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High dose fluticasone propionate, 1 mg daily, *versus* fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma

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on behalf of an International Study Group

High dose fluticasone propionate, 1 mg daily, versus *fluticasone propionate, 2 mg daily, or budesonide, 1.6 mg daily, in patients with chronic severe asthma. J.G. Ayres, E.D. Bateman, B. Lundbäck, T.A.J. Harris. ©ERS Journals Ltd 1995.*

ABSTRACT: Airway inflammation is now regarded as fundamental in the pathogenesis of asthma and treatment with inhaled corticosteroids has proved effective. There is a need for drugs in this category with higher topical potency but fewer side-effects than those presently available.

A double-blind, parallel group study was conducted in 671 patients with severe asthma (already taking between 0.8–2.0 mg of inhaled corticosteroid daily) to compare the safety and efficacy of 6 weeks of treatment with inhaled fluticasone propionate (FP), 1 mg daily, to fluticasone propionate, 2 mg daily, and budesonide (BUD), 1.6 mg daily, delivered *via* a metered-dose inhaler. Peak expiratory flow (PEF), asthma symptoms, and usage of rescue medication were recorded daily by the patient. At each clinic visit (-2, 0, 3 and 6 weeks) morning serum cortisol levels, bone markers and spirometry were assessed.

The changes in mean morning PEF from baseline (weeks 1–6) were: FP 2 mg daily +24 $l \cdot min^{-1}$; FP 1 mg daily +21 $l \cdot min^{-1}$; BUD 1.6 mg daily +13 $l \cdot min^{-1}$. A similar rank order for the three treatments was seen for evening PEF, clinic spirometry, reduction of diurnal PEF variation, symptom scores, and requirement for rescue bronchodilators. The mean serum cortisol levels remained well within the normal range in all three groups. Analysis of the geometric mean cortisol ratio (treatment/baseline ratio after 6 weeks treatment) showed a changed rank order, the values being: FP 1 mg daily 1.04; BUD 1.6 mg daily 0.97; FP 2 mg daily 0.88.

These data show that mg for mg, fluticasone propionate is more effective than budesonide in the treatment of patients with severe asthma.

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Inhaled beclomethasone dipropionate (BDP) and budesonide (BUD) have an established place in the management of adult and childhood asthma, as first line anti-inflammatory drugs [1]. Widespread clinical experience has shown budesonide to be an effective and well-tolerated treatment for asthma and rhinitis when administered by inhalation and intranasally, respectively. Whilst the anti-inflammatory properties of available corticosteroid esters vary quantitatively, there is still no clear efficacy advantage for any of these drugs. However, some clinical pharmacology studies suggest that budesonide has a more favourable ratio of anti-asthma to systemic glucocorticoid activity than beclomethasone dipropionate, and budesonide is preferred by some where high dosages of inhaled corticosteroids are needed to control asthma [2].

Although in adults, doses of up to 1 mg daily of these agents do not have a significant effect upon the hypothalamic-pituitary-adrenal axis (HPA-axis), or other serious adverse systemic effects, there is concern regarding their safety at doses above this level. Suppression of HPA-axis function has been observed in some patients, and their effect upon bone growth and turnover, particularly during long-term use, require clarification [3]. These concerns have prompted a search for drugs with higher topical potency but lower local and systemic side-effects.

Fluticasone propionate (FP), a trifluorinated glucocorticosteroid developed for topical use in asthma, has several promising properties. These include reduced mineralocorticoid activity, higher affinity and selectivity for the glucocorticosteroid receptor, and enhanced hepatic clearance. Results obtained in two studies with the McKenzie skin vasoconstrictor assay in humans have given different results. One study showed that FP has a more than nine times greater activity than fluocinolone acetonide and twice the activity of beclomethasone dipropionate and BUD, and the other found no significant difference between FP and BUD [4, 5]. Human pharmacology studies have shown that FP is poorly absorbed following oral administration, and absorbed drug is rapidly metabolized by the liver into an inactive metabolite. The hepatic extraction ratio for FP is almost 100%, resulting in an oral bioavailability of <1%, compared to that of

BUD (11%), flunisolide (20%) and prednisolone (>80%) [6].

We report the results of a 6 week double-blind, double-dummy, parallel group study designed to compare the efficacy and safety of FP given at high doses (1 and 2 mg daily) with high dose budesonide (1.6 mg daily) in subjects with symptomatic severe asthma, previously demonstrating a need for 0.8–2 mg of inhaled corticosteroids daily.

Patients and methods

Patients

Eight hundred and sixty two adult patients with a clinical history of severe asthma were recruited from 66 centres in 13 countries worldwide. All were out-patients and all required β_2-agonist treatment and inhaled corticosteroids at doses of either 1–2 mg daily of beclomethasone dipropionate or 0.8–1.6 mg daily of BUD. This dose could be delivered by metered-dose inhaler (MDI), or an equivalent dose delivered by dry powder.

Patients were required to be stable, having not changed their prophylactic asthma medications or been admitted to hospital because of their asthma during the month preceding the prestudy visit. Patients were entered into the treatment period if they had fulfilled the following criteria for symptomatic asthma in spite of continued treatment:

Asthma symptom scores of 1 or more (from the daily record card) on at least 4 out of the last 7 days, with either: 1) a forced expiratory volume in one second (FEV_1) reversibility of at least 15% (during the last 3 months); 2) a diurnal variation of ±15% on 4 out of the last 7 days; or 3) a need for two or more doses of β_2-agonist rescue medication each day for the last 7 days, with either: i) an FEV_1 of 80% or less of predicted; or ii) a mean morning peak flow of 80% or less of predicted, during the last 7 days.

Patients were excluded if they had: altered their normal asthma medication (apart from "rescue" doses of short acting β_2-agonists) during the run-in period; were on systemic corticosteroids above 10 mg daily or investigational therapies during the one month preceding the prestudy visit; were suspected of being hypersensitive to inhaled corticosteroids or components of the formulation; had concomitant disease likely to complicate the evaluation of the study drug; were pregnant or lactating (women of child-bearing potential were only included if the investigator considered that they were taking adequate contraceptive precautions); or were current cigarette smokers, or past smokers with a history of more than 10 pack years smoking.

Of the 862 adult patients screened, 671 were randomized to treatment and their results are detailed in this report. Two hundred and twenty five patients received FP, 1 mg daily, 225 patients received FP, 2 mg daily, and 221 patients received BUD, 1.6 mg daily. The patient characteristics are shown in table 1. All groups were well-matched for sex, age, race, smoking habits, use of a spacer, duration of asthma and prestudy medication. All patients gave their informed consent and the study was approved by local Ethics Committees.

Study design

The study was of a double-blind, double-dummy, parallel-group and randomized design (stratified for the use of oral corticosteroids prestudy). The study was designed to assess the relative safety and efficacy of the two inhaled corticosteroids at high doses in patients with severe

Table 1. – Patient characteristics

Parameter	FP 1 mg daily	FP 2 mg daily	BUD 1.6 mg daily	Total
Patients n	225	225	221	671
Sex % M/F	47/53	50/50	48/52	48/52
Caucasian n (%)	205 (91)	204 (91)	205 (93)	614 (92)
Smokers n (%)	21 (9)	17 (8)	26 (12)	64 (10)
Median age yrs (range)	51 (18–70)	48 (18–70)	50 (18–70)	49 (18–70)
Duration of asthma				
<1 yr n (%)	3 (1)	9 (4)	3 (2)	15 (2)
>10 yrs n (%)	143 (64)	128 (57)	125 (57)	396 (59)
Spacer used n (%)	133 (59)	138 (61)	132 (60)	403 (60)
Concurrent asthma medications*				
Methylxanthines n (%)	75 (33)	61 (27)	64 (29)	200 (30)
Anticholinergics N (%)	14 (6)	10 (4)	13 (6)	37 (6)
Other anti-inflammatory agents n (%)	10 (4)	8 (4)	6 (3)	24 (4)
Long-acting β_2-agonists n (%)	24 (11)	21 (9)	17 (8)	62 (10)
Oral steroids fixed dose (<10 mg·day^{-1}) n (%)	30 (13)	26 (12)	21 (10)	77 (11)
Run-in inhaled steroid mean dose mg·day^{-1}	1.24	1.20	1.16	1.20

*: excluding short acting β_2-agonists. FP: fluticasone propionate; BUD: budesonide; M: male; F: female.

asthma. Due to formulation differences, a direct dose comparison was not feasible. After a run-in period of 2 weeks, patients were randomized for 6 weeks, and then followed-up 2 weeks after treatment had ceased.

During the 2 week run-in period, patients took their inhaled bronchodilator on an as required basis and all other asthma medication, including their usual inhaled corticosteroid therapy, at a constant dose.

At the start of the treatment phase, patients stopped their current inhaled corticosteroid and were randomized to one of the following: 1) FP 1 mg daily (four 125 μg actuations inhaled from a pressurized inhaler twice daily, along with four actuations of placebo); 2) FP 2 mg daily (four 250 μg actuations inhaled as above, twice daily with four actuations of placebo); or 3) BUD 1.6 mg daily (four 200 μg actuations inhaled as above, twice daily with four actuation of placebo). Throughout the duration of the study, patients continued taking their other asthma medication at a constant dose. Rescue medication, such as salbutamol, was permitted on an as required basis. Appropriate large volume spacer devices were supplied for those patients who required them, provided that their use was constant throughout the study period.

Protocol

Patients measured their peak expiratory flow (PEF) with a Mini-Wright peak flow meter in the morning (at 7.00–8.00 a.m.) and evening (at 7.00–8.00 p.m.) before taking their treatment inhalers or using salbutamol. On each occasion, the highest of three readings was recorded on the daily record card. Their asthma symptoms, both day and night, using four-point rating scales were also recorded. Symptoms during the day were rated as follows: 0=no asthma, normal unrestricted activity; 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=asthma bad, could not go to work or do housework or carry out usual activities because of shortness of breath. Nocturnal symptoms were rated as follows: 0=good night, slept well no asthma; 1=good night, slept well but woke once early with wheeze or cough; 2=woken two or three times by the cough/wheeze/breathlessness/asthma; 3=bad night, awake most of the night with cough/wheeze/breathlessness/asthma. Patients also recorded the number of times they had used their salbutamol inhaler.

After the initial visit, patients attended the clinic at the end of the run-in period, after 3 and 6 weeks of treatment, and at the end of the 2 week follow-up period. At each of these visits, PEF, FEV_1 and forced vital capacity (FVC) were recorded. Where possible, measurements were made at the same time of day (preferably in the morning), and patients were asked not to use their inhaled bronchodilator for 4 h before attending the clinic. Oropharyngeal swabs, to determine the presence of *Candida albicans*, were taken if there was clinical evidence of infection on visual examination.

Adverse events

All serious and minor adverse events were recorded irrespective of their likely causality. Serious adverse events were defined as: death; life-threatening events; disabling or incapacitating events; events requiring or prolonging hospitalization; any congenital abnormality; cancer; drug overdose; and any other clinical or laboratory event with associated clinical signs or symptoms.

Laboratory tests

Blood samples for haematology, biochemistry, bone markers and cortisol levels were taken between 8.00 and 10.00 a.m. at each of 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 serum cortisol samples and bone markers were analysed centrally. Early morning urine samples were collected up to 4 h from waking at each of the clinic visits for the analysis of bone markers.

The procollagen type 1 (PICP) assay was carried out using a competitive immunoassay, double antibody technique (Orion Diagnostica, Finland). One hundred millilitres of sample was mixed with 200 ml of PICP antiserum and 200 ml of I^{125}-labelled PICP. After a 2 h incubation at 37°C, separation reagent (second antibody covalently bound to solid particles) was added and the tubes allowed to stand for a short while before centrifugation. The supernatant was discarded and the sediment counted in a gamma counter. At a concentration of 137 $mg \cdot l^{-1}$, the between batch coefficient of variation (CV) was found to be 3.7% (A. Marcham, Biochemical Markers of Bone Disease. MSc thesis, London University, UK, 1993).

The telopeptide (ICTP) (ICTP = carboxyterminal telopeptide region of type 1 collagen, cross-linked *via* pyridinoline cross-links) assay (Orion Diagnostica, Finland) was carried out as outlined for the PICP assay, except that I^{125}-ICTP was the tracer, and the separation reagent comprises polyethylene glycol (PEG) in PBS buffer, containing goat anti-rabbit gamma globulin. At a concentration of 6.2 $mg \cdot l^{-1}$, the between batch CV was 5.3% (A. Marcham, Biochemical Markers of Bone Disease. MSc thesis, London University, UK, 1993).

The osteocalcin assay was also based on a competitive radioimmunoassay, double antibody technique (CIS bio international, France). The 50 ml of sample was added to 200 ml of I^{125}-osteocalcin and 100 ml of anti-osteocalcin (rabbit anti-bovine) second antibody. The solution was mixed gently using a vortex type mixer and incubated for 20–24 hours at 2–8°C. After centrifugation, the sediment was counted in a gamma counter. At a concentration of 3.8 $mg \cdot ml^{-1}$, the between batch CV was 6.6% (A. Marcham, Biochemical Markers of Bone Disease, MSc thesis, London University, UK, 1993).

The serum cortisol assay was carried out using a coated tube method radioimmunoassay. The between batch CV was 7.0% (West Middlesex University Hospital, London, UK).

The urinary hydroxyproline assay measured both free and peptide bound hydroxyproline in the urine. The method measured both fractions, *i.e.* total urinary hydroxyproline. Urine samples were first hydrolysed with hydrochloric acid to release peptide bound hydroxyproline. The total hydroxyproline was then reacted with phenylisothiocyanate to form a phenylthiocarbonate. Phenylthiocarbonates formed with hydroxyproline and other amino acids are then separated using reversed phase high performance liquid chromatography (RP-HPLC), and quantitated by detection at 254 nm. Results may be expressed as a concentration or as a hydroxyproline/creatinine ratio. The between batch CV was 6.5% (West Middlesex University Hospital, London, UK).

Analysis

Statistical analyses were carried out using SAS (release 6.04) 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 1–42, 15–21 and 36–42. To be included in the analysis of a variable, patients were to have provided data for at least one day during the run-in period, and for at least one day in any treatment assessment period. The mean morning and evening PEF were calculated over each period for each patient, and expressed as absolute values and as percentage of predicted values. Predicted lung function values (European Coal and Steel Community (ECSC)) were calculated from sex, age and height using standard formulae [7].

Diary card PEFs and other lung function values, together with serum cortisol concentrations, were analysed by analysis of covariance, adjusting for baseline, country, sex, spacer, age, treatment and prestudy use of oral steroids. For the percentages of symptom-free days/nights the percentage of rescue-free days/nights, and the use of additional day/night-time salbutamol, the differences from baseline were obtained for each of the three treatment periods (days 1–42, 15–21, 36–42) and the differences between treatments compared using the Wilcoxon rank sum test, adjusted according to country using the van Elteren method [8]. The median symptom scores were also calculated, tabulated and analysed in the same way. The numbers of patients reporting an adverse event in each treatment group were compared using the Fisher's exact test [9]. For lung function and serum cortisol variables, p-values were calculated from adjusted mean data and values less than 0.05 were considered significant. Tabulated values may be subject to rounding.

Results

Efficacy

Daily PEF. Over the 42 days of treatment, all treatments increased the mean PEF, but patients taking FP 1 mg daily and FP 2 mg daily improved their mean morning PEF and % predicted mean morning PEF more than those on BUD ($p<0.05$) (fig. 1 and table 2). Mean evening PEF also improved on all treatments, and patients on FP 2 mg daily improved more than the other two treatments (difference in adjusted mean FP 2 mg *vs* 1 mg 7 $l \cdot min^{-1}$ (0–15 confidence interval), p=0.05, FP 2 mg *vs* BUD 12 $l \cdot min^{-1}$ (5–20); $p<0.001$ *vs* BUD) (fig. 2 and table 2). A reduction in the diurnal variation in PEF after 6 weeks of treatment was greater for the patients on FP than those on BUD ($p<0.05$) (table 2). An additional analysis was made of those patients who had shown a deterioration or improvement of 10% or more from baseline in their % predicted morning PEF. The ratio of patients showing improvement to deterioration was greater in those patients on FP 2 mg than those on BUD 1.6 mg (ratio of 10.6 and 2.1, respectively; p=0.004). No difference was seen when comparing FP 1 mg with BUD 1.6 mg daily (ratio of 4.5 and 2.1; p=0.23) (fig. 3).

Clinic lung function. Pulmonary function measurements (PEF, FEV_1, FVC) recorded after 6 weeks of treatment showed improvement in all parameters for all treatments (table 2). Patients taking FP at either dose improved more than those taking BUD for PEF and FEV_1 ($p<0.05$). Improvements in FVC were greater on FP 2 mg than on the other two treatments (p=0.001 *vs* BUD) (table 2).

Asthma symptom scores and rescue medication. The median values for daytime and night-time symptom scores were compared before and during teatment and found not to change for all three treatments. However, there were differences if these values were expressed as % of patients improving compared to the % of patients worsening on each treatment (table 3). More patients taking FP 1 mg daily had an improvement in % of symptom-free days and in the reduction of usage of rescue medication than patients on BUD. Fifty percent showed a improvement in symptom-free days, whereas on BUD it was 44% (p=0.048). In the FP 1 mg daily group 48%

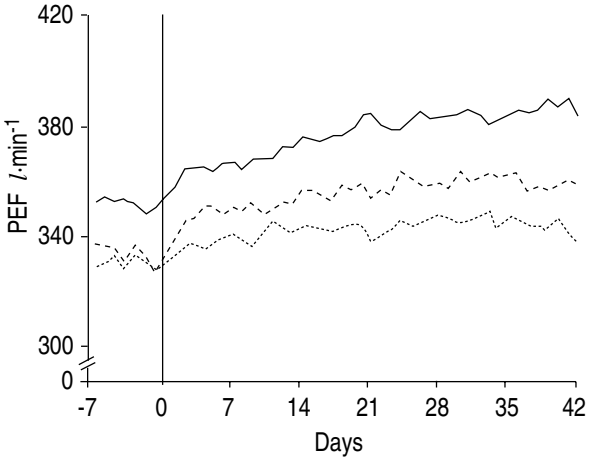

Fig. 1. – Mean morning peak expiratory flow rates (PEF) over the 6 weeks of treatment with FP 1 mg daily (- - - - - - -), FP 2 mg daily (———) and budesonide 1.6 mg daily (·····). Note that vertical axis is cut-off from zero. FP: fluticasone propionate.

Table 2. – Lung function data

	FP 1 mg daily			FP 2 mg daily			BUD 1.6 mg daily			Diff. in adjusted mean (95% CI)	
	Baseline mean	Mean change	Adjusted mean change	Baseline mean	Mean change	Adjusted mean change	Baseline mean	Mean change	Adjusted mean change	FP 1 mg *vs* BUD	FP 2mg *vs* BUD
Daily PEF a.m. (1–6 week) $l \cdot min^{-1}$	335	21	19	352	24	24	330	13	10	9* (2–17)	13† (6–21)
Daily PEF a.m. (1–6 week) % pred	75	5	4	77	5	5	73	3	2	2* (0–4)	3† (1–5)
Daily PEF p.m. (1–6 week) $l \cdot min^{-1}$	365	11	12	377	18	20	356	8	7	5 (-2–13)	12† (5–20)
Daily diurnal variation (6 week) $l \cdot min^{-1}$	29	-10	-5	24	-8	-5	25	-2	1	-6* (-11– -1)	-6* (-11– -1)
(n)	(223)	(223)	(223)	(222)	(222)	(222)	(216)	(216)	(216)		
Clinic PEF $l \cdot min^{-1}$	329	34	32	354	37	39	325	22	17	15* (1–30)	22** (8–37)
(n)	(210)	(210)	(210)	(208)	(208)	(208)	(210)	(210)	(210)		
Clinic FEV_1 l	1.91	0.21	0.22	2.02	0.26	0.28	1.9	0.12	0.12	0.1* (0.02–0.18)	0.17† (0.8–0.25)
(n)	(210)	(210)	(210)	(209)	(209)	(209)	(202)	(202)	(202)		
Clinic FVC l	3.0	0.18	0.18	3.14	0.24	0.26	3.07	0.11	0.11	0.07 (-0.02–0.16)	0.15† (0.06–0.24)
(n)	(209)	(209)	(209)	(207)	(207)	(207)	(202)	(202)	(202)		

(n): patient numbers. FP: fluticasone propionate; BUD: budesonide; 95% CI: 95% confidence interval; PEF: peak expiratory flow;

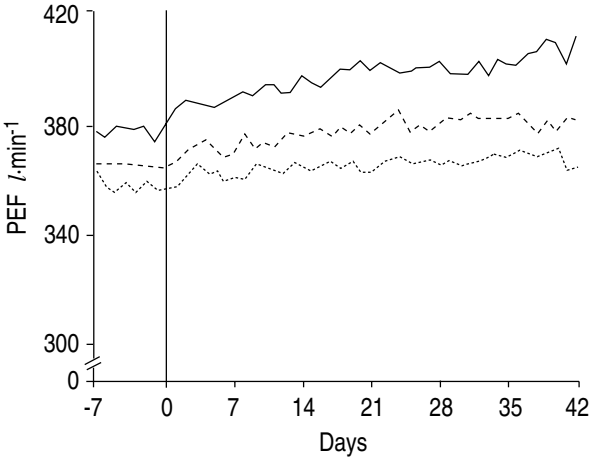

Fig. 2. – Mean evening peak expiratory flow rate (PEF) over 6 weeks of treatment with FP 1 mg daily (- - - - - - -), FP 2 mg daily (———) and budesonide 1.6 mg daily (·····). Note that the vertical axis is cut-off from zero. FP: fluticasone propionate.

of patients reduced their use of rescue medication, and in the BUD group it was 38% (p=0.017). However, there were no significant differences between FP 1 mg daily and BUD for daytime asthma scores, % symptom free nights, night-time asthma scores, % rescue-free days, frequency of daytime rescue and % rescue-free nights.

More patients taking FP 2 mg daily had an improvement in daytime symptom score, night-time symptom score, and in reduction of usage of rescue medication than patients on BUD. Twenty seven percent showed an improvement in daytime symptom scores, and 28% showed an improvement in night-time symptom scores. This compares with 23% both for daytime (p=0.029) and night-time symptom scores (p=0.050) in the BUD group.

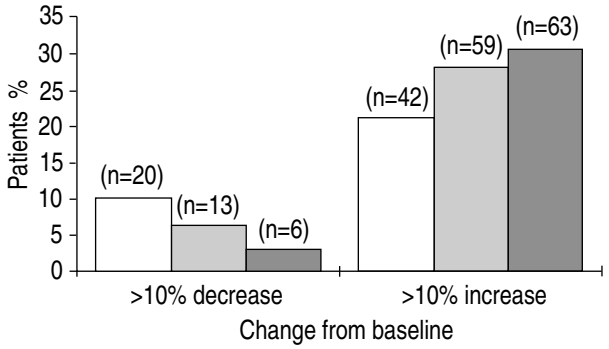

Fig 3. – Morning (% pred) peak expiratory flow rate changes from baseline at week 6. □ : budesonide, 800 µg *b.i.d.*; ▨ : FP 1 mg daily; ■ : FP 2 mg daily.

In the FP 2 mg daily group 50% of patients reduced their use of night-time rescue medication, and in the BUD group 38% (p=0.006). However, there were no significant differences between FP 2 mg daily and BUD for % symptom-free days, % symptom-free nights, % rescue-free days, frequency daytime rescue and % rescue-free nights.

Forty nine patients (22%) in the BUD group, 38 patients (17%) in the FP 1 mg group and 37 patients (16%) in the FP 2 mg group experienced asthma exacerbations. The proportion of patients requiring courses of rescue corticosteroids was 21 patients (10%) in the BUD group, 15 patients (7%) in the FP 1 mg group, and 10 patients (4%) in the FP 2 mg group (table 3).

Safety

Serum cortisol levels and biochemical markers of bone metabolism. The mean serum cortisol values of all groups

Table 3. – Asthma symptoms, rescue medication, asthma exacerbations and oral steroid requirements

		FP 1 mg daily	FP 2 mg daily	BUD 1.6 mg daily
Symptom-free days	% improved	50	51	44
(1–6 week)	% worsened	13	13	21
p-value *vs* BUD (1–6 week)		0.048	0.101	-
Day time asthma scores	% improved	30	27	23
(1–6 week)	% worsened	5	4	12
p-value *vs* BUD (1–6 week)		0.161	0.029	-
Symptom-free nights	% improved	44	52	46
(1–6 week)	% worsened	24	23	25
p-value *vs* BUD (1–6 week)		0.964	0.116	-
Night-time asthma score	% improved	21	28	23
(1–6 week)	% worsened	8	7	16
p-value *vs* BUD (1–6 week)		0.058	0.050	-
Rescue-free days	% improved	42	44	46
(1–6 week)	% worsened	26	23	26
p-value *vs* BUD (1–6 week)		0.592	0.275	-
Freq daytime rescue med	% improved	27	29	31
(1–6 week)	% worsened	12	14	13
p-value *vs* BUD (1–6 week)		0.964	0.975	-
Rescue-free nights	% improved	46	42	42
(1–6 week)	% worsened	10	15	12
p-value *vs* BUD (1–6 week)		0.055	0.635	-
Freq night time rescue	% improved	48	50	38
(1–6 week)	% worsened	11	10	18
p-value *vs* BUD (1–6 week)		0.017	0.006	-
Patients exacerbating	%	17	16	22
Patients requiring rescue oral steroids	%	7	4	10
p-value *vs* BUD (1–6 week)		0.354	0.054	-

Median values were measured for symptom scores and rescue medication usage before and during treatment and no significant changes were detected in the median values for any treatments. No differences were observed between FP 2 mg and FP 1 mg daily when % improved and % worsened analysis was performed. FP: fluticasone dipropionate; BUD: budesonide.

Table 4. – Serum and urine biochemical markers of bone metabolism

	FP 1 mg daily		FP 2 mg daily		BUD 1.6 mg daily	
	Baseline median	Post-treatment median	Baseline median	Post-treatment median	Baseline median	Post-treatment median
Serum calcium $nmol \cdot l^{-1}$	2.34 (198)	2.32 (198)	2.35 (200)	2.31 (200)	2.33 (191)	2.31 (191)
Serum osteocalcin $ng \cdot ml^{-1}$	3.7 (169)	4.3 (169)	4.1 (162)	4.1 (162)	4.1 (150)	4.4 (150)
Serum procollagen (PICP) $\mu g \cdot l^{-1}$	108 (176)	113 (176)	104 (176)	106 (176)	102 (167)	105 (167)
Serum cross-links (ICTP) $\mu g \cdot l^{-1}$	2.0 (181)	2.2 (181)	2.1 (162)	2.1 (162)	2.1 (157)	2.2 (157)
Urine hydroxyproline/ creatinine ratio	1527 (182)	1578 (182)	1629 (183)	1625 (183)	1624 (172)	1628 (172)

Values in parenthesis signify patient numbers. PICP: procollagen type 1; ICTP: carboxyterminal telopeptide region of type 1 collagen, cross-linked *via* pyrindinolone cross-links; FP: fluticasone propionate; BUD: budesonide.

Table 5. – Summary of most common adverse events: number of patients experiencing a particular adverse event

	FP 1 mg daily		FP 2 mg daily		BUD 1.6 mg daily	
Patients n	225		225		221	
Patients with adverse events n	137	(61)	110	(49)	112	(51)
Asthma and related events	30	(13)	26	(12)	39	(18)
Upper respiratory tract infection	25	(11)	22	(10)	14	(6)
Hoarseness	13	(6)	7	(3)	6	(3)
Headache	12	(5)	15	(7)	13	(6)
Musculoskeletal pain	11	(5)	12	(5)	8	(4)
Respiratory infection	10	(4)	3	(1)	4	(2)
Sore throat	10	(4)	9	(4)	4	(2)
Influenza	8	(4)	4	(2)	1	(<1)
Rhinitis	8	(4)	3	(1)	6	(3)
Candidiasis: mouth	7	(3)	9	(4)	10	(5)
Cough	7	(3)	13	(6)	10	(5)

Percentage values are presented in parentheses. Most common is defined as 4% or more patients experiencing an adverse event from any treatment group. FP: fluticasone propionate; BUD: budesonide.

before treatment were within the normal range (lower limit of normal 150 nmol·l^{-1}). The ratio calculated as the mean value after treatment divided by the mean value at baseline was 1.04 for FP 1 mg daily, 0.97 for BUD and 0.88 for FP 2 mg daily. All mean serum cortisols after treatment remained within the normal range and were similar between the three groups. The geometric mean value for patients on FP 1 mg rose during treatment (274 nmol·l^{-1} (Visit 1) to 286 nmol·l^{-1} (Visit 3)), whilst those on BUD and FP 2 mg fell (293 nmol·l^{-1} (Visit 1) to 285 nmol·l^{-1} (Visit 3)) and (276 nmol·l^{-1} (Visit 1) to 243 nmol·l^{-1} (Visit 3)), respectively. Serum cortisol levels were reduced after treatment in the FP 2 mg group when compared with the reduction for BUD ($p<0.01$) and the increase for FP 1 mg ($p<0.001$).

Markers of bone metabolism are shown in table 4. The median values before and after treatment showed no significant changes in any of the measurements of bone formation or resorption.

Adverse events

During treatment, adverse events were reported by a total of 359 patients. Of these, 137 (61%) received FP 1 mg daily, 110 (49%) received FP 2 mg daily and 112 (51%) received BUD. The most common adverse events (incidence >4% in a treatment group) are shown in table 5. Asthma and related events were reported with a higher incidence in the BUD group (39 patients; 18%) compared with FP 1 mg daily (30 patients; 13%) and FP 2 mg daily (26 patients; 12%). Other adverse events occurred with a similar frequency in all treatment groups, and there was no evidence that events were associated with a dose effect or treatment duration effect. Bruising, menstrual problems, weight gain and oedema were reported as adverse events in less than three patients per group.

Discussion

The aim of this study was to determine, in a controlled study in moderate to severe asthmatic patients, the comparative efficacy on morning peak flow of FP and BUD given by MDI. The lung function results showed consistently that FP was more effective than BUD when given *via* an MDI in improving all parameters measured, either daily by the patient or by the physician at the clinic visits. The rank order of effectiveness was FP 2 mg > FP 1 mg > BUD 1.6 mg. In some lung function parameters, *e.g.* FEV_1, the increases were higher than expected, considering that the patients were already being treated with relatively high doses of inhaled corticosteroid prior to the study. Although this study demonstrates that FP offers a statistically significant benefit over BUD when given *via* an MDI, the clinical relevance needs to be established with longer studies that examine parameters such as rates of exacerbations and asthma control. The results from this study help confirm the findings from two open studies in adult asthmatic patients, which have shown that when given *via* an MDI, FP at half the dose of BUD was just as effective in improving function and, in the second study, when given *via* dry powder devices (Diskhaler®/Turbuhaler®) FP, again at half the dose, was more effective than BUD ($p<0.05$) [10, 11].

Improvements in asthma symptom scores were not as consistent as seen with the lung function results, with only 5 out of 16 parameters being significant. One explanation for why the benefits were not consistent across all parameters may be that some symptom questions are more sensitive measures of the disease than others, or that in a short-term study lung function changes precede symptom improvements. Longer duration studies should help explain this disparity.

A double-blind, double-dummy study was used to overcome the different designs of the FP and BUD inhalers and the difference in unit doses per actuation. Ideally, the study would have examined equal doses both of FP and budesonide. Since we wished to study moderate to severe asthmatics, as we believed that FP may be beneficial in this population, we were therefore restricted to the 1.6 mg daily dose of budesonide, the maximum registered dose in most European countries. The FP doses

of 1 and 2 mg daily were placed on either side of the budesonide dose to enable a comparison to be made. Doses of the treatments were to be given morning and evening, therefore, the formulation of the drugs (200 μg per actuation MDI budesonide, 125 or 250 μg per actuation MDI FP) restricted the FP doses to 1 and 2 mg daily. The inclusion of additional placebo inhaler to enable either a 1.5 or 0.75 mg daily dose was considered, but rejected, as it was considered that patient compliance might be affected. With 220 patients per treatment and a residual standard deviation of 40 $l \cdot min^{-1}$, this study had approximately 90% power in declaring two treatments equivalent, when the 95% confidence interval (CI) for a treatment difference in PEF, was contained within ±13 $l \cdot min^{-1}$.

Safety monitoring showed that all treatments were well-tolerated. The incidence of side-effects was low and not related to the inhaled corticosteroid used, dose of corticosteroid or duration of treatment. Serum cortisol monitoring rather than bone markers seemed to be the most sensitive assay undertaken in this study for the measurement of the systemic effect of inhaled corticosteroids. The fall in mean cortisol level on FP 2 mg was significantly greater than the other two treatments, indicating some systemic activity possibly by absorption *via* the respiratory tract, however, the mean level remained well within the normal range.

This 2 mg daily dose would appear to be most beneficial to gain control of disease unresponsive to other treatments, and may reduce the need for oral corticosteroids [12]. Further studies with BUD and BDP have demonstrated a fall in serum cortisol of between 10–25% at a dose of 2 mg daily, which compares with a fall in serum cortisol of 12% on FP 2 mg daily, seen in the present study [13, 14]. A recent study comparing FP 2 mg daily, with BDP 1.6 mg daily, also showed an effect of FP 2 mg on serum cortisol comparable with that seen in this study. However, the lack of difference in clinical efficacy was likely to have been due to the low observed power (65% at $p<0.05$) [15]. This suggests that all three drugs have a similar systemic effect at equal doses.

Beclomethasone diproprionate and BUD appear to have a similar systemic activity at a dose of 2 mg daily when studying the effect on markers of bone metabolism [16]. Markers of bone metabolism, both in the serum and urine, showed no significant changes for any of the treatments in this study. Further studies and analysis of such parameters and studies examining bone density over longer periods are necessary to fully evaluate the effect of inhaled corticosteroids on growth and bone mass.

In conclusion, this study has shown FP, at 1 and 2 mg daily, to be more effective in treating patients with severe asthma than BUD, 1.6 mg daily, when given *via* an MDI, in terms of improved lung function, although the improvements in symptom scores were less marked.

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