

Fluticasone propionate – an update on preclinical and clinical experience

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Fluticasone propionate (FP) is a novel androstane glucocorticoid with potent anti-inflammatory activity which has been effectively used, intranasally, as therapy for seasonal and allergic perennial rhinitis. When taken by the inhaled route, FP has shown significant therapeutic efficacy in the management of asthma. Fluticasone propionate is a highly lipophilic molecule with good uptake, binding and retention characteristics in human lung tissue. Fluticasone propionate has high glucocorticoid receptor selectivity and affinity, demonstrating rapid receptor association and slow receptor dissociation. *In vitro*, FP has been shown to potently inhibit T lymphocyte proliferation, cytokine generation, tumour necrosis factor alpha (TNF- α)-induced adhesion molecule expression, interleukin-5-induced eosinophilia, mucosal oedema and toluene 2,4-diisocyanate-induced mast cell proliferation, while promoting secretory leucocyte protease inhibitor production and eosinophil apoptosis. In human studies, FP has demonstrated marked vasoconstrictor potency in normal subjects and inhibited antigen-induced mucosal platelet activating factor/eicosanoid production, T lymphocytes and CD25+ cells in patients with rhinitis. Biopsy data from mild asthmatics demonstrate FP-associated reduction in CD3, CD4, CD8 and CD25 cells, with an accompanying reduction in eosinophil and mast cell markers. Clinical studies have evaluated lung function, bronchial reactivity, exacerbation rates and oral corticosteroid-sparing effect. Results show that FP has at least twice the clinical potency of beclomethasone dipropionate and budesonide. This appears to be achieved without an accompanying increase in systemic effects, suggesting a therapeutic index which may be higher than other currently available inhaled corticosteroids.

Introduction

Fluticasone propionate (FP) is the latest in a range of inhaled corticosteroids indicated for the treatment of asthma. Evidence from clinical trials suggests that it has improved efficacy compared to other currently available inhaled corticosteroids, and that this heightened therapeutic effect is achieved without an accompanying increase in systemic activity. Overall, the data suggests that FP may have a higher therapeutic index than other currently available inhaled corticosteroids.

The aim of this review is to provide an update of the data from the many preclinical, pharmacokinetic and clinical studies which have examined the effects of FP in the management of asthma.

Preclinical Studies

DEPOT FORMATION AND TISSUE BINDING

Unlike most other corticosteroids, the structure of FP is based on the androstane, rather than the

pregnane, corticosteroid nucleus. It is a highly lipophilic molecule (1), a characteristic which has been shown to play a major role in dictating the drug's pharmacological profile, particularly with regard to lung tissue interaction. For example, FP has a dissolution time in human bronchial fluid of several hours, while more hydrophilic corticosteroids, such as flunisolide and budesonide have bronchial dissolution times of only a few minutes (2). This is relevant to both metered dose inhalers and powder delivery systems because particulate matter impacts on the airway mucosa. If this particulate matter has a long dissolution time, a drug depot can be formed within the airway tissue, enabling a sustained duration of action.

High lipophilicity also has important implications for the way in which corticosteroids are taken up and retained in lung tissue. A clear correlation has been observed (Fig. 1) (3) between lipophilicity and binding to lung tissue, with the lipophilic compounds FP, beclomethasone dipropionate (BDP) and beclomethasone-17-monopropionate (BMP), exhibiting more rapid and greater binding activity than

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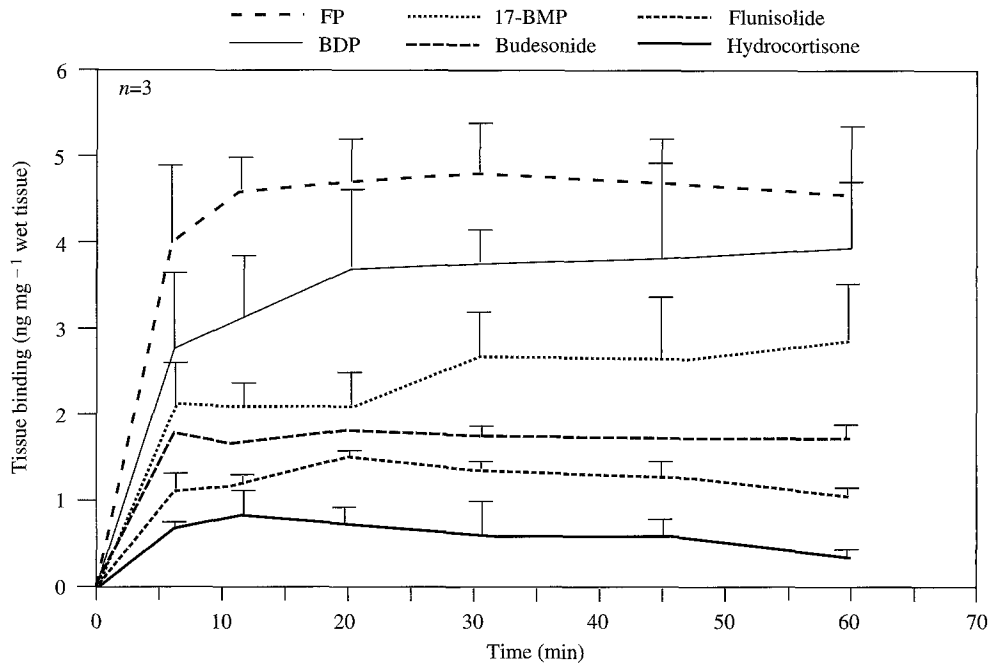


Fig. 1 Tissue binding of glucocorticoids to human lung tissue. FP, fluticasone propionate; BDP, beclomethasone dipropionate; 17-BMP beclomethasone-17-monopropionate. Source: Högger *et al.* (3).

more hydrophilic compounds such as budesonide, flunisolide and hydrocortisone. Fluticasone propionate had the highest level of lipophilicity among the compounds measured by Högger and Röhdewald (2) and also exhibits the greatest degree of lung tissue binding, approximately 4.89 ng mg^{-1} .

In therapeutic use, it is not just the rate and extent of uptake that is important, but also how much of the drug is subsequently retained in the lungs. This has also been studied *in vitro* by Högger and Röhdewald (2). In their study, once corticosteroid uptake into lung tissue had occurred, the tissue was placed into human plasma until equilibration took place. When the amount of drug remaining in the lung tissue was then determined, FP was found to have an equilibrium retention value of 2.2 ng mg^{-1} , while flunisolide and budesonide had values of 0.5 and 1.0 ng mg^{-1} , respectively, further demonstrating the potential advantage of high lipophilicity.

This is also reflected in preliminary data from patients undergoing lung resection. Subjects were given 1 mg of inhaled FP prior to surgery. Sample lung tissue and blood were taken during surgery and assayed for FP levels. During a period of 180–330 min after surgery, the ratio of FP in the lung compared to plasma ranged from 78:1 to 152:1 (4). Published data with budesonide using the same

methodology showed a lung to plasma ratio of approximately 9:1 (5).

RECEPTOR AFFINITY AND KINETICS

Having been retained in the lung tissue, a drug has to interact with its receptor to exert its pharmacological activity. The ability of corticosteroids to undergo such interaction can be determined by competition assays or by study of binding kinetics. Both of these methods have shown that FP has a high affinity for the human glucocorticoid receptor (2,6,7), approximately 20-fold greater than dexamethasone (2,7). In addition, FP has been found to have high glucocorticoid receptor selectivity (9), with fast receptor association and slow receptor dissociation (Table 1) (2).

These receptor kinetics may have implications for the biological response of corticosteroids. When a corticosteroid molecule enters a cell and interacts with its receptor in the cytosol, the resulting complex either interacts with transcription factors in the cytosol or forms a dimer and penetrates the nucleus to interact with the target gene. It is thus the receptor complex which triggers the biological response to the corticosteroid. Therefore, the different corticosteroid-receptor association/dissociation rates that have been identified, have important implications for

Table 1 Association and dissociation rates for a range of corticosteroids with the human lung glucocorticoid receptor

	Association rate constant ($1 \text{ mol}^{-1} \text{ min}^{-1}$)	Dissociation rate constant (min^{-1})
Dexamethasone	8.8×10^5	10.2×10^{-3}
Methylprednisolone	5.5×10^5	23.6×10^{-3}
Triamcinolone acetonide	4.9×10^5	3.0×10^{-3}
Fluticasone propionate	23.9×10^5	11.6×10^{-4}

Source: Högger and Röhdewald (2).

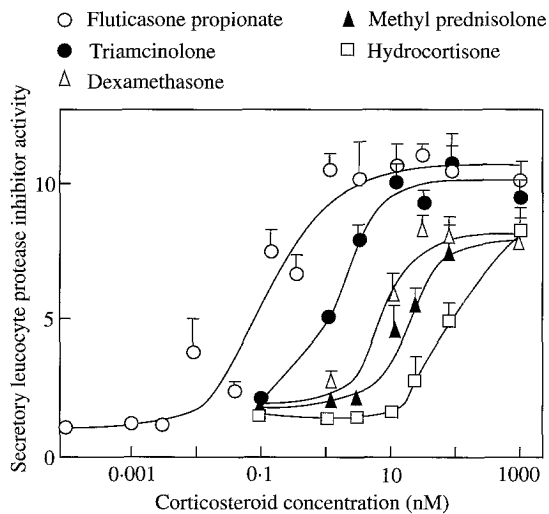


Fig. 2 Dose-dependent plateau response of secretory leucocyte protease inhibitor activity in the presence of a range of corticosteroids. Source: Abbinante-Nissen *et al.* (15).

corticosteroid differentiation. The rapid association and slow dissociation of FP for example, has been found to result in a corticosteroid-receptor complex with a half-life of 10 h, the longest half-life of any corticosteroid evaluated (2), compared with half-lives of 7.5 and 5.1 h for BMP and budesonide, respectively (2,6).

Biological activity in vitro

The anti-inflammatory activity of FP has been demonstrated by its effects on a number of inflammatory mediators and markers *in vitro*.

Fluticasone propionate has been found to potently inhibit anti-CD3-induced proliferation of T cells taken from normal volunteers, with a median effective dose (ED_{50}) value of approximately 0.3 nM. This compares with values of 0.8, 2.0 and 5.9 nM for budesonide, BMP and dexamethasone, respectively (9).

Table 2 Correlation of receptor affinity and protease inhibitor activity for a range of corticosteroids

	Receptor* affinity (EC_{50} ; ng ml^{-1})	Protease† inhibitor (EC_{50} ; nM)
Hydrocortisone	4.7	25.0
Dexamethasone	0.4	2.0
Methylprednisolone	1.0	5.0
Triamcinolone	0.2	1.0
Fluticasone propionate	0.02	0.1

*Human glucocorticoid receptor [See Derendorf *et al.* (7)];
†See Abbinante-Nissen *et al.* (15).

Fluticasone propionate also potently inhibits phytohaemagglutinin-stimulated proliferation of lymphocytes with almost complete inhibition at concentrations of FP as low as 10^{-10} M (10). The same level of inhibition required concentrations of between 10^{-8} M and 10^{-6} M for budesonide and BDP. Interestingly, in the same study, the proliferation of lymphocytes from corticosteroid-resistant patients could also be inhibited by FP with approximately 50% inhibition at 10^{-10} M. Inhibition was virtually complete at 10^{-8} M. Hydrocortisone was virtually inactive in the same system while budesonide and BDP showed only partial inhibition at high concentrations.

Cytokine generation is inhibited by FP in a range of human cells (11–14). In mast cell studies, for example, FP was found to have IC_{50} values of <1 nM for inhibition of interleukin-4 (IL-4), IL-6, IL-8 and tumour necrosis factor alpha (TNF- α) (14). In contrast, dexamethasone was found to have IC_{50} (inhibitory concentration of a receptor antagonist required to inhibit 50% of an agonist response) values of approximately 10 nM when assessed against the same individual parameters. This is consistent with the relative difference in receptor affinity, approximately 10-fold in favour of FP (4,7).

Table 3(a) Summary of clinical studies of fluticasone propionate vs. beclomethasone dipropionate

Reference	Patient numbers	FP daily dose (μg)	BDP daily dose (μg)	Treatment duration	Comparative efficacy*/safety	P-value
Dahl <i>et al.</i> (30)	$n=672$	100, 200 400,800 (MDI)	400 (MDI)	4 weeks	4:3 l min⁻¹ -Morning PEFR increase/daily dose -Evening PEFR increase/daily dose 3 l min ⁻¹	P=0.001 P=0.017
Fabbri <i>et al.</i> (31)	$n=274$	1500 (MDI)	1500 (MDI)	12 months	15 (CI 6,25) -Evening PEFR -Rescue medication -Clinic PEFR -FEV ₁ -Exacerbation rate -Cortisol	P<0.005 P<0.05 P<0.05 P<0.05 P<0.05 P<0.02 P=n.s.
Leblanc <i>et al.</i> (34)	$n=261$	200 (MDI)	400 (MDI)	4 weeks	4 (CI - 4,12) -Cortisol	P=0.368 P=0.006
Lundback <i>et al.</i> (35)	$n=585$ 6 weeks $n=489$ 12 months	500 (MDI) 500 (DH)	1000 (MDI)	6 weeks (12 months safety)	4 (CI - 5,14) MDI 6 (CI - 3,15) DH -Diurnal variation -Clinic PEFR -12 month clinic PEFR -12 month clinic FEV ₁ -Cortisol	P=0.361 P=0.214 P=0.03 P=0.013 P=0.02 P=0.025 P=n.s.
Bootsma <i>et al.</i> (58)	$n=281$	750 (MDI)	1500 (MDI)	3 weeks	Histamine PC₂₀ Ultra-nebulized distilled water FEV₁	P=0.094 P=0.926 P=0.365
Barnes <i>et al.</i> (32)	$n=154$	1000 (MDI)	2000 (MDI)	6 weeks	7 (CI - 21,7) -Diurnal variation -Clinic PEFR -Cortisol	P=0.346 P=0.038 P=0.046 P=0.026
Lorentzen and Dahl (36)	$n=235$	1000 (MDI)	2000 (MDI)	12 months	3 (CI - 19,24) (Clinic PEFR) -FEV ₁ 6 months -Reversibility 12 months -Cortisol 6 months -Cortisol 12 months	P=0.806 P=0.04 P=0.044 P=0.008 P=0.01

Concentrations required to inhibit epithelial cell cytokine production were slightly greater, with IC₅₀ values of 5 nM, 10 nM and 1 nM for inhibition of IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor, respectively. However, FP potently inhibited epithelial TNF- α generation, with an IC₅₀ value of 0.1 nM. Fluticasone propionate has also been shown to inhibit platelet-derived growth factor stimulated production of IL-1- β and IL-6 in human alveolar macrophage and fibroblast cells. The IC₅₀ value was found to be 0.1 nM for inhibition of IL-1- β and IL-6, respectively, in both cell types (13).

In addition to down-regulation of pro-inflammatory processes, corticosteroids also appear to exert anti-inflammatory activity by increasing endogenous anti-inflammatory mechanisms. One such mechanism is secretory leucocyte protease inhibitor (SLPI) produc-

tion. A study evaluating the ability of corticosteroids to increase SLPI production in human airway epithelial cells has demonstrated a clear concentration-dependent response (Fig. 2) (15). Potency is again seen to correlate with receptor affinity (Table 2) (7,15). Fluticasone propionate with the highest receptor affinity has the lowest EC₅₀ value in this assay compared with the other glucocorticoids tested.

Interestingly, receptor affinity has also been found to correlate with the level at which activity reaches a plateau; high affinity corticosteroids such as FP have a higher plateau of effect than lower affinity corticosteroids such as dexamethasone. This supports the emerging concept that corticosteroids may have differing levels of pharmacological efficacy. This concept has been clearly demonstrated for drugs acting at membrane receptors, but not as yet for drugs such

Table 3(b) Summary of clinical studies of fluticasone propionate vs. budesonide

Reference	Patient numbers	FP daily dose (µg)	Budesonide daily dose (µg)	Treatment duration	Comparative efficacy†/safety	P-value
Ayres <i>et al.</i> (37)	<i>n</i> =671	1000 (MDI) 2000 (MDI)	1600 (MDI)	6 weeks	9 (CI 2,17) 13 (CI 6,21) -Evening PEFR (2000 µg vs. BUD) -Diurnal variation (1000 µg and 2000 µg vs. BUD) -Clinic PEFR (1000 µg and 2000 µg vs. BUD) -Clinic FEV ₁ (1000 µg and 2000 µg vs. BUD) -Clinic FVC (2000 µg) -Cortisol (FP2 vs. BUD) -Cortisol (FP1 vs. BUD)	<i>P</i>=0.018 <i>P</i><0.001 <i>P</i> <0.001 <i>P</i> =0.028, <i>P</i> =0.024 <i>P</i> =0.041, <i>P</i> =0.003 <i>P</i> =0.015 <i>P</i> <0.01 <i>P</i> =0.001 <i>P</i> <0.01 <i>P</i> =n.s.
Langdon and Thompson (38)	<i>n</i> =157	200 (MDI)	400 (MDI)	8 weeks	8 (CI -15,31) -Cortisol	<i>P</i>=0.36 <i>P</i> =n.s.
Langdon and Capsey (39)	<i>n</i> =275	400 (DH)	800 (TH)	8 weeks	20 (CI 5,34) -Device preference -Cortisol	<i>P</i>=0.009 <i>P</i> =0.005 <i>P</i> =0.87

*Primary efficacy variable (**Bold text**)= Difference (FP minus BDP, or FP minus BUD mean and confidence intervals) in morning PEFR unless indicated. Other efficacy variables shown are those for which fluticasone propionate was statistically significantly better than BDP or BUD. FP, fluticasone propionate; BDP, beclomethasone dipropionate; BUD, budesonide; SCG, sodium cromoglycate; PEFR, peak expiratory flow rate; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; MDI, metered dose inhaler; DH, Diskhaler[®]; TH, Turbuhaler[®].

as corticosteroids, which exert their activity via intracellular receptor binding.

A relatively recently recognized property of corticosteroids is the ability to induce eosinophil cell death. Fluticasone propionate has been shown to be highly potent, with the ability to counter the effects of IL-5, an agent which attenuates the effects of corticosteroid-induced eosinophil cell death. While 1 ppm of IL-5 almost completely overcomes the effects of 100 nM dexamethasone, marked apoptosis is still observed when the same concentration of IL-5 is used in the presence of 1 nM FP (16).

Fluticasone propionate has also been studied for its effects on adhesion molecule expression. Human endothelial cells have been grown in culture and stimulated with TNF- α in the presence of increasing concentrations of FP (17). Although there is little inhibition of ICAM (intercellular adhesion molecule) expression, except at very high concentrations, FP does differ from earlier corticosteroids (18) in that there is a clear concentration-dependent inhibition of E-selectin and VCAM (vascular cell adhesion molecule) expression. In terms of ED₅₀, the potency of FP is around 20-fold and nine-fold greater than dexamethasone and budesonide, respectively.

In vivo anti-inflammatory activity

A range of *in vivo* studies have also demonstrated the anti-inflammatory activity of FP.

Guinea pigs treated with FP, 30 min before intratracheal administration of IL-5, have been compared to untreated and control animals also receiving IL-5. Eosinophil numbers in bronchoalveolar lavage fluid (BALF) were measured after 24 h. Fluticasone propionate was found to have potent inhibitory activity against IL-5-induced eosinophilia, with pretreated animals having BALF eosinophil concentrations similar to those of control animals (19).

Inhibition of histamine challenge-induced mucosal oedema, a model not traditionally recognized as being highly corticosteroid responsive, has also been investigated (20). There was some inhibition with BDP at the earliest time, but this was rapidly lost. In contrast, however, FP, at 10% of the dose of BDP, gave a marked and longer lasting response.

In a further study, a 5% toluene diisocyanate solution was administered intranasally to rats, over an 8-week period, to increase mast cell proliferation in rat nasal mucosa. Fluticasone propionate treatment was found to potently inhibit this response, an intranasal dose of 50 µg day⁻¹ reducing mast cell

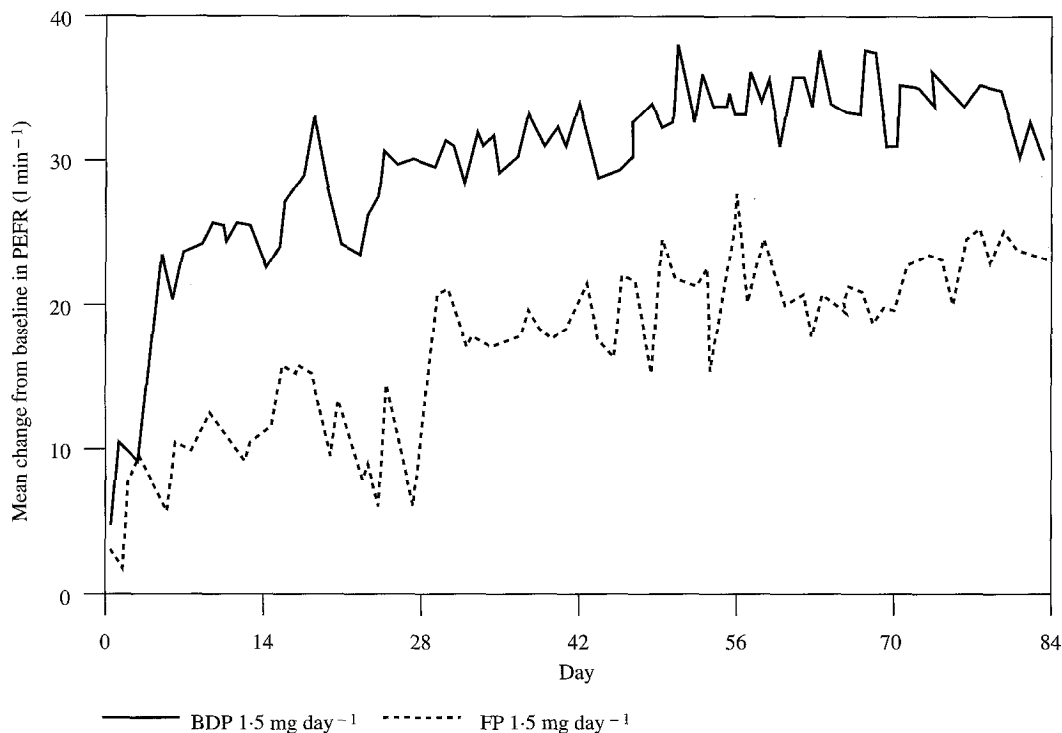


Fig. 3 Mean change from baseline in peak expiratory flow rate (PEFR) for the same dose of fluticasone propionate (FP) and beclomethasone dipropionate (BDP) (1.5 mg day^{-1}). Source: Fabbri *et al.* (31).

numbers to basal levels (21). The study demonstrates the ability of FP to decrease inflammatory cell accumulation induced by an intranasal stimulus.

Human volunteer studies

A number of *ex vivo* studies have evaluated the biological effects of FP. Two recent studies have used the MacKenzie skin vasoconstrictor test to rank the anti-inflammatory profile of corticosteroids by evaluating the blanching effect after topical administration (9,22). English *et al.* (9) found that FP had a vasoconstrictor potency at least two- to three-fold greater than budesonide and BDP over the linear portion of the dose-response curve. In contrast, Andersson *et al.* (22) concluded that FP had comparable effects to BUD. However, if only the linear portion of the dose-response curve, rather than the entire sigmoid curve, was analysed, the results were comparable to those of English *et al.* (9).

Fluticasone propionate has also been shown to inhibit antigen-induced mucosal platelet activating factor and eicosanoid production in normal volunteers (23). Additionally, in patients with rhinitis, FP has been shown to reduce nasal eosinophil and basophil numbers (24), while also inhibiting the pro-

duction of antigen-induced mucosal T lymphocytes and CD25+ cells (25).

When a 3-month study involving twice-daily administration of FP, 1 mg, was carried out in mild asthmatics, biopsy data showed a marked reduction in CD3, CD4, CD8 and CD25 cells, with an accompanying reduction of eosinophil and mast cell markers (26).

Clinical Studies

While *in vitro* and *in vivo* studies may show clear dose effects and differences between corticosteroids, demonstrating such differences clinically is less straightforward.

MEASURING DOSE-RESPONSE

Lung function data comprising peak expiratory flow rates (PEFR) are currently the standard means of measuring the clinical effect of corticosteroids. Using such methods, it is difficult to demonstrate differences between corticosteroids and, in particular, it has been thought that it was not possible to demonstrate a clear dose-related response to inhaled corticosteroids (ICS). In addition, important subgroup responses may be masked.

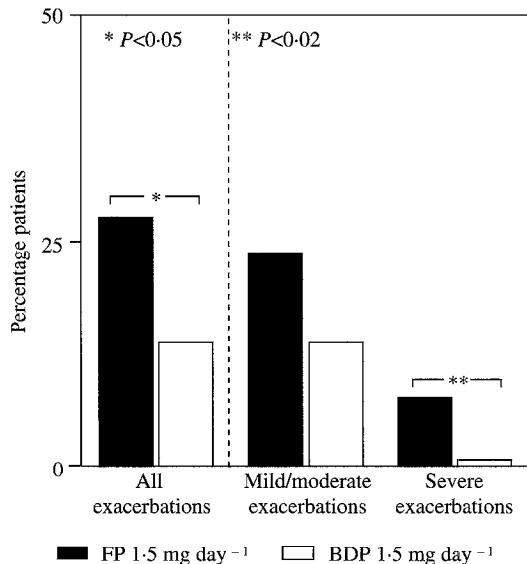


Fig. 4 Differing exacerbation rates for treatment with the same dose of fluticasone propionate (FP) and beclomethasone dipropionate (BDP) (1.5 mg day⁻¹). Source: Fabbri *et al.* (31).

A recent study has suggested that evaluation of bronchial reactivity using challenge with specific or non-specific stimuli may have an advantage over lung function data in that it can be used to show the differences between corticosteroids at low doses. Evaluation of rates of asthma exacerbation may also have utility for showing differences between low doses of inhaled corticosteroids. In the U.S.A., placebo-controlled studies with inhaled corticosteroids can be performed, using strict, pre-defined withdrawal criteria to remove patients from the study if treatment is ineffective. Therefore, it is possible to directly compare the rates of exacerbation in patients treated with different doses of inhaled corticosteroids or with placebo. Chervinsky *et al.* (27), using this method, showed a clear dose-related reduction in exacerbations of asthma with FP at doses of 50 µg day⁻¹, 200 µg day⁻¹ and 1000 µg day⁻¹.

The capacity of FP to allow reduction or withdrawal of oral corticosteroids has also been studied (28) and, most recently, preliminary data have been generated looking at the ability of FP to treat acute exacerbations of asthma (29).

Low dose-response

Pulmonary dose-response to low-dose inhaled FP has also been demonstrated. A study has compared histamine-induced bronchial reactivity in groups of 25 patients who received placebo, FP, 100 µg, or

FP, 200 µg. Change in PD₂₀ (provocation dose required to produce a 20% reduction in response) from baseline was monitored over 8 weeks. By the second week, a difference between the higher and lower dose was observed. This dose-dependent difference was maintained over the whole treatment period, the lower dose never becoming significantly more than placebo with regard to effect on histamine-induced bronchial reactivity. The method, therefore, appears to have utility for measuring the clinical difference between doses at the lower end of the dosage range.

High dose-response

Dose-response at the higher end of the dosage range has been demonstrated in an oral prednisone sparing study. Patients stabilized on prednisone, 5–10 mg day⁻¹ were randomized to receive either placebo, FP, 1.5 mg day⁻¹, or FP, 2.0 mg day⁻¹, for 16 weeks (28). Prednisone was then reduced by 2.5 mg week⁻¹. By the end of the study, oral prednisone could be completely withdrawn in 88% of patients receiving the higher dose of FP and in 69% of patients receiving the lower dose. Only 3% of patients in the placebo group could discontinue oral corticosteroid treatment. Patient withdrawal from the study due to exacerbation was higher in the FP, 1.5 mg, than the FP, 2.0 mg, group. In spite of the reduction in oral corticosteroids, lung function improved significantly in both of the FP-treated groups compared with placebo. A study performed in the same manner, but using budesonide, 0.8 mg and 1.6 mg, failed to show a dose-dependent association with prednisone-sparing effect or exacerbation rate (59).

COMPARATIVE STUDIES

A dose-ranging study by Dahl *et al.* compared FP at daily doses of 100, 200, 400 and 800 µg, with BDP at a dose of 400 µg (30). A significant dose-related increase in lung function was seen. In addition, changes in morning PEF were found to be similar for FP, 200 µg and BDP, 400 µg indicating a 2:1 efficacy advantage in favour of FP and reflecting the potency differences in experimental models. Importantly, a dose-related reduction in exacerbations of asthma was demonstrated. Based on the experimental observations and the results of this study, a number of studies were carried out comparing FP with other corticosteroids given at twice the dose. A list of the clinical studies comparing FP with placebo, BDP and budesonide is shown in Tables 3(a) and 3(b).

In order to demonstrate increased efficacy at comparable doses, a 12-month study by Fabbri *et al.* (31) was carried out comparing FP and BDP at 1.5 mg

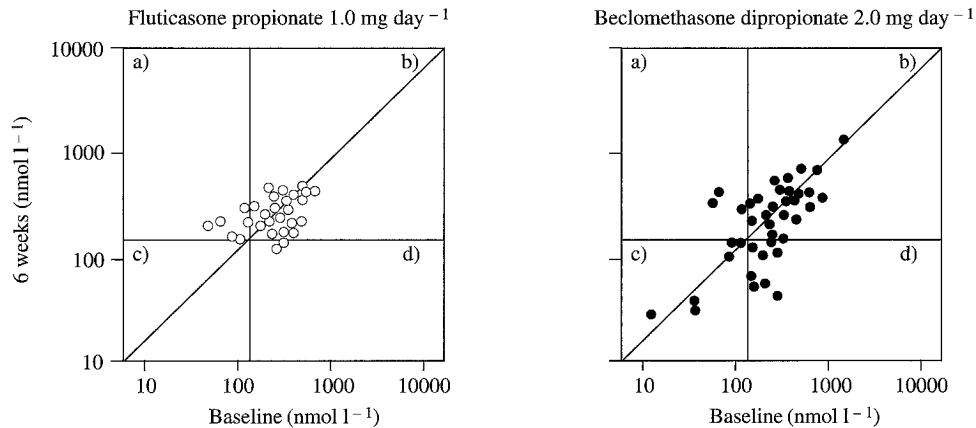


Fig. 5 Individual plasma cortisol levels at baseline and after 6 weeks treatment with fluticasone propionate and beclomethasone dipropionate, respectively. Source: Barnes *et al.* (32).

day⁻¹. It showed that improvement in morning PEFR is significantly greater with FP than with BDP given at the same dose (Fig. 3). Importantly, exacerbations, particularly severe exacerbations, were also significantly fewer in patients treated with FP compared to the same dose of BDP ($P < 0.02$) (Fig. 4) (31). However, despite the greater potency of FP, there was no difference between treatments in systemic activity determined by basal serum cortisol levels and response to adrenocorticotrophic hormone stimulation.

A potency advantage for FP over BDP without increased systemic activity has also been demonstrated in a double-blind, randomized, parallel group study by Barnes *et al.* (32). Fluticasone propionate, 1.0 mg day⁻¹, was found to be at least as effective as BDP, 2.0 mg day⁻¹, for control of severe asthma. The study monitored individual cortisol levels before and after the study period. Scatter plot analysis showed that the majority of patients in the FP-treated group had either similar cortisol levels before and after treatment or had increased levels after treatment (Fig. 5). In contrast, a number of BDP-treated patients had lower cortisol levels following treatment and the mean values at the end of treatment were significantly higher in the FP-treated group ($P = 0.026$).

A study by Boe *et al.* (33) set out to evaluate the clinical efficacy gained by severe asthmatics from increasing the dose of inhaled corticosteroids. The paper concluded that there was no difference in efficacy between BDP, 1.6 mg, and FP, 2.0 mg. However, examination of the study protocol raises a number of concerns.

It can be seen, for example, that one-half of the patients had had no incidences of hospitalization due

to exacerbations and did not meet any of the criteria for inclusion in the study. Many of the patients had asthma which was much milder than required for fulfilment of protocol criteria and the vast majority were not on BDP, 1.6 mg day⁻¹, or equivalent before the study. In fact, one-third of patients received BDP, 0.8 mg or less. As expected, because of the increase in corticosteroid dose, both treatments increased PEFR quite markedly. Interestingly, there is still a numerical, if not significant, difference in favour of FP in spite of the patient population studied and the low power of the study to detect a difference.

A further double-blind study by Ayres *et al.* has compared budesonide, 1.6 mg day⁻¹, with FP, 1.0 mg day⁻¹ and 2.0 mg day⁻¹ (37). The authors proposed that if budesonide had a similar clinical potency to FP, then budesonide would produce a response that lay between that of the two differing doses of FP. In fact, lung function data showed budesonide to have less effect than either dose of FP (Fig. 6). The magnitude of the changes are such, however, that it is difficult to ascertain the extent of their clinical relevance. To try and determine this, data were analysed in terms of proportion of patients showing a 10% change in predicted morning PEFR at 6 weeks. It can be seen from Fig. 7 that with budesonide, 1.6 mg day⁻¹, about twice as many patients showed an improvement of at least 10% of their predicted value than deteriorated by -10% of the predicted value. With FP, 1.0 mg day⁻¹, however, three-fold more patients improved by 10%, rising to 10-fold for FP, 2.0 mg day⁻¹. Interestingly, in about 66% of patients, no change in this lung function parameter occurred, irrespective of which drug or dose they were given. Clearly, if a way could

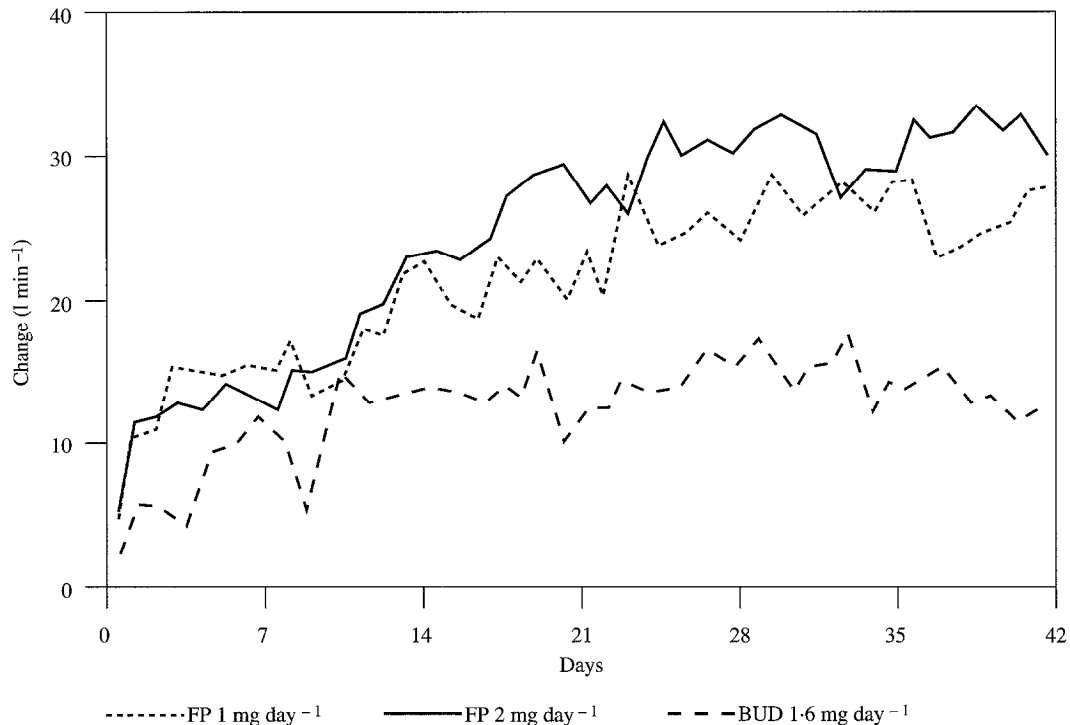


Fig. 6 Relative changes in morning peak expiratory flow rate for 1.6 mg day⁻¹ budesonide (BUD), 1 mg day⁻¹ fluticasone propionate (FP1) (FP2). Source: Ayres *et al.* (37).

be found to identify responsive patients clinically, it could markedly change clinical studies and clinical practice.

The study also showed dose-dependent decreases in morning serum cortisol levels, with budesonide, 1.6 mg day⁻¹, having a suppressive effect between that of FP, 1 mg and 2 mg. This lack of increased systemic activity with FP, despite its greater clinical potency, further supports the assertion that FP has a higher therapeutic index than budesonide.

Treatment of exacerbations

Inhaled corticosteroids are known to reduce the occurrence of asthma exacerbations. However, for the treatment of acute exacerbations, oral corticosteroids are generally recommended. A study has been performed in the U.K. involving patients presenting with acute exacerbations, which, in the opinion of their GP, necessitated a course of prednisone but not hospitalization (29). This randomized, double-blind study compared a reducing course of oral prednisone (40 mg daily, reduced by 5 mg every 2 days) with inhaled FP, 2 mg day⁻¹. Treatment success, defined as an improvement in forced expiratory volume in 1 s (FEV₁) of ≥10%, was approximately 48% in both

groups. Time course of improvement and onset of action were also very similar for both groups. In both groups around 25% of patients had to withdraw due to treatment failure. These preliminary results suggest that inhaled corticosteroids may be able to replace oral corticosteroids in the treatment of acute exacerbations of asthma.

TOLERABILITY

If the equivalent efficacy of FP at lower doses than other inhaled corticosteroids was merely a measure of higher potency, then the systemic side-effects of FP should also be greater. However, comparative studies of FP do not indicate that this is the case. In studies comparing FP dose for dose with BDP or budesonide, no significant increase in the suppression of plasma cortisol levels was seen with FP compared to BDP or BUD (31, 41). While one study claimed to show increased suppression of plasma cortisol, in this case FP had been administered at a higher dose (42).

In studies where FP was administered at one-half of the dose of BDP, FP was shown to have fewer side-effects at doses that gave comparable or better efficacy. At high doses of corticosteroids, (2.0 mg day⁻¹), a fall in serum cortisol levels of

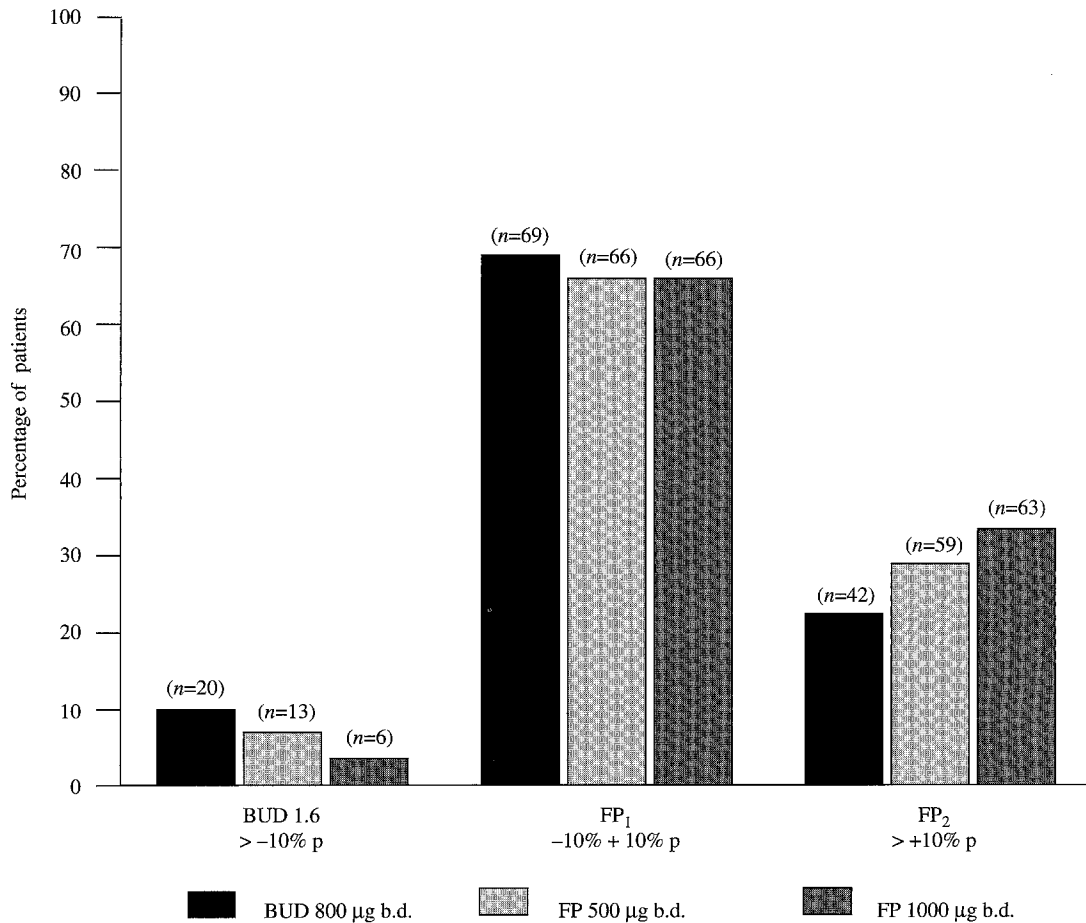


Fig. 7 10% change in predicted morning peak expiratory flow rate at 6 weeks for 1.6 mg day⁻¹ budesonide (BUD), 1 mg day⁻¹ fluticasone propionate (FP) and 2 mg day⁻¹. Source: Ayres *et al.* (37).

approximately 20% has been seen. Fluticasone propionate gave similar results to those previously seen with both budesonide and BDP (Table 4) (32,37,40). Thus, milligram for milligram, FP has a similar effect on cortisol levels as do BDP and budesonide.

PAEDIATRIC STUDIES

The clinical efficacy advantage of FP over other inhaled corticosteroids has also been demonstrated in children (Table 5). In a double-blind, placebo-controlled paediatric study, for example, FP, 400 µg day⁻¹, delivered *via* a Diskhaler was compared with budesonide, 400 µg day⁻¹, delivered *via* a Turbuhaler®. Morning PEFs were measured over an 8-week treatment period. Fluticasone propionate was found to produce a significantly greater improvement than budesonide (43). Overall, 40% of patients on FP improved by 10% of predicted PEF, despite the fact

that at the beginning of the study the lung function of the patients was near normal. Neither drug had a marked effect on cortisol values, although there was a significant difference in favour of FP.

A further study in children with mild and moderate asthma, has compared FP, 200 µg day⁻¹, with BDP, 400 µg day⁻¹. Results again appear to support the efficacy advantage of FP, with morning PEFs significantly greater in the FP-treated group even when used at the lower dose ($P < 0.05$) (44).

There was no significant difference between treatments with respect to safety parameters.

Paediatric safety

Clinical studies at doses of FP, up to 400 µg day⁻¹, support the safety profile of FP in children (Table 5). For example, one study (45) has compared FP, 100 µg day⁻¹, with sodium cromoglycate,

Table 4 Published studies: effects of high doses of corticosteroids on plasma cortisol levels

Reference	Changes in mean morning cortisol levels	
	Treatment	Ratio (pre:post)
Ayres <i>et al.</i> (37)	Fluticasone propionate 2.0 mg	0.88
Barnes <i>et al.</i> (32)	Beclomethasone dipropionate 2.0 mg	0.875
Toogood <i>et al.</i> (40)	Budesonide 2.0 mg	0.82

Table 5 Summary of clinical studies of fluticasone propionate in children

Reference	FP dose ($\mu\text{g day}^{-1}$)	Comparator daily dose (μg)	Treatment duration	Comparative efficacy/safety	P-value
Gustafsson <i>et al.</i> (44) <i>n</i> =398 Paediatric	200 (MDI)	BDP 400 (MDI)	6 weeks	1.7 (CI 0.1, 3.5) (NB. Percentage predicted PEFR)	<i>P</i> =0.069
				—Morning PEFR (weeks 3, 6)	<i>P</i> =0.044
				—Evening PEFR	<i>P</i> =0.043
				—Days with no exercise symptoms	<i>P</i> =0.041
				—Rescue-free days	<i>P</i> =0.04
				—Use of rescue	<i>P</i> =0.046
				—Cortisol	<i>P</i> =0.044
Hoecx and Hollingworth (43) <i>n</i> =229 Paediatric	400 (DH)	BUD 400 (TH)	8 weeks	3 (CI 1.5)(percentage predicted PEFR)	<i>P</i> =0.989
				7 (CI 1,14) (absolute PEFR)	<i>P</i> =0.007
				—Evening PEFR (percentage predicted)	<i>P</i> =0.017
				—Cortisol (weeks 4, 8)	<i>P</i> =0.02, 0.07
Price and Weller (45) <i>n</i> =225	100 (DH)	SCG 80 mg	8 weeks	Percentage predicted PEFR	<i>P</i> <0.001
				symptom-free days/nights	<i>P</i> <0.05
Wolthers and Pedersen (48) <i>n</i> =19	200 (DH)	BDP 400, 800 (DH)	2 weeks	Knemometry vs. BDP 400 μg	<i>P</i> =0.003
				vs. BDP 800 μg	<i>P</i> <0.001
Agertoft and Pedersen (49) <i>n</i> =2 \times 24*	200 (DH) 400 (DH)	BUD 200 (TH) BUD 400 (TH)	2 weeks	Knemometry	
				200 μg vs. 200 μg BUD	<i>P</i> =0.19
				400 μg vs. 400 μg BUD	<i>P</i> =0.39
				Urinary cortisol/creatinine	
				200 μg vs. 200 μg BUD	<i>P</i> =0.07
				400 μg vs. 400 μg BUD	<i>P</i> =0.29

*Each group treated at one dose level. See Table 3 for abbreviations.

20 mg, taken four times a day. While the efficacy difference in favour of FP was unsurprising, it was interesting to note that the incidence of withdrawals due to adverse events was greater in the cromoglycate group.

The effect of inhaled corticosteroid therapy on paediatric growth has been one area of particular concern. Height data have been recorded in 41 children (25 males, 16 females) aged 6–12.4 years treated

with FP, 100–200 $\mu\text{g day}^{-1}$ for a mean of 1.2 yr (46). Height velocity standard deviation scores were calculated for all patients. Growth during treatment was not significantly different from national standards (47). Although more studies are required, these data appear to support other observations that FP has a negligible effect on growth.

Separate studies have compared FP with BDP, and FP with budesonide using the technique of

knemometry. This technique, which accurately measures short-term changes in lower leg length, is apparently of little value for predicting final height, but is a very sensitive measure of systemic exposure.

Fluticasone propionate, at $200 \mu\text{g day}^{-1}$, compared with BDP, $400 \mu\text{g day}^{-1}$ and $800 \mu\text{g day}^{-1}$, had less of an effect on lower leg growth (48). In a separate placebo-controlled comparison with budesonide, FP was shown to have comparable effects at the same daily dose: FP, $200 \mu\text{g}$, vs. budesonide, $200 \mu\text{g}$; and FP, $400 \mu\text{g}$, vs. budesonide, $400 \mu\text{g}$ (49).

PHARMACOKINETICS

Experimental and clinical data clearly show that FP is more effective than other currently available inhaled corticosteroids, dose-for-dose. However, there does not appear to be a concomitant increase in systemic effects. This may be explained by the absorption characteristics and metabolic profile of the drug.

After intravenous dosing, FP displays a three-phase kinetic profile. At doses over the range 0.25 – 1.0 mg , there was no evidence of saturation of metabolism as the plasma profiles when normalized for dose were superimposed. Fluticasone propionate is extensively distributed in the body (volume of distribution is 318 l) and it is rapidly cleared (1.11 l min^{-1}). The terminal elimination half-life is 7.8 h , largely due to the third phase of the profile which is likely to represent re-equilibration from the tissues (50).

Metabolism of FP is by de-esterification in the liver. There is no evidence of any saturation of this process at intravenous doses up to 4 mg (51). In addition, the frequency distribution of clearance values shows that there is no evidence of genetic polymorphism of the metabolism of FP in the populations studied. Fluticasone propionate is a single enantiomer and, therefore, it is not necessary to take into account possible differences between enantiomers as is the case for racemic mixtures, such as budesonide.

When considering the pharmacokinetic behaviour of a drug after inhaled dosing, it is necessary to take into account a number of additional factors: the rate of absorption and the fate of the proportions of the dose which reach (1) the gut, and (2) the lungs.

The kinetic parameters of FP, in particular the high clearance rate which approaches that of liver blood flow, predict that any swallowed drug will be deactivated almost completely on first pass through the liver. This has been confirmed in a study comparing FP after intravenous (0.25 mg single dose) and

oral (0.1 mg , 1 mg and 10 mg twice daily) dosing over 3–5 days. The systemic availability of the oral doses was confirmed at less than 1% compared with approximately 11% for budesonide, 10% for triamcinolone and 20% for flunisolide.

A study in mild asthmatic patients compared oral FP, 20 mg day^{-1} , for up to 4 weeks with inhaled FP, 0.5 mg b.d. Plasma levels of FP were the same order in spite of the difference in dose (area under curve 1.4 ng h ml^{-1} after oral dosing, 0.5 ng h ml^{-1} after inhaled dosing). However, the oral dose was completely ineffective in improving FEV_1 and was no different from placebo, whereas inhaled FP improved lung function significantly compared with both oral FP and placebo, thus confirming the topical activity of FP (52).

There are a number of factors which determine the systemic activity of a corticosteroid after inhaled (and also intranasal) dosing: (1) rate of absorption through the lung (or nasal) mucosa; (2) dosage interval and (3) deposition of drug at the target organ.

(1) The concentration–time profile after inhaled dosing with FP is quite different from the intravenous profile. There is a slow appearance of drug in the plasma due to dissolution of drug at the mucosal surface followed by rapid uptake into the tissue because of the high lipophilicity of the molecule. This property also means that the drug is preferentially retained in the tissue and is released slowly into the plasma. This rate of absorption is slower than the elimination/clearance and, therefore, there is a prolongation of apparent half-life relative to that seen after intravenous dosing, with values of around 10 h (range 7–14 h).

As for intravenous dosing, the kinetic profiles after inhaled dosing are superimposable over a range of doses (0.5 – 2.0 mg) showing that there is no saturation of the kinetics of FP with this route of administration.

Taking into account the variability of deposition of drug in the lung, absolute bioavailability after inhaled dosing has been estimated at approximately 20% of the total delivered dose.

With intranasal dosing, plasma levels of FP were undetectable in a large proportion of cases, making it impossible to accurately determine pharmacokinetic parameters. The maximum possible bioavailability has been estimated at less than 2% using the limited samples where blood levels were detectable, and therefore this is likely to be an overestimate (53). This contrasts with published levels for budesonide of approximately 102% (54) and flunisolide of 49% (55).

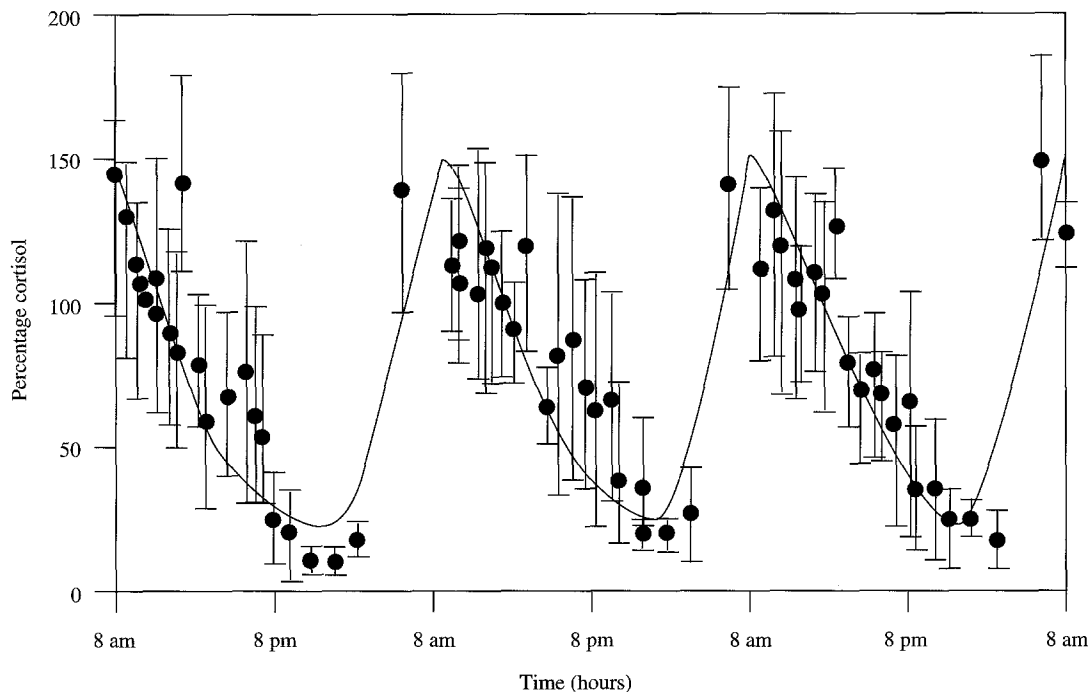


Fig. 8 Cortisol levels over a 3-day period showing an asymmetrical daytime/night-time distribution. Source: Rohatagi *et al.* (57).

(2) Inhaled FP has been given to volunteers repeatedly every 12 h for periods of 7 days with a maximum of 1.4-fold accumulation.

(3) A consistent observation throughout the large clinical pharmacology programme is that there is a large inter-patient variability of FP (approximately 10-fold) in blood levels after inhaled dosing, irrespective of the delivery system used. Measurements within any individual patient appeared to be more consistent. This appears to be a function of the deposition of drug in the lung and the ability of the patient to use the delivery system optimally, which strongly supports patient individualization of delivery system.

Thus, the chemical properties of FP, including low aqueous solubility and metabolic activation *in vivo*, result in slow absorption into the circulation after inhaled dosing, and rapid clearance from the body. Any swallowed dose is removed by almost complete first-pass metabolic inactivation. Drug levels at the site of action in the lung are maximized, which explains the observed separation of clinical and systemic potency.

Pharmacokinetic and Pharmacodynamic Modelling

The development of mathematical models, which allow the prediction of systemic pharmacodynamic

effects from corresponding pharmacokinetic parameters and *vice versa*, will provide us with additional information on the comparative systemic effects of inhaled corticosteroids.

Such models, originally developed by Holford and Sheiner (56), have been used to study the effects of FP on serum cortisol levels. Traditional measures of cortisol suppression are notoriously imprecise as cortisol levels fluctuate naturally throughout the course of the day. However, modelling techniques have been able to provide a mathematical link between the FP concentrations in the plasma and serum cortisol levels which is independent of time, dose, formulation and delivery route.

The models were used to relate the plasma levels of FP, after a single dose of FP, with the corresponding changes in serum cortisol levels (compared to placebo values) over a 12-h period from 10 a.m. to 10 p.m. These two sets of values, after computer manipulation using the Holford/Sheiner approach, give an EC_{50} value for FP's effects on serum cortisol. This, and the other model parameters, can be used to predict the systemic effects from any FP plasma level profile.

The predictive value of the model was validated using results from a study of a single dose of FP administered *via* a dry powder device to healthy

male volunteers in which FP of two different bioavailabilities was used (Glaxo data on file). All other pharmacokinetic parameters were identical. The data provided by the study results of the 50% bioavailable formulation of FP were used to construct a model that gave an accurate prediction of serum cortisol effect for the 100% bioavailable FP.

The validity of the pharmacokinetic/pharmacodynamic model has also been proved over a 24-h period following research which indicated that cortisol levels during the night follow a widely different pattern from those during the day. Tests over a 3-day period confirmed an asymmetrical variation of cortisol levels over the two 12-h periods (Fig. 8) (57).

These modelling techniques could be used to predict the concentration of circulating FP from cortisol measurements taken at a given time after FP dosing. In a similar way, serum cortisol levels can be predicted at intervals following FP dosing. Simulations show that following a single dose of FP, 500 µg, serum cortisol levels remain within the average distribution. Simulations can also predict the dose of FP that would produce a clinically significant cortisol suppression (defined as 70% suppression). The simulation predicted a result in normal volunteers of FP, 2.5 mg; suppression occurred during the day, with levels recovering to within the normal range at night.

Although not validated for multi-dose use, the model parameters, when applied to a twice-daily regimen of FP described in the literature (42) provided an accurate prediction of the levels of cortisol at steady state seen in the volunteers. The actual change was, however, exaggerated by the use of results over a 20-h period only, which leaves out the early morning 'catch-up'.

The results of these models are now being compared with historical control data from studies of FP in which cortisol measurements were taken. Although some inter-individual variation in cortisol levels occurs over the day, initial indications are that these are not sufficiently large to invalidate the model. Research has also shown that a similar relationship holds for asthma patients as for healthy volunteers. Therefore, much higher doses of FP will be needed before clinically significant cortisol suppression is seen in patients with asthma. These data also show the need to record both pharmacokinetics and cortisol levels; the two are closely related. Study designs which alter pharmacokinetics can give artificially high (or low) cortisol results.

Conclusion

Preclinical studies have demonstrated that FP is a highly lipophilic molecule, a characteristic which results in rapid penetration into the cells and retention in lung tissue. Fluticasone propionate has also been found to have high glucocorticoid-receptor selectivity with highly desirable 'fast-on, slow-off' receptor kinetics. The net effect is a FP-receptor half-life of 10 h, markedly greater than the receptor-drug half-lives of 7.5 and 5.1 h for beclomethasone-17-monopropionate (the active metabolite of BDP) and budesonide, respectively.

These differences in biological properties appear to be predictive of differing clinical effects. Studies evaluating lung function, exacerbation rate and oral corticosteroid-sparing effect all suggest that FP has a dose-dependent clinical potency which is at least two-fold greater than BDP and budesonide. Studies have also indicated that this increased clinical potency does not result in increased systemic activity. This separation between efficacy and systemic potency is a combination of negligible oral bioavailability, slow absorption from the lungs into the plasma and metabolic profile.

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