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Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids

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Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids. P. Faurschou, I. Steffensen, L. Jacques, on behalf of a European Respiratory Study Group.

ABSTRACT: The aim of this study was to assess the efficacy and safety of inhaled salmeterol 100 µg *b.d.* (SM) *versus* inhaled salbutamol 400 µg *q.d.s.* (SB), both *via* the Diskhaler™, when added to concurrent treatment, in asthmatic patients who were not controlled on high doses of inhaled steroids (≥1,500 µg beclomethasone dipropionate (BDP) or equivalent daily).

This was a multicentre, parallel group, double-blind study in which 190 patients with a forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEFR) of 30–75% predicted and 15% reversibility to inhaled bronchodilator were randomized to treatment for 6 weeks.

In the SM group, morning PEFR increased from 281 to 315 $L \cdot min^{-1}$ during treatment and in the SB group from 311 to 315 $L \cdot min^{-1}$ ($p<0.001$). The SM group showed significantly better reduction in diurnal variation, from 39 to 22 $L \cdot min^{-1}$ during treatment, than the SB group (34 to 37 $L \cdot min^{-1}$) ($p<0.001$). There was a significantly greater improvement in FEV_1 in the SM group (from 1.63 to 1.85 L) than in the SB group (from 1.79 to 1.84 L). The SM group had significantly more symptom-free nights than the SB group ($p<0.001$), and also more "rescue-free" nights ($p=0.04$). The adverse event profile was similar in both groups.

This study indicates that in asthmatic patients, not controlled on high-dose inhaled steroids, inhaled salmeterol 100 µg *b.d.* significantly improves lung function and reduces asthma symptoms.

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Salmeterol is a selective long-acting $beta_2$-agonist, which in a single 50 µg inhaled dose has been shown to produce bronchodilation for at least 12 h [1]. Dose-ranging studies in patients with mild-to-moderate asthma showed salmeterol 50 µg *b.d.* to be the optimum dose based on efficacy and side-effect information [2, 3]. Salmeterol 100 µg *b.d.* showed similar efficacy to 50 µg *b.d.*, but was associated with higher incidence of side-effects which are pharmacologically predictable of beta-agonists, such as tremor and subjective palpitations. In more severe asthmatics, a salmeterol dose of 100 µg *b.d.* has been shown to be more effective than the 50 µg *b.d.* dose in improving lung function and symptom control. However there was a higher incidence of tremor in the 100 µg group (8% of patients) compared with the 50 µg group (0.7% of patients) [4, 5]. In patients with mild-to-moderate asthma, studied over a 12 month period, salmeterol 50 µg *b.d.* was shown to be more effective than salbutamol 200–400 µg *q.d.s.* in lung function improvement and reducing symptoms [6, 7].

The aim of this study was to compare the effect of salmeterol 100 µg *b.d.* with salbutamol 400 µg *q.d.s.*, when added to current treatment, on lung function and symptom control in patients who remain symptomatic despite being on high doses of inhaled steroids. The dose of salmeterol used in this study was chosen because earlier work has shown this to be more effective than 50 µg *b.d.* in patients with severe asthma [4].

Patients and methods

Patients

A total of 286 chronic asthmatic male and female patients aged 18 yrs and over, currently receiving ≥1,500 µg beclomethasone dipropionate (BDP) or ≥1,200 µg budesonide daily were recruited. Patients were excluded if: they had changed their asthma medication; they had an acute respiratory infection, which required prescribed therapy; or they had been hospitalized for their airways disease in the 2 weeks prior to the start of the study. Patients who required maintenance therapy with oral steroids, or who had received a short course of oral steroids in the 4 weeks prior to the start of the study were also excluded.

At the end of the 2 week run-in period, patients who fulfilled the following inclusion criteria were randomized to one of two treatment groups, salmeterol 100 µg *b.d.* and salbutamol 400 µg *q.d.s.*: forced expiratory volume in one second (FEV_1) at baseline or mean peak expiratory flow rate (PEFR) over the last 7 days of 30–75% predicted normal (% pred); at least a 15% increase in FEV_1 15 min after inhaled salbutamol; and on at least four of the last seven days of the run-in, either a symptom score of ≥2 (see table 1 for symptom scoring system) or use of at least eight blisters of "rescue salbutamol in a 24 h period or diurnal variation in PEFR of ≥15%. Of the 286 asthmatic subjects recruited, 190 were randomized to treatment.

Study design

This study was a multicentre, double-blind, double-dummy, randomized, parallel group study performed in 20 centres in Denmark, Norway and the United Kingdom. Regulatory and Ethics Committee approval were obtained in all countries and centres, and all patients provided written informed consent.

Study procedure

The study consisted of a 6 week treatment period, which was preceded by a 2 week run-in period, and there was a 2 week follow-up period. Following the run-in period, eligible patients were randomized to receive salmeterol 100 µg *b.d. via* the Diskhaler™ (trade mark of the Glaxo Group of Companies) or salbutamol 400 µg *q.d.s. via* the Diskhaler™. Patients were instructed not to use their study medication on the day of clinic visits. At the first visit, all beta-receptor agonists were withdrawn and replaced with salbutamol Rotadisks™ to use on an "as required basis" for symptomatic relief throughout the run-in and treatment periods of the study. Patients were allowed to continue any other concurrent asthma medication provided the dose remained constant, and concurrent therapy for conditions other than asthma.

Patients kept a daily record during the run-in and the treatment periods of their morning and evening PEFR, daytime and night-time symptom score (table 1) and "rescue" salbutamol usage. FEV_1 and forced vital capacity (FVC) were measured at clinic visits at baseline and after 3 and 6 weeks of treatment. The physicians and the patients assessment of the study medication (rated on a four point scale: very effective; effective; satisfactory; ineffective) were noted at clinic visits. The safety and tolerability of salmeterol was assessed by monitoring adverse events (including exacerbations of asthma), blood pressure and heart rate at clinic visits throughout the study. An exacerbation of asthma was defined as any worsening of asthma symptoms sufficient to require a change in medication. Patients experiencing acute exacerbations during the study were treated as the investigator thought appropriate, and were not withdrawn from the study unless the investigator considered it to be to the patient's detriment to continue. Treatment for exacerbations could include oral steroids. All adverse events were recorded by the investigators throughout the study. The incidence of pharmacologically predictable adverse events, such as tremor and palpitations, was calculated from the adverse event recording.

Table 1. – Night-time and daytime symptom scores

Night-time symptom score
0 = no symptoms during the night
1 = symptoms causing you to wake once or twice early
2 = symptoms causing you to wake twice or more (including waking early)
3 = symptoms causing you to be awake for most of the night
4 = symptoms so severe that you did not sleep at all

Daytime symptoms score
0 = no symptoms during the day
1 = symptoms for one short period during the day
2 = symptoms for two or more short periods during the day
3 = symptoms for most of the day, which did not affect normal daily activities
4 = symptoms for most of the day, which did affect normal daily activities
5 = symptoms so severe that you could not go to work or perform normal activities

Statistical analysis

Analyses were carried out on an intent-to-treat basis. Data from patients who were withdrawn from the study after randomization were included up to the date of withdrawal. The size of the study was determined in relation to its statistical power to detect treatment differences in mean PEFR. Assuming an upper limit for the true standard deviation of mean morning or mean evening PEFR of 45 $L \cdot min^{-1}$ and the use of two-sided significance tests at the 5% level, then a total of 200 evaluable patients (100 per treatment) would give the study a power of 90% to detect mean differences of approximately 20 $L \cdot min^{-1}$ in PEFR. The primary end-point was based on PEFR (morning and evening PEFR and diurnal variations). Secondary end-points included: symptom scores; use of "rescue" bronchodilator; FEV_1; and patients and physicians assessment of efficacy.

The difference between treatments in change from baseline in lung function measurements (PEFR, % pred PEFR, diurnal variation, FEV_1) was analysed using analysis of covariance. The difference between treatments in increase from baseline in symptom scores and use of rescue medication were analysed using the Wilcoxon rank sum test. Diary card data were analysed over the 6 week treatment period. Baseline for diary card data was defined as the 7 days prior to randomization. FEV_1 was analysed after 3 and 6 weeks of treatment. P-values refer to difference between salmeterol and salbutamol in change from baseline, which was the value at the randomization visit. Patients' and physicians' assessment of effectiveness were analysed after 3 and 6 weeks of treatment using the Wilcoxon Rank Sum Test. The preselected significance level was 5% (two-sided).

Results

Patients

Of the 286 patients recruited, 190 were randomized to treatment. The main reason for withdrawal prior to

Table 2. – Patient demography

	Salmeterol 100 µg *b.d.*	Salbutamol 400 µg *q.d.s.*
Patients n	96	94
Sex n (%) M	45 (47)	55 (59)
F	51 (53)	39 (41)
Age yrs (range)	52 (27–80)	50 (18–79)
Patients with exacerbations in last 12 months requiring:		
Change in medication n (%)	67 (71)	71 (76)
Hospitalization n (%)	13 (14)	18 (19)
Mean baseline FEV_1 L	1.63	1.79
% pred	54	56
Mean baseline morning PEFR		
$L \cdot min^{-1}$	281	309
% pred	63	66
Patients using concurrent asthma medication:		
≥1,500 µg BDP n (%)	58 (60)	58 (62)
≥2,000 µg budesonide n (%)	39 (41)	36 (38)
methylxanthines n (%)	17 (18)	18 (19)
anticholinergics n (%)	7 (7)	10 (11)

M: male; F: female; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted normal; PEFR: peak expiratory flow rate; BDP: beclomethasone dipropionate.

randomization was ineligibility (70 patients). Ninety six patients were randomized to receive salmeterol 100 µg *b.d.* and 94 to receive salbutamol 400 µg *q.d.s.* The groups were well-matched for demographic details, except sex (table 2). The salmeterol group comprised 47% males and 53% females, but in the salbutamol group there were 59% male and 41% female. The majority of patients in both groups had a duration of asthma in excess of 10 yrs. Five patients were withdrawn from the salmeterol group after randomization (all because of adverse events, including two asthma exacerbations) and 12 patients were withdrawn from the salbutamol group (eight because of adverse event of which six were asthma exacerbations and the others either noncompliance or failure to return).

Lung function

At the end of the treatment period in the salmeterol group, mean morning PEFR improved by 33 $L \cdot min^{-1}$, while in the salbutamol group, mean morning PEFR only improved by 4 $L \cdot min^{-1}$. The difference was statistically significant ($p<0.001$; 95% confidence interval (95% CI) 17 to 40 $L \cdot min^{-1}$) (fig. 1). This improvement reflected an increase from 63% pred at baseline to 70% pred during treatment with salmeterol, and an increase from 66% pred at baseline to 67% pred during treatment with salbutamol. The evening PEFR for the salmeterol group improved by 16 $L \cdot min^{-1}$ from baseline and the salbutamol group by 6 $L \cdot min^{-1}$. The difference between the treatments approached significance ($p=0.084$; 95% CI -1 to 20). Diurnal variation was significantly reduced in the salmeterol group from 39 $L \cdot min^{-1}$ at baseline to 22 $L \cdot min^{-1}$ during treatment, compared with the salbutamol group, in which the diurnal variation was 34 $L \cdot min^{-1}$ at baseline, increased to 37 $L \cdot min^{-1}$ during the first week of treatment, and fell to 34 $L \cdot min^{-1}$ during the last 3 weeks of treatment ($p<0.001$; 95% CI -25 to -11).

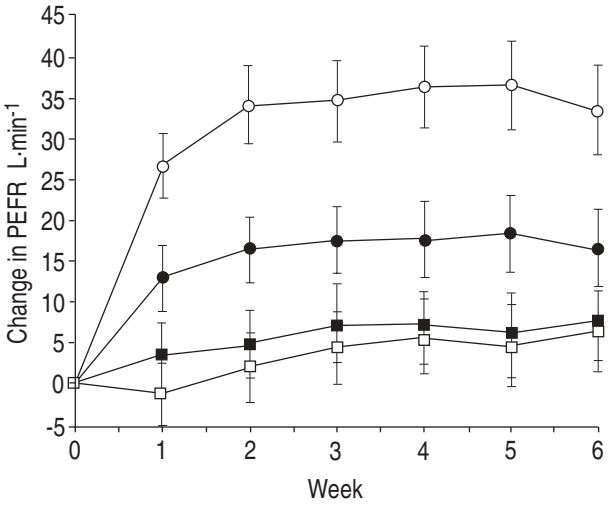

Fig. 1. – The change from baseline for morning and evening peak expiratory flow rate (PEFR) during the 6 weeks treatment. Values are presented as mean±SEM. —○—: salmeterol (*a.m.*); —●—: salmeterol (*p.m.*); —□—: salbutamol (*a.m.*); —■—: salbutamol (*p.m.*).

Salmeterol increased FEV_1 from 1.63 L (54% pred) at baseline to 1.85 L (61% pred) after 3 and 6 weeks treatment. The salbutamol group improved from 1.79 L (56% pred) at baseline to 1.89 L (58% pred) after 3 weeks and to 1.84 L (56% pred) after 6 weeks of treatment. The difference between treatments was significant both at three weeks (mean difference 0.15 L; 95% CI 0.02 to 0.28; $p<0.05$) and at 6 weeks (mean difference 0.15 L; 95% CI 0.03 to 0.27; $p<0.05$).

Symptom score and use of rescue bronchodilator

In the salmeterol group, the median percentage of symptom-free nights was 14% at baseline. This increased to 86% after 2 weeks of treatment and was 71% after 6 weeks. The improvement seen in the salbutamol group (28% symptom-free nights at baseline to 50% after 6 weeks treatment) was significantly lower than the improvement seen in the salmeterol group ($p<0.001$) (fig. 2).

There was no difference between the two groups for the number of symptom-free days. Over the 6 week treatment period, 53% of patients receiving salmeterol and 56% of patients receiving salbutamol showed an increase from baseline in the percentage of symptom-free days. Figure 3 shows the distribution of symptom scores at baseline and during treatment for each treatment group. The distribution of median daytime symptom scores did not differ significantly between the salmeterol and salbutamol groups.

The percentage of rescue-free days and nights is shown in figure 4. There was a significant increase in the percentage of rescue-free nights in the salmeterol-treated group compared with the salbutamol-treated group ($p=0.04$), and there was no difference between the treatment groups for rescue-free days.

Physicians and patients assessment of efficacy

The majority of patients in both treatment groups thought the study medication was either effective or very effective. However, significantly more patients in the salmeterol

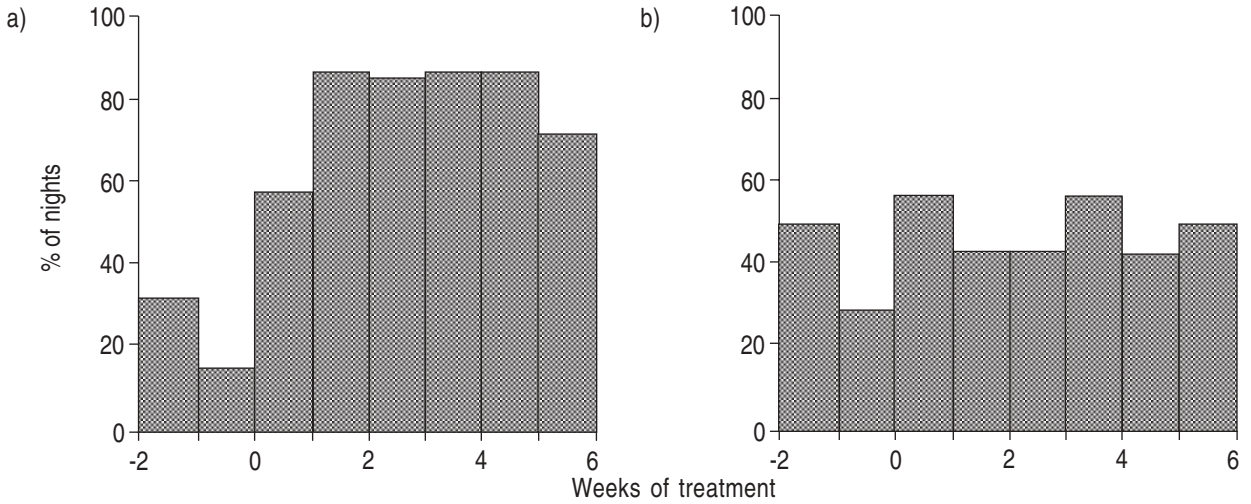

Fig. 2. – Median percentage of nights with no awakening due to asthma during the 6 weeks of treatment with: a) salmeterol 100 µg *b.d.*; and b) salbutamol 400 µg *q.d.s*. Median changes from baseline show salmeterol > salbutamol, p<0.01.

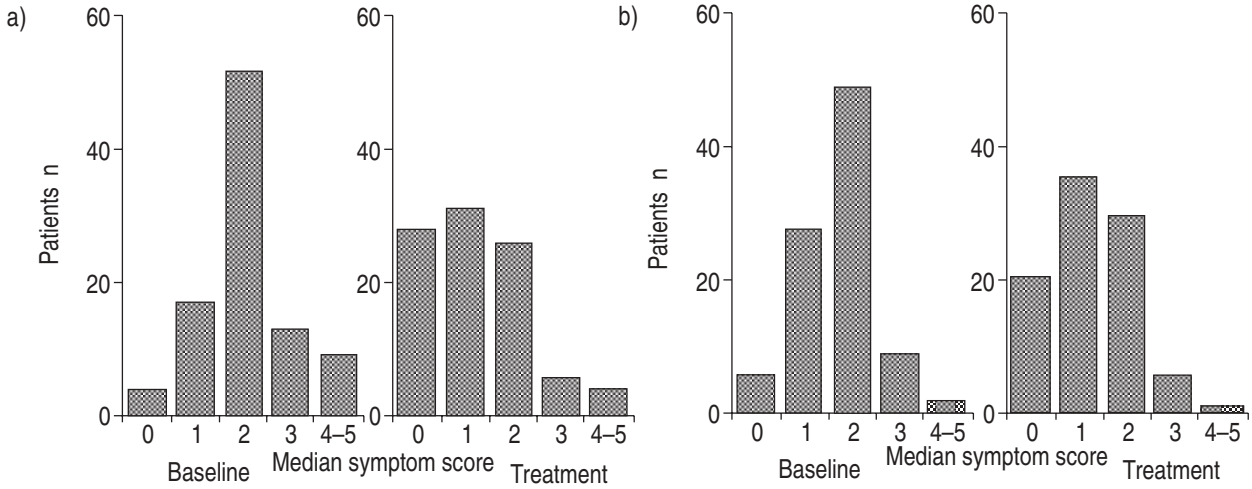

Fig. 3. – Distribution of median daytime symptoms scores at baseline over the 6 week treatment period with: a) salmeterol; and b) salbutamol. The number of patients who had a median score in each period is shown.

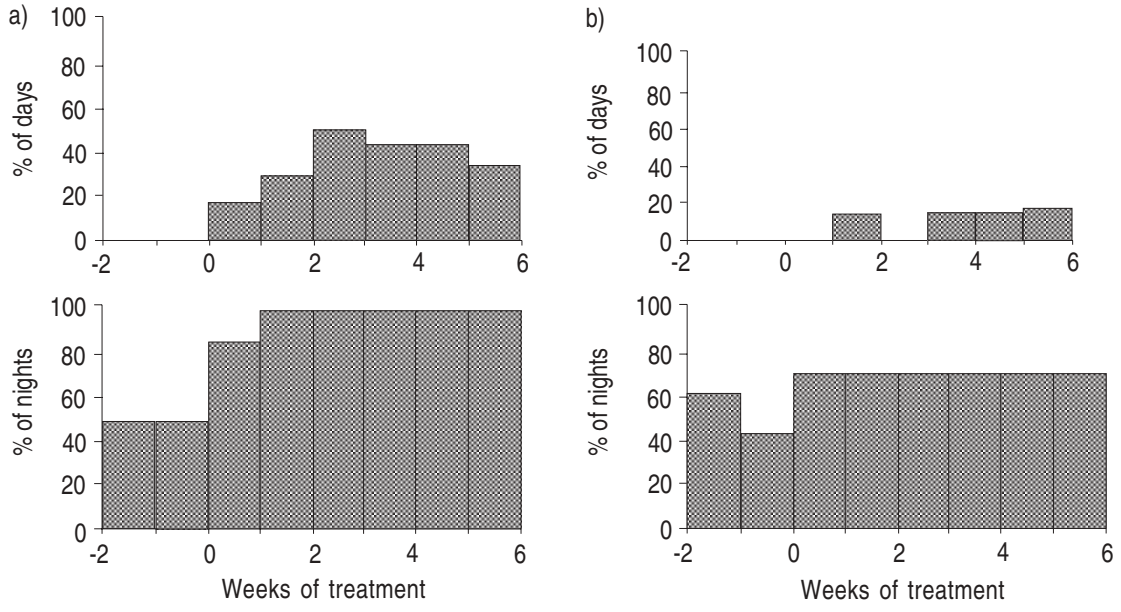

Fig. 4. – Median percentage of days and nights during which no rescue medication was used during treatment with: a) salmeterol 100 µg *b.d.*; and b) salbutamol 400 µg *q.d.s*. Median changes from baseline show salmeterol > salbutamol, p=0.04 for night-time use of rescue.

Table 3. – Adverse events during the 6 weeks of treatment

	Salmeterol 100 µg *b.d.* n (%)	Salbutamol 400 µg *q.d.s.* n (%)
Patients	96	94
Patients with any adverse event n	54 (56)	48 (51)
Asthma	14 (15)	16 (17)
Nasopharyngitis	12 (13)	7 (7)
Respiratory infection	4 (4)	7 (7)
Cough	6 (6)	4 (4)
Headache*	4 (4)	6 (6)
Dyspnoea	1 (1)	5 (5)
Tremor*	3 (3)	2 (2)
Dizziness	1 (1)	3 (3)
Muscle cramps*	1 (1)	2 (2)
Palpitations*	0 (0)	1 (1)

*: pharmacologically predictable adverse events for β_2-agonists.

group rated the treatment as very effective after 3 weeks of treatment (p=0.002). After 6 weeks of treatment the difference approached significance in favour of salmeterol (p=0.09). Similar results were seen for the physicians assessment of efficacy.

Safety

During the study, a total of 102 patients reported an adverse event, 54 whilst being treated with salmeterol and 48 whilst being treated with salbutamol. Table 3 shows the most common (reported by more than three patients in any treatment group) and the pharmacologically predictable adverse events. There was no difference in the incidence of adverse events between the two treatment groups. Serious adverse events were reported by one patient whilst being treated with salmeterol (epileptic convulsions), and by four patients whilst being treated with salbutamol (generally asthma-related and including one fatality). The patient who died was a 59 year old male. The cause of death was said to be cardiac and the investigator considered the fatality to be unrelated to salbutamol. During weeks 1–3 of treatment, 14% of patients in the salmeterol group and 15% of patients in the salbutamol group reported at least one exacerbation of asthma and during weeks 4–6, 5% of salmeterol patients and 2% of salbutamol patients reported exacerbations. Over the 6 weeks of treatment, no patients in the salmeterol group and three patients in the salbutamol group were hospitalized because of their asthma. Ten patients in each treatment group used oral steroids for exacerbations.

Mean systolic blood pressure did not change in either treatment group. The mean diastolic blood pressure decreased by 2 mmHg after 6 weeks of treatment with salmeterol but no change was seen in the salbutamol group. The adjusted mean change from baseline for heart rate at the end of 6 weeks treatment was 2 beats·min^{-1} for the salmeterol treated group and 1 beat·min^{-1} for the salbutamol-treated group.

Discussion

This study showed that in symptomatic asthmatic patients on ≥1,500 µg BDP or equivalent daily, addition of salmeterol 100 µg *b.d.* significantly improved lung function and night-time symptoms compared with addition of salbutamol 400 µg *q.d.s.* The incidence of adverse events did not differ between the two treatment groups. The dose of salmeterol chosen was 100 µg *b.d.*, as previous studies had shown this to be the optimum dose in severe asthmatics.

Nocturnal asthma is a common symptom of poorly controlled asthma. Salmeterol significantly reduced night-time awakenings and use of rescue medication during the night. Both salmeterol and salbutamol treatment groups showed an improvement in control of daytime symptoms but the degree of improvement did not differ between the two groups. This may be due to the fact that the control group used salbutamol 400 µg *q.d.s*. As the patients used salbutamol every 4–5 h whilst awake, this is very likely to have prevented the appearance of daytime symptoms. The fact that there was little improvement in use of "rescue" bronchodilator during the day in both groups may also be, in part, due to the fact that patients use their rescue, even on an as required basis, out of habit and not necessarily because of need. All patients were using beta$_2$-agonists either regularly or on an as required basis on entry to the study. This was replaced with salbutamol to use on an as required basis throughout the study.

Lung function, as determined by daily recording of PEFR and by measuring FEV1 at clinic visits, was significantly improved in the salmeterol group compared with the salbutamol group. There was relatively little improvement (≤7 L·min^{-1}) in either morning or evening PEFR in the salbutamol group (fig. 1). However, in the salmeterol group, the improvement in morning PEFR was approximately 35 L·min^{-1}. The greater improvement in morning PEFR than in evening PEFR in the salmeterol group was reflected in a reduction of 17 L·min^{-1} in diurnal variation in the salmeterol group, with no change seen in the salbutamol group. The results of this study confirm the findings of an earlier study, which showed salmeterol 100 µg *b.d.* significantly improved lung function and night-time symptoms compared with placebo in a group of severe asthmatic patients [8].

The International Consensus Report on Diagnosis and Treatment of Asthma recognizes that in severe asthmatics the outcome of treatment should be to achieve least symptoms and least use of rescue medication, least diurnal variation, best PEFR and least side-effects [9]. This study shows that in a group of moderate-to-severe asthmatic patients the addition of salmeterol 100 µg *b.d.* to existing therapy does achieve these outcomes. Morning PEFR improved from a mean of 63% predicted normal at baseline to 70% predicted normal during treatment with salmeterol. In this group of severe asthmatics, it is very unlikely that they could achieve a normal or near normal lung function. Salmeterol treatment also caused a significant reduction in diurnal variation from 39 L·min^{-1} to 22 L·min^{-1}.

Control of night-time symptoms and use of "rescue" bronchodilator was achieved with salmeterol treatment. Use of rescue medication during the day was reduced, but patients continued to have asthma symptoms on most days. However, on examining figure 3, which presents the distribution of median symptom scores during treatment both with salmeterol and salbutamol, there is an increase in the number of patients who had no symptoms. There was also a shift of patients moving from

more severe to less severe symptoms during the salmeterol treatment period. Again, in moderate-to-severe patients, such as were recruited in this study, the aim of treatment is to achieve minimum symptoms and it is unlikely that such severe asthma can be symptom free.

Although the incidence of adverse events reported during the treatment period was fairly high (56% for salmeterol and 51% for salbutamol), the incidence of individual adverse events was similar in both treatment groups. The incidence of tremor was lower than that seen in earlier studies, which assessed the safety and efficacy of chronic treatment with salmeterol 100 g *b.d.* [4, 8]. The reason for this difference is unclear. It may be due to different methods of assessment of tremor, or it is possible that the patients in this study become tolerant to the side-effects of $beta_2$-agonists as they all used bronchodilators either regularly or as required prior to entry into the study.

Even though this study was only of a 6 week duration, it is believed the results can be extrapolated to longer treatment periods. A number of long-term studies with salmeterol have shown that improvement seen within the first month are maintained throughout the 6–12 month periods studied [6, 7, 10]. It can, therefore, be concluded from this study that addition of salmeterol 100 µg *b.d.* to the treatment of moderate-to-severe asthmatics, symptomatic on daily inhaled beclomethasone dipropionate doses of ≥1,500 µg (or equivalent), significantly improves lung function and night-time symptoms compared with salbutamol 400 µg *q.d.s*.

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