

## Inhaled formoterol during one year in asthma: a comparison with salbutamol

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*Inhaled formoterol during one year in asthma: a comparison with salbutamol. P. Arvidsson, S. Larsson, C-G. Löfdahl, B. Melander, N. Svedmyr, L. Wåhlander.*

**ABSTRACT:** Eighteen patients, who had previously taken part in a 2 wk cross-over comparison between formoterol and salbutamol, now took part in a one year double-blind study comparing salbutamol 200 µg *b.i.d.* with formoterol 12 µg *b.i.d.*. Additional doses were taken when needed and were recorded. Ten patients were started on formoterol and eight on salbutamol. After one month, the patients were allowed to shift to the alternative drug.

Two patients withdrew from the study. At the end of the study, 13 of 16 patients were on formoterol, thus showing a long-lasting preference for this drug. Forced expiratory volume in one second (FEV<sub>1</sub>) dose-response curves for inhaled salbutamol were repeatedly recorded during the study, and no tachyphylaxis was found.

One patient stopped taking inhaled steroids but continued taking formoterol and theophylline. He deteriorated with a decreased response to salbutamol. After re-introduction of inhaled steroids his condition improved. This case indicates that effective bronchodilator therapy may mask the deterioration of asthma.

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Formoterol is a new  $\beta_2$ -adrenoreceptor agonist. It has been found *in vitro* to be about 50 times more potent than salbutamol, with regard to the effect on bronchial smooth muscle, and at least as  $\beta_2$ -selective as terbutaline and salbutamol [1-5].

Clinical studies of short-term effects in asthmatics have shown that formoterol is 50 times more potent than salbutamol after oral administration and 5-15 times more potent after inhaled administration [6]. The duration of action of inhaled formoterol is at least 8-12 h, compared to 4-5 h after salbutamol [6, 7]. We have reported a double-blind, cross-over comparison with salbutamol, in which formoterol and salbutamol were given for two weeks each. The study showed that the prolonged effect of formoterol could also be demonstrated in a clinical trial in asthmatics [8]. Furthermore, the patients preferred formoterol to salbutamol and there was no sign of tachyphylaxis.

We now report a one year follow-up of the patients in that study. The main objectives of the present investigation were to study the long-term preference (formoterol or salbutamol), the long-term effectiveness and tolerability of formoterol and the possibility of development of tachyphylaxis.

### Patients

Twenty patients had participated in the previous cross-over study. These patients were offered continued treatment with formoterol or salbutamol for one year. Eighteen patients accepted. They all had stable reversible airway obstruction, and used short-acting inhaled  $\beta_2$ -agonists at least three times daily.

Treatment with theophyllines, inhaled steroids and inhaled anticholinergics in unchanged dosage was allowed during the trial.

Oral and inhaled  $\beta_2$ -agonists other than the study medication were discontinued during the study.

### Methods

#### Study design

The 12 month study was started as a randomized, double-blind study with parallel groups of asthmatics treated twice daily with either two puffs of formoterol, 6 µg per puff, or two puffs of salbutamol, 100 µg per puff. The patients were told to take additional

inhalations (two puffs on each occasion) whenever needed and to record these inhalations during the week before each examination visit to the hospital. The patients were trained by an experienced assistant to use the correct inhalation technique

The patients were informed at the start of the trial that they would be allowed to shift to the alternative treatment after the first month, if they were dissatisfied with the drug to which they were randomized.

The patients were examined by forced expiratory volume in one second (FEV<sub>1</sub>) dose-response testing for increasing doses of salbutamol after 1, 3, 6, 9 and 12 months.

At the examinations after 9 and 12 months, two dose-response curves were constructed on two consecutive days. The patients were given a short-acting  $\beta_2$ -agonist (salbutamol) instead of the test drug between these two tests.

During the week before the examination visits to the hospital, the patients recorded their peak expiratory flow rate (PEFR) before each dose of the study medication. They also recorded the consumption of additional spray doses and symptoms on a diary card.

At each visit the patients were asked an open question concerning side-effects. The study was approved by the Ethics Committee at the University of Göteborg.

#### *Dose-response curves*

To study the potential for development of tachyphylaxis due to long-term treatment with formoterol, FEV<sub>1</sub> dose-response curves for increasing doses of inhaled salbutamol were recorded.

The patients were asked to abstain from the inhaled study medication for 12 h before the dose-response tests and from oral theophylline for 36 h before the tests. If this was not possible the test was postponed. The patients were allowed to stay on inhaled steroids.

The patients arrived at the laboratory at 7.30 a.m. after a light breakfast without coffee or tea. The patients rested seated for 50 min and then basal values for FEV<sub>1</sub> were recorded. Two baseline measurements were made with 20 min in between. Salbutamol was then given in three doses (100, 300 and 900  $\mu$ g, respectively) at intervals of 20 min. The inhalations were given by a dose-aerosol connected to a spacer, a Volumatic®. Only 100  $\mu$ g of salbutamol was released into the spacer before each inhalation. The patients rinsed their mouths with water after each inhalation, which was supervised by an experienced assistant.

FEV<sub>1</sub> was recorded 12 min after each dose on a Vitalograph Spirometer. The best of three values was used for the calculations.

#### *PEFR values and additional doses*

PEFR was measured before the prescribed study medication was taken in the morning and evening.

Recordings were also made before the intake of additional doses on the bronchodilators. The best of two values was recorded on a diary card. A Mini Wright peak flow meter was used and the patients were instructed how to record the values.

#### *Recording of symptoms*

The week before the examination visits, the patients recorded their subjective opinions about the severity of their asthma, every morning and evening on their diary cards, using a four-graded scale: 0 = no symptoms, undisturbed sleep; 1 = mild asthma, symptoms not interfering with activities or sleep; 2 = moderately severe asthma, symptoms only slightly interfering with activities or sleep; 3 = severe asthma, symptoms making daily activities impossible or seriously disturbing sleep.

#### *Statistical methods*

For the recordings at home, the mean values of the highest and lowest PEFR during 24 h, symptom scores and the number of additional doses were analysed for the six days preceding the visit. For comparisons within and between groups, the Wilcoxon signed rank and rank sum test, respectively, were used. Exceptions were made for age, height and weight, for which Student's t-test was used and for preferences, where the sign test was used.

## Results

Eighteen of the 20 patients included in the two week cross over study volunteered to take part in the present twelve month follow-up study. Ten patients were allocated to formoterol and eight to salbutamol therapy. Clinical details for the two groups of patients are given in table 1. No distinct differences between the groups are seen.

Table 1. - Patient details

	Formoterol n=10	Salbutamol n=8
Age yrs	58 (43-66)	59 (45-64)
Asthma duration yrs	17 (2-42)	16 (8-40)
FEV <sub>1</sub> % pred	54 (22-80)	35 (14-58)
Reversibility %	36 (22-64)	49 (22-80)
Concomitant medication n		
Inhaled steroids	8	5
Inhaled anticholinergics	0	1
Oral theophyllines	7	3

Data are given as mean (and range in parenthesis), with the exception of concomitant medication. FEV<sub>1</sub>: forced expiratory volume in one second.

Figure 1 shows shifts between treatments decided by the patients and discontinuations of treatment. Two patients withdrew from the study prematurely.

for these patients after two weeks of treatment with salbutamol and formoterol in the previous study are given for comparison. The dose response curves

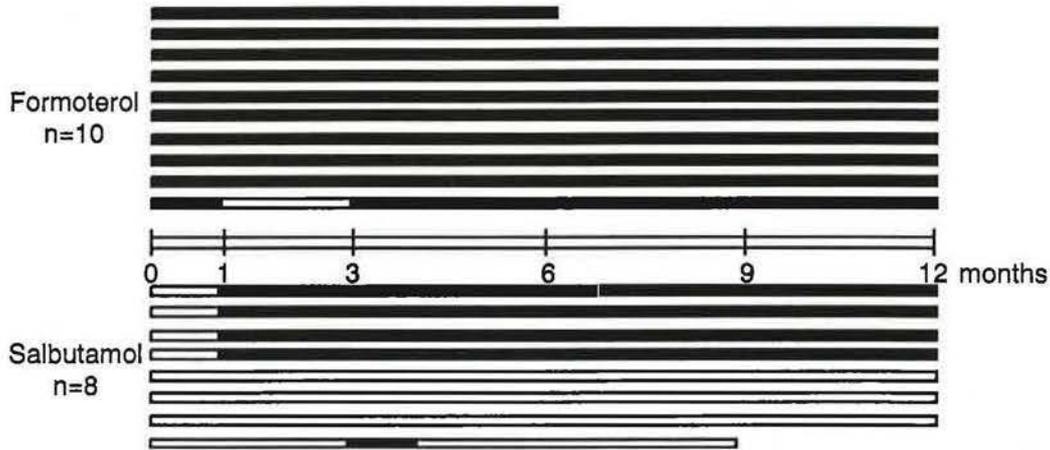


Fig. 1. - Randomization to treatment groups and treatment shifts. Filled lines: formoterol; open lines: salbutamol. Two patients withdrew from the study. Thirteen patients preferred formoterol and three salbutamol after twelve months of treatment ( $p < 0.05$ ).

One had been treated with formoterol for six months when she felt she did not want to continue in a clinical trial. The other patient, treated with salbutamol, travelled abroad. Almost all shifts between treatments occurred between one and three months. No shifts were allowed during the first month. All four patients who shifted from salbutamol to formoterol after one month showed improved baseline FEV<sub>1</sub>, improved PEF levels, and symptom scores and had less need of rescue medication. At the end of the trial, 13 patients were on formoterol and three on salbutamol. The difference is statistically significant ( $p < 0.05$ ).

#### Results after one month

Up to one month the study can be regarded as a study of parallel groups. The results after one month of treatment are similar to those from the previous cross-over study after two weeks. The mean dose-response curve recorded after one month with formoterol showed no evidence of development of tachyphylaxis. It was similar to the curve recorded in the previous cross-over study after salbutamol treatment in the same patients. The patients treated with formoterol took fewer additional inhalations, their mean PEF values were higher and their mean symptom scores were lower, compared with the results in the salbutamol group. However, the differences were not significant.

#### Results after 3-12 months

The results after 3-12 months are presented for the 13 patients who were on formoterol at the end of the study. These patients had then been treated continuously with formoterol for 9-12 months.

Figure 2 shows mean dose-response curves for these 13 patients. Mean dose-response curves recorded

during the year on formoterol are similar to the curve after two weeks on formoterol, although basal values and maximum values are slightly lower. The mean basal values after 3-12 months are higher than the basal value recorded after two weeks on salbutamol, while the maximum values are approximately the same.

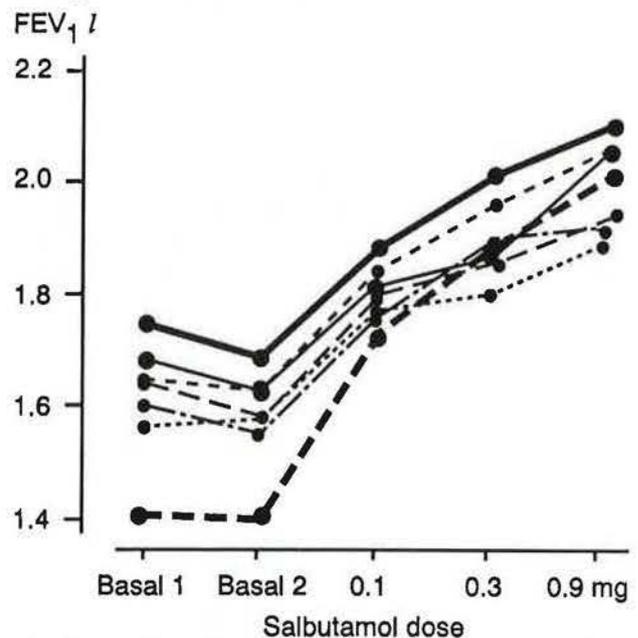


Fig. 2. - Mean dose-response curves for increasing doses of salbutamol, recorded 3, 6, 9 and 12 months after the start of the study in 13 patients on formoterol for 12 months. Mean dose-response curves for the same patients recorded after salbutamol and formoterol in the previous two week cross-over study are presented for comparison (bold lines). ●—●: 2 wks salbutamol; ●—●: 2 wks formoterol; ●---●: 1 month formoterol; ●---●: 3 months formoterol; ●- - -●: 6 months formoterol; ●- - -●: 9 months formoterol; ●—●: 12 months formoterol; FEV<sub>1</sub>: forced expiratory volume in one second.

Figure 3 shows the mean dose-response curves recorded after 9 and 12 months. At these examinations it was possible to record dose response curves on two consecutive days in 11 patients. Only a short-acting  $\beta_2$ -agonist, salbutamol, was given between the tests. The dose-response curves recorded on the second day after 9 and 12 months show lower basal and maximum values than those recorded on the previous day. After 9 months, the basal value on the second day was significantly lower than the day before ( $p < 0.05$ ). After 12 months the maximum value was significantly lower on the second day than the day before ( $p < 0.05$ ). The dose-response curves recorded on the second day are, however, similar to those recorded after two weeks on salbutamol in the previous cross-over trial.

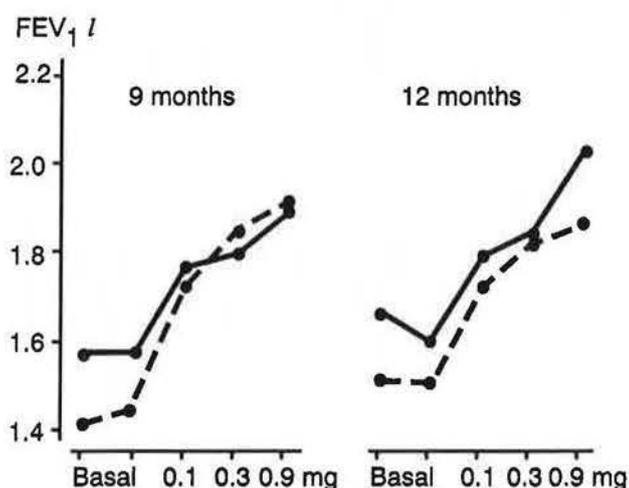


Fig. 3. — Mean dose-response curves for 11 patients. Recordings were done on two consecutive days after 9 and 12 months. ●—● : 12 h after last formoterol dose; —●—● : 36 h after last formoterol dose; FEV<sub>1</sub>: forced expiratory volume in one second.

Table 2 gives the number of additional doses, the symptom scores and the results of PEF<sub>R</sub> measurements recorded the week before the examination visits at 3–12 months. For comparison, results after two weeks treatment with salbutamol and formoterol are given. During 3–12 months the number of additional doses both during the night and the day are consistently lower than after two weeks of salbutamol therapy. The consumption is somewhat higher than after two weeks on formoterol. PEF values are higher than after salbutamol for two weeks and approximately the same as after two weeks on formoterol. Symptom scores are consistently lower than after two weeks on salbutamol but somewhat higher than after two weeks on formoterol.

#### Side-effects

Side-effects were reported by ten patients when on formoterol. Muscle cramps were reported by three patients. Tremor was reported by one patient. Two patients complained of dryness of the mouth; one of them consistently at all four visits. Single complaints of nasal congestion, irritation from the aerosol, insomnia and nausea when brushing the teeth were reported. All side-effects were considered mild by the patients, except for the muscle cramps reported by one patient, which was considered to be of moderate severity.

#### Case history

The following case history indicates that deterioration of asthma can be masked by a strong bronchodilator drug.

A 44 yr old smoker had had non-allergic asthma for 24 yrs. His medication was oral salbutamol, oral

Table 2. — Mean values for 13 patients on formoterol after 12 months treatment: symptom scores, PEF<sub>R</sub> values and number of additional doses

	Previous cross-over study		Current study			
	Salbutamol 2 wks	Formoterol 2 wks	Formoterol months			
			3	6	9	12
Symptom score						
Day	1.22	0.76	1.08	0.99	0.96	1.06
Night	1.20	0.59	0.73	0.86	0.85	0.97
PEFR l·min <sup>-1</sup>						
Lowest	291	334	340	336	324	331
Highest	355	370	385	375	368	371
Number of additional doses						
Day	1.58	0.65	1.12	1.05	1.06	1.05
Night	0.42	0.16	0.42	0.23	0.23	0.28

Each additional dose consists of two inhalations. PEF<sub>R</sub>: peak expiratory flow rate.

theophylline, inhaled formoterol and inhaled beclomethasone dipropionate 200  $\mu\text{g}$  *b.i.d.*. After three months he discontinued steroid therapy without consulting his doctor and gave up smoking. After four months there was a short period of deterioration of the asthma - probably due to a purulent bronchial infection - requiring acute asthma treatment. On the night before the six month dose-response test he became wheezy, and the FEV<sub>1</sub> in the morning was considerably lower than before. He showed a decreased dose-response to salbutamol and was given a short course of oral steroids. The same event occurred at the nine month test. A new dose-response test was performed one month later, without withdrawing the theophylline, and then the patient experienced no worsening at night and showed an improved response to salbutamol. It was now revealed that the patient had stopped taking the inhaled steroids, and this therapy was reinstated. One and two months later, at the end of the twelve month study, the patient again showed a good response to salbutamol, and theophylline and formoterol could be withdrawn before the test without any problems. During the whole study his PEF values remained very high (mean values between 450–550  $\text{l}\cdot\text{min}^{-1}$ ); also the PEF values the evening before all the response tests were within the same range.

### Discussion

This investigation was started as a study of parallel groups. However, during the previous two week cross-over study, the patients had expressed a strong preference for formoterol and it was considered necessary for ethical reasons to give them the possibility to shift to the alternative therapy. Randomized studies suffer from limitations when a strong preference for one treatment regime can be expected. Patients randomized to the least popular therapy will be prejudiced against this therapy. In this situation, study designs like the one used in the present study have been advocated [9]. The major advantage is that long-term preference can be studied.

As in the previous cross-over study, the patients in the present twelve month study expressed a clear preference for formoterol. This study shows that the patients consistently prefer formoterol during a period of one year.

*In vitro* studies have indicated that long-acting  $\beta_2$ -agonists have a slower onset of action [5, 10]. This may be a disadvantage, if these drugs are used when needed. In this study, however, formoterol was used not only for regular treatment but also on demand. The strong preference for formoterol indicates that the patients were satisfied with the long-acting drug also for use when needed.

In many respects, the results of the two week study are confirmed in the present investigation. The previous study concluded that the need for additional spray doses decreases with formoterol therapy and

that, in spite of this, PEF values are higher and symptoms better controlled than during salbutamol therapy. The same pattern is seen in this one year study (results after one month and table 2).

In the previous study no evidence was found of tachyphylaxis to the bronchodilating effect of beta-agonists after formoterol treatment. Similarly, WALLIN *et al.* [11] found no evidence of tachyphylaxis after one month of treatment with formoterol. The same conclusion must be drawn from the present study. Dose-response curves after one month and after 3–12 months (fig. 3) showed no evidence of tachyphylaxis. Basal values and maximum values were no lower than after salbutamol therapy in the previous study. On the contrary, the basal values recorded in the morning after cessation of formoterol therapy in connection with the dose response tests are higher than the values recorded in the morning after stopping salbutamol therapy. This can be interpreted as a remaining bronchodilating effect of formoterol after the last dose given the evening before the tests. One could argue that the remaining effect of formoterol seen in the previous study may mask development of tachyphylaxis. Dose-response tests were, therefore, carried out on two consecutive days after 9 and 12 months. Formoterol was substituted by salbutamol therapy between the test days. The dose-response recorded after 36 h of formoterol avoidance returned to the appearance after salbutamol therapy. Again, no evidence of tachyphylaxis was seen as the basal values and maximum values were no lower than after salbutamol therapy.

In our previous cross-over study, in the study by WALLIN *et al.* [11], and in the present study, the patients did not use their salbutamol inhaler frequently enough to produce the same PEF recordings and degree of freedom from symptoms as that obtained with their formoterol inhaler. This should have been possible at least during the day, as the patients were informed that they were allowed to take additional inhalations whenever needed. Moreover, the salbutamol and formoterol doses used produced equal bronchodilating peaks. This indicates that a major drawback with short-acting inhaled bronchodilators is that patients are reluctant to take them often enough to obtain the optimum effect. Fear of overdosing and simple practical reasons may be the explanation. Thus, with formoterol, more effective bronchodilating therapy can be achieved than has hitherto been possible.

It has recently been argued that treatment with long-acting beta-adrenoceptor agonists may disturb long-term control of asthma [12, 13]. In our study we did not find any long-term deterioration as regards PEF levels, symptom scores and additional intake of inhaled  $\beta_2$ -adrenoceptor agonists. The only long-term problem seen in this small study was related to one patient who stopped taking inhaled corticosteroids. As long as the patient took formoterol and theophylline continuously he felt unusually well. It was not until he stopped bronchodilator therapy abruptly before the

dose-response tests that the deterioration was revealed and he developed severe asthma and unresponsiveness to salbutamol. Before that, the patient noticed no deterioration, not even in the PEF values recorded the night before the dose-response tests. This could be due to the effective bronchodilatation obtained with formoterol, which could mask a deterioration of the asthmatic disease. Thus, we must warn patients against stopping steroid therapy in an uncontrolled way, even if their asthma is well controlled by effective bronchodilator therapy.

In conclusion, the promising results reported with formoterol in the previous two week study could also be found during the one year follow-up. With formoterol, more effective bronchodilating therapy can be achieved than with short-acting  $\beta_2$ -adrenoceptor agonists. This gives better asthma control, without any sign of development of tachyphylaxis. Side-effects seem to be a minor problem. One patient in the study indicates that effective bronchodilatation may mask deterioration of the asthma. This case supports the idea that during treatment with a long-acting drug such as formoterol, addition of inhaled steroids is as important as during treatment with short-acting  $\beta_2$ -agonists.

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*Le formoterol en inhalation pendant 1 an dans l'asthme. Comparaison avec le salbutamol.* P. Arvidsson, S. Larsson, C.G. Löfdahl, B. Melander, N. Svedmyr, L. Wählander.

RÉSUMÉ: Dix-huit patients, qui avaient pris part antérieurement à une comparaison de deux semaines en permutation croisée entre le formoterol et le salbutamol, ont participé ensuite à une étude aveugle d'un an, comparant 200  $\mu$ g de salbutamol 2 fois par jour avec 12  $\mu$ g de formoterol 2 fois par jour. Des doses complémentaires ont été prises en cas de besoin, et enregistrées. Dix patients ont commencé l'essai au formoterol, et huit au salbutamol. Après un mois, les patients ont été autorisés à passer à la drogue alternative.

Deux patients ont été retirés de l'étude. A la fin de l'étude, 13 des 16 patients étaient au formoterol, ce qui démontrait une préférence au long cours pour ce produit. Les courbes dose-réponse de VEMS pour l'inhalation de salbutamol ont été enregistrées à répétition au cours de l'étude, et l'on n'a observé aucune tachyphylaxie.

Un patient a cessé de prendre des stéroïdes en aérosol, mais a continué à prendre du formoterol et de la théophylline. Son état s'est détérioré et la réponse au salbutamol a diminué. Après réintroduction de l'inhalation de stéroïdes, son état s'est amélioré. Ce cas indique qu'une thérapeutique effective aux bronchodilatateurs pourrait masquer la détérioration de l'asthme.

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