A 6-month comparison between formoterol and salmeterol in patients with reversible obstructive airways disease

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The aim of this randomized, open, parallel group study was to compare the clinical efficacy of formoterol dry powder capsule 12 µg b.i.d. and salmeterol dry powder 50 µg b.i.d. in the treatment of patients with reversible obstructive airways disease. The 6-month treatment was preceded by a 2 week run-in period. Morning pre-dose peak expiratory flow (PEF) during the last 7 days of treatment was the primary variable. Throughout the study, patients recorded morning and evening pre-dose PEF, use of rescue medication, respiratory symptoms and adverse events. Clinic visits were scheduled at monthly intervals. Of the 482 patients randomized (equal numbers in the two treatment groups), 428 completed the study. Four hundred and twenty-five patients were included in the efficacy analysis for the primary variable.

For mean morning pre-dose PEF during the last 7 days of treatment, the 95% confidence interval (CI) for the treatment contrast formoterol minus salmeterol was included entirely in the predefined range of equivalence (CI limits = -8.69, +9.84 l min⁻¹). This was also the case for the morning PEF during the last week before each clinic visit. For mean evening pre-dose PEF, the estimated treatment contrasts showed a trend towards superiority of formoterol over salmeterol, which became statistically significant at 2, 3 and 4 months (P < 0.05; estimated contrasts 7.27, 10.45 and 10.51 l min⁻¹, respectively). No treatment group differences were found in use of rescue medication and respiratory symptom scores. The incidence of adverse events was similar in the two groups.

These findings demonstrate that formoterol 12 µg b.i.d. and salmeterol 50 µg b.i.d., both formulated as dry powders, have similar long-term efficacy and safety profiles in patients with reversible obstructive airways disease.

Introduction

β₂ agonists continue to be a cornerstone in the treatment of bronchial asthma. These agents are the most effective drugs available for the relief of acute asthma symptoms (1). Until recently, their therapeutic usefulness was limited by a relatively short duration of action, necessitating frequent administration and resulting in insufficient protection against, for example, nocturnal asthma.

Formoterol and salmeterol are the first drugs of a new generation of long-acting β₂-agonists (2). Both compounds, when administered as an aerosol by a metered dose inhaler (MDI) or when inhaled as a powder, induce symptomatic relief of wheezing and breathlessness, with a duration of action of at least 12 h. Whereas short-acting β₂-agonists have been recommended for use only as a relief medication, inhaled long-acting β₂-adrenoceptor agonists are usually prescribed for regular use in patients with asthma who are still symptomatic while receiving inhaled corticosteroid therapy. In these patients, clinical studies have indicated that chronic treatment with long-acting β₂-agonists improves symptom score, decreases nocturnal asthma, improves lung function, and decreases the use of short acting inhaled β₂-agonists (3-6).
In vitro comparative studies have shown evidence of differences between formoterol and salmeterol with respect to onset and duration of action and dose-dependency of effects (7). At the present time, four comparative single-dose studies have been published as full papers, two in patients with bronchial asthma (8,9) and two in patients with chronic obstructive pulmonary disease (COPD) (10,11). A direct comparison of efficacy and safety during long-term treatment is still lacking.

We conducted a multinational, randomized, open study using a population of patients with reversible obstructive airways disease who could benefit from the use of regular inhaled long-acting $\beta_2$-agonists. We compared the clinical efficacy and safety of 6-month treatment with either formoterol dry powder capsule 12 $\mu$g twice daily or salmeterol dry powder 50 $\mu$g twice daily.

**Methods**

**STUDY SUBJECTS**

Out-patients suffering from moderate-to-severe reversible obstructive airways disease were entered into the study. Patients were of both sexes, aged 18 years or older. Patients were required to have had a documented diagnosis of reversible obstructive airways disease for 1 yr or more and to be using regular inhaled corticosteroids at a constant dose of at least 400 $\mu$g day$^{-1}$ (or 200 $\mu$g day$^{-1}$ fluticasone) for at least 1 month before inclusion. Patients were excluded from participation if they had evidence of other clinically relevant diseases. Pregnant or lactating women were also excluded. Patients on $\beta$-blocker therapy or with hypersensitivity to sympathomimetic amines or inhaled lactose were excluded, as were those who were considered unable to comply with the study protocol. Inhaled corticosteroids were continued at a constant dose throughout the study.

Although the vast majority of patients selected according to the above inclusion criteria would have been patients with bronchial asthma, no attempt was made to exclude (or differentiate) patients with COPD, as long as bronchial reversibility had been demonstrated. This was done in order to obtain a sample which was representative of the patient population receiving inhaled long-acting $\beta_2$-agonists in daily clinical practice.

**STUDY DESIGN**

The trial was a randomized, parallel group, open study. A total of 41 centres, in France, Italy, Spain, Sweden, Switzerland and the U.K., participated. Following a 2 week run-in period, when patients recorded baseline symptoms, use of rescue medication (salbutamol MDI 100 $\mu$g puff$^{-1}$ or salbutamol dry powder 200 $\mu$g dose$^{-1}$) and twice daily peak expiratory flow (PEF) measurements, patients who, according to the investigator(s), could benefit from the regular use of a long-acting $\beta_2$-agonist were allocated to 6 months of twice daily treatment with 12 $\mu$g formoterol dry powder (FORADIL®) administered via the Aerolizer® or 50 $\mu$g salmeterol dry powder (SEREVENT® DISKHALER®). A computer-generated randomization scheme was used to provide balanced blocks of patient numbers for the two treatment groups within each country. A one-to-one treatment allocation and a block size of eight were used. No formal checks of patient compliance with dosing regimens were made.

**METHODS**

At home, using a mini-Wright peak flow meter, patients measured their PEF at about 12 h intervals, in the morning (6 to 9 a.m.) and evening (6 to 9 p.m.). PEF measurements (highest of three consecutive measurements) had to be performed before intake of trial medication and the values entered in diary cards. Patients were asked not to take rescue medication 6 h prior to the PEF measurements. If rescue medication was used, this was noted in the diary card. In addition, respiratory symptoms and adverse events were recorded. Day- and night-time respiratory symptoms were scored on a five grade scale (0=best to 4=worst). Patients visited the clinic before and after the run-in period and every 4th week of the treatment period. At each clinic visit, medication were reviewed and diary cards were collected. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice and was approved by the Ethics Committees of the participating centres. Signed informed consent was obtained from all patients before recruitment.

**ANALYSIS**

The primary variable was the mean morning pre-dose PEF during the last 7 days of treatment and the minimum sample size required for the study was determined in relation to its statistical power to detect treatment differences in mean PEF. Assuming an upper limit for the true standard deviation of mean morning PEF of 48 l min$^{-1}$ and the use of two-sided significance test at the 5% level, then a total of 180 evaluable patients (90 per treatment) would have given the study a power of 80% to detect mean differences in PEF of approximately 20 l min$^{-1}$. The sample size was then doubled in order to allow meaningful comparisons in a concomitant assessment of quality of life (manuscript in preparation). Secondary end-points included mean morning and evening pre-dose PEF during the last week before each clinic visit, overall mean morning and evening pre-dose PEF for the entire treatment period, day- and night-time use of rescue medication, and day- and night-time symptom scores.

The primary efficacy variable and the corresponding variable derived from the evening pre-dose PEF were analysed for the population of patient completing the entire treatment period. All other efficacy variables were analysed for those patients who received at least one dose of trial medication and who had at least one measurement during the treatment period. All randomized patients who received at least one dose of trial medication were included in the safety analysis. Tests for baseline homogeneity of treatment...
Table 1. Summary of demographic and baseline data

<table>
<thead>
<tr>
<th></th>
<th>Formoterol (n=241)</th>
<th>Salmeterol (n=241)</th>
<th>Total (n=482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (range)</td>
<td>48 (18–78)</td>
<td>47 (18–77)</td>
<td>48 (18–78)</td>
</tr>
<tr>
<td>Sex (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>108 (45)</td>
<td>113 (47)</td>
<td>221 (46)</td>
</tr>
<tr>
<td>Females</td>
<td>133 (55)</td>
<td>128 (53)</td>
<td>261 (54)</td>
</tr>
<tr>
<td>Smoking history (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>36 (14-9)</td>
<td>38 (15-8)</td>
<td>74 (15-4)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>70 (29-0)</td>
<td>77 (32-0)</td>
<td>147 (30-5)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>135 (56-0)</td>
<td>126 (52-3)</td>
<td>261 (54-1)</td>
</tr>
<tr>
<td>Duration of obstructive airways disease (years) Mean (range)</td>
<td>15.8 (1.1–54.0)</td>
<td>16.3 (0.7–64.0)</td>
<td>16.0 (0.7–63.0)</td>
</tr>
<tr>
<td>Morning PEF (1 min⁻¹) Mean (range)</td>
<td>377 (110–670)</td>
<td>371 (89–749)</td>
<td>374 (89–749)</td>
</tr>
<tr>
<td>Evening PEF (1 min⁻¹) Mean (range)</td>
<td>388 (97–744)</td>
<td>384 (149–800)</td>
<td>386 (97–800)</td>
</tr>
<tr>
<td>Day-time intake of rescue medication (number of puffs)* Mean (range)</td>
<td>2.1 (0–17-6)</td>
<td>1.9 (0–15-1)</td>
<td>2.0 (0–17-6)</td>
</tr>
<tr>
<td>Night-time intake of rescue medication (number of puffs)* Mean (range)</td>
<td>1.2 (0-10-9)</td>
<td>1.1 (0-10-9)</td>
<td>1.2 (0 10-9)</td>
</tr>
<tr>
<td>Day-time symptom score* Mean (range)</td>
<td>0.9 (0-40)</td>
<td>0.8 (0-37)</td>
<td>0.9 (0-40)</td>
</tr>
<tr>
<td>Night-time symptom score* Mean (range)</td>
<td>0.6 (0-40)</td>
<td>0.5 (0-30)</td>
<td>0.6 (0-40)</td>
</tr>
</tbody>
</table>

*Mean of the last seven days of the 2-week run-in phase.

groups were not performed. Instead, treatment group differences at baseline were adjusted for by including appropriate variables in the statistical model.

The primary efficacy variable was analysed by means of an analysis of covariance (ANCOVA) with fixed effects for treatment, country, centre within country and sex, and with the baseline value (last 7 days before the randomization visit) as a covariate. The treatment comparison was assessed by constructing, based on the ANCOVA, a two-sided 95% confidence interval (CI) for the contrast formoterol minus salmeterol. Equivalence was meant one-sided with a limit of 20 1 min⁻¹. Treatment equivalence would therefore have been demonstrated if the CI for the contrast formoterol minus salmeterol laid entirely above the –20 1 min⁻¹ value, i.e. if the mean morning pre-dose PEF during the last 7 days of treatment in the formoterol group was at most 20 1 min⁻¹ lower than in the salmeterol group. To account for the possible effect of the intake of rescue medication, a secondary exploratory analysis was performed, where all measurements for which an intake of rescue medication within the previous 6 h had been recorded were excluded. All other efficacy variables related to PEF were analysed in the same way as the primary variable. Differences in use of rescue medication were analysed with the van Elteren test (12) stratified for centre and, additionally, with the same ANCOVA model as the primary efficacy variable. Mean symptom scores were analysed with the van Elteren test stratified for centre.

Results

PATIENTS

This multicentre study enrolled 529 patients. Forty-seven patients were not randomized; the most frequent reasons were failure to meet the inclusion criteria (17 patients), non-compliance with study procedures (eight patients) and withdrawal of consent (eight patients). Thus, 482 patients were randomized to treatment.

Two hundred and forty-one patients were randomized to receive formoterol 12 μg b.i.d. and the same number to receive salmeterol 50 μg b.i.d. The groups were well-matched for demographical details. Patients' baseline characteristics are described in Table 1. Approximately 80% of patients used salbutamol MDI as rescue medication. There were no significant differences in terms of use of concomitant medications, including inhaled corticosteroids, between the two treatment groups.

Twenty-four patients from the formoterol group and 30 patients from the salmeterol group were withdrawn after randomization. Of these, 26 patients were withdrawn because of adverse events, five because of unsatisfactory
therapeutic effect, one for not meeting the protocol criteria, eight for non-compliance, six for withdrawal of consent, two because of administrative problems and six were lost to follow-up. There were no differences between treatment groups in the pattern of reasons for premature discontinuation of trial medication.

The efficacy primary end-point could be analysed for 425 of the 428 patients completing the study, since for three patients no PEF measurements were available in the diary for the last 7 days of treatment. All 482 patients who used the study medication were included in the safety analysis.

PEF MEASUREMENTS

The mean values for the run-in and treatment periods in morning and evening pre-dose PEF are presented in Fig. 1.

For the primary efficacy end-point, mean morning pre-dose PEF during the last 7 days of treatment, the 95% CI for the treatment contrast formoterol minus salmeterol was \(-8.69, +9.84\, \text{min}^{-1}\) and was included entirely in the pre-defined range of equivalence (Fig. 2). This was also the case for mean morning pre-dose PEF during the last week before each clinic visit. The analysis excluding measurement after intake of rescue medication essentially confirmed the primary analysis.

For mean evening pre-dose PEF, the estimated treatment contrasts showed a trend towards superiority of formoterol over salmeterol, which became statistically significant at 2, 3 and 4 months (\(P<0.05\), estimated contrasts 7.27, 10.45 and 10.51 \text{min}^{-1}, respectively) (Fig. 2). Also in this case, the analysis excluding measurements after an intake of rescue medication led to similar results.

USE OF RESCUE MEDICATION

At all visits, mean intake of rescue medication was found to be less than half of the baseline value for both treatment groups (Fig. 3). This was seen both at day- and night-time. No statistically significant difference between the two treatment groups was seen at any visit.

RESPIRATORY SYMPTOM SCORE

Mean symptom scores improved in both treatment groups in a similar way (Fig. 4). The percentage of days with a symptom score\(=0\) increased in both treatment groups by about the same extent. The symptom score improvements were similar for both day- and night-time periods. There was no statistically significant treatment group difference at any examination.
SAFETY

Both treatments were safe and well tolerated. Although adverse events were reported by 190 (79%) patients in the formoterol group and 193 (80%) patients in the salmeterol group, this is not unexpected in a trial of 6 month duration. No treatment group differences were seen. Most frequent adverse events included viral infection, asthma exacerbation, headache, rhinitis and chest infection. Exacerbation of asthma was reported as an adverse event by 41 patients (17%) in the formoterol group and 54 patients (22%) in the salmeterol group.

When considering only adverse events which were assessed by the investigator as possibly/probably trial drug-related, events were reported in 32 (13%) patients who received formoterol and 21 (9%) patients who received salmeterol. The most frequent possibly/probably trial drug-related adverse event was headache (seven patients in the formoterol group and 11 in the salmeterol group). Other possibly/probably trial drug-related adverse events included tremor (seven patients, five with formoterol and two with salmeterol), asthma exacerbation (eight patients, four in each group) and palpitations (four patients, all of them in the formoterol group).

Discussion

To our knowledge, this is the first study in which the long-term effects of formoterol and salmeterol on lung function and symptom control have been directly compared. In this mixed population of patients with reversible airways obstruction, which is likely to be representative of patients receiving inhaled long-acting &adrenoceptor agonists in clinical practice, formoterol dry powder capsule 12 &micro;g b.i.d. and salmeterol dry powder 50 &micro;g b.i.d. were equally effective in terms of PEF values and symptom control.

This was an open-label trial. The use of a double-dummy design would have been necessary to achieve double-binding. This would have added to the already fairly onerous long-term trial schedule. The use of an open design is unlikely, however, to have introduced significant bias. The patient information document merely stated that the two treatments would be compared, without indicating that formoterol was a newer medication. In addition, the main efficacy variable was derived from objective measurements (PEF).

In vitro studies have shown that formoterol is a more potent &beta;2-adrenoceptor agonist and has a faster onset of action than salmeterol, but that the duration of action is longer for salmeterol (7). In addition, the in vitro duration of action of formoterol, but not of salmeterol, was found to be dose-dependent.

There have been a number of studies comparing the effects of single doses of formoterol and salmeterol on airway tone. Rabe and co-workers found that 12 &micro;g formoterol and 50 &micro;g of salmeterol were equally effective in mild asthmatics in protecting against methacholine-induced bronchoconstriction for up to 24 h (8). In a study published as an abstract by Zellweger and colleagues, 50 &micro;g salmeterol
and 24 µg formoterol produced comparable protection against methacholine-induced bronchoconstriction during at least 16 h (13). Cazzola and co-workers compared the effects of 50 µg salmeterol and 24 µg formoterol in 16 patients with COPD and concluded that both compounds were equivalent in terms of maximum bronchodilatation and duration of action (10). However, in a second study in 12 patients with COPD, the same authors reported that 50 µg salmeterol had a longer duration of action than 12 or 24 µg formoterol (11), in contrast with their own previous findings. In a preliminary report on six patients with mild asthma, Dal Negro's group has shown that formoterol 24 µg and salmeterol 50 µg, but not formoterol 12 µg, protected against methacholine-induced bronchoconstriction for 12 h (14). In contrast, another preliminary report has claimed a longer duration of action of 12 µg formoterol over 50 µg salmeterol in nine patients with partially reversible COPD (15). Recently, van Noord and co-workers have compared single doses of formoterol 24 µg, salmeterol 50 µg and salbutamol 200 µg and have concluded that, in patients with moderately severe asthma, formoterol and salmeterol had an equal bronchodilatory capacity, which lasted for at least 12 h and that formoterol had a more rapid onset of action than salmeterol, equal to that of salbutamol (9). However, the clinical significance of the study was hampered by the lack of a formoterol 12 µg arm, which is the dose of formoterol recommended in the vast majority of patients (16).

During recent years, several guidelines for asthma and COPD treatments have been published. Although the role of inhaled long-acting β₂-agonists in the management of COPD patients remains to be determined (17), asthma guidelines agreed that regular bronchodilator drug use should be recommended when asthma symptoms and functional abnormalities are not completely controlled by regular use of inhaled corticosteroids (1). One of the issues to address is, therefore, the choice between formoterol and salmeterol.

Our study in a large number of patients with reversible airways obstruction demonstrates that, during 6 months of treatment, formoterol 12 µg b.i.d. and salmeterol 50 µg b.i.d. have similar clinical efficacy in terms of morning PEF, use of rescue medication and symptom score. This suggests that the in vitro longer duration of action of salmeterol does not have clinical relevance. A surprising result of the present study was the trend towards superiority of formoterol over salmeterol in terms of evening PEF, which became statistically significant at 2, 3 and 4 months. Further studies, including assessment of patients' compliance, are needed to investigate the reasons for this finding.

In conclusion, our study demonstrates that formoterol dry powder capsule 12 µg b.i.d. and salmeterol powder 50 µg b.i.d. are equally effective in controlling lung function and symptoms in patients with reversible airways disease who take regular inhaled steroids. In addition, they have similar safety profiles. Features other than the in vitro longer duration of action of salmeterol should, therefore, guide the therapeutic choice between these two drugs, including the impact of speed of onset of action (16) and type of inhalation device (18) on patients' compliance with treatment.

Acknowledgements

The authors would like to thank the following physicians for their co-operation. France: H. Benzaidane (Grenoble), J. Birnbaum (Marseille), M. Grosclaude (Guérrand Granges), C. Le Loet (Rouen), F. Macone (Nico), D. Muriciano (Clichy), J. P. Orlando (Aubagne), D. Piperno (Lyon), A. Prud'homme (Tarbes), G. Thomas (Marseille); Italy: R. Corsico (Montescano), C. F. Donner (Veruno), G. Moscato (Pavia), M. Neri (Tradate), C. M. Sanguinetti (Osimo), P. Zanon (Busto Arsizio); Spain: P. Casan Clara (Barcelona), F. M. Neri (Madrid), C. Picado Vallés (Barcelona), H. Verea Hernando (La Coruna), J. L. Viejo Buelos (Burgos); Sweden: P. Arvidsson (Göteborg), T. Winge (Skövde), O. Zetterstom (Stockholm), Switzerland: U. Aebi (Biel), W. Graf (Bern), M. Hacki (Zuerich), A. Paky (St. Gallen), M. Tschach (Lauzen); U.K.: D. Davies (South Glamorgan), R. J. Davies (London), D. O. Edwards (Merseyside), M. Rudolf (London), S. C. Stenton (Newcastle-upon-Tyne), J. R. Stradling (Oxford), J. A. Turner (Bournemouth). This study was supported by Novartis Pharma AG.

References


