Oxis® (formoterol given by Turbuhaler®) showed as rapid an onset of action as salbutamol given by a pMDI

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Thirty-six adult patients (16 women) with mild to moderate asthma with a mean baseline forced expiratory volume in 1 sec (FEV₁) of 73.8% (46–106%) of predicted normal value and mean reversibility of 24.2% (14–64–47-1%) were included in this double-blind, double-dummy, randomized, placebo-controlled and cross-over study. The patients inhaled single doses 4.5 or 9 μg of formoterol (Oxis®) via Turbuhaler® salbutamol (Ventolin®) 100 or 200 μg from a pressurized metered dose inhaler (pMDI) or placebo at five randomized visits. Efficacy was measured by FEV₁ pre-dose and then 1, 3, 5, 7, 10, 15, 20, 25 and 30 min after inhalation of the study drug. The primary variable of efficacy was the FEV₁-value 3 min after dose intake.

No statistically significant differences were found between active treatments. All active treatments gave a higher bronchodilating effect at 3 min than placebo: 10, 11-4% for salbutamol 100 and 200 μg and 11, 11-8% for formoterol 4.5 and 9 μg (P < 0.001 in all cases). There was a correlation between the measured response at 3 min and the subjective experience of the patients. The relative difference vs. placebo remained throughout the study period for all active treatments except for low dose salbutamol. All treatments were well tolerated.

In conclusion, formoterol Turbuhaler has as rapid an onset of action as salbutamol pMDI when given at recommended doses.

**Key words:** onset; Oxis; formoterol; salbutamol; Turbuhaler; pMDI.

**Introduction**

Inhaled β₂-agonists are used in the treatment of asthma both as rescue medication and as regular prophylaxis. They are divided into two groups: short-acting and long-acting β₂-agonists. Only the short-acting β₂-agonists are recommended to be used as needed for acute symptom relief in patients with mild to more severe asthma (1). The commonly used inhaled short-acting β₂-agonists have a disadvantage in having a duration of bronchodilation of only 4–6 h (2). As the long-acting inhaled β₂-agonists have a duration of action of at least 12 h (3,4), it would be beneficial to asthmatic patients if these drugs also could show an onset of action similar to that of the short-acting inhaled β₂-agonists.

Most of the previous observations on the onset of action of formoterol have been made in comparison with the other long-acting β₂-agonists approved for regular daily use, salmeterol. Salmeterol has been shown to have a slow onset of action, whereas formoterol administered via a pMDI (5) and via Turbuhaler® (6,7) has been shown to have a fast onset of action. One study has compared formoterol administered via a pMDI to the short-acting β₂-agonists salbutamol (8). This study showed that the onset of the bronchodilating action of formoterol was roughly similar to that of salbutamol.

The aim of this study was to investigate the bronchodilating effect within the first 30 min after inhalation of single doses of formoterol administered via the inspiratory flow driven multidose dry powder inhaler Turbuhaler. The delivered doses 4.5 and 9 μg were compared with salbutamol 100 and 200 μg delivered via a pMDI and placebo in adult patients with mild to moderate asthma.

A few studies have also made a comparison between the onset of action of formoterol dry powder (Aerolizer®, Novartis) and salbutamol in adult asthmatics (9–10). In none of these studies a comparison has been made in the same way as in the present day study i.e. measuring FEV₁ already within the first 3 min after inhalation.

**Patients and Methods**

**PATIENTS**

Patients of either gender aged 18 years or older were included. They all had a diagnosis of asthma in a stable...
condition with a minimum duration of 6 months. Only non-smokers or ex-smokers, who had stopped smoking at least 6 months prior to the first visit were to be included. They should have a baseline FEV1 ≥ 40% of predicted normal value and a FEV1 of at least 1·5 l and a reversibility of at least 15%, 15 min after inhalation of 0·5 mg terbutaline sulphate (Bricanyl® Turbuhaler). Patients who showed any signs of clinically relevant concomitant diseases were not included.

Prior to each study day, the patients discontinued inhaled short-acting β2-agonists for 6 h and inhaled ipratropium bromide for 8 h. Disodium cromoglycate, anti-histamines including ketotifen, inhaled and nasal glucocorticosteroids (GCS) were permitted during the study, provided that the doses were kept constant during 4 weeks prior to and throughout the study. Oral β2-agonists, inhaled long-acting β2-agonists, oral GCS, parenteral GCS, xanthines and oral adrenergics were not allowed during the study.

STUDY DESIGN

The study was multi-centred and placebo-controlled with a double-blind, double-dummy and cross-over design. The study consisted of one screening visit and five study visits. At the study visits, eligible patients were given either formoterol 4 mg or 9 mg via Turbuhaler, salbutamol 100 µg or 200 µg via a pMDI or placebo as single doses. On each occasion the patients inhaled one dose from two identical Turbuhaler inhalers and one dose from two pMDIs of the same appearance to preserve the blinding of the study. The doses used in the study are those recommended by the manufacturers for salbutamol pMDI and formoterol Turbuhaler. All four inhalations were performed within 1 min. The inhalations also had to be performed between 07:00 and 10:00 hours and varying at most by 30 min between visits for an individual patient and separated by a minimum of two days washout. Baseline FEV1 had to be within ± 12% of the FEV1 measured at the screening visit. If not, the patients were asked to come back another day. Three such attempts were allowed. The minimum duration of the study was estimated to be 12 days, including a post-study telephone contact for follow-up of adverse events.

Patients were randomized in Latin squares of size five. Stratification was made so that patients with even numbers inhaled from the Turbuhaler first and patients with odd numbers inhaled from the pMDI first. In order to ensure a correct inhalation technique, all patients received instructions on how to use both the Turbuhaler and pMDI at their first visit. At all visits, the patients also practised the inhalation technique with placebo inhalers and all study medication was taken under direct supervision of the investigational team.

The study was approved by the National Health Authorities in the Czech Republic and the local ethics committees. The patients gave their informed consent before enrolment in the study. They showed a mean baseline FEV1 of 2·75 l (range 1·60–5·19 l) at study entry, which corresponded to a mean FEV1 in % of predicted normal

ONSET OF ACTION—BRONCHODILATING EFFECT

For determination of onset of action, FEV1 was measured before and 1, 3, 5, 7, 10, 15, 20, 25 and 30 min after completed inhalation of the investigational products. The higher value out of two measurements, recorded by a Vitalograph® Alpha (Vitalograph Inc., Buckingham, England), was used. All measurements were made with the same spirometer for each patient.

ONSET OF ACTION—SUBJECTIVE EXPERIENCE

To evaluate the onsets of action, as judged by the patients, a question was asked 3 min after inhalation at every study visit. The question was: ‘Was the medication effective?’ The patients were instructed to preferably answer yes or no to the question. If they answered ‘not sure’, ‘don’t know’ etc, the answer was registered as ‘no’.

STATISTICAL METHODS

Onset of action measured as FEV1

The primary variable was the FEV1-value at 3 min after inhalation of study drug. It was compared between treatments by a multiplicative analysis of variance (ANOVA) model with patient, visit and treatment as fixed factors and the pre-dose FEV1 values as a covariate. The time to response, where response was defined as a 15% increase in FEV1 from the pre-inhalation value, was also compared between the active treatments, using survival analysis.

Differences in the time-response profile were investigated with an ANOVA model including patient, visit, treatment, time and interaction treatment by time as factors and the pre-dose FEV1 values as a covariate. In this analysis, only the high dose of each substance was included.

Correlation between FEV1 and the response experienced by the patients 3 min after inhalation

To investigate the correlation between the response measured as FEV1 3 min after drug administration and the answer to the above question, a mixed effects logistic regression model was applied using the General Estimating Equations (GEE) technique.

Results

PATIENTS

Thirty-six Caucasian patients, of whom 16 were women, with a mean age of 34 years (range 18–64 years) participated in the study. They showed a mean baseline FEV1 of 2·75 l (1·60–5·19 l) at study entry, which corresponded to a mean FEV1 in % of predicted normal
values of 73.8% (46–106%). They also exhibited a mean reversibility of 24.2% (14.6–47.1%).

Thirty-two patients were on regular treatment with inhaled GCS, since at least 1 month prior to enrolment. Twenty-six patients had one or more short-acting β₂-agonists, five patients used anti-histamines, two patients nasal GCS, and one patient anti-cholinergics. Twenty-nine patients had never smoked, seven patients were previous smokers. Thirty patients had extrinsic asthma, two intrinsic asthma, one chronic obstructive asthma and three unspecified asthma. The duration of asthma ranged between 1 and 47 years. All 36 patients were enrolled at five different centres in Czech Republic.

ONSET OF ACTION—BRONCHODILATING EFFECT

All enrolled patients completed the study and they were all considered fully eligible.

Figure 1 illustrates the mean value FEV₁ curves, where the FEV₁-values are given as percentage change from baseline.

The FEV₁ value measured 3 min after inhalation revealed no differences between active treatments. All active treatments gave a statistically significantly higher bronchodilating effect than placebo; 10-0, 11-4% for salbutamol 100 and 200 μg and 11-7, 11-8% for formoterol 4-5 and 9 μg, (P<0.001 in all cases). The relative difference vs. placebo remained throughout the 30 min of measurement for all active treatments except low dose salbutamol. A time-trend test including the high dose of formoterol and salbutamol was highly non-significant (P=0.94).

The median time to response ranged between 2.8 min (formoterol 9 μg) and 5.3 min (salbutamol 200 μg). No difference in this parameter between formoterol and salbutamol was found. Results are given in Table 1.

ONSET OF ACTION—SUBJECTIVE EXPERIENCE

The increase in FEV₁ was generally much higher for the patients who answered ‘yes’ to the question 3 min after inhalation of study drug, than for the patients who answered ‘no’. Mean increase in FEV₁ (%) was 18.1 in the ‘yes’ group and 5.6 in the ‘no’ group, as shown in Table 2.

Correlation between FEV₁ and the response experienced by the patients 3 min after inhalation

The estimated line became: Log odds = −0.15 + 0.14* FEV₁.

The individual FEV₁ values are plotted by answer (yes/no) in Fig. 2 together with the model fit. In the figure, a subdivision of the response in FEV₁ is plotted together with the resulting line. The slope was statistically different from 0 (95% CI 0.08–0.21; P<0.001), showing a statistically significant correlation.

Discussion

It is a common opinion that short-acting β₂-agonists are associated with a more rapid onset of action than long-acting β₂-agonists (11). In internationally accepted guidelines, short-acting β₂-agonists are classified as symptom ‘relievers’ and are recommended to be used as needed in patients with mild to more severe asthma or to prevent obstruction induced by exercise or allergen provocation. The long-acting β₂-agonists are only recommended for

<table>
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<th>Treatment</th>
<th>No. of responders</th>
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<tr>
<td></td>
<td></td>
<td>Mean</td>
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<td>Formoterol TBH 4.5 μg</td>
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<td>Formoterol TBH 9 μg</td>
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<td>9.4</td>
</tr>
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<td>11.2</td>
</tr>
<tr>
<td>Salbutamol pMDI 200 μg</td>
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regular use in patients whose symptoms are not controlled with inhaled GCS (1).

In the present study, no differences were found between formoterol and salbutamol regarding the bronchodilating effect 3 min after inhalation and in the time to response. These findings are in line with the results from other studies, in which a comparison regarding the onset of action between formoterol dry powder and salbutamol in adults has been made. However, in these studies increase in FEV₁ from pre- to 5 min post-dose (9) or increase in specific airway conductance (sGaw) (10) have been used. The same results have also been shown in a study evaluating the speeds of action of formoterol and salbutamol dry powder in reversing methacholine-induced bronchoconstriction (12). No other study, that we are aware of, has compared the onset of action between formoterol Turbuhaler and salbutamol pMDI.

The current data thus show that formoterol Turbuhaler has a rapid onset of action, comparable to that of the short-acting β₂-agonist salbutamol, at recommended doses. These data indicate that there is need for a revision of the opinion that short-acting is equal to fast onset and long-acting is equal to slow-acting. Maybe a better classification would be to describe the β₂-agonists as fast- and slow-acting with different duration of action.

The fast onset of action of formoterol via Turbuhaler, as shown in the present and previous studies (6,7) would make it possible to use it as needed for symptom relief in patients with mild to moderate asthma. The use of formoterol Turbuhaler on demand, in patients with moderate asthma, has been evaluated in a recent study (13). In this study, formoterol Turbuhaler prolonged the time to first asthma exacerbation and improved asthma control compared with terbutaline Turbuhaler.

One must also consider that true p.r.n. use of long-acting β₂-agonist could lead to a use of high doses in the case of an acute bronchoconstriction. However the use of high doses of formoterol has been documented in previous studies. One study compared formoterol Turbuhaler to terbutaline Turbuhaler in high doses (14). The results of this study showed that daily doses up to and including 120 μg formoterol (corresponding to 90 μg delivered dose) were safe and well tolerated in patients with chronic asthma and without concomitant ischaemic heart diseases, using

<table>
<thead>
<tr>
<th>Answer</th>
<th>Total No.</th>
<th>responders</th>
<th>non-responders</th>
<th>Mean increase FEV₁ (%)</th>
<th>Range increase FEV₁ (%)</th>
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<td>43</td>
<td>4</td>
<td>39</td>
<td>5.6</td>
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</table>

**Fig. 2.** Correlation between response in FEV₁ after 3 min and the answer to the subjective question.
Regarding the statistical issues.

The data mentioned above together with the data from the present study makes formoterol Turbuhaler a candidate for true p.r.n. use. Further studies where formoterol Turbuhaler is given p.r.n. compared to a short-acting $\beta_2$-agonist given p.r.n., in patients with mild persistent asthma, would therefore be of great interest.

In addition to the objectively measured onset of action, the subjective onset as judged by the patients was evaluated. No other study has compared the correlation between subjective and objective time to onset of action, although one non-placebo-controlled study has made a comparison regarding the duration of effect after inhalation of formoterol and salbutamol. This study indicated a good correlation between subjective and objective duration of effect (16). Data from the current study showed a positive correlation between the subjective and the objective onset of action. Thus, the fast onset of action of formoterol Turbuhaler measured by FEV$_1$ 3 min after inhalation was also experienced by the patients, further indicating that formoterol Turbuhaler given p.r.n. could be appreciated by the patients.

In conclusion we have demonstrated that formoterol administered via Turbuhaler at recommended doses, has as rapid an onset of action as salbutamol administered via pMDI at recommended doses.

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**References**


