Twelve month comparison of salmeterol and salbutamol as dry powder formulations in asthmatic patients

B Lundback, D W Rawlinson, J B D Palmer
on behalf of a European study group

Abstract

Background Salmeterol is a potent selective β_2 agonist that has been shown to have a duration of action in excess of 12 hours. In this study salmeterol and salbutamol were compared over a three month period with a further extension of nine months.

Methods Three hundred and eighty eight patients with mild to moderate reversible airways obstruction (forced expiratory volume in one second (FEV₁) >50% predicted) were randomised to receive salmeterol (50 μ g) twice daily or salbutamol (400 μ g) four times daily, both by dry powder, in a double blind parallel group study. During the first three months detailed assessment of efficacy was made with recording of morning and evening peak expiratory flow rates (PEF), asthma symptoms, and bronchodilator use when necessary for the relief of symptoms. Patients continued in the study for a further nine months with the salbutamol dose reduced to 400 μ g twice daily. Lung function was measured at the clinic and safety data were collected during this period.

Results Salmeterol produced a significantly higher mean morning PEF (mean difference compared with salbutamol 21 (95% CI 12-31) l/min), and a significant reduction in mean diurnal variation in PEF (from 30 l/min at baseline to 11 l/min during salmeterol compared with 34 l/min at baseline to 32 l/min during salbutamol treatment). Salmeterol also reduced day and night symptoms and use of rescue bronchodilator. FEV₁ increased with both salmeterol and salbutamol treatment over the 12 month treatment period. For both treatments the number of patients reporting exacerbations of asthma and the frequency of these exacerbations remained constant during the study. Thirty six patients in the salmeterol and 49 in the salbutamol group withdrew during the 12 months of the study.

Conclusions In this study salmeterol (50 μ g twice daily) was more effective than salbutamol (400 μ g four times daily) in the control of asthma over three months, and more effective than salbuta-

mol (400 μ g twice daily) over a further nine months. Neither salmeterol nor salbutamol was associated with any worsening of control of asthma.

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β_2 Adrenoceptor agonists are established treatment for asthma for patients of all ages. They are effective bronchodilators and protect against various constrictor challenges such as exercise, cold air, methacholine, and histamine.¹⁻⁴ The inhaled route is preferred as this delivers the drug directly to the lung and thus minimises potential systemic side effects.⁵ The major drawback of currently available inhaled drugs is their short duration of action—namely, less than six hours.^{6,7} Salmeterol is a potent selective β_2 agonist that has a duration of action in excess of 12 hours in vitro and in vivo.⁸ In a four week parallel group study in 692 patients with mild to moderate asthma salmeterol increased morning and evening peak flow, reduced the variation in diurnal peak flow, reduced the requirement for additional salbutamol, and lessened symptoms by comparison with placebo.⁹

This study was designed to investigate the safety and efficacy of salmeterol (50 μ g) twice daily and salbutamol (400 μ g) four times daily, both as dry powders, in patients with mild to moderate reversible airways obstruction over a three month period. The double blind study continued for a further nine months with the salbutamol treatment group on a reduced dose of 400 μ g twice daily. During this period lung function was measured at the clinic and safety data were collected.

Methods

PATIENTS

The inclusion criteria required patients (aged 18 or over) to have a forced expiratory volume in one second (FEV₁) or mean daily peak expiratory flow rate (PEF; mean of the highest morning and evening measurements) greater than 50% predicted, an increase in FEV₁ greater than 15% after taking 200 μ g inhaled salbutamol by a pressurised inhaler or 400 μ g inhaled salbutamol by a Diskhaler, a symptom score of 2 or more (for scale see

Medical Division,
National Institute of
Occupational Health,
Umea, Sweden
B Lundback

Department of
Respiratory Medicine,
Glaxo Group Research
Ltd, Greenford,
Middlesex UB6 0HE
D W Rawlinson
J B D Palmer

Correspondence to:
Mr D W Rawlinson

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Table 1 Asthma symptom scores

Night time asthma symptom score

- 0 = No symptoms during the night
 1 = Symptoms causing you to wake once or to wake early
 2 = Symptoms causing you to awake 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 asthma symptom 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 your normal daily activities
 4 = Symptoms for most of the day which did affect your normal daily activities
 5 = Symptoms so severe that you could not go to work or perform normal daily activities

table 1), or a diurnal variation in PEF of at least 15% on four of the last seven days of the run in period. Patients who required >20 mg prednisolone were excluded. A total of 460 patients with a clinical history of mild to moderate reversible airways obstruction and no other serious medical conditions entered the run in period and of these 388 (table 2) were randomised to receive treatment (190 received salmeterol, 198 received salbutamol). The study was performed in 47 centres in 11 countries (see acknowledgements). All patients gave informed consent. Regulatory permission was obtained from all countries where it was required and approval from the appropriate ethics committee was obtained for all centres.

STUDY MEDICATION

The study was of a randomised, double blind, double dummy, parallel group design. There was a two week run in period in which patients took either salbutamol by pressurised inhaler or a salbutamol Diskhaler when necessary for the relief of symptoms. This same rescue medication was also available during the treatment period. After the run in period, patients were randomised for three months to salmeterol (50 µg) twice daily and placebo four times daily or salbutamol (400 µg) four times daily and placebo twice daily. During the final nine months patients received either salmeterol (50 µg) twice daily or salbutamol

(200 µg) twice daily under double blind, double dummy conditions.

CONCOMITANT MEDICATION

At the start of the run in period all oral, parenteral, rectal, or inhaled β receptor agonists (other than the salbutamol inhaler provided), methylxanthines, and anticholinergic drugs were withdrawn. The patients continued inhaled corticosteroids (table 2), oral prednisolone (<20 mg per day), sodium cromoglycate, nedocromil, or ketotifen at unchanged doses throughout the study. Short courses of increased inhaled or oral corticosteroids were allowed during exacerbations.

PROTOCOL

Patients attended the clinic on seven occasions during the first three months of the study with three further visits during the next nine months. At the first visit demographic details were recorded and blood samples were taken for biochemical and haematological analysis. Patients were given a daily record card to record their morning and evening PEF with a mini-Wright peak flow meter (before study or relief medication). They were asked to record their daytime and night time symptoms according to a scoring system (see table 1), and to note their use of rescue salbutamol. If patients met the inclusion criteria they entered the treatment phase. They were seen initially at intervals of two weeks for four weeks (visits 3, 4, and 5) and then every four weeks (visits 6 and 7) to three months.

The patients then continued a nine month safety phase with visits at three-monthly intervals (visits 8, 9, and 10). At each visit the physician recorded changes in medication; intercurrent illnesses, adverse events, and withdrawal and measured blood pressure, heart rate, and FEV₁ and forced vital capacity (FVC). Blood and urine samples were collected at all visits (except visit 4) and 12 lead electrocardiograms were recorded at visit 3 (before study treatment), visit seven (after three months), and visit 10 (after 12 months).

POWER CALCULATION

From results of our previous experience with salbutamol it was estimated that the residual standard deviation of mean morning or evening PEF was unlikely to exceed 45 l/min. From this estimate of variability it was calculated that with 388 evaluable patients the study had a power of 0.91 to detect a mean difference in mean PEF between the two groups of 15 l/min, assuming a two sided *t* test and a 5% level of significance.

ANALYSIS

To be included in the analysis of a variable, patients must have provided at least four days of data for that variable during the run in period and data from at least half of the days in any period of assessment. The mean PEFs in the morning and evening were calculated for each patient together with the mean difference between salmeterol treatment and

Table 2 Patients' characteristics

	<i>Salmeterol</i> (50 µg twice daily)	<i>Salbutamol</i> (400 µg four times a day)
Number allocated to treatment	190	198
Men	89 (47)	100 (51)
Women	101 (53)	98 (49)
Median age (y)	42	46
Range	19–79	18–78
Median duration of asthma (y)	10.0	11.5
Mean PEF (l/min) (am/pm)	367/397	349/384
Mean FEV ₁ (l)	2.46	2.36
(% predicted)	76	73
Smoking history:		
Yes	23 (12)	27 (14)
No	108 (57)	110 (56)
Ex-smoker	59 (31)	61 (31)
Concurrent steroids		
Inhaled only	108 (57)	112 (57)
Oral only	7 (4)	11 (6)
Inhaled and oral	13 (7)	13 (7)

% in parentheses

Figure 1 Changes in mean morning peak flow (PEF; left hand panel) and mean evening PEF (right hand panel) during 12 weeks of treatment with salmeterol (50 µg twice daily; open circle) and salbutamol (400 µg four times daily; closed circle). Changes in morning PEF were significantly higher in patients taking salmeterol ($p < 0.001$).

salbutamol treatment for these responses.

The mean values obtained during treatment were subjected to analysis of covariance with the mean values recorded in the second run in period as covariates. Changes in the proportion of nights with asthma score 0, proportion of days with asthma score less than 2, proportion of nights with no additional salbutamol, and proportion of days with no additional salbutamol were subjected to analyses of variance after transformation to ranks.

Results

Of the 388 patients who were randomised to treatment (190 salmeterol, 198 salbutamol) 303 patients (154 salmeterol, 149 salbutamol) completed the 12 months of treatment. Forty five patients were withdrawn during the three month treatment period (20 salmeterol, 25 salbutamol). The primary reasons for withdrawal were poor compliance with protocol (seven salmeterol, 10 salbutamol) or asthma

ma (seven salmeterol, eight salbutamol). The two treatment groups were well matched for demographic details, smoking habits, and duration and severity of their reversible airways disease (table 2). During the treatment period 57% of patients receiving salmeterol and 57% of patients receiving salbutamol also received inhaled corticosteroids.

Figure 1 shows the changes in mean morning and evening PEFs over the 12 weeks of treatment. Increase in mean morning PEF was significantly higher in patients taking salmeterol than in patients taking salbutamol ($p < 0.001$); the mean difference was 21 l/min (95% confidence interval (95% CI) 12–31). Salmeterol also caused a significant reduction in the diurnal variation in PEF compared with salbutamol ($p < 0.001$); the mean variation was from 30 l/min at baseline to 11 l/min during salmeterol treatment compared with 34 l/min at baseline to 32 l/min during salbutamol treatment.

Figure 2 shows the weekly median percentage of nights with no symptoms of asthma.

Figure 2 Median % of symptom free nights during 12 weeks' treatment with salmeterol (50 µg twice daily; left hand panel) and salbutamol (400 µg four times daily; right hand panel). The median value was significantly greater for patients taking salmeterol ($p < 0.001$).

Figure 3 Median number of rescue doses of β_2 agonist taken during 12 weeks' treatment with salmeterol (50 μ g twice daily; left hand panel) and salbutamol (400 μ g four times daily; right hand panel). The number of doses was significantly less for patients taking salmeterol ($p = 0.013$).

The number of nights with no symptoms was higher during salmeterol treatment than with salbutamol treatment ($p < 0.001$). Median values were 29% during the run in period for both groups. During treatment with salmeterol the median value increased to 100%, and with salbutamol it increased to 71%. Treatment with salmeterol was associated with significantly less use of rescue salbutamol during the day (fig 3). The median percentage of days when no additional salbutamol was used was zero for both groups during the run in period. During treatment with salmeterol the median value increased to 75% and during salbutamol treatment it increased to 67% ($p = 0.013$). The percentage of nights when no additional salbutamol was used was also significantly lower in the salmeterol group than in the salbutamol group ($p < 0.001$). The percentage of nights when no salbutamol was used during the run in period was 43% for both groups. During salmeterol treatment the weekly median value increased to 86% after the first week of treatment and for the next 11 weeks of treatment it was 100%. During treatment with salbutamol the median value increased to 86%.

FEV₁ increased with both salmeterol and salbutamol treatment over the 12 month treatment period (mean change for salmeterol varied from 0.23 to 0.28 l and for salbutamol from 0.1 to 0.15 l). These changes were significantly greater for salmeterol at some but not all visits (see fig 4).

Both study drugs were well tolerated and

the overall incidence and nature of adverse events in the two groups were similar. The most commonly reported adverse event was exacerbation of asthma defined as episodes of acute asthma requiring additional or increased treatment other than relief β_2 agonists. Tables 3 and 4 show the number of patients with exacerbations of asthma and the frequency of exacerbations during each of the three monthly intervals for salmeterol and salbutamol respectively. The frequency of exacerbations was highest during the first three months of the study but this almost certainly reflects the greater frequency of study visits during this period. For both treatments the number of patients reporting exacerbations and the frequency of exacerbations did not increase during the last nine months of the study. This was also the case when the study population was subdivided into those not taking concomitant steroids, those taking inhaled steroids, and those taking oral steroids.

Table 3 Salmeterol: number of patients with asthma exacerbations during particular time intervals

	Time interval (months)			
	0-3	3-6	6-9	9-12
No of exacerbations:				
0	149	136	138	138
1	29	19	15	18
2	8	6	4	2
3	2	1	3	0
4	0	1	1	0
5	1	1	0	0
10	1	0	0	0
No of patients	190	164	161	158
No of patients with at least one exacerbation	41 (22%)	28 (17%)	23 (14%)	20 (13%)

Table 4 Salbutamol: number of patients with asthma exacerbations during particular time intervals

	Time interval (months)			
	0-3	3-6	6-9	9-12
No of exacerbations:				
0	144	124	133	126
1	36	26	22	20
2	9	9	2	3
3	6	1	1	2
4	2	0	0	0
5	1	1	0	0
6	0	1	0	0
10	0	0	1	0
No of patients	198	162	159	151
No of patients with at least one exacerbation	54 (27%)	38 (23%)	26 (16%)	25 (17%)

Figure 4 FEV₁ during 12 months' treatment with salmeterol (50 μ g twice daily; closed circle) and salbutamol (400 μ g four times daily) for 12 weeks and 400 μ g twice daily for the last nine months (open circle). * $p < 0.05$.

Table 5 summarises the incidence of the pharmacologically predictable and most common (>5%) adverse events for the first three months. There were no significant differences between the two groups. Twenty seven patients (12 receiving salmeterol, 15 receiving salbutamol) experienced serious adverse events requiring admission to hospital. Seventeen of these events involved exacerbations of asthma, of which seven occurred in patients receiving salmeterol and 10 in patients receiving salbutamol. One patient in the salbutamol group died as a result of a myocardial infarction, which was considered to be unlikely to be related to the study drug. There were also no significant changes in haematological and biochemical indices in either group and no significant changes were noted in heart rate, systolic and diastolic blood pressure, or 12 lead electrocardiograms.

Discussion

The data presented from this large multi-centre clinical trial show that compared with salbutamol (400 µg four times daily) salmeterol (50 µg twice daily) produced significantly greater improvements in lung function, including a reduction in the diurnal variation of peak flow to a normal level. Also both the requirement for bronchodilator treatment to relieve symptoms and the symptoms of asthma during the day and night were reduced. These improvements occurred during the first week of treatment and were sustained throughout the 12 weeks of detailed study with no evidence of deterioration in control of asthma. Both treatments were well tolerated with a similar low incidence of adverse events in the two groups.

The study was continued for a further nine months with the patients receiving salbutamol at a lower frequency (twice daily). This facilitated the continued use of a double dummy technique to maintain blinding. During this extension the control of asthma as assessed by exacerbation rate and lung function at the clinic was maintained. The incidence of exacerbations of asthma in both groups was higher during the first three months (almost certainly as a result of the greater frequency of clinic visits), and then declined during the next nine months. Thus there was no evidence of waning control of asthma or decline

in lung function as has been reported recently in patients having regular β_2 agonist treatment.^{10,11} Although this is reassuring there was no placebo group having treatment for relief of symptoms only for comparison and therefore further studies are required to answer the question over the long term safety of regular β_2 agonist treatment. This sustained control of asthma was achieved despite the fact that 40% of the patients were not receiving concurrent inhaled glucocorticosteroids. At the outset of this study it was considered appropriate to relate salmeterol to an active comparator given at its recommended regular dosage. Direct comparisons in adults in challenge studies between salmeterol and salbutamol, both administered as dry powders, have not been reported. Salmeterol (50 µg) given as a dry powder or metered dose aerosol, however, gave equal protection against histamine challenge¹² and salbutamol (200 µg) by metered dose aerosol gave acute protection equivalent to that of salmeterol (50 µg by metered dose aerosol) in most but not all¹² challenge studies.¹³⁻¹⁶ Salbutamol given as 200 µg by metered dose aerosol has been shown to be equivalent to salbutamol given as 400 µg of dry powder.¹⁷ We therefore believe that this dose of salbutamol would give an acute effect roughly equal to that of salmeterol (50 µg) although the effect would not be maintained for the same length of time. The change in the dose of salbutamol from four times to twice daily after three months was to aid continued compliance. During the final nine months lung function was measured at the clinic at regular intervals and this was usually in the morning so the maintained effect of salbutamol is to be expected.

Thus salmeterol given either as a dry powder or by metered dose aerosol¹⁸ is an effective treatment for asthma over at least 12 months compared with salbutamol.

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Table 5 Most common (> 5%) and pharmacologically predictable adverse events

	Salmeterol (50 µg twice daily)	Salbutamol (400 µg four times a day)
No of patients	190	198
Asthma and related events	29 (15.3)	42 (21.2)
Acute nasopharyngitis	12 (6.3)	20 (10.1)
Respiratory and chest infections	6 (3.2)	12 (6.1)
Tremor	2 (1.1)	5 (2.5)
Tachycardia (noted by physician)	0	3 (1.5)
Palpitations	1 (0.5)	3 (1.5)
Headache	11 (5.8)	6 (3.0)
Muscle cramp	2 (1.1)	3 (1.5)

% in parentheses.

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