Formoterol, a New Long-Acting $\beta_2$ Agonist, Inhaled Twice Daily, in Stable Asthmatic Subjects*

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Study objective: To determine whether formoterol, a new $\beta_2$ agonist with experimentally documented long duration, is clinically more effective than salbutamol in the maintenance treatment of chronic asthma.

Design: Randomized double-blind between-patient comparison between treatment with formoterol and with salbutamol during four weeks.

Setting: Asthma/allergy department in a university hospital.

Patients: Thirty-seven patients with chronic stable asthma, who during a two-week run-in period with inhaled salbutamol, 4 x 100 $\mu$g twice a day, used at least four additional doses (100 $\mu$g each) daily, were randomly assigned to use either formoterol or salbutamol. Thirty-five patients were evaluated for efficacy. One early withdrawal and one dropout were found in the salbutamol group. The groups were similar with respect to demographic data and baseline lung function.

Interventions: During the four-week study period, the patients used either formoterol (4 x 6 $\mu$g twice a day and as necessary, n=19) or salbutamol (4 x 100 $\mu$g twice a day and as necessary, n=16). Inhaled steroids and orally administered theophylline were allowed if doses were kept constant.

Measurements and main results: The median number of additional doses per 24 h (median of two weeks) of the test aerosols was 0 (range, 0 to 6) for formoterol and 4 (range, 0 to 14) for salbutamol (p<0.01). Morning and evening PEFRs were 422 (SEM = 31) and 443 (SEM = 30), respectively, for formoterol, and 335 (SEM = 30) and 360 (SEM = 26), respectively, for salbutamol (p=0.05 for both). Formoterol was superior (p<0.05) to salbutamol with respect to control of asthma symptoms, estimated duration of action and patient preference. Side effects did not differ.

Conclusions: Inhaled formoterol administered twice a day and as necessary was clinically more effective than the same regimen of salbutamol. (Chest 1992; 101:1019-22)

\[ \text{VAS} = \text{visual analogue scale} \]

Inhaled $\beta_2$ agonists are first-line drugs in the treatment of asthma. The main disadvantage is their short duration of action, necessitating frequent administration and resulting in insufficient protection against, eg, nocturnal, bronchoconstriction. The newly introduced long-acting $\beta_2$ agonists for topical use, salmeterol and formoterol,2 may allow longer intervals between inhalations without loss of control of the asthma. Formoterol is a highly selective $\beta_2$ agonist3 which is 5 to 15 times as potent as salbutamol when inhaled.4 Formoterol has a rapid onset of action4 and a duration of action of 8 to 12 h5,6 when inhaled. This suggests that a twice-a-day dosage regimen may be sufficient in order to control asthma symptoms in many patients. Previous crossover studies in adults and children have shown formoterol to be superior to salbutamol with respect to baseline lung function, use of additional inhalations and asthma symptoms8,9 as well as a prolonged suppression of the bronchial responsiveness to methacholine.5 We have studied the clinical effectiveness of formoterol and salbutamol in the maintenance treatment of chronic asthma in a parallel group design, without specific reference to baseline lung function data.11

Patients and Methods

The number of extra inhalations (puffs) of the test aerosols in addition to the fixed twice-a-day regimen was taken as the primary effect variable of the study, reflecting differences in the control of the disease. A reduction by two puffs daily (usually =one inhalation occasion) was considered clinically relevant in a group of patients using two to six additional puffs daily during the run-in period with a short-acting $\beta_2$ agonist. Assuming a type 1 error of 0.05 and a type 2 error of 0.20, the number of patients required in each group in a parallel group study was calculated to be 16.

Primary inclusion criteria were stable asthma, ≥15 percent reversibility on FEV1, after inhalation of 0.4 mg salbutamol, FEV1 after bronchodilatation (which reflects the irreversible component of the airflow obstruction) ≥50 percent of predicted,11 and use of inhaled bronchodilators (salbutamol or terbutaline) at least four times daily according to history. The definite inclusion criterion was the use of at least four additional puffs (or two inhalation occasions) of salbutamol daily during a two-week run-in period with a fixed regimen of inhaled salbutamol 0.4 mg (four puffs) morning and evening. Oral $\beta_2$ agonists were not allowed during this phase. Seventy-one patients were eligible according to the primary inclusion criteria and thus were included in the run-in phase of the study. In a considerable number of patients, this regular regimen of salbutamol, 400 $\mu$g twice a day, reduced their demand for extra inhalations during the rest of the day and night below the level for final inclusion. A total of 37 patients remained for the study, 35 of whom were finally evaluated. Two patients dropped out early (both in the salbutamol group) due to intercurrent infection and bad compliance (one) and $\beta_2$ side effects (one).
The randomization was balanced with respect to concomitant theophylline medication (which was kept constant during the study) and the patients were randomly assigned to either salbutamol (n = 18) or formoterol (n = 19). The study period was four weeks. During this period, the patients continued their inhaled steroids (n = 25; 12/13) and oral theophylline (n = 18; 10/6) but oral β2agonists and inhaled anticholinergic drugs were still withheld. Four puffs of the test spray were given morning and evening in a spacer. The salbutamol spray gave 100 μg per puff and the formoterol spray, 6 μg per puff. The patients were instructed to take additional puffs of the study medication whenever needed.

The number of additional inhalations (the primary effect variable) was recorded daily on a diary form. Peak expiratory flow rate (as measured by a mini-Wright peak flow meter) was recorded every morning and evening and before each occasion of additional inhalations. Asthma symptoms (as noted on a four-grade scale, where 0 = no symptoms and 3 = severe symptoms) and side effects were also recorded daily. At the end of the study period, the patients indicated their opinion about the duration of the spray (based on a five-grade scale where 0 = 0 to 2 h and 4 = >8 h), and whether better asthma control than that obtained with their usual medication had been attained (yes or no). They also indicated on a VAS (0 to 100 mm) their breathing ability, sleep and general well-being during the study, and the investigator indicated his opinion concerning the asthma control. Only data from the second of the two run-in weeks and from the middle two of the four study weeks were analyzed, since the first week was considered to be influenced by earlier treatment and the last week in some instances incomplete for practical reasons.

The number of additional inhalations, symptom score and VAS scores were analyzed with Wilcoxon's rank sum test, whereas PEFR and other lung function data were assumed to be normally distributed and therefore analyzed with the two-sided t test. Preferences were analyzed with Fisher's exact probability test.

The study was performed according to the rules of the declaration of Helsinki and was approved by the Medical Ethics Committee at the University of Lund and the National Board of Health and Welfare.

RESULTS

Thirty-seven patients were randomly grouped: 19 comprised the formoterol group and 18, the salbutamol group. In the latter group, one patient dropped out early due to infection. The side effect analysis was thus based on 36 patients. Another patient in the salbutamol group refused further treatment after only a few days because of side effects. A third patient discontinued treatment after three weeks while receiving formoterol due to adverse reactions, but this patient is included in the efficacy analysis. Thirty-five patients were thus evaluated for efficacy. At the time of inclusion and during the run-in period, the two treatment groups showed no differences with respect to any of the baseline demographic data or any of the variables under study (Table 1). Post-bronchodilator spirometric data are given instead of the conventional baseline VC and FEV1. The irreversible part of the airflow limitation is better quantified with this mode of presentation, whereas pre-bronchodilator values may be transiently affected by many factors; the so-called “baseline” may therefore fluctuate greatly.

The following variables differed significantly in favor

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salbutamol (n = 18)</th>
<th>Formoterol (n = 19)</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>(42 (3) NS)</td>
<td>(43 (3) )</td>
</tr>
<tr>
<td>VC (% of predicted)*</td>
<td>(79 (4) NS)</td>
<td>(85 (3) )</td>
</tr>
<tr>
<td>FEV1 (% of predicted)*</td>
<td>(69 (5) NS)</td>
<td>(77 (4) )</td>
</tr>
<tr>
<td>Reversibility of FEV1†</td>
<td>(37 (7) NS)</td>
<td>(40 (7) )</td>
</tr>
<tr>
<td>Additional puff‡</td>
<td>(5 (0-12) NS)</td>
<td>(6 (2-16) )</td>
</tr>
<tr>
<td>Symptoms during the day‡</td>
<td>(1 (0.1) NS)</td>
<td>(1.1 (0.1) )</td>
</tr>
<tr>
<td>Symptoms during the night‡</td>
<td>(0.7 (0.1) NS)</td>
<td>(1 (0.1) )</td>
</tr>
<tr>
<td>PEFR morning value‡</td>
<td>(338 (25) NS)</td>
<td>(352 (26) )</td>
</tr>
<tr>
<td>PEFR evening value‡</td>
<td>(376 (24) NS)</td>
<td>(391 (23) )</td>
</tr>
</tbody>
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*Post-bronchodilator.
†0.4 mg salbutamol.
‡Average of seven days.
§NS = p > 0.05.
of formoterol (Table 2): the number of extra inhalations per 24 h (p < 0.01 [Fig 1]); morning and evening PEFR (422 SEM = 31 and 443 SEM = 30, respectively, for formoterol and 335 SEM = 30 and 360 SEM = 26, respectively, for salbutamol [p = 0.05 for both; Fig 2]);
the average score for asthma symptoms during the day and during the night reported on the diary cards (p < 0.01); VAS score for "breathing" and the physician's estimation of the patients' control of asthma (p < 0.05); and estimated duration of the effect of the spray (p < 0.001) (Fig 3).

A significantly larger number of formoterol patients than salbutamol patients preferred the test aerosol compared with their usual medication (16 of 19 vs 4 of 16 patients [p < 0.001, Fisher's exact test]). Two patients (one receiving each treatment) discontinued the study after three days and three weeks, respectively, due to unacceptable side effects (tremor, anxiety, muscle cramps and palpitations). The patient who discontinued after three weeks stated that his asthma had "never been better" and he used no rescue medication during the study period. The code was not broken at this time, and the patient was thus eligible for final evaluation and it was found that he had been given formoterol. The other patient (receiving salbu-

Table 3—Adverse Effects (No. of Patients)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salbutamol (n = 17)</th>
<th>Formoterol (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cramps</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

dtamol) had been heavily overdosing the aerosol when she experienced the side effects. The total number of patients reporting side effects was not significantly different between the groups (Table 3).

**DISCUSSION**

The β₂ agonists for inhalation available at present must generally be administered four times a day or even more frequently due to their short duration of action (Fig 3). This schedule may cause problems with compliance and patients therefore run the risk of being undertreated. The antiasthmatic treatments available at present, with a twice-a-day dosage regimen, include oral slow-release β₂ agonists, theophylline (with more side effects) and inhaled steroids (with an entirely different mode of action). Long-acting β₂ agonists for inhalation would therefore offer advantages to the asthmatic patients with improved disease control, fewer symptoms and less demand for extra medication.

The selection of patients with a documented need for inhaled β₂ agonist at least four times a day provided us with a clinically relevant model for the study of the differences between the effectiveness of long- vs short-acting β₂ agonists in the treatment of asthma. The patients were instructed to take additional inhalations of β₂ agonists whenever required. More than half of the patients in the salbutamol group thus used three or more additional puffs (median value), whereas in the formoterol group 11 of 19 patients managed without extra inhalations for most of the study days (median = 0 [Fig 1]). Due to the non-normal distribution of data, the number of puffs was analyzed with nonparametric statistical methods; therefore, medians rather than means are given in tables and figures. Comparison of the mean number of inhalations with

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21642/ on 06/25/2017)

**Figure 2.** Graphic presentation of PEFR in relation to run-in and study periods. Comparisons of evening and morning values for both formoterol and salbutamol groups.
the t test yields the same significance level, p<0.01, although this numeric difference is less impressive (4.5 for salbutamol and 1.5 for formoterol, as compared with the medians of 4 and 0, respectively).

Although the patients in both groups used as much aerosol as they felt they needed, asthma control was better in the formoterol group (Fig 2), indicating that the optimum inhalation frequency in the salbutamol group would be even higher than that spontaneously chosen by the patients. This suggests that a long-acting β2 agonist may provide better asthma control and not merely greater convenience for the patients.

Although the nocturnal symptom score was lower in the formoterol group, we found no significant differences with respect to self-reported sleep disturbances and morning PEFR. The reason may be that the patients were not selected with respect to nocturnal asthma and their scoring of nocturnal asthma symptoms before the study was low (average 0.8 on the 0 to 3 scale). This impairs the ability of our study to detect clinically relevant differences between the treatments with respect to nocturnal asthma.

Side effects were of the well recognized β2-adrenergic type and slightly more frequent in the formoterol group. One patient in each treatment group discontinued the study prematurely because of side effects. The patient who reported side effects while receiving formoterol had excellent control of asthma without extra medication; in an ordinary clinical situation he would probably have continued receiving formoterol in a lower dose. In this study, we actively asked about side effects. It should thus be borne in mind that the reported frequency of side effects may be higher than in studies in which only spontaneously reported side effects are recorded.

We are well aware of the current concern about possible negative consequences of continuous treatment with sympathomimetics. However, a significant number of patients need frequent inhalations of β2 agonists to achieve good control of asthma in spite of maintenance treatment with inhaled steroids and long-acting theophylline. For this type of patient, i.e., the type that we included in our study, the long-acting β2 agonists may provide better control of asthma and therefore can be defended in their place in anti-asthmatic pharmacotherapy.

We conclude that formoterol, 24 μg twice a day and as necessary was superior to salbutamol, 400 μg twice a day and as necessary with respect to the use of additional medication, control of asthma and PEFR scores in this group of asthmatic patients with regular use, at least four times a day, of inhaled short-acting β2 agonists.

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