Salmeterol in paediatric asthma

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Abstract

Background—The addition of long acting inhaled β_2 agonists is recommended at step 3 of the British guidelines on asthma management but a recent study suggested no additional benefit in children with asthma.

Methods—The aim of this study was to compare, in a double blind, three way, crossover study, the effects of the addition of salmeterol 50 μ g bd, salmeterol 100 μ g bd, and salbutamol 200 μ g qds in asthmatic children who were symptomatic despite treatment with inhaled corticosteroids in a dose of at least 400 μ g/day over a one month period. Symptom scores, morning and evening peak expiratory flow (PEF) rates, use of rescue medication, spirometric indices, and histamine challenge were measured.

Results—Forty five children aged 5–14 years were enrolled. All three treatments improved asthma control, morning and evening PEF rates, and spirometric indices with no change in bronchial hyper-reactivity. Mean morning PEF was significantly better during the salmeterol treatment periods than with salbutamol treatment ($p < 0.05$). The analysis of mean morning PEF gave an estimated treatment difference of 9.6 l/min for salmeterol 50 μ g bd versus salbutamol 200 μ g qds (95% confidence interval (CI) 2.1 to 17.1), and an estimated treatment difference of 13.8 l/min for salmeterol 100 μ g bd versus salbutamol 200 μ g qds (95% CI 6.0 to 21.5). There were no significant differences between the two doses of salmeterol and all treatments were well tolerated.

Conclusions—In this population of moderate to severe asthmatic children on inhaled corticosteroids, salmeterol in a dose of either 50 μ g bd or 100 μ g bd is significantly more effective at increasing the morning PEF rate over a one month period than salbutamol 200 μ g qds. The data provided no significant evidence of a difference in efficacy between the two doses of salmeterol, 50 μ g and 100 μ g. A trial of salmeterol 100 μ g bd may be worth considering in those still symptomatic on the lower dose.

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treatment in children¹ recommend the early introduction of inhaled corticosteroids to treat airway inflammation. If a child fails to respond to the equivalent of 800 μ g/day of beclomethasone (step 2 of the British guidelines), then either the dose of inhaled corticosteroids may be increased or a long acting inhaled β_2 agonist added to the regime. Studies in mixed populations of adult and paediatric asthmatic subjects have shown that the addition of salmeterol^{2,3} or formoterol⁴ results in better lung function and control of exacerbations than doubling the dose of inhaled corticosteroids, thereby apparently establishing an important role for long acting β_2 agonists at step 3. Studies in children have given conflicting results. Russell *et al*⁵ showed improvement in morning and evening peak flow rate, recorded symptoms, and bronchodilator use when salmeterol was added to inhaled steroids. However, a more recent paediatric study showed no benefit from either doubling the dose of inhaled steroids or adding inhaled salmeterol in children with asthma,⁶ which suggests that long acting β_2 agonists have a lesser role in children than in adults. We designed this study to compare the effects of salmeterol 50 μ g bd, salmeterol 100 μ g bd, and salbutamol 200 μ g qds in children with inadequately controlled asthma despite treatment with ≥ 400 μ g/day inhaled beclomethasone or equivalent.

Methods

PATIENTS

Children were eligible to enter the study if at the screening visit they were aged 5–16 years and required ≥ 400 μ g/day inhaled beclomethasone or equivalent, and showed evidence of reversible airflow obstruction—namely, a 15% increase in peak expiratory flow (PEF) or forced expiratory volume in one second (FEV₁) after inhaling 400 μ g salbutamol from a Diskhaler, short acting bronchodilators having been withheld for more than four hours. Exclusion criteria were admission to hospital for any reason, treatment with oral corticosteroids or change in regular asthma treatment during the four weeks before starting the study, serious concomitant disease, and an acute respiratory infection requiring new prescribed treatment during the four weeks before starting the study. Treatment with oral β agonists, theophylline, or inhaled anticholinergic agents was not permitted.

STUDY DESIGN

This was a double blind, double dummy, three way, crossover study with a run in and three treatment periods. During the run in period the children took their regular inhaled corticosteroids and were asked to use inhaled salbutamol from a Diskhaler for relief of symptoms. In

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Asthma is characterised by variable airflow obstruction related to bronchial hyperreactivity to a variety of stimuli owing to underlying airway inflammation. Guidelines for asthma

order to be eligible for the treatment periods, at the end of the two week run in period (see below) they were required to have either (1) an $FEV_1 < 80\%$ predicted four hours after last inhaling a short acting β_2 agonist or (2) a mean morning PEF over the last seven days of the run in period of $< 80\%$ of the predicted normal or (3) a diurnal variation in PEF of at least 20% on at least four of the last seven days of the run in period where diurnal variation was defined as:

$$[(PEF_{\text{previous evening}} - PEF_{\text{following morning}}) / (PEF_{\text{previous evening}})] \times 100\%.$$

The treatment periods were a double blind comparison of salmeterol 50 µg bd with salmeterol 100 µg bd and salbutamol 200 µg qds for four weeks each. Treatment order was randomised by a computer generated random code. Between six and nine subjects were randomised to each of the six possible treatment sequences. Each child inhaled from three Diskhalers regularly during each of the three study periods to ensure blinding. In addition, active salbutamol 200 µg/dose could be used up to six times a day from a Diskhaler for relief of symptoms. Adherence to treatment was assessed by counting the number of blisters returned. There was no washout between treatment periods. At the end of the study there was a final two week period of monitoring during which the child used only inhaled salbutamol as required.

Based on a residual standard deviation of 35 l/min, 54 evaluable patients would give a power of at least 80% to detect a treatment difference in mean morning PEF of 13 l/min between any two treatments at a 5% significance level. It was therefore planned that approximately 72 boys and girls would be recruited with the aim of providing 54 evaluable subjects.

MEASUREMENTS

There were a total of six visits (start of study, end of run in period, end of each treatment period, end of two week post-study period). At each visit the child was assessed, record cards (below) were examined, and medication was returned as appropriate. The investigator and the child or guardian assessed the effectiveness of treatment independently but subjectively. Spirometric tests were performed at each visit using a Compact Vitalograph (Hamburg, Germany) which was calibrated before each set of measurements with a one litre syringe. The best of three reproducible measurements of FEV_1 was recorded. PEF was measured separately using a Wright peak flow meter (London, UK). Histamine challenge was performed in a subgroup of children (below). The baseline results are shown in table 1.

Children were asked to keep a diary card throughout the study. They were asked to record daytime and night time symptoms and use of rescue medication. They were provided with a Wright mini-peak flow meter and asked to record the best of three peak flows in the morning and in the evening before taking their study medication. Only the last two weeks of

Table 1 Mean (SD) baseline lung function results

Baseline measure	n	Mean (SD)
Mean morning PEF (l/min)	43	249 (69)
Morning PEF (% predicted)	43	94 (19)
Mean evening PEF (l/min)	43	255 (43)
Evening PEF (% predicted)	43	96 (19)
FEV_1 (l)	44	1.60 (0.50)
PC_{20} (mg/ml)	21	0.28 (1.94)*

PEF = peak expiratory flow; FEV_1 = forced expiratory volume in one second; PC_{20} = concentration of histamine provoking a fall in FEV_1 of 20%.

*Geometric mean and coefficient of variation.

the diary card data were used in the final analysis.

BRONCHIAL HYPERREACTIVITY

Bronchial challenge was performed in children who had an FEV_1 of more than 75% predicted and an absolute value of more than one litre at the end of each of the three study periods. Study medications were omitted on the morning of the challenge. Test medications were given in a Wright nebuliser, airflow 8 l/min from an air cylinder, with the child breathing tidally and wearing a noseclip. Nebulisation time was two minutes at each dose, with FEV_1 and PEF measured at the end of nebulisation. Normal saline was inhaled first, followed by histamine acid phosphate in doubling doses from 0.03 to 32 mg/ml. The test was halted when FEV_1 had fallen by $\geq 20\%$ and the concentration of histamine producing a 20% fall in FEV_1 (PC_{20}) was determined by linear interpolation.

STATISTICAL METHODS

Only patients with at least one day's data during weeks 3 or 4 in at least two periods and at least one day's data during the last week of the run in period were included in the efficacy analyses. The primary efficacy end point was the mean morning PEF. An analysis of covariance, appropriate for a three way crossover,⁷ was used to analyse these data. The covariates used were subject, randomisation treatment sequence, period effects, treatment effects, and period $\times$ treatment interaction. The carryover effect was tested but was not found to be significant ($p = 0.62$). The period and period $\times$ treatment interaction effects were also found not to explain significantly the variation in the data. However, these terms were left in the model as they were included in the planned analysis.

Secondary end points—mean evening PEF, percentage predicted morning and evening PEF ($-425.5714 + 5.2428 \times \text{height}$), and the log transformed histamine PC_{20} —were also analysed using the described method of analysis of covariance. The median number of blisters of day and night rescue salbutamol were analysed using the Wilcoxon rank sum test via Koch's method⁸ which performs pairwise treatment comparisons whilst adjusting for period effects. The day and night symptom scores and the patient's and physician's assessments were also analysed using this method.

Pairwise comparisons of the most common adverse events were tested using Prescott's test.

Table 2 Comparison of lung function results for the three treatments over a four week period

Treatment	n	Adjusted mean	Estimated treatment difference versus salbutamol 200 µg	95% CI	p value
<i>Mean morning PEF (l/min)</i>					
Salmeterol 50 µg	40	262.0	9.6	2.1 to 17.1	0.013
Salmeterol 100 µg	38	266.2	13.8	6.0 to 21.5	0.001
Salbutamol 200 µg	40	252.4			
<i>Predicted morning PEF (%)</i>					
Salmeterol 50 µg	40	98.7	3.6	0.4 to 6.7	0.028
Salmeterol 100 µg	38	99.4	5.4	2.1 to 8.6	0.002
Salbutamol 200 µg	40	95.5			
<i>Mean evening PEF (l/min)</i>					
Salmeterol 50 µg	40	268.0	4.6	-4.0 to 13.3	0.288
Salmeterol 100 µg	38	268.0	7.5	-1.4 to 16.4	0.097
Salbutamol 200 µg	40	261.6			
<i>Predicted evening PEF (%)</i>					
Salmeterol 50 µg	40	100.5	1.3	-2.2 to 4.7	0.471
Salmeterol 100 µg	38	100.8	2.4	-1.1 to 6.0	0.178
Salbutamol 200 µg	40	98.7			
<i>Clinic visit FEV₁ (l)</i>					
Salmeterol 50 µg	41	1.75	0.03	-0.04 to 0.1	0.439
Salmeterol 100 µg	40	1.70	-0.02	-0.09 to 0.05	0.585
Salbutamol 200 µg	41	1.72			
<i>Clinic visit PC₂₀</i>					
Salmeterol 50 µg	14	0.47*	1.54†	0.65 to 3.70	0.306
Salmeterol 100 µg	15	0.37*	1.23†	0.55 to 2.78	0.598
Salbutamol 200 µg	16	0.30*			

PEF = peak expiratory flow; FEV₁ = forced expiratory volume in one second; PC₂₀ = concentration of histamine provoking a fall in FEV₁ of 20%.

*Adjusted geometric mean.

†Ratio of treatment:salbutamol.

Results

All statistical analyses were performed on the intent-to-treat population which consisted of 45 of the 52 subjects screened. A further five subjects withdrew from the study after randomisation. Three of the withdrawn subjects failed to return. These subjects were randomised to treatment sequences ACB, CAB, and ACB (where A = salmeterol 50 µg, B = salmeterol 100 µg, and C = salbutamol 200 µg) and withdrew during periods 1, 2, and 2, respectively. One subject, randomised to sequence ACB, withdrew due to non-compliance in the third period. The other withdrawal, randomised to sequence BCA, withdrew due to lack of efficacy in the first period. All subjects returned at least 80% of the prescribed study medication with the blisters pierced.

Thirty one (69%) of the 45 subjects in the intent-to-treat population were boys with 24 (77%) being less than 12 years of age. Of the 14 girls, 10 (71%) were less than 12 years of age. The overall mean (SD) age of the subjects was 9 (2.8) years.

Eighty two percent of the subjects had a family history of asthma, 80% had a history of seasonal rhinitis, and 60% had a positive skin test to common allergens. All children had at least one exacerbation requiring a change in medication in the previous year, but only five had been admitted to hospital in that period. The main asthma triggers identified were exercise (96%) and cold air (91%).

The overall incidence of adverse events experienced during treatment was slightly higher with salbutamol 200 µg (79%) than with salmeterol 50 µg (64%) or 100 µg (70%). However, for the most common adverse events (asthma, upper respiratory tract infection, cough, headache, and sore throat) there were no statistically significant differences between the treatment groups. Headache was the most

commonly reported drug related adverse event in all three treatment groups. Nine patients in the intent-to-treat population experienced at least one serious adverse event during the run in period, study period, or follow up. Two subjects had serious adverse events that were considered to be possibly or probably related to study medication. However, on further follow up the investigator concluded that one these was unlikely to be related to study medication. No subjects died in the study and no patients were withdrawn because of an adverse event.

The primary efficacy analysis identified the two salmeterol treatments to be significantly more effective at increasing the mean morning PEF than salbutamol. For salmeterol 50 µg versus salbutamol 200 µg the estimated treatment difference was 9.6 l/min (95% confidence interval (CI) 2.1 to 17.1), $p = 0.013$. For salmeterol 100 µg versus salbutamol 200 µg the estimated treatment difference was 13.8 l/min (95% CI 6.0 to 21.5), $p = 0.001$. No significant difference was found between the two doses of salmeterol ($p = 0.280$, table 2).

Analysis of the percentage predicted mean morning PEF gave similarly significant results to the treatment differences. However, for the mean evening PEF and percentage predicted mean evening PEF, no significant treatment differences were identified. The clinic visit FEV₁ also showed no differences between treatments. Only 14 subjects were tested for bronchial hyperreactivity (PC₂₀) on salmeterol 50 µg, 15 on salmeterol 100 µg, and 16 on salbutamol 200 µg and no significant differences were found between the treatment groups.

The median percentage of days during which no rescue medication was required was greatly increased from baseline (42%) for all three treatments: 61% for salmeterol 50 µg, 72% for salmeterol 100 µg, and 65% for salbutamol 200 µg. However, Koch's method provided no evidence to suggest that any one treatment was more effective in increasing the percentage of days with no rescue medication. No significant differences were found between the treatment groups for the percentage of nights during which no rescue medication was required.

The median daytime symptom score improved from a baseline score of 1 to a score of 0 for all three treatments and the daytime symptom score remained at 0 for all treatments throughout the study. The percentage of symptom free days increased from baseline for all three treatments but there were no significant differences between them. The physician and child assessments of efficacy were the same for all study periods, with more than 50% rating the study medication as effective or very effective. These results provide no further evidence of any differences between treatments.

Discussion

This study has shown that, in addition to inhaled corticosteroids in doses of at least 400 µg/day, the use of salmeterol 50 µg bd and salmeterol 100 µg bd provides significantly greater improvement in mean morning PEF (9.6 l/min and 13.8 l/min, respectively) than

Figure 1 Mean morning peak expiratory flow rate (PEFR) over the four week treatment period, using the raw data.

regular salbutamol 200 µg qds in children with symptomatic asthma over a four week period. There was no significant difference in efficacy between the two doses of salmeterol. There were no significant treatment differences for the symptom scores, evening peak expiratory flow, use of rescue medication, spirometric indices, and histamine challenge.

This study was double dummy and double blind with a random order of treatments to control for the tendency for children with asthma to improve spontaneously over time. There are potential limitations to any conclusions that can be drawn because of the nature of the study design. Firstly, the treatment periods were for four weeks only, and thus we cannot exclude that a longer time period would have revealed loss of efficacy or increased side effects in any of the treatments. We decided to opt for a shorter treatment period because of concerns about the possible ill effects of regular short acting β_2 agonists during the control period, and also to enable us to complete a dose response study in a reasonable length of time. The alternative would have been a parallel group design over 12 weeks but this would have required far more patients to achieve comparable statistical power. However, inspection of the raw data showed no compelling evidence of any trends for improvement or deterioration with time during the last three weeks of the treatment periods, implying that a plateau had been reached which is, to some extent, reassuring (fig 1). Furthermore, Russell *et al*⁷ showed no loss of benefit in their parallel group study over a 12 week period and Verberne *et al*⁸ showed no deterioration in bronchoprotection with salmeterol treatment over a four month period in 30 children with mild asthma. A more recent study¹⁰ did show a reduction in the duration of the protective action of salmeterol against exercise induced bronchoconstriction. The short duration of the study means that we were precluded from detecting any effect (positive or negative) on acute exacerbations of asthma.

Secondly, the study lacked a placebo period. However, in these very symptomatic children we felt that a placebo period would not be ethical and that a two week run in was the longest acceptable time without instituting a change in treatment. We accept that an alternative study

design would have been to provide as needed rather than regular salbutamol,⁵ but the children were already in effect using this strategy before joining the study and were still symptomatic, so we felt we had to offer an alternative strategy. The further alternative, that of doubling the dose of inhaled corticosteroids, would have been likely to require a longer study period and the comparison of these two strategies was not the aim of this study. We do not have any direct data on changes in airway inflammation. Clearly we could not have carried out bronchoscopy, lavage, and biopsy at the end of each treatment period in this group of children. At the time the study was carried out we did not have access to measurements of exhaled nitric oxide^{11,12} or induced sputum¹³ that would undoubtedly have supplemented our findings. However, even these techniques would have been difficult to apply in some of the younger children. We were able to measure bronchial hyperreactivity as a surrogate for airway inflammation^{14,15} in about one third of the group, and reassuringly there was no change with treatment. However, this study cannot exclude the possibility of either short term or long term worsening of airway inflammation in any treatment arm.

Nonetheless, within the constraints of the study, the data provided no evidence of a significant advantage, in terms of the primary or secondary end points, of doubling the conventional dose of salmeterol. Previous dose response studies have compared salmeterol in doses up to 50 µg bd¹⁶⁻¹⁸ with conflicting results. Lenney *et al*¹⁶ compared 25 µg with 50 µg bd and showed that symptoms and morning and evening peak flow were higher with salmeterol 50 µg bd. By contrast, de Benedictis *et al*¹⁷ found that a single dose of 25 µg salmeterol was equally as good as 50 µg in preventing exercise induced bronchoconstriction. Weinstein *et al*¹⁸ reported a trend to greater bronchodilatation with 42 µg than with 21 µg salmeterol in 243 children but found no statistically different changes between the two doses. Primhak *et al*¹⁹ did show additional bronchoprotective effect against methacholine induced wheeze with an increase in a single salmeterol dose from 25 to 100 µg, but this was in younger children using a mask and spacer. It is difficult to compare airway deposition with this device and a dry powder device. Some of these apparent contradictions may be because the plateau of the dose response curves are at different doses for bronchodilatation and bronchoprotection. Our data imply that, at least for bronchodilatation, symptom score and use of rescue medication, the plateau has been reached by 50 µg salmeterol twice daily in most individuals. This does not exclude the possibility that some individuals may benefit from a higher dose and, indeed, four children (10%) did appear to show additional benefit at the higher dose.

The role of long acting β_2 agonists in paediatric asthma is still to be defined. They should only be used in children already taking inhaled corticosteroids, and not used as sole preventive treatment.^{20,21} Several previous investigators

have demonstrated benefit in children with asthma who had inadequate control on moderate doses of inhaled corticosteroids.^{16 22 23} However, the role of long acting β_2 agonists in paediatric asthma was called into question by Verberne *et al*⁶ who performed a randomised, double blind, parallel group study comparing beclomethasone 200 μg bd plus placebo, beclomethasone 200 μg bd plus salmeterol 50 μg bd, and beclomethasone 400 μg bd in 177 children. They showed no difference in lung function, bronchial hyperreactivity, and asthma control in any of the three groups. This may be because they were studying children whose asthma was already well controlled (average rescue bronchodilator usage <1 dose/week). In our study, in which a much more symptomatic group of patients was studied, differences in the mean morning PEF were seen over the four week period with the different treatments, both doses of salmeterol giving significantly greater improvements in PEF than salbutamol. The symptomatic control of patients and use of rescue therapy improved over the four week period in all treatment groups, although the differences were not significant.

What then is the role of long acting β_2 agonists in paediatric asthma? They should never be used as monotherapy but, when added to inhaled corticosteroids, there is evidence for improved asthma control and better lung function with no deterioration in bronchial hyperreactivity, at least in the short term. For most children there will be no additional benefit in increasing the dose of salmeterol above 50 μg bd, although a few children may benefit from a trial of 100 μg bd. Although benefit can be obtained with regular short acting β_2 agonists, the improvement is less and the inconvenience of a four times daily regime is likely to make it less acceptable. The stage at which long acting β_2 agonists should be added rather than the dose of inhaled steroids increased remains to be agreed, at least in paediatric asthma.

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