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ORIGINAL ARTICLE

Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction

Anne LINDBERG,[1] Zsuzsanna SZALAI,[2] Teet PULLERITS[3] AND Eva RADECZKY[4]

[1]*Department of Respiratory Medicine, Sunderby Central Hospital of Norrbotten, Luleå, Sweden,* [2]*Department of Pulmonology and Allergology, Karolina Hospital, Mosonmagyarovar, Hungary,* [3]*Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Gothenburg, Sweden,* [4]*Szazhalom Outpatient Polyclinic, Szazhalombatta, Hungary*

Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with COPD and reversible airway obstruction
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Background and objectives: Data on the onset of action of COPD medications are lacking. This study compared the onset of bronchodilation following different inhaled therapies in patients with moderate-to-severe COPD and reversible airway obstruction.
Methods: In this double-blind, double-dummy, crossover study, 90 patients (aged ≥40 years; FEV_1 30–70% predicted) were randomized to a single dose (two inhalations) of budesonide/formoterol 160/4.5 μg, salmeterol/fluticasone 25/250 μg, salbutamol 100 μg or placebo (via pressurized metered-dose inhalers) on four visits. The primary end-point was change in FEV_1 5 min after drug inhalation; secondary end-points included inspiratory capacity (IC) and perception of onset of effect.
Results: Budesonide/formoterol significantly improved FEV_1 at 5 min compared with placebo ($P < 0.0001$) and salmeterol/fluticasone ($P = 0.0001$). Significant differences were first observed at 3 min. Onset of effect was similar with budesonide/formoterol and salbutamol. Improvements in FEV_1 following active treatments were superior to placebo after 180 min (all $P < 0.0001$); both combinations were better than salbutamol at maintaining FEV_1 improvements ($P \leq 0.0001$) at 180 min. Active treatments improved IC at 15 and 185 min compared with placebo ($P < 0.0001$). Maximal IC was greater with budesonide/formoterol than salmeterol/fluticasone ($P = 0.0184$) at 65 min. Patients reported a positive response to the perceptions of the onset of effect question shortly after receiving active treatments (median time to onset 5 min for active treatments vs 20 min for placebo), with no significant difference between active treatments.
Conclusion: Budesonide/formoterol has an onset of bronchodilatory effect in patients with COPD and reversible airway obstruction that is faster than salmeterol/fluticasone and similar to salbutamol.

Key words: budesonide/formoterol, COPD, lung function, onset of effect, salmeterol/fluticasone.

Correspondence: Anne Lindberg, Department of Respiratory Medicine, Sunderby Hospital, SE-971 80 Luleå, Sweden. Email: anne.lindberg@nll.se

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INTRODUCTION

Most patients with moderate-to-severe COPD are symptomatic and can experience an increase in their respiratory symptoms.[1–3] COPD patients tend to adhere poorly to their maintenance medication,[4–6] often resulting in adverse clinical outcomes and increases in the number of physician visits and risk of hospitalization.[7,8] Although it is a complex issue, involving several medication-, physician- and patient-related factors, poor perception of the benefit of treatment and delayed onset of effect are believed to contribute to poor adherence.[9,10] A maintenance medication that has a rapid beneficial effect on symptoms and lung function may therefore be an attractive therapeutic option.

Current international guidelines recommend maintenance therapy with a long-acting β_2-agonist (LABA) and an inhaled corticosteroid (ICS) in patients with severe COPD who experience repeated exacerbations.[1] In these patients, the combination of an ICS and a LABA is preferred over individual components because of improved efficacy.[1] In addition, as patient adherence is known to decrease as the number of medications increases,[10,11] combining both the ICS and LABA components in one inhaler has the potential to increase patients' confidence in their medication, potentially leading to improved adherence and patient outcomes.[12,13]

Budesonide/formoterol has been shown to improve lung function and patient-reported outcomes in patients with COPD[14] and to maintain the improvements achieved with optimal treatment.[15] Szafranski *et al.*[14] observed improvements in FEV_1 with budesonide/formoterol from as early as the first day of treatment, and data from a small study in 16 patients with moderate-to-severe COPD suggest a trend towards a faster onset of effect with budesonide/formoterol compared to salmeterol/fluticasone.[16] While COPD is characterized by airflow limitation that is not fully reversible,[1] many patients do have a reversible component, and as a result, can benefit from treatment with bronchodilators.[17,18]

The aim of the present study was to evaluate the onset of bronchodilation in patients with moderate-to-severe COPD and reversible airway obstruction following administration of single doses of inhaled budesonide/formoterol, salmeterol/fluticasone, salbutamol and placebo. An additional aim was to investigate the effect of these treatments on inspiratory capacity (IC)—an exploratory outcome measure linked to exercise capacity and lung hyperinflation[19–22]—and to assess the utility of an exploratory questionnaire designed to ascertain patients' perceptions of the onset of effect (POE) of their medication.

METHODS

Patients

This multicentre, randomized, double-blind, double-dummy, placebo-controlled, crossover study (study code D5899C00748) was conducted in 19 centres across Sweden and Hungary. Patients who fulfilled the following criteria were eligible for inclusion: age ≥40 years; clinical diagnosis of COPD and COPD symptoms for >2 years; FEV_1 30–70% of predicted normal, prebronchodilator (≤85% postbronchodilator); FEV_1/VC ≤70%; reversibility in FEV_1 of 9–25% following administration of terbutaline (Bricanyl; AstraZeneca, Lund, Sweden) 0.5 mg (metered dose), two inhalations; current or previous smoker with a smoking history of ≥10 pack-years; and no history of asthma or allergic rhinitis within the last 20 years. Patients were excluded if they had had any respiratory disorder other than COPD or any exacerbation of COPD requiring medical intervention in the 30 days prior to Visit 1 or during run-in.

Patients were permitted to use ICS (stable dose) and short-acting β_2-agonists or ipratropium as reliever medication (except within the 8 h before, and during, clinic visits). Inhaled LABA were to be discontinued 48 h before Visit 1 for the duration of the study. Patients using ICS/LABA combination inhalers were to stop using the combined treatment and continue with the same dose of the ICS monoproduct.

Study design

Patients attended the clinic six times during the study period. Eligibility was assessed at Visit 1 and a randomization code was assigned at Visit 2, when lung function tests were also performed. At each of the subsequent four visits (each separated by a washout period of ≥3 days), eligible patients received a single dose (two inhalations each) of one of the four treatments: budesonide/formoterol (Symbicort, AstraZeneca, Lund, Sweden) 160/4.5 μg; salmeterol/fluticasone (Seretide, GlaxoSmithKline, Uxbridge, UK) 25/250 μg; salbutamol (Ventolin, GlaxoSmithKline) 100 μg; or placebo. Treatments were administered using appropriate hydrofluoroalkane pressurized metered-dose inhalers. All patients received each of the four treatments, which were administered in a randomized order; each patient received a specific treatment once only.

Randomization was performed by allocating eligible patients consecutively using a computer-generated randomization code; the drug treatment schedule was generated using a computer-based system. Study medication came in three inhalers with different appearances. To maintain blinding, patients always took two inhalations from each of the three different inhalers in a predefined and balanced sequence. On three of the visits, one device contained active medication and two contained placebo; on the remaining visit, all three inhalers contained placebo.

The study complied with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. An independent ethics committee approved the study protocol and patient consent form. Written informed consent was obtained from all patients.

Assessments

The primary objective of the study was to evaluate the bronchodilatory effect of the four treatments within the first 180 min after dosing. The primary outcome variable was the change in FEV_1 at 5 min (expressed as the ratio (in per cent) between the FEV_1 measured at 5 min after study drug administration and the baseline FEV_1 before study drug administration).

Secondary outcomes were: change in FEV_1 at 3 min and 180 min (expressed in the same way as change in FEV_1 at 5 min); maximal change in FEV_1 (the ratio between the maximal change in FEV_1 and baseline FEV_1); average effect on FEV_1 during the observation interval after dosing, calculated as the area under the curve (determined using the trapezoidal method) divided by the observation time; change in IC at 15 min; maximal change in IC; average effect on IC during the observation interval; POE question; and adverse events. IC outcome variables were expressed in the same way as FEV_1 variables.

Spirometry was performed in accordance with European Respiratory Society recommendations[23] between 7 AM and 10 AM on the first day of the study and within an hour of the time of the first assessment at each subsequent visit. At each randomized visit, FEV_1 was assessed before and at 3, 5, 10, 20, 30, 60, 120 and 180 min after administration of the study medication. IC was measured before and at 15, 35, 65, 125 and 185 min after inhalation of the study medication.

Perceptions of the onset of effect was evaluated using a self-administered questionnaire that was originally developed for use in patients with asthma. Prior to the study, a cognitive debriefing exercise performed in patients with COPD indicated that the POE questionnaire might provide useful data in this patient population. Patients answered 'yes' or 'no' to a question concerning whether they felt that the study medication was working. The POE question was answered immediately prior to FEV_1 measurements and the time to the first 'yes' response to the POE question was recorded. The questionnaire was translated into Swedish and Hungarian according to a linguistic validation process.

The nature, incidence and intensity of adverse events were recorded at Visits 2–6. Vital signs were recorded and a physical examination was performed at Visits 1 and 6.

Statistical analysis

The full study cohort, that is, all randomized patients with efficacy data after randomization, was used for all efficacy analyses. All patients who took at least one dose of any randomized investigational product, and for whom data were collected post randomization, were included in the safety analysis. Power calculations indicated that 80 patients were required for 90% power to detect a difference of 4.4% in FEV_1 at 5 min between budesonide/formoterol and salmeterol/fluticasone (primary comparison) using a *t*-test, assuming a residual SD of 0.083 (logarithmic scale).

Spirometric data were log transformed and analysed using an additive analysis of variance (ANOVA) model with back-transformation by exponentiation, resulting in geometric means. The mean change in FEV_1 at 5 min (primary variable) was compared between treatments using a multiplicative ANOVA with patient, period and treatment as fixed factors and baseline FEV_1 as a covariate. Similar analyses were performed for all secondary end-points derived from the FEV_1 and IC measurements. The time to first POE (i.e. a 'yes' answer) was compared between treatments using Wilcoxon's signed-rank test and the difference described using the Hodge–Lehmann estimate and its associated 95% confidence interval (CI). Patients reporting no POE were censored at 180 min. Adverse-event data were analysed using descriptive statistics.

RESULTS

Patients

Two hundred patients were enrolled, 90 of whom were randomized to study treatment. The most common reasons for not being randomized were failure to satisfy eligibility criteria; in particular, the criteria relating to FEV_1/VC and postbronchodilator FEV_1 values and FEV_1 reversibility (102 patients); adverse events (three patients); and five patients were not randomized for other reasons. For the primary variable, 89 of the 90 randomized patients had post-randomization data. One patient had data from just one treatment period and thus did not contribute to the analysis, as data from at least two treatment periods were required and missing data were not imputed. Therefore, the efficacy analysis is based on 88 patients and the safety analysis is based on 89 patients. Three patients discontinued the study prematurely: two because of adverse events and one for other reasons. Patient demographics and clinical characteristics at baseline are shown in Table 1.

Efficacy

Lung function

Budesonide/formoterol improved FEV_1 at 5 min (primary variable) to a greater extent than either salmeterol/fluticasone (ratio, 105% (95% CI: 103–108%); $P = 0.0001$) or placebo (ratio, 116% (95% CI: 113–119%); $P < 0.0001$) and to a similar extent as salbutamol (ratio, 99% (95% CI: 97–101%); $P = 0.35$) (Table 2; Fig. 1). Similar findings were observed for FEV_1 at 3 min—the earliest assessment point. Compared with placebo, FEV_1 was significantly improved over 180 min after all three active treatments (all $P < 0.0001$), although improvements were maintained more effectively with budesonide/formoterol and salmeterol/fluticasone than with salbutamol, as demonstrated by the FEV_1 at 180 min after study drug administration (ratio, 107% (95% CI: 104–109%) for budesonide/formoterol and 106% (95% CI: 103–108%) for salmeterol/fluticasone vs salbutamol; both

$P \leq 0.0001$). Maximal increases in FEV_1 were 0.35 L, 0.32 L, 0.34 L and 0.14 L for budesonide/formoterol, salmeterol/fluticasone, salbutamol and placebo, respectively. There were no statistically significant differences between the three active treatments in maximal FEV_1 or average FEV_1 over 180 min and all three active treatments were superior to placebo for both variables (all $P < 0.0001$) (Table 2).

Inspiratory capacity was significantly improved at 15 min following all three active treatments compared with placebo (all $P < 0.0001$); there were no significant differences between the active treatments (Table 2; Fig. 2). Maximal increases in IC were 0.65 L, 0.53 L, 0.54 L and 0.28 L for budesonide/formoterol, salmeterol/fluticasone, salbutamol and placebo, respectively, representing a 4% greater increase for budesonide/formoterol versus salmeterol/fluticasone (ratio, 104% (95% CI: 101–107%); $P = 0.0184$) and a 13% greater increase vs placebo (ratio, 113% (95% CI: 110–117%); $P < 0.0001$). There were no differences between the active treatments in average IC over 185 min. The effect of budesonide/formoterol and salmeterol/fluticasone on IC was of a longer duration than that of salbutamol (Table 2; Fig. 2).

Table 1 Patient demographics and baseline characteristics

Characteristic	Value ($n = 90$)
Men, *n* (%)	50 (56)
Mean age, years (range)	62 (41–79)
Median time since diagnosis, years (range)	5 (0–34)
Median time with symptoms, years (range)	9 (2–44)
Smoking status, *n* (%)	
Previous	54 (60)
Occasional	3 (3)
Habitual	33 (37)
Median pack-years (range)	35 (10–114)
ICS at study entry, *n* (%)	44 (49)
Dose, μg/day (range)	633 (200–1600)
Mean prebronchodilator FEV_1	
% predicted (range)†	48 (30–69)
L (range)	1.3 (0.6–2.4)
Reversibility, mL (range)	344 (180–680)
Reversibility, % predicted (range)	13 (9–24)
Mean post-bronchodilator FEV_1	
% predicted (range)†	60.2 (38.9–83.1)

†Calculation of predicted normal FEV_1 values was based on European Respiratory Society reference values.[23]

ICS, inhaled corticosteroids.

Perception of onset of effect

The proportion of patients answering 'yes' to the question regarding whether they felt their medication working was 84%, 81%, 84% and 61% following treatment with budesonide/formoterol, salmeterol/fluticasone, salbutamol and placebo, respectively. Time to POE was 10 min faster (95% CI: −75.0, −3.5) for budesonide/formoterol and 10.5 min faster (95% CI: −80.0, −3.5) for salbutamol compared with placebo; time to POE was slightly slower with salmeterol/fluticasone, being observed 5 min faster (95% CI: −75.0, 0.0) than placebo (Hodge–Lehmann estimate). All active treatments resulted in a significantly faster time to POE than placebo (all $P < 0.001$). The median time to POE was 5 min for each of the three active treatments and 20 min for placebo. There were no statistically significant differences between active treatments.

Safety

All treatments were well tolerated and no new or unexpected safety concerns were identified. There were 24 adverse events in total (all mild to moderate

Table 2 Spirometry variables after study drug administration

Variable	Adjusted ratio (%)‡‡			
	Budesonide/ formoterol	Salmeterol/ fluticasone	Salbutamol	Placebo
FEV_1				
3 min	111*,†	105*	113*,†	99
5 min‡	115*,§	110*	117*,†	100
180 min	122*,¶	121*,¶	115*	103
Maximal	126*	125*	126*	111
0–180 min	119*	118*	119*	103
IC				
15 min	114*	114*	115*	103
Maximal	128*,††	124*	127*	113
0–185 min	118*	115*	117*	104

*$P < 0.0001$ versus placebo. †$P < 0.0001$ versus salmeterol/fluticasone. ‡Primary end-point. §$P < 0.001$ versus salmeterol/fluticasone. ¶$P < 0.001$ versus salbutamol. ††$P < 0.05$ versus salmeterol/fluticasone.

‡‡Multiplicative ANOVA with treatment, patient and period as factors and baseline as covariate.

IC, inspiratory capacity; ICS, inhaled corticosteroids.

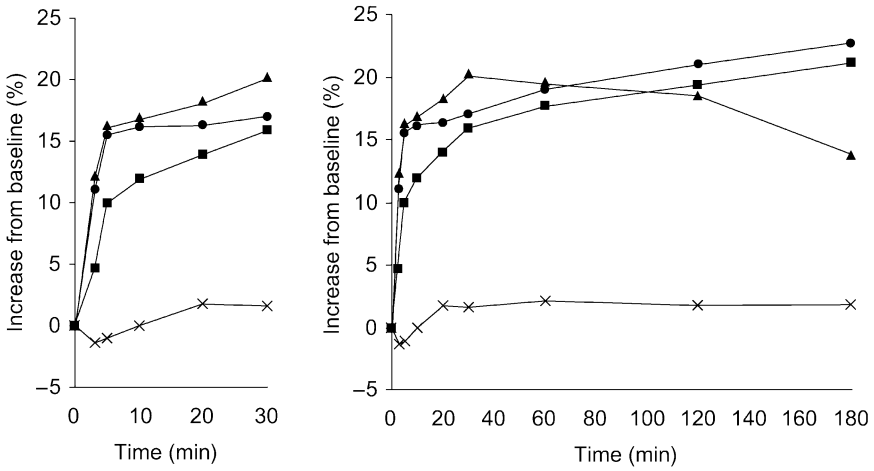

Figure 1 Mean FEV_1 during the first 180 min after inhalation of budesonide/formoterol (pMDI $2 \times 160/4.5$ μg; ●), salmeterol/fluticasone (pMDI $2 \times 25/250$ μg; ■), salbutamol (2×100 μg; ▲) or placebo (**X**) (% increase from predrug value). Inset shows mean FEV_1 during the first 30 min. pMDI, pressurized metered-dose inhaler.

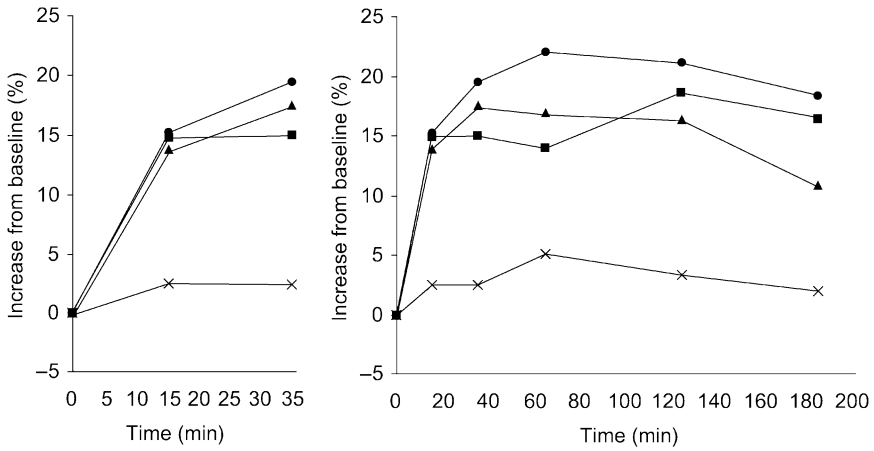

Figure 2 Mean IC during the first 180 min after inhalation of budesonide/formoterol (pMDI $2 \times 160/4.5$ μg; ●), salmeterol/fluticasone (pMDI $2 \times 25/250$ μg; ■), salbutamol (2×100 μg; ▲) or placebo (**X**) (% increase from predrug value). Inset shows mean IC during the first 35 min. IC, inspiratory capacity; pMDI, pressurized metered-dose inhaler.

in intensity), none of which was considered to be related to study treatment. Two patients discontinued treatment because of adverse events: one patient had a COPD exacerbation (placebo) and another experienced acute nasopharyngitis (salbutamol). No serious adverse events or deaths were reported.

No clinically important differences between treatments, changes over time or abnormalities were reported with respect to vital signs and physical findings.

DISCUSSION

The results of the present study show that budesonide/formoterol provides a rapid onset of bronchodilation in patients with moderate-to-severe COPD and a reversible component to their airflow limitation. The onset of the bronchodilatory effect following inhalation of budesonide/formoterol was similar to that seen with the gold standard reliever medication, salbutamol, and faster than that observed with salmeterol/fluticasone. All three active treatments were superior to placebo. As expected, improvements in lung function were maintained after treatment with both budesonide/formoterol and salmeterol/fluticasone over the study period, whereas the bronchodilatory effect of salbutamol declined over time. All four treatments were well tolerated and no safety concerns were identified.

The beneficial effect of budesonide/formoterol on objective measures of lung function agrees with results from previous long-term studies in COPD, in which budesonide/formoterol provided improvements in FEV_1[14] and maintained the improvements achieved following an optimized run-in period during which patients received intensified treatment.[15] The present study is the first to clearly demonstrate a rapid onset of effect in patients with COPD similar to that observed in patients with asthma.[24–27] Asthma and COPD are not directly comparable, however, and it has been suggested that the onset of effect of bronchodilators is probably slower in COPD than in asthma.[1] Our results suggest that this may not be the case for the budesonide/formoterol combination, as the mean improvement in FEV_1 in the budesonide/formoterol group at the 5-min assessment was 0.2 L or 15% of the baseline value. As we recruited patients who had significant reversibility, these results should not be generalized to all patients with COPD; they are,

however, applicable to the 50–75% of patients with a reversible component to their airflow limitation.[17,18]

There are difficulties associated with the determination of what constitutes a clinically relevant difference in FEV_1 among COPD patients. The American Thoracic Society/European Respiratory Society Task Force Guidelines[28] state that small increases in FEV_1, induced by bronchodilator therapy, are often related to larger changes in lung volume and an associated reduction in perceived breathlessness. The significance of a change in lung volume relative to FEV_1 is dependent on the stage of COPD. Previously, Redelmeier *et al.* [29] identified that a difference of 4% in predicted FEV_1 was necessary for patients to perceive a change in dyspnoea from being 'a little bit better/worse' and 'about the same'. In addition, Newton *et al.* have defined a change of at least 200 mL (or 10% of predicted normal) in IC as being clinically meaningful.[22] Furthermore, additional significant effects on lung function have been observed in individuals receiving combination therapy compared with either monocomponent alone.[15,30] Therefore, the improvement observed in FEV_1 and IC with budesonide/formoterol combination therapy, in the present study, can be considered clinically meaningful, as well as being similar to the improvements provided by salbutamol. The reasons for enhanced efficacy of budesonide/formoterol in combination compared with monocomponents remain unclear. However, corticosteroids can up-regulate the number of β_2-receptors on the cell membrane and β_2-agonists may enhance nuclear localization of glucocorticoid receptors.[31] Furthermore, a combination of budesonide/formoterol reduces the proliferation of airway smooth muscle, via synchronized cellular signalling, compared with either component alone.[32] It is likely that a combination of these mechanisms is responsible for the improved efficacy reported with budesonide/formoterol combination therapy.

The rapid onset of bronchodilatory effect of budesonide/formoterol is believed to be related directly to the formoterol component. In patients with COPD, formoterol has an onset of effect comparable with that of salbutamol[33,34] and faster than that of salmeterol.[35–38] One possible explanation for its faster onset of action may be that formoterol is a full β_2-agonist, whereas salmeterol is a partial agonist.[39–41] Based on results from a double-blind crossover study in patients with COPD, Cazzola *et al.* [42] suggested that the addition of budesonide to formoterol influenced the fast onset of action of formoterol, although the design of their study prevented them from concluding whether the effect was synergistic or merely additive. Whatever the underlying mechanism, the rapid onset of effect of budesonide/formoterol has the potential to improve patients' adherence to medication.[9,10]

In addition to FEV_1, the effects of treatment on IC were assessed in order to provide additional information to conventional spirometry on the acute effects of bronchodilators. Patients with COPD can develop dynamic hyperinflation, which contributes to dyspnoea and exercise intolerance. As IC is determined by the degree of hyperinflation, improvements in resting IC can be used to predict improvements in dyspnoea and exercise tolerance.[20,43] In line with their effects on FEV_1, all three active treatments improved IC to a greater extent than placebo, with significantly greater increases in IC at 15 min after drug administration. In addition, budesonide/formoterol increased maximal IC to a greater extent than salmeterol/fluticasone and to a similar extent as salbutamol, with an increase of 28% in maximal IC. O'Donnell *et al.* [20] demonstrated that a 10% increase in IC was associated with a significant (25%) improvement in exercise endurance time in patients with COPD, therefore budesonide/formoterol may help to rapidly improve exercise tolerance, dyspnoea and the ability of patients to carry out normal daily activities,[19–22] as well as improving health status.[44] Although further work is required to verify these exploratory results, functional improvements in patients with COPD have been reported with long-term budesonide/formoterol treatment in two large-scale trials.[14,15]

Patients in the present study were able to perceive the onset of effect soon after receiving each of the active treatments, whereas the time to POE was significantly longer following placebo. In contrast to the effects on spirometric measures, which demonstrate an advantage for budesonide/formoterol over salmeterol/fluticasone, patients' POE was similar for all three active treatments. With regard to time to POE, a difference of 10 min was observed between budesonide/formoterol and placebo, while the difference between salmeterol/fluticasone and placebo was 5 min. Statistically, however, there was no significant difference in median time to POE among the three active treatments. Although the study was neither designed nor powered to show differences in POE, the lack of a statistically significant difference between active treatments suggests that the instrument used was not sensitive enough to detect differences in COPD patients' perceptions of treatment effects. Previously, considerable variability has been reported in the perception of onset of symptoms between COPD patients. Redelmeier *et al.* reported that differences in FEV_1, which were expected to be related to dyspnoea were not consistently associated with patients' perception of dyspnoea.[29] In the present study there was a large placebo effect, with 61% of patients reporting a POE after receiving placebo. This may be another limitation of the POE question, which appears to be a blunt tool for measuring the effect of treatment. Patients may have been in steady state with respect to symptoms and many may have been relatively asymptomatic during the study, thus affecting the ability of the POE questionnaire to assess treatment effects. Alternatively, the large placebo effect may have been a consequence of diurnal variation in lung function in COPD patients, as lung function in COPD patients is known to be worst early in the morning, when the first assessments took place, and to improve spontaneously during the day.[45] It is also likely that the repeated FEV_1 measurements may have affected the POE.

Other tools have been developed for the measurement of onset of effect. A study in patients with asthma successfully demonstrated differences in

POE of effect between budesonide/formoterol and salmeterol/fluticasone. van der Woude *et al.* [27] used the modified Borg scale[46] in patients with methacholine-induced bronchoconstriction to demonstrate a significantly faster onset of effect following budesonide/formoterol treatment compared with salmeterol/fluticasone.[27] The Borg scale has also been used in patients with COPD,[47,48] although it has been suggested that the perception of dyspnoea during adenosine 5′-monophosphate- and methacholine-induced bronchoconstriction may be lower in patients with COPD than in those with asthma.[47]

This study shows that budesonide/formoterol has an onset of bronchodilatory effect in patients with COPD that is similar to the onset of the fast-acting β_2-agonist salbutamol, faster than that of salmeterol/fluticasone and placebo, and is perceived by patients within the first few minutes after administration.

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