Eur Respir J, 1995, 8, 1494–1498
DOI: 10.1183/09031936.95.08091494
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy

G. Boyd on behalf of a UK Study group

Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy. G. Boyd on behalf of a UK Study Group. ©ERS Journals Ltd 1995.

ABSTRACT: In severe chronic asthma, long-term oral steroids may be necessary to control symptoms. In patients in whom such treatment was under consideration, the efficacy and safety of salmeterol xinafoate 100 μg *b.i.d.* was investigated in a randomized, double-blind, placebo-controlled parallel-group, multicentre study.

One hundred and nineteen chronic symptomatic asthmatics were randomized to receive either salmeterol, 100 μg *b.i.d.* (n=55; baseline % predicted morning peak expiratory flow (PEF) 59%; forced expiratory volume in one second (FEV_1) 66%) or placebo (n=64; baseline % predicted morning PEF 63%; FEV_1 66%) both *via* the Diskhaler. Morning and evening PEF and asthma symptoms were recorded in daily record booklets by the patient over a 12 week period.

A significant improvement in morning PEF was achieved after 1 month in the salmeterol treated group; this persisted throughout the treatment period (estimated treatment difference 22 $L \cdot min^{-1}$). There was a significant increase in the proportion of symptom-free nights experienced by the salmeterol treated group (33 (SD 32) %) compared with placebo (13 (26) %), and a significant decrease in daily use of relief medication (mean decrease 5.1 (4.7) doses per day with salmeterol, 2.5 (4.0) doses with placebo). Both treatments were well-tolerated, with no evidence of any difference in the side-effects associated with $beta_2$-agonists.

In conclusion, the addition of salmeterol (100 μg daily) to the existing treatment of chronic asthmatics under consideration for maintenance oral corticosteroid therapy is well-tolerated, improves lung function and provides additional symptom control.

Eur Respir J., 1995, 8, 1494–1498.

Dept of Respiratory Medicine, Stobhill Hospital, Glasgow, UK.

Correspondence: G. Boyd
Stobhill Hospital
Glasgow
G21 3UW
UK

Keywords: $Beta_2$-agonists
chronic asthma
nocturnal asthma control
salmeterol

Received: November 8 1994
Accepted after revision April 13 1995

This study was supported by Allen & Hanburys Ltd. Stockley Park West, Uxbridge UB11 1BT, UK.

Corticosteroids are generally considered to be the most effective anti-inflammatory therapy available for the treatment of asthma. Current guidelines recommend the introduction of inhaled corticosteroids into the treatment regimen of all but the mildest asthmatics [1]; the dose of inhaled corticosteroid increasing with the severity of asthma up to a recommended maximum of 2 mg daily. In more severe cases, the introduction of long-term oral corticosteroid therapy may be necessary to achieve control of symptoms. Whilst the clinical efficacy of oral corticosteroids is well-established, chronic treatment is often associated with significant systemic side-effects, such as suppression of the hypothalmic-pituitary-adrenal axis (HPA) and changes in bone metabolism [2]. An important aspect of the management of chronic asthma is to minimize the risk of such drug effects. Concern over the systemic effects of oral corticosteroids is reflected in the current management guidelines [1], where in more severe patients it is recommended that sequential trials of long-acting bronchodilators in conjunction with maximal inhaled corticosteroids are performed before the introduction of long-term oral corticosteroids.

Salmeterol xinafoate is a potent, long-acting, inhaled $beta_2$-adrenoceptor agonist which has been shown to have a bronchodilator effect of up to 12 h both in adults and children [3, 4]. Studies in adult asthmatics have shown that salmeterol is capable of improving lung function and symptom control [5–7].

A study of 283 symptomatic moderate-to-severe adult asthmatics showed that salmeterol at a dose of 100 μg *b.i.d.* afforded significantly better control than salmeterol 50 μg *b.i.d.*, even when given concurrently both with inhaled and oral corticosteroids [8]. With reference to this, and given the good tolerability and low side-effect profile of salmeterol, this study investigated the efficacy and safety of salmeterol in the management of chronic asthmatics currently being considered for maintenance oral corticosteroid therapy.

Patients and methods

Patients

A total of 181 asthmatics aged at least 18 yrs, with a requirement for at least 1,500 μg daily of inhaled

beclomethasone dipropionate (or equivalent), and who were under consideration for maintenance oral corticosteroid therapy, as judged by their physician, were recruited into the study at 15 out-patient departments in the UK.

Patients were required to have a documented history of at least 15% improvement from baseline in lung function following inhaled salbutamol, and of acute exacerbations of asthma on at least two occasions in the preceding 18 months. An exacerbation was defined as an acute episode requiring either emergency hospital attendance or treatment with a short course of oral corticosteroids. Patients were excluded if they had a concurrent uncontrolled systemic disease, had received treatment for an acute respiratory infection in the last 2 weeks, or were unable to demonstrate at least 40% of their predicted forced expiratory volume in one second (FEV_1) at baseline.

The study was approved by the local Ethics Committee for each participating centre, and written informed consent was obtained from each patient.

Methods

On entry to the 2 week baseline period, $beta_2$-agonist therapy was withdrawn and replaced with commercially available salbutamol metered-dose inhalers (MDIs) (100 $\mu g \cdot actuation^{-1}$) for symptomatic relief. A medical history was taken and concurrent illnesses and medication were noted. PEF was measured using a mini-Wright peak flow meter (Clement-Clarke International Ltd, Harlow, UK), and FEV_1 and forced vital capacity (FVC) were measured using a Micromedical pocket spirometer (Micromedical Ltd, Rochester, UK). For each measure the best of three attempts was recorded. Blood samples were taken for routine laboratory safety investigations (haematology and biochemistry) and a resting 12-lead electrocardiograph (ECG) was recorded. During the baseline period, patients were provided with diary booklets and were asked to assess the severity of their daytime and night-time asthma symptoms based on 5-point scales (table 1), and to record the number of puffs of relief medication taken each day. Before taking their first morning and last evening doses of medication, patients were asked to record the best of three PEF measurements.

At the end of the baseline period, patients' symptoms, peak flow rates and relief medication use were reviewed. Randomization criteria were at least two of the following: a night-time symptom score of at least 1, a daytime score of at least 2, use of at least eight puffs of relief medication or a diurnal variation in PEF (defined as ((evening PEF - next morning PEF) divided by evening PEF) × 100%) of at least 15%; on at least three of the last 7 days.

Patients were randomized in a double-blind fashion to receive either salmeterol 100 μg (2×50 μg blisters) *b.i.d.* or matching placebo *via* the Diskhaler™ for 12 weeks. Patients continued to receive salbutamol by MDIs for relief and their usual prophylactic asthma therapy throughout the study.

Throughout the treatment period, the severity of daytime and night-time symptoms, daily relief medication use and morning and evening PEF were recorded by patients in the daily record booklets. Patients were seen at 4 weekly intervals during the treatment period. At each clinic visit PEF, FEV_1 and FVC (clinic lung function) were measured and treatment compliance assessed. Adverse events were recorded throughout the study.

Table 1. – Symptom score rating scale

Daytime symptom score scale		
0	=	no symptoms during the day
1	=	occasional symptoms during the day but not troublesome
2	=	frequent symptoms during the day, which did not interfere with the day's activities
3	=	symptoms throughout the day, which interfered to some extent with the day's activities
4	=	symptoms so bad during the day that the day's activities were greatly restricted.
Night-time symptom score scale		
0	=	no symptoms during the night
1	=	symptoms which caused the patient to wake once or to wake early
2	=	symptoms which caused the patient to wake two to three times (including waking early)
3	=	symptoms which caused the patient to be awake for much of the night
4	=	symptoms so severe that the patient was prevented from sleeping

Statistical analysis

The study was analysed on an intention-to-treat basis. All patients randomized to treatment were evaluable.

The primary efficacy variables were changes in the morning and evening PEF between the baseline and treatment periods. Using a standard deviation for morning and evening PEF of 45 $L \cdot min^{-1}$, it was estimated that a sample size of 120 evaluable patients (60 per treatment group) was required to give the study a 90% power to detect a mean treatment difference in morning and evening PEF of 30 $L \cdot min^{-1}$ (two-sided test, 0.05 significance level).

Analysis of variance was used to compare changes from baseline in morning and evening PEF, the proportion of symptom-free days and nights, and relief medication use between treatments. Wilcoxon's rank sum test was used to compare changes in daytime and night-time symptoms between treatments. For each of these variables the average treatment difference was estimated and 95% confidence intervals were calculated.

Results

One hundred and eighty one patients entered the study, 62 of whom were withdrawn prior to randomization. The reasons for withdrawal were: ineligible/protocol violation (44); adverse events (8); noncompliance/default (6); withdrawal of consent (2); and others (2).

Table 2. – Demographic details and lung function on entry into the study

	Salmeterol n=55	Placebo n=64
Sex M/F	22/33	29/35
Age yrs*	47 (18–79)	47 (18–73)
Inhaled corticosteroids at entry n (%)		
1000–2000 mg·day^{-1}	47 (85)	55 (86)
2001–3000 mg·day^{-1}	6 (11)	7 (11)
3001–4000 mg·day^{-1}	2 (4)	2 (3)
Baseline FEV1 L*	1.92 (0.65–3.30)	1.93 (0.52–3.24)
% predicted*	66 (33–105)	66 (16–115)
Baseline morning PEF L·min^{-1}**	267±94†	289±111†
% pred**	59±19†	63±22†
Baseline evening PEF L·min^{-1}	309±103†	321±104†
% pred	68±21†	70±21†

*: values are presented as mean, and range in parenthesis; **: values are presented as mean±SD. M: male; F: female; FEV1: forced expiratory volume in one second; PEF: peak expiratory flow. †: no significant differences between values.

One hundred and nineteen patients entered the treatment phase (68 females and 51 males), 97 of whom completed the study (47 salmeterol and 50 placebo). The reasons for the 22 withdrawals (8 salmeterol and 14 placebo) were: failure to meet inclusion/exclusion criteria (4 in each group); poor compliance (1 and 4, respectively); patient request (1 and 3); worsening asthma (2 in each group); and code break violation (1 in the placebo group). Demographic details were well-matched for both treatment groups (table 2). Ninety one percent of patients in the salmeterol group and 92% in the placebo group were receiving inhaled salbutamol prior to the study. Of these, in the salmeterol group, 57% were prescribed salbutamol on an as-needed basis, 20% on a regular basis, and 14% on a regular/*p.r.n.* basis. Corresponding figures for the placebo group were 58, 24 and 10%. All other patients were receiving terbutaline. There was a difference in lung function during the baseline period (table 2), mean morning PEF was 22 L·min^{-1} higher in the placebo-treated group. The difference in mean evening PEF was lower (12 L·min^{-1}) (table 2). Relief medication use and symptom scores were comparable for both groups (table 3).

Salmeterol significantly increased the mean morning PEF when compared to placebo. This effect was present after 1 month of treatment and persisted throughout the treatment period (table 4). The overall improvement in mean morning PEF was 45 (SD 41) L·min^{-1} for salmeterol and 23 (45) L·min^{-1} for placebo (p=0.006; mean estimated treatment difference 22 L·min^{-1}; 95% confidence interval (95% CI) 7–38 L·min^{-1}) (table 4).

There were no significant changes in mean evening PEF (table 4), although there was a trend in favour of salmeterol. The overall mean change in evening PEF was 23 (38) L·min^{-1} for salmeterol and 15 (45) L·min^{-1} for placebo (p=0.28; mean estimated treatment difference 8 L·min^{-1}; 95% CI -7–24 L·min^{-1}) (table 4). There were no significant changes in clinic FEV1 (table 4) or FVC.

Throughout the treatment period, control of night-time asthma symptoms was better for the salmeterol treated group (table 3). There was a significant increase in the proportion of symptom-free nights when compared to placebo (33 (32) %, salmeterol, 13 (26) %, placebo

Table 3. – Analysis of the overall changes in daytime and night-time symptom scores, proportion of symptom-free days/nights and relief medication usage between baseline and treatment

	Baseline	Treatment	Change*	p-value (95% CI)
Daytime symptom scores				
Salmeterol n=53	0.94±0.23	0.74±0.45	-0.21±0.41	p=0.24
Placebo n=62	0.94±0.22	0.82±0.39	-0.12±0.32	
Night-time symptom scores				
Salmeterol n=53	0.91±0.28	0.45±0.50	-0.45±0.49	p=0.002
Placebo n=62	0.73±0.44	0.58±0.50	-0.15±0.48	
Proportion of symptom-free days				
Salmeterol n=53	0.08±0.17	0.30±0.36	0.22±0.30	p=0.07 (-0.002 to 0.20)
Placebo n=62	0.07±0.19	0.20±0.31	0.13±0.22	
Proportion of symptom-free nights				
Salmeterol n=53	0.20±0.25	0.53±0.38	0.33±0.32	p=0.001 (0.09 to 0.29)
Placebo n=62	0.29±0.33	0.42±0.38	0.13±0.26	
Relief medication**				
Salmeterol n=53	11.3±6.0	6.3±6.2	-5.1±4.7	p=0.002 (-4.15 to -1.01)
Placebo n=62	9.7±4.0	7.2±4.9	-2.5±4.0	

Values are presented as mean±SD. *: change=treatment period - baseline period; **: number of puffs required from salbutamol MDI per 24 h. MDI: metered dose inhaler; 95% CI: 95% confidence interval.

Table 4. – Analysis of the changes in mean morning PEF, mean evening PEF and clinic FEV_1 between baseline and treatment by month and overall changes

	Baseline	Month 1	Month 2	Month 3	Overall Change*
Morning PEF					
Salmeterol	267±94 n=53	308±102 n=53	311±101 n=51	319±98 n=48	45.2
Placebo	289±111 n=62	305±113 n=62	317±119 n=59	321±121 n=52	22.8
Estimated treatment difference** for change from baseline (95% confidence interval)		24.6 (9.7 to 39.5)	25.8 (8.4 to 43.3)	26.0 (7.9 to 44.1)	22.4 (6.7 to 38.2)
p-value		0.002	0.005	0.006	0.006
Evening PEF					
Salmeterol	309±103 n=53	328±101 n=53	332±99 n=48	330±98 n=47	23.1
Placebo	321±104 n=62	330±109 n=62	346±114 n=56	344±115 n=52	14.7
Estimated treatment difference** for change from baseline (95% confidence interval)		10.3 (-4.6 to 25.1)	13.5 (-3.8 to 30.8)	11.1 (-6.9 to 29.2)	8.4 (-7.0 to 23.9)
p-value		0.17	0.12	0.23	0.28
Clinic FEV_1					
Salmeterol	1.78±0.71 n=55	1.93±0.78 n=52	2.07±0.78 n=48	1.99±0.78 n=47	0.19
Placebo	1.87±0.74 n=63	2.00±0.75 n=58	1.98±0.73 n=52	2.01±0.68 n=49	0.15
Estimated treatment difference** for change from baseline (95% confidence interval)					0.03 (-0.13 to 0.19)
p-value					0.68

Values are presented as mean±SD. *: change=treatment period - baseline period; **: salmeterol group - placebo group. For abbreviations see legend to table 2.

p=0.001), and a significant fall from baseline in nighttime symptom scores (-0.45 (0.49) salmeterol, -0.15 (0.48) placebo; p=0.002) (table 3). There were no significant treatment differences for either proportion of symptom-free days or daytime symptom scores (table 3). The increases in proportion of symptom-free days were 22 (30) %, salmeterol, and 13 (22) %, placebo (p=0.07), and changes in daytime symptom scores were -0.21 (0.41), salmeterol, and -0.12 (0.32), placebo (p=0.24) (table 3).

Consistent with treatment differences observed for the symptomatic assessment, relief medication use was also significantly reduced by salmeterol. The mean decrease in the number of puffs of salbutamol taken per day was 5.1 (4.7) in the salmeterol and 2.5 (4.0) in the placebo group (p=0.002) (table 3).

Both treatments were generally well-tolerated. Minor adverse events were experienced by 44 patients in the salmeterol group and 53 in the placebo group. Respiratory disorders, (40 patients (73%) in the salmeterol group and 47 patients (73%) in the placebo group), most commonly cold symptoms and upper respiratory tract infections, and nervous disorders, most commonly headache (17 patients in each group, 31 and 27%, respectively), were most frequently reported with each treatment. Most adverse events were of mild to moderate severity and resolved spontaneously without discontinuing the study treatment. Serious adverse events were reported by seven patients in each treatment group during the treatment period. Five of these in the salmeterol group and four in the placebo group were events associated with respiratory tract. Three patients in the placebo group were hospitalized for unrelated surgical procedures. One patient in the salmeterol group suffered a severe leg injury and the remaining patient suffered abdominal pain and fever. There was no significant difference (p=0.19) in exacerbations of asthma (defined as an event requiring a short course of oral corticosteroid therapy) between the two treatments. Nineteen patients in the salmeterol group and 15 in the placebo group experienced an exacerbation.

Pharmacologically predictable side-effects were similar for both treatment groups. Seventeen patients in each group reported headache, three in each group reported tremor, three patients in the salmeterol group and one in the placebo group reported cramps, two and one reported palpitations, and one in each group reported tachycardia.

Discussion

The addition of oral corticosteroids to the treatment regimen of poorly controlled chronic asthmatics on maximum doses of inhaled corticosteroids is widely-accepted. However, this may be associated with significant side-effects and may not be appropriate in every case. Current guidelines for the management of chronic asthma [1] include minimalizing adverse drug effects in these patients. It is recommended that one or more of the

longer acting bronchodilators are assessed in this group of patients prior to the introduction of regular corticosteroids.

This study has shown that the introduction of salmeterol into the treatment regimen of chronic asthmatics on maximum inhaled corticosteroids significantly and persistently increased morning peak expiratory flow rate when compared to placebo, and this was associated with a trend to improvement in evening peak expiratory flow rate. There was a difference in baseline morning PEF in favour of the placebo-treated group, however, by analysing the overall change in morning PEF, this difference in baseline values is adjusted for and any change seen can be assumed to be true treatment effects. Symptomatically, compared to placebo, there were statistically significant improvements in the proportion of symptom-free nights, night-time symptom scores and proportion of symptom-free days for the salmeterol-treated group. In addition, patients treated with salmeterol used significantly less relief medication.

These findings are consistent with those of PALMER *et al.* [8], and represent an overall improvement in asthma management. They also concur with the results of other studies, which have demonstrated that symptomatic patients receiving inhaled corticosteroids benefit more following the introduction of salmeterol than a doubling in dose of their inhaled corticosteroid [9, 10] therapy. In these studies, the patients were symptomatic, but did not have a history of exacerbations, unlike the patients in the present study.

This study showed salmeterol was well-tolerated and the adverse events experienced were generally related to the patient's existing condition. The adverse events were unremarkable considering the severe nature of these asthmatics. For the category of patient included in this study the most advantageous outcomes defined in current asthma management guidelines [1] are: to achieve the least possible symptoms; the least possible use of relief bronchodilators; to reduce limitation of activity; to improve PEF and variation in PEF; and to have the least adverse drug effects.

This study has shown that when administered twice daily, salmeterol 100 μg satisfies the majority of these criteria and is an effective therapeutic option, which should be considered prior to the introduction of regular oral corticosteroids for patients who are symptomatic despite high doses of inhaled corticosteroids.

Acknowledgements: The author would like to thank the following for their participation in the study: J. Ayres (Birmingham), M.G. Britton (Chertsey), P. Corris (Newcastle-Upon-Tyne), A. Fairfax (Stafford), T. Higginbottom (Cambridge), S.T. Holgate (Southampton), A.J. Johnson (Canterbury), D. Lane and M.J. Morris (Oxford, J. McMahon (Belfast), F. Stanford (Belfast), J. Stableforth (Birmingham), J. Stradling (Oxford), M. Peake (Pontefract), and H. Walters (Newcastle-Upon-Tyne).

References

1. British Thoracic Society and others. Guidelines on the management of asthma. *Thorax* 1993; 48 (Suppl.): S1–S24.
2. Jennings B, Anderson K, Johannson S. Assessments of systemic effects of inhaled glucocorticosteroids; comparison of the effects of inhaled budesonide and oral prednisolone on adrenal function and markers of bone turnover. *Eur J Clin Pharmacol* 1991; 40: 77–82.
3. Sandstrom T, Frederiksen B, Rosenhall L, Sandstrom B. Salmeterol: a dose response study with a long-acting inhaled β_2-agonist. *Am Rev Respir Dis* 1989; 139 (4, part 2): A64.
4. Verberne A, Hop W, Bos A, Kerrebijn K. Effect of a single dose of inhaled salmeterol on baseline airway caliber and methacholine-induced airway obstruction in asthmatic children. *J Allergy Clin Immunol* 1993; 91: 127–134.
5. Britton M. Salmeterol, three month comparison with salbutamol in asthmatic patients. *Eur Respir J* 1990; 3: 786.
6. Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. *Eur Respir J* 1991; 4: 1178–1184.
7. Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992; 5: 1062–1067.
8. Palmer JBD, Stuart AM, Shepherd GC, Viskum K. Inhaled salmeterol in the treatment of patients with moderate to severe obstructive airways disease: a 3 month comparison of the efficacy and safety of twice daily salmeterol (100 μg) with salmeterol (50 μg). *Respir Med* 1992; 86: 409–417.
9. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol *versus* higher dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994; 344: 219–224.
10. Woolcock A, Lundback B, Ringdal O, Jacques L. Comparison of the effect of addition of salmeterol with doubling the inhaled steroid dose of asthmatic patients. *Am J Respir Crit Care Med* 1994; 149: A280.