Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis®

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This study aimed to compare the duration of protection against exercise-induced bronchoconstriction (EIB) after inhalation of formoterol (Oxis®) Turbuhaler® with that of terbutaline Turbuhaler® and placebo Turbuhaler® in asthmatic patients treated regularly with formoterol Turbuhaler® 9 µg b.i.d. and inhaled steroids.

The study, performed at three centres (Göteborg and Lund, Sweden, and Trondheim, Norway), consisted of an open-label part with formoterol Turbuhaler® 9 µg b.i.d. and a randomized, double-blind, cross-over part with a single dose (on top of the regular treatment) of either formoterol Turbuhaler® 9 µg, terbutaline Turbuhaler® 0·5 mg or placebo Turbuhaler®. The patients attended the clinic six times: twice for screening visits, three times for randomized treatment and once for a follow-up visit. Patients received regular b.i.d. treatment with formoterol 9 µg for a mean period of 16 days.

Formoterol gave a post-exercise fall of 12, 10, 15 and 17% in forced expiratory volume in 1 sec (FEV1) 15 min, 4, 8 and 12 h after inhalation. The differences compared with placebo (falls of 26, 22, 23 and 22%) and terbutaline (falls of 17, 18, 22 and 22%) were all statistically significant (P < 0·05 for all comparisons).

Patients on regular treatment with formoterol Turbuhaler® 9 µg b.i.d. have a significant protection against EIB up to 12 h after inhalation of formoterol 9 µg. The protection was also significantly better than that of terbutaline Turbuhaler® 0·5 mg.

Key words: formoterol turbuhaler®; asthma; exercise; cold air.

Introduction

The airway response to exercise is a feature of bronchial responsiveness. Although the mechanism is not fully understood, it involves bronchial smooth muscle cells, mast cells and neurons (1), with the release of mediators (2). Respiratory heat loss, resulting in water loss, is one of the hypotheses for the cause of exercise-induced bronchoconstriction (EIB) (3). Cold air inhalation during exercise has been shown to enhance the magnitude of EIB (4).

Inhaled β2-adrenoceptor agonists are the most effective drugs for preventing EIB in patients with asthma (5,6). However, the usefulness of most currently available β2-agonists is limited by a rather short duration of protection (7,8). Formoterol fumarate dihydrate (hereafter ‘formoterol’) is a long-acting β2-agonist with a rapid onset of action and maintained bronchodilatory effect for at least 12 h (9,10). Single doses of formoterol and the other long-acting β2-agonist salmeterol have been shown to give significant protection up to 12 h against bronchoconstriction induced by exercise and methacholine challenge. However, it has been reported that regular use of these drugs is associated with tolerance development resulting in a reduced bronchoprotection (11,12).

The present placebo-controlled study was performed to investigate whether patients on regular treatment with formoterol Turbuhaler® 9 µg b.i.d. and using inhaled corticosteroids would have protection against repeated EIB for 12 h after inhalation of formoterol (Oxis®) Turbuhaler® 9 µg compared with terbutaline Turbuhaler® 0·5 mg. To avoid a carry-over effect, the evening dose of formoterol, scheduled to be taken 12 h prior to exercise challenge test, was omitted.
Materials and methods

STUDY DESIGN AND PATIENTS

The study, performed at three centres (Göteborg and Lund, Sweden, and Trondheim, Norway), included adult asthmatics, diagnosed at least 6 months prior to inclusion, who had been on regular treatment with a constant dose of inhaled glucocorticosteroids (GCSs) for at least 30 days before the start of the study. Lung function measured as forced expiratory flow in 1 sec (FEV₁) had to be > 70% of predicted normal value and the patient had to document a fall in FEV₁ of at least 15% after the exercise challenge test (ECT). To exclude a late-phase reaction to exercise, peak expiratory flow (PEF) was measured at the clinic before ECT and at home 4, 8 and 12 h after ECT at visit 1.

The study consisted of six visits to the clinic: two screening visits, three visits for drug tests and a follow-up visit (Fig. 1). At visit 1, a screening ECT was performed. Patients who demonstrated a fall in FEV₁ of at least 15% after the ECT received 9 μg formoterol Turbuhaler® (corresponding to 12 μg metered dose) to be used twice daily throughout the study, except in the evening before visits 2–5. A second screening visit (visit 2) took place after a minimum of 4 days and another ECT was performed. Only patients who once again showed a fall of at least 15% in FEV₁ after exercise were allowed to continue the study and proceeded with the open-label treatment with formoterol.

Visits 3–5 were scheduled for the morning, and a single dose of formoterol 9 μg or terbutaline 0.5 mg or placebo, on top of the regular b.i.d. formoterol treatment, was administered via Turbuhaler® in a double-blind, cross-over and randomized fashion. Fifteen minutes after drug administration, ECT was performed. The ECT was repeated 4, 8 and 12 h after drug administration. Visit 6 was a follow-up visit.

Between visits 1 and 5, patients were asked to fill in diaries at home. The time of inhalation of study medication and any use of relief medication during the night before visits 2–5 were recorded.

ECT

EIB was determined using a standardized ECT. Patients ran continuously for 4–8 min on a treadmill with an inclination of about 10% and at a speed that was adjusted step-wise to produce a final pulse ≥80% of the predicted maximum value. During the ECT, the patients wore a nose-clip and breathed cold dry air (−18°C) generated by a Turboaire® challenger (Equilibrated Bio Systems, U.S.A.) through a mouth-piece. For each patient the individual workload determined at visit 1 was maintained throughout the study.

SPIROMETRY

FEV₁ measurements were performed using a standard spirometer (Vitalograph® Alpha; Vitalograph Ltd, U.K.) in accordance with American Thoracic Society (ATS) acceptability and reproducibility guidelines (13).

For establishment of baseline, two FEV₁ determinations (15 min apart) were performed before study drug administration. The mean of the two FEV₁ values had to be > 70% of predicted normal value at visits 1–5. Moreover, baseline FEV₁ at visits 3–5 had to be within ±12% of the baseline FEV₁ measured at visit 2.

Pulmonary function was evaluated by the best of two FEV₁ measurements, immediately before and after exercise, and 5, 10 and 20 min after exercise. If FEV₁ was lower after 20 min than after 10 min, further measurements were made every 10 min until the maximum fall was observed.

STATISTICAL ANALYSIS

The bronchial response to exercise was expressed as the maximum fall in FEV₁ from the pre-exercise value:

$$\text{Maximum percentage fall} = \frac{\text{pre-exercise FEV}_1 - \text{lowest post-exercise FEV}_1}{\text{pre-exercise FEV}_1} \times 100$$

The maximum percentage fall was compared between treatments with an additive analysis of variance (ANOVA) model with factors patient, period and treatment. Ninety-five per cent confidence intervals (CI) were constructed for the pair-wise treatment contrasts. The values from each ECT within a single study day were treated in separate analyses. Formoterol was first compared with placebo and if a statistically significant difference was found, formoterol was then compared with terbutaline. The duration of the
protective effect was evaluated by comparing active treatment with placebo, first at 15 min and then at increasing time points for as long as the difference was statistically significant.

The bronchodilator effect was compared between treatments with a multiplicative ANOVA model with factors patient, period and treatment and using FEV\(_1\) as covariate. The bronchodilator effect was expressed as the FEV\(_1\) value before ECT and as the 12-h average FEV\(_1\) (AUC/12) based on the before ECT values.

SAFETY

As safety parameters, serum potassium, pulse and blood pressure were measured. Also, the patients were asked about adverse events (AEs) at all visits and routine physical examinations were performed at visits 1 and 6.

ETHICS

The independent ethics committees of all participating centres approved the study, and a signed consent to participate in the study was obtained from each patient prior to admission. The study followed the guidelines in the Declaration of Helsinki.

Results

PATIENT DEMOGRAPHICS

In all, 52 patients with asthma (ATS definition) were enrolled in the study. Thirty-two were given the open-label treatment with formoterol for a mean time of 16 days (range 8–44 days) and 26 were randomized to the double-blind treatment. Twenty-six patients were withdrawn prior to randomization because of a fall in FEV\(_1\)<15% (22 patients), a baseline FEV\(_1\)<70% (two patients), a late-phase reaction (one patient) and other reasons (one patient).

Of the 26 randomized patients, 22 had a diagnosis of extrinsic asthma, three patients of intrinsic asthma and one patient unspecified asthma. All 26 patients had been on regular treatment with inhaled GCSs for at least 1 month prior to visit 1; 12 patients used low-dose equivalent to 400 \(\mu\)g budesonide day\(^{-1}\), 12 used medium-dose equivalent to 800 \(\mu\)g budesonide day\(^{-1}\) and two used high-dose equivalent to 1600 \(\mu\)g budesonide day\(^{-1}\). One patient used disodium cromoglycate on an 'as-needed' basis until 8 days before visit 1. Three patients were on anti-histamines and two patients used nasal GCSs. Nine patients used a long-acting \(\beta_2\)-agonist (salmeterol) until 3–8 days before visit 1.

Table 1 shows patient characteristics. All 26 randomized patients were considered eligible for evaluation of efficacy data and are included in the analysis.

BRONCHODILATORY EFFECT

The mean baseline FEV\(_1\) values (visits 3, 4 and 5) obtained prior to drug inhalation were similar for all treatments: 3·101 for terbutaline and 3·111 for formoterol and placebo.

Formoterol increased FEV\(_1\) 15 min after inhalation, just before the ECT, significantly more than placebo and terbutaline. Terbutaline was also significantly better than placebo (see Fig. 2). The 12-h average bronchodilatory effect, based on the area under the curve of time vs. effect, gave the same picture as that seen 15 min after inhalation. Results of the analyses are given in Table 2.

BRONCHOPROTECTIVE EFFECT

Formoterol gave a significantly higher degree of protection against EIB than placebo and terbutaline at 15 min, 4, 8 and 12 h after drug administration (Fig. 3).

The degree of protection declined with time. The placebo fall was slightly smaller during the randomized study day (21·7–26%) than during visits 1 (28·3%) and 2 (27·6%). The results of the statistical analyses are given in Table 3.
TABLE 2. Single dose effects on FEV\(_1\) (l)

<table>
<thead>
<tr>
<th>Contrast(^\dagger)</th>
<th>Number of patients</th>
<th>Baseline FEV(_1) (l) (unadjusted raw arithmetic means)</th>
<th>Mean FEV(_1) (l) (15 min after drug inhalation)</th>
<th>Average FEV(_1) (l) (during 12 h after drug inhalation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (range)</td>
<td>Est.*</td>
<td>95% CI</td>
</tr>
<tr>
<td>Terbutaline 0·5 mg</td>
<td>26</td>
<td>3·15 (2·25-4·17)</td>
<td>3·25</td>
<td>3·20-3·30</td>
</tr>
<tr>
<td>Formoterol 9 µg</td>
<td>26</td>
<td>3·17 (2·09-4·26)</td>
<td>3·33</td>
<td>3·28-3·38</td>
</tr>
<tr>
<td>Placebo</td>
<td>26</td>
<td>3·17 (2·08-4·26)</td>
<td>3·07</td>
<td>3·02-3·12</td>
</tr>
<tr>
<td>Formoterol/placebo</td>
<td>—</td>
<td>—</td>
<td>108·5</td>
<td>106·2-111·0</td>
</tr>
<tr>
<td>Terbutaline/placebo</td>
<td>—</td>
<td>—</td>
<td>105·9</td>
<td>103·6-108·2</td>
</tr>
<tr>
<td>Formoterol/terbutaline</td>
<td>—</td>
<td>—</td>
<td>102·5</td>
<td>100·3-104·8</td>
</tr>
</tbody>
</table>

CI: Confidence interval.
*Geometric means adjusted for period effects and baseline differences; \(^\dagger\) treatment ratios in %.
SAFETY

There was no clinically relevant difference between treatments regarding serum potassium levels, blood pressure, pulse or AEs throughout the study.

Discussion

In this study, formoterol 9 μg gave a statistically significantly better bronchoprotection against repeated exercise challenge than both terbutaline 0.5 mg and placebo from 15 min up to 12 h after inhalation, in adult asthmatics on regular treatment with formoterol. This supports the findings of another study in children and adolescents, which demonstrated that a single dose of inhaled formoterol 4.5 or 9 μg gave significantly better protection against repeated exercise challenge for up to 12 h compared with placebo and from 4 h compared with terbutaline 0.5 mg (14). The sustained bronchoprotective effect of at least 12 h seen with formoterol contrasts with that reported for short-acting β2-agonists. The latter usually have a protection against EIB that lasts for a shorter time than the bronchodilatory effect (15,16). The benefit of maintained protection is obvious; the patient can carry out all kinds of physical activities for up to 12 h after treatment without needing to fear bronchoconstriction.

For both formoterol 9 μg and terbutaline 0.5 mg the bronchodilatory effect was limited (8–5% and 5–9%, respectively), which could be explained by the selection of

### Table 3. Maximum fall (%) in FEV<sub>1</sub> at different time points and differences between treatments

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Maximum % fall in FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>ECT 15 min after drug inhalation</th>
<th>ECT 4 h after drug inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimation</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Terbutaline 0.5 mg</td>
<td>16.6</td>
<td>13.7–19.4</td>
<td>—</td>
</tr>
<tr>
<td>Formoterol 9 μg</td>
<td>12.1</td>
<td>9.25–15.0</td>
<td>—</td>
</tr>
<tr>
<td>Placebo</td>
<td>26.2</td>
<td>23.3–29.2</td>
<td>—</td>
</tr>
<tr>
<td>Placebo-formoterol</td>
<td>14.1</td>
<td>10.0–18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo-terbutaline</td>
<td>9.65</td>
<td>5.55–13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Terbutaline-formoterol</td>
<td>4.47</td>
<td>0.43–8.50</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Maximum % fall in FEV<sub>1</sub>

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Maximum % fall in FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>ECT 8 h after drug inhalation</th>
<th>ECT 12 h after drug inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimation</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Terbutaline 0.5 mg</td>
<td>22.2</td>
<td>19.6–24.8</td>
<td>—</td>
</tr>
<tr>
<td>Formoterol 9 μg</td>
<td>15.0</td>
<td>12.4–17.6</td>
<td>—</td>
</tr>
<tr>
<td>Placebo</td>
<td>22.5</td>
<td>19.8–25.1</td>
<td>—</td>
</tr>
<tr>
<td>Placebo-formoterol</td>
<td>7.44</td>
<td>3.71–11.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo-terbutaline</td>
<td>0.23</td>
<td>–3.50–3.97</td>
<td>0.90</td>
</tr>
<tr>
<td>Terbutaline-formoterol</td>
<td>7.20</td>
<td>3.53–10.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: Confidence interval.
mild asthmatics, using GCSs, who had a mean baseline FEV₁ value (at visit 2) of 89-6% (range 70-2-110-0%) of predicted normal. Moreover, the patients’ ability to respond to a β₂-agonist was not required for inclusion into this study. Although all patients had been using inhaled GCSs on a regular basis for at least 1 month prior to inclusion in the study, they had a maximum fall in FEV₁ ≥15%.

The decrease in the maximum percentage fall in FEV₁ after the 4-h ECT in the placebo group could be explained by diurnal variation or by attenuation in the response after repeated testing. However, the latter is unlikely because the interval between ECTs in this study was 4 h and the recovery time after an ECT is normally 2 h (17). The bronchoprotective effect shown in this study confirms the benefit of adding formoterol to inhaled GCS treatment, not only as a regular treatment in patients with persistent asthma (18) but also when needed for bronchoprotection against EIB.

The primary objective of this study was to evaluate the protective effect of adding formoterol 9 μg against repeated exercise during 12 h compared with placebo and terbutaline 0-5 mg, so to avoid a carry-over effect from the last dose prior to first ECT; the evening dose scheduled to be taken 12 h prior to the exercise challenge was omitted. Considering that formoterol in fact showed protective effect vs. placebo at 12 h justifies this procedure. The bronchoprotective effect of formoterol after 12 h was small and its clinical importance may be questioned. However, it was measured at the end of the recommended dosing interval and the following dose of formoterol would renew the protection. In contrast, an earlier study demonstrated that formoterol 12 μg significantly protected against methacholine-induced bronchoconstriction for up to 24 h compared with placebo, perhaps suggesting that the type of stimulus may influence the duration of protective effect (19).

Although the patients in this study received 9 μg formoterol b.i.d. (in addition to inhaled corticosteroids) for a mean treatment period of 16 days (range 8-44 days), tolerance development was not investigated. Hence, to what degree tolerance occurred, if any, remains unknown as no ECT was performed prior to the start of regular treatment with formoterol. Other studies have indicated that there is an association between regular use of long-acting β₂-agonists and development of tolerance, resulting in reduced bronchoprotective effect against exercise and methacholine challenge but maintained bronchodilating effects (11,12). Nevertheless, one of these studies demonstrated that after 2 weeks of continuous dosing with formoterol the resulting bronchoprotection was significantly better than placebo and similar to terbutaline (12).

The impact of withdrawal of β₂-agonist treatment for a short time on the tolerance development has also been investigated. In one study, it was observed that stopping β₂-agonist treatment for a short time enhances the recovery of tolerance against systemic effects in patients using inhaled steroids (20). However, other studies, published by the same group, have shown that stopping treatment with formoterol for up to 36 h did not influence the tolerance development to bronchoprotective effect against methacholine (12,21).

Different bronchoconstrictor stimuli appear to have varying effects on the ability of β₂-agonists to provide and maintain bronchoprotection. For instance, the protective effect induced by terbutaline has shown a more rapid decline against inhaled adenosine 5'-monophosphate (AMP) than methacholine (22). Methacholine is a direct stimulus whereas exercise and AMP are both indirect bronchoconstrictors. AMP probably induces bronchoconstriction in subjects with asthma through release of histamine from airway mast cells, and exercise-induced bronchoconstriction may be mediated by hypertonic mast-cell degranulation (23). In one study, regular formoterol 24 μg once daily induced a similar degree of subsensitivity to AMP bronchial challenge as formoterol 24 μg twice daily, suggesting that even with a 24-h dosing interval, tolerance may develop to formoterol (24). However, in a second study, a single dose of formoterol 12 μg had a greater protective effect against AMP than against histamine challenge, suggesting that formoterol may have a mast-cell stabilizing effect in vivo in mild asthma (25). Hence, preliminary evidence suggests that formoterol may provide better protection against indirect than direct stimuli. Furthermore, any tolerance development following regular treatment plateaus after a short time to remain at a level significantly better than seen with placebo and at least as good as that observed with short-acting β₂-agonists.

In conclusion, this study showed that a single 9 μg dose of formoterol Turbuhaler® gave significantly better protection against EIB than either terbutaline Turbuhaler® 0-5 mg or placebo for up to 12 h after inhalation, in patients on regular treatment with formoterol Turbuhaler® 9 μg b.i.d.

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