Formoterol via Turbuhaler® gave better protection than terbutaline against repeated exercise challenge for up to 12 hours in children and adolescents

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We aimed to compare the protective effect of single doses of 4·5 and 9 µg of formoterol fumarate (F), 0·5 mg terbutaline sulphate (T) and placebo (P), all via Turbuhaler®, against exercise-induced bronchoconstriction (EIB) in children.

Twenty-seven asthmatic children, showing a fall of ≥20% in FEV₁ after a standardized exercise challenge test (ECT) combined with cold air (−10°C) inhalation, were randomized in this cross-over, double-blind study. They had a mean age of 12·6 years (range 8–17 years), mean baseline FEV₁ 90% (73–9–105–6%) of predicted normal value. Seventeen children used inhaled glucocorticosteroids (120–750 µg day⁻¹). ECTs were performed 15 min and 4, 8, and 12 h after drug administration.

F significantly reduced the fall in FEV₁ after ECT to 5·4% (15 min), 5·2% (4 h), 8·2% (8 h) and 9·3% (12 h) after 4·5 µg, and 2·5%, 3·0%, 5·0% and 5·4% after 9 µg, compared with a fall of 18·4%, 15·7%, 15·6% and 16·5% in FEV₁ after P. The fall after T was 3·3%, 11·6%, 14·4% and 19·1% after 15 min, 4, 8 and 12 h respectively. The difference between F and T was statistically significant from 4 h and onward (P-value for all comparisons <0·05).

Children using a single dose of either formoterol Turbuhaler 4·5 or 9 µg had significantly better bronchoprotection against repeated exercise challenge up to 12 h compared with placebo and from 4 h onward compared with terbutaline Turbuhaler® 0·5 mg.

Key words: formoterol; Turbuhaler; children; adolescents; asthma; exercise.

Introduction

Strenuous physical activity is often associated with symptoms of airway obstruction in children suffering from asthma. In some children exercise is the only trigger, whereas in others it is one of several stimuli which trigger symptoms (1). In clinical investigations, exercise tests resulted in bronchoconstriction in more than 70% of asthmatic children (2–4). Exercise-induced bronchoconstriction (EIB) is thought to be elicited by airway cooling (5) and respiratory water loss (6), which causes a change in osmolality of the pericilliary fluid lining the respiratory tract (7). Cold air in combination with exercise, which represents a commonly encountered stimulus during the daily life of many asthmatic individuals, especially in winter, markedly worsened EIB in children with asthma (8).
adults, formoterol Turbuhaler at both 4.5 and 9 \( \mu g \) b.i.d. was statistically significantly better in the control of asthma (19,20). Concerning the protection against EIB in children, a single dose of formoterol (metered dose) 12 \( \mu g \) via pressurized metered dose inhaler gave a significantly prolonged protection compared with salbutamol 200 \( \mu g \); the protection persisted for 12 h (21). Similar outcomes were seen in adults in a study comparing 9 \( \mu g \) formoterol Turbuhaler and 0.5 mg terbutaline Turbuhaler (22).

This study compared the bronchoprotection of single doses of formoterol Turbuhaler at delivered doses of 4.5 \( \mu g \) and 9 \( \mu g \) with that of 0.5 mg terbutaline Turbuhaler and of placebo, against repeated exercise challenge combined with cold air in children during a period of 12 h.

Patients and methods

PATIENTS

Patients with asthma, as defined by the ATS (23), stratified into two age groups; 6–12 and 13–17 years were enrolled. To be included, they should have a baseline FEV\(_1\) of ≥80% of predicted normal value (24) and had to show a fall of ≥20% in FEV\(_1\) following a standardized exercise challenge test (ECT).

DESIGN

This was a randomized, double-blind, placebo-controlled, cross-over study performed at two centres: one in Norway and one in Germany. The study consisted of five visits comprising one screening and four 12-h study days (visits 2–5), separated by washout periods of at least 72 h.

On study days, the patients inhaled 4.5 or 9 \( \mu g \) formoterol fumarate dehydrate (hereafter formoterol), 0.5 mg terbutaline sulphate (hereafter terbutaline) or placebo, all via Turbuhaler, in a randomized order.

### Spirometry

Schedule of spirometry test during study days is presented in Fig. 1. Two FEV\(_1\) determinations (separated by 15 min) were performed before study drug administration. The mean of the two was used as baseline FEV\(_1\) and had to be ≥80% of predicted normal value at visits 1–5. The variation in baseline FEV\(_1\) at visits 2–5 had to be within 20% of the mean baseline FEV\(_1\) value at visit 1.

FEV\(_1\) was measured before, immediately after, and 5, 10 and 20 min after ECT. If FEV\(_1\) was lower after 20 min than after 10 min, measurements continued every 10 min until the maximum fall was observed.

### Exercise challenge test (ECT)

ECTs were performed 15 min and 4, 8 and 12 h after drug administration. The ECT at visit 1 was carried out to determine if the patient responded to exercise with a decline in FEV\(_1\) of at least 20% of his/her baseline value. The patients performed a continuous running test on a treadmill (25) with a workload adjusted to produce a maximum pulse (approximately 180 beats min\(^{-1}\)). During exercise the patients inhaled cold dry air (−10°C) generated by the Turboaire® challenger through compressed medical air with a pressure of 6 bar, through a mouthpiece. The duration of the test varied between 4 and 8 min, depending on the time required to reach a maximum pulse. The individual workload established at enrolment for each patient was maintained throughout the study. Pulse was measured before, during and immediately after the running period.

Before each ECT, the investigator had to judge whether it was possible and safe for the patient to perform the ECT. If not, the patient has to rest until the next scheduled ECT. To exclude a possible late phase reaction, PEF was measured at the clinic and then at home at 4, 8 and 12 h after the ECT at visit 1.

<table>
<thead>
<tr>
<th>Time</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>−30 min</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>−15 min</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>0 min</td>
<td>Study drug inhalation</td>
</tr>
<tr>
<td>+15 min</td>
<td>ECT</td>
</tr>
<tr>
<td></td>
<td>before ECT</td>
</tr>
<tr>
<td></td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>Start of ECT</td>
<td>pulse</td>
</tr>
<tr>
<td>End of ECT</td>
<td>pulse</td>
</tr>
<tr>
<td>immediately after ECT</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>+5 min after ECT</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>+10 min after ECT</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>+20 min after ECT</td>
<td>FEV(_1) (2 attempts)</td>
</tr>
<tr>
<td>+4 h</td>
<td>ECT</td>
</tr>
<tr>
<td>+8 h</td>
<td>ECT</td>
</tr>
<tr>
<td>+12 h</td>
<td>ECT</td>
</tr>
</tbody>
</table>

Fig. 1. Spirometry tests during study days.
Patients discontinued any concomitant use of bronchodilators 6–72 h prior to visits, depending on the duration of drug action. Anti-histamines and disodium cromoglycate were discontinued 48 and 24 h, respectively, prior to visits. Inhaled and nasal glucocorticosteroids (GCSs) were allowed, provided that they were used at constant doses 30 days prior to visit 1 and throughout the study.

**Pharmacodynamic parameters**

- **AUC<sub>0–20</sub>:** The area under the time-effect curve in the interval 0–20 min was computed using the trapezoidal rule.
- **AUC<sub>0–12 h</sub>:** The area under the time-effect curve in the interval 0–12 h.
- **E<sub>base</sub>:** The mean of the two FEV<sub>1</sub> measurements at the beginning of each study day (before study drug at visits 2–5).
- **E<sub>pre</sub>:** FEV<sub>1</sub> just before each ECT.
- **E<sub>min</sub>:** The minimum post-exercise value measured.
- **E<sub>avg</sub>:** The average effect based on E<sub>pre</sub> within the study day, i.e. AUC<sub>0–12 h/12</sub>.
- **Index<sub>EIB</sub>:** The bronchial response to exercise was expressed as maximum fall in FEV<sub>1</sub> from the pre-exercise value (the % fall index):
  \[
  \text{Index}_{EIB} = \frac{E_{pre} - E_{min}}{E_{pre}} \times 100
  \]
- **Average<sub>EIB</sub>:** The mean post-exercise lung function relative to the FEV<sub>1</sub> value measured just before each ECT (E<sub>pre</sub>):
  \[
  \text{Average}_{EIB} = \frac{\text{AUC}_{0–20}}{20 \times E_{pre}}
  \]

**Safety**

Information about adverse events was obtained by means of an open standardized question to the patient at the clinic visits: ‘Have you/your child had any health problems since the previous visit/questioning?’.

**Statistics**

In a previous study in children, the within patient coefficient of variation in the lowest post-exercise vs. pre-exercise FEV<sub>1</sub> ratio was 13%. With similar variation in this study, a sample size of 24 evaluable patients would give a probability of 80% to detect an effect of 11%. This assumed a two-sided test on a 5% significance level.

Index<sub>EIB</sub> was compared between treatments with an additive analysis of variance (ANOVA) model with factors patient, visit and treatment. 95% confidence intervals were constructed for the pair-wise treatment comparisons. The values from each exercise test within a study day were treated in separate analyses. The duration of the protective effect was evaluated by comparing the active treatments with placebo at 15 min and then for as long as the difference was statistically significant.

Possible differences in treatment effects between the two age groups (6–12 and 13–17 years) were investigated using a separate ANOVA model.

**Ethics**

Independent Ethics Committees in Norway and Germany approved the study. Signed informed consent was obtained from the parent and from the patient if he/she was older than 12 years or oral consent if the child was younger than 12 years, prior to enrolment in the study.

**Results**

Twenty-seven patients (15 males and 12 females) were randomized into the study. Their mean age was 12.6 years (range 8–17 years), mean weight 47 kg (25–71 kg) and mean height 154 cm (135–180 cm). All but two were Caucasians. Thirteen children belonged to the younger age group (6–12 years) and 14 to the older age group (13–17 years). The mean baseline FEV<sub>1</sub> (E<sub>base</sub>) at visit 1 was 2.56 l (1.66–4.15 l) corresponding to 90% of predicted normal value (74–106%). The mean percentage fall in FEV<sub>1</sub> after exercise at enrolment (Index<sub>EIB</sub>) was 32% (19.7–49.5%). The distribution of some patient characteristics at entry is shown in Fig. 2.

Seventeen patients were on regular treatment with inhaled GCSs (120–750 µg) and four patients were using a long-acting β<sub>2</sub>-agonist (salmeterol) on a regular basis. Eight patients used anti-histamines; one patient used inhaled disodium cromoglycate, one patient used nasal disodium cromoglycate and two patients used nasal GCSs.

**FEV<sub>1</sub> BEFORE ECT**

Mean baseline FEV<sub>1</sub> measured before drug administration (E<sub>base</sub>) was about the same for all treatments; 2.501 (placebo), 2.56 l (formoterol 4.5 µg), 2.551 (formoterol 9 µg) and 2.521 (terbutaline 0.5 mg). Both doses of formoterol as well as terbutaline gave statistically significantly higher FEV<sub>1</sub> values than placebo, 15 min after administration (Table 1). No statistically significant difference was seen between the 4.5 and 9 µg dose of formoterol (Fig. 3).

Concerning a 12 h average of pre-exercise FEV<sub>1</sub> (E<sub>avg</sub>), both formoterol doses gave significantly higher bronchodilating effects than both placebo and terbutaline.

**PROTECTION AGAINST EIB**

Both formoterol doses gave a significantly higher degree of protection against EIB than placebo, between 15 min and 12 h after study drug administration. Compared with terbutaline, both formoterol doses gave a significantly better protection at 4, 8 and 12 h after drug administration. Fifteen minutes after drug administration, terbutaline gave a significantly better protection than placebo. The effect
declined, reaching the same level as placebo at the exercise test performed 4 h after administration (Fig. 4). The mean fall in FEV₁ after placebo during the randomized study days was 18.4% at the 15-min test, which was less than the mean fall measured at the screening visit (32.0%). The results of the statistical analyses are given in Table 2. No major differences were seen between the age groups concerning the treatment effects (Fig. 5). Statistical tests comparing treatments were not made due to the limited number of patients in each subgroup.

SAFETY

There were no adverse events of clinical relevance or considered causally related to treatment.

Discussion

The current guidelines (11) recommend the use of short-acting β₂-agonists for prevention and treatment of acute
Fig. 3. Mean $E_{pre}$ at different time points after administration of study drugs, presented as changes from baseline (%). Placebo (○), formoterol 4·5 μg (□), formoterol 9 μg (△), terbutaline 0·5 mg (+).

Table 2. Analyses of $\text{Index}_{\text{EIB}}$ at different time points

<table>
<thead>
<tr>
<th>Contrast</th>
<th>15 min</th>
<th>4 h</th>
<th>8 h</th>
<th>12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est.</td>
<td>95% CI</td>
<td>$P$-value</td>
<td>Est.</td>
</tr>
<tr>
<td>Placebo</td>
<td>18·4</td>
<td>14·5</td>
<td>22·3</td>
<td>15·7</td>
</tr>
<tr>
<td>Formoterol 4·5 μg</td>
<td>5·40</td>
<td>1·46</td>
<td>9·35</td>
<td>5·19</td>
</tr>
<tr>
<td>Formoterol 9 μg</td>
<td>2·50</td>
<td>-1·43</td>
<td>6·44</td>
<td>3·02</td>
</tr>
<tr>
<td>Terbutaline 0·5 mg</td>
<td>3·34</td>
<td>-0·60</td>
<td>7·28</td>
<td>11·6</td>
</tr>
<tr>
<td>Placebo-formoterol 9 μg</td>
<td>15·9</td>
<td>10·3</td>
<td>21·5</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Placebo-formoterol 4·5 μg</td>
<td>13·0</td>
<td>7·41</td>
<td>18·6</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Placeo-terbutaline 0·5 mg</td>
<td>15·0</td>
<td>9·48</td>
<td>20·6</td>
<td>&lt;0·001</td>
</tr>
<tr>
<td>Terbutaline 0·5 mg-formoterol 9 μg</td>
<td>0·84</td>
<td>-4·73</td>
<td>6·41</td>
<td>0·76</td>
</tr>
<tr>
<td>Terbutaline 0·5 mg-formoterol 4·5 μg</td>
<td>-2·06</td>
<td>-7·65</td>
<td>3·53</td>
<td>0·46</td>
</tr>
<tr>
<td>Formoterol 4·5 μg-formoterol 9 μg</td>
<td>2·90</td>
<td>-2·67</td>
<td>8·47</td>
<td>0·30</td>
</tr>
</tbody>
</table>

Fig. 4. $\text{Index}_{\text{EIB}}$ at different time points after drug administration. Placebo (○), formoterol 4·5 μg (□), formoterol 9 μg (△), terbutaline 0·5 mg (+).

Exacerbation associated with exercise and other stimuli, which trigger bronchoconstriction. The present results demonstrate that long-acting formoterol Turbuhaler is a superior alternative to short-acting terbutaline in protection against bronchoconstriction induced by a repeated exercise during a period of 12 h. The technique of repeated exercise test after a single dose reflects the daily life situation for many children, which includes scheduled physical activities...
such as school sporting activities and other unplanned activities, during the day. A practical implication of the present results is that the children need only to take one single dose in the morning and may then feel confident to take part in physical activities without needing to carry any rescue inhaler or to think about timing an extra inhalation before exercise. The children will not feel different from other children, which should have positive impact on their self-confidence and quality of life (12–14).

The fall in FEV₁ during the randomized placebo day was smaller than the mean fall seen at the screening day (18% compared with 32%), indicating a placebo effect. A similar effect on EIB has been reported before (26,27). Both formoterol and terbutaline had a limited bronchodilating effect, 7 and 6% after 4.5 and 9 µg formoterol respectively and 5% after terbutaline. This is what would be expected in patients with relatively high baseline FEV₁ (74–106% of predicted normal value). A reversibility test was not performed in these patients; the main inclusion criterion was a fall in FEV₁ after exercise. A high baseline FEV₁ was chosen as a safety measure to avoid very low post-exercise FEV₁ and to eliminate the contribution of bronchodilating effect to the protection against EIB.

In contrast to the long acting β₂-agonists, the short-acting drugs have demonstrated shorter duration of bronchoprotective effect against exercise than that of the bronchodilatory effect (25). This was also applicable in the present study. Both formoterol and terbutaline gave statistically significant protection relative to placebo against bronchoconstriction induced by exercise performed at 15 min after drug administration. The protection of formoterol lasted for 12 h, while that of terbutaline was the same as after placebo during exercise performed 4 h after administration. Prolonged bronchoprotection of formoterol during exercise was also shown in adults on regular treatment with formoterol Turbuhaler 9 µg b.i.d. A statistically significant protection against EIB for up to 12 h was shown after a mean treatment period of 16 days (range 8–44 days). Although the protection was somewhat lower at the 12-h ECT compared to what was seen earlier in the day, formoterol had about three times longer duration of effect than the short-acting bronchodilators normally used for the prevention of EIB (22). A prolonged protective effect of long-acting β₂-agonists against bronchoconstriction induced by other stimuli has been reported in previous investigations (28–30).

Despite the fact that a majority of the patients were on regular use of inhaled GCSs, they all showed a fall in FEV₁ after exercise. In these patients, a single dose of formoterol 4.5 or 9 µg was seen to give the protection they needed against EIB.

In conclusion formoterol was shown to be a better alternative to terbutaline against bronchoconstriction induced by repeated exercise challenge for up to 12 h in children.

References


