

The anti-inflammatory profile of fluticasone propionate

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Fluticasone propionate is a new corticosteroid based on the androstane nucleus. It is more lipophilic than beclomethasone dipropionate (BDP) and budesonide, and binds more avidly to human lung tissue. It has an absolute affinity (K_D) of 0.5 nM for the glucocorticoid receptor and a relative receptor affinity 1.5- and 3.0-times greater than that of beclomethasone-17-monopropionate (17-BMP) and budesonide, respectively. The rate of association with the receptor is faster and the rate of dissociation slower than with standard corticosteroids. As a result, the half-life of the corticosteroid-receptor complex is > 10 h. Fluticasone propionate is also highly selective for the glucocorticoid receptor, with little or no activity at other steroid receptors. Pretreatment with fluticasone propionate significantly inhibits the increase in mast cell numbers in the nasal mucosa of rats chronically exposed to toluene di-isocyanate (TDI), and suppresses TDI-induced mast cell degranulation. It is more potent *in vitro* than dexamethasone, BDP and budesonide in inhibiting anti-CD3-induced human T-lymphocyte proliferation, in attenuating tumour necrosis factor- α -induced endothelial cell adhesion molecule expression, and in increasing secretory leucocyte protease inhibitor levels in airway epithelial cells. It is also more potent and longer-acting than other corticosteroids in inhibiting oedema formation, interleukin-5 (IL-5)-induced blood eosinophilia, and IL-5- or platelet activating factor-stimulated eosinophil accumulation in the lung. Fluticasone propionate therefore has increased intrinsic glucocorticoid potency and high topical anti-inflammatory activity.

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Introduction

Fluticasone propionate is a topically-active corticosteroid molecule based on the androstane nucleus (11). A key feature is the 17 β -carbothioate ester, which is metabolised on first pass through the liver to yield the 17 β -carboxylic acid, an inactive metabolite. Since first pass metabolism is virtually complete, oral bioavailability is very low, resulting in minimal systemic adverse effects, when administered by the intranasal or inhaled route.

Fluticasone propionate is highly lipophilic in nature – some three-fold more lipophilic than beclomethasone dipropionate (BDP) and 300-fold more lipophilic than budesonide. Lipophilicity is an important property in a corticosteroid for topical use, since it increases both drug uptake and retention in tissues. For example, fluticasone propionate and BDP exhibit a higher degree of binding to human lung tissue compared with more hydrophilic molecules such as beclomethasone-17-monopropionate

(17-BMP) – the active metabolite of BDP, budesonide and flunisolide (3). This pattern is also observed in the amount of drug remaining in the tissue after equilibration in plasma, the residual concentration of fluticasone propionate being approximately four-fold greater than that of budesonide and flunisolide (4).

Receptor binding properties

In terms of affinity for the human glucocorticoid receptor, fluticasone propionate has an absolute affinity (K_D) of 0.5 nM, 14–18 times that of dexamethasone, 2–4-fold greater than budesonide, and 1.5–2 times higher than 17-BMP (3). In addition to having higher affinity, the fluticasone propionate molecule associates with the glucocorticoid receptor faster than standard corticosteroids (4). However, in contrast, the rate of dissociation from the glucocorticoid receptor is markedly slower than with triamcinolone, dexamethasone and methylprednisolone

(4). Rapid association and slow dissociation from the receptor suggests that the fluticasone propionate-receptor complex will be more stable. Indeed, when the half-life of the receptor complex for different corticosteroids is determined, fluticasone propionate has a half-life in excess of 10 h with the receptor, compared with 1 h for dexamethasone, 4 h for triamcinolone and 5 h for budesonide (4). Since it is the receptor complex which mediates the biological actions of the steroid, this may have important therapeutic implications. Despite these receptor pharmacokinetic differences, fluticasone propionate retains high selectivity for the glucocorticoid receptor, with little or no activity at mineralocorticoid, oestrogen, androgen and progestagen receptors (2). The receptor pharmacology of fluticasone propionate may thus be summarised as: high affinity for the glucocorticoid receptor; fast association and slow dissociation, leading to increased stability of the receptor complex; and high selectivity for the glucocorticoid receptor.

Effects on cell activation

The receptor profile of fluticasone propionate determines the anti-inflammatory properties of the molecule which are relevant to its use in allergic rhinitis. The efficacy of this agent can be observed by its effects on the various types of cells involved in the different stages of the allergic inflammatory reaction in the nasal mucosa.

There is clinical evidence of increased mast cell numbers and mast cell activation in patients suffering from allergic rhinitis. When rats were pretreated with the occupational sensitiser, toluene di-isocyanate (TDI), this promoted an increase in mast cell numbers in the nasal mucosa of these animals, as measured in terms of the histamine content of the tissue (Fig. 1). Treatment with intranasal fluticasone propionate throughout the sensitisation procedure

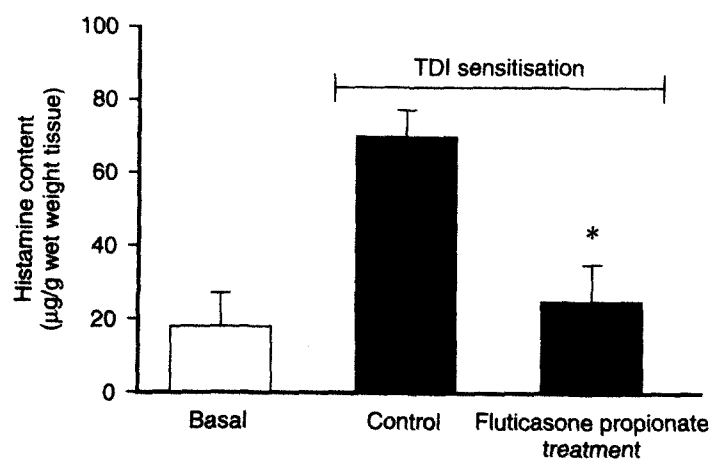


Fig. 1. Effect of intranasal fluticasone propionate treatment (50 µg b.d.) on mast cell numbers in nasal mucosa (as determined by histamine content) after TDI sensitisation in rats. *Fluticasone propionate significantly different from control ($P < 0.01$).

reduced the number of mucosal mast cells towards basal levels. Alternatively, in sensitised animals, subsequent challenge with TDI leads to mast cell activation and degranulation. This process is inhibited by a single dose of fluticasone propionate (50 µg) administered 30 min before challenge (Fig. 2). These findings are similar to those reported by Kubo et al. (9).

A key cell in the inflammatory response in perennial rhinitis is the T-lymphocyte, activation of which leads to a proliferative response. Corticosteroids inhibit anti-CD3-induced T-cell proliferation in a concentration-dependent manner, with fluticasone propionate being 20-fold more potent than dexamethasone, and 3- and 6-times more potent than budesonide and BDP respectively (Table 1).

Release of inflammatory mediators

One of the consequences of cell activation and inflammatory cell recruitment is the release of inflammatory mediators, which may then act on the microvasculature to initiate protein extravasation and oedema formation. Fluticasone propionate, administered to guinea-pigs at nebuliser concentrations of 100 and 1000 µg/ml, 4 h before challenge with histamine, was effective in inhibiting lung oedema and had a duration of action of up to 16 h (7). Under these conditions, fluticasone propionate was more potent and longer-acting than BDP.

A characteristic of both seasonal and perennial rhinitis is infiltration by eosinophils into the nasal mucosa (12), and it has been suggested that the number of eosinophils in nasal lavage fluid is a marker of ongoing allergic inflammatory activity (5). The first stage in the process of tissue eosinophilia is the mobilisation of cells from the bone marrow and vascular margination sites into the circulation. Indeed, the intravenous administration of the T-cell-derived cytokine, interleukin-5 (IL-5), results in a marked increase in blood eosinophils over the subsequent

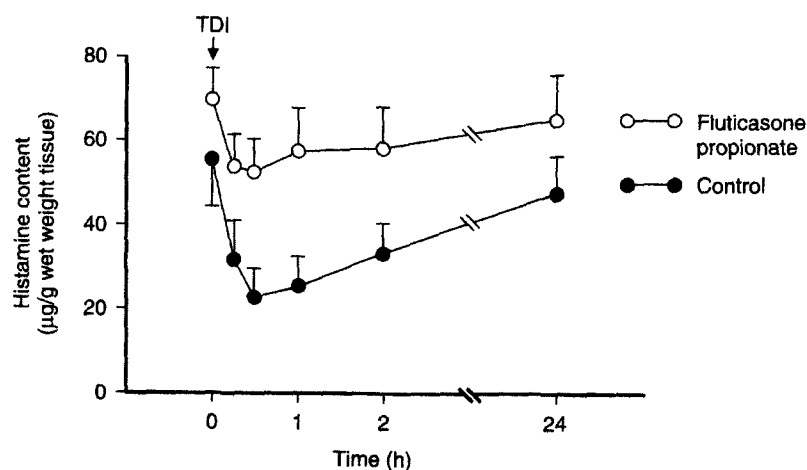


Fig. 2. Intranasal fluticasone propionate (50 µg) in sensitised rats subjected to TDI challenge – effect on mast cell activation and degranulation.

Table 1. Inhibition of anti-CD3-induced human T-lymphocyte proliferation by corticosteroids

	IC ₅₀ (nM)
Dexamethasone	5.9
BDP	2.1
Budesonide	0.9
Fluticasone propionate	0.3

6–12 h. Fluticasone propionate, given systemically at 25 µg/kg i.v. inhibits IL-5-induced eosinophilia towards basal levels (Fig. 3).

The second stage in inflammatory cell recruitment is adhesion to the vascular endothelium. This is orchestrated by interaction between complementary pairs of adhesion molecules on the granulocyte and endothelial cell, activated under the influence of locally-generated cytokines and other inflammatory mediators (14). Fluticasone propionate (0.1–10 nM) inhibits the expression of adhesion molecules, such as ELAM or E-selectin on human endothelial cells in culture, stimulated by tumour necrosis factor-α (TNFα), and at higher concentrations (100 nM) will also inhibit VCAM, although it has little effect against ICAM (Fig. 4). When compared with other corticosteroids, fluticasone propionate is more potent than BDP, 17-BMP, and budesonide in inhibiting TNFα-induced E-selectin expression, with an IC₅₀ of 1 nM (8).

Inflammatory cell accumulation

Inhibition of cell activation and cell adhesion mechanisms should result in a decrease in the number of inflammatory cells recruited into the tissue and airway lumen. Indeed, inhaled fluticasone propionate (100 µg/ml) completely suppresses the increase in eosinophils which occurs in bronchoalveolar lavage fluid, 24 h following local challenge with IL-5 (Fig. 5). Similarly, at increasing nebuliser concentrations, flu-

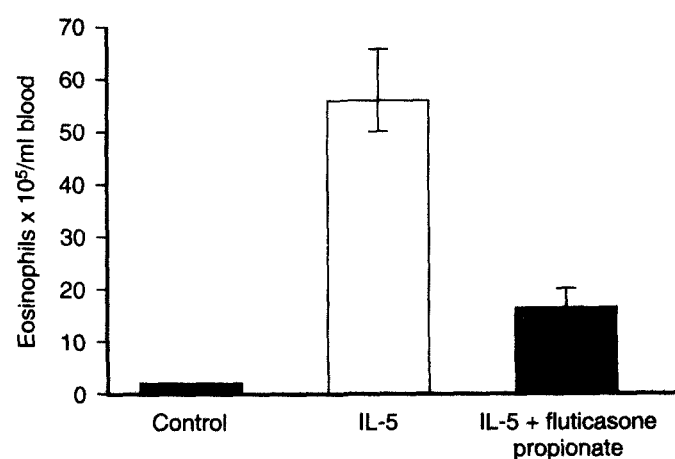


Fig. 3. Inhibition of IL-5-induced blood eosinophilia in the guinea-pig by fluticasone propionate.

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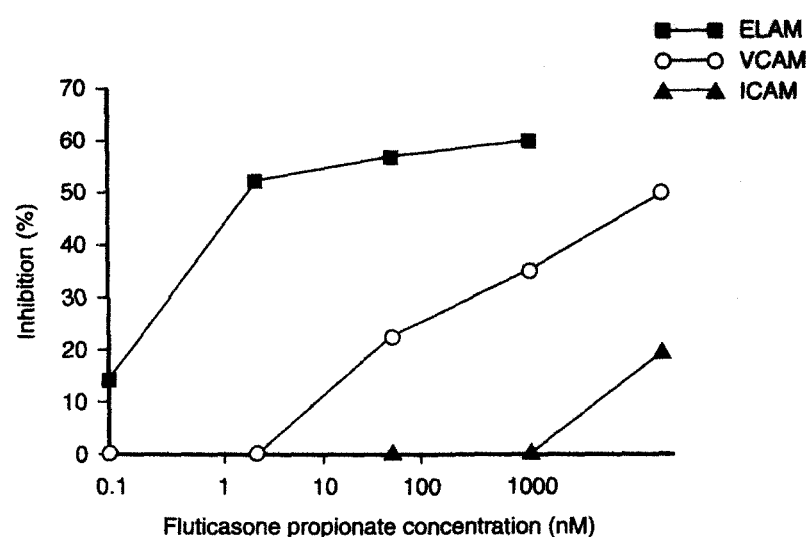


Fig. 4. Inhibition of TNFα-induced expression of adhesion molecules on human endothelial cells by fluticasone propionate.

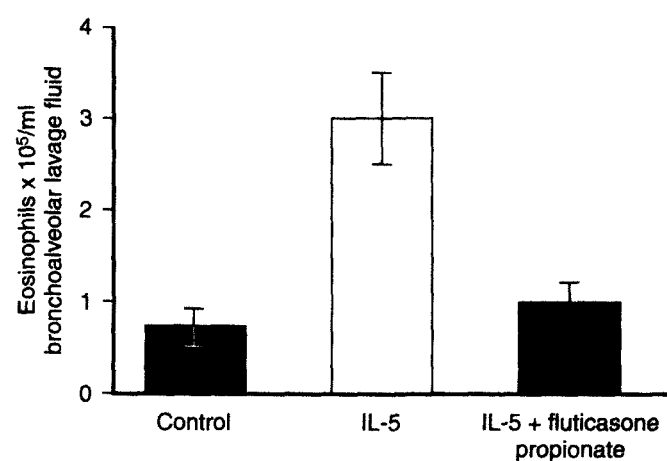


Fig. 5. Inhibition of IL-5-induced lung eosinophilia in the guinea-pig by fluticasone propionate.

ticasone propionate inhibits eosinophil accumulation under the influence of the inflammatory mediator, platelet activating factor (PAF) (6). In this context, fluticasone propionate is markedly more potent than BDP, dexamethasone and budesonide (6).

Finally, in sensitised animals, the total number of inflammatory cells and the number of eosinophils, lymphocytes and macrophages recruited into the airway lumen, 24 h after challenge with ovalbumin, was reduced to baseline by a single administration of

Table 2. Antigen-induced inflammatory cell accumulation in the airway lumen (bronchoalveolar lavage fluid) after challenge with ovalbumin: effect of pretreatment with fluticasone propionate

	Cell count x 10 ⁵ /ml			
	Total cells	Eosinophils	Lymphocytes	Macrophages
Basal	8.6	0.7	0.08	4.8
Ovalbumin	15.4	5.4	0.24	6.0
Fluticasone propionate + ovalbumin	6.8	1.1	0.08	3.8

Table 3. Stimulatory effect of corticosteroids on secretory leucocyte protease inhibitor in human airway epithelial cells (Abbinante-Nissen et al., 1994)(1)

	EC ₅₀ (nM)
Dexamethasone	2.0
Triamcinolone	1.0
Methylprednisolone	5.0
Hydrocortisone	25.0
Fluticasone propionate	0.1

fluticasone propionate (0.5 mg) by dry powder insufflation (Table 2) (10).

The accumulation of activated inflammatory cells, such as eosinophils and macrophages, in the nasal mucosa results in local tissue damage due to the release of cytotoxic products, including proteases (13). Epithelial cells release an inhibitor of leucocyte proteases which can be induced by corticosteroids (15). Fluticasone propionate was shown to be markedly more potent (EC₅₀ 0.1 nM) than comparator corticosteroids in stimulating levels of secretory leucocyte protease inhibitor in human airway epithelial cells (1), being 20-times more potent than dexamethasone and 10-times more potent than triamcinolone (Table 3).

Conclusions

In summary, nasal inflammation has a number of similarities to the processes of acute and chronic inflammation in the lung, involving cell activation, mediator release, cell trafficking and tissue damage. Fluticasone propionate, as a result of its increased affinity and improved glucocorticoid receptor pharmacokinetics, has increased intrinsic potency as an effective topical anti-inflammatory agent.

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