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Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose–response study

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When testing the response to β_2-agonist drugs in severe chronic obstructive pulmonary disease (COPD), a dose–response assessment should be undertaken. This study compares the time course of inhaled salmeterol (25, 50 and 75 μg) and formoterol (12, 24 and 36 μg) at different doses in a group of 12 patients with partially reversible, but severe COPD (FEV_1 of 12–32% of predicted values after β_2-agonist drugs had been withheld for 24 h). All doses of salmeterol and formoterol induced a significant ($P<0{\cdot}01$) spirometric improvement over the 12-h monitoring period, when compared to the spirometric improvement after placebo, but while formoterol induced a dose-dependent increase of the FVC, FEV_1 and FEF_{50}, this was not the case for salmeterol. In fact, 75 μg salmeterol did not produce a further improvement of these parameters. Mean peak bronchodilation, expressed as the increase in FEV_1 over baseline values, occurred 2 h after inhalation of the three doses of salmeterol, and 1 h after inhalation of the three doses of formoterol. A comparison of 50 μg salmeterol with 12 μg or 24 μg formoterol (clinically recommended doses), showed that improvement of FEV_1 after salmeterol was statistically ($P<0{\cdot}05$) higher than that after the two doses of formoterol, although the mean peak bronchodilations were similar. This was because salmeterol has a longer duration of action than formoterol. These data demonstrate that salmeterol is equally effective as, but longer-acting than, formoterol at clinically recommended doses in patients suffering from COPD, with severe airway obstruction. Moreover, these data suggest that 50 μg is the best dosage for salmeterol in these patients.

Introduction

The aim of bronchodilator therapy in patients with chronic obstructive pulmonary disease (COPD) is to treat any airflow obstruction which is reversible (1). However, clinicians are sometimes reluctant to prescribe β_2-agonists to these patients because the airflow obstruction is often 'irreversible'. Indeed, the response to inhaled β_2-agonists varies among patients with chronic bronchitis and emphysema, presumably reflecting the different mechanisms responsible for airway obstruction, e.g. smooth muscle-induced bronchospasm and luminal obstruction in patients with predominant bronchitis *vs.* airway collapse in patients with emphysema, but also because the dose of bronchodilator is inadequate for the severity of the airflow obstruction.

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When the response to β_2-agonist drugs in severe COPD is tested, a dose–response assessment should be undertaken. In fact, in patients classified as chronic bronchitics, there is clearly a wide variation of response to bronchodilators and a surprising degree of reversibility can be achieved. Due to this variation in response, conventional drug doses may be too small in some cases (2). Barclay *et al.* (2) demonstrated that a group of chronic obstructive bronchitics were non-responsive to 200 μg inhaled salbutamol, but by gradually increasing the dose, a response was obtained in all patients. Similar results were reported by other authors (3).

Salmeterol and formoterol are new, highly potent β_2-adrenoceptor agonists characterized by a long duration of action when inhaled (4). Clinical efficacy of these two bronchodilators indicate that they might be a major step forward in the therapy of chronic reversible airway disease, exceeding the therapeutic efficacy of the β_2-agonists available to date (5–7).

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Table 1 Anthropometric data and pulmonary function of patients

Patient	Sex	Age (years)	Height (cm)	Weight (kg)	FEV_1 (l)	FEV_1 (% predicted)	% reversibility
1	M	62	165	74	0·45	16	+31
2	M	63	154	46	0·32	14	+34
3	M	58	157	47	0·68	26	+43
4	M	67	163	62	0·82	32	+40
5	M	66	168	80	0·50	18	+20
6	M	62	164	74	0·50	18	+34
7	M	64	162	77	0·59	22	+27
8	M	57	168	81	0·98	32	+24
9	M	53	160	54	0·52	18	+25
10	M	74	167	49	0·51	20	+25
11	M	58	165	54	0·89	30	+20
12	M	67	154	100	0·25	12	+24

Moreover, salmeterol has been demonstrated to lead to a long lasting improvement of exercise capacity in patients with COPD (8).

In this study, comparisons have been made between the time course of inhaled salmeterol and formoterol at different doses, in a group of patients with partially reversible COPD.

Patients and Methods

Twelve male patients with severe COPD participated in the study after giving their informed consent. All fulfilled the criteria proposed by the American Thoracic Society (9): i.e. they were current or former smokers without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both, were non-atopic, had had no change in symptom severity or treatment in the preceding 4 weeks, had shown no signs of a respiratory tract infection in the month preceding or during the trial, were not taking oral corticosteroids and had a FEV_1 between 12–32% (after β_2-agonist drugs had been withheld for 24 h) of predicted values. Only patients who had an increase in FEV_1 of at least 15%, 15 min after inhalation of 200 μg salbutamol from a metered dose inhaler, but a post-bronchodilator FEV_1 or FEV_1/FVC below the predicted range, were included. Table 1 outlines the baseline characteristics of the population studied.

The study, approved by the Ethics Committee at the A. Cardarelli Hospital of Naples, was performed using a single-blind, cross-over, randomized study. The bronchodilator activity of 25, 50 and 75 μg salmeterol hydroxynaphthoate (Glaxo, Verona, Italy), 12, 24 and 36 μg formoterol fumarate (Ciba, Basel, Switzerland) and placebo, which were all inhaled from a metered dose inhaler and holding chamber (AeroChamber) with mouthpiece, was investigated on several non-consecutive days. The subjects had not taken any inhaled bronchodilator drug for at least 12 h, or oral bronchodilators for at least 24 h before the investigation started, and consumption of cola drinks, coffee, tea, and smoking in the hours immediately before and during the investigation were also avoided. All experiments began at 8 a.m. to avoid well-known interference of the circadian rhythm on bronchomotor tone.

Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for FVC and FEV_1. The best FVC, FEV_1 and instantaneous forced expiratory flow after 50% of the FVC is exhaled (FEF_{50}), obtained from one or the other of the reproducible curves, were kept for analysis. Measurements were performed at the following times: immediately before inhalation of treatment, and at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 min after inhalation of the individual treatment.

The functional indices' increases from baseline after salmeterol, formoterol and placebo were assessed. Comparisons of baseline characteristics among the three groups were performed by ANOVA analysis, and Fisher's exact test. Analysis of spirometric data was performed using the Student's *t*-test for paired variables. The time-averaged changes in the 12 h after drug administration, between each treatment and placebo, and between drugs were compared by means of the distribution free cross-over analysis (10). With respect to the multiple testing of three lung function parameters, the significance level of 0·05 was considered as relevant. The FEV_1

Table 2 Number of patients with FEV_1 response to bronchodilator 15 min after inhalation ($n=12$)

	25 Salm	50 Salm	75 Salm	12 Form	24 Form	36 Form
Basal FEV_1 range (l)	0·19–1·04	0·30–1·09	0·26–1·05	0·27–1·09	0·22–1·15	0·27–1·21
PI 15% responders	8	12	11	11	10	11
PI 25% responders	6	5	6	10	10	9
AI responders	4	6	6	8	8	9

Salm, Salmeterol; Form, formoterol; PI 15%, patients showing a percentage increase of >15%; PI 25%, patients showing a percentage increase of >25%; AI, patients showing an absolute increase of >160 ml.

areas under the curve were analysed by the trapezoidal rule. The baseline values were always indicated as 100%.

Results

All 12 patients completed the 7-day study. There were no significant differences between the baseline spirometric values of the seven treatment groups ($P>0·05$).

RATE OF ONSET OF ACTION

Eight out of 12 patients presented an increase in FEV_1 of at least 15%, 15 min after inhalation of 25 μg salmeterol, 12 patients presented this increase after 50 μg salmeterol, 11 patients presented this increase after 75 μg salmeterol, 12 μg formoterol or 36 μg formoterol, and 10 patients presented this increase after 24 μg formoterol (Table 2). Choosing a 25% cut-off, six patients out of 12 responded to 25 μg or 75 μg salmeterol 15 min after drug inhalation, five patients responded to 50 μg salmeterol 15 min after drug inhalation, 10 patients responded to 12 μg or 24 μg formoterol 15 min after drug inhalation, and nine patients responded to 36 μg formoterol after 15 min. Using an increase in FEV_1 of 0·16 l as cut-off, as suggested by Tweeddale *et al.* (11), only four out of 12 patients achieved such a response 15 min after the inhalation of 25 μg salmeterol, six patients after inhalation of 50 μg or 75 μg salmeterol, eight patients after 12 μg or 24 μg formoterol, and nine patients after 36 μg formoterol.

MAXIMUM RESPONSE

The mean individual peak bronchodilation, expressed as the maximum increase in FEV_1 over baseline values, occurred 2 h after inhalation of the three doses of salmeterol, and 1 h after inhalation of the three doses of formoterol (range 25 μg salmeterol, 30–360 min; 50 μg salmeterol, 60–360 min; 75 μg salmeterol, 60–360 min; 12 μg formoterol, 30–300 min; 24 μg formoterol, 30–360 min; 36 μg formoterol, 30–480 min). However, patients varied in their maximum response to the different doses of the two drugs (Fig. 1).

TIME COURSE OF BRONCHODILATING EFFECT

The mean percent changes of FEV_1 from baseline after administration of salmeterol, formoterol or placebo are shown in Fig. 2, and the changes of FVC and FEF_{50} in Fig. 3. All doses of salmeterol and formoterol induced a significant ($P<0·01$) spirometric improvement over the 12-h monitoring period when compared to that after placebo, but while formoterol induced a dose-dependent increase of FEV_1, FVC and FEF_{50}, this was not the case for salmeterol. In fact, 75 μg salmeterol did not produce a further improvement of these parameters. However, when individual subjects were considered, there was a heterogenous response to the various bronchodilator regimens. A comparison of 50 μg salmeterol with 12 μg or 24 μg formoterol (clinically

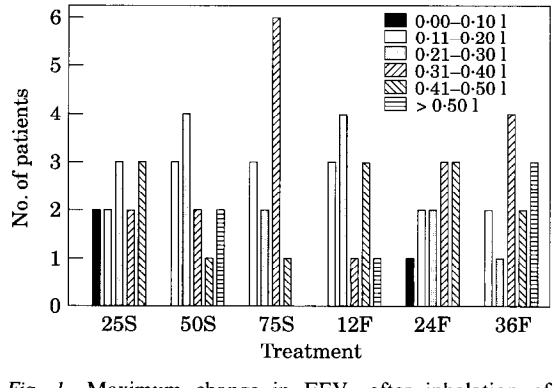

Fig. 1 Maximum change in FEV_1 after inhalation of salmeterol or formoterol for all the subjects and six subgroups. 25S, 25 μg salmeterol; 50S, 50 μg salmeterol; 75S, 75 μg salmeterol; 12F, 12 μg formoterol; 24F, 24 μg formoterol; 36F, 36 μg formoterol.

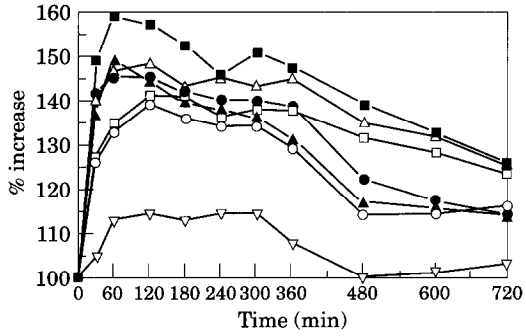

Fig. 2 Mean percentage changes in FEV_1 from baseline at different times after inhalation of salmeterol, formoterol or placebo. ○, 25 μg salmeterol; △, 50 μg salmeterol; □, 75 μg salmeterol; ●, 12 μg formoterol; ▲, 24 μg formoterol; ■, 36 μg formoterol; ▽, placebo.

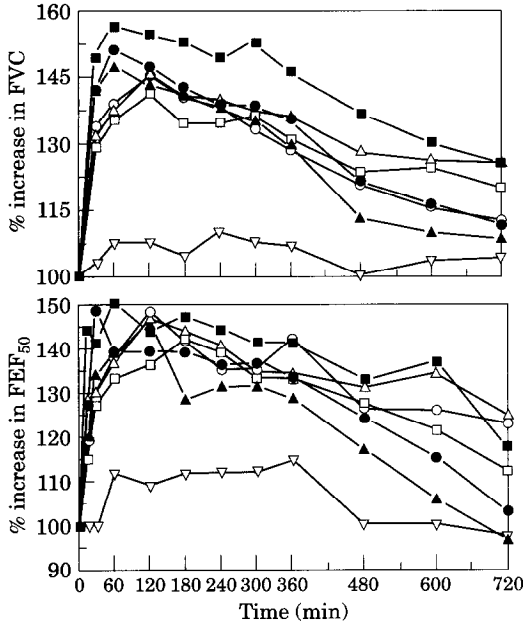

Fig. 3 Mean percentage of changes in FVC and FEF_{50} from baseline at different times after the inhalation of salmeterol, formoterol or placebo. ○, 25 μg salmeterol; △, 50 μg salmeterol; □, 75 μg salmeterol; ●, 12 μg formoterol; ▲, 24 μg formoterol; ■, 36 μg formoterol; ▽, placebo.

recommended doses) showed that improvement of FEV_1 after salmeterol was statistically ($P<0.05$) higher than that after the two doses of formoterol, although the mean peak bronchodilations were similar. This was because salmeterol has a longer duration of action than formoterol. The highest dose of formoterol increased FEV_1 more than salmeterol,

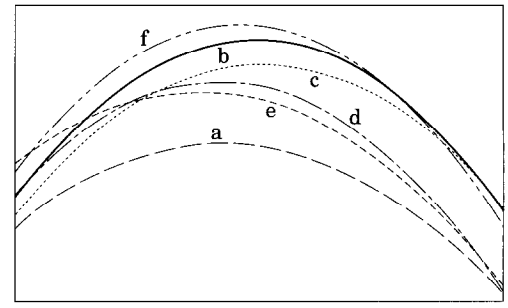

Fig. 4 Polynomial regression lines, order 2, for FEV_1 values. a, 25 μg salmeterol; b, 50 μg salmeterol; c, 75 μg salmeterol; d, 12 μg formoterol; e, 24 μg formoterol; f, 36 μg formoterol.

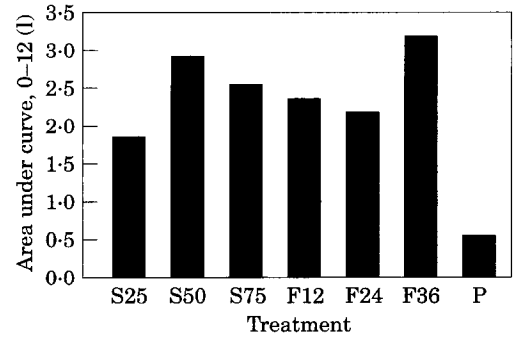

Fig. 5. Area under the time–response curve after the inhalation of salmeterol (S25, S50, and S75), formoterol (F12, F24, and F36) or placebo (P).

but was shorter-acting. The FEV_1 dose–response curves, shown as polynomial regression lines, confirmed this pattern (Fig. 4).

FEV_1 AREA UNDER THE CURVES

The mean FEV_1 area under the curve was significantly ($P<0.05$) larger after 50 μg when compared to that after 12 μg or 24 μg formoterol (Fig. 5). However, there was no significant difference ($P>0.05$) between 50 μg salmeterol and 36 μg formoterol.

Discussion

The effects of salmeterol and formoterol on airway tone have been investigated in asthmatic patients. Ullman and Svedmyr (12) found that doses of 50 or 100 μg salmeterol had a long-lasting effect on peak expiratory flow, and Derom and Pauwels (13) reported on the effects of prolonged bronchodilation after 12 or 24 μg inhaled formoterol on FEV_1; in neither of these studies did these doses have a dose-dependent effect. In a recent study, Rabe *et al.*

(14) demonstrated that 50 μg salmeterol and 12 μg formoterol have a duration of action up to 24 h and induce bronchodilation equally effectively in patients with mild bronchial asthma.

From our present study, it seems that 50 μg salmeterol induces a good and long-lasting bronchodilation, but 75 μg salmeterol does not elicit additional improvements in partially reversible severe COPD. Formoterol at doses from 12–36 μg induces a dose-dependent increase of bronchodilation. However, a 50 μg salmeterol elicits a similar mean peak bronchodilation and a longer lasting bronchodilator effect than 12 μg or 24 μg formoterol.

It has been previously demonstrated that salmeterol and formoterol, administered at the recommended doses for regular inhaled therapy (50 μg and 24 μg, respectively) by metered dose inhaler, appear to be very effective in improving airway limitation in patients suffering from COPD (15). The time-averaged values over 12 h were significantly higher after salmeterol and formoterol, when compared to that after salbutamol and placebo, while differences between salmeterol and formoterol were not significant at any of the observed times, although there was a trend for a longer-lasting duration of action of salmeterol. The disparity between the results of that study and the present research could be partly explained by the fact that a different patient population was studied. Patients recruited for the first study had moderate COPD, whereas those in the present study had more severe disease, as indicated by their low baseline FEV_1 and bronchodilator responses at the time of initial assessment. In any case, the fact that only a single dose of each agent being compared was used, severely limited the information obtained.

If a study comparing single doses of different agents fails to show a statistically significant difference between the compared preparations, this is not equivalent to saying that they are identical. The failure to show a difference could be due to type II statistical error, i.e. insufficient sample size and, consequently, lack of sufficient statistical power in the study, or the fact that the specific subjects studied in the specific clinical situation in which they were studied were at the top of their β-agonist dose–response curve (16).

A much more effective study design for comparing the effects of inhaled β-agonists is to use each of the agents being studied at various differing doses. However, the clinical value of establishing the optimal bronchodilation and the optimal dose of β-agonist, required to produce such bronchodilation in patients with COPD, is limited by the large within-patient variability in the response to bronchodilator, resulting in poor reproducibility (17).

Lung function tests, including FEV_1, PEFR and FVC, have been used to measure the degree of bronchodilation, and thereby assess bioequivalence and bioequipotency of inhaled drug products (18). At present, it is generally agreed that the acute increase in FEV_1 in response to increasing doses of β-agonist may be employed as the method of choosing the dose to be prescribed.

One of the most common ways of expressing the bronchodilating response is to quantify the change in FEV_1 as a percentage of the basal obstruction (pre-bronchodilator FEV_1). However, this change is strongly dependent on the initial FEV_1, especially in patients with COPD (19). The absolute increase in FEV_1 necessary to distinguish, with 95% confidence, between natural variability and a response to bronchodilator in these patients is 160 ml (11), but even small changes in FEV_1 (100 ml) may be important to patients with severe chronic airway limitation (20). It must be highlighted that the use of a cut-off of 15% to define response in FEV_1 selects a greater proportion of more severely than less severely impaired patients (21), and our patients were suffering from severe obstructive ventilatory defects.

In any case, if one uses a cut-off of 15%, the sensitivity of acute bronchodilator response in predicting long-term symptomatic response in subjects with chronic airflow limitation is good, but the specificity is poor (21). Using higher cut-off, specificity improves, but at the expense of sensitivity. Even a 15% cut-off would still leave some patients, who gain symptomatic benefit from the drugs, untreated. It is clear that an acute response to inhaled β-agonists is not useful for identifying patients with chronic airflow limitation who are likely to benefit from acute bronchodilator treatment (21,22).

In conclusion, this study has demonstrated that salmeterol is equally effective as, but longer-acting than, formoterol at clinically recommended doses in patients suffering from COPD, with severe airway limitation. This study also suggests that 50 μg is the best dosage for salmeterol in these patients, even though future bronchodilator therapy should be based on individual assessment, as mechanisms behind a similar degree of airway obstruction may differ. Considering that a single measurement of the response to a bronchodilator has limited validity, since short-term changes in spirometry following bronchodilators fail to predict the long-term response, controlled studies evaluating clinically relevant outcomes and home PEFR recordings in

response to different doses of salmeterol and formoterol over longer periods of time are needed.

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