Fluticasone propionate 1 mg daily and beclomethasone dipropionate 2 mg daily: a comparison over 1 yr

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This study was designed primarily to assess the safety and tolerability of fluticasone propionate (FP) 1 mg day⁻¹ by comparison with beclomethasone dipropionate (BDP) 2 mg day⁻¹ over a 12-month study period. Lung function data were also recorded and used to determine whether the potency ratio between the two inhaled corticosteroids observed in previous studies was maintained in the long-term. Two hundred and thirteen patients with an established clinical history of severe chronic asthma and who were currently receiving between 1000 μg and 2000 μg day⁻¹ of inhaled steroids were randomized to treatment in a ratio of 3:1 for FP:BDP (159 patients FP; 54 patients BDP), both via metered dose inhalers. Both treatments were well tolerated with a similar adverse event profile. No unexpected adverse events were recorded. Most adverse events were related to the patients’ asthma, an intercurrent infection or underlying atopy. The incidence of pharmacologically predictable adverse events was equally low in both treatment groups as was the incidence of events suggestive of systemic steroid effect. Mean serum cortisol levels remained within the normal range at all visits for both treatments. At 12 months, however, the mean cortisol levels for the FP group had risen 4% above the baseline value but had dropped 15% below for the BDP group, giving a ratio of FP:BDP of 1.22; P=0.01; 95% confidence limits (CL) 1.05–1.43. Fluticasone propionate 1 mg day⁻¹ was at least as effective as BDP 2 mg day⁻¹ in improving lung function (PEF, FEV₁ and FVC) over this period. Moreover, the difference in FEV₁ values at 6 months was significantly greater for the FP group than for the BDP group (P=0.04; difference=0.12 l; 95% CL=0.01, 0.24 l). The difference between treatments in the amount of FEV₁ reversibility was also significantly greater for FP at 12 months (difference in treatments=−3%; 95% CL=−7.0%; P=0.044). This study supports previous studies and suggests that FP is likely to be of benefit in the long-term treatment of chronic severe asthma.

Introduction

Asthma management guidelines now stress the importance of prompt treatment with inhaled corticosteroids, even in cases of mild asthma (1,2). These guidelines recommend that the dose of corticosteroid should be titrated against the severity of disease, gradually reducing treatment in patients whose asthma has been stable for 3–6 months (3). Whilst the therapeutic benefits of corticosteroids are generally accepted, their safety, particularly when used long-term or in progressively greater doses, remains a cause for concern.

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Inhaled steroids are associated with both local and systemic side-effects. Of these, local side-effects are typically oropharyngeal candidiasis, sore throat and cough (4). Their incidence appears to be related to dose, frequency and type of inhaler used, and may be reduced with the use of spacer devices (5). Overall, local side-effects of inhaled steroid treatment do not appear to represent a hazard to the patient. Systemic side-effects are potentially more serious. These may include suppression of the hypothalamic-pituitary-adrenalin (HPA) axis, osteoporosis, skin thinning, weight gain, hypertension and reduced glucose tolerance (4–6). Whilst it is generally agreed that HPA-axis function is unlikely to be affected by doses of inhaled corticosteroids up to 1500 μg day⁻¹ (4,5,7), individual susceptibility to adrenal suppression, and other unwanted systemic effects, varies
wide. Therefore, it is recognized that patients would benefit from the introduction of inhaled steroids which combine a high level of topical potency with minimum potential for systemic activity (5,8).

Preclinical and clinical studies indicate that fluticasone propionate (FP), a new topically active, tri-fluorinated glucocorticosteroid, may possess a better efficacy: risk ratio than other commonly prescribed inhaled corticosteroids. Fluticasone propionate has been shown to be less systemically available than other inhaled steroids by the oral route (9) and to be at least as effective as beclomethasone dipropionate (BDP) at half the microgram dosage (10–14). Studies comparing FP with budesonide in both metered-dose and dry powder inhalers, at low and high doses, suggest that the 2:1 potency ratio also exists between these corticosteroids (15–18). In other studies which have compared equivalent doses, FP has been shown to have significantly better clinical efficacy than BDP and is as well tolerated (19,20) with no increased effect on basal or stimulated plasma cortisols (19).

There are, however, only two published controlled studies which have evaluated the efficacy of FP for a period of more than 6 or 12 weeks (14,19). In a previous study in patients with severe chronic asthma, FP 1 mg day\(^{-1}\) was shown to have the efficacy of BDP 2 mg day\(^{-1}\) over a 6-week treatment period (12). This present study was designed primarily to assess the safety and tolerability of FP 1 mg day\(^{-1}\) by comparison with BDP 2 mg day\(^{-1}\) over a 1-yr study period. Lung function data were also recorded and used to determine whether the potency ratio between the two inhaled corticosteroids was maintained in the long term.

Patients and Methods

**Patients**

Patients with an established clinical history of severe chronic asthma, requiring and responding to \(\beta_2\)-agonist therapy and treatment with high doses of inhaled corticosteroids, were recruited on an outpatient basis at 20 centres in seven countries in Europe. All the patients, aged between 18 and 77 years, were receiving between 1000 \(\mu\)g and 2000 \(\mu\)g day\(^{-1}\) of BDP or budesonide, and had no change to their regular asthma medication for at least 1 month.

Patients entered a 2-week run-in period during which they recorded the following details on daily record cards: the best of three assessments of peak expiratory flow (PEF), recorded once in the morning and once in the evening; asthma symptoms experienced by day and by night; and use of rescue medication. Asthma symptoms were assessed during the day from a scale which ranged from 0 = no asthma, to 3 = unable to carry out usual activities, and during the night from a scale which ranged from 0 = slept well, no asthma, to 3 = awake most of the night.

As the study was designed primarily to provide safety data over 1 yr, patients were recruited from those who were already stable on 1500–2000 \(\mu\)g day\(^{-1}\) inhaled corticosteroid or those who were mildly symptomatic on 1000–1500 \(\mu\)g day\(^{-1}\) inhaled corticosteroid.

During the run-in period, patients receiving more than 1500 \(\mu\)g day\(^{-1}\) of an inhaled steroid were required to demonstrate that their asthma was stable. Stability was assessed from the results of lung function tests, daily PEF data and a clinical examination. Patients receiving less than 1500 \(\mu\)g day\(^{-1}\) of an inhaled steroid had either: (1) to exhibit asthma symptoms (with a score of at least 1) on no less than 4 of the last 14 days of the run-in period; or (2) to demonstrate at least 15% reversibility in forced expiratory volume in 1 s (FEV\(_1\)) 15 min after inhaling 200 \(\mu\)g salbutamol from a metered dose inhaler or 400 \(\mu\)g salbutamol from a Diskhaler.

Patients were excluded from the study if any of the following applied: serious uncontrolled systemic disease; recent admission to hospital with asthma; infection of the upper or lower respiratory tract within the previous month; treatment with systemic corticosteroids during the last month or on at least three occasions during the last 6 months; hypersensitivity to inhaled corticosteroids; treatment with other investigational drugs during the previous month; lactation, pregnancy or inadequate contraceptive precautions in women of child-bearing potential; evidence of alcohol abuse; inability to use a pressurized metered dose inhaler correctly; or inability or refusal to comply with any of the trial procedures.

All the patients gave their written informed consent to participate in the study which had been approved by the local Ethics Committee.

**Design**

This was a multi-centre, randomized, double-blind, parallel-group study of 12 months treatment. After a 2-week run-in period, eligible patients were allocated randomly to receive either FP, two 250 \(\mu\)g actuations twice daily via a metered dose inhaler (MDI), with four actuations twice daily from a placebo MDI; or BDP four 250 \(\mu\)g actuations twice daily via an MDI plus two actuations twice daily from a placebo MDI. Three patients were randomized to receive FP for every one patient randomized to receive BDP.
At the start of the 2-week run-in period, all pre-study bronchodilator therapy was replaced by inhaled salbutamol administered via MDI to be used as required. All inhaled steroid medication was stopped at the end of the run-in period and replaced with the randomized study medication. Patients were allowed to use a Volumatic spacer device at the discretion of their physician.

**ASSESSMENTS**

There were eight clinic assessments during the study: at the beginning and end of the run-in period, after 1 and 2 months treatment, and at 3-monthly intervals thereafter until the end of the 12-month treatment period. A follow-up visit was scheduled to take place 2 weeks after the cessation of study treatment. A full clinical history was obtained for each patient together with a physical examination which was repeated at the end of treatment. Vital signs and weight were measured at each clinic visit.

Respiratory function tests at each clinic visit were: the best of three measurements of PEF, FEV₁ and forced vital capacity (FVC). Where possible, these were measured at the same time of day and when inhaled bronchodilator therapy had been withheld for at least 4 h. Reversibility of FEV₁ was measured 15 min after inhaling salbutamol (200 μg or 400 μg).

**ADVERSE EVENTS**

Irrespective of their supposed causal relationship to study treatment, details of all adverse events were recorded, as were any clinically significant shifts in the results of laboratory tests. Serious adverse events were defined as death, any life-threatening, disabling or incapacitating events, events requiring hospitalization, congenital anomalies and cancer or drug overdose.

**ASTHMA EXACERBATIONS**

Asthma exacerbations recorded throughout the study were defined as an increase in asthma symptoms which necessitated a change in therapy other than inhaled β₂-agonist. Patients with a worsening of asthma symptoms were instructed to measure their PEF using the mini-Wright peak flow meter provided, then to record their symptoms and increase their use of inhaled bronchodilator. Patients were also advised to contact their investigator and report to the hospital clinic within 24 h of the onset of the symptoms. Where a short course of corticosteroids was considered necessary, patients were prescribed 30–40 mg oral prednisolone daily. Patients whose symptoms improved after 48 h were gradually weaned off, whereas those who continued to require oral steroid therapy for longer than 3 weeks were withdrawn from this study. Patients were also withdrawn if they required systemic corticosteroids on more than four occasions during the course of the study.

**LABORATORY EVALUATIONS**

Blood samples for routine testing (haematology and biochemistry) were taken at the start of treatment, after 1, 2 and 3 months treatment, and thereafter at 3-monthly intervals. When abnormal results had been obtained at the final clinic visit, blood sampling was repeated at the follow-up visit. Samples were taken from fasted patients between 0800 and 1000h. A urine sample was also tested for the presence or absence of blood, protein or glucose using a dipstick. Serum cortisol concentrations were measured from blood samples taken at the same clinic visits. All samples were analysed by West Middlesex Laboratories, Clinical Biochemistry Department, Isleworth, Middlesex, U.K. The serum cortisol samples were analysed by radioimmunoassay, using the coated-tube method with a between-batch coefficient of variation of 7%.

Oropharyngeal swabs for Candida albicans were taken where indicated clinically by visual examination at each clinic visit.

**STATISTICAL METHODS**

All statistical analyses were performed using SAS (release 6.07) programs and procedures. The analysis presented here is that of the total randomized population on an 'intent to treat' basis. In the analyses, two countries were identified with low patient numbers (Austria (n=14) and Ireland (n=4)). All other countries recruited in excess of 24 patients. The results from Austria and Ireland were therefore grouped together. This action was unlikely to have had an effect on the study outcome since the number of patients involved was small.

For each of the lung function, vital signs, weight and serum concentration parameters, analyses included adjusted means, treatment differences and 95% confidence limits (95% CL) for the treatment differences. Lung function parameters (PEF, FEV₁, FVC and reversibility in FEV₁), vital signs and weight were analysed by analysis of covariance at 6 and 12 months. The analysis accounted for variations due to country (with Austria and Ireland grouped), sex, age, use of spacer device and baseline. A log transformation was applied to the serum cortisol concentration data before it was subjected to the same statistical analyses as the clinic lung function data. Therefore, a treatment ratio rather than a difference was obtained for the serum cortisol data.
Common adverse event rates were compared using Fisher's exact test by doubling the one-sided test. The distribution of asthma exacerbations was analysed by Wilcoxon rank sum test.

Results

Patients were randomized to treatment in a ratio of 3:1 for FP:BDP. Of the total 213 patients randomized to treatment from 20 centres in seven different countries, 159 received FP and 54 received BDP. The two treatment groups were well matched for baseline characteristics, use of spacer device (Table 1), concomitant diseases and concurrent medications. Compliance to treatment was not assessed formally but inspection of returned medication revealed only a small percentage of ‘non-compliant’ patients (see below).

During the study, 17% of patients in each treatment group withdrew from the trial for the following reasons: adverse events (13% and 9% in the FP and BDP groups, respectively), non-compliance (1% and 2%, respectively), failure to return (3% in the FP group only) and treatment failure (1% and 6%, respectively).

ADVERSE EVENTS

The incidence of adverse events and drug-related adverse events was similar in both treatment groups. Seventy-two percent of the patients in each treatment group reported adverse events, the most common of which were related to asthma itself, an intercurrent infection or underlying atopy. The incidence of headache, more marked in patients taking BDP (four patients, 7%) than FP (one patient, 1%), was the only adverse event to show a significant difference between the two groups (P=0.03). In both treatment groups, the incidence of pharmacologically predictable adverse events such as oral candidiasis and hoarseness was low (Table 2). In the FP treatment group, there were two reports of fluid retention/oedema and one each of menstrual disorders, weight gain and diabetes mellitus. The report of diabetes mellitus was considered to be unrelated to the study drug. In the BDP treatment group, there was one report of low cortisol and one of fluid retention/oedema.

Of the 25 patients who withdrew from the study due to an adverse event, 20 (13%) patients were receiving FP and five (9%) patients were receiving BDP. Some patients reported more than one adverse event as reason for withdrawal. A summation of events showed that the most common reason for withdrawal was asthma and related events (nine and four reports for FP and BDP, respectively). Other reasons for withdrawal included: ear, nose and throat disorders (four and one, respectively), cardiovascular disorders (three reports FP), gastrointestinal disorders (three reports FP), neurological disorder (three reports FP), mouth and teeth disorders (two reports FP), abnormal cortisols (one report BDP),...
Table 2  Summary of adverse events

<table>
<thead>
<tr>
<th></th>
<th>FP 500 µg bd</th>
<th>BDP 1000 µg bd</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>159</td>
<td>54</td>
</tr>
<tr>
<td>No. of patients with an adverse event (%)</td>
<td>114 (72)</td>
<td>39 (72)</td>
</tr>
</tbody>
</table>

Most common (>5% of patients) adverse events and those pharmacologically predictable

Asthma and related events (%) 56 (35) 25 (46)
Rhinitis (%) 16 (10) 2 (1)
Bronchitis (%) 13 (8) 5 (9)
Cough (%) 11 (7) 1 (2)
Respiratory infection (%) 9 (6) 5 (9)
Expectoration (%) 8 (5) 3 (6)
Influenza (%) 8 (5) 7 (13)
Sore throat (%) 7 (4) 4 (7)
Urinary problems (%) 5 (3) 3 (6)
Headache* (%) 1 (<1) 4 (7)
Hoarseness† (%) 10 (6) 4 (7)
Oral candidiasis‡ (%) 7 (4) 2 (4)

FP, fluticasone propionate; BDP, beclomethasone dipropionate.
*Statistically significant difference between treatments (P=0.03).
†Pharmacologically predictable.

hypersensitivity disorder (one report FP) and urogenital disorder (one report FP).

Serious adverse events were reported by 11 patients (7%) in the FP group and three patients (6%) in the BDP group. Serious adverse events in the FP group were: Type 1 diabetes mellitus (one patient); myocardial infarction (two patients); hysterectomy (one patient), cataract operation (one patient) and salpingitis (one patient); and exacerbations of asthma or intercurrent infections (five patients). The three serious adverse events in the BDP group were: carcinoma of the prostate, syncope and exacerbation of asthma. Only one serious adverse event from the FP group (exacerbation of asthma) was considered by the investigator to be possibly related to study treatment. All other serious adverse event reports were considered to be unrelated to study treatment.

LABORATORY EVALUATIONS

No clinically significant abnormalities were detected in routine laboratory haematology, biochemistry or urinalysis parameters.

CORTISOLS

Figure 1 presents all the individual serum cortisol values as a scatter plot. The lower limit of the normal value of serum cortisol (150 nmol l\(^{-1}\)) is indicated on both axes. Patients in ‘Quadrant a’ are those who started the study with a lower than normal serum cortisol value which increased by the end of the study period; patients in ‘Quadrant b’ are those who started the study with a cortisol value above the lower limit which remained so at the end of the 12-month study period; patients in ‘Quadrant c’ are those who had a lower than normal value at baseline which remained low at the end of the study; and patients in ‘Quadrant d’ are those who started the study with a cortisol value above the lower limit which then fell below the lower limit at the end of the study.

A comparison of the scatter plots shows that for both treatments, the majority of patients fell into ‘Quadrant b’ and were above the lower limit of normal values after 12 months. Five patients (3%) in the FP treatment group and one patient (2%) in the BDP group had falls in serum cortisol values from above normal range to below the lower limit of the normal range (Quadrant d). Only one of these reports (from the BDP treatment group) was judged to be clinically significant.

Whilst mean geometric serum cortisol levels in both treatment groups remained above the lower limit of the normal range throughout the study, the mean for patients taking FP was significantly higher at both the 6 and 12 month assessments (Table 3). After 12 months treatment, the adjusted geometric mean serum cortisol concentration in these patients had risen by 4% from baseline. By contrast, in patients taking BDP, the adjusted geometric mean fell by 15% from baseline. After 6 and 12 months of treatment, the respective adjusted geometric mean ratios of FP to BDP were: 1.23, 95% CI, 1.06–1.43; P=0.008 and 1.22; 95% CI, 1.05–1.43; P=0.01.

VITAL SIGNS

No clinically relevant changes in weight, pulse rate, systolic or diastolic blood pressure were detected.

EFFICACY

The potency ratio between the two inhaled corticosteroids was maintained over the 12-month study period. In terms of PEF, FEV\(_1\), and FVC, FP 1 mg day\(^{-1}\) was as effective as BDP 2 mg day\(^{-1}\) over this period. Mean FEV\(_1\) is shown in Fig. 2. The difference in FEV\(_1\) between treatments at 6 months was significantly greater for the FP group than for the BDP group (P=0.04; difference=0.12 l; 95% CL=0.01–0.24 l). Fluticasone propionate was also associated with a significantly greater improvement in FEV\(_1\) reversibility at 12 months (difference in treatments in favour of FP= -3%; 95% CL= -7–0%; P=0.044).
Fig. 1 Scatter plots of individual serum cortisol means at baseline and after 12 months treatment with (a) fluticasone propionate 1 mg day\(^{-1}\) (n=159) or (b) beclomethasone dipropionate 2 mg day\(^{-1}\) (n=54). The lower limit of the normal range of serum cortisol values (150 nmol l\(^{-1}\)) is indicated on both axes. Patients in ‘Quadrant a’ were those who started the study with a lower than normal serum cortisol value which increased by the end of the study period; patients in ‘Quadrant b’ are those who started the study with a cortisol value above the lower limit which remained so at the end of the 12-month study period; patients in ‘Quadrant c’ are those who had a lower than normal visit at baseline which remained low at the end of the study; and patients in ‘Quadrant d’ are those who started the study with a cortisol value above the lower limit which then fell below the lower limit at the end of the study.

Table 3 Geometric mean serum cortisol levels

<table>
<thead>
<tr>
<th></th>
<th>FP 500(\mu)g bd</th>
<th>BDP 1000(\mu)g bd</th>
<th>Adjusted† mean ratio (FP/BDP)</th>
<th>95% CL</th>
<th>P value</th>
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<tbody>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients†</td>
<td>123</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (nmol l(^{-1}))</td>
<td>349</td>
<td>299</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months (nmol l(^{-1}))</td>
<td>331</td>
<td>254</td>
<td>1.23</td>
<td>1.06-1.43</td>
<td>0.008</td>
</tr>
<tr>
<td>Ratio*</td>
<td>0.95</td>
<td>0.85</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients†</td>
<td>113</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline (nmol l(^{-1}))</td>
<td>365</td>
<td>312</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months (nmol l(^{-1}))</td>
<td>377</td>
<td>291</td>
<td>1.22</td>
<td>1.05-1.43</td>
<td>0.010</td>
</tr>
<tr>
<td>Ratio*</td>
<td>1.03</td>
<td>0.93</td>
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</table>

†FP, fluticasone propionate; BDP, beclomethasone dipropionate.
*Ratio is calculated for each patient as the response at each clinic visit divided by the response at baseline.
†Mean ratios adjusted for baseline, country, age, sex and use of spacer device.
†Patients with data at start of treatment and at specified visit.

There was no difference between treatments at any of the other time points.

ASTHMA EXACERBATIONS

Table 4 shows the frequency and rate of occurrence of asthma exacerbations over the 12-month treatment period. Sixty-one percent of patients on FP and 52% of patients on BDP remained free of exacerbations throughout the study period. There was no statistical difference between the two treatment groups in the frequency of asthma exacerbations. The rate of occurrence of exacerbations remained fairly constant over the 12-month period.

Discussion

A substantial amount of data comparing FP with BDP indicate that FP at half the dose is at least as
effective in improving lung function and symptoms over the whole range of asthma severity and dosage (10–14). Furthermore, these studies demonstrate that the effect of FP on the HPA-axis is minimal, and either similar or significantly better than that of BDP. Very few published studies, however, have examined the effects of FP for longer than 12 weeks (14,19). The present study was, therefore, designed to assess the safety and tolerability of FP 1 mg day$^{-1}$ by comparison with BDP 2 mg day$^{-1}$ over 12 months and to determine whether the 2:1 efficacy ratio for BDP:FP was maintained at these doses over this period.

As the objective was not to demonstrate efficacy, the subject population was drawn from patients with severe chronic asthma whose condition was either currently stable on 1500–2000 $\mu$g day$^{-1}$ inhaled corticosteroid, or who suffered from only mild symptoms on 1000–1500 $\mu$g day$^{-1}$ inhaled corticosteroid. Since BDP has been studied extensively (4), the randomization schedule for this present study was structured in a 3:1 ratio (FP:BDP) in order to increase the number of patients receiving FP.

Lung function (FEV$_1$, PEFR, and FVC) improved from baseline values for both treatments, and the 2:1 ratio for the doses of BDP:FP was maintained over the 12-month period. The rate of occurrence of asthma exacerbation confirmed that 1 mg day$^{-1}$ FP and 2 mg day$^{-1}$ BDP provided good asthma control for up to 1 yr.

Both treatments were well tolerated with similar adverse event profiles. No unexpected adverse events were recorded, and most of those recorded were related to the patients' asthma, an intercurrent infection or underlying atopy. The incidence of headache was significantly different between treatments with one report in the FP treatment group and four in the BDP treatment group. This finding is unlikely to hold any clinical significance since it has not been detected in previous studies (10–14) and the

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Asthma exacerbations*</th>
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<tr>
<td></td>
<td>Frequency of asthma exacerbations</td>
</tr>
<tr>
<td></td>
<td>Number of exacerbations</td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>5</td>
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<td>6</td>
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Number of patients (%) with at least one exacerbation during each 3-monthly time interval

<table>
<thead>
<tr>
<th>Time interval (months)</th>
<th>0–1</th>
<th>1–3</th>
<th>3–6</th>
<th>6–9</th>
<th>9–12</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP 500 $\mu$g bd</td>
<td>11 (7%)</td>
<td>24 (15%)</td>
<td>16 (11%)</td>
<td>16 (11%)</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>BDP 1000 $\mu$g bd</td>
<td>7 (13%)</td>
<td>8 (15%)</td>
<td>13 (25%)</td>
<td>5 (10%)</td>
<td>6 (13%)</td>
</tr>
</tbody>
</table>

FP, fluticasone propionate; BDP, beclomethasone dipropionate.

*Asthma exacerbations were defined as asthma or related adverse events.
sponses of headache are not uncommon in asthmatic patients.

The incidence of pharmacologically predictable adverse events was equally low in both treatment groups, and too low to determine whether the use of a spacer device (40% of population) had affected the results. The incidence of events suggestive of systemic steroid effect (weight gain, menstrual disorders, fluid retention, diabetes mellitus) was low with a collective incidence of 3% of patients in the FP treatment group and less than 2% in the BDP group. The report of diabetes mellitus was considered to be unrelated to the study drug.

In terms of serum cortisols, although all mean values were well within the normal range after 12 months of treatment, they were 4% above mean baseline values in the FP group and 15% below baseline values in the BDP group.

Several approaches have been used to assess HPA-axis function both in terms of basal function and adrenal reserve. These include measurements of morning serum cortisol levels, integrated serum cortisol levels, urinary free cortisol levels and serum cortisol response to tetracosactrin (4,21). There is, however, no general consensus as to the best method to use. Brown et al. (22) in one study found that low 24-h urinary excretion of cortisol correlated well with low post-tetracosactrin cortisol concentrations, whereas plasma cortisol showed less sensitivity. However, in a subsequent study, the same authors found that plasma cortisol was similar in sensitivity to post-tetracosactrin cortisol concentrations and urinary free cortisol (23). Other authors have suggested repeated serum cortisol determinations are more sensitive than single serum cortisol levels. (4) Clearly, however, serial serum cortisol measurements over 24 h are impractical in asthmatic patients, and morning serum cortisol thus remains the most appropriate measure of HPA-axis function in large-scale, multicentre clinical trials.

It must be remembered, however, that the relationship between different measures of HPA-axis function and the clinical relevance of changes in these measures is by no means clear (4). The HPA-axis is a very sensitive feedback system and small detectable changes in cortisol production are to be expected when exogenous corticosteroids are given. A decrease in basal cortisol production or an attenuation in the adrenal response to stimulation do not necessarily mean suppression of the HPA-axis function, merely that a corticosteroid is systemically available and pharmacologically active. Several studies investigating the effects of inhaled corticosteroids have identified so-called 'suppression' of HPA-axis function in the absence of clinical adrenal insufficiency (24,25).

The effect of treatments on bone metabolism was not assessed in the present study. Although there is some concern regarding the effects of inhaled corticosteroids on bone metabolism (6), there is no definite evidence from the literature that long term treatment with inhaled corticosteroids is associated with an increased risk of osteoporosis or fracture in children or adults (4,21). Often the interpretation of the effects of inhaled corticosteroids in patients with asthma is complicated by previous oral corticosteroid therapy (6). More long-term, prospective, controlled clinical studies are required to evaluate fully the effect of inhaled corticosteroids on growth and bone density which may not become apparent for several years. In a recent study, Ayres et al. found that serum cortisol monitoring rather than biochemical markers of bone metabolism appeared to be the most sensitive assay for measurement of systemic effect of high-dose inhaled steroids (18).

Whilst treatment guidelines (1,2) are unanimous in recommending inhaled corticosteroids, even for patients with mild asthma, many patients and physicians are wary of their long-term use and potential for systemic side-effects. The present study demonstrated that FP 1 mg day$^{-1}$ and BDP 2 mg day$^{-1}$ were well tolerated and unassociated with significant systemic effect over a 12-month period. In terms of lung function, FP 1 mg day$^{-1}$ was shown to be at least as effective as BDP 2 mg day$^{-1}$ throughout the 12 months. The findings of this study support those of previous studies and suggest that FP is likely to be of benefit in the long-term treatment of asthma without affecting serum cortisols significantly.

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References

Long-term safety of fluticasone propionate


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