 30	Placebo n = 30	Formoterol n = 30
Any		11 (36.7)	4 (13.3)	1 (3.3)
General and administration site	Chest discomfort	1 (3.3)	1 (3.3)	0
Infections and infestations	Nasopharyngitis	0	1 (3.3)	0
Musculoskelelal and connective tissue	Back pain	1 (3.3)	1 (3.3)	1 (3.3)
	Myalgia	1 (3.3)	0	0
Nervous system	Headache	0	0	1 (3.3)
Respiratory, thoracic and mediastinal	Cough	6 (20.0)	1 (3.3)	0
	Dry throat	1 (3.3)	0	0
	Dyspnoea	2 (6.7)	2 (6.7)	0

occurring most frequently following indacaterol, and was suspected to be related to treatment. There were no serious adverse events reported during the study, and no discontinuations due to adverse events.

4. Discussion

The primary objective of this study was to compare and contrast indacaterol, placebo and formoterol in terms of their effects on two measures reflecting the airflow limitation of COPD, namely FEV_1 and resting IC. Comparing peak effects, indacaterol and formoterol had similar effects on FEV_1, whereas indacaterol had a significantly greater peak effect than formoterol on IC, although additional work is needed to determine clinical relevance. This pattern is reflected in the profile of relative effects over 24 h, where indacaterol was superior to formoterol for FEV_1 towards the end of formoterol's 12-h duration of bronchodilator effect. At 8 h following the morning dose, FEV_1 increased from pre-dose by 20% with indacaterol and 11% with formoterol. At 24 h following the morning dose of indacaterol (i.e. 12 h after the second formoterol dose), the 18% increase in FEV_1 compared favourably with the increase of 8% 12 h following the second dose of formoterol. For IC, indacaterol had a significantly greater effect than formoterol during most of the post-dose period.

These results are unlikely to be the result of underlying differences in treatment period baseline lung function, since pre-dose measures of FEV_1 and IC were consistent between treatments. The choice of doses is another possible factor that may partly account for the present results. However, the formoterol dose was chosen as the commercially available therapeutic dose, the indacaterol dose is within the range previously shown to provide effective bronchodilation over 24 h [8] and an approximate equivalence between the effects of formoterol and the chosen indacaterol dose on FEV_1 (the differences at the later time points reflecting their differing durations of effect) was demonstrated (as shown in Fig. 3). Nevertheless, the comparative results between indacaterol and formoterol need to be interpreted with a degree of caution, given the open-label nature of the latter treatment, and the results of this exploratory study should be confirmed using appropriate blinding and a double-dummy comparative design.

Previous studies have demonstrated the 24-h bronchodilator efficacy of indacaterol in subjects with COPD [7,8]; this is the first comparison with formoterol. In addition to the potential advantages of greater convenience for the patient of once-daily vs twice daily dosing, the superior bronchodilator efficacy at time points when formoterol's effect is tailing off may be reflected in a smoother and more sustained control of symptoms and, importantly, peripheral lung emptying under resting conditions, which may be reflected by the superior effect of indacaterol on trough IC at 24 h post-dose. This is also the first study to report on the effect of indacaterol on IC, which was significantly greater than placebo throughout the 24-h post-dose period. The effect was significant as early as 5 min post-dose and remained significant at 24 h post-dose.

Previous studies of up to 8 weeks in duration have shown significant (pre-dose) effects on resting IC at trough after treatment with tiotropium (differences vs placebo ranging from 0.10 L [$p < 0.05$] to 0.22 L [$p < 0.001$]) [4,12,13] and salmeterol/fluticasone (0.23 L vs placebo; $p \leq 0.008$) but not salmeterol (0.11 L vs placebo) [14]. It has been suggested that a bronchodilator-induced increase in resting IC of the order of 0.3 L, or 15–17% of baseline value, is clinically meaningful in terms of important improvements in exercise endurance and exertional dyspnoea [15]. In the present study indacaterol increased IC by 0.30–0.45 L relative to placebo, and by 15–25% from pre-dose values, during the 24-h study period. Other studies comparing the acute effects of formoterol and salmeterol on IC have suggested that formoterol has a greater effect than salmeterol 1–2 h post-dose, reflecting its faster onset of action [16,17]. The present data show that indacaterol may provide a greater effect than formoterol in the early hours post-dose and at trough.

Lung IC has been shown to correlate significantly with increased exercise endurance and with reduced dyspnoea during exercise [5,18]. It has been shown that the reduction in breathlessness during exercise and improved exercise tolerance are closely related to the bronchodilator-induced change in IC at rest, regardless of the change in resting FEV_1 [19]. Furthermore, though not tested here, increases in IC were shown to correlate much better than increased FEV_1 with patients' perceptions of improved symptoms [20]. Measurement of IC may therefore be useful in predicting the beneficial effects of bronchodilator therapy on dyspnoea and exercise tolerance.

In terms of the data from the present study, IC appears to be a more sensitive measure than FEV_1 in discriminating between the effects of indacaterol and formoterol on the airflow limitations of subjects with COPD. It is hoped that these early observations will translate into a beneficial effect on exercise capacity and associated breathlessness in subjects with COPD, and results of further studies in which these endpoints will be specifically evaluated are awaited.

In conclusion, indacaterol proved an effective and well tolerated bronchodilator in this population of subjects with moderately severe COPD. Both indacaterol (single dose) and formoterol (twice daily) had a significant bronchodilator effect in patients with COPD, measured either by FEV_1 or IC. The results of this exploratory study suggest that indacaterol had the greater effect on IC compared with formoterol, which may translate into more marked benefits on other clinical endpoints.

Acknowledgements

The authors thank patients and staff involved in this study, and the investigators at the other participating centres: Dr Rikke Riisbro, Cyncron (ex-Medicon Clinical Pharmacology) A/S, Copenhagen,

Denmark, and Dr Pauline A. Palmer, Chiltern's Clinical Research Unit (CCRU), Slough, UK. The study was sponsored by Novartis Pharma AG. The authors were assisted in the preparation of the manuscript by Sarah Filcek (this support was funded by the study sponsor). The authors thank David Young of Novartis Horsham Research Centre for reviewing this manuscript.

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