Comparison of fluticasone propionate with beclometasone dipropionate in moderate to severe asthma treated for one year

L Fabbri, P S Burge, L Croonenborgh, F Warlies, B Weeke, A Ciaccia, C Parker on behalf of an International Study Group

Abstract

Background—High dose inhaled glucocorticosteroids are increasingly used in the management of patients with moderate to severe asthma. Although effective, they may cause systemic side effects. Fluticasone propionate is a topically active inhaled glucocorticosteroid which has few systemic effects at high doses.

Methods—Fluticasone propionate, 1·5 mg per day, was compared with beclometasone dipropionate at the same dose for one year in patients with symptomatic moderate to severe asthma; 142 patients received fluticasone propionate and 132 received beclometasone dipropionate. The study was multicentre, double blind and of a parallel design. For the first three months patients attended the clinic every four weeks and completed daily diary cards. For the next nine months they were only seen at three monthly intervals in the clinic.

Results—During the first three months diary card peak expiratory flow (PEF) rate and lung function measurements in the clinic showed significantly greater improvement in patients receiving fluticasone propionate (difference in morning PEF 15 l/min (95% CI 6 to 25)), and these differences were apparent at the end of the first week. The improved lung function was maintained throughout the 12 month period and the number of severe exacerbations in patients receiving fluticasone propionate was reduced by 8% compared with those receiving beclometasone dipropionate. No significant differences between the two groups were observed in morning plasma cortisol levels, urinary free cortisol levels, or response to synthetic ACTH stimulation. In addition, both the rates of withdrawal and of adverse events were low, and there were fewer exacerbations of asthma with fluticasone propionate than beclometasone dipropionate.

Conclusions—This study shows that fluticasone propionate in a daily dose of 1·5 mg results in a significantly greater increase in PEF and asthma control than the same dose of beclometasone dipropionate, with no increase in systemic or other side effects.

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up to 90% of an inhaled dose may be swallowed if a spacing chamber is not used, fluticasone propionate appears to have an advantage over existing inhaled corticosteroids. There is no evidence for local metabolism in the lung.

This study was designed to compare the efficacy and safety of fluticasone propionate with an equal daily dose of beclomethasone dipropionate. Preclinical and clinical studies have suggested that fluticasone propionate has at least twice the potency of beclomethasone dipropionate with a greater local to systemic activity ratio.\(^5\) Patients with moderate to severe uncontrolled asthma taking a daily dose of at least 1000 \(\mu g\) beclomethasone dipropionate or budesonide were recruited into a comparative study of fluticasone propionate, 1·5 mg per day, with beclomethasone dipropionate, 1·5 mg per day, for 12 months. Throughout the study period detailed assessments of asthma control were made for three months, and safety and lung function values were assessed for a further nine months.

**Methods**

**Patients**

A total of 274 patients with symptomatic moderate to severe asthma aged between 17 and 80 years recruited from 25 centres in 10 countries were randomised to treatment. All patients were currently receiving at least 1000 \(\mu g\)/day beclomethasone dipropionate or budesonide. Following a two week run-in period on 1·5 mg beclomethasone dipropionate per day, patients were randomised to treatment with fluticasone propionate or beclomethasone dipropionate, 750 \(\mu g\) twice daily, both administered via a pressurised metered dose inhaler. Patients were allowed to use a spacer device but this was at the discretion of individual physicians. One hundred and forty two patients received fluticasone propionate (1·5 mg/day) and 132 received beclomethasone dipropionate (1·5 mg/day).

Patients were randomised if they had at least two of the following: mean morning peak expiratory flow (PEF) during the last seven days of the run in period \(\leq 70\%\) predicted; 15\% reversibility of forced expiratory volume in one second (FEV\(_1\)) following 200 \(\mu g\) salbutamol during the run in period or within three months before the start of the study; \(\geq 20\%\) diurnal variation in PEF on at least four of the last seven days of the run in period; asthma symptoms on at least four of the last seven days of the run in period.

Exclusion criteria were as follows: treatment with \(2000 \mu g/day\) or more of beclomethasone dipropionate or budesonide; treatment with systemic corticosteroids within one month of the study period or on more than three occasions during the six months before the run in period; treatment with other investigational drugs within four weeks of the study; hypersensitivity to inhaled corticosteroids; concomitant diseases likely to complicate the evaluation of the study drug; pregnancy or lactation. Women of childbearing potential were only included if the investigator considered that they were taking adequate contraceptive precautions. All patients gave their informed consent and the study was approved by local ethical committees.

**Study Design**

During the two week run in period the patients discontinued use of their usual inhaled corticosteroid therapy and received 1·5 mg beclomethasone dipropionate per day. The dose of all other asthma medication remained constant, except for inhaled \(\beta_2\) agonists which were only to be continued on an "as required" basis. If, during that period, the patients achieved the criteria for randomisation they entered the double blind portion of the study. These patients were randomly allocated in a double blind manner to receive either fluticasone propionate, 1·5 mg/day, or beclomethasone dipropionate, 1·5 mg per day, for one year. Investigators were, however, permitted to increase the dose of study drug to 2 mg at any time after the first three months, either transiently or long term. For the first three months the patients attended the clinic every four weeks and completed daily diary cards. After this they were seen at three monthly intervals in the clinic and did not complete daily assessments. They were also seen at a follow up visit two weeks after withdrawal of study medication.

**Measurements**

Using the mini Wright peak flow meter, patients measured their PEF in the morning (between 07:00 and 08:00 hours) before using a bronchodilator, and in the evening (19:00–20:00 hours), preferably not within four hours of bronchodilator therapy. On each occasion they took three readings and entered the highest measurement on a daily record card on which they also noted the severity of their asthma symptoms by day and at night, using four-point rating scales. Symptoms during the day were rated as 0 = very well, no symptoms; 1 = a few symptoms (not troublesome); 2 = asthma troublesome; or 3 = asthma bad, not able to carry out daily activities as normal. Symptoms during the night were rated as: 0 = slept through the night; 1 = slept well, woken early or once by asthma or cough; 2 = woken two or three times by cough or asthma; or 3 = bad night, kept awake most of the night by asthma. Patients also recorded their use of the study medication and of the salbutamol inhaler.

At each of the clinic visits three measurements were made of PEF, FEV\(_1\), and forced vital capacity (FVC) and the best of the three measurements were recorded. Where possible these measurements were made at the same time of day (preferably in the morning) on each visit, and patients were asked not to use their inhaled bronchodilator for four hours before attending the clinic. Oropharyngeal swabs to determine the presence of *Candida albicans* were taken if there was clinical evidence of infection following visual examination.
Adverse events
At each clinic visit assessments of safety were performed. All serious and minor adverse events were recorded, irrespective of their apparent cause in relation to the study drug.

Laboratory evaluations
At the pre-study visit, at the end of the run in period, and after three, six, nine, and 12 months, patients were asked to collect a 24 hour urine sample for determination of urinary free cortisol excretion. Blood samples for routine testing (haematology, biochemistry) were taken between 08:00 and 10:00 hours at the clinic visits before and during treatment, and at the follow up visit if any abnormal results had been noted at the previous visit. The samples were analysed locally. Plasma cortisol concentrations were assessed from blood samples taken at the pretrial visit and at all other visits throughout the 12 months of study. The plasma cortisol samples were analysed by radioimmunoassay at the West Middlesex Laboratory, UK using the coated tube method with a between batch coefficient of variation of 7%.

In addition, at some centres patients had assessments of adrenal reserve made using a short tetracosactrin test after 12 months of treatment. Patients were asked to withhold treatment with inhaled glucocorticosteroids for at least 12 hours before the test. A blood sample was taken between 08:00 and 10:00 hours for determination of basal plasma cortisol concentration. Patients then received a single intramuscular injection of tetracosactrin 250 μg. Exactly 30 and 60 minutes later further blood samples were obtained for plasma cortisol measurements.

Asthma exacerbations
Asthma exacerbations were defined as increasing asthma symptoms requiring a change in therapy other than inhaled β₂ agonist rescue therapy, and these were recorded throughout the study by the investigators.

Table 1  Demographic details of the study patients randomised to fluticasone propionate and beclometasone dipropionate

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone propionate</th>
<th>Beclometasone dipropionate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>142</td>
<td>132</td>
</tr>
<tr>
<td>Withdrawals</td>
<td>25 (18)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Male/female</td>
<td>91/51 (64/36)</td>
<td>64/68 (48/52)</td>
</tr>
<tr>
<td>Age (range) (y)</td>
<td>17–77</td>
<td>19–80</td>
</tr>
<tr>
<td>Caucasian</td>
<td>137 (96)</td>
<td>130 (98)</td>
</tr>
<tr>
<td>Smokers</td>
<td>19 (13)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Asthma &gt;1y</td>
<td>139 (98)</td>
<td>129 (98)</td>
</tr>
<tr>
<td>Asthma &gt;10y</td>
<td>81 (57)</td>
<td>73 (55)</td>
</tr>
<tr>
<td>Spacer used</td>
<td>69 (49)</td>
<td>60 (45)</td>
</tr>
<tr>
<td>Mean morning PEF (l/min)</td>
<td>350</td>
<td>314</td>
</tr>
<tr>
<td>Mean morning PEF (% predicted)</td>
<td>74</td>
<td>73</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.

The occurrence of an exacerbation was not a dropout criterion so the patient could continue in the study at the doctor’s discretion.

The procedure to be followed in the event of an exacerbation of asthma was detailed in the protocol and explained to the patients. Patients who experienced worsening symptoms were instructed to increase their use of bronchodilator therapy and to report to the hospital within 24 hours. The investigator would decide whether to commence oral steroid therapy or increase the dose of inhaled corticosteroid up to 2000 μg/day. If a short course of oral corticosteroids was considered necessary patients took 30–40 mg prednisolone daily for one week in addition to their trial medication. If their symptoms had improved and were stable for 48 hours the dose of oral corticosteroids was gradually reduced and stopped. Those patients who did not improve continued to take oral corticosteroids for a further two weeks and were reassessed. Patients who did not improve after three weeks were withdrawn from the study, as were patients who required systemic corticosteroids on more than four occasions during the study.

Analysis
Data from the daily record cards completed during the last 14 days of the run in period were used to establish a baseline. For the treatment period data were analysed for weeks 1–4, weeks 5–8, and weeks 9–12. A further analysis was undertaken using summarised data from the whole 12 week period.

To be included in the analysis of a variable, patients had to provide data for at least seven days during the run in period and for at least 14 days in any treatment assessment period. The analysis presented here is that of the total randomised population on an ‘intent to treat’ basis.

Daily record card data were collected over the first 12 weeks of the study. Clinic lung function measurements were recorded over 12 months. The mean morning and evening PEF was calculated over each period for each patient and expressed as absolute values. Predicted lung function values were calculated from sex, age, and height using standard formulae.8 Diary card PEF rates and other lung function values, together with plasma cortisol concentrations, were analysed by analysis of covariance using SAS-GLM procedure (SAS Release 6.04). Tests for interactions between baseline (the last 14 days of the run in), country, use of spacer device, and treatment were performed.

The non-parametric data such as symptom scores and relief β₂ agonist use were analysed by Wilcoxon rank sum test adjusted for country by the van Elteren method.7 The adverse events and withdrawals were analysed by the Mantel-Haenszel test10 and Fisher’s exact test, respectively. In addition, exacerbations reported as a single diagnosis were analysed by the Wilcoxon rank sum test and the occurrence of severe exacerbations by the Fisher’s exact test.
Results
Table 1 shows the demographic details of the randomised patients. There were no apparent differences between the groups on entry to the study. Approximately 50% of the patients in each treatment group had been receiving >1.5 mg inhaled corticosteroid per day before the run in period.

During the trial 18 patients withdrew from the beclomethasone dipropionate group and 25 from the fluticasone propionate group. One patient from the beclomethasone dipropionate and four from the fluticasone propionate group withdrew because of asthma. Fifteen patients in total, all in the fluticasone propionate group, temporarily increased their study drug from 1.5 mg/day to 2 mg/day to control symptoms during the last nine months of treatment. This small number of patients had no apparent influence on the three monthly clinic lung function measurements or on the exacerbation rates.

Diary card data
The morning PEF values increased in both groups from the baseline value. The mean differences between the treatment groups, however, at weeks 1–4, 5–8, and 9–12 were all significantly in favour of fluticasone propionate (fig 1). Overall the mean difference was 15 l/min (95% confidence intervals (CI) 6 to 25; p < 0.005) when averaged over the 12 weeks of diary card completion and adjusted for differences in baseline values, country, and use of spacer device. Analysis of changes from baseline morning PEF values showed that the difference between treatments was significant for both days 1–7 (adjusted mean difference = 9 l/min; 95% CI 1 to 17; p < 0.005) and days 8–14 (adjusted mean difference = 16 l/min; 95% CI 6 to 25; p = 0.002). Moreover, these results were obtained after a two week run in period on 1500 μg/day beclomethasone dipropionate.

Increases in mean evening PEF in favour of fluticasone propionate were also observed throughout the 12 week period, the adjusted mean evening PEF being significantly greater on fluticasone propionate by 10 l/min (95% CI 0 to 19; p < 0.05).

Patients in both treatment groups reported fewer symptoms by day or night compared with the run in values. The mean percentage of symptom free days was 19% and 22% during the run in period for the fluticasone propionate and beclomethasone dipropionate groups, respectively. This increased to 38% and 41% over the 12 weeks, the differences between the groups being not significant. The mean percentage of symptom free nights was 47% and 50% during the run in period for the fluticasone propionate and beclomethasone dipropionate groups, respectively. This increased to 61% and 63% over the 12 weeks, again the mean differences not being significant between treatments. Patients in both treatment groups were well controlled.

For all treatment time periods analysed fewer than 10% of patients given fluticasone propionate or beclomethasone dipropionate had median symptom scores of 2 or more.

Both treatments also reduced the number of days and nights in which patients had to use their salbutamol inhaler. The mean percentage of β₂ agonist rescue free days was 20% and 13% during the run in period for the fluticasone propionate and beclomethasone dipropionate groups, respectively. This increased to 29% and 19% over the 12 weeks. There were no significant differences between treatments. The use of rescue medication was very low with β₂ agonist requirement during the run in period varying from 25 to 27 times per week. During the treatment period patients on beclomethasone dipropionate tended to use more rescue medication than those in the fluticasone propionate treatment group. This difference was significant for weeks 5–8 (p < 0.05).

Clinic lung function
Figure 2 shows the mean change from baseline values in clinic PEF values over the 12
month treatment period. The mean clinic PEF values, which were 369 l/min and 323 l/min at the end of the run in period for fluticasone propionate and beclomethasone dipropionate groups respectively, increased over the 12 months in both treatment groups to 405 l/min and 348 l/min. Analysis of the results, which took baseline values, country, and use of spacer into account, showed that the increase was significantly greater on fluticasone propionate by 20 l/min (95% CI 1 to 40; p < 0.05) at 12 months.

The mean FEV₁ increased from 2.141 and 1.811 for fluticasone propionate and beclomethasone dipropionate to 2.391 and 1.971 respectively, over the 12 months (fig 3), and the adjusted treatment difference was greater on fluticasone propionate by 0.151 (95% CI 0.01 to 0.29; p < 0.05). Significant treatment differences in favour of fluticasone propionate were also found after eight and 12 weeks of treatment (p < 0.05).

Mean FVC values showed a similar increase from 3.371 and 2.891 for fluticasone propionate and beclomethasone dipropionate groups to 3.561 and 3.041, respectively. The adjusted mean differences, both between absolute values and as a percentage of predicted normal values, were not significantly different at any of the clinic visits.

**Asthma exacerbations**
The number of patients experiencing an exacerbation of asthma during the study is shown in table 2. The number of exacerbations experienced was low with the majority (>70%) of patients experiencing no exacerbations. There was significant difference in the distribution of exacerbations, reported as a single diagnosis adverse event, between patients receiving fluticasone propionate and these receiving beclomethasone dipropionate (p < 0.02), with statistically fewer patients experiencing exacerbations in the fluticasone propionate group than in the beclomethasone dipropionate group (p < 0.05). Furthermore, significantly fewer patients had severe exacerbations on fluticasone propionate (3/142 patients, 2%) than on beclomethasone dipropionate (13/132 patients, 10%) (p < 0.02).

**Corticosteroids**
Analysis of geometric mean plasma cortisol values at baseline and after three, six, nine, and 12 months include only those patients with data at baseline and at the specified visit. There was no difference between the geometric mean plasma cortisol concentrations in patients receiving fluticasone propionate and beclomethasone dipropionate at any of the visits (table 3), nor were there any differences in the percentage of patients with a plasma cortisol level below the lower limit of normal (150 nmol/l). Likewise there were no differences between treatment groups in the 24 hour urinary free cortisol levels; 25/110 (23%) patients treated with fluticasone propionate and 26/115 (23%) treated with beclomethasone dipropionate showed a change from high or normal values to below the lower limit of the normal range.

The tetracosactrin test was performed in 35 and 30 patients in the fluticasone propionate and beclomethasone dipropionate groups respectively, after 12 months of treatment. The results from both treatment groups showed a “normal response”—that is, after 30 minutes mean plasma cortisol concentrations had risen by at least 200 nmol/l to almost 500 nmol/l and after 60 minutes were greater than 500 nmol/l.

**Adverse events**
There were no consistent changes in biochemical or haematological indices on either treatment. During the study there were 276 and 267 adverse events during treatment with fluticasone propionate and beclomethasone dipropionate in 70% and 73% of patients, respectively. This included serious adverse events in 16% and 23% for fluticasone propionate and beclomethasone dipropionate respectively, leading to 8% of patients withdrawing in both groups. There were three deaths during the study, two while receiving fluticasone propionate and one while receiving beclomethasone dipropionate, none of which were asthma related. The adverse events which occurred most commonly—that is, more than 5%—and those which were pharmacologically predictable are shown in table 4. The most common were related to the patient’s disease (asthma, rhinitis). The incidence of expected pharmacologically predictable adverse events such as *Candida* infec-

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**Table 2: Asthma exacerbations**

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone propionate</th>
<th>Beclomethasone dipropionate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>142</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Total number of exacerbations</td>
<td>33</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Number of patients with exacerbation</td>
<td>23 (16)</td>
<td>37 (28)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Number of patients with severe exacerbations</td>
<td>3 (2)</td>
<td>13 (10)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Number of patients with mild/moderate exacerbations</td>
<td>22 (16)</td>
<td>30 (23)</td>
<td>NC</td>
</tr>
</tbody>
</table>

*Exacerbation reported as a single diagnosis adverse event. Values in parentheses are percentages. NC—not calculated.
were significantly different. Data were cortisol
6 months 20/124 (16)
3 months 24/115 (21) 14/111 (13)
12 months 26/105 (25) 11/101 (11)

Pharmacologically predictable adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Fluticasone propionate</th>
<th>Beclomethasone dipropionate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Influenza</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Sore throat</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

All of these values were significantly different.

Discussion
This study suggests that a daily dose of 1-5 mg fluticasone propionate causes a greater increase in both diary card and clinic lung function measurements than 1-5 mg beclomethasone dipropionate in adult patients with moderate to severe asthma. Furthermore, the improvement with fluticasone propionate was more rapidly apparent than with beclomethasone dipropionate, occurring during the first week. There was also a tendency for symptom scores and rescue β2 agonist use to be reduced more on fluticasone propionate than on beclomethasone dipropionate, although only the difference in β2 agonist use was significant. These improvements occurred in patients who were receiving between 1000 and 2000 μg/day beclomethasone propionate or budesonide before entering the study and then had a two week run in period on 1-5 mg/day beclomethasone dipropionate. The improvement in lung function was maintained over 12 months with no increase in adverse events or systemic effects in patients receiving fluticasone propionate. In addition, the number of severe exacerbations was significantly reduced in this group of patients. These data are compatible with the clinical and preclinical studies17 which showed fluticasone propionate to be more potent than beclomethasone dipropionate with less systemic activity.

Beclomethasone dipropionate has been compared with budesonide over a wide range of doses which show that the two have similar effects on asthma control.11-13 Clinically significant effects on the HPA axis have not been shown with either drug in doses up to 1-5 mg/day.14 In normal volunteers at high doses of 2 mg/day it has, however, been suggested that there may be greater systemic effects with beclomethasone dipropionate.15

In a recent study by Brown et al14 more than 20% of their population of adult asthmatic patients taking long term high dose (>1500 μg/day) inhaled beclomethasone dipropionate were found to have adrenal suppression to an extent which may be of clinical relevance. In the 12 month study presented here, however, neither beclomethasone dipropionate nor fluticasone propionate, in a dose of 1-5 mg/day, was associated with reduced HPA axis function as measured by serum cortisol levels or assessment of adrenal reserve by the short tetracosactrin test as no firm conclusions could be made from the 24 hour urinary free cortisol data. Moreover, fluticasone propionate was well tolerated as indicated by the low incidence of adverse events. Further studies are required to establish the effects of fluticasone propionate, if any, on other possible systemic side effects such as growth retardation, osteoporosis, and skin thickness.15

Several national16 and international17 guidelines recommend the use of inhaled glucocorticosteroid as first line prophylactic therapy. If these gain acceptance they will lead to greater numbers of asthmatic patients taking such drugs. Already in the UK more than 50% of treated asthmatic patients receive inhaled glucocorticosteroids. The guidelines recommend treatment in a stepwise manner. To achieve the goals of asthma management, plans such as abolition of symptoms will therefore require that some patients receive higher doses of glucocorticosteroids than are currently given as maintenance. Indeed, this study has shown that patients taking at least 1 mg/day beclomethasone dipropionate or budesonide who, in addition, were regularly taking β2 agonist and/or oral methylxanthines showed considerable improvement in lung function and symptom scores when their dose of inhaled glucocorticosteroid was increased. The change to higher doses in greater numbers of patients will therefore require the use of drugs with the greatest margin of safety. The potential hazards from extended use of inhaled glucocorticosteroids were highlighted by Brown et al18 and Boe and Skoogh19 who concluded that more long term studies are required.
The results of this study suggest that fluticasone propionate may be more effective than beclomethasone dipropionate. This, taken together with the observation that it has minimal effect on the HPA axis function at high doses, suggests that fluticasone propionate will be of benefit in the long term treatment of asthma.

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13 Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high-dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 µg/day) and budesonide (1600 µg/day) for chronic asthma. Thorax 1986;41:869-74.
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