

## A study with cumulative doses of formoterol and salbutamol in children with asthma

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**ABSTRACT:** In a double-blind, cross-over study, 9 children (7-13 yrs old) with stable, moderate asthma inhaled formoterol (6, 18 and 54 µg) and salbutamol (100, 300 and 900 µg) at hourly intervals, in order to compare the peak effect of cumulative doses of the two drugs. One hour after the last dose, 1 mg salbutamol was inhaled to ensure that maximum bronchodilatation was obtained. The forced expiratory volume in one second (FEV<sub>1</sub>), peak expiratory flow rate (PEFR), forced vital capacity (FVC), pulse rate, blood pressure and tremor were measured regularly after each dose and the PEFR 5, 7, 9 and 20 h after the last dose.

The first dose of each drug improved the FEV<sub>1</sub>, PEFR and FVC substantially while the following doses only gave minor improvement. The final addition of 1 mg salbutamol produced no further improvement. No statistically significant difference in bronchodilating effect was seen between the two drugs at any point in time. Side-effects were minimal.

Our data indicate that doses of 6-24 µg formoterol can be recommended for school children. For most patients with mild to moderate bronchial asthma higher doses will not add much to the bronchodilating effect.

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Inhaled formoterol fumarate is a new potent selective beta<sub>2</sub>-agonist with much longer bronchodilating effect than other inhaled beta<sub>2</sub>-agonists currently in use [1, 2]. Compared with 200 µg salbutamol, inhalation of 12 or 24 µg formoterol has the same rapid onset of action, a somewhat delayed peak effect but a much more prolonged duration of effect [3-6]. The aim of the present study was to evaluate appropriate doses of formoterol for use in children with asthma symptoms in a cumulative dose response study, with salbutamol as the comparative drug.

### Material

Nine children, 4 boys and 5 girls, 7-13 yrs old (mean 10 yrs) with chronic stable asthma and no other serious diseases were included in the study. They were allowed to use their regular dosage of sodium cromoglycate (7 patients) and inhaled steroids (7 patients) if these had not been changed during the past month. Oral drugs (n=8) were withdrawn at least 12 h, (slow release terbutaline (n=5) 24 h, and slow release theophylline (n=8) 36 h) before the tests.

Within two weeks before the start of the study the patients should have shown at least 20% reversibility of their peak expiratory flow rate (PEFR) value (mean 44%, range 20-81%) after inhalation of 0.2 mg × 3 of salbutamol metered dose inhaler (MDI) in a spacer. Informed consent to the child's participation was obtained from the parents.

### Methods

Spirometry was performed with a Vitalograph® and the forced expiratory volume in one second (FEV<sub>1</sub>) was registered. The PEFR was measured in the laboratory with a Wright peak flow meter and at home with a mini-Wright peak flow meter (Clement Clarke International Ltd). The best of three attempts was recorded in all measurements.

Tremor was registered by two simple tests. The examiner subjectively assessed the tremor of the fingers of the patient's extended right hand with a small sheet of paper held between the three middle fingers and graded the tremor on a scale from 0 to 3. In the other "circle" test, the patient was instructed to



trace a line between two concentric circles (diameters 11 and 10 cm) with a pencil and the number of contacts and overcrossings was recorded. The middle part of an 18 cm long pencil was held between three fingers and without any support for the arm. The tracing should take about 30 s.

### Study design

The study was performed as a double-blind, cross-over study with three different doses of formoterol (6, 18 and 54  $\mu$ g) and salbutamol (100, 300 and 900  $\mu$ g). At least one week should have passed between the two test days. To ensure that the test conditions were comparable, the patients PEFR values were measured in the morning and evening on the last two days before each test day and the best of three measurements was recorded. No more than a 10% difference between the PEFR values obtained in the morning of the two test days were allowed.

FEV<sub>1</sub> and PEFR were the principal effect parameters of the study. Each test day started at 8 a.m. with a 30 min rest, followed by measurement of the PEFR, FEV<sub>1</sub>, forced vital capacity (FVC), pulse rate, blood pressure and tremor. The measurements were repeated after 15 min. The patients were then given one puff of either test substance from a metered dose aerosol via a spacer (Volumatic®). One hour later three puffs were given and after another hour, nine more puffs. Every 15 min after each dose, the FEV<sub>1</sub>, FVC, heart rate and tremor were measured, and every 30 min, the PEFR and blood pressure. The maximum value reached after each dose was used in the calculations. One hour after the last dose the patients were given 5  $\times$  0.2 mg salbutamol in a Volumatic® spacer and all the tests mentioned above were performed 15 min later. The PEFR value and the pulse rate were measured at home 4, 6, and 8 h later and in the morning the following day. Any asthma symptoms, side-effects and need for extra medication were noted.

### Statistics

Analysis of variance was used to test the relationship between dose and effect or systemic effects of each drug. The difference in effect between the dose levels (0-1, 1-2, 2-3, 3 to final administration of 1 mg salbutamol) of each drug was tested by Wilcoxon's signed rank test.

For comparison between the two treatments at each dose level, absolute values were applied to pulse rate, blood pressure and the two tremor tests. The PEFR, FEV<sub>1</sub> and FVC were calculated as percentages of the maximum value during the day, and the calculated values were used to compare the two treatments. This calculation was chosen as the patients did not always reach the same maximum value on the two test days, although the baselines for the PEFR and FEV<sub>1</sub> were almost the same at both visits. In this way, the

patient's capacity at each examination was taken into account. In the comparison of the results, the Wilcoxon's signed rank test was used as there were no period effects. The Wilcoxon's rank-sum test was used for the test of period effect.

The study was approved by the Ethics Committee of the Medical Faculty, Uppsala University.

### Results

#### Pulmonary function variables

The first dose of each drug already markedly improved the FEV<sub>1</sub> value. The mean FEV<sub>1</sub> ( $\pm$ SEM) increased from 1.45 ( $\pm$ 0.11) l before to 1.77 ( $\pm$ 0.13) l after 6  $\mu$ g formoterol. Further administration of formoterol doses of 18 and 54  $\mu$ g increased the mean FEV<sub>1</sub> to 1.92 ( $\pm$ 0.17) and 1.98 ( $\pm$ 0.17) l, respectively. The corresponding FEV<sub>1</sub> values for salbutamol were 1.42 ( $\pm$ 0.13) l before and 1.90 ( $\pm$ 0.21), 1.99 ( $\pm$ 0.18) and 2.08 ( $\pm$ 0.21) l after 100, 300 and 900  $\mu$ g salbutamol, respectively. The effect of cumulative doses of formoterol and salbutamol on FEV<sub>1</sub> is shown as percentages of the maximum in figure 1.

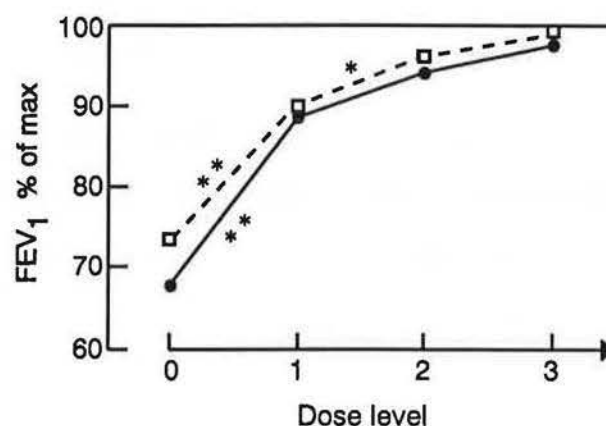


Fig. 1. — FEV<sub>1</sub> in percentage of the maximum FEV<sub>1</sub> after any dose on the test day. The dose levels of formoterol and salbutamol were 1=6, 2=18, 3=54  $\mu$ g and 1=100, 2=300, 3=900  $\mu$ g, respectively. \*\*:  $p < 0.01$ ; \*:  $p < 0.05$ ; □ - - □: formoterol; ● — ●: salbutamol; FEV<sub>1</sub>: forced expiratory volume in one second.

The final inhalation of 1 mg salbutamol did not improve the FEV<sub>1</sub> further, indicating that the maximum effect had been obtained by the greatest dose of each drug. There was no statistically significant difference between the two drugs at any dose level. For both drugs there was a highly significant ( $p = 0.001$ ) increase in FEV<sub>1</sub> with increasing doses, as shown by analysis of variance. The FVC also increased with dose with both drugs ( $p < 0.01$ ). Most of the effect, up to about 95% of the maximum, was already reached after the first dose (data not shown).

The PEFR values after cumulative doses of the two drugs are shown in figure 2 as percentages of the maximum. The general pattern is similar to that for the



FEV<sub>1</sub>. The mean PEFR increased from 247 ( $\pm 14$ ) l·min<sup>-1</sup> before to 308 ( $\pm 15$ ), 332 ( $\pm 20$ ) and 343 ( $\pm 20$ ) l·min<sup>-1</sup> after doses no. 1–3 of formoterol, respectively. The PEFR was 238 ( $\pm 16$ ) l·min<sup>-1</sup> before and 324 ( $\pm 25$ ), 342 ( $\pm 22$ ), and 343 ( $\pm 22$ ) l·min<sup>-1</sup> after doses no. 1–3 of salbutamol. There was no statistically significant difference in PEFR between the drugs at any dose level.

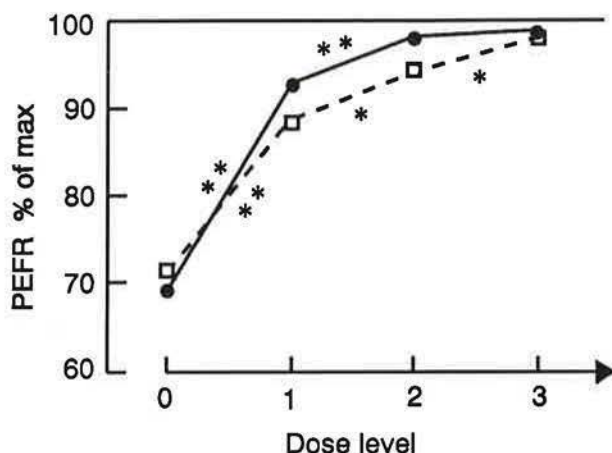


Fig. 2. — PEFR in percentage of the maximum on the test day. Dose levels and symbols as in legend to figure 1. PEFR: peak expiratory flow rate; □ — □: formoterol; ● — ●: salbutamol.

The duration of effect on the PEFR is shown in figure 3. There was no statistically significant difference between the test drugs at any point of time. PEFR 20 h after administration of the last dose was 86% ( $\pm 2.8$ ) of the maximum for formoterol and 82% ( $\pm 5.0$ ) of the maximum for salbutamol. This is significantly better than the basal PEFR pre-test value for formoterol ( $p < 0.01$ ) but not for salbutamol.

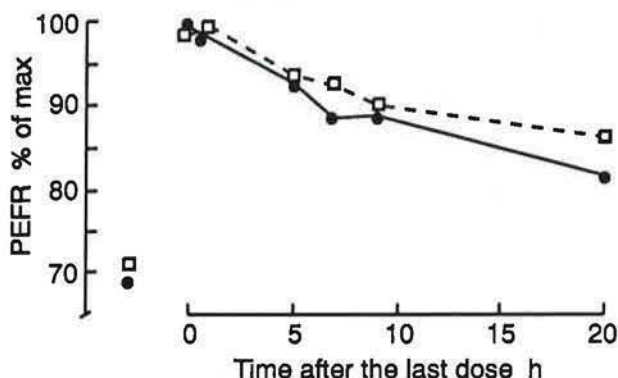


Fig. 3. — PEFR in percentage of the maximum reached on the test day. The values are corrected, which means that if a patient had used rescue medication, the last value before the rescue medication was carried forward for the following time points. The time is given as the number of hours after the last test dose. N.B. 1 mg salbutamol was inhaled by all patients 1 h after dose level 3. The symbols before time 0 represent the pre-test values. PEFR: peak expiratory flow rate; □ — □: formoterol; ● — ●: salbutamol.

After leaving the laboratory, two patients on each treatment had to use their regular inhaled beta<sub>2</sub>-stimulant (one was the same individual). Asthma symptoms during the night after the test day were reported after each drug with similar symptom scores by three children.

#### Systemic effects

The pulse rate before and after treatment is shown in table 1. There was no statistically significant difference in pulse rate between the two drugs at any given point in time. Analysis of variance showed an effect of dose on the pulse rate for salbutamol ( $p < 0.001$ ) but not for formoterol. The reason for the higher pulse rate after 900  $\mu$ g salbutamol than after the following administration of 1 mg salbutamol is, however, unclear.

Table 1. — Pulse rate

Dose level	Formoterol	Salbutamol
0	90 $\pm$ 3.4	87 $\pm$ 3.6
1	91 $\pm$ 4.2	88 $\pm$ 3.3
2	92 $\pm$ 5.6	92 $\pm$ 4.0
3	94 $\pm$ 5.0	97 $\pm$ 3.5
1 mg salbutamol	95 $\pm$ 6.8	89 $\pm$ 4.3

Mean $\pm$ SEM beats·min<sup>-1</sup>.

The mean systolic and diastolic blood pressure before the start of the study and after the highest dose of formoterol was 107/70 and 110/68, respectively. After salbutamol, the corresponding figures were 112/72 and 110/69. Analysis of variance showed no effect of dose on the blood pressure for either drug.

Tremor tests yielded low scores with no tendency to increase with dose for any of the drugs. Figure 4 shows the results of the "circle test". After the first dose of each drug there was a tendency for the tremor to increase, which was followed by a tendency towards a decrease after the following doses. This may be due to development of tolerance, a training effect in performing the test, or both.

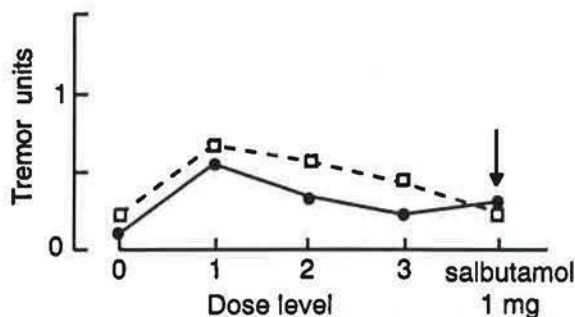


Fig. 4. — Tremor test. Units on the Y axis are the numbers of failures to trace a line with a pencil ("circle test"). Dose levels as in legend to figure 1. □ — □: formoterol; ● — ●: salbutamol.



### Adverse effects

One patient reported slight headache and tiredness after formoterol. No other adverse effects were reported or observed during the study.

### Discussion

In adults a cumulative dose response study has shown that formoterol by the inhaled route was 5–15 times more potent than salbutamol with respect to bronchodilatation [2]. After cumulative doses of 39 and 123 µg of formoterol, approximately 90 and 95%, respectively, of the bronchodilating capacity of the patients was reached. Only minor changes in heart rate and no changes in blood pressure were observed. The tremor increased significantly with the greatest dose.

No similar studies have been performed in children to our knowledge. Only doses of 6–24 µg of inhaled formoterol have been tested on school children. In one study 24 µg of formoterol showed a tendency (ns) towards a better bronchodilating effect than 12 µg, without any difference with regard to adverse reactions [5]. Another study showed a similar bronchodilating effect with 6, 12 and 24 µg of formoterol up to 12 h after administration, but better protection against exercise-induced asthma after 24 µg of formoterol than after the lower doses [7].

In the present study, the smallest dose of formoterol tested (6 µg) already significantly improved the FEV<sub>1</sub> and PEF. Administration of 18 µg formoterol (total 24 µg) caused further improvement. Increase of the dose beyond that added nothing or only little to the effect on the FEV<sub>1</sub> and PEF. There was no significant effect of formoterol on pulse rate, tremor, systolic or diastolic blood pressure. No side-effects were reported or observed after formoterol, except for one report of slight headache and tiredness. There were no significant differences in bronchodilating effect or systemic effects between formoterol in the cumulative doses of 6, 18, and 54 µg (total 78 µg) and salbutamol 100, 300 and 900 µg (total 1,300 µg). This does not prove dose-equivalence, however, since that would require a study with more dose steps and a greater number of patients.

It has been shown in several studies that the duration of effect of formoterol is longer than that of salbutamol [1–6]. In our study, no significant difference between the PEF values was seen between the two drugs up to 20 h after the test. The reason is that our investigation was designed to compare the peak effect of cumulative doses of formoterol and salbutamol rather than to study the duration of effect. Therefore, a very high dose of salbutamol was administered after the last dose of each test drug to determine whether maximum bronchodilatation had been attained. This high dose of salbutamol may have influenced the results even 20 h after administration, as the duration of effect is influenced by the magnitude of dose.

In summary, our findings indicate that doses of 6–24 µg formoterol MDI can be recommended for school children. For most patients with mild to moderate bronchial asthma higher doses will not add much to the bronchodilating effect.

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*Etude en permutation croisée et en double aveugle avec des doses cumulatives de formoterol et de salbutamol chez des enfants asthmatiques. T. Foucard, G. Lönnnerholm.*

**RÉSUMÉ:** Au cours d'une étude en permutation croisée et en double aveugle, 9 enfants (âgés de 7 à 13 ans) et atteints d'un asthme modéré stable ont inhalé du formoterol (6, 18 et 54 µg) et du salbutamol (100, 300 et 900 µg) à des intervalles horaires, pour comparer l'effet maximal de doses cumulatives des deux produits. Une heure après la dernière dose, 1 mg de salbutamol a été inhalé pour s'assurer que la bronchodilatation maximale avait été obtenue. Le VEMS, le DEP, la CVF, le pouls, la pression artérielle et le tremblement, ont été mesurés régulièrement après chaque dose, et le DEP également 5, 7, 9 et 20 heures après la dernière dose.

La première dose de chacun des produits améliore le VEMS, le DEP et la CVF de façon substantielle, alors que les doses suivantes n'ont donné qu'une amélioration mineure. L'addition finale de 1 mg de salbutamol n'a pas produit d'amélioration complémentaire. L'on n'a noté aucune différence statistiquement significative dans l'effet bronchodilatateur entre les deux drogues à un point quelconque de temps. Les effets collatéraux ont été minimaux.

Nos données indiquent que les doses de 6 à 25 µg de formoterol peuvent être recommandées pour les enfants en âge d'école. Pour la plupart des patients atteints d'asthme léger à modéré, des doses plus importantes n'ajouteront pas grand chose à l'effet bronchodilatateur.

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