Comparison of fluticasone propionate and beclomethasone dipropionate on direct and indirect measurements of bronchial hyperresponsiveness in patients with stable asthma

G P Bootsma, P N R Dekhuijzen, J Festen, P G H Mulder, C L A van Herwaarden

Abstract

Background – Fluticasone propionate is a new inhaled corticosteroid with a 2:1 efficacy ratio compared with beclomethasone dipropionate with regard to lung function and symptom scores, without increased systemic activity. The aim of this study was to investigate whether this was also the case for bronchial hyperresponsiveness, assessed by both a direct (histamine) and an indirect (ultrasonically nebulised distilled water (UNDW)) provocation test.

Methods – Fluticasone propionate, 750 μg/day, and beclomethasone dipropionate, 1500 μg/day, were compared in a randomised, double blind, crossover study consisting of two six week treatment periods, each preceded by a three week single blind placebo period. Twenty non-smoking asthmatics (mean forced expiratory volume in one second (FEV1) 74.7% predicted, mean PC20 histamine 0.36 mg/ml) completed the study.

Results – Fluticasone propionate and beclomethasone dipropionate improved FEV1, peak flow rates, asthma symptoms, and bronchial hyperresponsiveness to the same extent. Both fluticasone propionate and beclomethasone dipropionate caused an increase in PC20 histamine (mean 2.29 [95% confidence interval 1.45 to 3.13] and 1.95 [1.07 to 2.84] doubling doses, respectively) and in PD20 UNDW (1.12 [0.55 to 1.70] and 1.28 [0.88 to 1.70] doubling doses, respectively). Neither treatment changed morning serum cortisol levels, but fluticasone propionate decreased the number of peripheral blood eosinophils less than beclomethasone dipropionate, indicating smaller systemic effects of fluticasone propionate.

Conclusions – These findings show that fluticasone propionate is as effective as twice the dose of beclomethasone dipropionate on bronchial hyperresponsiveness, assessed by provocation with both histamine and UNDW, without increased systemic activity.

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Keywords: bronchial hyperresponsiveness, fluticasone propionate, beclomethasone dipropionate.
a final evaluation was made to check if the patient met all inclusion criteria. If so, they randomly received fluticasone propionate 750 μg daily or beclometasone dipropionate 1500 μg daily for six weeks.

Throughout the study the patients took three inhalations of the study medication twice daily. The inhalations were taken from a metered dose inhaler containing either placebo, fluticasone propionate 125 μg, or beclometasone dipropionate 250 μg per dose. The patients used a salbutamol metered dose inhaler (100 μg) as required as rescue medication. Patients were instructed on the correct usage of their inhaler. No other pulmonary medication was allowed.

SUBJECTS
Thirty adult non-smoking patients with asthma according to the criteria of the American Thoracic Society were recruited from the outpatient department. Baseline characteristics of these subjects are shown in table 1. All but one used inhaled corticosteroids before entering the study, with a mean (SE) daily dose of 790 (54) μg. At the start of the first placebo (washout and run in) period patients discontinued their inhaled steroids. Allergy was defined as raised specific IgE levels or positive skin tests for house dust mite or two of seven other common aeroallergens tested. To be included in the study patients needed to be asymptomatic, defined as having ≥4 symptom days during the last week, or ≥7 symptom days during the last two weeks of the first placebo (run in) period. Days were considered as symptom days when patients recorded at least one asthma symptom on the record cards (see below) during that day. At the end of the run in period, FEV1 had to be ≥50% of predicted and patients needed to have a provocative concentration of histamine causing a 20% fall in FEV1 (PC20histamine) below 4 mg/ml, indicating overt bronchial hyperresponsiveness. Subjects with seasonal allergy did not participate in the study during that specific season. None of the patients had used systemic corticosteroids in the six months preceding the study. Patients with an upper or lower respiratory tract infection within six weeks before the start of the study were excluded. The study was approved by the Nijmegen University medical ethics committee. All subjects gave written informed consent.

FIGURE 1. Design of the study. FP = fluticasone propionate 750 μg daily; BDP = beclometasone dipropionate 1500 μg daily.

BRONCHIAL HYPERRESPONSIVENESS AND LUNG FUNCTION
At the end of the four periods a histamine and a UNDW provocation test were performed at the same time on two different days in order to avoid tachyphylaxis for the different tests. Subjects did not use rescue or study medication for at least eight hours before each visit, and rested 15 minutes before the measurements were started.

Lung function and responses to provocation with histamine (PC20histamine) and UNDW (PD20UNDW) were assessed by FEV1, measured with a flow-volume curve recorded on a heated pneumotachograph (Spiro analyser ST 250; Fukuda Sangyo Co, Tokyo, Japan). Baseline lung function was recorded as the best of three reproducible values of FEV1 (within 5%) before the provocation tests.

The histamine provocation test was carried out according to the method of Cockcroft et al. For two minutes patients inhaled doubling concentrations of histamine acid phosphate by tidal breathing, increasing from 0.03 to 16 mg/ml. Histamine was nebulised with a DeVilbiss 646 nebuliser (DeVilbiss, Somerset, Pennsylvania, USA) with a fixed output of 0.13 ml/min. PC20histamine was determined in mg/ml by interpolating the last two points of the dose-response curve on a semilogarithmic scale.

The UNDW provocation test was performed according to the method of Groot et al. UNDW was generated with an ultrasonic nebuliser (Ultraneb 99, DeVilbiss, Somerset, Pennsylvania, USA) at a fixed output of 2.00 (0.05) ml/min. After inhalation of 20 litres of ambient air through the system, patients inhaled doubling volumes of air with UNDW (3, 5, 10, up to 100 litres), measured with a Wright respirometer (British Oxygen Co, London, UK). The respirometer was placed between the aerosol hose and the mouthpiece by means of a two way valve. Before and after each test the nebuliser chamber and aerosol hose were weighed to determine the exact amount of distilled water inhaled. The cumulative amount of inhaled water (ml H2O) causing a 20% fall in FEV1 from post-air values (PD20UNDW) was calculated by linear interpolation on a semilogarithmic curve.

DAILY RECORD CARDS
During the last three weeks of each of the four periods, patients recorded PEFR, use of study and rescue inhaler, asthma symptoms, and adverse events every day. The best of three PEFR measurements with a mini-Wright peak flow meter was recorded every morning and evening, before medication. The severity of dyspnoea during the day, during the night, and during exercise was registered on a visual analogue scale ranging from 0 to 100 mm.
LABORATORY EVALUATION
At the end of the four treatment periods a peripheral blood sample was taken between 0700 and 0900 hours (individual patients always at the same time) for measurement of total numbers of eosinophils and cortisol.

Total numbers of eosinophils were measured with a Technicon H1 analyser (Technicon Instrument Co, Tarrytown, New York, USA). Cortisol levels were immediately determined using an in-house radioimmunoassay involving heat inactivation of corticosteroid binding globulin. The lower limit of normal for morning serum cortisol levels in our laboratory is 0·19 μmol/l.

STATISTICAL ANALYSIS
Treatments were randomly allocated to five groups of six patients each according to the PACT computer programme. Each consecutive patient was allocated the next randomisation number after meeting the entry criteria at visit 1.

Four repeated measurements were made, at the start and at the end of each of both treatment periods (measurements 1–4, fig 1). The carryover effect of the first treatment at the start of the second treatment period (measurement 3) is a first order carryover effect, which may still be partly present at the end of the second treatment period (measurement 4). This latter part is the second order carryover effect which may interfere with the treatment effect. The first order carryover effect was tested by comparing the differences of measurements 3 and 1 between the two randomised treatment groups. Theoretically, the second order carryover effect is tested by comparing the sum of measurements 2 and 4 between the treatment order groups.15 However, in the present study some imbalance was present in several outcome variables between the two treatment groups at the start of the study, despite randomisation. In order to correct for this imbalance present at measurement 1, the second order carryover effect was tested by comparing the sum of two differences—that is, 2 minus 1 and 4 minus 1—between the two treatment groups. Provided that there was no second order carryover effect, the treatment effect was tested next by comparing the difference of measurements 2 and 4 between the treatment order groups. The treatment effect “fluticasone propionate (FP) minus beclomethasone dipropionate (BDP)” was estimated by taking half the difference between the two treatment order groups of the within group mean differences of measurements 2 and 4: \((\text{FP} - \text{BDP}) - (\text{BDP} - \text{FP})/2\).17 Alternatively, the clinical efficacy of each treatment was also expressed by taking the differences between the measurements at the end of either treatment period and the associated baseline measurement at the start of the treatment period considered.

All \(\text{PC}_{20}\text{histamine}\) and \(\text{PD}_{20}\text{UNDW}\) data were \(\log_{10}\) transformed before analysis, hence changes in \(\text{PC}_{20}\text{histamine}\) and \(\text{PD}_{20}\text{UNDW}\) were expressed as doubling doses of inhaled histamine and UNDW. The standard deviation of the differences between two repeated measurements (SD-rm) for these provocation tests was calculated between the two baseline values.16 From the parameters recorded on the diary card (PEFR, symptom scores, additional use of bronchodilator) the mean of all values recorded during the last two weeks of each period was used for statistical analysis. PEFR variability was defined as the difference between morning and evening reading (highest minus lowest value), expressed as a percentage of the mean of both readings.14 The Wilcoxon signed rank test or the paired \(t\) test were used for analysis when appropriate. Correlations were calculated by means of the Spearman rank correlation coefficient, \(p\) values of \(<0·05\) being considered significant. Data are reported as mean (SE) values unless specified otherwise.

Results
Thirty patients entered the first placebo (run in) period. Two patients did not meet the final criteria after the run in period because they

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Mean (SD) baseline characteristics of the patients</th>
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<tbody>
<tr>
<td></td>
<td>At start of study (n = 30)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30·3 (7·4)</td>
</tr>
<tr>
<td>Allergy (positive)</td>
<td>25</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
<td>84·8 (18·8)</td>
</tr>
<tr>
<td>(\log_{10}) PC20 histamine (mg/ml)</td>
<td>2·85 (1·98)</td>
</tr>
<tr>
<td>(\log_{10}) PD20 UNDW (ml H2O)</td>
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</table>

\(\text{PC}_{20}\text{histamine} = \) provocative concentration of histamine causing a 20% fall in FEV1; \(\text{PD}_{20}\text{UNDW} = \) provocative dose of ultrasonically nebulised distilled water causing a 20% fall in FEV1.

![Figure 2](http://thorax.bmj.com/) Mean (SE) values of (A) \(\text{PC}_{20}\text{histamine}\) (provocative concentration of histamine causing a 20% fall in FEV1) and (B) \(\text{PD}_{20}\text{UNDW}\) (provocative dose of ultrasonically nebulised distilled water causing a 20% fall in FEV1). □, beclomethasone dipropionate (BDP); ■, fluticasone propionate (FP).
experienced no asthma symptoms during that period. Seven patients dropped out in the run in period because of an exacerbation of their asthma after withdrawal of their inhaled cortico-}
costeroid. The remaining 21 patients all completed the study. Of these patients, 14 started with beclomethasone dipropionate and seven with fluticasone propionate. Since patients actually dropped out on the basis of pre-randomisation criteria, this did not affect the validity of the study.

There were no first and second order carry-over effects for any variable measured. The treatment effects of fluticasone propionate and beclomethasone dipropionate were therefore compared by analysing the difference of measurements 2 and 4 between the treatment order groups (table 2). Furthermore, the clinical efficacy of both inhaled steroids was analysed by comparing the treatment effects with their own baseline value (table 2) (A effects). No significant differences were found in any variable at the end of each placebo period.

BRONCHIAL HYPERRESPONSIVENESS AND LUNG FUNCTION

Both fluticasone propionate and beclomethasone dipropionate caused a significant decrease in bronchial hyperresponsiveness. On average, PC_{20}histamine increased by 2.29 [95% confidence interval (CI) 1.45 to 3.13] and by 1.95 [1.07 to 2.84] doubling doses, respectively (both p<0.001). PD_{20}UNDW increased by 1.12 [0.55 to 1.70] and by 1.28 [0.88 to 1.70] doubling doses, respectively (p<0.001 and p<0.005, respectively) (fig 2). The SD-rm of the two baseline measurements was 0.33 doubling doses for the histamine provocation test and 0.23 doubling doses for the UNDW provocation test.

PC_{20}histamine and PD_{20}UNDW were significantly correlated both after placebo (r = 0.74; p<0.001) and after treatment with fluticasone propionate (r = 0.54; p<0.05) and beclomethasone dipropionate (r = 0.51; p<0.05). There were no significant differences between the effects of fluticasone propionate and beclomethasone dipropionate on bronchial hyperresponsiveness and FEV_{1} (table 2). FEV_{1} increased by 0.45 (0.12) after fluticasone propionate (from 74.1% to 86.9% predicted; p<0.005), and by 0.34 (0.09) after beclomethasone dipropionate (from 76.4% to 85.8% predicted; p<0.001).

DAILY RECORD CARDS

Compared with baseline values, PEFR showed increases in morning and evening values after both fluticasone propionate and beclomethasone dipropionate (all p<0.01). The diurnal variation in PEFR decreased significantly after fluticasone propionate but not after beclomethasone dipropionate (table 2, fig 3). The treatment effects of fluticasone propionate and beclomethasone dipropionate were not significantly different (table 2).

The use of β_{2} agonists decreased significantly compared with baseline, both with fluticasone propionate and beclomethasone dipropionate, the treatment effect not being different with either steroid (table 2). Dyspnoea scores, recorded on a visual analogue scale, decreased...
There were no ticasone ing methasone methasone dipropionate times fluticasone between headache after mm three groups order.

LABORATORY EVALUATION

The total number of eosinophils in the peripheral blood decreased from 0-45 to 0-22 × 10^9/l (p<0.001) after beclomethasone dipropionate, and from 0-41 to 0-30 × 10^9/l (p<0.001) after fluticasone propionate. This treatment effect was significantly different, with a mean difference between fluticasone propionate and beclomethasone dipropionate of 0-076 × 10^9/l (95% CI 0-024 to 0-13).

Table 2 Clinical efficacy and mutual comparison of fluticasone propionate (FP) and beclomethasone dipropionate (BDP)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (mean SE)</th>
<th>After 6 weeks of treatment (mean SE)</th>
<th>Difference in treatment effects†</th>
<th>Mean (SE)</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>PC_{20} histamine (mg/ml)</td>
<td></td>
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<tr>
<td>FP</td>
<td>0.41 (0.17)</td>
<td>2.42 (0.17)***</td>
<td>0.55 (0.3) DD</td>
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<tr>
<td>BDP</td>
<td>0.49 (0.24)</td>
<td>1.63 (0.61)***</td>
<td>−0.10 to 1.21</td>
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<tr>
<td>PD_{20} UNDW (ml H_{2}O)</td>
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<tr>
<td>FP</td>
<td>3.77 (1.00)</td>
<td>8.62 (1.93)***</td>
<td>−0.63 to 0.65</td>
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<tr>
<td>BDP</td>
<td>3.29 (0.91)</td>
<td>7.63 (1.78)**</td>
<td>0.03 (0.3) DD</td>
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<tr>
<td>FEV_{1/2} (l)</td>
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<tr>
<td>FP</td>
<td>2.83 (0.18)</td>
<td>3.28 (0.13)**</td>
<td>0.06 (0.07)</td>
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<tr>
<td>BDP</td>
<td>2.90 (0.15)</td>
<td>3.24 (0.14)**</td>
<td>−0.08 to 0.21</td>
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<tr>
<td>BDP PEFR morning (l/min)</td>
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<tr>
<td>FP</td>
<td>438.4 (21.2)</td>
<td>489.9 (17.3)***</td>
<td>5.57 (5.5)</td>
<td>6.31 to 17.5</td>
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<tr>
<td>BDP</td>
<td>436.5 (20.8)</td>
<td>479.9 (17.7)***</td>
<td>2.69 (6.5)</td>
<td>10.9 to 16.3</td>
<td></td>
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<tr>
<td>Diurnal variation (%)§</td>
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<tr>
<td>FP</td>
<td>6.89 (0.90)</td>
<td>3.97 (0.50)**</td>
<td>−0.59 (0.64)</td>
<td>−1.93 to 0.76</td>
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<tr>
<td>BDP (agonist use (puffs/day)</td>
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<tr>
<td>FP</td>
<td>2.23 (0.35)</td>
<td>1.03 (0.29)***</td>
<td>−0.25 (0.22)</td>
<td>−0.72 to 0.21</td>
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<tr>
<td>BDP</td>
<td>2.36 (0.43)</td>
<td>1.40 (0.34)**</td>
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† A treatment effect is calculated as treatment versus corresponding baseline values. NS= not significant; **p<0.01; ***p<0.001.
§ Treatment effects of FP and BDP are directly compared by analysing the difference of their treatment effects between treatment order groups (FP − BDP) − (BDP − FP)/2.

**Discussion**

This study in patients with stable asthma shows that, after six weeks of treatment, fluticasone propionate 750 μg daily is as effective as beclomethasone dipropionate 1500 μg daily. No significant differences in beneficial effects were found with regard to bronchial hyper-responsiveness, FEV_{1}, PEFR, and asthma symptoms. Both fluticasone propionate and beclomethasone dipropionate caused a significant decrease in bronchial hyper-responsiveness, assessed by both the histamine and the UNDW provocation test.

Neither fluticasone propionate nor beclomethasone dipropionate affected morning cortisol levels significantly, as shown in fig 4. The seven patients with high values of morning cortisol (>0.70 μmol/l) were all women, six of whom were taking oral contraceptive drugs. Oestrogens in oral contraceptive drugs are known to increase the production of corticosteroid binding globulin, which probably accounts for the high values of cortisol in these patients. The only patient with a large decrease (0.45 μmol/l) in morning cortisol levels after treatment with beclomethasone dipropionate also showed a substantial decrease (0.25 μmol/l) after treatment with fluticasone propionate. In no patient did the cortisol level fall below the lower limit of normal after treatment. Mean cortisol values did not change significantly (from baseline 0.64 to 0.61 μmol/l after fluticasone propionate, and from baseline 0.60 to 0.59 μmol/l after beclomethasone dipropionate). There was no difference in treatment effect between fluticasone propionate and beclomethasone dipropionate.

During daytime from 18.1 (2-7) to 7.3 (2.1) mm after fluticasone propionate and from 14.8 (3.0) to 6.4 (1.9) mm after beclomethasone dipropionate (both p<0.001). Night time dyspnoea scores decreased from 17.1 (2.9) to 5.6 (2.0) mm after fluticasone propionate and from 14.9 (3.6) to 5.9 (2.2) mm after beclomethasone dipropionate (both p<0.001). There were no significant treatment effects between fluticasone propionate and beclomethasone dipropionate.

No serious adverse events were reported during the study. During treatment with both fluticasone propionate and with beclomethasone dipropionate three subjects reported a sore throat not related to a common cold. Other adverse events, unlike to be related to the use of the study drugs, included common cold (seven times with fluticasone propionate, four times with beclomethasone dipropionate, and six times with placebo), nausea and stomach ache (twice with beclomethasone dipropionate), headache (once with fluticasone propionate, three times with beclomethasone dipropionate and five times with placebo), diarrhoea (once both with fluticasone propionate and beclomethasone dipropionate), and generalised itching (three times with placebo).
Comparison of fluticasone propionate and beclomethasone dipropionate on bronchial hyperresponsiveness

steroid significantly changed morning cortisol levels.

This is the first study to test the hypothesis that fluticasone propionate may provide an equal effect on bronchial hyperresponsiveness, a major characteristic of asthma, at half the microgram dose of beclomethasone dipropionate. Until now all comparative studies in mild, moderate, and severe asthmatics have shown a 2:1 ratio in clinical effects. This was shown over a wide dose range, from 200 to 1000 μg fluticasone propionate (400–2000 μg beclomethasone dipropionate,4–7 and 400 μg budesonide6). Furthermore, in an open study 400 μg fluticasone propionate was more effective than 800 μg budesonide,9 and both 1000 and 2000 μg fluticasone propionate were significantly more effective than 1600 μg budesonide.10 Fabbri et al12 compared fluticasone propionate and beclomethasone dipropionate in an equal dose (1500 μg daily) in patients with moderate to severe asthma. Fluticasone propionate caused a significantly greater increase in asthma control than beclomethasone dipropionate. The present study confirms a similar ratio with regard to lung function, PEFR, symptom scores, and use of β2 agonists as that shown in previous comparative trials.6–9 On all parameters fluticasone propionate was as effective as twice the dose of beclomethasone dipropionate (table 2).

The extent to which fluticasone propionate and beclomethasone dipropionate reduced bronchial hyperresponsiveness is in line with that in previous studies. In mild asthmatics fluticasone propionate 1000 μg daily for two weeks improved PC20histamine by 1:3 doubling doses.20 The average increase in PC20histamine or methacholine after chronic treatment with beclomethasone dipropionate or budesonide, as recently reviewed by Barnes et al,2 is also of the order of one or two doubling doses. The extent of the response depends on dose, duration of treatment, and degree of steroid responsiveness. Treatment with a similar dose of budesonide (1600 μg daily) during six weeks improved PC20histamine by 2:4 doubling doses24 compared with 2-3 doubling doses for fluticasone propionate and 2:0 doubling doses for beclomethasone dipropionate in this study. The extent of the increase in PD50UNDW (1:1 and 1:3 doubling doses) is slightly less than in the study of Groot et al25 (1:8 doubling doses after four weeks of beclomethasone dipropionate 800 μg daily). This may be explained by the fact that at baseline our patients were less responsive to UNDW, the PD50UNDW being 3:3 and 3:8 ml H2O, compared with 1:3 ml H2O in the study by Groot et al25.

To assess efficacy of treatment an indirect challenge, as with UNDW, may be preferable because it mimicks naturally occurring bronchoconstrictor stimuli and because it reflects the severity of asthma better.10,11 Inhaled histamine acts mainly directly on the airway smooth muscle.10 In contrast, UNDW induces bronchoconstriction by cell-mediated events.11 Challenge with UNDW may increase bronchial hyperresponsiveness and induce a late asthmatic response, just as exposure to allergens.26 It has been suggested that inhaled corticosteroids may have a greater effect on indirect than on direct challenges, because they not only affect smooth muscle responsiveness but also reduce the airway mast cell function.27 This concept could not be confirmed in the present study because both fluticasone propionate and beclomethasone dipropionate caused a strong decrease in bronchial hyperresponsiveness in both tests. Compared with the SD-rm of the challenges, both steroids improved the PC20histamine about sixfold, and the PD50UNDW about fivefold, indicating equal effects on both parameters. Similarly, the study of Groot et al25 showed no advantage of UNDW over histamine. Nevertheless, the low correlation coefficient between PC20histamine and PD50UNDW after treatment indicates that both challenges test different aspects of bronchial hyperresponsiveness.

A potential drawback of our study was the crossover design, because it may take several weeks before bronchial hyperresponsiveness returns to baseline values after discontinuation of inhaled steroids.28 However, after the second washout period (measurement 3) all parameters, including bronchial hyperresponsiveness, returned to pretreatment levels (measurement 1). Therefore, carryover effects are not likely to have affected the outcome in the present study both from a statistical point of view and in terms of clinical relevance. Fluticasone propionate may offer some advantages over previous inhaled steroids due to its negligible oral bioavailability.29 However, the systemic effects of inhaled corticosteroids are mainly due to their resorption from the airways. The use of a spacer device may increase lung deposition and thus systemic absorption.30 There is no evidence for local metabolism of fluticasone propionate in the lung. The systemic concentration will be reduced by continuous recirculation and inactivation in the liver; the hepatic extraction ratio of fluticasone propionate is almost 100%.31 This may offer some improvement over budesonide and fluticasone dipropionate. In the lung beclomethasone dipropionate is hydrolysed to its much more active metabolite beclomethasone-17-monopropionate (17-BMP), and the majority of 17-BMP will reach the circulation. We did not use a spacer device in the present study. It is possible that the use of a spacer would have increased the systemic effects. However, the use of a spacer is not likely to have changed the difference between the two drugs.

With regard to the systemic effects of inhaled corticosteroids, two studies have shown significant differences in the effect on the hypothalamic-pituitary-adrenal (HPA) axis between fluticasone propionate and beclomethasone dipropionate in adult asthmatics. In the study by Leblanc et al26 200 μg fluticasone propionate daily increased serum cortisol levels compared with a (non-significant) decrease after 400 μg beclomethasone dipropionate. In addition, tetracosactrin-stimulated cortisol levels were significantly higher after fluticasone propionate. In the study of Barnes and coworkers'
serum cortisol levels rose from 0.29 to 0·31 μmol/l after fluticasone propionate 1000 μg daily, and decreased from 0·26 to 0·22 μmol/l after beclomethasone dipropionate 2000 μg daily, the treatment effects being significantly different. In our study serum cortisol levels did not change significantly with relatively high doses of inhaled steroids, which corresponds with the findings by Ayres et al.11 However, most studies (including ours) only measured morning serum cortisol levels, a simple but insensitive method to detect changes in the adrenal function. This was demonstrated in the study by Nicolaizik et al.12 who showed that morning serum cortisol levels did not change during treatment with budesonide and beclomethasone, but that 24 hour urinary secretion of free cortisol was decreased. In addition, our patients inhaled steroids without a spacer, and the duration of active treatment with each of the drugs studied was only six weeks. These factors may partly explain our inability to detect any change in adrenal function. On the other hand, we did detect a significant difference in absolute eosinophil counts in the peripheral blood, also a sensitive indicator of systemic activity.13 Absolute numbers of eosinophils decreased less with fluticasone propionate than with beclomethasone dipropionate, the treatment effect being significantly different (p<0·01). In this respect fluticasone propionate showed less systemic activity than beclomethasone dipropionate.

In conclusion, fluticasone propionate 750 μg daily is as effective as beclomethasone dipropionate 1500 μg daily with regard to bronchial hyperresponsiveness and clinical efficacy, while the systemic activity is not increased.

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