Anti-Inflammatory Properties of Fluticasone Propionate

M.

Johnson

Glaxo Research and Development, Uxbridge, UK

Key Words

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Correspondence to: Dr. M. Johnson, Respiratory Commercial Strategy, Glaxo plc, Stockley Park West, Uxbridge, Middlesex UB11 1BU (UK)

Fluticasone propionate (FP) is a new corticosteroid based on the androstane nucleus [1]. It is more lipophilic than beclomethasone dipropionate (BDP) and budesonide, and both binding and retention in human lung tissue in vitro is in the rank order: FP > BDP > beclomethasone 17-mono-propionate (17-BMP) > budesonide > flunisolide > hydro-cortisone [2]. FP has an absolute affinity (Kd) for the gluco-corticoid receptor of 0.5 nM, and a relative receptor affinity 1.5- and 3-fold higher than 17-BMP and budesonide, respectively. The rate of association with the receptor is 4-fold faster, and the rate of dissociation 10-fold slower than with standard steroids. The resulting half-life of the active steroid-receptor complex is > 10 h, compared with 1, 5, 7.5 and 4h for dexamethasone, budesonide, 17-BMP and triamci-nolone, respectively [2]. FP is also highly selective for the glucocorticoid receptor, with little or no activity at proges-tagen, androgen, oestrogen or mineralocorticoid receptors [1].

The properties of FP have been investigated in a number of systems relevant to the pathophysiology of allergic inflammation. FP is more potent in vitro than dexamethasone, BDP and budesonide in inhibiting anti-CD3-induced human T lymphocyte proliferation, with IC50 values of 0.3, 5.9,

2.0 and 0.8 nM, respectively. Similarly, FP attenuates the expression of adhesion molecules (E-selectin, VCAM) on human endothelial cells in culture stimulated with the cyto-kine, tumour necrosis factor (TNF)- α . The IC50 against E-selectin was 1 nM, compared with 23 nM for dexamethasone and 9.5 nM for budesonide. Higher concentrations of FP (100 nM) were required to inhibit TNF- α -induced VCAM and there was little effect on ICAM expression. In human airway epithelial cells, FP (10 nM) increased mRNA levels for secretory leukocyte protease inhibitor within 24 h and maximal transcript accumulation occurred at 48 h [3]. The rank order of potency of corticosteroids was: FP (EC50: 0.1 μ M) > triamcinolone (1 nM) > dexamethasone (2nM) > methylprednisolone (5 nM) > hydrocortisone (25 nM).

In vivo, by the inhaled route in the guinea pig, FP had an approximately 100-fold higher potency than dexamethasone, BDP and budesonide in inhibiting eosinophil accumulation in the airway

lumen 24 h after exposure to interleukin-5 or platelet-activating factor. In sensitised guinea pigs, antigen challenge leads to a marked infiltration of the lung by CD4⁺ T lymphocytes, eosinophils and macrophages. Treatment with FP (0.5 mg) markedly reduced antigen-induced eosinophil (basal: $0.7 \times 10^5/\text{ml}$; ovalbumin:

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$5.4 \times 10^5/\text{ml}$; FP $1 \times 10^{-6}\text{M}$) and lymphocyte (basal: $0.08 \times 10^5/\text{ml}$; ovalbumin: $0.24 \times 10^5/\text{ml}$; FP: $0.08 \times 10^5/\text{ml}$) accumulation in the bronchoalveolar lavage fluid. There was also a reduction in the total number of T lymphocytes, CD4⁺ cells and macrophages in the airway wall, following FP pretreatment. This agrees with previous findings in a similar model [4].

FP has increased intrinsic activity at the glucocorticoid receptor, and as a result exhibits high topical anti-inflammatory potency. Such activity, coupled with its improved safety profile, suggests that fluticasone propionate will have good efficacy in allergic inflammatory disease.

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