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A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma

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A comparison of fluticasone propionate, 1 mg daily, with beclomethasone dipropionate, 2 mg daily, in the treatment of severe asthma. N.C. Barnes, G. Marone, G.U. Di Maria, S. Visser, I. Utama, S.L. Payne, on behalf of an International Study Group. ©ERS Journals Ltd 1993.

ABSTRACT: We wanted to compare the efficacy and safety of fluticasone propionate, a new topically active inhaled corticosteroid, to that of high dose beclomethasone dipropionate, in severe adult asthma.

Patients currently receiving between 1.5–2.0 mg·day^{-1} of an inhaled corticosteroid were treated for six weeks in a double-blind, randomized, parallel group study with 1 mg·day^{-1} fluticasone propionate (n=82), or 2 mg·day^{-1} beclomethasone dipropionate (n=72).

Mean morning peak expiratory flow rates (PEFR) increased from 303 to 321 *l*·min^{-1} with fluticasone propionate, and from 294 to 319 *l*·min^{-1} with beclomethasone dipropionate. There was an increase in evening PEFR, asthma symptoms improved, and rescue beta$_2$-agonist use decreased for both treatment groups. None of these differences between treatments were statistically significant. However, diurnal variation was significantly reduced with fluticasone propionate, when compared with beclomethasone dipropionate (difference = 7 *l*·min^{-1}; p=0.038). Clinic lung function also improved with both treatments and, apart from % predicted PEFR, which showed no difference after beclomethasone dipropionate but increased from 73 to 78% with fluticasone propionate, there were no differences between treatments. Forced expiratory volume in one second (FEV$_1$) increased with both treatments. The geometric mean plasma cortisol concentration rose after treatment with fluticasone propionate (from 293 to 309 nmol·*l*$^{-1}$) and fell after beclomethasone dipropionate (from 256 to 224 nmol·*l*$^{-1}$); the difference between treatments was significant. The incidence of adverse events was low in both treatment groups.

In conclusion, 1 mg·day^{-1} fluticasone propionate was as effective as 2 mg·day^{-1} beclomethasone dipropionate in the control of severe asthma. However, adrenal function was affected less by fluticasone propionate, which gives it a better overall safety profile. This study, therefore, demonstrates the increased therapeutic potential of fluticasone propionate over beclomethasone dipropionate in severe asthma.
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The efficacy of oral corticosteroids in the treatment of chronic asthma is undisputed, but their long-term use is associated with adverse side-effects, including suppression of the hypothalamo pituitary adrenal (HPA) axis function, osteoporosis, weight gain, hypertension and reduced glucose tolerance [1, 2]. The introduction of inhaled corticosteroids in the early 1970s represented a significant therapeutic advance in the management of asthma, since these compounds combined high topical potency with low systemic activity. It has been repeatedly shown that doses of up to 800 μg·day^{-1} of inhaled corticosteroids, such as beclomethasone dipropionate and budesonide, do not have clinically significant effects on HPA-axis function, and are not thought to be associated with other adverse systemic effects [3–5]. However, high doses of ≥1,500 μg·day^{-1} may suppress HPA-axis function in some patients [6–8].

Fluticasone propionate is a new, topically active, synthetic glucocorticosteroid, which has negligible oral bioavailability, due to a combination of poor gastrointestinal absorption and extensive first pass hepatic metabolism [9]. This feature would suggest that fluticasone propionate has advantages over currently used inhaled corticosteroids, since, as with any inhaled drug, a large proportion of the dose (approximately 90%) will be swallowed [10]. The lack of systemic action of fluticasone propionate has been demonstrated in a study in healthy volunteers, who were treated for 10 days with either, 1.5 mg·day^{-1} fluticasone propionate, 15 mg·day^{-1} beclomethasone

dipropionate, or with placebo. At the end of the treatment period, morning plasma cortisol levels after fluticasone propionate showed no significant differences compared with placebo. In contrast, after treatment with beclomethasone dipropionate, morning cortisol levels were significantly decreased [11].

Fluticasone propionate has been shown to be twice as potent as beclomethasone dipropionate both in preclinical studies and in dose ranging studies in asthmatic patients [12, 13]. It is believed, therefore, that fluticasone propionate, administered at higher doses, will have a wider safety margin compared with beclomethasone dipropionate or budesonide.

The present study was designed to compare the efficacy and safety of fluticasone propionate treatment (1 mg·day^{-1}), with high-dose beclomethasone dipropionate treatment (2 mg·day^{-1}), in adult patients with severe asthma.

Methods

Patients

One hundred and seventy–two patients, with a clinical history of severe chronic asthma, were recruited from outpatients at 18 centres in seven countries worldwide. All patients required 1.5–2.0 mg·day^{-1} beclomethasone dipropionate or budesonide and inhaled beta$_2$-adrenergic receptor agonist (beta$_2$-agonist) therapy. Of the 172 patients, 154 were randomized to treatment, and their results are presented in this paper. Eighty two patients received fluticasone propionate (1 mg·day^{-1}), and 72 received beclomethasone dipropionate (2 mg·day^{-1}). The patient characteristics are shown in table 1; the two treatment groups were well-matched for sex, age, weight, height, ethnic origin, smoking habits, use of a spacer device, duration of asthma, prestudy asthma medication, and baseline pulmonary function. All patients gave their informed consent, and the study was approved by local ethics committees.

In the month preceding the run-in to the study, none of the patients had changed their prophylactic inhaled or oral medications, which they used to control their asthma, and none had been admitted to hospital in connection with their respiratory disease. Inclusion criteria were based on lung function and asthma symptoms. Patients were entered into the treatment period if they had demonstrated at least two of the following: mean morning peak expiratory flow rate (PEFR) ≤70% of predicted during the last 7 days of the run-in period; ≥15% reversibility in forced expiratory volume in one second (FEV_1) following inhalation of a beta$_2$-agonist during the run-in period or within 3 months before the start of the study; ≥20% diurnal variation in PEFR on at least 4 of the last 7 days of the run-in period; asthma symptoms on at least 4 of the last 7 days of the run-in period.

Exclusion criteria were as follows: changes in asthma medication (except inhaled beta$_2$-agonist) during the run-in period; treatment with systemic corticosteroids within one month of the study period, or on more than four 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.

Thirteen patients taking fluticasone propionate, and five taking beclomethasone dipropionate, were withdrawn by the investigator during the study. Withdrawals from the fluticasone propionate group were made because of exacerbation of asthma (six patients), other adverse events (two patients: oral candidiasis, abnormal hepatic function), or non-compliance (five patients). Two patients were withdrawn from the beclomethasone dipropionate group because of exacerbation of asthma, and three were withdrawn because of other adverse events (diabetes; chest infection and oral candidiasis; pityriasis rosea).

Table 1. – Patient characteristics

Parameter	FP 1 mg·day^{-1}	BDP 2 mg·day^{-1}	Total
Patients n	82	72	154
M/F n	44/38	41/31	85/69
Caucasian n (%)	78 (95)	71 (99)	149 (97)
Smokers n (%)	14 (17)	17 (24)	31 (20)
Median age yrs (range)	50 (18–78)	52 (20–75)	51 (18–78)
Duration of asthma			
>1 yr n (%)	82 (100)	71 (99)	153 (99)
>10 yrs n (%)	48 (59)	38 (53)	86 (56)
Spacer used n (%)	26 (32)	22 (31)	48 (31)
Prestudy asthma medications*			
Methylxanthines n (%)	38 (46)	31 (43)	69 (45)
Ipratropium bromide n (%)	22 (27)	17 (24)	39 (25)
Sodium cromoglycate n (%)	4 (5)	2 (3)	6 (4)
Other n (%)	9 (11)	4 (6)	13 (8)

FP: fluticasone propionate; BDP: beclomethasone dipropionate; *: excluding inhaled beta$_2$-agonists.

Study design

The study was double-blind, parallel-grouped and randomized in design. Treatment was for six weeks, after a run-in period of two weeks, and there was a follow-up period of two weeks after treatment.

During the two week run-in period the patients discontinued use of their usual inhaled bronchodilator (beta$_2$-agonists, anticholinergic agents and combination inhalers) and replaced them with inhaled salbutamol, taken as required. All other asthma medication, including their usual inhaled corticosteroid therapy was continued at a fixed dose.

At the end of the run-in period, the patients' usual inhaled corticosteroid treatment was replaced by fluticasone propionate or beclomethasone dipropionate. Fluticasone propionate was given as two 250 μg actuations inhaled from a pressurized inhaler twice daily, along with two actuations of placebo, inhaled twice daily. Beclomethasone dipropionate was administered as two 250 μg actuations from each of two pressurized inhalers, twice daily. Throughout the duration of the study patients continued using their other asthma medication at constant dose. They were allowed to use salbutamol inhalers (100 μg per actuation) as required for symptomatic relief of airways obstruction.

Patients were withdrawn from the study if a change or increase in the dose of their current asthma medication proved necessary, or if any additional medication, including oral corticosteroids, was required.

Protocol

Using the mini-Wright peak flow meter, patients measured their PEFR morning (between 07.00–08.00 h) and evening (19.00–20.00 h), before taking fluticasone propionate or beclomethasone dipropionate or using salbutamol. On each occasion, they took three readings. They entered these measurements 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 follows: 0=none; 1=wheezing or shortness of breath on strenuous exercise/hurrying, otherwise asthma not unduly troublesome; 2=wheezing or shortness of breath most of the day, normal activities difficult; 3=unable to carry out normal activities because of shortness of breath. Symptoms during the night were rated as follows: 0=none: 1=symptoms caused waking once or early waking; 2=woken 2 or 3 times by cough/wheeze/breathlessness/asthma; 3=awake most of the night with cough/wheeze/breathlessness/asthma. Patients also recorded their use of the study medication and of the salbutamol inhaler.

After the initial visit, patients attended the clinic on four more occasions: at the end of the run-in period, after three and six weeks of treatment, and at the end of the two week follow-up period. At each of these visits three, measurements were made of PEFR, FEV_1, and forced vital capacity (FVC) before, and 15 min after inhalation of 2 puffs (200 μg) salbutamol. 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. The patients assessed their asthma as compared to the previous visit according to the following scale: 1=much improved; 2=improved; 3=unchanged; 4=worse; 5=much worse. Oropharyngeal swabs, to determine the presence of *Candida albicans,* were taken if there was clinical evidence of infection following visual examination.

Adverse events

All serious and minor adverse events were recorded, irrespective of their causality in relation to the study drug. Serious adverse events were defined as death, life-threatening, disabling or incapacitating events, events requiring hospitalization, any congenital abnormality or cancer or drug overdose, and any other clinical or laboratory event leading to withdrawal of the study drug.

Laboratory evaluations

Blood samples for routine testing (haematology, biochemistry) were taken between 08.00 and 10.00 h 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 the clinic visits at the end of the run-in period, and after 6 weeks of treatment. The plasma cortisol samples were analysed centrally by the West Middlesex Laboratory, UK. The samples were analysed by radioimmunoassay, using the coated tube method with a between batch coefficient of variation of 7%.

Analysis

All statistical analyses were carried out using SAS (release 6.03) programs and procedures.

Data from the daily record cards completed during the run-in period were used to establish a baseline. For the treatment period, data were analysed for days 1–21, 22–42 and 1–42. To be included in the analysis of a variable, patients were to have provided data for at least seven days during the run-in period, and for at least 11 days in any treatment assessment period. The mean morning and evening PEFR was calculated over each period for each patient, and expressed as absolute values and as percentage of predicted values. Predicted lung function values were calculated from sex, age, and height using standard formulae [14].

Diary card PEFRs and other lung function values, together with plasma cortisol concentrations, were analysed by analysis of covariance, adjusting for baseline, country, use of spacer and treatment. For the percentages of symptom-free days/nights and the mean frequency of use of the salbutamol inhaler, the differences from

baseline were obtained for each of the three treatment periods (days 1–21, 22–42, 1–42), and the differences between treatments compared using the Wilcoxon rank sum test, adjusted according to country using the van Elteren method [15]. The median symptom scores were also calculated and tabulated. The assessments of treatment efficacy made by patients after three and six weeks of treatment were compared, adjusting for country, using an extended Mantel-Haenszel test with standardized mid-rank scores [16]. The numbers of patients reporting an adverse event in each treatment group were compared using the Mantel-Haenszel test [16]. For all variables p values <0.05 were considered significant.

Results

Efficacy

Both fluticasone propionate and beclomethasone dipropionate were highly effective in the control of severe asthma, and analysis of the parameters measured showed very few significant differences between the two treatments.

Tests for baseline by treatment interaction, country by treatment interaction, and use of spacer device by treatment interaction were performed, and in each case there was no evidence of an interaction effect.

Daily record card

Over days 1–42 of treatment, mean morning PEFR increased on both treatments (table 2 and fig. 1). Analysis of covariance, which takes into account the baseline values, country and use of spacer device, showed that there was no difference between the treatment means (adjusted mean difference, -7 $l \cdot min^{-1}$; 95% confidence interval (95% CI), -21 to 7 $l \cdot min^{-1}$; p=0.346). Mean evening PEFR also improved with both treatments (table 2). Again, analysis of covariance showed no significant differences between treatments (adjusted mean difference, -13 $l \cdot min^{-1}$; 95% CI, -26 to 1 $l \cdot min^{-1}$; p=0.07).

When the morning PEFR value was subtracted from the previous evening's PEFR value to obtain diurnal variation in PEFR, there was, however, a significantly greater reduction over the six weeks of treatment with fluticasone propionate, when compared with beclomethasone dipropionate (the difference was 7 $l \cdot min^{-1}$, p=0.038; fig. 2).

At the end of the six week treatment period, patients given fluticasone propionate or beclomethasone dipropionate reported fewer asthma symptoms by day and at night, with no significant differences between treatments (table 2 and fig. 3). The percentage of patients with a median daytime or night-time symptom score of 0 increased with both treatments (table 2). For all treatment-time periods analysed, less 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 (table 2). In both treatment groups, there was a small decrease in the number of times salbutamol was used during the day or at night (table 2).

There were no significant differences between fluticasone propionate and beclomethasone dipropionate for any of these parameters during any treatment period.

Table 2. – Dairy card data

Parameter	Fluticasone propionate			Beclomethasone dipropionate			Difference in adjusted means (95% CI)	p value
	Baseline mean	Means after treatment	Adjusted means*	Baseline mean	Means after treatment	Adjusted means*		
PEFR AM $l \cdot min^{-1}$	303 (77)	321 (77)	317 (77)	294 (70)	319 (70)	324 (70)	-7 (-21 to 7)	0.346
PEFR PM $l \cdot min^{-1}$	337 (75)	339 (75)	336 (75)	333 (70)	349 (70)	348 (70)	-13 (-26 to 1)	0.07
Diurnal variation $l \cdot min^{-1}$	37 (75)	20 (75)	23 (75)	39 (69)	28 (69)	30 (69)	-7	0.038**
Symptom–free days %	38	52	-	28	37	-	-	0.212
Symptom–free nights %	46	59	-	38	50	-	-	0.854
Days=0 %	38	58	-	28	38	-	-	-
Nights=0 %	49	61	-	35	57	-	-	-
Rescue–free days %	28	36	-	23	30	-	-	0.733
Rescue–free nights %	47	53	-	39	47	-	-	0.935
Mean usage† salb·day^{-1} n	13	10	-	14	11	-	-	0.866
Mean usage† salb·night^{-1} n	6	5	-	8	6	-	-	0.875

Numbers in parenthesis indicate number of patients. *: mean adjusted for baseline, country and use of spacer; **: statistically significant in favour of fluticasone proprionate; †: mean number of times rescue medication used per day/night. Days=0: days with median symptom score =0; Nights=0: nights with median symptoms score =0; -: not calculated; PEFR: peak expiratory flow rate. AM: morning; PM: evening.

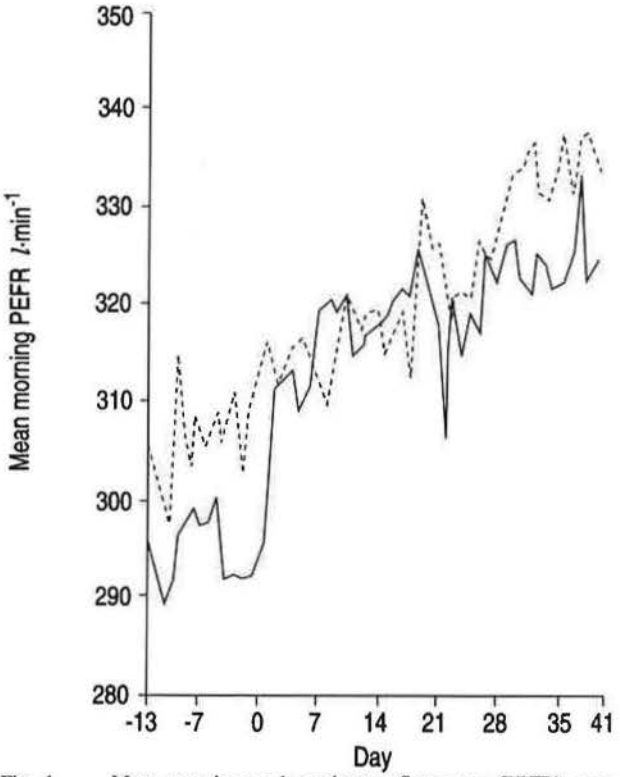

Fig. 1. – Mean morning peak expiratory flow rates (PEFR) over baseline and six weeks of treatment with fluticasone propionate 1 mg·day^{-1}, and beclomethasone dipropionate, 2 mg·day^{-1}. ——— : beclomethasone dipropionate; - - - - : fluticasone propionate.

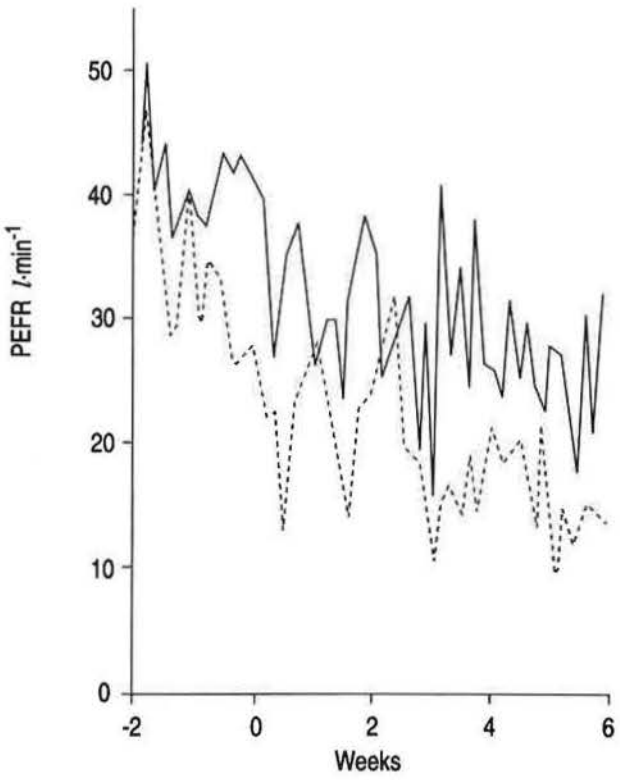

Fig. 2. – Diurnal variation in peak expiratory flow rates (PEFR) over baseline and 6 weeks of treatment with fluticasone propionate (FP) 1 mg·day^{-1}, or beclomethasone dipropionate (BDP), 2 mg·day^{-1}. There was a significantly greater reduction in diurnal variation in the fluticasone propionate treated group than in the beclomethasone dipropionate treated group (p=0.038). ——— : BDP; - - - - : FP.

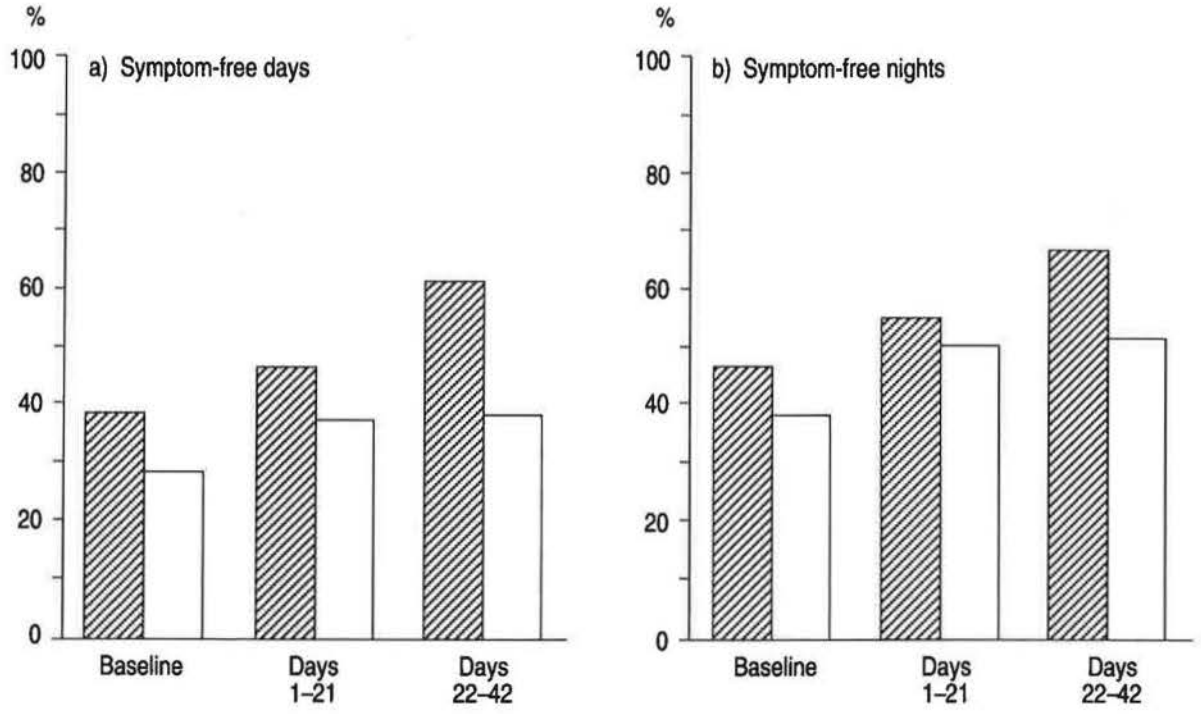

Fig. 3. – Mean percentage of: a) symptom-free days; and b) symptom-free nights at baseline, during days 1–21 and during days 22–42 of treatment with fluticasone propionate (FP) 1 mg·day^{-1} (▨); or beclomethasone dipropionate (BDP), 2 mg·day^{-1} (▭) (73≥ n ≥65).

Clinic lung function

Pulmonary function measurements taken before salbutamol inhaled showed improvements after three and six weeks of treatment (table 3). For PEFR as percentage predicted, the improvement in PEFR was significantly greater in the fluticasone propionate treated group (p=0.046). There were no other significant differences between the treatment groups. There were improvements in FEV_1 and FVC at three and six weeks, with no significant differences between treatments.

At both clinic visits, more patients reported that their asthma had improved after taking treatment when compared with the run-in period. At six weeks, 44% of patients taking fluticasone propionate, and 38% taking beclomethasone dipropionate, assessed their asthma to be improved or much improved, in comparison with 21% (fluticasone propionate), and 18% (beclomethasone dipropionate), at baseline after a two week run-in period. There was no significant difference between the two treatments.

Adverse events

The incidence of adverse events is summarized in table 4. Statistical analysis showed no significant differences (p>0.15) between treatments in the incidence or nature of adverse events.

Adverse events that occurred in more than 2% of patients during treatment are shown in table 4. The most common adverse events were related to disease, *e.g.* asthma, rhinitis. Three serious adverse events (including two of exacerbation of asthma) were reported during the study drug period, all in patients taking fluticasone propionate, but none of these was assessed as being related to treatment. In total, during the treatment period, six patients taking fluticasone propionate and two taking beclomethasone dipropionate were withdrawn from the study because of an exacerbation of asthma.

The incidence of pharmacologically predictable adverse events, *i.e. Candida albicans* and hoarseness, was low, and there was no difference between the treatment groups.

Table 3. – Clinic lung function at baseline and after six weeks of treatment

Parameter	Fluticasone propionate n=68			Beclomethasone dipropionate n=68			Difference in adjusted mean (95%CI)	p value
	Baseline mean	Means after treatment	Adjusted means*	Baseline mean	Means after treatment	Adjusted means*		
PEFR $l \cdot min^{-1}$	333	364	357	323†	331†	330†	27 (-2 to 56)	0.072
% pred	73	80	78	72†	72†	72†	6 (0 to 12)	0.046**
FEV_1 l	1.88	2.07	1.95	1.73	1.89	1.89	0.66 (-0.07 to 0.19)	0.343
% pred	61	67	64	57	62	61	2 (-2 to 6)	0.358
FVC l	2.97	3.18	3.09	2.78	2.93	3.00	0.09 (-0.07 to 0.25)	0.265
% pred	80	85	83	75	79	81	2 (-2 to 7)	0.274

*: mean adjusted for baseline, country and use of space; % pred: % predicted normal value; †: n=67. PEFR: peak expiratory flow rate; **: statistically significant in favour of fluticasone proprionate. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Table 4. – Summary of adverse events

	Run-in	FP	BDP	Follow-up
Patients n	172	82	72	151
Adverse events n	53	71	60	25
Patients with an adverse event n (%)	46 (27)	43 (52)	37 (51)	25 (16)
Severe adverse event n (%)	6 (3)	8 (10)	5 (7)	1 (1)
Drug-related adverse event n (%)	3 (2)	15 (18)	18 (25)	4 (3)
Withdrawal due to adverse event n (%)	9 (5)	8 (10)	5 (7)	0 (0)
Most common (>2% of patients) adverse event during treatment				
Asthma and related events n (%)		12 (15)	7 (10)	
Rhinitis n (%)		6 (7)	2 (3)	
Oral candidiasis n (%)		5 (6)	3 (4)	
Upper respiratory tract infection n (%)		5 (6)	2 (3)	
Sore throat n (%)		4 (5)	4 (6)	
Headache n (%)		3 (4)	1 (1)	
Cough n (%)		3 (4)	0	
Respiratory infection n (%)		2 (2)	2 (3)	

FP: fluticasone propionate; BDP: beclomethasone dipropionate.

Candida was reported in five patients (6%) on fluticasone propionate, and in three patients (4%) on beclomethasone dipropionate; one patient (on beclomethasone dipropionate) was withdrawn as a result of this infection. Two patients on fluticasone propionate and one on beclomethasone dipropionate reported hoarseness as an associated symptom of oral candidiasis. No patient given fluticasone propionate reported hoarseness as a single symptom, but two patients on fluticasone propionate reported hoarseness as one of several symptoms, and one patient reported aphonia and huskiness. Hoarseness was reported as a single symptom in two patients taking beclomethasone dipropionate.

Laboratory evaluations

No abnormalities were detected in the routine laboratory haematology, biochemistry and urinalysis.

Plasma cortisol concentrations from before and after treatment were recorded from 117 patients, 57 of whom received fluticasone propionate, and 60 of whom received beclomethasone dipropionate. Statistical analysis of the cortisol data showed a significant interaction of treatment with baseline (p=0.04). Patients who started the study with a low plasma cortisol concentration showed a greater improvement on fluticasone propionate than those on beclomethasone dipropionate. Overall, when compared with baseline values, mean early morning plasma cortisol concentrations rose after treatment with fluticasone propionate and fell after treatment with beclomethasone dipropionate. The geometric mean morning serum cortisol rose from a baseline of 293 to 309 nmol·l^{-1} after treatment with fluticasone propionate, and fell from a baseline of 256 to 224 nmol·l^{-1} after treatment with beclomethasone dipropionate. Statistical analysis of the means, which were adjusted for differences in baseline values, country and use of spacer device, showed that they were significantly different (p=0.026), with the mean plasma cortisol concentration rising 27% higher in the fluticasone propionate group than in the beclomethasone dipropionate group (the ratio of the fluticasone propionate mean to the beclomethasone dipropionate mean=1.27; 95% CI, 1.03–1.56).

These findings are illustrated in figure 4, which is a scatter plot of all the individual plasma cortisol values. The lower limit of the normal value of plasma cortisol (150 nmol·l^{-1}) is indicated on both axes. Patients who fell into "quadrant a" were those who started the study with a lower than normal plasma cortisol value, which increased over the study period; patients who fell into "quadrant b" were those who started the study with a cortisol value above the normal value, which remained above after six weeks of treatment; patients who fell into "quadrant c" were those who had a lower than normal value at baseline, which remained low after study treatment; and patients who fell into "quadrant d" were those who had a value above the lower normal limit at baseline, which then fell after the study treatment.

A comparison of the scatter plots shows that whilst the majority of patients who received fluticasone propionate fell into "quadrants a and b" and were above the lower limit of normal values after treatment, the individual plots for beclomethasone dipropionate were more scattered, and several patients fell into "quadrants c and d" indicating that they had lower than normal values after treatment.

Vital signs

No significant changes in weight, pulse rate, or systolic or diastolic blood pressure were detected in the total population.

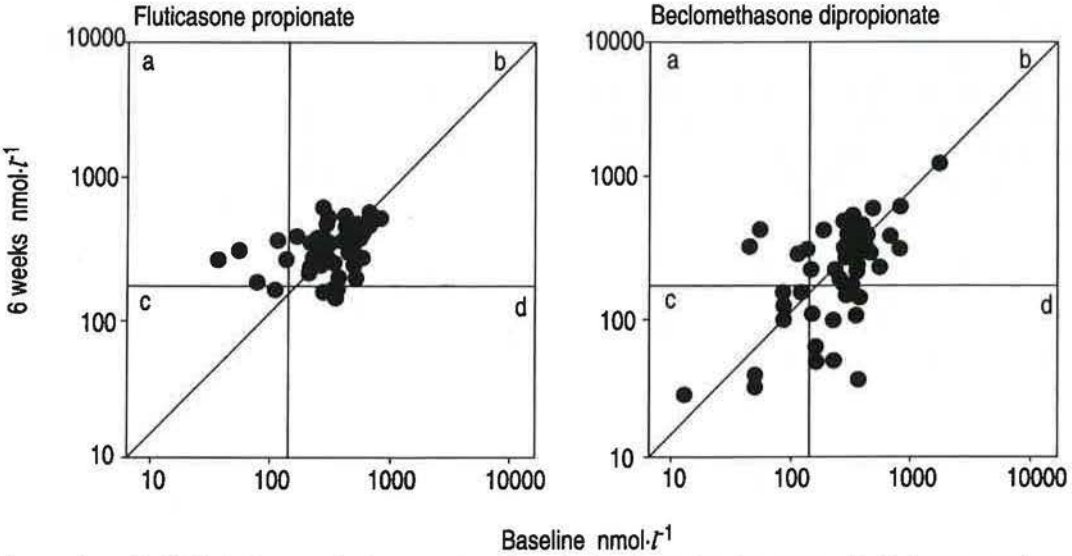

Fig. 4. – Scatter plots of individual plasma cortisol means at baseline and after six weeks of treatment with fluticasone propionate (1 mg·day^{-1}; n=57) or beclomethasone dipropionate (2 mg·day^{-1}; n=60). The lower limit of the normal range of cortisol values (150 nmol·l^{-1}) is indicated by a continuous line on both axes, Patients who fell into: "quadrant a" = started the study with a lower than normal plasma cortisol value, which increased over the study period; "quadrant b" = started the study with a cortisol value above the normal value, which remained above after treatment; "quadrant c" = had a lower than normal value at baseline, which remained low after treatment; "quadrant d" = had a value above the lower normal limit at baseline, which then fell after treatment. As can be seen from the plots, most patients on fluticasone propionate finished the study with normal cortisols, whereas fewer patients on beclomethasone dipropionate did.

Discussion

This study has demonstrated that 1 mg·day^{-1} fluticasone propionate is approximately equipotent to 2 mg·day^{-1} beclomethasone dipropionate in the control of severe chronic asthma. Over the six week study period, both treatments improved pulmonary function, reduced daytime and night-time asthma symptoms and, as a consequence, reduced the use of relief bronchodilator medication. Furthermore, the reduced diurnal variation in PEFR was significantly greater on fluticasone propionate. This improvement on both treatments was reflected in the patients' own assessment of their asthma. These results are consistent with the 2:1 potency ratio of fluticasone propionate to beclomethasone dipropionate, which has been observed in earlier studies [12, 13].

The overall incidence of adverse events was low. There were no significant differences between treatment groups, and no unexpected adverse effects were observed in either treatment group. The most frequently reported event was associated with the disease itself (asthma was reported by 12 patients in the fluticasone propionate group and 7 patients in the beclomethasone dipropionate group).

Oral candidiasis and hoarseness are pharmacologically predictable adverse events of inhaled corticosteroid therapy [17, 18]. Candida is present in many normal throats [19–21], and has been cultivated from throat swabs in up to 71% of normal subjects [22]. The incidence of candidiasis in patients taking inhaled corticosteroids has also varied considerably from 3% [23] to 77% [24]. It has been suggested that the incidence is related to dose [25], and frequency of use [26], and may be reduced with spacer devices [27]. In this study, the incidence of hoarseness was low in both treatment groups, and candidiasis was reported in 6% of the patients treated with fluticasone propionate, and 4% of those treated with beclomethasone dipropionate. The incidence of candidiasis was too low to determine whether the use of a spacer device had affected the results.

The study compared the effects of fluticasone propionate with that of high-dose beclomethasone dipropionate on HPA-axis function. High doses of beclomethasone dipropionate (≥1,500 μg·day^{-1}) are known to produce adrenal suppression in some patients [6–8]. In the present study, there was no evidence of any clinically significant effect on the HPA-axis in any patient treated with fluticasone propionate. Overall, mean plasma cortisol levels fell following treatment with beclomethasone dipropionate (2 mg·day^{-1}). In contrast, in patients on fluticasone propionate (1 mg·day^{-1}), mean plasma cortisol levels rose. The difference between the treatment groups was statistically significant.

The present study indicates that in the control of severe asthma, fluticasone propionate at 500 μg *b.d.* (1 mg·day^{-1}) is at least as effective as beclomethasone dipropionate at 1,000 μg *b.d.* (2 mg·day^{-1}). Furthermore, in terms of safety, fluticasone propionate has significant benefits, exerting significantly less effect on the function of the HPA-axis in comparison with beclomethasone dipropionate. This favourable ratio of therapeutic effects to systemic side-effects should make fluticasone propionate a useful drug in the treatment of severe asthma.

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