

Formoterol, a new long acting beta₂ agonist for inhalation twice daily, compared with salbutamol in the treatment of asthma

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Abstract

Sixteen patients with stable chronic asthma participated in a double blind crossover study comparing the new inhaled long acting beta₂ agonist formoterol with salbutamol. Inhaled (n = 15) and oral steroid (n = 1) treatment were maintained at the same daily dose throughout the study. For four weeks the patients received either formoterol 24 µg twice daily or salbutamol 400 µg twice daily, plus additional puffs (with the same drug) when needed. Asthma symptoms, additional puffs of beta₂ agonist, peak expiratory flow (PEF), and side effects were recorded daily. During treatment with formoterol the patients used fewer additional puffs of beta₂ agonist, had better symptom scores, less disturbed sleep, more days without additional aerosol, and higher PEF both morning and evening than during salbutamol treatment. Thus formoterol 24 µg twice daily gave long lasting bronchodilatation and asthma symptoms were well controlled with regular twice daily administration.

Inhaled beta₂ agonists are first line treatment for asthma in most countries. One disadvantage of currently available drugs is their relatively short duration of action. If inhaled beta₂ agonist treatment is insufficient to provide good control of asthma inhaled steroid treatment is usually added. Some patients will nevertheless need supplementary medication with a long acting oral bronchodilator. Side effects often limit the use of such oral drugs. An inhaled long acting beta₂ agonist that combined long lasting bronchodilatation with few side effects would be useful for treating such patients.

Formoterol is a new potent beta₂ agonist that is at least as beta₂ adrenoceptor selective as salbutamol in animal and human studies.¹⁻³ It is about 50 times more potent than salbutamol when given orally.^{3,4} Inhaled formoterol is 5-15 times more potent than salbutamol in asthmatic patients³ and the duration of action is usually at least 8-12 hours.^{3,5-7}

The aim of this study was to compare formoterol with salbutamol, given as aerosols, in patients with a proved high requirement for inhaled bronchodilator treatment.

Methods

PATIENTS

Eighteen patients with stable asthma were entered in the study. None had had a respiratory infection for at least one month before the study. No patient had any concomitant disease apart from one who had mild hypertension. Sixteen patients (five women, 11 men) completed the study. They had a mean age of 62 (range 33-69 years), a mean duration of asthma of 17 (range 2-48) years, a mean FEV₁ of 60% predicted (range 33-106%), and a mean percentage increase in FEV₁ after inhaling 400 µg salbutamol of 28% (range 16-71%).

All patients inhaled beta₂ agonists regularly and 15 also inhaled corticosteroids (daily dose 600-1600 µg), one taking oral steroids also. The steroid dose was kept constant for four weeks before and during the study. One patient inhaled an anticholinergic drug and six were treated with oral beta₂ agonists and theophylline, two with oral beta₂ agonists, and one with theophylline. These drugs were withdrawn when the patient entered the run in period. The study was approved by the ethical committee of the University Hospital of Umeå.

STUDY DESIGN

The study had a randomised double blind crossover design consisting of a run in period of two weeks followed by two treatment periods of four weeks each. During the run in period the patients were asked to inhale salbutamol 400 µg (100 µg per puff) twice daily from a metered dose inhaler with a Volumatic spacer. Two additional puffs were taken from the same aerosol, but without the spacer, whenever needed. Peak expiratory flow (PEF) was taken as the best of three measurements with a mini Wright peak flow meter before the regular trial medication every morning and evening. Asthma symptoms, side effects, additional puffs of bronchodilator, and PEF were recorded daily. Asthma symptoms were graded: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. In the morning the patients also recorded whether they had woken up during the night because of asthma symptoms.

All patients included in the active treatment periods fulfilled the inclusion criterion of having taken at least four additional salbutamol puffs per 24 hours during the last 10 days of the run in period. Before randomisation patients were balanced according to their additional spray consumption during the run in period and a randomisation table was used for allocating them to the two treatment groups. During

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the treatment periods the patients inhaled salbutamol, four puffs (100 µg a puff) twice daily, or formoterol, four puffs (6 µg a puff) twice daily, plus two additional puffs of the same aerosol whenever needed, for four weeks followed by the other bronchodilator for four weeks. The aerosols were administered in the same way and the diary cards were the same as during the run in period.

After the run in period and each treatment period patients were asked about side effects by direct questioning and reversibility tests were performed. FEV₁ was measured with a dry spirometer (Vitalograph) before and 15 minutes after inhalation of salbutamol 400 µg with a Volumatic spacer. The patients were told not to take their inhaled beta₂ agonist for at least eight hours before the test. Serum potassium concentrations were measured before and at the end of the study. Blood samples were taken 20 minutes after beta₂ agonist inhalation.

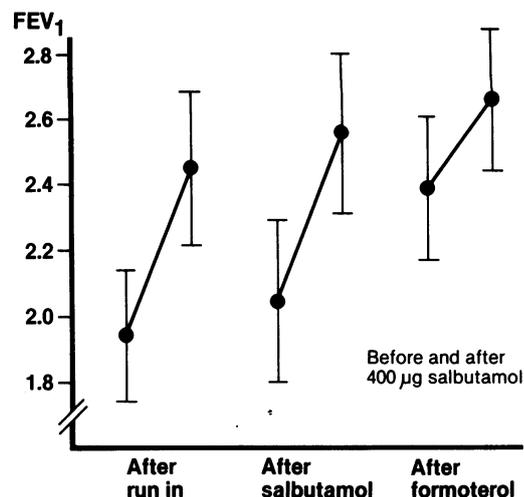
STATISTICAL ANALYSIS

For calculations based on the patients' own recordings mean values or sum totals were used. The last 10 days of the pretreatment period were used for the description of patients and the last 14 days of each treatment period for analysis of efficacy. Significant interactions and period or drug effects were sought according to Hills and Armitage.⁸ Differences in efficacy (as judged by number of additional puffs of beta₂ agonist, number of disturbed nights, asthma symptom scores, PEF, FEV₁) between patients taking the drugs in different sequence were assessed by the Wilcoxon rank sum test; data on preferences were analysed by the sign test.

Results

Two patients were withdrawn during their first treatment period, one in each treatment group, owing to deterioration of their asthma.

During treatment with formoterol 24 µg twice daily there was a significant reduction in the number of additional puffs of beta₂ agonists used, lower asthma symptom scores, higher PEF values, and less disturbed sleep due to asthma compared with the salbutamol treatment period ($p < 0.01$ in each case; table 1). During the formoterol treatment period the mean total number of additional puffs of beta₂



Mean (SEM) FEV₁ (litres) in reversibility tests performed after two weeks' run in period and after four weeks' treatment with salbutamol and four weeks' formoterol. FEV₁ values were recorded at least eight hours after the last dose of the test medication and 15 minutes after inhalation of 400 µg salbutamol.

agonists was 1.9, compared with 6.2 during the salbutamol treatment period, and patients had a mean number of 1.3 nights with disturbed sleep compared with 4.9 nights when taking salbutamol. They had a mean number of 6.6 (range 0–14) days when they did not require additional aerosol inhalations when taking formoterol, compared with 1.0 (range 0–5) days when receiving salbutamol. Ten patients managed more than five days without additional puffs during the last two weeks of the treatment period while having formoterol but none while having salbutamol.

The mean basal value of FEV₁ before the reversibility test was higher after four weeks' treatment with formoterol ($p < 0.05$). The reversibility was greater after four weeks' treatment with salbutamol than after formoterol, the difference corresponding to the increased basal value of FEV₁ after formoterol. There was no significant difference between the mean maximum FEV₁ values after inhaled salbutamol (figure).

Side effects were mild and few with both treatments (table 2). No significant changes in serum potassium concentrations were observed after the two treatments (table 3).

When patients were asked after completing the study which treatment period they preferred, 13 said they preferred formoterol and one salbutamol, and two had no preference ($p < 0.01$).

Table 1 Additional inhalations of beta₂ agonists, number of nights with disturbed sleep, symptom scores, and peak flow during four weeks' treatment with salbutamol and with formoterol: mean (SEM) values for the last 14 days of both treatment periods and the last 10 days of the run in period

	Run in	Salbutamol	Formoterol	<i>p</i> value: salbutamol v formoterol
No of additional inhalations				
Day	6.5 (0.6)	4.4 (0.9)	1.6 (0.4)	
Night	2.4 (0.5)	1.8 (0.8)	0.3 (0.2)	
Total/24 h	8.9 (1.0)	6.2 (1.6)	1.9 (0.5)	< 0.01
No of nights with disturbed sleep	6.1 (1.0)	4.9 (1.5)	1.3 (0.9)	< 0.01
Symptom score (4 point scale)				
Day	1.1 (< 0.1)	1.1 (< 0.1)	0.6 (< 0.1)	
Night	0.8 (< 0.1)	0.5 (< 0.1)	0.2 (< 0.1)	
Mean/24 h	1.0 (< 0.1)	0.8 (< 0.1)	0.4 (< 0.1)	< 0.01
Peak flow (l/min)				
Morning	363 (23)	374 (25)	432 (24)	< 0.01
Evening	397 (23)	394 (25)	443 (24)	< 0.01

Table 2 Number of patients who reported side effects during the last 10 days of the run in period and during the last two weeks of each treatment period

	No of patients		
	Run in	Salbutamol	Formoterol
Any side effect	8	6	6
Palpitation	3	1	1
Tremor	3	2	3
Muscle cramps	2	1	1
Anxiety	2	0	0
Headache	5	4	3
Others	3	2	3

Table 3 Mean (SEM) serum potassium concentrations before and after the study in the groups treated with salbutamol followed by formoterol and with formoterol followed by salbutamol

	Serum potassium concentration (mmol/l)	
	Salbutamol/ formoterol	Formoterol/ salbutamol
Before study (n=8)	4.17 (0.17)	3.91 (0.17)
After study (n=8)	4.16 (0.15)	4.14 (0.17)

Discussion

In this study formoterol 24 µg had a longer duration of action, and when given twice daily led to less need for additional puffs of beta₂ agonist than salbutamol 400 µg. The doses of formoterol and salbutamol were based on the results of a cumulative dose-response study by Löfdahl *et al.*,³ in which formoterol 24 µg caused at least as much bronchodilation as salbutamol 400 µg; and our findings agree with those of their study and of others.⁵⁻⁷ They indicate clinical benefit in terms of less aerosol use, fewer day and night time symptoms, and better lung function with the formoterol treatment.

To compare a long acting with a short acting bronchodilator we selected the patients on the basis of a high requirement for additional beta₂ agonist aerosol despite regular treatment with inhaled steroids. A twice daily regimen using salbutamol was insufficient for these patients, and they were therefore told to use additional aerosol whenever they needed it. The greater need for additional aerosol during salbutamol treatment was expected. We had anticipated that a greater need for salbutamol would lead to a similar degree of asthma control with the two treatments. Even though the patients used considerably more aerosol during the salbutamol treatment period, however, asthma control and lung function were much better during the formoterol treatment period.

Early morning dyspnoea in asthmatic patients relates to a circadian rhythm in airway calibre.^{9,10} Oral theophylline, oral beta₂ agonists and high dose beta₂ agonists by metered dose inhaler at bedtime have up to now been the therapeutic approaches for treating this sometimes dangerous symptom.¹¹⁻¹⁵ Long acting inhaled bronchodilators would be expected to be beneficial in these circumstances, and our patients had more undisturbed nights during the formoterol treatment period.

The duration of bronchodilation with formoterol has not yet been compared with oral beta₂ agonists in sustained release forms but it seems to be of the same magnitude. As the side effects with formoterol 24 µg were similar to those with inhaled salbutamol 400 µg, the use of formoterol may improve patients' compliance.

Reversibility tests were performed after the treatment periods to investigate whether tachyphylaxis developed (figure). The tests were made at least eight hours after inhalation of the

beta₂ agonist. After four weeks' treatment with formoterol the mean basal value of FEV₁ was considerably increased, however, despite the eight hour interval, presumably owing to the residual effect of the last dose, as the duration of action is at least 8-12 hours. The mean maximum value was about the same for both treatment limbs.

The timing of the reversibility test was not ideal for assessing tachyphylaxis but for these patients, with their high requirement for a beta₂ agonist, it was clinically impossible to withhold bronchodilator treatment for at least 12 hours. We believe that if clinically important tachyphylaxis had developed both the baseline and the maximum value would have diminished after four weeks' treatment with formoterol, which they did not.^{16,17}

We conclude that formoterol 24 µg gave a long lasting bronchodilator effect and that, with regular twice daily administration, asthma symptoms were well controlled in a group of asthmatic patients with a frequent daily requirement for inhaled salbutamol despite regular treatment with inhaled steroids.

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