Long-term treatment of asthmatic patients with salmeterol vs slow-release theophylline

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The aim of the present multicentre, open, randomized, parallel group study was to evaluate the efficacy and safety of salmeterol versus theophylline in asthmatic patients. A total of 112 patients were randomized: 56 received inhaled salmeterol (50 μg twice daily) and 50 oral dose titrated theophylline twice daily. The study lasted 12 months. The efficacy of both drugs was evaluated for the first 3 months of the study and the safety for a further 9 months. Spirometric measurements were carried out for the total duration of the study. Salmeterol showed a greater and more significant efficacy than theophylline in reducing both day- and night-time symptoms (P<0.001) and in reducing additional salbutamol requirement (P<0.001). The subjective assessment of efficacy by physicians and patients was in favour of salmeterol from the first month of treatment (P<0.001). Both drugs improved the quality of life as measured by the specific questionnaire ‘Living with Asthma’ with no significant differences. The total number of adverse events was slightly higher in the theophylline group compared with salmeterol (18 vs 9; P n.s.). Both salmeterol and theophylline increased morning and evening PEFR with no significant difference. FEV₁ and FVC increased in both groups of patients; the difference between the effects of the two treatments was not statistically significant at 12 months. Our study suggests that salmeterol has higher efficacy and safety than theophylline in long-term treatment of asthmatic patients.

Introduction

According to the International Asthma Report (1), the use of long-acting bronchodilator is recommended for basic symptomatological treatment. Among the bronchodilating drugs, slow-release theophylline is commonly used for the control of nighttime symptoms because of its prolonged action (2-4); however, close monitoring of blood concentrations is indispensable for maintaining a correct dosage while avoiding toxic side-effects which may even be potentially dangerous (5,6).

Slow-release oral β₂-agonists are effective in controlling symptoms, but they expose the patient to the risk of systemic side-effects such as cardiovascular stimulation, tremors and hypokalaemia (7,8). Several studies have shown that salmeterol is an effective drug in asthma treatment, especially for nocturnal and exercise-induced asthma (9-15) and that its use is not associated with relevant side-effects (16-19).

The efficacy and safety of salmeterol versus theophylline, both administered over a short period (from 7 to 28 days) to asthmatic patients have been recently evaluated (20-23). In these studies salmeterol was found to be more efficacious and safer than theophylline.

Patients and Methods

PATIENTS

Patients aged over 18 years affected with bronchial asthma who fulfilled the following criteria at the end of the run-in period were enrolled.

1. Forced expiratory volume in 1 s (FEV₁) between 50 and 80% of predicted value.
2. There was an increase of FEV₁ after 200 μg of salbutamol administered by a metered-dose inhaler, equal to or greater than 15% from basal values.
3. Total symptom score was equal to or greater than 2, with a daily score of 1 or more, on at least 4 days during the last 7 days of the run-in period. The symptom score was graded from 0 (no symptoms at all) to 5 (symptoms with complete impairment of normal daily activity) for daily symptoms and from 0 to 4 (symptoms which prevented sleep throughout the night) for nocturnal symptoms.

The exclusion criteria were severe steroid-dependent asthma, lower respiratory tract infections or admittance to
hospital for asthma in the previous 28 days, serious systemic disease, renal insufficiency or liver insufficiency, congestive heart failure, active or asymptomatic peptic ulcer, variable smoking habit, pregnancy or breast-feeding, hypersensitivity to $\beta_2$-receptor agonists and/or to theophylline, and treatment with $\beta$-blockers, cimetidine, erythromycin, allopurinol, propranolol, labetalol, phenytoin, rifampicin, sulphinpyrazone, lithium, influenza vaccine, cyproflaxacin and interferon. Patients who were not able to use the metered-dose aerosol, or who were taking research drugs in the last month were also excluded.

The trial was conducted according to the Helsinki declaration; each patient gave his or her informed consent at the moment of the enrolment.

STUDY DESIGN

The result was randomized, multicentre, open and with parallel groups. The choice of this type of design was a result of organizing difficulties for the management of a long-term treatment based on two different modalities of administration (oral versus aerosol) in a multicentre study.

The trial design was as follows.

Two-week Run-in

Patients were not allowed to use the following drugs: $\beta_2$-agonists except rescue salbutamol; anticholinergics, methylxanthine. The patient was asked to record the peak flow values daily at morning and at evening and to note in his or her daily diary the symptoms. The use of rescue salbutamol as needed was also reported. These parameters were recorded by the patients up to the end of the first treatment period (3 months).

Theophylline Titration of Varying Duration

At the end of the run-in 150 mg of theophylline was administered twice daily to eligible patients; the dose was then increased by 150 mg twice daily every 4–7 days until a plasma theophyllinaemia level of 10–20 $\mu$g ml$^{-1}$ was reached. The theophyllinaemia level was determined with Acculevel Theophylline Assay Kits (24).

First 3 Month Treatment Period (Evaluation of Efficacy)

At the end of the titration period, the patients were randomly assigned to one of the following treatments: (1) 50 $\mu$g inhaled salmeterol b.d. or (2) individually dose-titrated slow-release oral theophylline twice daily.

Second 9 Month Treatment Period (Evaluation of Safety)

The patients continued to take the drug for which they had been randomized. During this period, the patients were asked to record compliance with the treatment, additional salbutamol or other drugs and adverse events on the weekly record card. Respiratory functional data FEV$_1$ and forced vital capacity (FVC) were assessed during each medical visit.

Two-week Follow-up

The patients suspended the drug and were controlled after 2 weeks.

ASSESSMENTS

Medical Visits

The number and frequency of medical visits were as follows: run-in period, three visits (one at the beginning, one after 1 week and two after 2 weeks); titration period, up to four visits, each at an interval of 2–7 days; first treatment period, three visits, each at 4 week intervals; second treatment period, three visits, each at 3 month intervals; follow-up, one visit at the end of follow-up.

Data from the Patient’s Record Card

The following were noted: peak flow assessed by mini-Wright’s peak flow meter (normal range) every day at morning and at evening; daily and nocturnal symptom score; use of additional salbutamol.

Data Collected by the Researcher at each Visit

FEV$_1$, FVC, arterial blood pressure, heart rate, chest auscultation and evaluation of the efficacy of the treatment were noted. The highest FEV$_1$ value of three recordings was chosen. Bronchodilators were suspended for at least 4 h before the test.

Data Collected from Questionnaire on Quality of Life (Living with Asthma, Italian Version)

The questionnaire consisted of 12 questions. A score from 0 to 2 was assigned to each response. The questionnaire was administered at the end of run-in, and after 3, 6, 9 and 12 months of treatment.

Laboratory Tests

Electrocardiographic recording and haematochemical tests (haemochrome; sodium; potassium; calcium; bilirubinemia; total proteins; SGOT, SGPT, glycemia, urea, creatinine; uric acid; alkaline phosphate; urine test) were performed at the beginning and at the end of the trial.

ADVERSE EVENTS

All the adverse events were recorded, regardless of their apparent correlation with the test drug. The following events were considered serious: death; events which placed the patients in danger of life; events which were disabling or unabling for patients; events which required or prolonged
hospitalization; any congenital anomaly; cancer; overdose. Other events were considered minor.

STATISTICAL EVALUATION

The statistical evaluation was carried out according to the 'intent to treat' logic on all the 112 randomized patients.

Analysis of Efficacy

Peak expiratory flow variations were analysed as variations of the means in the two groups of patients assessed at the end of the run-in, after 1 month and after 3 months of treatment, and as the mean of the 3 months of treatment; the difference between the effects of the two treatments was evaluated using the analysis of covariance.

The symptom score over time was evaluated by calculating the proportion of days (nights) free of symptoms at the end of the first, second and third months of treatment, as well as the mean of all 3 months of treatment. The comparative analysis between the groups was determined using the $\chi^2$ test.

The analysis of the mean amount of additional salbutamol was evaluated with a similar method to that for the symptom score.

The values of FEV$_1$ and FVC over time, the effect of treatments and the comparison between these were evaluated using the same method employed for the analysis of PEFR variations. The evaluations were made after 1, 3, 6, 9 and 12 months of treatment.

A $\chi^2$ test was used to evaluate the overall efficacy of the two drugs and the variations in the auscultation results in both groups of patients.

Analysis of Safety

Arterial blood pressure and heart rate data were analysed in each group at the beginning and at the end of run-in and at all the other visits during the treatment period. The arithmetic mean, standard deviation and range were the descriptive synthetic indicators of the evolution of these variables.

The result of the electrocardiographic record was evaluated separately for each patient.

The haematological parameters were analysed by calculating the number and percentage of patients in whom an increase or decrease in values was observed at the end of the study compared with the pre-treatment values.

The significance of the changes was statistically evaluated with Student's $t$ test for paired data or with the sign test.

Analysis of the Effects on the Quality of Life

The quality of life was measured by evaluating the overall synthetic score for each patient (obtained by finding the arithmetic mean of the weight of the items to which the patient responded and multiplying by 10 to remove decimals). The overall score could range from a minimum of 0, an index of good quality of life, to a maximum of 20, an index of bad quality of life.

The effect of each treatment on the overall synthetic score was evaluated by calculating the mean values of the index at the end of run-in and after 3, 6, and 9 months of treatment.

The comparison between treatments was made by comparing the mean values of the index after 3, 6, 9 and 12 months of treatment using Student's $t$ test for independent data.

Results

Thirteen centres took part in the trial. Of the 112 patients randomized, 56 were treated with salmeterol and 56 with theophylline.

Thirty-one of the randomized patients withdrew from the trial after the beginning of treatment. The reasons for withdrawal were the following: failure to return (12 patients); adverse events (12 patients); concomitant diseases (three patients); other reasons (four patients). Withdrawal from the study due to adverse events was 3 times more frequent in the theophylline-treated group than in the salmeterol-treated one (nine cases versus three).

Anthropometric, clinical and functional respiratory data (Table 1) of the patients were similar in both groups.

Seven of the patients of the salmeterol group and five of the theophylline group were receiving inhalated anti-inflammatory agents (steroids or chomons); two patients of the salmeterol group and two of the theophylline group were receiving oral methyl prednisolone <20 mg day$^{-1}$. These treatments remained unchanged throughout the trial.

EVALUATION OF THE EFFICACY

PEFR

Both salmeterol and theophylline increased morning and evening PEFR values after 1 and 3 months of treatment as compared with the values found at the end of the run-in (Table 2). The difference between the two treatments was not statistically significant.

The mean increase in morning PEFR over the 3 months of treatment was $35.1 \text{ l min}^{-1}$ in the salmeterol-treated group and $28.1 \text{ l min}^{-1}$ in the theophylline-treated group. The mean increase in evening PEFR in the 3 months of treatment was $41.2 \text{ l min}^{-1}$ in the salmeterol group and $26.5 \text{ l min}^{-1}$ in the theophylline group.

Symptoms

Salmeterol showed a greater and more significant efficacy than theophylline in reducing both daytime and nighttime symptoms (Fig. 1). The rate of symptom-free days in the salmeterol-treated group increased by 31.3% at the end of the run-in to 60.4 and 70% after 1 and 3 months of treatment, respectively. In the theophylline-treated group this rate passed from 28% at the end of run-in to 51.7 and 63.7% after 1 and 3 months of treatment, respectively. The rate of symptom-free days evaluated as the mean over the
Table 1. Anthropometric, clinical and functional respiratory data of the two groups of treated patients

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol</th>
<th>Theophylline</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>56</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Age (years)*</td>
<td>45.5 (14)</td>
<td>47.9 (16.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>31:25</td>
<td>37:18</td>
<td></td>
</tr>
<tr>
<td>No. of smokers</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>No. of patients with allergological positivity</td>
<td>33</td>
<td>28</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of disease (yr)*</td>
<td>12.8 (9.5)</td>
<td>10.3 (8.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>No. of re-exacerbations in last year*</td>
<td>2.6 (2.2)</td>
<td>2.1 (1.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>No. of hospitalizations in last year*</td>
<td>0.5 (0.8)</td>
<td>0.7 (1.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FVC (l)*</td>
<td>3.4 (1-1)</td>
<td>3.2 (1-0.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PEFR (l/min - ')</td>
<td>359.9 (138.6)</td>
<td>331.6 (119.2)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Mean (SD); n.s., no statistical significance.

Table 2. Mean values in litres per minute of PEFR measured in the morning and evening of the two patient groups

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol [mean (SD)]</th>
<th>Theophylline [mean (SD)]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning PEFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of run-in</td>
<td>359.9 (138.6)</td>
<td>331.6 (119.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>After 1 month</td>
<td>385.7 (131)</td>
<td>358.8 (107.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>After 3 months</td>
<td>406.9 (135.6)</td>
<td>371.7 (104.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>1–3 months</td>
<td>387.6 (133.8)</td>
<td>368.2 (105.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Evening PEFR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of run-in</td>
<td>364.7 (139.2)</td>
<td>340.7 (122.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>After 1 month</td>
<td>396 (130-4)</td>
<td>364.6 (106-2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>After 3 months</td>
<td>420.1 (135-6)</td>
<td>380-4 (103-6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>1–3 months</td>
<td>398.4 (132-9)</td>
<td>373-9 (104-4)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

3 months of treatment was 65.7% in the salmeterol group and 56.8% in the theophylline group.

The difference between the effects of the two treatments was statistically significant after 1 month (P<0.001), after 3 months (P<0.005) and as the mean value over the 3 months (P<0.01).

In the salmeterol group the rate of symptom-free nights increased from 32.8% at the end of run-in to 60.8% after 1 month of treatment and 72.1% after 3 months. In the theophylline group these rates passed from 43.4 to 56.3 and 61.2% after 1 and 3 months of treatment, respectively. The rate of symptom-free nights evaluated as the mean over the 3 months was 65.7% in the salmeterol group and 60.2% in the theophylline group. The difference between the effects of the two treatments was statistically significant after 1 month (P<0.05), 3 months (P<0.001) and as the mean value over the 3 months of treatment (P<0.01).

Use of Rescue Salbutamol

The theophylline-treated patients had more frequent recourse to additional salbutamol during both the day and the night than the salmeterol-treated ones (Fig. 2).

The rate of days during which no additional salbutamol was required increased from 34.2% at the end of run-in to 64.1 and 75.5 after 1 and 3 months of salmeterol treatment, respectively, and from 41.8% to 54.8 and 57.5% respectively in the theophylline group. The difference between the effects of the two treatments was statistically significant in favour of salmeterol after both 1 month (P<0.01) and 3 months (p<0.01). The percentage of days without recourse to additional salbutamol, evaluated as the mean over the 3 months, was 68.7% in the salmeterol-treated group and 57.2% in the theophylline-treated one. This difference was statistically significant (p<0.001).

In the salmeterol group the percentage of nights without the need for additional salbutamol passed from 37.9% at the end of the run-in to 66.4% after 1 month of treatment and 74.3% after 3 months. In the theophylline group these percentages passed from 53.3% at the end of run-in to 63.5% after 1 month and to 58.1% after 3 months. The percentage of nights during which patients did not use salbutamol, evaluated as a mean value over the 3 months,
Days
Nights

FIG. 1. Percentage of symptom-free days and nights in salmeterol and theophylline groups: ■, run-in; □, 1 month; △, 3 months.

was 70.1 and 63.0% respectively in the salmeterol and theophylline groups.

The difference between the effects of the two treatments was significant in favour of salmeterol both at the end of the third month of treatment (P<0.001) and as regards the mean over the 3 months (P<0.001).

FVC and FEV₁

Both salmeterol and theophylline produced an increase in FVC and FEV₁ values (Table 3). The difference between the effects of the two treatments was in favour of salmeterol at 3 and 9 months for FVC and at 6 and 9 months for FEV₁, but no difference was observed at the end of the study.

Investigator's and Patient's Assessment

Salmeterol obtained more favourable assessments than theophylline from both investigator and patient and this difference was already statistically significant from the first month. After 1 month, salmeterol was considered very effective or very effective by the investigator in 72.7% of patients, vs 34% for theophylline (P<0.001). At the third month, these percentages became 76.4% for salmeterol and 52.3% for theophylline (P<0.001), while at the 12th month they went up to 78.1% for salmeterol and down to 48.7% for theophylline (P<0.004). After 1 month, salmeterol was considered effective or very effective by the patient in 67.9% of cases, vs 38% for theophylline (P<0.001). At the third month, these percentages became 78 and 45.4%, respectively (P<0.003), while at the 17th month they increased to 81.4% for salmeterol and 50% for theophylline (P<0.02).

Chest Auscultation

The percentage of patients free of bronchospasm increased from 13% at the screening to 57.1% after 12 months of treatment in the salmeterol group, and from 18.1 to 55.3% in the theophylline group. The difference between the two groups of patients was not statistically significant.

Quality of Life

Both salmeterol and theophylline improved the quality of life.

In the salmeterol group the synthetic index passed from 10.2 at the end of run-in to 9.7 after 3 months of treatment, 8.6 after 6 months and 8.0 after 12 months. In the theophylline group the synthetic index passed from 10.4 at the end of run-in to 8.6 after 3 months of treatment, 7.5 after 6 months and 6.7 after 12 months.

The comparison between the two treatments showed no statistically significant differences.

EVALUATION OF SAFETY

The cardiovascular parameters (arterial blood pressure and heart rate) did not change during the treatment period with either of the tested drugs. Neither salmeterol nor theophylline modified the electrocardiographic records.

At the end of the trial the following haematological parameters changed as compared with baseline values: lymphocytes increased in 85.3% (P<0.001) of salmeterol subjects and in 83.9% (P<0.001) of theophylline subjects; monocytes and calcium decreased in 64% (P=0.01) and in 58.8% (P=0.05) respectively of salmeterol patients; eosinophils and alkaline phosphate decreased in 71% (P<0.001) and 64.5% (P=0.05) respectively of theophylline patients.

Of the 56 patients treated with salmeterol, six (10.7%) reported at least one minor adverse event; these events were judged by the researcher as being almost certainly related to the administration of the drug in three patients. The total number of minor events was eight, and of these four (50%) were considered severe by the investigator. In the salmeterol-treated group, a serious adverse event occurred (death); this was judged by the investigator as not being related to the drug.

Of the 56 patients treated with theophylline, three (5.3%) reported at least one minor adverse event; five (8.9%) an adverse event which was not classified by the investigator and two (3.5%) a serious adverse effect (one 'pain all over', and one 'road traffic accident', both judged by the investigator as not being related to the administration of the drug). In five of the eight patients reporting at least one minor or unclassified adverse effect, such effects are judged
Table 3. Mean values in litres of FEV₁ and FVC measured at the different examinations and mean between the values at the various examinations and the value at the end of run-in in the two patient groups

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol [mean (SD)]</th>
<th>Theophylline [mean (SD)]</th>
<th>Salmeterol [mean ∆]</th>
<th>Theophylline [mean ∆]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FVC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of run-in</td>
<td>3.35 (1.2)</td>
<td>3.26 (1.0)</td>
<td>+0.13</td>
<td>+0.12</td>
<td>n.s.</td>
</tr>
<tr>
<td>1 month</td>
<td>3.49 (1.2)</td>
<td>3.46 (0.9)</td>
<td>+0.23</td>
<td>+0.21</td>
<td>n.s.</td>
</tr>
<tr>
<td>3 months</td>
<td>3.63 (1.2)</td>
<td>3.48 (0.9)</td>
<td>+0.48</td>
<td>+0.34</td>
<td>n.s.</td>
</tr>
<tr>
<td>6 months</td>
<td>3.61 (1.2)</td>
<td>3.54 (0.9)</td>
<td>+0.12</td>
<td>+0.11</td>
<td>n.s.</td>
</tr>
<tr>
<td>9 months</td>
<td>3.70 (1.2)</td>
<td>3.53 (0.9)</td>
<td>+0.21</td>
<td>+0.18</td>
<td>n.s.</td>
</tr>
<tr>
<td>12 months</td>
<td>3.70 (1.2)</td>
<td>3.64 (0.9)</td>
<td>+0.27</td>
<td>+0.27</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>FEV₁</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of run-in</td>
<td>2.22 (0.8)</td>
<td>2.14 (0.6)</td>
<td>+0.25</td>
<td>+0.20</td>
<td>n.s.</td>
</tr>
<tr>
<td>1 month</td>
<td>2.45 (0.9)</td>
<td>2.36 (0.7)</td>
<td>+0.34</td>
<td>+0.24</td>
<td>n.s.</td>
</tr>
<tr>
<td>3 months</td>
<td>2.60 (0.9)</td>
<td>2.50 (0.7)</td>
<td>+0.40</td>
<td>+0.22</td>
<td>n.s.</td>
</tr>
<tr>
<td>6 months</td>
<td>2.65 (1.0)</td>
<td>2.49 (0.7)</td>
<td>+0.43</td>
<td>+0.19</td>
<td>n.s.</td>
</tr>
<tr>
<td>9 months</td>
<td>2.74 (0.9)</td>
<td>2.56 (0.7)</td>
<td>+0.45</td>
<td>+0.28</td>
<td>n.s.</td>
</tr>
<tr>
<td>12 months</td>
<td>2.75 (0.9)</td>
<td>2.56 (0.7)</td>
<td>+0.45</td>
<td>+0.28</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 4. Minor or unclassified adverse events occurring during the trial

<table>
<thead>
<tr>
<th></th>
<th>Salmeterol</th>
<th>Theophylline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Excitability</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Precordial pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Tremors</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Re-exacerbation of asthma</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pyrosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Epigastralgia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Discussion

The results of our trial show that inhaled salmeterol in asthmatic patients at the dosage of 50 μg b.d. for a period of 12 months is associated with a better control of asthma and lower frequency of adverse events than individually dose-titrated, sustained-release theophylline administered twice daily.

Salmeterol showed a greater and more significant efficacy than theophylline in reducing both day- and night-time symptoms and in reducing additional salbutamol requirement. The subjective assessment of efficacy by physicians and patients was in favour of salmeterol from the first month of treatment. These findings are in agreement with those of previous studies (20–24) which had tested salmeterol versus theophylline for shorter periods of time (from 7 to 28 days). In asthmatic patients treated for 28 days, the complete disappearance of nocturnal symptoms was reported in 46-39% of those treated with salmeterol and in 15-36% of those treated with theophylline (20). Also, the treatment of asthmatic patients for a shorter period of time (7-15 days) resulted in a greater reduction in symptoms and use of additional salbutamol in the salmeterol-treated group than in the theophylline-treated one (21,22). More recently in a large multicentre European study which lasted 4 weeks (23), the median percentage of nights with no asthma symptoms rose from 14% to 71% in patients treated with salmeterol and from 14% to 46% in patients treated with theophylline. Moreover, in the salmeterol group, rescue salbutamol use was significantly reduced during the night in comparison with the theophylline group.

Also our study, carried out for a longer period of time (3 months) than the other studies previously reported, confirms the higher efficacy of salmeterol than theophylline in reducing daily (21) and nocturnal (21-23) symptoms and rescue salbutamol use (21–23).

The improvement of quality of life is a desirable target in the treatment of bronchial asthma. A recent study has reported that patients with nocturnal asthma treated with salmeterol had more nights without awakenings, fewer nocturnal arousals and improved quality of life in comparison with patients treated with theophylline (25). In our patients the improvement of quality of life was observed in both groups without significant difference, even though
salmeterol was associated with a better control of daily and nocturnal symptoms than theophylline. We have no explanations for this discrepancy; probably quality of life is influenced by many other complex factors in addition to symptoms.

Concerning the adverse effects which may be induced by bronchodilating agents the data of our study showed that the patients treated with salmeterol had fewer adverse events than those treated with theophylline, even though the difference was not statistically significant. These results were in agreement with those of previous studies, which reported five times less frequent adverse effects in salmeterol-treated patients than in theophylline-treated ones (20) and association of headache, nausea and vomiting with theophylline treatment (21,23).

While all the studies previously cited indicate a greater efficacy of salmeterol in reducing asthma symptoms, which is associated with less need for additional salbutamol administration, the analysis of the respiratory function findings in both our trial and previous ones indicates an improvement with both salmeterol and theophylline, with salmeterol at only a slight advantage.

In asthmatic patients treated for 28 days with salmeterol a statistically significantly higher increase in FEV₁ was found than in patients treated with theophylline + ketotifen for a similar period, while no significant differences were ascertained in either FVC or PEFR (20).

Salmeterol showed a significantly greater efficay than theophylline in inducing both morning and evening PEFR improvement over a 15-day administration period; FEV₁ improved without any significant differences in both groups (21).

The administration of salmeterol for 7 days led to a reduction in the number of days with PEFR decrease during the night and this effect was significantly higher than with theophylline. The effect of the two treatments on FFV₁ and FVC was not evaluated (22).

No significant difference between salmeterol versus theophylline was observed for PEFR in a recent study during 4 weeks of treatment (23).

The different behaviour of the various respiratory function parameters in these studies is difficult to interpret. One explanation might be the difference in trial design as regards duration and the influence of the accuracy of patient training as regards the performance and hence the result of PEFR measurement.

In our study both treatments determined an improvement over time in morning and evening PEFR, FEV₁ and FVC without significant difference at the end of the study.

In conclusion, our trial suggests that salmeterol has higher efficacy and safety than theophylline in long-term treatment of asthmatic patients. It may thus be considered a first-choice long-lasting bronchodilator for those asthmatic patients who have clinical indications for treatment with this class of drugs.

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References


**Appendix**

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