Salmeterol reduces the need for inhaled corticosteroid in steroid-dependent asthmatics

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Previous results have demonstrated addition of long-acting β2-adrenergic agonists to be beneficial in asthma patients already receiving inhaled corticosteroid. The purpose of this study was to determine, qualitatively as well as quantitatively, the steroid-sparing properties of salmeterol in stable asthma patients receiving maintenance inhaled corticosteroids (800–1600 μg day⁻¹).

In these patients, the daily dose of beclomethasone dipropionate was reduced by 200 μg each week until asthma deteriorated, with the minimal acceptable dose (MAD) being defined as the dose one step above deterioration (sensitivity period). Following this, patients received three times the MAD for 2 weeks. Patients were randomized to receive either salmeterol 50 μg twice daily or placebo and the MAD was again determined (treatment period).

Fifteen patients received salmeterol and 19 placebo. The MAD was significantly lower in the salmeterol group compared with placebo during the treatment period (P<0.01). A 50% reduction of the MAD was achieved by more patients treated with salmeterol than placebo (P=0.001). Salmeterol caused a significantly greater reduction in daytime symptom score and use of as-needed β2-agonist therapy between sensitivity and treatment periods compared with placebo (P<0.05 for both).

The results demonstrate, that the addition of salmeterol to corticosteroid treatment offers a clinically relevant potential for reduction of inhaled corticosteroid dose in steroid sensitive asthmatics.

Introduction

The use of inhaled corticosteroids as a first-line treatment for asthma is well established. If patients remain symptomatic during low- to moderate-dose inhaled corticosteroid therapy, previous recommendations have been to increase the dose of corticosteroid. However, recent guidelines propose an alternative strategy, i.e. the addition of a long-acting bronchodilator when symptoms persist (1,2).

Salmeterol xinafoate is a highly selective, long-acting β2-agonist that can be administered by inhalation. Regular treatment of asthma with salmeterol has been shown to reduce symptoms and improve lung function (3–6). Long-term clinical studies have indicated that in patients remaining symptomatic on inhaled corticosteroid therapy, the addition of salmeterol to ongoing inhaled corticosteroid therapy is superior to doubling the dose of the inhaled corticosteroid (7,8). However, the corticosteroid level at which to commence salmeterol treatment and, particularly, the extent to which the asthma patient can clinically benefit from such treatment remain unclear. Furthermore, it is unknown whether patients with stable asthma receiving inhaled corticosteroid treatment would benefit from salmeterol treatment.

The present study was conducted to determine whether salmeterol had steroid-sparing properties in stable asthma patients already receiving maintenance inhaled corticosteroids.

Methods

PATIENTS

All patients were diagnosed with having asthma (9) and achieved the criteria of stable asthma defined for this study (Table 1). For all patients entering the study their asthma was controlled by a dose of inhaled corticosteroid...
TABLE 1. Definition of stable asthma

At least five out of the six criteria in each section must be fulfilled:

1) At the end of the baseline period:
   a) FEV₁ > 60% of predicted normal (before β₂-agonist) and during the last seven days of the period;
   b) mean morning PEF > 60% of predicted normal (before β₂-agonist);
   c) mean evening PEF > 60% of predicted normal (before β₂-agonist);
   d) diurnal variation of PEF < 20% on each day;
   e) total symptom score ≤ 2 on each day;
   f) total daily use of salbutamol ≤ 1.2 mg on average.

2) In all other periods:
   a) FEV₁ > 60% of predicted normal (before β₂-agonist) and during the last three days of the period;
   b) mean morning PEF > 60% of predicted normal (before β₂-agonist) and within 80% of baseline morning PEF;
   c) mean evening PEF > 60% of predicted normal (before β₂-agonist) and within 80% of baseline evening PEF;
   d) diurnal variation of PEF < 20% on each day;
   e) total symptom score ≤ 2 on each day;
   f) total daily use of salbutamol ≤ 1.2 mg on average and less than 0.6 mg in addition to baseline average.

FEV₁: forced expiratory flow in 1 sec; PEF: peak expiratory flow rate.

STUDY DESIGN

This was a multicentre, double-blind, randomized, placebo-controlled trial. During the study period, patients attended the clinic each week for evaluation of asthma deterioration. At each visit FEV₁ was measured by spirometry (Vitalograph®, Spiropharma, Copenhagen, Denmark). In addition, patients kept a diary card in which they recorded morning and evening PEF, asthma symptom score (day and night-time), the need for rescue β₂-agonist medication and any adverse events. PEF was measured every morning and evening using a MiniWright® (Spiropharma) peak flow meter. Daytime symptoms were scored using a scale ranging from 0 (no symptoms) to 5 (disabling symptoms), and at night-time using a scale ranging from 0 (no symptoms) to 4 (severe symptoms).

The study consisted of five periods (Fig. 1). During the baseline period of 2 weeks, patients received BDP via a Diskhaler® (GlaxoWellcome, London, U.K., at a dose equivalent to their previous corticosteroid dose. If using budesonide, this was changed to BDP at a 1:1 ratio. Throughout the study, patients were allowed to use salbutamol 200 µg per actuation via a Diskhaler® as needed in addition to BDP and study medication. Patients meeting the entry criteria for stable asthma (Table 1) progressed to the 'sensitivity period'. In this period, the daily dose of inhaled corticosteroid for each patient was reduced by 200 µg each week. Reduction in the dose of inhaled corticosteroid continued until asthma became unstable, i.e. patients did not achieve the criteria for stable asthma. The minimal acceptable dos (MAD) of BDP was defined as the dose one step above the dose resulting in unstable asthma. Patients who were able to completely withdraw from corticosteroid therapy without their asthma becoming unstable were excluded. Patients whose asthma became unstable were treated with a dose of inhaled corticosteroid that was three times the MAD (maximum dose level 3000 µg daily) for 2 weeks. Patients, who were stable at the end of the second week, were then randomized to either salmeterol 50 µg twice daily or placebo (treatment period). The daily dose of BDP was again reduced by 200 µg each week and the MAD determined. A 2-week follow-up period on appropriate medication concluded the study.

STATISTICS

All statistical analyses were carried out using SAS software (v. 6-11, SAS Institute, Carg, NC, U. S. A.). The proportion
of patients that decreased their use of corticosteroids by at least 50% during the treatment period was analysed using a chi-square test. The MADs in the treatment period of the two treatment groups, as well as the difference between MADs during treatment and sensitivity periods, were analysed using a Wilcoxon 2-sample test with normal approximation.

Lung function parameters (morning and evening PEF and FEV₁) were tested by analysis of variance. PEF was analysed as the mean of the last three recordings while receiving the MAD. This procedure was also carried out for day and night-time symptom scores and use of rescue bronchodilator medication. These variables, as well as lung function parameters, were all analysed using logistic regression (proportional odds model).

**ETHICS**

The study was approved by the local scientific ethics committee (County of Aarhus), as well as the Danish National Board of Health. All patients gave informed consent in writing before entering the study.

**Results**

In total, 77 patients aged 19–65 years entered the study. All patients' asthma was controlled by a dose of inhaled corticosteroid of 800–1600 µg daily. Forty-three patients were excluded at the end of the sensitivity period; the most common reason for exclusion was complete withdrawal of corticosteroid treatment (36 patients). Thirty-four patients were randomized to study medication. Fifteen patients received salmeterol and 19 patients received placebo. Baseline characteristics of patients are listed in Table 2. No significant differences in baseline characteristics were found between the two treatment groups.

There was no significant difference in corticosteroid dose at baseline between the two groups. No difference in the MAD of corticosteroid was seen in the sensitivity period between patients randomized to salmeterol or placebo (Fig. 2). During the treatment period the MAD of corticosteroid was significantly lower in salmeterol-treated patients compared with those receiving placebo ($P<0.01$). Comparison of the MAD difference of salmeterol and placebo treatment between the sensitivity and treatment periods revealed a larger difference in the treatment period ($P<0.01$). The difference in MADs between the treatment and sensitivity periods (Table 3) was significantly larger in the salmeterol group compared to placebo ($P=0.001$) (Fig. 3).

The number of patients in each treatment group who were able to reduce their MAD by at least 50% during the treatment period was significantly greater in the salmeterol-treated group compared to the placebo-treated group ($P=0.001$) (Fig. 3).

The treatment given, whether salmeterol or placebo, did not influence lung function. FEV₁ and morning and evening PEF were not significantly different between the two groups.

**TABLE 2. Baseline characteristics of study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Salmeterol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>10/9</td>
<td>5/10</td>
<td>15/19</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43.0</td>
<td>45.0</td>
<td>43.9</td>
</tr>
<tr>
<td>Smokers (n)</td>
<td>9</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Patients with an allergy (n)</td>
<td>9</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Mean asthma duration (yr)</td>
<td>12.9</td>
<td>15.4</td>
<td>14.0</td>
</tr>
<tr>
<td>Mean FEV₁ (l/min⁻¹) (% predicted)</td>
<td>2.98 (86.7)</td>
<td>2.80 (86.1)</td>
<td>2.90 (86.4)</td>
</tr>
<tr>
<td>Mean BDP dose (µg daily)</td>
<td>1179</td>
<td>1280</td>
<td>1224</td>
</tr>
</tbody>
</table>

FEV₁: forced expiratory volume in 1 sec; BDP: beclomethasone dipropionate.

**TABLE 3. Difference between periods (treatment-sensitivity) for the two treatment groups**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Salmeterol</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAD (µg)</td>
<td>42 (118)</td>
<td>-253 (196)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Morning PEF (l/min⁻¹)</td>
<td>3.7 (8.5)</td>
<td>17.4 (9.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Evenning PEF (l/min⁻¹)</td>
<td>3.2 (9.6)</td>
<td>14.1 (10.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>-40 (170)</td>
<td>160 (210)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Daily use of salbutamol (µg)</td>
<td>42 (54)</td>
<td>-214 (102)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Results are given as mean (SE). MAD: minimal acceptable dose; PEF: peak expiratory flow; FEV₁: forced expiratory volume in 1 sec.
Fig. 3. Number of patients able to reduce their minimal acceptable dose of inhaled corticosteroid by at least 50% or less than 50% during treatment with either placebo (■) or salmeterol 50 μg twice daily (▲). **: \( P = 0.001 \).

evening PEFs in the treatment period were not significantly different from those observed during the sensitivity period, when comparing treatment groups (Table 3).

Salmeterol-treated patients experienced significantly fewer symptoms during the daytime \( (P < 0.01) \) and more days without symptoms \( (P < 0.001) \) than placebo-treated patients (Fig. 4). There was no difference between the two treatments with regard to night-time symptom score (data not shown).

Daily use of as needed bronchodilator medication increased slightly between sensitivity and treatment periods for the patients receiving placebo, whereas the salmeterol-treated group had a marked decrease in salbutamol consumption. Daily use of as needed salbutamol (Table 3) was significantly lower in salmeterol—compared with placebo-treated patients \( (P < 0.05) \).

No differences of steroid dosage and lung function parameters were observed between treatment groups at the end of the high dose period.

In the placebo-treated group, patients had significantly lower morning PEF \( (P < 0.05) \), increased daytime symptom score \( (P < 0.05) \) and more frequently used as needed bronchodilator medication \( (P < 0.05) \) during the treatment period compared with baseline (data not shown). No such differences were observed in the salmeterol-treated group.

There was no difference between the two treatment groups in the incidence of adverse events during the study. A total of 82 adverse events were reported and only one was classed as serious: this was a placebo-treated patient experiencing syncope, which was unrelated to study medication.

Discussion

A number of large studies have shown the addition of a long-acting \( \beta_2 \)-agonist, such as salmeterol or formoterol, to be an alternative to increasing the dose of inhaled corticosteroid in symptomatic asthma patients \( (7,8,10) \). Indeed, with regard to improving asthma symptoms, these studies have shown the addition of a long-acting \( \beta_2 \)-agonist to be superior to doubling the dose of corticosteroid in unstable asthma patients. Significant improvements in symptom control following the addition of salmeterol have also been reported in patients with severe asthma who are being considered for oral corticosteroid treatment \( (11) \).

The present study is the first to evaluate whether salmeterol has a steroid-sparing effect. It is possible that the weekly reduction in corticosteroid dosage might be too short a time period for asthma to deteriorate. However, the design of the study has previously proven useful \( (12) \) and in this study only the most steroid-sensitive patients were randomized to treatment, which strengthens the results of the study.

A significantly greater decrease in the MAD of corticosteroid could be obtained when patients were treated with salmeterol compared with placebo. This demonstrates the ability of salmeterol to reduce the dose of inhaled corticosteroid required in stable asthma patients without affecting short-term disease control. This finding is supported by a previous study showing salmeterol to allow a 17% reduction in steroid dose compared with placebo, while maintaining disease control \( (13) \). Perhaps more importantly, 80% of salmeterol-treated patients were able to reduce their inhaled corticosteroid dose by more than half, compared with 21% of placebo-treated patients. Thus, the potential for reduction seemed clinically useful.

Lung function parameters were stable throughout the study period in the salmeterol-treated group. Other studies have reported improved lung function in patients treated with salmeterol compared with those receiving higher doses of inhaled corticosteroid \( (7,8) \). However, the aim of this study was not to improve lung function but to maintain asthma control while reducing the dose in inhaled corticosteroid.

Generally, the addition of salmeterol to existing therapy has resulted in reduced asthma symptoms and patients having less need for short-acting bronchodilators \( (7,8,13) \). Similar results were obtained for daytime symptom score in
this study even though the corticosteroid dosage was constantly being reduced. A little surprisingly, no treatment effect was seen for night-time symptoms, when comparing salmeterol and placebo groups. A possible explanation could be, that the asthma worsening elicited was intentionally slight and short.

Salmeterol treatment has proved beneficial in other aspects of asthma disease. Bronchial hyper-responsiveness has been shown to remain stable (8) or improve (13) in salmeterol-treated patients. This agrees with data demonstrating salmeterol to completely inhibit the increase in non-specific bronchial responsiveness following allergen challenge in allergic asthma patients (14). Moreover, in patients with moderate-to-severe asthma the frequency of exacerbations were found to be equal whether they were treated with salmeterol in combination with inhaled corticosteroid or a double-dose of inhaled corticosteroid (7,8).

Although inhaled corticosteroids are considered as safe and effective treatment for asthma, there has been some concern over long-term dose-dependent systemic and local side effects (15-18). In order to avoid potential side-effects, the dose of inhaled corticosteroid required for maintenance therapy should be as low as possible. The addition of salmeterol serves two purposes. Firstly, as illustrated by the results of this study, salmeterol treatment offers the possibility for further reduction in corticosteroid dose without affecting disease control. Secondly, the potential risk of under-treatment when reducing the inhaled corticosteroid dose would be avoided by the addition of salmeterol. Although the reduction in corticosteroid dose in this study was performed using current standard measurements of disease activity, this data has shown that placebo-treated patients had significantly lower morning PEF and daytime symptom score, and a greater need for 'as needed' bronchodilator medication during the treatment period compared with baseline. Thus, reduction of the inhaled corticosteroid dose to an acceptable minimum level according to current disease parameters might increase the risk of some patients’ asthma becoming unstable and symptoms ensuing.

At present, the reason for the steroid-sparing effect of salmeterol is unclear. One simple explanation would be that the bronchodilator activity of salmeterol enables the inhaled corticosteroid to reach the inflammatory site in the bronchi more effectively, and thereby reduces the steroid dose required. However, previous data using short-acting $\beta_2$-agonist prior to inhalation of a corticosteroid have not supported the theory of bronchodilation permitting a reduction in steroid dose (19).

The efficacy of inhaled corticosteroid treatment in asthma is based upon its anti-inflammatory activity. Indeed, the population selected in the present study represented the most steroid-sensitive asthma patients. It could, therefore, be speculated that the steroid-sparing effect of salmeterol was the result of an effect on the inflammatory process. Salmeterol has been reported to have some anti-inflammatory properties. In one study of corticosteroid-treated asthma patients, salmeterol caused a reduction in T-lymphocyte activation that was considerably greater and of longer duration than that observed with salbutamol (20). A separate study demonstrated a reduction in blood eosinophil number in corticosteroid-treated asthma patients over a 12-month treatment period with salmeterol (21). In vitro, salmeterol has been shown to inhibit mediator secretion, i.e. histamine, leukotrienes and prostaglandins, from immunocompetent cells and tissues (22,23), supporting the anti-inflammatory effect of salmeterol. However, these findings are supported by other studies, such as an unchanged bronchoalveolar lavage cell profile in asthma patients after salmeterol treatment (24).

Concerns against the use of salmeterol for steroid-sparing purposes can be made as some studies have shown a reduction in $\beta_2$-adrenoceptor sensitivity and number to occur after treatment with long-acting $\beta_2$-agonists (25,26). However, the importance of this finding remains unclear as, to date, there have been no reports of the clinical relevance of this finding. Large, longitudinal clinical studies have reported decreased consumption of short-acting $\beta_2$-agonists (8,10,13) and unaltered $\beta_2$-adrenoceptor sensitivity (21) following treatment with salmeterol. A possible explanation for the difference in findings could be that the studies presented evidence of tachyphylaxis were performed on patients or healthy volunteers that were not regularly receiving $\beta_2$-agonist therapy, whereas the clinical reality is that almost all asthma patients use short-acting $\beta_2$-agonists to some extent.

In conclusion, the results of this study clearly demonstrate a larger potential for reduction of inhaled corticosteroid dose after addition of salmeterol to the treatment regimen compared with placebo. Quantitatively, this findings is potentially clinically relevant when considering the number of patients able to reduce inhaled corticosteroid dose by at least 50%. Salmeterol treatment did not affect lung function parameters, and, in fact, decreased daytime symptoms and need for bronchodilators.

In contrast, placebo treatment resulted in poorer lung function, more symptoms and increased need for bronchodilation, when compared to baseline, although steroid tapering was based on parameters according to current recommendations. Thus, the addition of salmeterol to existing corticosteroid treatment should be considered when attempting to obtain the lowest possible dose of inhaled corticosteroid required for optimal disease control in patients with moderate asthma.

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References


