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Time course of bronchodilating effect of inhaled formoterol, a potent and long acting sympathomimetic

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Abstract

Background **Most of the currently available inhaled β_2 agonists are short acting bronchodilators. The aim of this study was to compare the rate of onset and duration of the bronchodilating activity of formoterol and salbutamol.**

Methods **Fourteen patients with reversible airways obstruction received placebo, 200 μg salbutamol, and 12, 24, and 48 μg formoterol from a metered dose inhaler, according to a double blind, randomised crossover design. Forced expiratory volume in one second (FEV_1) and specific airways conductance (sGaw) were measured over 12 hours.**

Results **Salbutamol and all doses of formoterol caused a significant and substantial increase in sGaw one minute after inhalation. The mean maximum increase in FEV_1 was 58% (8%) after 200 μg salbutamol compared with 63% (11%), 62% (10%), and 74% (10%) after 12, 24, and 48 μg formoterol, respectively. The mean maximum increase in FEV_1 occurred 57 (12) minutes after administration of salbutamol compared with 137 (16), 141 (21), and 161 (33) minutes after 12, 24, and 48 μg formoterol respectively. The bronchodilating effect of salbutamol did not differ from placebo after six hours. In contrast, the mean increase in FEV_1 12 hours after 12 μg formoterol (26% (8%) of baseline) significantly exceeded the change after placebo. Tremor was recorded in four patients after 48 μg formoterol.**

Conclusion **Formoterol is a potent, fast acting bronchodilator with a long duration of action.**

Inhaled β_2 adrenoreceptor agonists are often used as first line treatment in the management of acute and chronic asthma. However, most of the currently available inhaled β_2 agonists have the disadvantage of being short acting and must therefore be given three to four times a day as maintenance treatment. As their duration of action is not sufficiently long to prevent nocturnal bronchoconstriction and early morning dyspnoea,[1] treatment with an inhaled β_2 agonist often has to be combined with an oral slow release preparation containing theophylline or β_2 agonist.

Formoterol is a new selective and potent β_2 agonist with a long duration of action when administered orally to asthmatic subjects.[2] Inhalation of 12 μg formoterol results in long lasting bronchodilatation and is well tolerated.[3] The bronchodilating effect of higher doses of formoterol and its rate of onset have not been studied systematically. Our randomised, placebo controlled, crossover study was designed to investigate the onset of action, the magnitude, and the duration of the bronchodilator effect of 12, 24, and 48 μg formoterol in comparison with a standard dose of inhaled salbutamol (200 μg).

Patients and methods

Fourteen patients with a documented history of asthma were studied. All patients were taking inhaled β_2 agonist regularly; some were being treated with an inhaled corticosteroid (n = 9) or theophylline (n = 8) and one with oral prednisolone 8 mg on alternate days (table 1). All patients had an initial forced expiratory volume (FEV_1) of 40% to 70% of predicted values[4] and an increase in FEV_1 of at least 20% 15 minutes after inhalation of 400 μg fenoterol from a metered dose inhaler. All were studied during a stable period of their disease and none had signs of a respiratory tract infection in the month preceding or during the trial. The initial FEV_1 on each test day had to be within 15% of the baseline value on each study day. Informed consent was given by the patients and the study was approved by the ethical committee of the University Hospital of Ghent.

LUNG FUNCTION MEASUREMENTS

FEV_1 was measured with a water sealed spirometer (Expirograph Godart) and taken as the highest of three consecutive measurements. Specific airways conductance (sGaw) was calculated from airways resistance and thoracic gas volume, measured with a constant volume body plethysmograph (Jaeger, Würzburg, Germany); each value was the mean of eight consecutive measurements.

DESIGN OF THE STUDY

The bronchodilator activity of placebo, 200 μg salbutamol, and 12, 24, and 48 μg formoterol was investigated on five non-consecutive days (at least two days apart, and at most seven days). The study was double blind, randomised and crossover. All inhalers looked identical and their contents did not differ in taste or smell. The patients were instructed carefully on how

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Table 1 Patients' characteristics

Case No	Sex	Age (years)	FEV_1 Baseline (l)	FEV_1 Reversibility (% change from baseline)	Smoking history	Current asthma treatment
1	M	30	3·01	35	Non-smoker	Bi, Si
2	F	58	1·58	44	Non-smoker	Bi, Si, T
3	M	40	1·29	55	Non-smoker	Bi, Si, T
4	M	23	2·90	66	Non-smoker	Bi
5	M	18	3·29	30	Non-smoker	Bi, Si, T
6	M	21	1·99	37	Ex-smoker	Bi, Si
7	F	39	2·55	26	Non-smoker	Bi, Si, T
8	M	22	3·49	35	Non-smoker	Bi
9	M	40	1·24	96	Non-smoker	Bi, T
10	M	50	2·26	23	Smoker	Bi, Si
11	M	52	1·29	70	Ex-smoker	Bi, T
12	M	57	1·02	100	Ex-smoker	Bi, Si, T, So
13	M	46	1·72	20	Smoker	Bi, Si, T
14	M	47	2·36	37	Ex-smoker	Bi

Bi = inhaled β_2 agonist, Si = inhaled steroids, So = oral steroids, T = oral theophylline.

to take two inhalations from the metered dose inhaler.

Patients arrived at the laboratory at 7.45 am on the five study days. Inhaled β_2 agonists and anticholinergic drugs were withdrawn 12 hours before the start of the trial, and oral β_2 agonists, long acting theophylline preparations, caffeinated drinks, and diuretics 24 hours before. Oral and inhaled corticosteroids were continued at constant dose. Serum theophylline concentrations were determined on each study day.

After 30 minutes baseline measurements of heart rate, blood pressure, sGaw, and FEV_1 were performed. Since deep inspirations are known to cause bronchoconstriction in asthmatic subjects,[5] sGaw was always measured first. Patients were then asked to inhale two puffs of the test drug. Heart rate and blood pressure were measured 10, 30, 60, and 120 minutes after inhalation. sGaw was measured 1, 3, 5, and 10 minutes after inhalation and sGaw and FEV_1 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 minutes after inhalation.

Toleration of the trial drug was assessed during the study day by questioning the patient about potential adverse effects. All patients were provided with rescue treatment (terbutaline metered dose aerosol), which they were allowed to use 12 hours before the study and throughout the examination day if necessary. Each extra inhalation was reported to the physician supervising the trial.

ANALYSIS

All data obtained after rescue treatment was used were discarded and replaced by the data obtained immediately before the extra inhalation.

The maximum increases from baseline FEV_1 and sGaw with the different drugs were compared and the FEV_1 and sGaw at 12 hours were assessed and compared by analysis of variance for treatment and time. The mean times after inhalation at which FEV_1 and sGaw were maximal were also compared.

To investigate the rate of onset of the bronchodilating effect of the different treatments after 1, 3, and 5 minutes, the absolute increase in sGaw and the increase in sGaw relative to the peak response in sGaw were calculated.

Maximal changes and mean changes at fixed time points in FEV_1 and sGaw were expressed as the mean (SE) percentage changes from the baseline value. Time to maximal bronchodilatation was also expressed as mean (SE).

Results

There was no significant difference in mean baseline FEV_1 or sGaw on the five study days (table 2). Serum theophylline concentrations at the start of each test day were below 4 mg/l in all patients.

RESCUE TREATMENT

On a total of 70 examination days rescue treatment was needed on only three occasions. Two patients receiving placebo used two puffs of terbutaline 30 and 240 minutes after the beginning of the trial. At these time points FEV_1 had decreased by 28% from baseline values in both patients. The third patient initially responded well to 48 μg formoterol, but he then developed a progressive decrease in FEV_1 (−17% of baseline values after 10 hours) and chose to inhale two puffs of terbutaline.

TIME COURSE OF BRONCHODILATING EFFECT

All doses of formoterol caused a greater increase in FEV_1 than placebo or salbutamol (both $p < 0·001$) (figures 1 and 2). Inhalation of 12 and 24 μg formoterol resulted in an almost identical increase in FEV_1 over 12 hours; 48 μg formoterol caused a greater response than 12 and 24 μg (both $p < 0·001$). The formoterol induced increase in sGaw was dose dependent.

MAXIMUM RESPONSE

Maximum changes in FEV_1 and sGaw are given both in absolute (table 2) and in relative (table 3) terms. The maximum increase in FEV_1 after 200 μg salbutamol was 52% (8%) of baseline values, which was more than the maximum change observed on the placebo day ($p < 0·01$). The maximum increase in FEV_1

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Table 2 Mean (SE) baseline and maximum values of FEV_1 and sGaw with different treatments

	Placebo	Salbutamol 200 μg	Formoterol (μg) 12	24	48
			FEV_1 (l)		
Baseline	2·00 (0·20)	2·11 (0·24)	1·98 (0·24)	2·05 (0·24)	1·96 (0·20)
Maximum	2·36 (0·22)	3·03 (0·26)	3·05 (0·29)	3·16 (0·28)	3·22 (0·27)
			sGaw (cm H_2O.s)		
Baseline	0·031 (0·003)	0·041 (0·005)	0·041 (0·006)	0·038 (0·006)	0·035 (0·003)
Maximum	0·066 (0·008	0·130 (0·016)	0·133 (0·018)	0·151 (0·022)	0·167 (0·021)

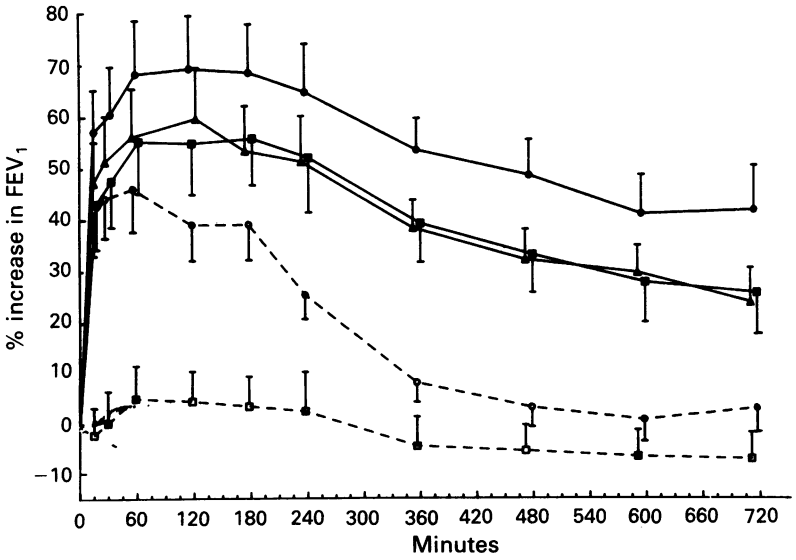

Figure 1 Time course of change in FEV_1 (mean (SE) in 14 patients) after inhalation of placebo (□— — — —□), salbutamol (○— —○), 12 μg formoterol (■——■), 24 μg formoterol (▲——▲), and 48 μg formoterol (●——●).

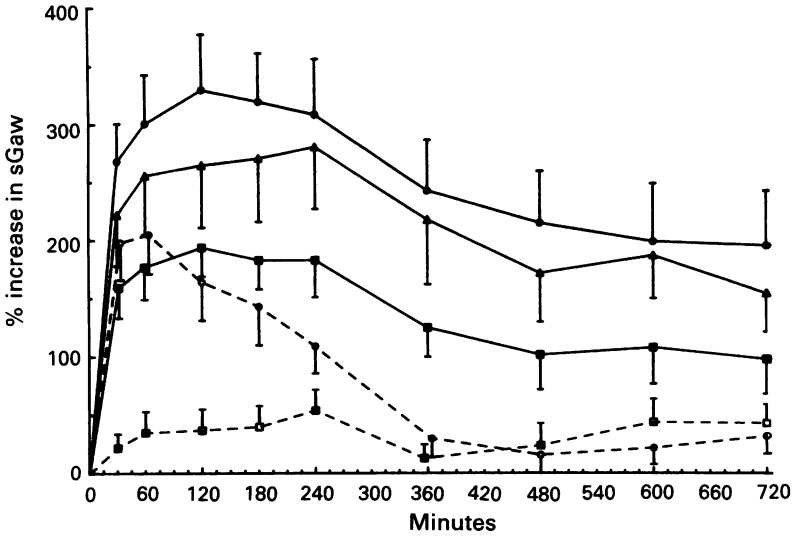

Figure 2 Time course of change in sGaw after inhalation of placebo, salbutamol, and formoterol (same key as figure 1).

after 12 and 24 μg formoterol was not significantly different from that after salbutamol. The maximum increase in FEV_1 after 48 μg formoterol was greater than the increase after salbutamol ($p < 0·01$) or 12 μg formoterol ($p < 0·05$). The maximum increase in sGaw after salbutamol was similar to that obtained after 12 μg formoterol. Maximum sGaw achieved with 24 and 48 μg formoterol was greater than that with salbutamol ($p < 0·01$).

DURATION

At 12 hours the mean increase in FEV_1 and sGaw (figures 1 and 2 and table 3) produced by all doses of formoterol was greater than the effect observed after placebo or salbutamol (all $p < 0·05$).

TIME OF MAXIMUM RESPONSE

The mean time of maximum increase in FEV_1 for salbutamol was 57 (SE 12) minutes after inhalation and more than 120 minutes for all doses of formoterol ($p < 0·01$).

RATE OF ONSET OF ACTION

sGaw increased at 1, 3, and 5 minutes after inhalation of salbutamol and all doses of formoterol (figure 3). When the bronchodilating effect was expressed as a percentage of the maximum response, the rate of onset after salbutamol was more rapid than after formoterol. One minute after inhalation of salbutamol sGaw was 63% (6%) of its maximum response compared with 47% (7%) of its maximum response after 24 μg formoterol ($p < 0·01$). sGaw further increased at three and five minutes after each active treatment.

BLOOD PRESSURE AND HEART RATE

Changes in systolic or diastolic blood pressure were small and not significant. The maximum increase in heart rate did not exceed 5 beats/min and differences between treatments were not significant (paired *t* test).

SIDE EFFECTS

Treatments were generally well tolerated. Only after inhalation of 48 μg formoterol was a mild but not disturbing tremor noted by four of the 14 patients. Headache was reported by one patient after formoterol, salbutamol, and placebo.

Discussion

Our results show clearly that 12 μg inhaled formoterol produces a maximal bronchodilating effect that equals the bronchodilator effect of 200 μg of inhaled salbutamol. At this equipotent dose inhaled formoterol results in a significantly longer duration of action. Indeed, 12 hours after the inhalation of 12 μg formoterol a significant effect on FEV_1 and sGaw was apparent. The rate of onset of the bronchodilating action of formoterol is roughly similar to that of salbutamol (figure 3). When our data were expressed as a percentage of the maximum response or as time at which the maximum response was reached the rate of

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Table 3 Maximum increase in FEV_1 and sGaw and change at 12 hours with different treatments. Values are means (SE) as percentages of baseline values

	Placebo	Salbutamol 200 μg	Formoterol (μg) 12	24	48
		FEV_1 (l)			
Maximum increase	13 (7)	52 (8)	63 (11)	62 (10)	74 (10)
Change at 12 hours	−6 (5)	4 (5)	26 (8)	24 (7)	42 (9)
		sGaw			
Maximum increase	83 (2)	236 (32)	231 (27)	330 (56)	366 (49)
Change at 12 hours	43 (16)	32 (15)	98 (30)	154 (33)	195 (47)

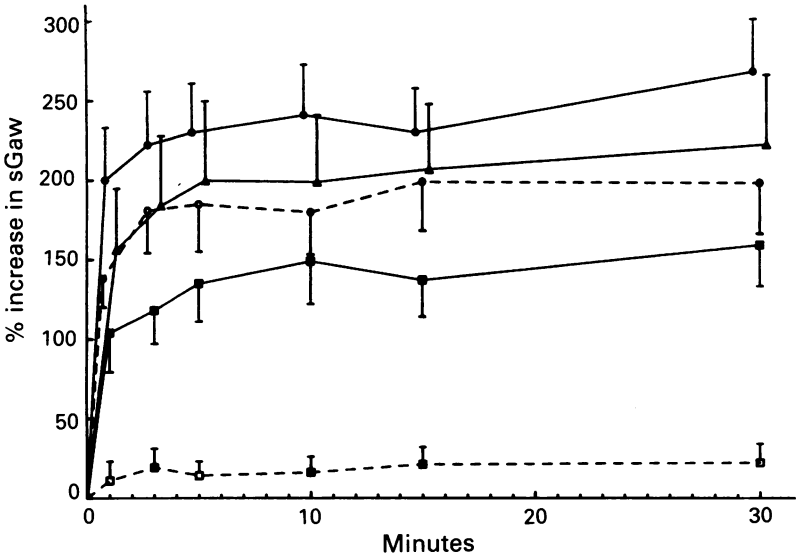

Figure 3 Time course of change in sGaw after inhalation of placebo, salbutamol, and formoterol for the first 30 minutes (same key as figure 1).

onset of action of salbutamol was faster than that of formoterol.

Our study does not allow a final conclusion to be made about the relative potency of salbutamol and formoterol. To do this the dose of inhaled formoterol that is equivalent to the dose of inhaled salbutamol would have to be determined systematically in each patient as differences in duration of action may be expected when non-equivalent doses of β_2 agonists are compared. As a consequence, only a dose-response curve for both drugs allows a proper comparison of the potency and duration of action of the two drugs.

The longer duration of action observed with 24 and 48 μg formoterol was probably partly due to a greater relative dose of β_2 agonist. Indeed, at these doses the maximum increase in FEV_1 and in sGaw clearly exceeded the maximum increase after 200 μg salbutamol. This explanation, however, does not seem to be valid for 12 μg formoterol, whose maximum effect on FEV_1 was only slightly greater than the increase produced by 200 μg salbutamol. The increase in sGaw after 12 μg formoterol did not exceed the increase after 200 μg salbutamol. Thus 200 μg salbutamol and 12 μg formoterol probably differ only slightly in their bronchodilating potency. This is in line with a recent study in which cumulatively increasing doses of salbutamol and formoterol were administered to asthmatic subjects.[6] Thus the longer duration of action of 12 μg formoterol may be ascribed to long lasting β_2 stimulating activity at the level of bronchial smooth muscle. The mechanism, however, remains to be elucidated.

We observed a significant dose-response relation in the bronchodilating effect of formoterol, that of the 48 μg dose being clearly superior to that of 12 μg. Measurement of change in FEV_1 could not distinguish between the 12 and the 24 μg dose, though the increase in sGaw was significantly lower for the two lowest doses of formoterol.

Formoterol was well tolerated. No cardiovascular effects were observed, and only after the 48 μg dose of formoterol was a mild, but not disturbing, tremor reported by four of the 14 patients.

Our observations may have important clinical implications in the treatment of asthmatic patients. Firstly, the long acting bronchodilating effect of formoterol should enable the frequency of regular inhalation of sympathomimetic agents to be reduced from four to two times a day, thus increasing therapeutic compliance. Secondly, our study is the first to provide convincing evidence that formoterol, even at higher than recommended doses, presents a slower rate of onset of action than a standard dose of salbutamol. The clinical relevance of this finding should be evaluated by comparing salbutamol and formoterol in a dose-response study in the treatment of acute asthma.

In conclusion, we found that inhaled formoterol is a potent bronchodilator that produces a rapid and long lasting bronchodilatation in asthmatic patients and has few side effects. Further investigations with inhaled formoterol at 12 and 24 μg twice daily are required to assess its clinical value over a longer period of time.

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