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Effect of Salmeterol and Formoterol in Patients with Chronic Obstructive Pulmonary Disease

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SUMMARY: In the present trial we investigated the time course of inhaled salmeterol and formoterol bronchodilation in comparison with that of inhaled salbutamol and placebo in 16 patients with moderate to severe chronic obstructive pulmonary disease (COPD).

The study was performed using a single-blind crossover randomized study. The bronchodilator activity of 200 μg salbutamol, 50 μg salmeterol, 24 μg formoterol and placebo, which were all inhaled from a metered dose inhaler, was investigated.

Our results showed that salmeterol and formoterol are efficacious in reducing airflow obstruction in patients suffering from COPD. We found similar times of onset to improve FEV_1 by 15% for salmeterol and formoterol (salbutamol behaving faster), while the duration of action showed the expected differences between the two long-acting drugs and salbutamol.

The results indicate that long-acting β_2-agonists appear to be very effective in improving airway limitation in patients suffering from COPD. Although the onset of bronchodilation after inhaling salmeterol and formoterol is slightly delayed compared with salbutamol, this is of little clinical importance since in these patients salmeterol and formoterol must be intended for maintenance treatment and not immediate symptomatic relief.

KEY WORDS: Inhaled β_2-agonists, Salmeterol, Formoterol, Salbutamol, Chronic obstructive pulmonary disease.

INTRODUCTION

Inhaled β_2-agonists are often used as first-line treatment in COPD. However, the β_2-adrenoceptor agonists in clinical use over the past years have a short duration of action (4–6 h). Therefore, patients are required to use these agents frequently in order to improve airflow.

The recent development of β_2-agonists with a prolonged duration of action (approximately 12 h) compared with those previously available may represent a useful therapeutic advance in the treatment of airways disease.[1] Salmeterol and formoterol belong to this new generation of β_2-selective adrenoceptor agonists and are characterized by a long duration of action when inhaled.[2]

In the present study the time course of inhaled salmeterol and formoterol in comparison with that of salbutamol in a group of patients with COPD was evaluated.

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PATIENTS AND METHODS

Sixteen patients (all men) with moderate to severe COPD participated in the study after giving their informed consent. All fulfilled the American Thoracic Society criteria for chronic bronchitis,[3] were non-atopic, were heavy smokers (between 40.3 and 72.8 pack years) but had not smoked cigarettes within the preceding 4 months, 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 an FEV_1 (after β_2-agonist drugs had been withheld for 24 h) of between 15–69% of predicted value. Only patients who had an increase in forced expiratory volume in one second (FEV_1) of at least 15%, 15 min after inhalation of

Table 1 Anthropometric data and pulmonary function of patients.

Patient	Sex	Age (yrs)	Height (cm)	Weight (kg)	FEV_1 (l)	FEV_1 % predicted	Maximum reversibility %
1	M	60	1.72	72	1.47	47	+47
2	M	69	1.71	73	1.10	38	+40
3	M	70	1.70	80	0.72	26	+29
4	M	61	1.63	68	0.96	35	+66
5	M	68	1.63	69	0.99	39	+24
6	M	54	1.62	70	1.48	51	+62
7	M	50	1.61	82	1.54	52	+41
8	M	65	1.66	66	0.88	32	+49
9	M	73	1.66	74	0.64	25	+42
10	M	67	1.59	57	0.35	15	+138
11	M	76	1.59	76	0.57	27	+41
12	M	80	1.68	73	0.94	56	+30
13	M	59	1.77	90	2.24	69	+46
14	M	80	1.55	48	0.54	29	+31
15	M	45	1.57	75	1.69	57	+44
16	M	51	1.68	86	0.97	30	+26

Reversibility = % change from baseline after 200 µg inhaled salbutamol.

200 µg salbutamol from a metered dose inhaler, but a postbronchodilator FEV_1 or FEV_1/VC below the predicted range were included. All patients were taking oral theophylline and inhaled β_2-agonists regularly. 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 crossover randomized study. The bronchodilator activity of 200 µg salbutamol sulphate (Glaxo, Verona, Italy), 50 µg salmeterol hydroxynaphthoate (Glaxo, Verona, Italy), 24 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 eight non-consecutive days. Dosages were those recommended for regular inhaled therapy. At least 48 h elapsed between each experimental day. FEV_1 baseline values varied by no more than 15% on different study days. The patients were instructed carefully on how to take two inhalations from the metered dose inhaler. The subjects had not taken any inhaled bronchodilator drug for at least 12 h and oral bronchodilators for at least 48 h before the investigation started, and consumption of cola drinks, coffee and tea and smoking in the hours immediately before and during the investigation were also avoided. All experiments began at 8 am to avoid well-known interference with the circadian rhythm on bronchomotor tone. Spirometric measurements were made by electrical integration of a signal from a pneumotachygraph (Fleisch No. 3) (Pneumodata, Cosmed, Rome, Italy). Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for the forced vital capacity (FVC) and the FEV_1. The best FVC, FEV_1 and peak expiratory flow rate (PEFR) obtained from one or the other of the reproducible curves were kept for analysis.

To investigate the rate of onset of the bronchodilating effect of the different treatments, in the first four study days measurements were performed immediately before (as baseline value) and every 3 min after inhalation of drugs until patients achieved an increase in FEV_1 of at least 15%. In the last four study days, measurements were performed at the following times: immediately before and at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 min after inhalation of the individual treatment.

To overcome the drawbacks of current MEFV curve indices, we have examined the area under the MEFV curve (AUC) [AUC = (FVC × PEFR)]. The potential advantage of the AUC is that it should increase more on bronchodilation than other MEFV curve indices. This is because the concavity of the MEFV curve flattens out on bronchodilation and a small increase in PEFR and FVC should be accompanied by larger increases in AUC.[4]

The functional indices' increases from baseline after salbutamol, salmeterol, formoterol and placebo, which are presented as percentage of change [100 × (value after treatment − value before treatment)/(value before treatment)], were assessed. Descriptive statistics included median and central 68%-range. For the interference statistical analysis, FVC and FEV_1 were considered as key parameters of lung function. The time-averaged changes within the first 12 h after drug administration, between each drug and placebo, and between drugs, were compared by means of the distribution-free crossover analysis.[5] With respect to the multiple testing of three lung function parameters, the significance level of $\alpha = 0.05$ was considered as relevant. The baseline values are always indicated as 100%.

Table 2 Mean time of onset of the bronchodilating effect (increase in FEV_1 of at least 15%) after inhalation of salbutamol, salmeterol and formoterol.

Treatment	Time	95% Confidence level
Salbutamol	3 min 56 s	53 s
Salmeterol	10 min 8 s	3 min 50 s
Formoterol	10 min 52 s	6 min

RESULTS

All 16 patients completed the 8-day study. There were no significant differences between the baseline spirometric values of the four treatment groups ($P > 0.05$). The mean basal FEV_1 ($\pm$SEM) value on the salmeterol day was 1.04 ± 0.31 l, on the formoterol day was 1.13 ± 0.26 l, on the salbutamol day was 1.02 ± 0.29 l and on the placebo day was 1.10 ± 0.32 l.

Rate of onset of action

The onset of action was more rapid after salbutamol than after formoterol and salmeterol (Table 2); the difference was significant ($P < 0.05$). Formoterol and salmeterol were similar when mean values were evaluated, but nine out of 16 patients presented a more rapid onset of action after formoterol compared to salmeterol and only five after salmeterol compared to formoterol. Moreover, formoterol was faster than salbutamol in four out of 16 patients. However, the variability in formoterol-treated patients was larger than in salmeterol-treated patients. Placebo induced a 15% increase in FEV_1 in only three out of 16 patients.

Maximum response

Mean peak bronchodilation, expressed as the increase in FEV_1 over baseline values, occurred 5 h after inhalation of salmeterol ($+32.81 \pm 4.0\%$), 4 h after inhalation of formoterol ($+35.63 \pm 6.3\%$) and 60 min after inhalation of salbutamol ($+39.1 \pm 6.33\%$).

Time course of bronchodilating effect

The change in FEV_1 was chosen as the primary outcome variable to demonstrate bronchodilation.[6] Figure 1 shows the mean percentage increase in FEV_1 from baseline for the four treatment groups. The mean changes were higher after salbutamol than after salmeterol and formoterol, but all patients receiving salbutamol returned to baseline after 6 h. In contrast, after a rapid improvement, salmeterol and formoterol reached the highest levels at 360 min and soon after there was a slow decline in percentage improvements. The time-averaged values over 12 h were significantly higher after salmeterol and formoterol ($P < 0.01$) when compared to that after salbutamol, while differences between salmeterol and formoterol were not significant ($P > 0.05$) at each of the observed times.

The percentage improvement of FVC was also evaluated (Fig. 2) because a minority of patients may show improvement in FVC without change in FEV_1;[7] it was rather similar after salmeterol and formoterol. The time-averaged value difference over 12 h between these two drugs was not significant ($P > 0.05$), but it was significant ($P < 0.01$) between salmeterol and salbutamol and between formoterol and salbutamol.

When individual subjects were considered, there was a heterogenous response to the various bronchodilator regimens.

Area under the MEFV curves

The mean areas under the MEFV curves at 8, 10 and 12 h after salmeterol were higher than that after formoterol (Fig. 3).

Blood pressure and heart rate

The heart rate and blood pressure did not change significantly ($P > 0.05$) during the tests.

DISCUSSION

Several studies have confirmed the finding that 50 µg salmeterol and 24 µg formoterol produce a significantly longer duration of bronchodilation than salbutamol. Formoterol caused significant bronchodilation lasting 8–12 h in asthmatic adult patients[8] and children[9] and in healthy smokers and non-smokers.[10] With salmeterol the bronchodilator effect lasted approximately 12 h in adult asthmatics and in patients with nocturnal asthma.[11,12] To our knowledge, ours is the first study to compare the effectiveness of salmeterol and formoterol in patients with COPD. Our data showed that the duration of bronchodilation was similar to previously published results with differences between the two long-acting drugs and salbutamol. However, the mean areas under the MEFV curves at 8, 10 and 12 h after salmeterol were higher than that after formoterol.

We have used 24 µg formoterol and 50 µg salmeterol, which are the recommended doses for regular inhaled therapy. These dosages differed only by a factor of 1.5 base on molecular weight. Thus, the agonist-activation provided by salmeterol was greater than that obtained with formoterol and this may explain why there was no observed slower onset of action for salmeterol than for formoterol, as has been previously reported.[13,14]

Both salmeterol and formoterol improved FEV_1, PEFR and MEF_{50} with a rapid onset of action fol-

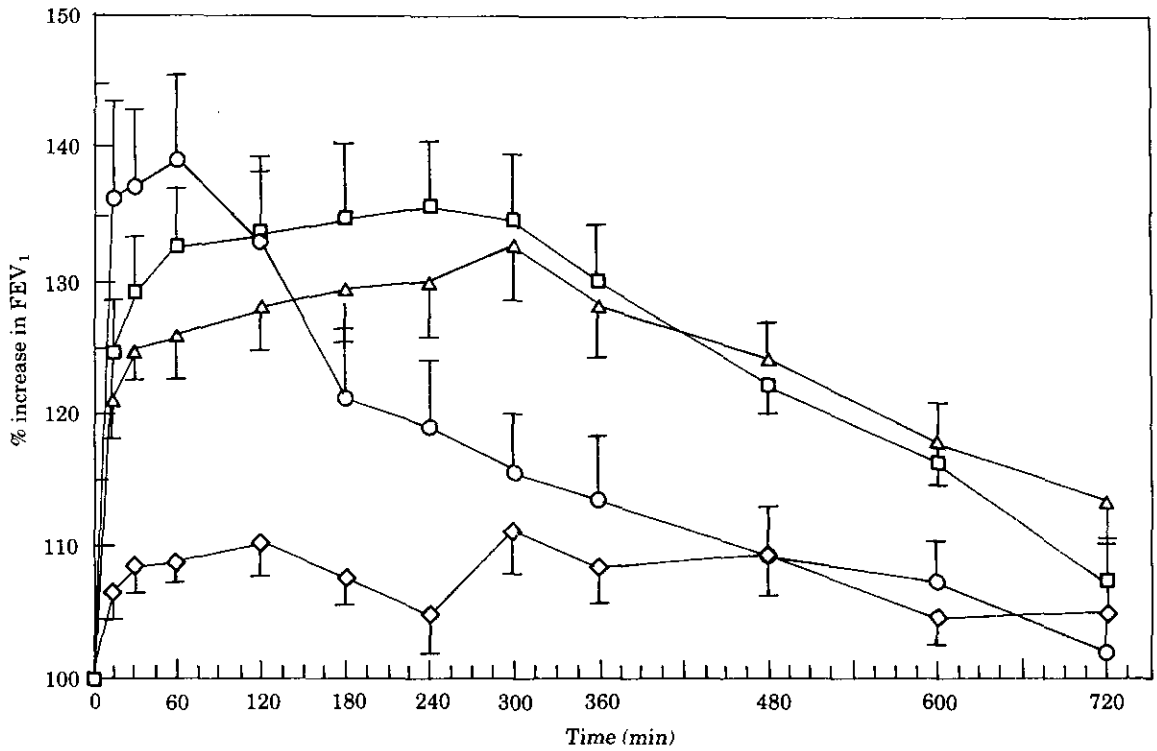

Fig. 1 Mean individual percentage of change in FEV_1 from baseline after inhaled salbutamol (○), salmeterol (△), formoterol (□) and placebo (◇).

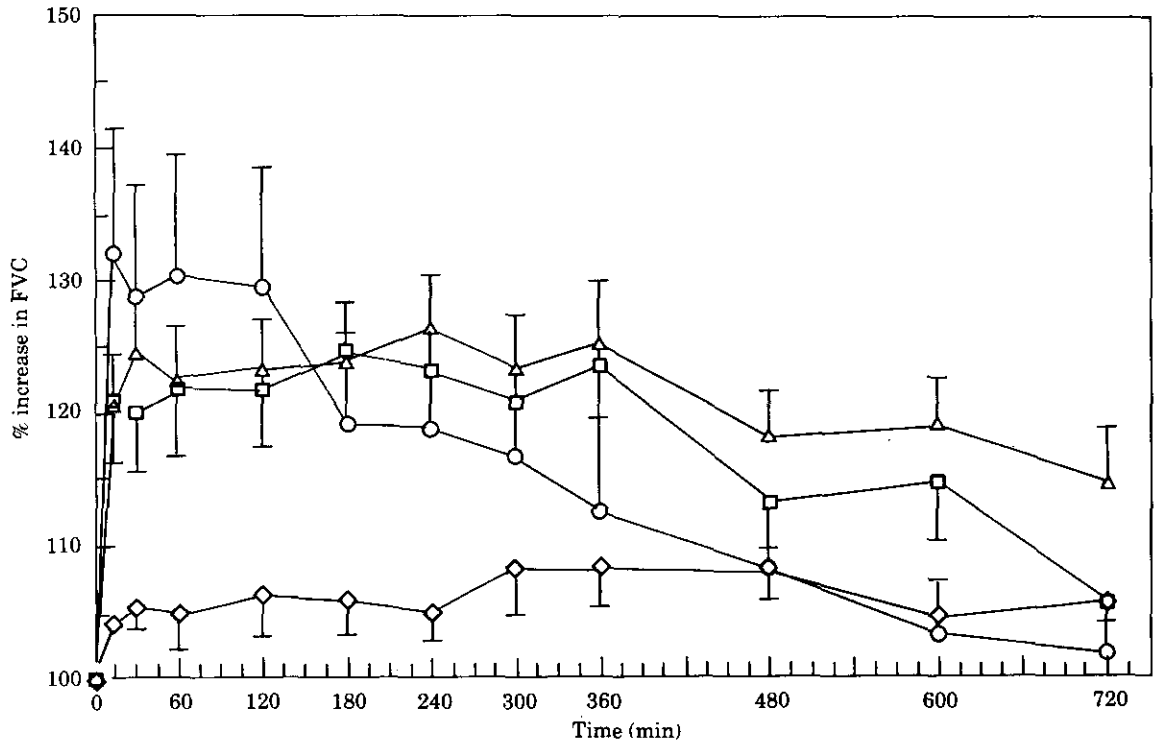

Fig. 2 Mean individual percentage of change in FVC from baseline after inhaled salbutamol (○), salmeterol (△), formoterol (□) and placebo (◇).

lowed by a gradual increase with time. This may mean that after a relatively rapid agonist-receptor association, a secondary effect was also present. Since salmeterol and formoterol exhibit persistent inhibition of both preformed and newly generated mediators from lung tissues with a greater potency than

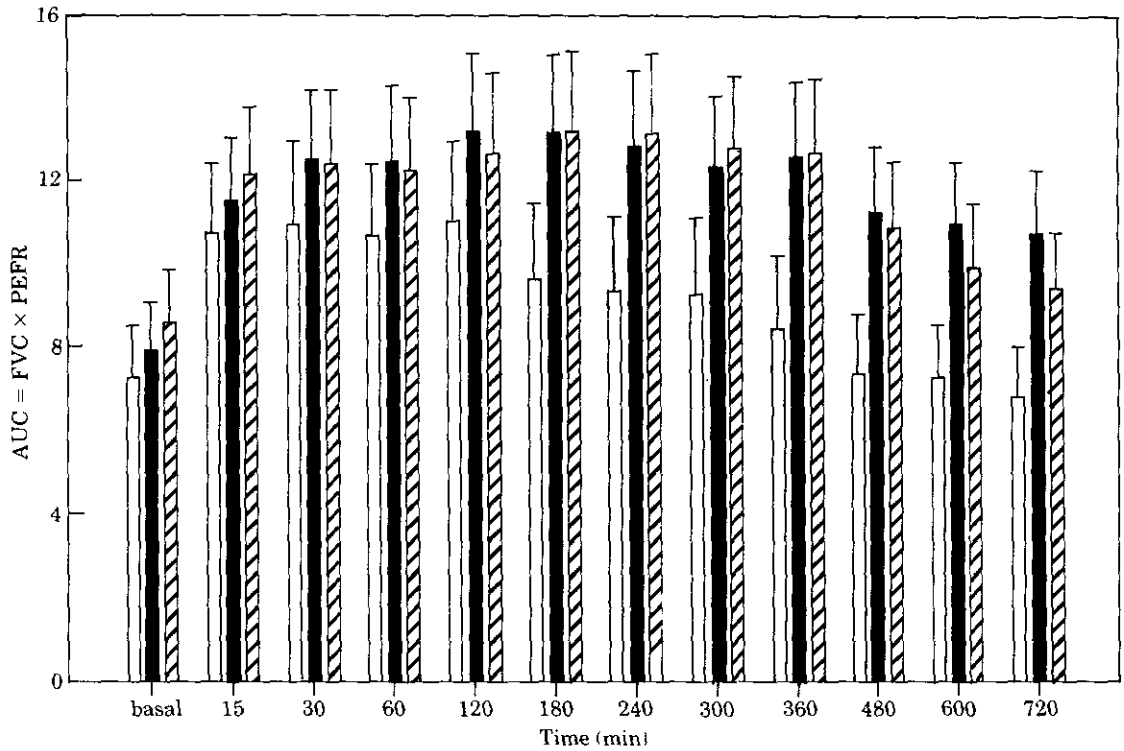

Fig. 3 Mean (± SE) changes in area under the MEFV curve after inhalation of salbutamol (□), salmeterol (■) and formoterol (▨).

salbutamol,[15,16] this additional effect may explain the present observation.

In conclusion, our results show that long-acting β_2-agonists appear to be effective in improving airway limitation in patients suffering from COPD. Although the onset of bronchodilation after inhaling salmeterol and formoterol is slightly delayed compared with salbutamol, this is of little clinical importance since in these patients salmeterol and formoterol must be intended for maintenance treatment and not immediate symptomatic relief.

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