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The bronchodilator response to salmeterol is maintained with regular, long-term use in patients with COPD

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Abstract

Long-acting beta$_2$-agonists (LABAs) are recommended in the management of patients with chronic obstructive pulmonary disease (COPD). Previous studies have demonstrated that the LABA, salmeterol, improves lung function, symptoms and quality of life in patients with COPD. In this study, we have performed additional analyses of the combined data from two previous double-blind, placebo-controlled, parallel studies of salmeterol (50 μg, b.i.d) in patients with COPD. The new analyses reveal that the significant improvements seen in pre-dose and 2-h post-dose forced expiratory volume in 1 s (FEV_1) compared to placebo, occur early in the treatment period, and are sustained for at least 24 weeks. Moreover, improvements in peak expiratory flow rate occur as early as Day 1, and are sustained throughout the 24-week period. Additional analyses of 12-h FEV_1 data also show that salmeterol is associated with an increase in the area under the curve at Week 12 compared with Day 1, adding further support to evidence that it results in a sustained bronchodilator response, with no evidence of tolerance.

Keywords: Bronchodilator; Chronic obstructive pulmonary disease (COPD); Long-acting beta$_2$-agonist (LABA); Salmeterol

1. Introduction

Salmeterol is a long-acting beta$_2$-agonist (LABA) used for the maintenance treatment of chronic obstructive pulmonary disease (COPD), a disease state characterized by airflow limitation that is not fully reversible. Patients with COPD experience a progressive decline in lung function associated with an increase in symptoms of breathlessness, cough and sputum production. In addition, patients with more advanced disease experience increasingly frequent acute exacerbations which may require hospitalisation, and in the most severe cases, can result in death. Current international guidelines (i.e. the Global Initiative for Chronic Obstructive Lung Disease) recommend the use of LABAs, such as salmeterol, as first-line therapy [1]. A number of studies have shown that treatment with salmeterol is associated with improvements in lung function, reductions in symptoms and use of rescue therapy, as well as reduced exacerbation risk and improvements in quality of life in patients with COPD compared with ipratropium bromide treatment or placebo [2–4]. The present analysis was undertaken to further evaluate data on the bronchodilatory effect of salmeterol (inhalation powder) twice daily via the Diskus® over 24 weeks in patients with COPD. In particular, the available data were examined for any evidence of tolerance to the bronchodilator effect of long-term treatment of patients with COPD with salmeterol.

2. Materials and methods

Data were combined and integrated from two similarly designed double-blind, parallel group multicenter studies based in the US (protocol numbers SFCA3006 and SFCA3007), where patients were randomized to receive either salmeterol (50 μg twice daily), salmeterol/fluticasone propionate (50/250 or 500 μg twice daily), fluticasone

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ANCOVA, analysis of covariance.

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propionate (250 or 500 μg twice daily) or placebo, all via the Diskus® device, for 24 weeks. Full individual results of these studies are published elsewhere [5,6]. In the present study we examine only data from the salmeterol and placebo arms. Patients ($n=711$) were 40 years of age or older, current or former smokers with at least a 20 pack-year history of smoking, and had a diagnosis of COPD [7]. Inclusion criteria required a baseline forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) of $\leq 70\%$ and a baseline FEV_1 of $<65\%$ of predicted, but >0.70 l. Patients were required to have chronic bronchitis (cough productive of sputum on most days for 3 months of the year for two consecutive years) and dyspnea. Key exclusion criteria included a current diagnosis of asthma, oral corticosteroid use in the previous 6 weeks, and clinically significant medical disorders besides COPD. All patients received inhaled or nebulized albuterol as rescue medication, but were not permitted to use inhaled or oral corticosteroids, ipratropium bromide, nedocromil and cromolyn sodium, or leukotriene modifiers.

2.1. Post-dose FEV_1

The primary efficacy outcome in this analysis was post-dose FEV_1, which represents the maximum bronchodilatory effect due to salmeterol. Patients were evaluated weekly for the first 4 weeks of treatment, every 2 weeks until Week 8, and then at 4-week intervals for the remainder of the treatment period. Differences between groups were analyzed by analysis of covariance (ANCOVA).

2.2. 12-h AUC FEV_1

An additional efficacy endpoint in these studies was 12-h FEV_1 area under curve, above baseline (AUC(BL)) which represents the duration and onset of effect of salmeterol over a 12-h period. This parameter was assessed only in a subset of patients at Day 1 (baseline) (placebo: $n=99$, salmeterol: $n=91$) and Week 12 (placebo: $n=69$, salmeterol: $n=75$). Mean values were calculated by visit, not controlled for study drop-outs. FEV_1 measurements were taken at 30 min pre-dose, immediately pre-dose (time 0) and 0.5, 1, 2, 4, 6, 8, 10 and 12 h post-dose. The AUC of the serial 12-h FEV_1 data (above the pre-dose FEV_1 at 0 h recorded on Day 1), AUC(BL), was calculated as:

$$\begin{aligned}\text{AUC(BL)} = {} & 0.25(\text{FEV2}) + 0.5(\text{FEV3}) + 0.75(\text{FEV4}) \\ & + 1.5(\text{FEV5}) + 2(\text{FEV6} + \text{FEV7} + \text{FEV8} \\ & + \text{FEV9}) + \text{FEV}_1 0 - 12(\text{FEVBL})\end{aligned}$$

FEV2 to $FEV_1 0$ were the measurements at 0, 0.5, 1, 2, 4, 6, 8, 10 and 12 h, respectively, and FEVBL was the average of the measurements at -0.5 and 0 h.

Onset of effect was defined as the time point (within 4-h post-dose) at which FEV_1 exceeded 100 ml above the baseline recorded at Day 1. If a subject did not respond within 4 h, the onset was defined as 12 h. Duration of effect was defined as the time of offset minus time of onset. Offset of effect was taken as the time post-dose at which FEV_1 dropped below the 100 ml improvement limit for two consecutive time points. Treatment comparisons for AUC(BL) were based on analysis of variance F-test. Comparisons for onset and duration of the response were performed using the van Elteren test [8] (a generalization of the Wilcoxon rank sum test that controls for investigator).

2.3. Peak expiratory flow (PEF) rates

Morning peak expiratory flow (PEF) data, which represent maximal flow rate, were also analysed. Patients were trained to measure morning PEF using a hand-held Mini–Wright peak flow meter. The technique of performing the peak flow maneuvers was reviewed by study staff at each clinical visit. Triplicate maneuvers were performed each morning prior to the first medication dose, and the highest value was recorded on by patients using diary cards.

3. Results

A total of 711 patients were randomized to treatment; 341 and 370 in the salmeterol and placebo groups, respectively. A total of 709 patients were evaluated; 339 and 370 in the salmeterol and placebo groups, respectively, as two patients in the salmeterol group did not have FEV_1 data at baseline. The baseline characteristics in the two treatment groups were well matched (Table 1).

Significant improvements in both pre-dose and 2 h post-dose FEV_1, compared to baseline, were seen in patients receiving salmeterol throughout the 24-week period (Fig. 1a and b). Significant improvements in 2-h post-dose FEV_1 for salmeterol versus placebo were also seen at Day 1 of treatment (0.2 ± 0.01 versus 0.04 ± 0.01 l; $p<0.001$), and

Table 1
Patient demographics and baseline characteristics

	Salmeterol ($n=341$)	Placebo ($n=370$)
Mean age (SE, years)	64 (0.5)	64 (0.4)
Male (%)	61	72
White (%)	94	93
Current smokers (%)	49	50
Mean smoking history (SE, pack years)	63 (1.7)	65 (1.6)
Mean % predicted FEV_1 (SE)	39.8 (0.7)	40.1 (0.7)
Mean FEV_1/FVC ratio (SE)	0.5 (0.006)	0.5 (0.006)
Reversible to albuterol[a] (%)	53	56
Mean FEV_1 reversibility (%)	21.2 (0.9)	40.1 (0.7)

[a] ≥ 200 ml and $\geq 12\%$ improvement in FEV_1.