Effects of 2 weeks of treatment with fluticasone propionate 100 mcg b.d. by comparison with zafirlukast 20 mg b.d. on bronchial hyper-responsiveness in patients with mild to moderate asthma

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This study was designed to compare the effects of low-dose inhaled fluticasone propionate (100 mcg twice daily) with those of the leukotriene antagonist, zafirlukast (20 mg twice daily), on bronchial hyper-responsiveness. The study recruited 30 patients (nine men, 21 women; mean age 45 years) with forced expiratory volume in 1 sec (FEV₁) >50% and airway reversibility to salbutamol ≥15%. This was a single centre, double-blind, double-dummy crossover study, composed of two successive 2-week treatment periods, each preceded by a 2–4 week single-blind placebo period. Following 2 weeks of treatment with fluticasone propionate and zafirlukast, the mean provocational concentration causing a 20% fall in FEV₁ (PC₂₀) histamine was 1.61 mg ml⁻¹ (SD 2.34) and 0.99 mg ml⁻¹ (SD 1.74) respectively. Taking baseline differences into account, the difference between treatments was equivalent to 0.77 doubling doses of histamine (95% CI, 0.05–1.50; P=0.037). Morning peak flow values were significantly higher (17 l min⁻¹; P=0.049) after treatment with fluticasone propionate during the second week of treatment. Both treatments were well tolerated. The results of this short-term study show that compared with zafirlukast, a low dose of fluticasone propionate offers greater clinical benefit and is more cost effective.

Key words: bronchial hyper-responsiveness; fluticasone propionate; zafirlukast; asthma; histamine.

Introduction

Fluticasone propionate, an inhaled corticosteroid established in the treatment of asthma, has been shown to benefit from an improved efficacy to safety ratio when compared with other inhaled steroids. Studies in both adults and children assessing lung function, symptoms and extra bronchodilator usage have shown that fluticasone propionate is more effective than beclomethasone dipropionate (1–3) or budesonide (1,4,5) when used at half the dose of these inhaled corticosteroids. When used in chronic treatment, fluticasone propionate at doses of 750 mcg day⁻¹ and above have been shown to be very effective in decreasing bronchial hyper-responsiveness (6–8). Its efficacy in this respect was achieved at half the dose of beclomethasone dipropionate (8).

Although many mediators are involved in the pathogenesis of asthma, there is evidence to suggest that cysteinyl leukotrienes are important mediators of the asthmatic response (9). A number of studies have demonstrated that leukotrienes are potent bronchoconstrictors (10) as well as inducers of mucus hypersecretion (11) and airway oedema (12). It has been shown that the urinary leukotriene E₄ (LTE₄), used as a marker for whole body cysteinyl leukotriene production, increases following allergen challenge (13) and during acute asthma attacks (14). However, no correlation has been found between the severity of clinical asthma and the level of LTE₄ in the urine of stable asthmatic patients (15).

Several placebo-controlled studies have demonstrated that chronic treatment with leukotriene antagonists results in decreased asthmatic symptoms, improved lung function and decreased use of bronchodilator (16–19) with measurable effects being achieved within 3–14 days of therapy (19). Leukotriene receptor antagonists, as well as drugs which interfere with leukotriene formation, have been shown to attenuate the obstructive response induced by cold, dry air hyperventilation, exercise, allergen and aspirin (20–22).
There is also some suggestion that these agents can reduce the bronchial hyper-responsiveness provoked by pharmacological stimuli (23–25). It has been proposed, therefore, that leukotriene antagonists may constitute alternative first-line preventative therapy for patients with mild to moderate asthma who are receiving intermittent inhaled \( \beta_2 \)-agonist therapy (26). However, there are very few comparative data to support this proposal.

Asthma is characterized by reversible airways obstruction, oedema and inflammation as well as hyper-responsiveness to provocative stimuli. Non-specific bronchoconstrictor stimuli such as histamine and methacholine are widely used to demonstrate bronchial hyper-responsiveness. The provocative concentration \( (PC_{20}, \text{histamine}) \) producing a 20% fall in forced expiratory volume in 1 sec \( (\text{FEV}_1) \) is used as a measure of sensitivity. This is lowered in asthmatics (27). This study was designed to compare the effects on bronchial hyper-responsiveness of 2 weeks’ treatment with low-dose fluticasone propionate \( (100 \text{ mcg twice daily}) \) and the leukotriene antagonist, zafirlukast \( (20 \text{ mg twice daily}) \) respectively. Bronchial hyper-responsiveness was assessed by histamine provocation.

**Methods**

**SUBJECTS**

Non-smoking, adult patients aged 18–70 years with a documented clinical history of reversible airways disease were recruited into the study. None of the patients had used oral or inhaled corticosteroids, sodium cromoglycate, nedocromil or long-acting \( \beta_2 \)-agonists for at least 4 weeks before the start of the study. Other entry criteria, established during the run-in period, included: \( \text{FEV}_1 \) of at least 50% of predicted normal value; reversibility of airway obstruction of at least 15% following 200 mcg salbutamol from a metered dose inhaler \( (\text{MDI}) \) or 400 mcg salbutamol from a Diskhaler inhaler; and \( PC_{20}, \text{histamine} \leq 4 \text{ mg ml}^{-1} \).

Patients were excluded from the study if they had been admitted to hospital with asthma or had received antibiotics for an upper or lower respiratory tract infection within the previous month. Other exclusion criteria included: ketotifen therapy within the previous 3 months; lactation, pregnancy or inadequate contraceptive precautions in women of child-bearing potential; inadequate inhaler and peak flow meter techniques. Approval was obtained from the local research ethics committee and all patients provided their written informed consent.

**STUDY DESIGN**

This was a randomized, double dummy, cross-over study; patients were recruited from two hospital centres. Initially, patients entered a 2–4 week, single-blind, placebo run-in period. During this period all asthma medication (apart from regular methyloxanthines and anticholinergies) was replaced by inhaled salbutamol from a Diskhaler inhaler or MDI, which was to be used as necessary to relieve symptoms. Therapy for all other medical conditions was to remain constant throughout the study. Patients who fulfilled the eligibility criteria were then randomly assigned to 2 weeks’ double-blind treatment (treatment period 1) with either inhaled fluticasone propionate 100 mcg twice a day \( (\text{b.d.}) \) administered by Diskhaler inhaler or oral zafirlukast 20 mg b.d. Thereafter, patients entered a 2–4 week single-blind, wash-out period on placebo followed by a subsequent 2-week period where, again under double-blind conditions, they received the alternative active treatment (treatment period 2). Patients were instructed to use their medication in the morning \( (\text{around} 0800 \text{ h}) \) and in the evening \( (\text{around} 2000 \text{ h}) \).

Assessments were performed in the clinic at the beginning and end of the placebo run-in period, at the end of treatment period 1, after the placebo washout period and at the end of treatment period 2.

At the first clinic visit, demographic details and a full clinical history were recorded and a physical examination was performed. Investigators also confirmed that patients could use an inhaler and a peak flow meter correctly. In addition, \( \text{FEV}_1 \) was measured using a spirometer and the highest of three values was recorded. At the beginning or end of the run-in period, airway reversibility was determined by recording \( \text{FEV}_1 \) before and 15 min after the inhalation of 200 mcg salbutamol from a MDI or 400 mcg salbutamol via Diskhaler inhaler. Histamine challenge tests were also performed at the end of the run-in period, at the end of treatment period 1 and at the end of treatment period 2 on separate days to the pulmonary function tests, but within 3 successive days. All pulmonary function and airway challenge tests were performed at \( 0900 \text{ h} \) \( (\pm 1 \text{ h}) \), patients were therefore requested not to use their bronchodilators for at least 4 h before each clinic visit.

Baseline lung function was recorded as the best of three reproducible values of \( \text{FEV}_1 \) \( (\text{within} 5\%) \) before the provocation tests. The histamine provocation test was performed according to the method of Cockcroft et al. (28). Aerosols of histamine were generated by a jet nebuliser with a fixed output of \( 0\text{-}13 \text{ ml min}^{-1} \). A nose clip was worn and the aerosol was inhaled by tidal breathing for 30 sec. The first aerosol was saline and was followed at 5-min intervals by doubling concentrations of histamine \( (0\text{-}125\text{-}32 \text{ mg ml}) \). \( \text{FEV}_1 \) was measured before and 1 min after each inhalation until the reading had fallen by 20% or more from the lowest post-saline value. The results were expressed as \( PC_{20}, \text{histamine} \). The exact value for \( PC_{20}, \text{histamine} \) was determined in \( \text{mg ml}^{-1} \) by linear interpolation of the last two points of the concentration–response curve.

All patients kept daily record cards throughout the study, recording morning and evening peak expiratory flow \( (\text{PEF}) \), study medication, use of relief medication and symptoms by day and by night. Symptoms related to daily activities were rated as follows: 0 = none; 1 = symptoms for one short period; 2 = symptoms for two or more short periods; 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 perform normal daily activities. Symptoms during the night
related to sleep disturbance and were rated as follows: 0 =
one; 1 = symptoms caused you to wake once or wake
early; 2 = symptoms caused you to wake twice or more
(including waking early); 3 = symptoms caused you to be
awake for most of the night; 4 = symptoms so severe that
you did not sleep at all. Patients were also requested to
record the number of times salbutamol was required for
symptomatic relief both during the day and at night.
At the beginning and end of the treatment period, blood
samples were taken for routine haematology and biochem-
istry. In addition, the oropharynx was examined at each
clinic visit and a swab was taken if clinically indicated to
determine the presence of *Candida* spp.

**STATISTICAL ANALYSIS**

The level of significance for all analyses was 5%, all tests
were two-sided and all were based on the intention-to-treat
sample. Predicted lung function values were calculated
from sex, age and height using standard formulae (29).

The primary measure of efficacy was PC_{20} histamine
values. Only patients who provided data for both treatment
periods were included in the statistical analysis. The
presence of carry-over effects was investigated using
Wilcoxon’s rank-sum test. Log-transformed PC_{20} values
were analysed by analysis of covariance (ANCOVA)
adjusting for study period, patient and pre-treatment value
(obtained at the start of each treatment period) as
covariates and treatment as main effect.

The daily morning/evening PEF values were averaged
over patients and plotted by treatment group. Baseline PEF
was established by taking the mean of the last 7 days of
the run-in period for each patient. Average weekly values (for
week 1 and week 2) were analysed using ANCOVA as
described for PC_{20} histamine values and the presence of
carry-over effects was investigated using Wilcoxon’s rank-
sum test. No formal analysis was applied to symptom score
data and the use of rescue bronchodilator medication.

It was estimated that 30 evaluable patients would provide
90% power to detect a treatment difference of at least 0-7
doubling doses of histamine with a 5% level of significance.
This assumed a within-patient standard deviation of up to
0-75 of a doubling dose.

**Results**

Of the 30 patients who completed the placebo run-in
period, the majority were women. Seventy-seven percent
were atopic (diagnosed by skin test) and 80% had been
suffering from asthma for over 6 years. There were no
significant differences in baseline characteristics between the
two treatment sequence groups (Table 1). The mean PC_{20}
values prior to treatment were similar in both groups (0-57
mg ml^{-1} for fluticasone propionate; 0-58 mg ml^{-1} for
zafirlukast). Only one patient was receiving concurrent
anticholinergic therapy and none were receiving methyl-
xanthines. Three patients were withdrawn from the study,
two because of adverse events and one because incorrect
medication was taken during the wash-out period. The
remaining 27 patients completed the study.

**BRONCHIAL HYPER-RESPONSIVENESS**

Baseline FEV_{1} values taken before histamine challenges did
not differ significantly between active treatment groups.
Pre-saline FEV_{1} values before treatment were 2-52 ±0-71
and 2-0 ±0-69 l, for the fluticasone propionate (n = 29) and
zafirlukast (n = 30) groups, respectively, and post-saline
values were 2-55 ±0-91 and 2-49 ±0-67 l.

There was no evidence of carry-over with respect to PC_{20}
(P = 0-289) and all data were therefore combined. At the
start of treatment PC_{20} values were similar for both
treatment groups. (Table 1, Fig. 1). The change in reac-
tivity, however, after 2 weeks’ treatment with each agent,
was significantly different: the mean PC_{20} histamine was
1-61 mg ml^{-1} (so 2-34) after treatment with fluticasone
propionate, compared with 0-99 mg ml^{-1} (so 1-74) after
treatment with zafirlukast (Fig. 1). Using ANCOVA where
period, patient and baseline were used as covariants, this
difference was equivalent to 0-77 doubling doses of
histamine (95% CI, 0-05–1-50; P = 0-037).

**DAILY RECORD CARD DATA**

Mean morning and evening PEF values tended to be higher
in the fluticasone propionate group than in the zafirlukast
group both during the first and second week of treatment.
Mean morning peak flow is shown in Fig. 2. A significant
treatment difference (17-71 min^{-1}; P = 0-049) was observed
in morning PEF values during the second week (Table 2).

The majority of patients had no symptoms or suffered
from very mild symptoms throughout the study. They used
very little extra relief bronchodilator and no obvious
differences were detected between the two treatments.

**ADVERSE EVENTS**

No serious adverse events were reported during the study.
Overall, nine patients reported 14 adverse events; six
patients reported 10 adverse events during treatment with
fluticasone propionate and three patients reported four
adverse events during treatment with zafirlukast. Only one
event (asthma attack during zafirlukast therapy) was judged
to be related to study medication. During treatment with
fluticasone propionate, there were three reports of head-
ache, two of common cold and one report each of back
pain, diabetes, dizziness, ear infection and fatigue. Further
investigation into the report of ‘diabetes’ revealed that this
patient had elevated blood glucose levels prior to the study.
This event therefore, bears no relation to study treatment.

During treatment with zafirlukast, there was one report
each of headache, asthmatic attack, fever and pyrosis. Two
patients were withdrawn from the study during wash-out
periods, one following fluticasone propionate treatment
(dyspnoea), the other following zafirlukast treatment
(dyspnoea plus chest pains).
Liver function was assessed by monitoring levels of aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT) and gamma glutamyltransferase (GGT). No trends were apparent from the summary data and none of the changes recorded was judged to be clinically significant. Apart from one patient who had an abnormal oropharyngeal throat examination at one visit, all throat examinations from all patients were normal. The physician did not, however, recommend further investigation.

**Discussion**

The results of this study showed that, after 2 weeks' therapy, inhaled fluticasone propionate 100 mcg b.d. decreased bronchial hyper-responsiveness to a significantly greater extent than oral zafirlukast 20 mg b.d. Lung function also tended to improve more with fluticasone propionate than with zafirlukast. There was a clinically significant difference between treatments (17.71 min⁻¹) in morning PEF during the second week of therapy, being higher after treatment with fluticasone propionate.

The extent to which fluticasone propionate 100 mcg b.d. reduced bronchial hyper-responsiveness in this study is consistent with the results of a previous study involving mild asthmatic subjects during which fluticasone propionate 1000 mcg daily for 2 weeks improved PC₂₀ histamine by 1.3 doubling doses (6). The only study to have reported the effects of chronic treatment with zafirlukast on bronchial hyper-responsiveness showed that by comparison with placebo, zafirlukast 20 mg b.d. for 2 weeks was associated with a significant mean shift in log PC₂₀ methacholine of 0.38 log dose units and that PC₂₀ methacholine was on average 2.5 times higher during active treatment than during placebo treatment (23).

Two other studies have examined bronchial hyper-responsiveness after a period of treatment with a leukotriene antagonist. The first was a double-blind, cross-over study which observed the effects of oral pranlukast 225 mg b.d. in the treatment of 11 stable asthmatics (24). After 1 week of treatment, pranlukast produced a small but significant improvement in bronchial hyper-responsiveness (half of one doubling dose of methacholine). The second study, in 11 subjects, found pranlukast 450 mg b.d. to be associated with improved clinical symptoms as well as improved histamine reactivity to bronchial challenge performed 12 and 24 weeks post-treatment (25).

**TABLE 1. Baseline patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>FP followed by zafirlukast (n = 15)</th>
<th>Zafirlukast followed by FP (n = 15)</th>
<th>Total (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>4/11</td>
<td>5/10</td>
<td>9/21</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean (sd)</td>
<td>46 (17)</td>
<td>44 (14)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Atopic, n (%)</td>
<td>13 (87%)</td>
<td>10 (67%)</td>
<td>23 (77%)</td>
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<tr>
<td>Duration of asthma (years)</td>
<td></td>
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<tr>
<td>&lt; 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td>1–5</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>&gt; 6</td>
<td>12</td>
<td>12</td>
<td>24</td>
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<tr>
<td>FEV₁</td>
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<td></td>
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<tr>
<td>% predicted FEV₁ mean (sd)</td>
<td></td>
<td></td>
<td>77(14)*</td>
</tr>
<tr>
<td>Before FP (l) mean (sd)</td>
<td></td>
<td></td>
<td>2.52 (0.7)</td>
</tr>
<tr>
<td>Before zafirlukast (l) mean (sd)</td>
<td></td>
<td></td>
<td>2.50 (0.69)</td>
</tr>
<tr>
<td>PC₂₀ histamine (mg ml⁻¹)</td>
<td></td>
<td></td>
<td>0.57 (0.93)**</td>
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<tr>
<td>Before FP mean (sd)</td>
<td></td>
<td></td>
<td>0.58 (0.91)</td>
</tr>
<tr>
<td>Before zafirlukast mean (sd)</td>
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</table>

FP fluticasone propionate.

* n = 22; ** n = 29.

Not calculated.

**Fig 1. The change in reactivity (mean PC₂₀) following 2 weeks of treatment with zafirlukast and fluticasone propionate.**
It has been suggested that the effect of zafirlukast on bronchial hyper-responsiveness may vary depending on the duration of the medication, short-term or single dose studies failing to reflect the ultimate capability of anti-leukotriene medication. That being the case, the acute benefits of these drugs could not be assessed from bronchial provocation using methacholine or histamine. The same argument would apply in the case of inhaled corticosteroids, the degree of response being dependent on the severity of disease, the dose, the duration of treatment and steroid responsiveness of the patient. Indeed, it may be 12 months before inhaled steroids exert their maximum effect on bronchial reactivity (30).

While the pathogenesis of airway hyper-responsiveness is unclear, in asthma it is linked with inflammation (31). In stable asthmatic patients, airway responsiveness is related to the numbers of eosinophils and mast cells which are present in bronchoalveolar lavage fluid (BAL), the extent of mucosal inflammation and peripheral blood eosinophilia (31). Eosinophils are one of the predominant inflammatory cells in the asthmatic lung and they play a central role in asthma (32). A correlation has been observed between activated eosinophils and pulmonary function or non-specific bronchial hyper-responsiveness (33–35). The documented effect of fluticasone propionate and zafirlukast on eosinophils is therefore worthy of mention. In a placebo-controlled, cross-over study involving 16 asthmatic patients, fluticasone propionate 500 mcg day\(^{-1}\) taken over a 6-week period, significantly improved methacholine provoked bronchial hyper-responsiveness and significantly reduced both BAL eosinophil count and peripheral blood eosinophil count (36). By comparison in another study,

![Graph showing peak flow values over time](image)

**Fig. 2.** Unadjusted daily mean morning peak flow (l min\(^{-1}\)) values during the placebo run-in period and wash-out periods and through the 2-week treatment periods. The mean values shown at the start and end of the study (days 14, 40 and 42) were taken from a reduced sample of patients since data were only available from those patients who had completed diary cards on those days. (○: treatment group 1; □: treatment group 2; vertical lines represent the last day of a period.)

<table>
<thead>
<tr>
<th>Table 2. Peak flow values (l min(^{-1}))</th>
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<tbody>
<tr>
<td><strong>FP</strong> ((n = 29))</td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Mean morning PEF</strong> *</td>
</tr>
<tr>
<td>1st week</td>
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<tr>
<td>2nd week</td>
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<tr>
<td><strong>Mean evening PEF</strong> *</td>
</tr>
<tr>
<td>1st week</td>
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<tr>
<td>2nd week</td>
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</table>

*Means adjusted for period, patient and baseline (where baseline is the average PEF during the week prior to beginning treatment).

†\(n = 28\).

FP, fluticasone propionate.
zafirlukast 20 mg b.d. has been shown to reduce the numbers of some of the inflammatory cells (basophils, $P < 0.01$ and lymphocytes, $P < 0.01$) in BAL fluid following segmental allergen challenge 5 days post-treatment, but to have no effect on number of eosinophils and macrophages (37). Pranlukast, however, has been observed to decrease BAL macrophages, neutrophils and epithelial cells (38). The comparative effects of inhaled corticosteroids and leukotriene antagonists may account for their differing capacity to reduce bronchial hyper-responsiveness.

The treatment of asthma focuses on diminishing the inflammatory process and bronchial hyper-responsiveness. Corticosteroids are by far the most effective and most commonly used anti-inflammatory agents available (39). Leukotrienes are just one of the many groups of mediators involved in the complex inflammatory process leading to the clinical manifestations of asthma. In this study we found, even at a low dose and for a short treatment period, that the effects of fluticasone propionate could be clearly differentiated from those of zafirlukast in mild asthma. This present study suggests that the extent to which inhibiting one set of inflammatory mediators can be expected to attenuate the asthmatic response can be questioned. In these patients, fluticasone propionate offers greater clinical benefit than zafirlukast.

Acknowledgements

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