

# A 4-week comparison of salmeterol and terbutaline in adult asthma\*

Hermansson BA, Jenkins RJ. A 4-week comparison of salmeterol and terbutaline in adult asthma.

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This was a 4-week, open-label, parallel-group study designed to compare the efficacy and safety of the long-acting inhaled bronchodilator, salmeterol, with the established inhaled bronchodilator, terbutaline, in the treatment of patients with mild to moderate asthma. A total of 243 adult patients was randomized to receive treatment with either salmeterol 50 µg bd via a Diskhaler<sup>TM</sup> (Glaxo) inhaler ( $n = 121$ ) or terbutaline 500 µg qds via a reservoir powder inhaler device ( $n = 122$ ). Apart from all bronchodilator treatment which was withdrawn at the start of the run-in period and replaced by inhaled salbutamol to be used as required for symptom relief, all concurrent medications were kept constant throughout the study. Salmeterol produced a significantly greater increase in mean morning peak expiratory flow (PEF) than terbutaline (difference in adjusted means after treatment = 28 l/min; 95% CI = 19–37 l/min;  $P < 0.001$ ). Likewise, the increase in mean evening PEF was significantly greater following treatment with salmeterol than with terbutaline (difference in adjusted means = 9 l/min; 95% CI = 0–17 l/min;  $P = 0.045$ ). Salmeterol was associated with a significant reduction in diurnal variation in PEF by comparison with terbutaline (difference in adjusted means = –18 l/min; 95% CI = –24, –12 l/min;  $P < 0.001$ ). Significant improvements with salmeterol by comparison with terbutaline were also observed in daytime and night-time asthma scores, percentage of symptom-free days and nights, use of additional inhaled bronchodilator, and percentage of days and nights when no additional inhaled bronchodilator was needed. The greater overall improvement in the control of asthma and its symptoms after treatment with salmeterol was further evident from the lower incidence of asthma-related adverse events in patients taking salmeterol compared with those taking terbutaline (2% and 15%, respectively). While both treatments were well tolerated, more patients withdrew from the terbutaline group than from the salmeterol group (12 and 3 patients, respectively) and terbutaline was associated with a higher incidence of drug-related adverse events (26% and 9% in the terbutaline- and salmeterol-treated groups, respectively). This study demonstrated that salmeterol 50 µg bd via a Diskhaler was significantly more effective and associated with fewer adverse events than terbutaline 500 µg qds via a reservoir powder inhaler device.

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Inhaled short-acting beta<sub>2</sub>-adrenergic agonists, such as salbutamol and terbutaline, are the most effective bronchodilator agents available for the treatment of acute symptoms of asthma (16). The disadvantage of both agents is that they have only a relatively short duration of action. Measurable bronchodilatation following inhalation of a standard dose of 200 µg

salbutamol or 500 µg terbutaline persists for 4–6 h although protection from exercise and other challenges seldom exceeds 2 h in the majority of asthmatic patients (3, 34). Therefore, the availability of an inhaled beta<sub>2</sub>-adrenoceptor agonist which has a longer duration of action but a similar side-effect profile would offer distinct advantages over the short-acting alternatives. The most important of these advantages in terms of asthma management would be the possibility of improved symptom control by day and by night and the convenience of a reduced dos-

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ing schedule which might facilitate better compliance with treatment.

Salmeterol is a selective, long-acting, inhaled  $\beta_2$ -agonist which has a duration of action of at least 12 h (2). Various large multicentre studies (6, 9, 18, 25–27), some of them lasting up to 12 months (6, 18), have confirmed the safety and efficacy of a twice daily dose of salmeterol 50  $\mu$ g whether inhaled as an aerosol from a metered-dose inhaler, or as a dry powder from a Diskhaler<sup>TM</sup> inhaler. Salmeterol 50  $\mu$ g twice daily has also been shown to be more effective than salbutamol 200  $\mu$ g four times daily when administered by metered-dose inhaler (6), and salbutamol 400  $\mu$ g four times daily when both drugs were inhaled as dry powder (18).

The present study compared the efficacy and safety of twice daily salmeterol with four times daily terbutaline when both drugs were administered in dry-powder form to adult patients with mild to moderate asthma.

## Material and methods

### *Patients*

A total of 243 patients aged over 18 years with mild to moderate asthma was enrolled by 23 centres in six European countries. Patients were allowed to continue their usual asthma therapy provided the dose remained constant throughout the study with the exception of any  $\beta_2$ -agonist therapy or anticholinergic treatment, which was replaced by inhaled salbutamol via a Diskhaler inhaler to be used as required.

Patients were considered eligible for the study if they could demonstrate either a forced expiratory volume in 1 s ( $FEV_1$ ) at the clinic, or a mean daily peak expiratory flow rate (PEF) over week 2 of the run-in period, of at least 50% of predicted normal value and reversibility in  $FEV_1$  of greater than 15% following inhalation of salbutamol (400  $\mu$ g from a Diskhaler inhaler). On at least four of the last seven days of the run-in, the total daily symptom score was found to be at least 2 for each patient, with a minimum score of 1 during the day, or a diurnal variation in daily PEF of greater than 15%. Daytime asthma symptom scores were rated from a scale which ranged from 0 (no symptoms) to 5 (symptoms so severe that patients could not go to work or perform normal daily activities), and nighttime symptoms were scored from a scale which ranged from 0 (no symptoms) to 4 (symptoms so severe that patients did not sleep at all).

Patients were excluded from the study if they were suffering from a serious uncontrolled systemic disease, had recently been admitted to hospital with asthma, or had suffered infection of the lower respiratory tract within the previous month. Other rea-

sons for exclusion were as follows: a requirement for oral steroid therapy in excess of 20 mg prednisolone or its equivalent per day; lactation, pregnancy, or inadequate contraceptive precautions in women of child-bearing potential; known hypersensitivity to  $\beta_2$ -receptor agonists; concurrent treatment with  $\beta$ -receptor antagonists; and treatment with other research medication during the previous month.

### *Design and methods*

This was a multicentre, open-label, randomized, parallel-group study comparing the effects of salmeterol 50  $\mu$ g twice daily with terbutaline 500  $\mu$ g four times daily. A run-in period of 2 weeks preceded a 4-week treatment period, which was followed by a 2-week follow-up period.

At the first clinic visit, a full clinical history was documented and a physical examination performed. Blood and urine samples were taken, and a 12-lead electrocardiogram was performed as a safety screen. Vital signs and weight were recorded at the first visit and again on two subsequent occasions: at the end of both the run-in and the 4-week treatment periods.

Patients were shown how to use the mini-Wright peak flow meter and the Diskhaler inhaler. They were also issued with daily record cards on which they were asked to record morning and evening PEF, asthma symptom scores, and use of additional inhaled salbutamol. These measurements were to be made before inhaling the next dose of study medication or salbutamol.

Patients fulfilling the entry criteria at the end of the run-in period were randomized to receive either salmeterol 50  $\mu$ g morning and evening to be administered via the Diskhaler inhaler, or terbutaline 500  $\mu$ g to be inhaled morning, noon, late afternoon, and at bedtime, administered via the reservoir powder inhaler device. Prior to commencing treatment, patients allocated terbutaline were shown how to use the reservoir powder inhaler device. Salbutamol blister packs (400  $\mu$ g/blister) were provided for use as required to relieve symptoms.

There was a total of six clinic visits: at the beginning, middle and end of the 2-week run-in period; after 2 and 4 weeks' treatment; and at the end of the 2-week follow-up period. At the second clinic visit and at each clinic visit thereafter, three measurements of  $FEV_1$  and forced vital capacity (FVC) were also recorded.

Patients and physicians were asked to make a subjective assessment of the efficacy of study medication immediately before and after 2 and 4 weeks' treatment.

Safety and tolerability were assessed by recording any adverse events and by analysing cardiovascular parameters and weight before, during, and after treat-

ment. The treatment of acute asthma exacerbations was left to the discretion of the investigator.

Prior to the start of the study, ethics committee approval was obtained from each centre where such a committee existed, and patients provided their written or oral informed consent to participate in the trial. The study was conducted in accordance with the conditions agreed in the Declaration of Helsinki (Hong Kong Amendment, 1989).

### Statistical methods

All statistical tests were conducted on the total population randomized to receive study treatment on an "intent-to-treat" basis. With 243 patients randomized to treatment, the study had approximately 93% power to detect a mean difference of 20 l/min in the primary end point, morning PEF, at the 5% level of significance. Centres were grouped into countries for the purpose of analysis. A two-tailed significance test was used for declaring differences.

Morning and evening PEF were recorded in triplicate by the patients, and the highest value of each was used in the analysis. Daily PEF, additional bronchodilator medication, and daytime and night-time asthma scores were summarized for each patient and included in the analysis if data were available for at least 14 days of the treatment period and at least 4 days of week 2 of the run-in period. Data from the last 7 days of the run-in period were used as baseline values.

Morning and evening PEF, diurnal variation in PEF, clinic lung function measurements (FEV<sub>1</sub> and FVC), and vital signs were analysed by analysis of covariance, with baseline as a covariate, adjusting for variation due to country. Treatment mean values, adjusted for these covariates, were calculated, and the significance of differences between treatments and 95% confidence intervals (CI) for the difference were based on the "*t*" distribution. The data were also evaluated for interactions, at the 10% significance level, between treatment and baseline and between treatment and country.

Median responses were calculated for daytime and night-time asthma scores, the percentage of days with a score of zero, the percentage of nights with a score of zero, the percentage of days and nights with no additional salbutamol, and the number of times salbutamol was taken in the day and at night. Median daytime and night-time asthma symptom scores (scores of 2 and higher were pooled together), together with physicians' and patients' assessment of overall efficacy of treatment, were analysed with logistic regression models, allowing for variation due to differences at baseline and due to country. Treatment effects were estimated (with 95% CI) for the probability of observing any specified response cat-

egory or better. For all the other assessments, the median change from baseline for each variable was subjected to a nonparametric analysis by the Wilcoxon rank sum test, stratified by country by van Elteren's method (32).

## Results

### Patients

Of the total 243 patients randomized to treatment, 121 received salmeterol 50 µg bd, and 122 received terbutaline 500 µg qds. Table 1 shows the demographic details of the study population. Other than differences in the ratio of women to men and in the percentage of previous smokers, the two treatment groups were similar in terms of baseline characteristics, lung function, concomitant diseases, and medication. Any differences in baseline demography between the two treatment groups did not significantly affect the study outcome. The most commonly used drugs during the study were inhaled steroids taken by 92 patients (79%) and 85 patients (70%) in the salmeterol and terbutaline groups, respectively.

Fifteen patients (6%) were withdrawn from the study after randomization (three and 12 from the salmeterol and terbutaline groups, respectively). Nine patients withdrew because of an exacerbation of asthma (one and eight in the salmeterol and terbutaline groups, respectively), four withdrew because of adverse events (one and three in the salmeterol

Table 1. Patient characteristics

|                                            | Salmeterol<br>50 µg bd | Terbutaline<br>500 µg qds | Total    |
|--------------------------------------------|------------------------|---------------------------|----------|
| No. of patients                            | 121                    | 122                       | 243      |
| Men <i>n</i> (%)                           | 52 (43)                | 68 (56)                   | 120 (49) |
| Women <i>n</i> (%)                         | 69 (57)                | 54 (44)                   | 123 (51) |
| Caucasian <i>n</i> (%)                     | 120 (99)               | 120 (98)                  | 240 (99) |
| Age (years)                                |                        |                           |          |
| Median                                     | 49                     | 48                        | 48       |
| Range                                      | 18–78                  | 18–74                     | 18–78    |
| Height (cm)                                |                        |                           |          |
| Mean (SD)                                  |                        |                           |          |
| Men                                        | 176 (6)                | 175 (7)                   | 175 (7)  |
| Women                                      | 163 (6)                | 164 (7)                   | 163 (7)  |
| Weight (kg)                                |                        |                           |          |
| Mean (SD)                                  |                        |                           |          |
| Men                                        | 81 (11)                | 81 (12)                   | 81 (11)  |
| Women                                      | 67 (11)                | 64 (11)                   | 66 (11)  |
| Smokers <i>n</i> (%)                       |                        |                           |          |
| Yes                                        | 20 (17)                | 22 (18)                   | 42 (17)  |
| No                                         | 67 (55)                | 60 (41)                   | 117 (48) |
| Previous                                   | 34 (28)                | 50 (41)                   | 84 (35)  |
| Duration of asthma <i>n</i> (%)            |                        |                           |          |
| 0–10 years                                 | 68 (56)                | 72 (60)                   | 140 (58) |
| 11–30 years                                | 38 (31)                | 36 (30)                   | 74 (31)  |
| > 30 years                                 | 115 (12)               | 13 (11)                   | 28 (12)  |
| Asthma medication continued into study (%) |                        |                           |          |
| Inhaled steroids                           | 92 (76)                | 85 (70)                   | 177 (73) |
| Oral and inhaled steroids                  | 4 (3)                  | 4 (3)                     | 8 (3)    |
| Sodium cromoglycate                        | 11 (9)                 | 7 (6)                     | 18 (7)   |
| Others                                     | 5 (4)                  | 10 (8)                    | 15 (6)   |

and terbutaline groups, respectively), and one patient in each group failed to return.

Physicians recorded a total 14 (6%) patients who were noncompliant and failed to take study medication as prescribed; five (4%) in the salmeterol group and nine (7%) in the terbutaline group. Data from these patients were included in the analyses.

#### Daily record card data

**PEF.** Compared with terbutaline, salmeterol produced significant improvements in both morning and evening PEF (Figs. 1 and 2) and in diurnal variation in PEF.

Over 4 weeks' treatment, mean morning PEF increased from 374 to 407 l/min and from 374 to 378 l/min for salmeterol and terbutaline, respectively. The difference in adjusted means after treatment (28 l/min) was statistically significant ( $P < 0.001$ ; 95% CI = 19 to 37 l/min) in favour of salmeterol (Table 2).

Mean evening PEF over 4 weeks' treatment increased from 405 to 421 l/min and from 402 to 409 l/min for salmeterol and terbutaline, respectively. The difference in the adjusted means after treatment for morning PEF (9 l/min) was statistically significant ( $P = 0.045$ ; 95% CI = 0 to 17 l/min) in favour of salmeterol (Table 2).

Mean diurnal variation in PEF decreased from 32 l/min at baseline to 14 l/min during treatment in the salmeterol group, whereas it remained unaltered in the terbutaline group (Table 2). This difference between treatments (adjusted mean difference = -18 l/min) was statistically significant (95% CI = -24 to -12 l/min;  $P < 0.001$ ; Table 2). A treatment-by-country and a treatment-by-baseline interaction was observed ( $P < 0.001$ ). Inspection of the data showed that the treatment-by-country interaction was probably due to the fact that the diurnal variation in PEF for the Finnish patients, unlike all the other nationalities, was smaller for the terbutaline

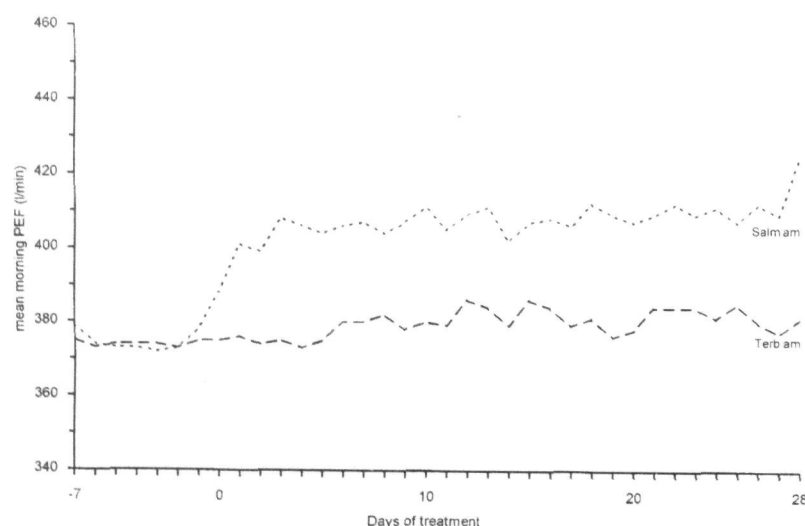


Fig. 1. Daily mean morning peak expiratory flow (PEF). Terb am = terbutaline 500 µg qds; Salm am = salmeterol 50 µg bd.

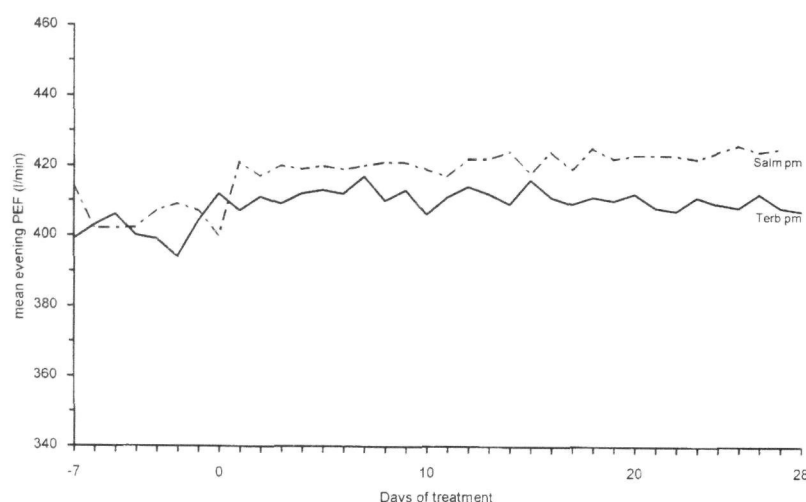


Fig. 2. Daily mean evening peak expiratory flow (PEF). Terb pm = terbutaline 500 µg qds; Salm pm = salmeterol 50 µg bd.

group than the salmeterol group. However, there was no evidence of a treatment-by-country interaction for Finland in any of the other parameters. Likewise, the treatment-by-baseline interaction was not consistently seen through the results, suggesting that it was a spurious finding.

**Asthma symptoms.** At the end of the run-in period, both treatment groups had median values of 0% of days with no symptoms. After 4 weeks' treatment, 42% of patients in the salmeterol group had a median daytime asthma score of zero compared with 22% in the terbutaline group (Fig. 3). Statistical analysis showed that there was a significant difference ( $P < 0.001$ ) in the frequency of daytime asthma scores in favour of salmeterol (odds ratio = 3.52; 95% CI = 2.07, 5.99).

Night-time asthma scores at the end of the run-in were also comparable, both groups having a median value of 29% of nights with an asthma score of zero. Following treatment, 67% of patients taking salmeterol had a median night-time asthma score of zero compared with 52% of patients using terbutaline (Fig. 3). The difference in frequency of night-time asthma scores was also statistically significant in favour of salmeterol (odds ratio = 2.29; 95% CI = 1.24, 4.23;  $P = 0.008$ ).

As a corollary, the median percentage of symptom-free days was significantly higher in the salmeterol group (0% at baseline to 43% at the end of treatment) than in the terbutaline group (no change from 0% at baseline ( $P < 0.001$ )). A similar improvement was observed in the median percentage of symptom-free nights, which rose from 29% at baseline to 86% at the end of treatment in patients taking salmeterol. In the terbutaline group, the median percentage of symptom-free nights rose from 29% at baseline to 71% at treatment week 4 ( $P = 0.012$ ).

**Use of rescue medication.** Only a small amount of additional inhaled salbutamol was used during the

Table 2. Analysis of peak expiratory flow (PEF) data

|                                   | Salmeterol<br>50 µg bd | Terbutaline<br>500 µg qds | Difference in<br>adjusted means<br>(Sal-Terb) | 95% CI   | P value |
|-----------------------------------|------------------------|---------------------------|-----------------------------------------------|----------|---------|
| <b>Morning PEF</b>                |                        |                           |                                               |          |         |
| No. of patients                   | 119                    | 113                       |                                               |          |         |
| Mean during baseline (l/min)      | 374                    | 374                       |                                               |          |         |
| Mean during treatment (l/min)     | 407                    | 378                       |                                               |          |         |
| Adjusted* mean                    | 407                    | 379                       | 28                                            | 19, 37   | <0.001  |
| <b>Evening PEF</b>                |                        |                           |                                               |          |         |
| No. of patients                   | 117                    | 110                       |                                               |          |         |
| Mean during baseline (l/min)      | 405                    | 402                       |                                               |          |         |
| Mean during treatment (l/min)     | 421                    | 409                       |                                               |          |         |
| Adjusted* mean                    | 418                    | 410                       | 9                                             | 0, 17    | 0.045   |
| <b>Diurnal variation in PEF**</b> |                        |                           |                                               |          |         |
| No. of patients                   | 117                    | 112                       |                                               |          |         |
| Mean during baseline (l/min)      | 32                     | 26                        |                                               |          |         |
| Mean during treatment (l/min)     | 14                     | 30                        |                                               |          |         |
| Adjusted* mean                    | 12                     | 30                        | -18                                           | -24, -12 | <0.001  |

\* Means adjusted for baseline and country.

\*\* Mean morning-evening decrease in PEF.

treatment period. The highest weekly median value observed was two blisters per day during week 1 of the treatment period for patients receiving terbutaline. The highest weekly median value observed for patients receiving salmeterol was one blister per day. Statistical analysis showed that, compared with baseline values, patients in the salmeterol group took less rescue salbutamol by day and by night than did those in the terbutaline group. In the day, 87% of patients in the salmeterol group exhibited a decrease compared with 67% in the terbutaline group ( $P < 0.001$ ). At night, 42% of patients in the salmeterol group exhibited a decrease compared with 24% in the terbutaline group ( $P = 0.002$ ).

The percentage of days and nights during which patients required no additional salbutamol was significantly higher among patients taking salmeterol than among those taking terbutaline. Daytime values increased from a median 0% at baseline to a median 67% and 17% after 4 weeks' treatment in the salmeterol and terbutaline groups, respectively (median difference in increases = 27.8%;  $P = 0.002$ ). Night-time values increased from a median 50% at baseline to 100% in the salmeterol group and from 59% at baseline to 86% in the terbutaline group (median difference in increases = 11%;  $P = 0.007$ ).

### Clinic assessments

**Lung function.** There were no significant differences between treatments in terms of mean FEV<sub>1</sub> or FVC after 4 weeks' treatment. The mean FEV<sub>1</sub> at baseline was 2.43 l for the salmeterol group and 2.31 l for the

terbutaline group. These increased to 2.62 l and 2.47 l, respectively (difference in adjusted means = 0.03; 95% CI = -0.08, 0.14;  $P = 0.598$ ).

The mean FVC at baseline was 3.42 l for the salmeterol group and 3.21 l for the terbutaline group. These increased to 3.63 l and 3.43 l, respectively (difference in adjusted means = 0.01; 95% CI = -0.13, 0.14;  $P = 0.916$ ).

**Overall assessment of efficacy.** At the end of treatment, both the physicians' and patients' assessments of efficacy judged salmeterol to be significantly more effective than terbutaline (odds ratio for physicians' assessment = 4.57,  $P < 0.001$ ; odds ratio for patients'

Table 3. Most common adverse events\*

|                                         | Salmeterol<br>50 µg bd | Terbutaline<br>500 µg qds |
|-----------------------------------------|------------------------|---------------------------|
| Total no. of patients                   | 121                    | 122                       |
| No. of patients reporting adverse event | 47 (39%)               | 54 (44%)                  |
| Asthma                                  | 3 (2%)                 | 18 (15%)                  |
| Acute nasopharyngitis                   | 15 (12%)               | 7 (6%)                    |
| Headache**                              | 8 (7%)                 | 4 (3%)                    |
| Bronchitis                              | 3 (2%)                 | 3 (2%)                    |
| Respiratory infection                   | 3 (2%)                 | 1 (<1%)                   |
| Tremor**                                | 2 (2%)                 | 8 (7%)                    |
| Viral infection                         | 2 (2%)                 | 3 (2%)                    |
| Palpitations**                          | 1 (<1%)                | 0                         |
| Tachycardia**                           | 1 (<1%)                | 0                         |
| Muscle cramps**                         | 0                      | 1 (<1%)                   |

\* Reported as overall diagnosis or symptom without diagnosis.

\*\* Pharmacologically predictable.

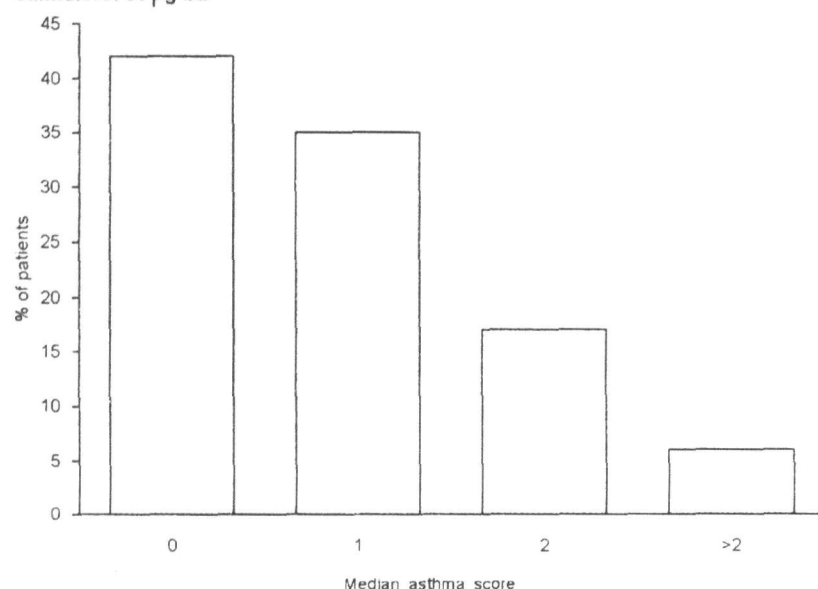
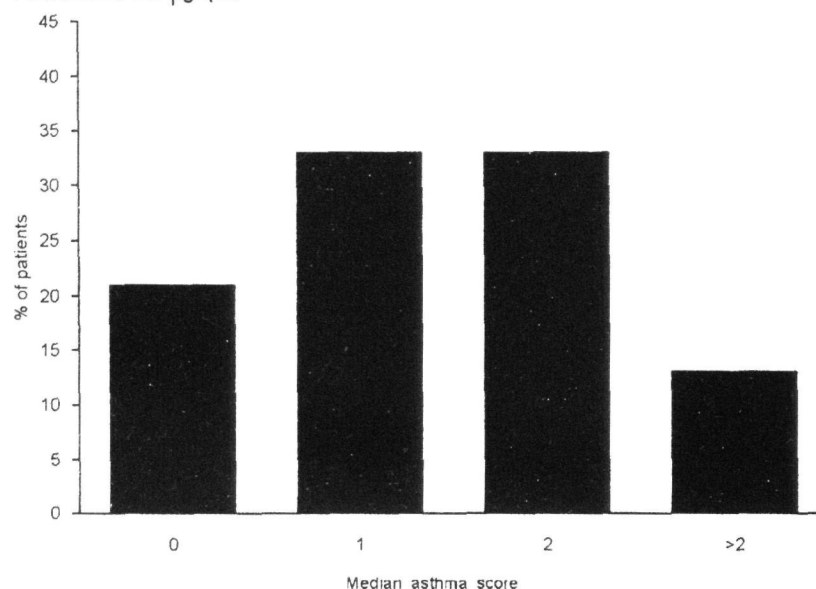
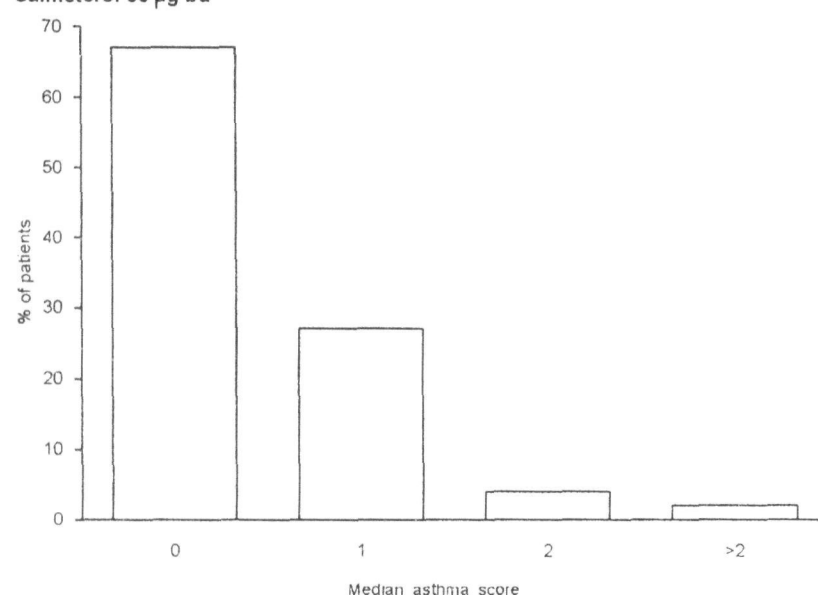
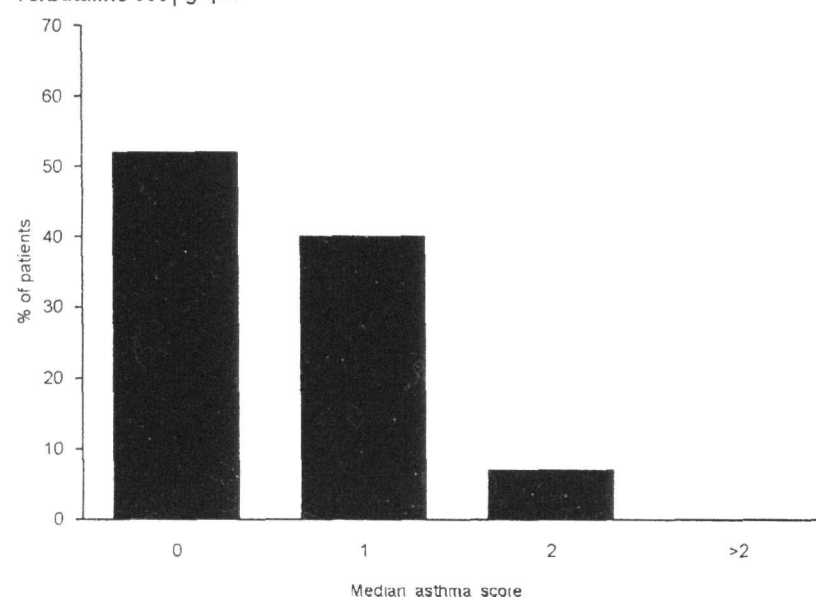
**DAYTIME SCORES**  
**Salmeterol 50 µg bd**

**Terbutaline 500 µg qds**

**NIGHT-TIME SCORES**  
**Salmeterol 50 µg bd**

**Terbutaline 500 µg qds**


Fig. 3. Median daytime and night-time asthma scores for salmeterol 50 µg bd and terbutaline 500 µg qds over 4-week treatment period.

assessment = 4.02,  $P < 0.001$ ). The relative percentages judging treatment as "effective" or "very effective" were, for salmeterol and terbutaline, respectively, 84% and 61% of patients and 84% and 58% of physicians.

#### Adverse events

Adverse events were reported by 47 patients (39%) taking salmeterol (65 adverse events) and 54 patients (44%) taking terbutaline (81 adverse events). Asthma was the most common event in the terbutaline group (reported by 18 patients (15%)) compared to three patients (2%) in the salmeterol group. Acute nasopharyngitis and headache were the events most commonly reported by patients taking salmeterol (Table 3).

Headache and tremor were the most commonly reported pharmacologically predictable adverse events. Tremor was higher in patients treated with

terbutaline than in those treated with salmeterol, affecting 7% and 2% of patients, respectively. On the other hand, headache was more common in the salmeterol group than in the terbutaline group (7% and 3%, respectively).

Twenty-one of the 81 adverse events (26%) reported by patients taking terbutaline were considered to be drug-related. There were eight cases of tremor, two of nervousness, and one each of leg cramps, sleeping difficulties, dizziness, headache, nausea, and hypersensitivity reaction to terbutaline. The five remaining drug-related adverse events appeared to indicate inadequate control of asthma symptoms.

Of the six drug-related adverse events (9%) reported by patients in the salmeterol group, the majority were pharmacologically predictable. There were two cases of headache, two of tremor, and one each of tachycardia and laryngitis.

*Vital signs*

No clinically relevant changes in weight, pulse rate, or systolic and diastolic blood pressure were detected.

**Discussion**

The results of this study demonstrated that the addition of salmeterol 50 µg twice daily administered via a Diskhaler inhaler to patients' usual prophylactic asthma therapy was significantly more effective in the control of symptomatic moderate asthma than the addition of terbutaline 500 µg four times daily administered via a reservoir powder inhaler device. The improvement was further evident from the lower incidence of exacerbations of asthma in patients taking salmeterol compared with those taking terbutaline (2% (3/121 patients) and 15% (18/122 patients), respectively). Additionally, more patients withdrew from the terbutaline group than from the salmeterol group (12 and three patients, respectively). There were no significant differences in clinic lung function measurements, but this was not surprising since no attempt was made to withhold bronchodilators before clinic visits.

In general, both treatments were well tolerated and associated with a similarly low incidence of pharmacologically predictable adverse events, although more drug-related adverse events (26%) were reported by patients taking terbutaline than by those taking salmeterol (9%).

The study opted for an open design in preference to a double-blind, double-dummy method, which would have relied on dosing from multiple inhalers and complicated dose regimens, factors which could have affected patient compliance. Compliance with treatment was in fact good, with only 4% of patients in the salmeterol group and 7% of patients in the terbutaline group being reported as noncompliant. The main drawback of an open study design is the potential for bias, which is dependent on both the patients' and physicians' preconceptions about a particular treatment. Bias was reduced in this present study by the use of a parallel-group design and a large subject population. All efficacy variables were significantly in favour of salmeterol, and it is therefore unlikely that terbutaline was more effective than salmeterol. In addition, fewer drug-related adverse events and fewer exacerbations of asthma were reported in the salmeterol group than in the terbutaline group.

Furthermore, the results of this present study concur with those of Venables (33), who, in a 4-week crossover study in 102 patients, found that salmeterol 50 µg bd administered via a Diskhaler inhaler had significant advantages over terbutaline 500 µg

qds administered via a reservoir powder inhaler device in terms of efficacy, safety, and frequency of dosing. Also, more patients preferred salmeterol via the Diskhaler inhaler than terbutaline via the reservoir powder inhaler device.

These data also compare favourably with previous studies comparing salmeterol (50 µg twice daily) with the short-acting beta<sub>2</sub>-agonist salbutamol (200–400 µg four times daily) which showed that salmeterol produced significantly better asthma control, fewer asthma exacerbations, and a decreased requirement for rescue inhaled-bronchodilator therapy (6, 18, 27).

This study confirms that, despite widespread use of inhaled corticosteroids, persistent symptoms of asthma continue to affect a number of patients (17). Patients particularly affected are those who are prone to nocturnal symptoms and symptoms induced by cold air and exercise (17). In the past, these patients were treated with slow-release oral bronchodilators (theophylline and/or beta<sub>2</sub>-agonists) and/or regular inhalations of short-acting beta<sub>2</sub>-agonist three to four times daily (5, 17). However, while theophyllines and oral beta<sub>2</sub>-agonists do provide prolonged bronchodilatation, their use is associated with frequent side-effects (14, 21, 22). For these patients, regular treatment with inhaled salmeterol is an alternative which has been shown to have good efficacy and few side-effects (8, 10, 19, 20, 23, 24).

Some studies have suggested that regular use of beta<sub>2</sub>-agonists may lead to loss of asthma control (11, 15, 28, 30, 32). Others have found no evidence of such an effect, observing, on the contrary, that both asthma symptoms and lung function improved (1, 4, 6, 7, 12, 18, 29). Although the present study was not specifically designed to study this aspect of beta<sub>2</sub>-agonist therapy and did not include a placebo treatment group, the results agree with those of other studies showing that regular inhaled beta<sub>2</sub>-agonist therapy has no deleterious effect on asthma control. This was evident from the improvements shown in both treatment groups for morning and evening PEF, diurnal variation in PEF, night-time asthma symptoms, and use of rescue inhaled bronchodilator. Furthermore, the incidence of asthma exacerbations was in keeping with previous findings (13, 29).

In summary, this study demonstrated that in patients with moderate asthma, the majority of whom were concurrently receiving inhaled corticosteroids, twice daily salmeterol 50 µg administered via a Diskhaler inhaler provided significantly better asthma control and was associated with fewer adverse events than terbutaline 500 µg administered four times daily via a reservoir powder inhaler device.

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