

Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease

R. Dahl*, J.S. Earnshaw**, J.B.D. Palmer**

Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. R. Dahl, J.S. Earnshaw, J.B.D. Palmer.

ABSTRACT: A total of 1,068 patients, aged 18-70 yrs, with mild to moderate reversible airways disease, were recruited into a multi-centre, double-blind, parallel group study in 76 European centres. Following a 2 week run-in period, the 692 patients fulfilling the entry criteria were randomized to 4 weeks treatment with either salmeterol 12.5, 50 or 100 µg or placebo *b.d.* all given by pressurized inhaler, with assessments of symptoms and ventilatory lung function prior to dosing.

All three doses of salmeterol had significant efficacy, manifested by increased morning and evening peak expiratory flow rate (PEFR) (by 35-59 l·min⁻¹ and 11-38 l·min⁻¹, respectively), by reduced diurnal variation in PEFR, and by reduced requirement for additional bronchodilator for symptomatic relief. These effects were dose-related. Daytime asthma symptoms and nocturnal awakenings were significantly reduced by salmeterol treatment, although these reductions were not dose-related. The incidence of adverse events was low. Pharmacologically predictable events (*e.g.* tremor) were more frequent after treatment with 100 µg *b.d.* than with placebo.

On the basis of the efficacy and side-effect information, 50 µg *b.d.* is considered to be the optimum dose for the treatment of this group of asthmatics.

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*Dept of Respiratory Diseases, University Hospital, Århus C, Denmark.

** Dept of Respiratory Medicine, Glaxo Group Research, Greenford, Middlesex, UK. Fax: 44 81 864 9438.

Correspondence: J.S. Earnshaw, Dept of Respiratory Medicine, Glaxo Group Research, Greenford Road, Greenford, Middlesex, UK.

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Inhaled beta₂-adrenoceptor agonists have become established as one of the cornerstones of the treatment of airways obstruction [1-4]. However, their principal disadvantage is a short duration of action [5, 6]. The development of an inhaled beta₂-agonist with a longer duration of action would, therefore, represent a considerable advance in the treatment and management of asthma and airways obstruction.

Salmeterol hydroxynaphthoate is one of a new class of beta₂-adrenoceptor agonists for inhaled use, which has been shown to produce long-lasting bronchodilation *in vitro* and *in vivo* [7, 8]. Salmeterol has also been shown to be a potent and long-acting inhibitor of the release of inflammatory mediators from the human lung *in vitro* [9] and to abolish both the allergen-induced late asthmatic response and increase in bronchial hyperresponsiveness in atopic subjects, indicating that it may have some additional non-bronchodilator properties [10].

A single-dose, crossover study in patients with asthma demonstrated that doses of 50, 100 or 200 µg salmeterol produced peak increases in lung function

similar to those achieved with inhaled salbutamol 200 µg. However, the improvements in lung function with salmeterol were sustained for a significantly greater period with bronchodilation throughout the 12 h study period [11]. These data suggested that salmeterol administered twice daily on a regular basis should be effective in the treatment of reversible airways disease.

Regular use of beta-agonists has not been universally accepted in the treatment of asthma. Some reports demonstrate the benefits of the regular use of bronchodilator [12, 13], whilst another shows no difference from salbutamol taken when required for the control of symptoms [14]. This correlates with studies showing no increase in bronchial responsiveness after long-term beta₂-agonist treatment [15-17] but contrasts with three reports of a small increase in bronchial responsiveness after long-term beta₂-agonist treatment [18-20].

This multicentre, international study was conducted to determine the optimal dose for twice daily dosing and to compare the efficacy of this dose with that of placebo, as well as examining further the safety profile of salmeterol in asthmatic patients.

Patients and methods

Patients

Male and female patients, aged 18–70 yrs, with a clinical history of mild to moderate reversible airways obstruction were recruited at 76 centres in 12 European countries. Of the initial 1,068 patients who entered a 2 week run-in period, 692 were eligible for randomization to treatment at the end of this period, a mean of nine patients per centre. The range of recruitment was 1–34 patients per centre, with at least six patients recruited by 58 of the centres. The relatively high drop-out rate (35%) in the run-in phase was a reflection of the stringent entry criteria. These were a forced expiratory volume in one second (FEV_1) of 60–90% predicted normal values; reversibility in FEV_1 to inhaled salbutamol (200 μ g) of 15% above baseline and either a symptom score >2 or diurnal variation in peak expiratory flow rate (PEFR) >15% on 4 out of 7 days during the second run-in week.

Exclusion criteria were lower respiratory tract infection or hospitalization for reversible airways obstruction within the last 28 days, treatment with above 20 mg oral steroids or with beta-receptor antagonists, hypokalaemia or concurrent serious systemic disease. Females were not included if pregnant or lactating and those of childbearing potential were to be using adequate contraceptive precautions.

Regulatory permission and Ethical Committee approval were obtained in all countries and centres where it was required. The study was carried out under the Declaration of Helsinki and all patients provided informed written or oral consent.

Study design

The study was of a double-blind, parallel group design and compared three dosages of salmeterol (12.5, 50 and 100 μ g *b.d.*) with placebo, all administered from pressurized inhalers. Treatments were randomly allocated to patients in blocks of twelve. This ensured that within each block three patients received each treatment. Patients attended hospital on five occasions and the four week study was preceded by two consecutive run-in periods, each lasting for seven days.

At the first visit demographic details were recorded and blood samples taken for the determination of baseline biochemical parameters. Any oral, rectal or parenteral beta-receptor agonists, methylxanthines, inhaled anticholinergics, ketotifen, hypnotics or sedatives were withdrawn from the treatment regimen. Continued therapy with inhaled steroids, oral steroids (<20 mg prednisolone or equivalent per day), sodium cromoglycate, nedocromil, and non-sedating antihistamines was allowed, but the dosages of these drugs were to remain unchanged during the study.

A salbutamol pressurized inhaler (100 μ g per puff) was provided specifically for symptomatic relief. With

the aid of a special counter on the inhaler the patients were asked to note the extent of its use on daily record cards. In addition, each morning and evening, patients recorded three successive PEFrs using mini-Wright peak flow meters.

The patients also noted the frequency of nocturnal awakening due to reversible airways obstruction and assessed their asthma symptoms each evening according to a 6 point scoring system: 0 = no symptoms during the day; 1 = symptoms for one short period during the day; 2 = symptoms for two short periods during the day; 3 = symptoms for most of the day but not affecting normal daily activities; 4 = symptoms for most of the day which did affect normal daily activities; 5 = symptoms so severe that the patient could not go to work or perform normal daily activities.

After the two run-in weeks, patients eligible for treatment (table 1) were randomized to trial medication. For technical reasons this was packaged as two inhalers, and the patients were instructed to inhale one metered actuation from each on waking in the morning and again at bedtime each night. The inhaler was test-fired to ensure that the valve chamber was full before the dose was released. Salbutamol was supplied for symptomatic relief. PEFrs were to be recorded before inhaling the next dose of study medication.

Visits 3, 4 and 5 were at fortnightly intervals, when the physician recorded any changes in medication, intercurrent illnesses, adverse events and/or patient withdrawals. At each visit, blood and urine samples were collected, heart rate and blood pressure were measured and lung function was assessed by recording the FEV_1 and the relaxed vital capacity (RVC). Twelve-lead electrocardiograms were performed at all centres during visits 3 and 5. Twenty four hour ambulatory monitoring of electrocardiograms was also performed before and during treatment at those centres willing to undertake this. Both the physician and the patient gave their assessments of treatment effectiveness at baseline and after two and four weeks treatment by selecting one of four descriptions (very effective, effective, satisfactory, ineffective).

Statistical methods

The number of patients required was calculated using the results of a previous large study with salbutamol from which it was estimated that the true residual standard deviation of mean morning and evening PEFr was unlikely to exceed 50 $l \cdot min^{-1}$.

Using this estimate of variability, it was calculated that a total of 600 evaluable patients (150 per treatment group) would give this study a power of >0.99 to detect a slope of 10 $l \cdot min^{-1}$ in PEFr per doubling of the salmeterol dose and a power of 0.95 to detect a mean difference of 20 $l \cdot min^{-1}$ between any two treatments. This assumed the use of two-sided t-tests conducted at the 5% significance level. Data from all patients randomized to treatment were used

in the analyses of efficacy. Means obtained during treatment were subjected to analysis of covariance using the means recorded in the second run-in period as covariates. The analysis allowed for variation between centres and treatments.

Peak flow rates

All three doses of salmeterol gave significantly greater increases in morning and evening peak expiratory flow rate than placebo. Mean increases over

Table 1. — Patient characteristics

| Patient characteristics | Placebo <i>b.d.</i> | | Salmeterol μg <i>b.d.</i> | | | |
|---|---------------------|--|--------------------------------------|-----------------|-----------------|--|
| | | | 12.5 | 50 | 100 | |
| Allocated to treatments n | 172 | | 174 | 171 | 175 | |
| Sex | | | | | | |
| Male n (%) | 94 (55) | | 91 (52) | 83 (49) | 92 (53) | |
| Female n (%) | 78 (45) | | 83 (48) | 88 (51) | 83 (47) | |
| Mean age yrs | 43 | | 40 | 43 | 42 | |
| FEV ₁ mean \pm SD l | 2.23 \pm 0.64 | | 2.36 \pm 0.73 | 2.21 \pm 0.73 | 2.38 \pm 0.77 | |
| RVC mean \pm SD l | 3.46 \pm 1.01 | | 3.58 \pm 0.97 | 3.44 \pm 1.05 | 3.60 \pm 1.10 | |
| Smoking history n (%) | | | | | | |
| Yes | 33 (19) | | 32 (18) | 33 (19) | 30 (17) | |
| No | 97 (56) | | 91 (52) | 92 (54) | 91 (52) | |
| Previous | 42 (24) | | 51 (29) | 46 (27) | 54 (31) | |
| Current steroid therapy | | | | | | |
| Inhaled n (%) | 113 (66) | | 106 (61) | 115 (67) | 111 (63) | |
| Oral n (%) | 2 (1) | | 4 (2) | 2 (1) | 3 (2) | |
| Both n (%) | 14 (8) | | 11 (6) | 14 (8) | 17 (10) | |
| Mean dose inhaled (range) μg | 862 (100–2000) | | 916 (100–2000) | 886 (100–2000) | 796 (100–2000) | |
| Mean dose oral (range) mg | 7.6 (1–20) | | 9.0 (0.25–30) | 6.25 (1–10) | 7.3 (0.5–20) | |
| Completing trial | 144 | | 158 | 156 | 156 | |

FEV₁: forced expiratory volume in one second; RVC: relaxed vital capacity.

Changes in the incidence of nocturnal awakening and in the proportion of days during treatment with symptom scores <2 were subjected to analysis of variance allowing for variation between centres and treatments after transformation to ranks [21]. The median number of nocturnal awakenings and median symptom scores were analysed by ordinal regression methods, grouping centres into countries to avoid instability in the model fitting procedure [22].

Results

Patient characteristics

After the run-in periods, 692 patients were eligible for treatment and 614 of these completed the study. Twenty eight patients from the placebo group were withdrawn as compared with 16, 15 and 19 patients from the 12.5, 50 and 100 μg salmeterol groups, respectively. Twenty one of the patients were withdrawn from the placebo group because of adverse events compared to 12, 13 and 16 for the 12.5, 50 and 100 μg doses, respectively.

All four patient groups were well matched with respect to demographic details, lung function and smoking habits. Patient characteristics are summarized in table 1. There were no centre or treatment interactions detected for any of the efficacy parameters.

placebo were 35–44 $\text{l}\cdot\text{min}^{-1}$, 95% confidence limits 26–54 ($p<0.001$) and 15–25 $\text{l}\cdot\text{min}^{-1}$, 95% confidence limits 7–33 ($p<0.001$) for morning and evening, respectively. In addition the extent of these increases was significantly related to the salmeterol dose; the slope per doubling dose of salmeterol was 3 $\text{l}\cdot\text{min}^{-1}$ for both morning ($p=0.049$) and evening values ($p=0.011$).

When compared with placebo, all three salmeterol doses produced a corresponding significant reduction in diurnal variation of PEF of 13–20 $\text{l}\cdot\text{min}^{-1}$ (95% confidence limits of 7–25, $p<0.001$), the extent of which was dose-related (slope per doubling dose of salmeterol of 2 $\text{l}\cdot\text{min}^{-1}$, 95% confidence limits 0–4, $p<0.05$) (fig. 1). These improvements were observed within 24 h of the commencement of treatment and were maintained throughout the 4 week treatment period.

Approximately 75% of patients from all treatment groups were receiving concurrent treatment with either inhaled or oral steroids at similar dosages (table 1). No difference was observed in PEF changes between these patients and those not taking steroids (fig. 2).

Use of rescue inhalation and nocturnal awakenings

All three doses of salmeterol also gave a highly significant reduction in the median weekly number of additional actuations of inhaled salbutamol taken during the day ($p<0.001$, fig. 3).

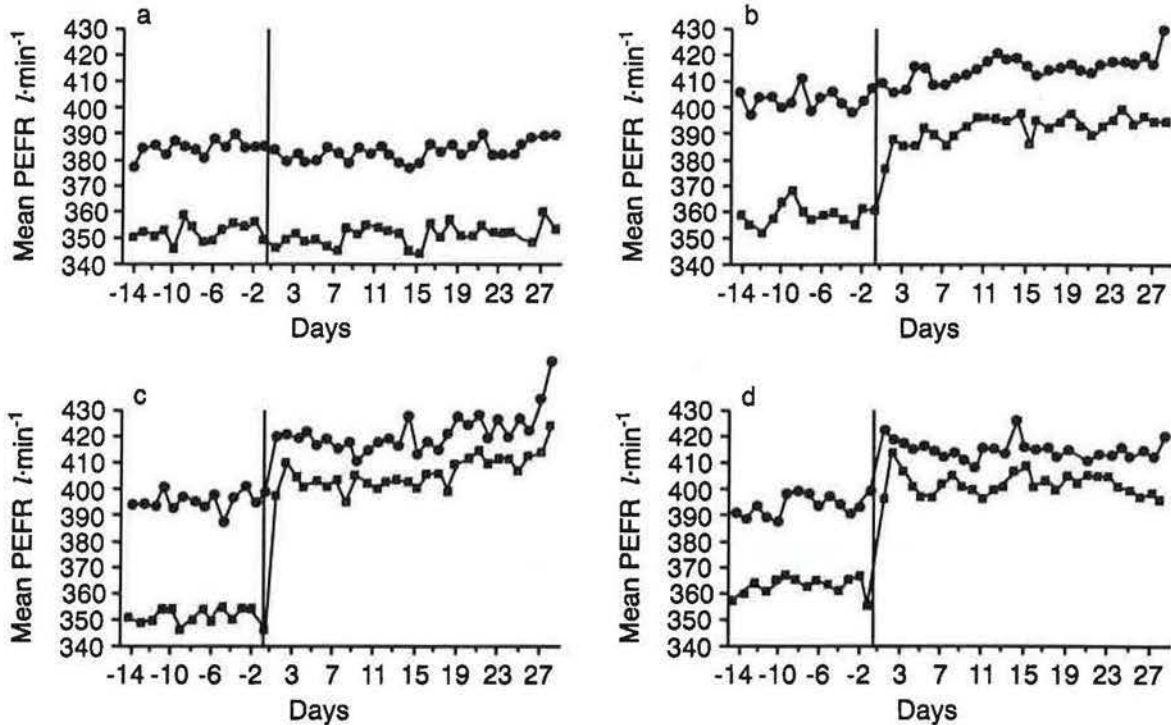


Fig. 1. — Mean morning (■) and evening (●) peak expiratory flow rate (PEFR) after treatment with: a) placebo (n=172); b) salmeterol 12.5 µg b.d. n=174; c) salmeterol 50 µg b.d. (n=171); and d) salmeterol 100 µg b.d. (n=175). Initiation of treatment indicated by vertical line.

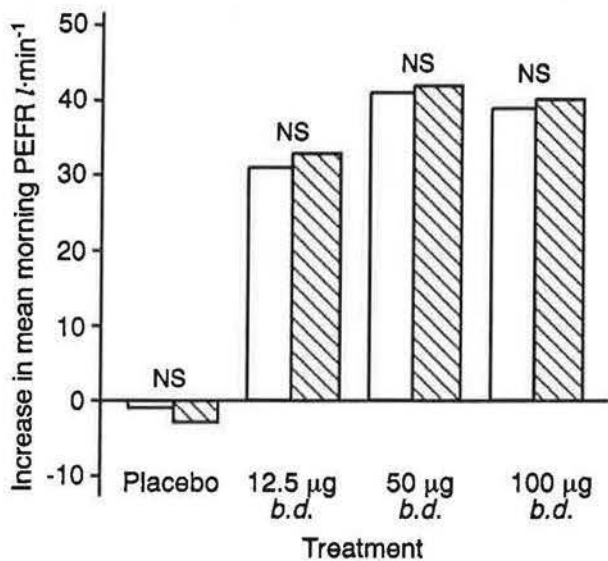


Fig. 2. — Increase in mean morning PEFR from run-in to during 4 weeks treatment in patients receiving regular concurrent (inhaled or oral) corticosteroid treatment (steroid) and those not on steroids (non-steroid). □: non-steroid; ▨: steroid; PEFR: peak expiratory flow rate; ns: nonsignificant.

In addition the median percentage of nights per week without awakenings due to the symptoms of reversible airways obstruction, e.g. cough, wheeze and breathlessness, increased with all salmeterol treatments compared with placebo ($p < 0.001$). The effects of the 50 and 100 µg b.d. dose were similar but greater than that of 12.5 µg b.d.; the odds for a median of zero night-time awakenings increased in a dose-related

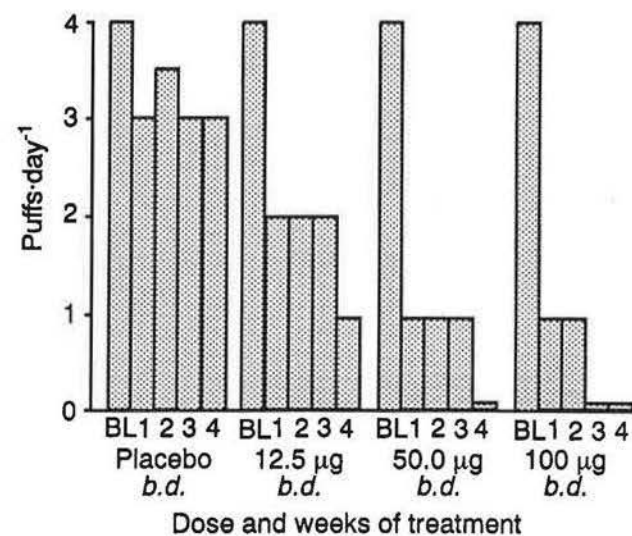


Fig. 3. — The use of additional daytime salbutamol (weekly median number of actuations·day⁻¹). BL: Baseline, median value in 7 days prior to randomization.

fashion by 1.27 per doubling dose of salmeterol (95% confidence limits 1.05–1.54, $p < 0.05$) (fig. 4).

Symptoms scores and assessments

All salmeterol dose schedules resulted in significantly more days where the asthma scores were < 2 compared with placebo; median increase from run-in was 23.1–33.3% for salmeterol, compared to 2.9% for placebo, $p < 0.001$. This effect was not clearly dose-related.

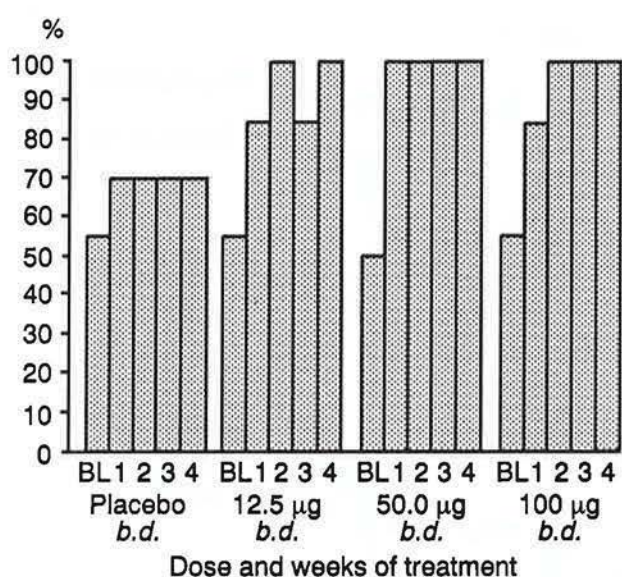


Fig. 4. - The weekly median percentage of nights with-out awakenings. BL: baseline, weekly median for 7 days prior to randomization.

Table 2. - The number of patients with pharmacologically predictable adverse events during the treatment phase

| Adverse event | Placebo | Salmeterol µg b.d. | | |
|---------------|---------|--------------------|-------------|--------------|
| | n=172 | 12.5 n=174 | 50 n=171 | 100 n=175 |
| Tremor | 4 | 0 | 5 | 21 |
| Palpitations | 4 | 0 | 1 | 8 |
| Tachycardia | 0 | 1 | 0 | 3 |
| Muscle cramp | 2 | 0 | 3 | 2 |
| Headache | 6 | 7 | 3 | 9 |

1.44–5.42, $p < 0.001$) for the investigators' and patients' assessment, respectively. The improvements were dose-related with an increase in the odds per doubling of the salmeterol dose of 1.25 (95% confidence 1.01–1.43, $p < 0.001$) for the investigators' opinion and 1.18 (95% confidence of 1.03–1.35, $p < 0.05$) for the patients' opinion. The effects of 50 and 100 µg b.d. were similar but greater than that of 12.5 µg b.d.

Spirometry

Dynamic lung volumes recorded at clinic visits showed that all three doses of salmeterol produced significant increases in the FEV₁ compared with placebo. Mean values pretreatment were 2.23, 2.36, 2.21 and 2.38 l for the placebo, 12.5, 50 and 100 µg b.d. doses, respectively, and rose to 2.44, 2.71, 2.63 and 2.67 l at the end of 4 weeks' treatment; mean differences over placebo were 0.13–0.2 l (95% confidence limits 0.01–0.31, $p < 0.05$). There was no clear difference between any dose of salmeterol and placebo in improvement in RVC (mean values before treatment for placebo, 12.5, 50 and 100 µg b.d. doses of 3.46, 3.58, 3.44 and 3.60 l, respectively, increasing to 3.73, 3.70, 3.75 and 3.73 l after 4 weeks' treatment).

Adverse events

The overall incidence of adverse events was low; most frequently reported were acute nasopharyngitis (this covered a range of conditions including rhinitis and the common cold) and events related to asthma (defined as worsening of symptoms requiring a change in prescribed medication).

These did not appear to be dose-related or to differ in incidence between the placebo and active treatment

Table 3. - Mean systolic and diastolic blood pressure and pulse rate before and after 4 weeks treatment

| | Placebo | | 12.5 | | Salmeterol 50 µg b.d. | | 100 | |
|--|---------|-------|--------|-------|-----------------------|-------|--------|-------|
| | Before | After | Before | After | Before | After | Before | After |
| Systolic blood pressure mmHg | | | | | | | | |
| Mean | 127 | 127 | 126 | 123 | 129 | 128 | 126 | 125 |
| SD | 18 | 18 | 17 | 15 | 19 | 19 | 17 | 19 |
| n | 171 | 129 | 168 | 140 | 169 | 142 | 173 | 145 |
| Diastolic blood pressure mmHg | | | | | | | | |
| Mean | 79 | 79 | 78 | 77 | 79 | 80 | 78 | 78 |
| SD | 11 | 11 | 10 | 9 | 11 | 10 | 11 | 11 |
| n | 171 | 129 | 168 | 140 | 169 | 142 | 173 | 145 |
| Pulse rate beats·min⁻¹ | | | | | | | | |
| Mean | 76 | 74 | 74 | 75 | 73 | 77 | 74 | 77 |
| SD | 10 | 9 | 11 | 10 | 11 | 11 | 11 | 12 |
| n | 171 | 128 | 170 | 142 | 169 | 142 | 173 | 145 |

The physicians' and patients' assessment of treatment efficacy showed that all doses of active treatment caused a significant improvement after both 2 and 4 weeks treatment with the odds of obtaining any specified degree of effectiveness or better increasing by 2.17–4.12 fold (95% confidence 1.44–6.29, $p < 0.001$) and 2.16–3.40 fold (95% confidence

groups: incidence rate 2.9, 5.3, 4.6 and 4.1% for acute nasopharyngitis, and 2.3, 5.3, 2.3 and 3.5% for asthma in the placebo, 12.5, 50 and 100 µg groups, respectively.

Events which are pharmacologically predictable for beta-agonists (subjective palpitations and tachycardia, headache and tremor) showed a higher incidence in the

salmeterol 100 µg group (table 2). There was no difference in the incidence of these effects between the salmeterol 12.5 and 50 µg groups and placebo.

There was no significant change in systolic or diastolic blood pressure at any dose of salmeterol (table 3). There was a small increase in mean pulse rate of 4 beats·min⁻¹ difference between both the salmeterol 50 and 100 µg groups and placebo. Pulse rate on the 12.5 µg salmeterol dose did not differ significantly from placebo (table 3).

Twenty four hour ambulatory electrocardiograms from 46 patients and 12-lead electrocardiograms from 489 patients were Minnesota coded [23] and assessed in a blinded manner by an independent physician. No clinically relevant changes from baseline values were recorded.

A review of both haematological and biochemical data showed no clinically important abnormalities with respect to any dose of salmeterol or duration of treatment and in particular no significant changes in serum potassium levels were noted during the treatment period.

Discussion

The data presented show that compared to placebo all doses of salmeterol significantly increased morning and evening peak flow, reduced diurnal peak flow variation, reduced the requirement for additional rescue salbutamol and reduced the symptoms of asthma, both during the night and day.

There is some evidence of a dose-response relationship for salmeterol. On reviewing all the data it is apparent that, overall, control of asthma with the 12.5 *b.d.* dose is not as good as with the higher doses of salmeterol, whilst at 100 µg *b.d.* pharmacologically predictable adverse events begin to occur. It is, therefore, recommended that 50 µg *b.d.* is the optimal dose for the treatment of mild to moderate asthmatics. However, it is possible that salmeterol at the higher dose of 100 µg *b.d.* may be of further benefit to those patients with more severe reversible airways disease.

The reduction in nocturnal symptoms observed during this study is particularly important, as this is an aspect of the disease which in the past has proved difficult to control; indeed, in a recent study it was found that at least 73% of asthmatics woke with symptoms at least once a week and 39% woke nightly [24]. Theophyllines and oral beta-agonists have been shown to improve control of nocturnal symptoms [25, 26]; however, both have been associated with an increased side-effect load. Salmeterol appears to provide a considerable advance in the control of nocturnal symptoms, and this was confirmed in a recent paper in which 50 µg *b.d.* salmeterol was shown to be effective treatment for nocturnal asthma and to improve sleep quality [27].

Over the 4 week treatment period there was no evidence of deterioration in lung function, in either patients taking or not taking inhaled steroid medica-

tion. This suggests that there is no tachyphylaxis to inhaled salmeterol and that concurrent use of inhaled steroids are not in any way protecting against tachyphylaxis. This finding is supported by another recent study which demonstrated that there was no tachyphylaxis to the effects of cumulative doses of inhaled beta-agonist (salbutamol) following regular dosing with salmeterol [28].

The use of regular beta-agonists in the treatment of asthma is currently the focus of much discussion. Indeed a recent study has demonstrated a deterioration in asthma control in patients treated regularly with a relatively non-selective beta-agonist fenoterol compared to use of beta-agonist on an "on demand" basis [20]. A second study has highlighted the differences between fenoterol and other short-acting beta₂-agonists such as terbutaline or salbutamol in terms of extrapulmonary effects, *e.g.* heart rate, QTC interval, serum potassium and tremor [29]. It is, therefore, a matter of debate whether the deterioration in asthma control with regular fenoterol can be considered a class or a drug specific effect.

In this study, regular twice daily dosing with salmeterol was clearly an extremely effective treatment in patients on either concurrent inhaled or oral steroids as well as in those on bronchodilator therapy only. There is no evidence of any deterioration in lung function or loss of asthma control in comparison with placebo and additional symptomatic salbutamol.

This latter finding has been supported by data from longer term studies with salmeterol where the rate of exacerbations did not increase during a year's treatment [30] and asthma control was better in patients receiving salmeterol treatment for three months than in a parallel group receiving placebo and symptomatic salbutamol [31]. This suggests that twice daily treatment with salmeterol will be of benefit in a wide spectrum of patients with mild to moderate asthma.

Conclusion

Salmeterol has been shown to be a highly efficacious and well-tolerated drug. From these data, it is recommended that 50 µg *b.d.* is the optimal dose for the regular treatment of patients with mild to moderate reversible obstructive airways disease.

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Salmeterol: une étude de quatre semaines d'un agoniste bêta-adrénorécepteur à action prolongée, pour le traitement des maladies réversibles des voies aériennes. R. Dahl, J.S. Earnshaw, J.B.D. Palmer.

RÉSUMÉ: Un total de 1.068 patients, âgés de 18 à 70 ans, avec une maladie des voies aériennes légère à modérée, ont été placés dans une étude multicentrique en double aveugle, à groupe parallèle, dans 76 centres européens. Après une période de mise en route de 2 semaines, les 692 patients répondant aux critères d'admission ont été randomisés à un traitement de 4 semaines, soit au moyen de salmeterol (12.5, 50 ou 100 µg), soit au placebo deux fois par jour, au moyen d'aérosol doseur, avec appréciation des symptômes et de la fonction pulmonaire ventilatoire avant l'administration.

Les trois doses de salmeterol avaient une efficacité significative, manifestée par une augmentation du débit expiratoire de pointe le matin et le soir (respectivement de 35 à 59 litres/minute - 1, et de 11 à 38 litres/minute - 1), par une diminution de la variation diurne du débit expiratoire de pointe, et par des besoins réduits de traitement bronchodilatateur complémentaire pour soulagement symptomatique. Ces effets sont en relation avec la dose. Les symptômes d'asthme diurne et les réveils nocturnes sont significativement diminués par le traitement au salmeterol, quoique ces réductions ne soient pas liées à la dose. L'incidence des effets collatéraux est basse. Les effets pharmacologiques prédictibles, par exemple le tremblement, sont plus fréquents après traitement qu'après placebo. *Eur Respir J*, 1991, 4, 1178-1184.