Comparison of the Effects of Salmeterol and Formoterol in Patients With Severe Asthma*

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**Study objective:** Several studies have demonstrated the superiority of salmeterol and formoterol to either regular treatment with albuterol or placebo. However, to date there have been no trials comparing the efficacy of salmeterol and formoterol in patients with severe asthma.

**Design:** We undertook a randomized, placebo-controlled, crossover study to compare 4 weeks of treatment with inhaled formoterol (12 µg twice daily) or salmeterol (50 µg twice daily) in patients with severe asthma whose conditions were not being adequately controlled by therapy with high doses of inhaled corticosteroids (ie, ≥ 1,500 µg daily) or with regular oral corticosteroid treatment. Morning pretreatment peak expiratory flow (PEF) during the last 14 days of the treatment period was the primary outcome variable. Patients recorded morning and evening pretreatment PEF, daytime and nighttime symptom scores, and any use of rescue medication. Spirometry and bronchial reversibility were performed after each treatment.

**Results:** Forty-two nonsmoking patients (29 women; mean age, 45 ± 2 years; mean [± SEM] FEV1, 61.8 ± 3.4% of predicted) took part in the trial, and 27 patients completed the trial. The mean morning PEF was greater in patients receiving formoterol (mean increase, 14.4 L/min; 95% confidence interval [CI]. 0.2 to 28.6) or salmeterol (mean increase, 14.8 L/min; 95% CI, 0.5 to 29.1) compared with those receiving placebo, but there was no difference between these treatments. There were no significant treatment effects for any of the secondary outcome variables (ie, FEV1, FVC, mean evening PEF, mean daytime symptom score, or nighttime symptom score).

**Conclusion:** We conclude that the long-acting β2-agonists salmeterol and formoterol improve morning PEF in patients with severe asthma, but that there is no difference in efficacy between the two drugs.

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**Key words:** formoterol; salmeterol; severe asthma

**Abbreviations:** CI = confidence interval; MDI = metered-dose inhaler; PEF = peak expiratory flow

Inhaled β2-agonists are recognized as effective bronchodilators for the relief of and prophylaxis for airway narrowing in the treatment of patients with asthma. Formoterol and salmeterol are long-acting β2-agonists with a duration of action of >12 h, making them suitable for twice-daily treatment and for providing protection from nocturnal symptoms. Additionally, both drugs protect against airways challenge with methacholine for a period of 12 h. International guidelines on asthma management have recommended that they be added to the treatment of patients with symptoms that are not controlled by therapy with regular high-dose inhaled corticosteroids.

Several studies have demonstrated the superiority of salmeterol and formoterol to regular treatment with either albuterol or placebo. However, most of these trials included patients with mild-to-moderate asthma rather than very severe asthma. Although salmeterol and formoterol have a similar duration of action in asthma patients, these two β2-agonists differ pharmacologically, in that salmeterol acts as a partial agonist and formoterol acts as a full agonist. This difference may be of clinical relevance, particularly in patients with more severe asthma. There are few clinical studies comparing salmeterol and formoterol, and those studies that have been performed have looked at patients with mild-to-moderate asthma rather than those with...
Materials and Methods

Patients

Forty-two nonsmoking patients who met the American Thoracic Society criteria for asthma (13 men and 29 women; mean [± SEM] age, 45.4 ± 2.1 years) took part in the study. British Thoracic Society guidelines on asthma management currently define severity in terms of the treatment step needed to control symptoms, maintain lung function, and allow the activities of a normal life. All patients were receiving treatment with dosages of at least 1,500 µg of an inhaled steroid (eg, beclomethasone dipropionate, budesonide, or fluticasone propionate) or of regular oral steroids and had an FEV₁ < 80% of predicted, reported daily asthma symptoms, and were using their rescue inhaler on most days. According to these criteria, all patients were at steps 4 or 5 of the British Thoracic Society guidelines. No patient had taken long-acting β₂-agonists for at least 4 weeks prior to the study. All patients continued to receive the same maintenance medication throughout the trial to prevent bias between treatment periods. If patients had an exacerbation of their asthma requiring a change in the maintenance treatment, they were withdrawn from the study. All patients had documented bronchial reversibility of at least 15%, either spontaneously during the run-in period or following the inhalation of 200 µg albuterol. Patients who experienced an exacerbation of asthma or an upper respiratory tract infection in the 4 weeks prior to the study, and all were nonsmokers. Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of The Royal Brompton Hospital.

Study Design

This was a randomized, placebo-controlled study of crossover design comparing the effects of 4 weeks of treatment with salmeterol, 50 µg twice daily, (Serevent diskhaler [50 µg]; GlaxoSmithKline; Stockley Park West, UK), formoterol, 12 µg twice daily (Foradil dry powder inhaler [12 µg per capsule]; Novartis; Frimley, UK), or placebo. A salmeterol placebo was not available, therefore an identical formoterol inhaler device with identical capsules was used as the placebo. Investigators were blinded throughout the trial. Patients were only partially blinded. They were unaware of whether they were receiving formoterol or placebo but were aware of the treatment with salmeterol because the inhaler differed in appearance.

At the initial screening visit, a full medical history was taken and a physical examination was performed. Baseline spirometry and peak expiratory flow (PEF) were measured, and airways reversibility was established by repeating these tests 15 min after inhaling 200 µg albuterol. Venous blood (5 mL) was taken for determination of serum potassium levels. All patients had normal ECG findings.

Patients then underwent a 2-week run-in period, during which they were asked to keep a daily diary card. The diary card was used to record morning and evening PEF measurements (prior to β₂-agonist use), daytime and nighttime symptom scores, and rescue inhaler use. Patients were trained in the proper use of the peak flowmeter during their initial visit. Following the run-in period, patients returned to the laboratory where spirometry, PEF, and bronchial reversibility were reassessed. Patients then were randomized to receive salmeterol (50 µg), formoterol (12 µg), or placebo (1 capsule), which they were asked to take twice daily for 4 weeks. They were seen again after this 4-week period for identical measurements. Patients then were switched to the second study inhaler and were reassessed after 4 weeks. They were then given the final inhaler, and at the end of 4 weeks of treatment returned to the hospital for a final visit.

Patients were asked to record symptoms, PEF, and daily rescue inhaler use throughout the study. Patients were asked not to use their short-acting β₂-agonist medication for 6 h and not to use their long-acting β₂-agonist medication for 12 h prior to each visit if possible. Patients receiving therapy with long-acting β₂-agonists prior to the trial stopped them after the screening visit and underwent a 4-week run-in period. Baseline data for these patients was recorded during the final 2 weeks of the run-in period (ie, 2 weeks after stopping therapy with long-acting β₂-agonists), and they entered the initial treatment period after a 4-week washout from therapy with long-acting β₂-agonists. Patients were given either albuterol (Diskhaler) or terbutaline (Turbohaler; AstraZeneca; Kings Langley, UK) to use as rescue medication to coincide with their prescribed relief medication prior to the study. Capsule/disk counts were made at each visit as a check on compliance.

Spirometry and PEF

FEV₁ and FVC were measured using a dry wedge spirometer (Vitalograph; Buckingham, UK). All volunteers were trained in the use of the apparatus prior to beginning the study. Baseline values were measured after 15 min of rest and were recorded as the highest of three readings made at 1-min intervals. Single readings only were taken at other times. PEF was measured using a standard peak flowmeter (Mini-Wright; Clement Clarke International Ltd; Harlow, Essex, UK). These meters were used for measurements in the laboratory and were given to patients for the daily measurement of PEF at home.

Bronchial Reversibility

Bronchial reversibility was assessed by the measurement of spirometry before and 15 min after the inhalation of 200 µg albuterol from a metered-dose inhaler (MDI) via a spacer. Percentage reversibility was calculated as

$$\frac{FEV_1 (post-albuterol) - FEV_1 (pre-albuterol)}{FEV_1 (pre-albuterol)} \times 100$$

Symptom Scores

Patients were asked to record a daytime and a nighttime symptom score. Symptom scores were recorded every 12 h in the diary card using a 4-point scale (0, no symptoms; 1, mild; 2, moderate; 3, severe).

Statistical Analysis

Statistical analysis consisted of comparisons between treatments using a generalized linear model. This model consisted of fitting patient, period, and treatment effects. Since formoterol and salmeterol have proven efficacy in a twice-daily regimen, the sensitivity of the trial was established by analyzing the contrast of the mean effect of the active treatments compared with placebo performed one-sided at the 5% significance level. Should the trial have proven sensitivity, the efficacy of formoterol and salmeterol was to be compared using a two-sided test at the 5% level. All
three possible pairwse contrasts were calculated, together with 95% confidence intervals (CIs) and associated p values for both primary and secondary efficacy variables. The mean prebronchodilator morning PEF was the primary outcome variable, other measurements (ie, evening PEF, symptom scores, rescue inhaler use, and spirometry) were secondary outcome variables. Mean values were calculated from the final 2 weeks of diary card values for each treatment period, with the first 2 weeks of each treatment period acting as an active washout period. All patients with data recorded for two or more treatment periods were included in the analysis. Values are expressed as the means with 95% CIs or the mean ± SEM. Assuming that an increase of 20 L/min in the median morning PEF is clinically relevant, a sample size of 36 patients would have 85% power to detect such a difference, and a sample size of 30 patients would have 78% power.

RESULTS
Withdrawals, Adverse Events, and Compliance

Forty-two patients were randomized, and of these 38 (90%) were included in the intention-to-treat population. Fifteen of the 42 randomized patients (36%) withdrew from the study, and therefore 27 patients completed the trial. Of these 27 patients, 11 had taken long-acting β2-agonists prior to the trial. Seven patients withdrew while taking the placebo, five patients withdrew while taking formoterol, and three patients withdrew while taking salmeterol (Table 1). All withdrawals were due to asthma exacerbations requiring treatment with oral steroids, except for one patient who did not attend follow-up sessions. The number of reported adverse events was higher for patients receiving placebo (18 of 37 patients; 49%) and formoterol (17 of 35 patients; 49%) than for those receiving salmeterol (13 of 33 patients; 39%). There were two serious adverse events. One patient experienced attacks of angina while taking the placebo, and one patient experienced a transient ischemic attack while taking formoterol.

Compliance was assessed by capsule/disk count at the end of each treatment period. Medication was not returned for 12 visits. For the remaining visits, the mean compliance was 91% (SEM, 1%). There was no difference in compliance between treatments.

Concomitant Medications

All patients were receiving at least 1,500 μg inhaled steroid daily, and 11 patients were treated with regular oral steroids (Table 2). All patients who were receiving regular oral steroids also were receiving inhaled steroids. Fifteen patients were taking long-acting β2-agonist medications prior to entry into the trial (salmeterol, 14 patients; formoterol, 1 patient), and these patients were stopped from taking more of the medications at the screening visit and underwent a 4-week run-in period to allow for a sufficient washout period.

Baseline Lung Function

At the initial screening visit, patients had a mean FEV1 of 1.83 ± 0.12 L (61.8 ± 3.4% predicted) with an average reversibility of 17 ± 2.2%, and a mean PEF of 333 ± 14 L/min. During the run-in period, patients had a mean morning PEF of 290 ± 14 L/min, a mean evening PEF of 317 ± 14 L/min, a mean daytime symptom score of 1.2 ± 0.1, and a mean nighttime symptom score of 0.9 ± 0.1. The mean rescue inhaler use during the run-in period was 6.1 ± 0.7 puffs per day, and in the five patients using home nebulizers, mean nebulizer use was 5.3 ± 2.2 nebulizers per day.

Lung Function

Following treatment, there was a statistically significant increase in the mean morning PEF for patients receiving both formoterol and salmeterol compared with placebo (p < 0.05 for both) [Fig 1]. The mean increase for formoterol was 14.4 L/min (95% CI, 0.5 to 29.1), and the mean increase for salmeterol was 14.8 L/min (95% CI, 0.5 to 29.1). There was no significant difference in the mean morning PEF between the two active treatments.

There were no significant treatment effects for any of the secondary outcome variables (ie, FEV1, p = 0.2; FVC, p = 0.7; mean evening PEF, p = 0.5; mean daytime symptom score, p = 0.5; mean nighttime symptom score, p = 0.2) [Tables 3 and 4].

Table 2—Concomitant Medication Use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients, No.</th>
<th>Mean Dose, mg</th>
<th>Dose Range, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>11</td>
<td>10</td>
<td>2.5–30</td>
</tr>
<tr>
<td>Prednisolone plus inhaled steroid</td>
<td>11</td>
<td>1.6</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>Inhaled budesonide</td>
<td>15</td>
<td>2.0</td>
<td>1.6–4.0</td>
</tr>
<tr>
<td>Inhaled fluticasone</td>
<td>7</td>
<td>2.0</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Inhaled beclomethasone</td>
<td>9</td>
<td>1.8</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Theophylline/aminophylline</td>
<td>15</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1—Summary of Patients Who Withdrew From the Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Formoterol</th>
<th>Salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>37</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Patients withdrawn, No.</td>
<td>7 (19%)</td>
<td>5 (14%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Cause of withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma exacerbation</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Nonattendance</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There was a trend for improvement in spirometry and PEF measurements following treatment with salmeterol and formoterol compared with placebo treatment (Table 3), but no significant differences among the three groups. Bronchial reversibility to albuterol was greater following placebo treatment compared with active treatments, although not significantly so. However, the postbronchodilator FEV₁ measurements were the same for all three treatments.

### Table 3—Lung Function Parameters at the End of Treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo</th>
<th>Formoterol</th>
<th>Salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, L</td>
<td>1.75 ± 0.13</td>
<td>1.96 ± 0.14</td>
<td>1.91 ± 0.13</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>61.6 ± 4.0</td>
<td>67.0 ± 4.0</td>
<td>66.2 ± 3.8</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.62 ± 0.15</td>
<td>2.80 ± 0.17</td>
<td>2.78 ± 0.14</td>
</tr>
<tr>
<td>PEF, L/min</td>
<td>333 ± 16</td>
<td>357 ± 17</td>
<td>363 ± 16</td>
</tr>
<tr>
<td>Postbronchodilator</td>
<td>2.02 ± 0.13</td>
<td>2.11 ± 0.15</td>
<td>2.01 ± 0.13</td>
</tr>
<tr>
<td>Reversibility, %</td>
<td>17.3 ± 2.8</td>
<td>8.6 ± 2.6</td>
<td>6.9 ± 1.6</td>
</tr>
</tbody>
</table>

*Values given as mean ± SEM.

### Table 4—Summary of Data From Diary Cards for Last 2 Weeks of Each Treatment Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Formoterol</th>
<th>Salmeterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean evening PEF, L/min</td>
<td>334 ± 16</td>
<td>342 ± 18</td>
<td>341 ± 16</td>
</tr>
<tr>
<td>Symptom score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>Nighttime</td>
<td>0.6 ± 0.1</td>
<td>0.6 ± 0.1</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>Rescue inhaler use, puffs/d</td>
<td>5.0 ± 0.7</td>
<td>4.1 ± 0.9</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>Nebulizer use, nebulezer/d</td>
<td>3.6 ± 0.5</td>
<td>2.7 ± 2.1</td>
<td>3.7 ± 2.1</td>
</tr>
</tbody>
</table>

*Values given as the mean ± SEM.
†Four patients.

There was a trend for improvement in spirometry and PEF measurements following treatment with salmeterol and formoterol compared with placebo treatment (Table 3), but no significant differences among the three groups. Bronchial reversibility to albuterol was greater following placebo treatment compared with active treatments, although not significantly so. However, the postbronchodilator FEV₁ measurements were the same for all three treatments.

### Discussion

The present study compared the clinical effects of 4 weeks of treatment with inhaled formoterol (12 μg twice daily) or inhaled salmeterol (50 μg twice daily) in patients with severe asthma whose symptoms were not controlled by treatment with high-dose inhaled or regular oral corticosteroids. We found that the mean morning PEF was greater for patients receiving both formoterol and salmeterol compared with placebo, but with no difference between the active treatments.

Formoterol and salmeterol are both highly selective and potent β₂-adrenoceptor agonists that relax bronchial smooth muscle in vitro. However, formoterol is more potent than salmeterol in vitro, with a faster onset but a shorter duration of action. In addition, formoterol is a nearly full agonist, and salmeterol is only a partial agonist at the β₂-adrenoceptor.

Single-dose studies with salmeterol and formoterol found that formoterol has a more rapid onset of bronchodilator action than salmeterol in asthmatic patients but has a similar bronchodilator effect at 12 h. Relative potency estimates show that 50 μg salmeterol corresponds to 9 μg formoterol. In addition, formoterol has a faster action in reversing methacholine-induced bronchoconstriction than salmeterol. Also, 12 μg formoterol and 50 μg salmeterol provide equal protection against methacholine-induced bronchoconstriction for up to 24 h. However, formoterol has a greater maximal protective effect than salmeterol against methacholine-induced bronchoconstriction in asthmatic patients, confirming that salmeterol is a partial agonist compared with formoterol in human airways in vivo.

Previous studies have demonstrated the effectiveness of regular treatment with salmeterol or formoterol compared with albuterol or placebo. In common with the present study, these studies showed improvements in morning PEF with long-acting β₂-agonist treatment. However, unlike the present study, these studies demonstrated improvements in evening PEF, decreased symptom scores, and decreased use of rescue inhalers. There are two possible reasons for these discrepancies. First, many of the previous studies looked at patient populations with milder asthma. Previous studies included patients with mild-to-moderate asthma and patients receiving either low-dose inhaled cortico-
roids or those receiving no regular steroid treatment. Second, some studies\textsuperscript{7,22} used a higher dose of formoterol (ie, 24 $\mu$g twice daily) than was used herein. Three trials\textsuperscript{25–27} of salmeterol in severe asthmatics demonstrated improvements in PEF values, symptom scores, and rescue inhaler usage. However, in two of these trials the dose of salmeterol used was 100 $\mu$g twice daily\textsuperscript{25,26} compared with the present dose of 50 $\mu$g twice daily. The third trial\textsuperscript{27} used the same dose of salmeterol as was used herein, although the patients may have had milder disease than those in the present study. They included patients receiving doses of 500 $\mu$g daily of inhaled steroids (compared with >1,500 $\mu$g daily in the present study), and only 1 of 20 patients was receiving regular oral steroid treatment (compared with 11 of 42 patients herein).

The present study is one of the few to examine the effects of therapy with long-acting $\beta_2$-agonists in patients with severe and uncontrolled asthma. Our data suggest that both salmeterol and formoterol are less effective in this population than has been reported previously in patients with less severe asthma. The study of patients with severe asthma poses problems, including a high dropout rate, with 33\% of patients being withdrawn from the study due to asthma exacerbations. This meant that the power of the study was reduced to 65\%. Another explanation for the apparently poor response could be down-regulation of $\beta_2$-adrenergceptors by the use of high doses of short-acting $\beta_2$-agonists.\textsuperscript{28} This also may explain the lack of difference in efficacy between treatments. Third, the addition of a leukotriene antagonist to the treatment of patients with severe asthma did not result in any clinical benefit.\textsuperscript{29} This, together with the results of the present study, suggests that in patients with continuing unsatisfactory control of their asthma despite treatment with high doses of inhaled steroids, the lack of benefit from additional treatments may not be purely related to lack of efficacy. Other factors such as compliance and psychosocial issues also may be relevant. Also, 11 of the patients who completed the present trial received therapy with long-acting $\beta_2$-agonists prior to entering the study. Of these patients, some remained symptomatic despite this therapy. This may have preselected a proportion of patients that would not respond favorably to the trial medications. In addition, in allergic asthma patients, the morning PEF may be affected by allergen exposure, which is affected by various measures including high-efficiency particulate air filtration and air conditioning.\textsuperscript{8} However, we do not have any information regarding the use of such devices by patients in the present study.

Two previous studies\textsuperscript{11,12} have compared salmeterol and formoterol treatment in asthmatic patients. The first was a large parallel-group study of 6 months of treatment using the same doses as those used herein.\textsuperscript{12} Like the present study, there was no difference in mean morning PEF, rescue medication use, or symptom scores, although the evening PEF was better with formoterol at 2, 3, and 4 months. The second study\textsuperscript{11} also showed improvements in morning and evening PEF values, symptom scores, and rescue inhaler use with two formulations of salmeterol (MDI and Serevent Accuhaler; GlaxoSmithKline) and with formoterol compared with baseline values. The only difference between treatments was a greater improvement in daytime symptoms in patients receiving formoterol compared with those using the salmeterol inhaler (Accuhaler) but not compared with the salmeterol MDI. These two studies differed from the present study in three ways. There was no placebo control, both trials were of an open-label design, and the patients who were studied had milder cases of asthma, with higher PEF rates, lower rescue inhaler use, and lower steroid doses than those recorded herein.

A large trial\textsuperscript{30} investigating the cost-effectiveness of inhaled formoterol compared with salmeterol in asthma patients found no difference in median medical costs over a 6-month treatment period. This finding coupled with our finding of no difference in efficacy between treatments suggests that it is not possible to recommend the use of one drug over the other for patients with severe asthma. However, long-term treatment with formoterol added to budesonide decreases the exacerbation rate in patients with less severe asthma.\textsuperscript{31} The present short-term study did not investigate exacerbation rates, and a longer trial in this severe patient group, similar to that performed by van der Molen and colleagues,\textsuperscript{22} would be of interest.

We conclude that the long-acting $\beta_2$-agonist medications salmeterol and formoterol improve morning PEF in patients with severe asthma but without any difference in efficacy between the two drugs.

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