Comparison between formoterol 12 µg b.i.d. and on-demand salbutamol in moderate persistent asthma

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IN ASSOCIATION WITH THE FRENCH FOR-F-01 STUDY GROUP

Inhalation of on-demand salbutamol (ODS) several times daily is sometimes the only β2-agonist prescribed in moderate persistent asthma, whereas a long-acting β2-agonist should be added. This trial aimed to compare the efficacy of formoterol dry-powder capsule 12 µg b.i.d. (Foradil®) and ODS in patients with moderate persistent asthma treated with inhaled corticosteroids, in the conditions of real practice. Two hundred and fifty-nine patients were randomized (formoterol; 130; ODS: 129) in this open, parallel-group trial. The mean increases in morning peak expiratory flow (PEF primary variable) and evening PEF over the 3-month treatment period were statistically significantly higher with formoterol: +25.7 and +24.11 min⁻¹, respectively vs. +4.5 and +0.51 min⁻¹ respectively with ODS. The increase in FEV₁ was statistically significantly higher with formoterol at months 1 and 3. Formoterol reduced the use of salbutamol as rescue medication by two-thirds. The percentages of symptom-free days and nights statistically significantly increased with formoterol (+20% and +33% respectively), but did not significantly change with ODS. Clinically relevant and statistically significant improvement in the mean total score of the St George’s Hospital Respiratory Questionnaire was observed in the formoterol group. Adverse events were similar in the two groups. The results show that treatment with formoterol has significant advantages over ODS in patients with moderate persistent asthma.

Key words: asthma; β2-agonists; formoterol; salbutamol; inhalation therapy; efficacy.


Introduction

Formoterol is a long-acting β2-agonist bronchodilator available as dry-powder capsules containing 12 µg of formoterol fumarate administered via a single dose breath-actuated inhaler (1). It is mainly used in patients presenting with moderate or severe persistent asthma [according to the classification of the Global Initiative for Asthma (2)] not optimally controlled with inhaled corticosteroids, i.e. in case of persistent symptoms or in patients with nocturnal symptoms or using too many puffs of short-acting β2-agonists (3). Conversely to long-acting β2-agonists, the use of short-acting β2-agonists at a fixed dosage is not recommended (2), because this has no advantage compared with use on an as-needed basis (4,5). On-demand short-acting β2-agonists such as salbutamol are usually the only β2-agonists used for the treatment of intermittent asthma and mild persistent asthma.

The use of long-acting β2-agonists is not questioned in patients with severe persistent asthma. In patients with moderate persistent asthma, on-demand short-acting β2-agonists are sometimes only prescribed whereas long-acting β2-agonists are recommended to be introduced.

Formoterol has never been directly compared with a short-acting β2-agonist given on an on-demand basis, but with salbutamol given at a fixed dosage of 200 µg or 400 µg two or four times daily (6–11), or indirectly during trials comparing formoterol with a placebo matched to formoterol in combination with on-demand salbutamol (11,12). However, in this case, results may not be strictly extrapolated because of the possible interference of the placebo effect.

The aim of this pragmatic study was to directly assess the efficacy and the safety of formoterol given at the standard dosage of 12 µg twice daily vs. on-demand (ODS) salbutamol given in patients with a moderate persistent asthma.

Methods

STUDY POPULATION

Male and female outpatients aged 18 years or over with moderate persistent asthma were eligible for inclusion.
These patients had to take daily treatment with an inhaled corticosteroid (the same product at a stable dose for at least 1 month prior to the first visit) and require daily treatment with inhaled bronchodilators (taken regularly or on-demand). The inhaled corticosteroid was kept at a constant dose throughout the trial, up to the maximal daily dose permitted in moderate persistent asthma (i.e. 1000 μg of beclomethasone, 800 μg of budesonide, 500 μg of fluticasone). However in case of asthma exacerbation, a transient increase in the daily dose of the inhaled corticosteroid therapy, a course of oral corticosteroid therapy or a symptomatic β2-agonist nebulizer therapy were allowed. Asthma was defined according to the criteria of the American Thoracic Society (13). The FEV1 had to be superior or equal to 60% of the predicted normal value for the patient. Reversibility test (increase in FEV1 ≥ 10% of the predicted value) had to be documented at the first visit or within 3 months prior to this visit. Patients had to refrain from taking salbutamol 6 h before each spirometry.

The patients were excluded if they presented one of the following criteria: known hypersensitivity to sympathic amine or to lactose; pregnancy or breast-feeding; women of childbearing potential who did not use a reliable contraceptive method; significant change in the regular asthma medication, asthma exacerbation or respiratory tract infection in the month prior to the first visit; incapacity to use a metered-dose inhaler correctly or to complete the patient diary. Concomitant treatments with theophylline, anticholinergic bronchodilators and inhaled or oral β2-agonists other than the trial medications were not allowed.

**STUDY DESIGN**

This multicentre study was performed by 42 specialists in France, from February 1998 to March 1999, as a randomized, open, parallel-group trial in two groups of asthmatic patients who were treated for 3 months with either one dry-powder capsule containing 12 μg of formoterol fumarate every morning and evening (Foradil®; Novartis Pharma S.A) with salbutamol as rescue medication, or ODS via a metered-dose inhaler (100 μg puff−1). The trial had two periods. The first period was a 2- to 3-week run-in, baseline period during which all patients received ODS. The second period was a 3-month treatment period in which patients were assigned at random to one of the two treatment groups. Centralized phone randomization was used to avoid inclusion bias. Patients underwent five visits during the trial: one at the start of study (visit 1), a randomization visit (visit 2), then three monthly visits during treatment (visits 3, 4 and 5). An Ethics Committee approved the study protocol and all participants gave their written consent.

**CLINICAL ASSESSMENTS**

Patients completed a diary card twice daily throughout the whole trial. The following data were recorded: pre-dose peak expiratory flow (PEF) (morning and evening) using a mini-Wright peak flow meter; night-time asthma symptom score (0=no breathing problems; 1=one waking up because of breathing problems, but no use of rescue medication; 2=one waking up because of breathing problems, controlled by rescue medication; 3=more than one waking up because of breathing problems, controlled by rescue medication; 4=difficult sleep because of breathing problems, despite use of rescue medication; daytime asthma symptom score (0=no breathing problems at all, activity not restricted; 1=breathing problems with little or no discomfort, and no activity restriction; 2=breathing problems with some discomfort and limitation of strenuous activity; 3=breathing problems with discomfort and limitation of routine activity; 4=breathing problems at rest with major discomfort and limitation of routine activity); number of inhalations of rescue medication (salbutamol) used during the night and during the day.

A spirometry was performed at each visit before the morning dose of trial medication and the best of three determinations of FEV1 was recorded.

The St George’s Hospital Respiratory Questionnaire (SGRQ) was used to measure quality of life. The SGRQ was self-administered by the patient at the investigator’s site at visits 2 (baseline) and 5 (after 3 months). The total score was calculated, just as the three sub-scores: ‘Activity’ (assessing the effects of breathlessness on mobility and physical activity), ‘impacts’ (assessing the psychosocial impact of disease), ‘Symptoms’ (assessing distress due to respiratory symptoms). A change of 4 units was considered to be clinically relevant (14,15).

The safety of the treatments was assessed by measuring the vital signs (heart rate and blood pressure) before each spirometry, and by recording adverse experiences (AE) (nature, severity and causal relationship), as well as reasons for premature treatment discontinuations.

**STATISTICAL ANALYSIS**

Data processing and statistical analyses were performed using SAS under Windows release 6.12. The primary efficacy variable was the mean change in morning predose PEF for the entire treatment period. The calculation of the minimum sample size required for the study was based on this variable. Assuming an upper limit for the true standard deviation of mean morning PEF of 50 l min−1 and the use of a two-sided significance test at the 5% level, then a total of 198 patients (99 per treatment) would have given the study a power of 80% to detect a difference of 20 l min−1 between formoterol and ODS. Secondary efficacy endpoints included mean increase in evening predose PEF for the entire treatment period, mean morning and evening predose PEF averaged 1-monthly, changes in morning predose FEV1 at visits 3, 4 and 5, day- and night-time use of salbutamol, day- and night-time symptom scores and SGRQ scores.

The analyses were carried out in the intent-to-treat population, i.e. in all randomized patients with a post-baseline efficacy measurement. Peak expiratory flow, use of salbutamol and symptom scores were analysed by analysis
of covariance (ANCOVA) with treatment, centre and sex as factors, and with the baseline value (run-in average) as a covariate. For the primary variable (morning predose PEF for the entire treatment period), treatment-by-centre, treatment-by-baseline and treatment-by-sex interactions were also tested. The same ANCOVA model as specified above (without interactions) was used for predose FEV₁ and vital signs.

Results

A total of 266 patients were screened, of whom 259 were randomized at visit 2. Of the seven patients who discontinued before the randomization, three failed to fulfill the selection criteria, two withdrew their consent and two were lost to follow-up. Thirty patients withdrew from the study prematurely after the randomization (formoterol, 12; ODS, 18). The reasons for these premature discontinuations were lost to follow-up (formoterol, five; ODS, seven), adverse events (formoterol, three; ODS, three), withdrawal of consent (formoterol, one; ODS, two), not meeting protocol criteria (formoterol, one; ODS, three), unsatisfactory therapeutic effect (formoterol, 0; ODS; three) and administrative problems (formoterol, two; ODS, 0). Six patients were excluded from the intent-to-treat efficacy analysis because of the absence of efficacy data. The two treatment groups were similar with respect to demographics, asthma history and lung function (Table 1).

LUNG FUNCTION

The mean increase (± SD) in morning PEF over the 3 months was significantly higher in the formoterol group than in the ODS group: +25.7 (± 36.5) l min⁻¹ and +4.5 (± 32.7) l min⁻¹ respectively (P < 0.0001). Formoterol also induced a significantly higher mean increase in evening predose PEF: +24.1 (± 35.3) l min⁻¹ and +0.5 (± 31.5) l min⁻¹ respectively (P < 0.0001). The mean changes in morning and evening PEF compared with baseline values are shown in Fig. 1.

![Graph showing mean changes from baseline in morning and evening peak expiratory flow (PEF)](image)

**Table 1. Patient demographics, asthma duration, baseline lung function**

<table>
<thead>
<tr>
<th></th>
<th>Formoterol (n=130)</th>
<th>On-demand salbutamol (n=129)</th>
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<tbody>
<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Mean age ± SD (years)</td>
<td>38.5 ± 14.9</td>
<td>39.5 ± 15.0</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>76:54</td>
<td>71:58</td>
</tr>
<tr>
<td>Mean height ± SD (cm)</td>
<td>167.3 ± 9.5</td>
<td>167.3 ± 9.6</td>
</tr>
<tr>
<td>Mean weight ± SD (kg)</td>
<td>67.3 ± 15.1</td>
<td>67.0 ± 11.8</td>
</tr>
<tr>
<td>Smoking status: n(%)</td>
<td></td>
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<tr>
<td>Never</td>
<td>91 (70)</td>
<td>88 (68)</td>
</tr>
<tr>
<td>Past</td>
<td>20 (15)</td>
<td>23 (18)</td>
</tr>
<tr>
<td>Current</td>
<td>19 (15)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Mean asthma duration ± SD (years)</td>
<td>14.7 ± 13.0</td>
<td>15.1 ± 11.5</td>
</tr>
<tr>
<td>Baseline lung function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean FEV₁ ± SD (% of predicted value)</td>
<td>72.7 ± 10.0</td>
<td>73.7 ± 9.4</td>
</tr>
<tr>
<td>Mean PEF ± SD (l min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>387.4 ± 108.2</td>
<td>396.2 ± 85.0</td>
</tr>
<tr>
<td>Evening</td>
<td>399.1 ± 111.0</td>
<td>406.0 ± 89.0</td>
</tr>
<tr>
<td>Mean reversibility ± SD (% of predicted FEV₁)</td>
<td>15.1 ± 5.6</td>
<td>15.8 ± 7.8</td>
</tr>
</tbody>
</table>
Improvement in predose FEV₁ was significantly greater with formoterol at visits 3 and 5 (P<0.01 and P<0.05, respectively). The mean changes in FEV₁ compared with baseline values are shown in Fig. 2.

SALBUTAMOL USE

Over the 3 months, the mean (±SD) number of puffs of salbutamol during the day decreased from 1·2 (±1·46) to 0·4 (±0·65) in the formoterol group and increased from 1·0 (±1·24) to 1·1 (±1·29) in the ODS group. Similarly, the mean (±SD) number of puffs of salbutamol during the night changed from 0·7 (±0·85) to 0·2 (±0·46) and from 0·5 (±0·76) to 0·7 (±0·88), respectively.

The mean (±SD) changes from baseline in the number of puffs of salbutamol during day and night respectively, were −0·8 (±1·32) and −0·4 (±0·72) with formoterol, and +0·1 (±0·85) and +0·1 (±0·69) with ODS (P<0·0001 for day and night).

The percentages of days and nights with no puff of salbutamol are shown in Fig. 3 and the rescue use patterns in Fig. 4.

During the run-in period, 91% of the patients used salbutamol at least once in the formoterol group and 85% in the ODS group. Of these patients, 54% of the formoterol patients and 20% of the ODS patients did not use salbutamol throughout the 3-month treatment period or used it less than once monthly. Conversely, 45% of the ODS patients used salbutamol daily or at least once a week compared with only 15% of the patients in the formoterol group.

ASTHMA SYMPTOM SCORES

The mean (±SD) baseline daytime symptom score was 0·7 (±0·66) in the formoterol group and 0·6 (±0·66) in the ODS group. Over the 3-month treatment period, the mean decrease in this score was significantly higher with formoterol (−0·3±0·48) than with ODS (−0·1±0·43) (P<0·0001). Similar changes were observed in night-time symptom scores (baseline values: 0·5±0·54 and 0·3±0·54, changes vs. baseline: −0·1±0·43 and 0·0±0·35, respectively) (P<0·0001).

Over the 3 months, the increase in the mean (±SD) percentage of symptom-free days was significantly higher in the formoterol group (from 53·5±38·2% to 71·3±35·0%, i.e. a 20% increase in symptom-free days) than in the ODS group (from 56·8±38·2% to 63·4±36·0%) (P<0·0001). The respective values of the mean (±SD) percentages of symptom-free nights were 68·2 ± 33·8% to 81·7 ± 28·4% (i.e. a 33% increase in symptom-free nights) and 78·0 ± 30·0% to 76·4 ± 29·7% (P=0·003).
QUALITY OF LIFE

After 3 months, the mean decreases in the SGRQ total score and in the ‘activity’ and ‘symptoms’ sub-scores statistically significantly exceeded the threshold for a clinically relevant change in the formoterol group. The mean decrease in the total SGRQ score was significantly higher with formoterol ($-6.4 \pm 10.0$) than with ODS ($-3.5 \pm 13.7$) ($P=0.05$). The changes in the mean sub- and total SGRQ scores are shown in Fig. 5.

SAFETY

At least one AE was reported by 47 (36%) and 46 (36%) of the formoterol and ODS patients, respectively. Five patients of the formoterol group (4%) and four patients of the ODS group (3%) presented at least one drug-related AE with no relevant differences between the two groups. Drug-related AE induced premature withdrawal of the treatment in two patients (2%) of the formoterol group and in three patients (2%) of the ODS group. Bronchitis or asthma worsening was reported in 17 patients (13%) and 20 patients (15%), respectively. No drug-related serious AE was reported. No clinically relevant changes in heart rate or blood pressure were observed in any group throughout the study.

Discussion

Although a treatment with a long-acting bronchodilator is recommended in patients with moderate persistent asthma in addition to inhaled corticosteroids (2), some physicians are reluctant about a continuous treatment with a long-acting $\beta_2$-agonist and prefer to limit the bronchodilator therapy to a short-acting $\beta_2$-agonist used on an on-demand basis. The causes for the reticence about regular use of a long-acting $\beta_2$-agonist are various (safety, tolerance, loss of asthma control, etc.) (16,17), despite the fact they have never been demonstrated in large clinical studies. The results of this study demonstrate that, in patients with a moderate persistent asthma, the addition of formoterol 12 $\mu g$ b.i.d. to treatment with inhaled corticosteroid and ODS, reduces use of salbutamol, asthma symptoms and improves lung function and quality of life.

Reduction in short-acting $\beta_2$-agonist use is balanced by the use of a long-acting $\beta_2$-agonist so that the overall $\beta_2$-agonist consumption is not reduced by addition of formoterol. However, as opposed to on-demand inhalation of salbutamol, use of formoterol may be scheduled only in the morning and evening, making it more convenient. The time of requirement of on-demand therapy is not predictable. Consequently patients with only on-demand salbutamol therapy take their treatment frequently and only when dyspnoea is present. More than the absolute $\beta_2$-agonist consumption, the frequency of rescue medication requirement is one of the major handicaps for patients. So 54% of patients in the formoterol group vs. 20% of patients in the ODS group had to take rescue salbutamol less than once a month, allowing a quite normal life. This contributes to the clinically significant improvement in quality of life observed in the formoterol group. The reduction in rescue medication requirement observed with formoterol may be partly explained by a protective effect of formoterol. Indeed, ODS treatment being taken after the beginning of chest discomfort has no protective effect whereas a sustained bronchoprotective effect over a 6-month period has been demonstrated for formoterol (12). Subsequently Fitzgerald et al. demonstrated a reduction in the exacerbation rate in the formoterol group compared to the salbutamol group in agreement with the reduction in the exacerbation rate observed with formoterol in the FACET study (18). The pattern of exacerbation was however no different with or without formoterol (19), confirming the lack of interaction of formoterol on rescue medication observed on human bronchi (20).

To the authors’, knowledge, this is the first study in which formoterol has been compared with ODS only and not with ODS in combination with a placebo matched to formoterol. The open design of the study made this comparison possible. Whereas the improvements in lung function, symptom scores and salbutamol use observed with formoterol are similar to those presented in previously published studies (11,12,21,22), the results observed with the ODS confirm the elimination of the placebo effect. In a double-blind study comparing formoterol with ODS plus placebo matched to formoterol, the reduction in salbutamol use during the entire treatment period was 60% with formoterol and 27% with ODS, i.e. almost half the effect of formoterol (12). In the present study no change in salbutamol use was found in the ODS group throughout the 3-month treatment period. Comparable results in symptom scores suggest the existence of a significant placebo effect for these criteria of asthma control.

The improvement in quality of life observed in the formoterol group at the end of this 3-month study complement the traditional indicators of asthma efficacy. A significant improvement in the total score of the St George’s Hospital Respiratory Questionnaire has already
been found after longer treatment with formoterol (6 months) (23).
In conclusion, this study carried out in the conditions of real practice shows that adding formoterol to treatment in patients with moderate persistent asthma treated with ODS and inhaled corticosteroid, results in improved lung function, reduced symptoms and rescue salbutamol use, and an improved quality of life.

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