Formoterol, a new long-acting bronchodilator for inhalation

P. Arvidsson, S. Larsson, C-G. Löfdahl, B. Melander, L. Wahlander, N. Svedmyr

Abstract: The aim of this study was to evaluate if treatment with inhaled formoterol is appreciated by asthmatics and whether it causes tachyphylaxis. Twenty stable asthmatics were included in a randomized, double-blind, crossover study. They were treated for two weeks either with formoterol or salbutamol, with one week washout inbetween. They were given 12 µg formoterol or 200 µg salbutamol twice daily and instructed to use additional spray doses on demand. On a diary card they recorded the number of doses, asthma symptoms and peak expiratory flow rate (PEFR) before every dose. Forced expiratory volume in one second (FEV1) dose-response curves for salbutamol (total dose 1.3 mg) were performed before and after each treatment period to evaluate development of tachyphylaxis. There was a significant difference in favour of formoterol concerning symptoms, PEFR recordings, spray consumption, and preference. Fifteen patients preferred formoterol and two salbutamol. The dose-response curves before formoterol and before, as well as after salbutamol were almost identical. After formoterol the curve had changed; both basal and maximum values were higher than before. Thus, no evidence of tachyphylaxis was found, compared to the ordinary β-stimulant treatment.


Formoterol fumarate (BD-40A, YM-08316) is a new β2-adrenoceptor agonist which has been found in vitro to be about 50 times more potent than salbutamol on bronchial smooth muscle (1, 2) and at least as β2-selective as salbutamol and terbutaline (2). In vivo animal studies gave similar results (3, 4).

Since 1986, formoterol has been registered for oral administration in Japan. However, as an inhalant this preparation has not been tested in Japan.

An earlier study performed in Sweden has shown that when inhaled, the potency of formoterol is 5-15 times that of salbutamol, according to a double-blind, cumulative dose-response study, and studies in West Germany gave similar results (5, 6). Most important, however, is the finding that the duration of effect of inhaled formoterol is much longer than after equipotent doses of salbutamol. Eight hours after administration, forced expiratory volume in one second (FEV1) was still significantly increased compared with the basal value, and was approximately 75% of the maximum PEFR, value. After inhalation of salbutamol, FEV1 returned to the basal value after approximately 4 h (5, 6). In other studies, a residual effect after a single dose of inhaled formoterol has been shown after 12 h (7, 8).

This prolonged bronchodilating effect of inhaled formoterol, which has been demonstrated in studies over one day under laboratory conditions, may be of great clinical significance. The aim of the present study was to determine whether patients would notice the prolonged effect and appreciate it when formoterol was given in a controlled study over a longer period of time. We also studied whether this long-lasting stimulation of the β2-adrenoceptors of the bronchi led to development of increased tachyphylaxis during two weeks of treatment, compared to their ordinary treatment with an inhaled β2-stimulant.

Patients

Twenty one patients with non-allergic bronchial asthma using β2-agonists by inhalation at least three times daily were included in the trial. A reversibility of FEV1 of at least 20% after inhalation of a β2-agonist was required on the first day of the investigation. One patient was excluded as his reversibility was less than 20%. Twenty patients are thus presented (table 1). Treatment with theophyllines, inhaled steroids and inhaled anticholinergics in unchanged dosage was allowed during the trial. Oral β2-agonists were withdrawn. Thirteen patients used oral theophylline, fifteen patients inhaled corticosteroids and two patients inhaled anticholinergics.

Pregnant women, patients with serious diseases and asthmatics on oral steroids or β-blockers were excluded from participation. Patients who were considered unable to comply with the study protocol were not included.
Table 1. - Patient characteristics (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>48</td>
<td>43-66</td>
</tr>
<tr>
<td>Duration of disease yrs</td>
<td>16</td>
<td>2-42</td>
</tr>
<tr>
<td>Basal FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</td>
<td>44</td>
<td>14-78</td>
</tr>
<tr>
<td>Reversibility %</td>
<td>44</td>
<td>20-80</td>
</tr>
</tbody>
</table>

Seventeen of the patients were men and five were smokers. Three patients had hypertension treated with diuretics or verapamil. One patient had experienced slight cardiac decompensation, treated with a diuretic. FEV<sub>1</sub>: forced expiratory volume in one second.

Methods

The study was carried out as a randomized, double-blind crossover study with two weeks of treatment with either inhaled salbutamol or inhaled formoterol and with a washout period of one week between treatment periods. The patients were examined before and after each treatment period, with FEV<sub>1</sub> dose-response curves for salbutamol to evaluate tachyphylaxis. During the treatment periods peak expiratory flow rate (PEFR) was recorded by the patients themselves before each dose of the study medication. They also recorded on a diary card additional doses of the tested drugs and symptom scores. Asthma symptoms were also recorded using visual analogue scales at each visit, when side-effects were also recorded. At the last visit, the patients were asked about their treatment preference.

The study was approved by the Ethical Committee at the University of Gothenburg.

PEFR values and need for additional doses of bronchodilators

PEFR was measured every morning and evening during the study before the prescribed study medication was taken. Recordings were also made before every additional dose (two puffs) of the study medication. A Wright mini peak-flow meter was used. The patients were given thorough instructions about the recording technique. The best of two values was recorded on a diary card. In this way every additional dose was recorded. The values for the last 10 days of each treatment were evaluated.

Continuous recording of symptoms

The patients made subjective recordings of the severity of their asthma every morning and evening on their diary card by using a four-grade scale:

- 0 = No symptoms, undisturbed sleep;
- 1 = Mild asthma, symptoms not interfering with activity or sleep;
- 2 = Moderate asthma, symptoms only slightly interfering with activities and sleep;
- 3 = Severe asthma symptoms making daily activities impossible and seriously disturbing sleep.

Recordings made during the 10 last days of the treatment periods were used for the calculations.

Visual analogue scales

Before and after each treatment period the patients were asked about their subjective view of symptoms and duration of effect of the study medication. Visual analogue scales were used for this investigation. The patients were asked to give their answers by placing a mark on a 100 mm long horizontal line. Separate sheets of paper were used for each question. The four questions asked are presented in figure 1.

Further interviews

At each visit the patients were asked for any side-effects that they considered attributable to the tested drugs. They were also asked to give their opinion concerning the duration of the effect by using a five-grade scale with the following alternatives; 0-2 h, 2-4 h, 4-6 h, 6-8 h, and more than 8 h. At the last visit the patients were asked which treatment period they preferred.
The patients were treated with either salbutamol from a dose aerosol delivering 100 µg per puff or formoterol 6 µg per puff. Two puffs were given regularly morning and evening. A spacer, Volumatic®, was used for the inhalations. The patients were taught the correct inhalation technique by an experienced assistant. The patients were instructed to use additional inhalations when needed. During the washout period, the patients used their ordinary medication.

**Dose-response curves**

To study the possibility of tachyphylaxis of the bronchial β₂-adrenoceptors, FEV₁, dose-response curves for inhaled salbutamol were recorded before and after each treatment period. The patients were asked to abstain from inhaled bronchodilators during 12 h before the dose-response tests and from oral theophyllines for 36 h before the tests. They arrived at the laboratory at 7.30 am after a light breakfast without coffee or tea. The patients rested seated for 30 min and basal values for FEV₁ were then recorded. Two measurements were made with 20 min in between. Salbutamol was then given in three doses (100, 300 and 900 µg, respectively) at intervals of 20 min. The inhaled doses were given by a dose aerosol connected to a Volumatic® spacer. Only 100 µg salbutamol was released into the space before each inhalation. The inhalations were supervised by an experienced assistant and the patient's mouth was rinsed with water after each inhalation. FEV₁ was recorded 12 min after each dose with a Vitalograph spirometer. The best of three values was used for calculations. If the patient could not abstain from inhaled bronchodilators during the night before the test, this was postponed.

**Statistics**

The results were analysed with regard to interactions, period and treatment effects according to HILL and ARMITAGE [9]. Thus, while all the results given are based on the actually recorded unadjusted figures, the p-values presented for treatment effects are adjusted for period effects. Wilcoxon's mid rank-sum test was used for comparisons between the sequences and p<0.05 was chosen as the level of significance. The SAS programme package was used for all the calculations.

**Results**

**PEFR measurements**

The highest and lowest PEFR values on each treatment day were used in the calculation of data presented in table 2. The table presents mean values for the last 10 days of each treatment period. Maximum and minimum values were significantly higher during formoterol treatment and the difference between maximum and minimum values decreased significantly during formoterol treatment, showing a decrease in diurnal variation during that treatment.

<table>
<thead>
<tr>
<th>Table 2. – Daily PEFR values, number of additional doses and symptoms, during salbutamol and formoterol treatment periods (mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily PEFR l/min</strong></td>
</tr>
<tr>
<td>Maximal</td>
</tr>
<tr>
<td>Minimal</td>
</tr>
<tr>
<td>&quot;Diurnal variation&quot;</td>
</tr>
<tr>
<td>Additional doses</td>
</tr>
<tr>
<td>(2 puffs each)</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>Night</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Symptom score (0-3)</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>Night</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Visual analogue scales (0-100 mm)</td>
</tr>
<tr>
<td>Asthma severity</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Quality of sleep</td>
</tr>
<tr>
<td>Duration of spray effect</td>
</tr>
</tbody>
</table>

PEFR: peak expiratory flow rate.
Additional doses

Besides the regular inhalations of 2 puffs b.i.d. the patients took, on average, 2 additional puffs 1.9 times during 24 h when treated with salbutamol, whereas their average number of additional dosage occasions during 24 h was 0.9 with formoterol. The number of additional doses (2 puffs each) both at night and day was significantly smaller during the formoterol treatment period (table 2).

Symptom evaluation

Mean values for each patient during the last 10 days of each treatment period were used for calculations of the values presented in table 3. When treated, these patients had mild symptoms, reflected in low symptom scores. During both day and night, the symptom scores were significantly better during the formoterol treatment period. The effect was most pronounced at night.

Table 3. - Subjective evaluation of spray duration (number of patients)

<table>
<thead>
<tr>
<th>Spray duration</th>
<th>Salbutamol</th>
<th>Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 h</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2-4 h</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>4-6 h</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>6-8 h</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>&gt;8 h</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Difference between drugs (p<0.001).

Mean values for visual analogue scale recordings before and after each treatment are presented in table 2. The parameters, asthma severity, quality of night sleep, and breathlessness were significantly better during formoterol treatment.

Duration of effect

The patient's own opinion concerning the duration of effect of the tested drugs was estimated using both visual analogue scales and a five-grade scale. According to the visual analogue scales, the patients experienced significantly longer duration of effect with formoterol than with salbutamol (table 2). There was also a significant difference in favour of formoterol when the five-grade scale was analysed (table 3). During formoterol treatment, eight patients estimated the duration to be more than 8 h, whereas during salbutamol treatment only three patients gave the same estimate.

Side-effects

The patients had only slight complaints. One patient on salbutamol complained of slight dizziness and tachycardia, and another patient on salbutamol of tiredness and coughing. On formoterol one patient complained of dryness of the mouth in the morning.

Preferences

After the last treatment period, we asked the patients which of the two treatment periods they preferred. Fifteen patients preferred the formoterol treatment period, two patients preferred the salbutamol period and three patients could not state a preference (p<0.01).

Studies of tachyphylaxis.

Figure 2 shows the mean FEV₁ dose-response curves for 20 patients. The curves before and after the salbutamol treatment period are almost identical, showing no indication of a change in the β₂-adrenoceptor response.
before the formoterol treatment period the FEV₁ curve was at approximately the same level as the curves recorded before and after the salbutamol treatment period. After treatment for two weeks with formoterol both the baseline and maximal FEV₁ value were higher than the values recorded before the formoterol treatment period. Thus, there was no indication that formoterol produced a more pronounced tachyphylaxis to β₂-adrenoceptor stimulation in the bronchial muscle of asthmatics than the β₂-adrenoceptor agonists normally used, e.g. salbutamol.

We also studied separately the five patients who were not treated with inhaled corticosteroids. Their dose-response curves showed the same pattern as those of the whole group, i.e. there was no indication of tachyphylaxis in these patients either.

**Discussion**

This study has demonstrated that the prolonged effect of inhaled formoterol shown in acute studies is also evident during longer periods of clinical use. The patients noticed the long duration of effect and stated that the effect lasted considerably longer than that of salbutamol. They also noted the longer duration of action of formoterol as a need for fewer additional inhalations.

The patients included in this study had moderate to fairly severe asthma as evidenced by baseline FEV₁, values, when no bronchodilators had been given since the previous evening. No patients with the most severe form of asthma participated, as patients on oral steroids were not included. The reason for their exclusion was the difficulty of studying patients with very severe asthma, as they tend to be unstable and unable to complete a five-week study. This means, however, that we do not know whether patients with more severe asthma will find formoterol as advantageous as the patients in the present study.

Bronchodilators with a prolonged effect on the bronchial β₂-adrenoceptors may involve a greater risk of tachyphylaxis compared to the short-acting drugs. Studies of tachyphylaxis to this new bronchodilator are therefore essential. In this study, with a limited number of patients, no evidence of tachyphylaxis to formoterol was found compared to their ordinary treatment with a β₂-agonist. Fourteen days of treatment is a rather short period but probably long enough for a study of tachyphylaxis. Tachyphylaxis to β₂-agonists develops very rapidly after the start of treatment in almost all receptors studied, except the bronchial β₂-adrenoceptors in asthma patients [11–15]. It has been shown that healthy people develop tachyphylaxis to the bronchial effects of β₂-agonists (contrary to asthmatics) even after one week of therapy [12]. It is therefore likely that tachyphylaxis would have developed in this group of patients within 14 days, if such a development were to occur. The patients in this study are now on continuous formoterol therapy for one year and will be followed with repeated dose-response curves to elucidate this matter further.

Fifteen patients were treated with inhaled corticosteroids, which is the standard treatment of asthma of this severity in Sweden. Inhaled corticosteroids are the recommended second choice after inhaled β₂-adrenoceptor agonists for the treatment of asthma. This may have blunted the development of tachyphylaxis [12]. However, separate evaluation of patients without inhaled corticosteroid treatment did not indicate tachyphylaxis. Moreover, as this is the recommended treatment for this type of patient, our data elucidate the most important question, namely, whether a long-acting β₂-adrenoceptor agonist such as formoterol induces tachyphylaxis in the clinical situation. However, studies of tachyphylaxis to this drug in mild asthmatics without previous steroid or β₂-stimulant therapy would be of interest.

The dose of formoterol used in this study, 12 μg, was chosen to be approximately equipotent with 200 μg of salbutamol, with regard to the maximum bronchodilating effect. Actually, 200 μg salbutamol is somewhat more potent. This has been shown in a double-blind cumulative dose-response comparison to salbutamol in asthmatics [5]. Available data indicate that the duration of effect of 12 μg formoterol would be 12 h [7, 8]. For this reason two administrations a day were chosen for continuous use in this study. On average, the patients used formoterol once more per day. Our patients are used to taking bronchodilators prophylactically when attacks can be anticipated, as for example before physical exercise. The dose used may, therefore, have been slightly higher than was actually needed. However, on the basis of data from this study, regular dosage of 12 μg formoterol 3 times daily can be expected to be a reasonable recommendation for asthmatics with moderate to severe asthma. However, several patients in this study felt well on only two doses of formoterol a day. It was not the original intention of the present study to compare formoterol with recommended salbutamol dosage. Such a comparison seems possible, however, since the patients in this study took 200 μg salbutamol approximately 4 times daily, on average, which is in fact the recommended regular dose [16]. Our results indicate that 12 μg formoterol 3 times daily is clearly superior to 200 μg salbutamol 4 times daily with regard to symptom relief and improved PEFR values.

The crossover design may give rise to certain problems [9, 10]. In this study a tendency towards interaction between treatment and treatment order was noticed, with respect to the dose-response recordings. This means that it cannot be ascertained that the change towards "improvement" of the dose-response curves for FEV₁ after the formoterol treatment period was in fact caused by the therapy. However, this is highly likely, since the same pattern was evident when the results from the first treatment period were analysed as a study with parallel groups. We are therefore inclined to believe that the high basal values for FEV₁ after formoterol therapy were caused by remaining bronchodilatation after the last dose, given about 12 h before the test.

It has been shown that a long-acting inhaled bronchodilator would improve asthma therapy significantly [17]. This paper supports this assumption. The patients did not only notice the prolonged effect of formoterol, but also stated that their asthma was better controlled during both


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Le formoterol, un nouveau bronchodilatateur à action prolongée en inhalation. Une comparaison pendant deux semaines avec étude de la tachyphylaxie. P. Arvidsson, S. Larsson, C.G. Löfdahl, B. Melander, L. Wålinder, N. Svedmyr. RÉSUMÉ: L'objectif de cette étude est d'évaluer si le traitement au moyen du formoterol en inhalation est bien apprécié par les asthmatiques, et s'il provoque une tachyphylaxie. Nous avons introduit 20 asthmatiques en état stable dans une étude randomisée, en double anonymat, avec permutation croisée. Ils ont été traités pendant deux semaines, soit par le formoterol, soit par le salbutamol, avec une semaine intermédiaire de washout. On leur a donné 12 lg de formoterol ou 200 lg de salbutamol deux fois par jour et on leur a donné comme instruction d'utiliser des doses supplémentaires d'aérosols à la demande. Ils ont noté sur une fiche d'observation quotidienne le nombre de doses utilisées, les symptômes asthmatiques, ainsi que le DEP avant chaque dose. Les courbes dose-réponse du VEMS pour le salbutamol (dose totale 1.3 mg) ont été réalisées avant et après chaque période de traitement, pour évaluer le développement d'une tachyphylaxie. On a noté une différence significative en faveur du formoterol en ce qui concerne les symptômes, les enregistrements du DEP, la consommation d'aérosols, et la préférence. Quinze patients préféraient le formoterol et deux le salbutamol. Les courbes dose-réponse réalisées avant formoterol ainsi qu'avant et après salbutamol, s'avèrent quasiment identiques. Après formoterol, la courbe s'est modifiée, les valeurs basses et maximales étant plus élevées qu auparavant. On n'a donc trouvé aucune preuve de tachyphylaxie par comparaison avec un traitement \( \beta \)-stimulant classique.