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LANDMARKS IN FLUTICASONE PROPIONATE

London, United Kingdom
February 27, 1997

Guest Editor

Peter Barnes, DSc, FRCP

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CONTENTS

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Landmarks in Fluticasone Propionate

Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma — S427

Peter J. Barnes, DSc, FRCP, London, United Kingdom

Development of fluticasone propionate and comparison with other inhaled corticosteroids — S434

Malcolm Johnson, PhD, Middlesex, United Kingdom

Pharmacokinetics and pharmacodynamics of inhaled corticosteroids — S440

H. Derendorf, PhD, G. Hochhaus, PhD, B. Meibohm, PhD, H. Möllmann, MD, and J. Barth, MD, Gainesville, Fla., and Bochum, Germany

Clinical relevance of inhaled corticosteroids and HPA axis suppression — S447

Robert G. Dluhy, MD, Boston, Mass.

Effects of inhaled corticosteroids on growth — S451

Carrie MacKenzie, MD, Sheffield, United Kingdom

Effects of inhaled corticosteroids on bone density and metabolism — S456

Ashley Woodcock, MD, FRCP, Manchester, United Kingdom

Relative safety and efficacy of inhaled corticosteroids — S460

Neil Barnes, FRCP, London, U.K.

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Development of fluticasone propionate and comparison with other inhaled corticosteroids

Malcolm Johnson, PhD *Middlesex, United Kingdom*

Fluticasone propionate (FP) is a trifluorinated glucocorticoid based on the androstane nucleus. It was selected for development from structure-activity relationships (topical anti-inflammatory, cutaneous vasoconstriction, and hypothalamic-pituitary-adrenal axis suppression) of a series of 17β-carbothioates. FP is 3-, 300-, and 1000-fold more lipophilic than beclomethasone dipropionate, budesonide, and triamcinolone acetonide, respectively. FP has an absolute affinity (K_D) for the glucocorticoid receptor of 0.5 nmol/L and a relative receptor affinity 1.5-fold higher than beclomethasone-17-monopropionate (17-BMP) and mometasone furoate, 3-fold higher than budesonide, and 20-fold higher than flunisolide and triamcinolone acetonide. The rate of association of FP with the receptor is faster and the rate of dissociation slower than other corticosteroids. The resulting half-life of the FP active steroid-receptor complex is >10 hours, compared with approximately 5, 7.5, and 4 hours for budesonide, 17-BMP, and triamcinolone acetonide, respectively. FP has high selectivity for the glucocorticoid receptor, with little or no activity at other steroid receptors. FP is more potent than beclomethasone dipropionate, budesonide, triamcinolone acetonide, and mometasone furoate in inhibiting human T-cell migration and proliferation, inhibiting CD4+ T-cell cytokine and basophil histamine release, attenuating adhesion molecule expression, stimulating inflammatory cell apoptosis, and inducing cellular antiprotease release. In asthma patients, FP decreases the number of CD3+, CD4+, CD8+, and CD25+ T cells, mast cells, and eosinophils in bronchial biopsies, in addition to suppressing CD1a-dendritic and IgE+ cells and HLA-DR. FP, therefore, has a good pharmacologic profile for a topical steroid with increased intrinsic glucocorticoid potency and potent anti-inflammatory activity.

(J Allergy Clin Immunol 1998;101:S434-9.)

Key words: *Fluticasone propionate, inhaled corticosteroids, structure-activity relationships, asthma*

Abbreviations used	
BDP:	Beclomethasone dipropionate
17-BMP:	Beclomethasone-17-monopropionate
FP:	Fluticasone propionate
GR:	Glucocorticoid receptor
GRE:	Glucocorticoid-responsive element
RBA:	Relative receptor binding affinity

To exert anti-inflammatory activity, a corticosteroid molecule must penetrate the cellular membrane and demonstrate affinity for the steroid binding site on the glucocorticoid receptor (GR), leading to activation of the receptor.[1] Dimerization of the active steroid-receptor complex occurs, and this can then enter the nucleus, bind to glucocorticoid-responsive elements on a target gene, influence gene transcription, and either inhibit proinflammatory or potentiate endogenous anti-inflammatory mechanisms. Alternatively, a direct interaction of the GR complex with transcription factors may also be an important determinant of steroid action and a key mechanism by which glucocorticoids exert some anti-inflammatory activity.[1]

The early development of corticosteroids based on the structure of cortisol focused on increasing topical potency and improving glucocorticoid selectivity. The first structure-activity studies attempted to find compounds with greater anti-inflammatory activity. This was achieved either by the insertion of an additional double bond at the 1,2 position in the steroid nucleus; by the introduction of 6α-fluoro, 6α-methyl, or 9α-fluoro substituents; or by a combination of these changes (Fig. 1). Although anti-inflammatory potency was potentiated, mineralocorticoid activity was increased to an even greater extent.[2] This effect was counteracted by further substitutions with α-hydroxyl, α-methyl, or β-methyl at the 16 position, for example, in dexamethasone (Fig. 1). A novel finding was that an ester function at the 16α, 17α, or 21α hydroxyl group was preferred, and this gave rise to betamethasone 17-valerate, triamcinolone 16,17-acetonide, and beclomethasone-17,21-dipropionate.[2] These compounds have proved to be of value in the treatment of the inflammatory component of bronchial asthma and rhinitis and have shown little detectable systemic activity when delivered by the topical route. However, concern that long-term therapy may result in a wide range of unacceptable systemic side effects such as adrenal suppression, bone fracture, osteoporosis, and inhibition of growth in children highlighted the need for steroids with a better therapeutic index.

DEVELOPMENT OF FLUTICASONE PROPIONATE

The development of fluticasone propionate was an attempt to produce a potent corticosteroid that exhibited improved airway selectivity (Table I) compared with earlier compounds. Lipophilicity was identified as an important physicochemical property for increased uptake and retention in lung tissue, resulting in enhanced lung-systemic distribution and greater affinity for the

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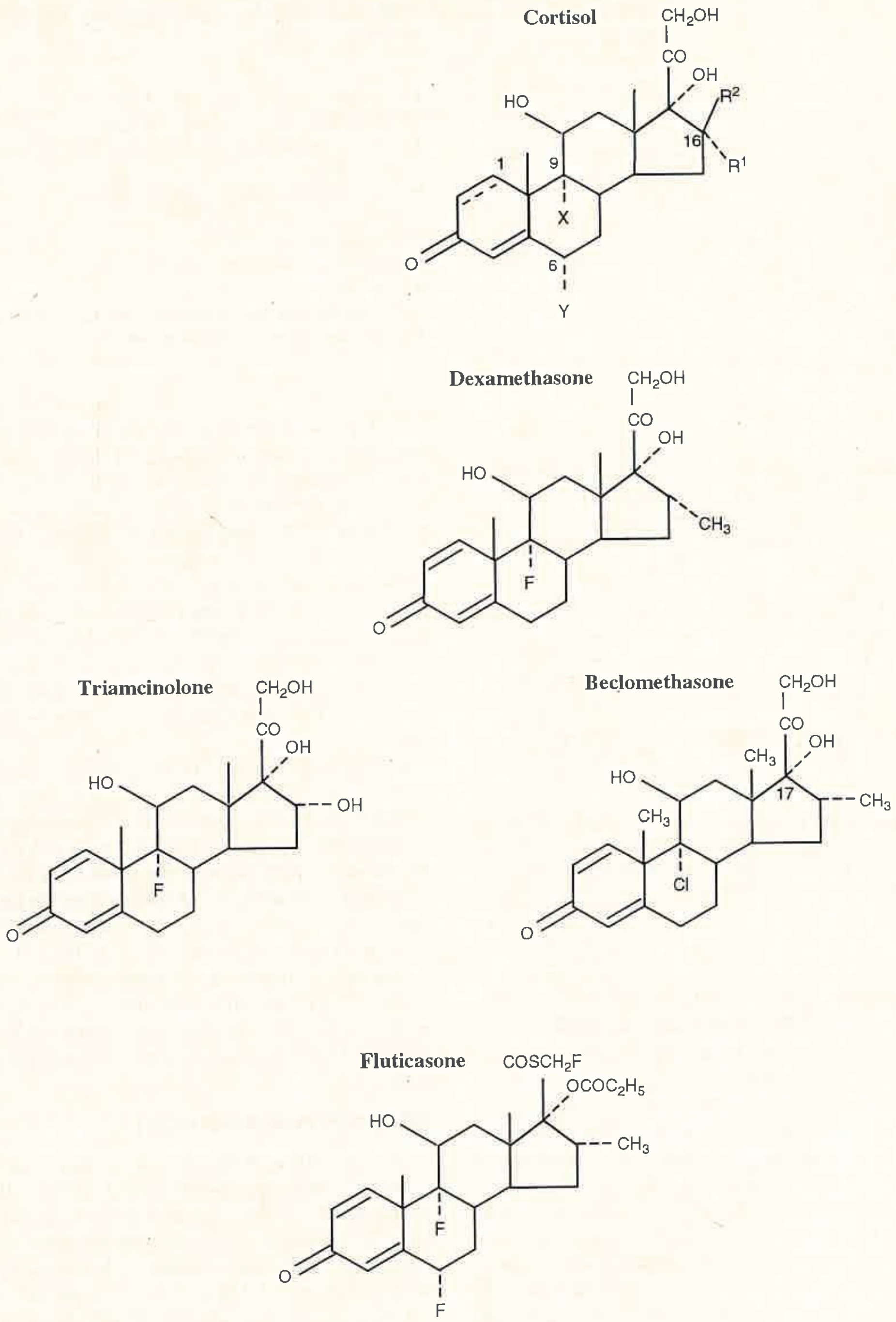

FIG. 1. Structural modifications of cortisol that produced the corticosteroids: dexamethasone, triamcinolone acetonide, beclomethasone dipropionate, and fluticasone propionate.

GR. The androstane nucleus, which is highly lipophilic, was therefore selected as the basis of the chemical program.[3] Topical activity was assessed by inhibition of croton oil–induced inflammation of the ear in a mouse model[4] and inhibitory activity at the hypothalamic-pituitary-adrenal (HPA) axis assessed by measuring reductions in circulating corticosteroids in response to ether stress.[5] The vasoconstriction/skin blanching assay[6]

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