Glucocorticoids & Mechanisms of Asthma

Clinical & Experimental Aspects

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Glucocorticoids and Mechanisms of Asthma

The symposium and these Proceedings are dedicated to Dr John H. Toogood (London, Ontario, Canada) in recognition of his many years of contribution to the research of respiratory disease. Dr Toogood has been a pioneer in the area of inhaled steroids and their impact on the inflammatory processes of asthma.

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Introduction

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On behalf of Astra Pharma, the organizers of this symposium, and the chairmen and speakers, I am pleased to welcome you to this meeting on corticosteroids and asthma. The last 20 years represent a real breakthrough in our understanding of the mechanisms and treatment of asthma. A vast amount of literature on mediators, cells and new therapeutic products, including inhaled steroids, has been published. This symposium will summarize these findings and outline new research developments.

First, however, I would like to give a brief historical account of the use of steroids in asthma.

In 1855 and 1856, the role of the adrenal glands was clearly determined by the description of what was subsequently called Addison's disease and by Brown-Sequard's finding that removal of adrenal glands caused early death in animals. At the beginning of the twentieth century, several investigators described the role of the adrenal glands in glucose and electrolyte metabolism and adrenal extracts became available. In 1932, Cushing first described the syndrome which would later be named after him. Between 1935 and 1940 the natural glucocorticoids were isolated, structurally identified and synthesized. ACTH was purified in 1943. Austrian-born Hans Selye, who later worked at the Université de Montréal, described his General Adaptation Syndrome, his stress theory, in 1946. The first therapeutic trials with compound E, now known as cortisone, and with ACTH took place from 1948 to 1950. The Nobel Prize was given to P.S. Hench, E.C. Kendall and T. Reichstein for their discovery of compound E. The first therapeutic trials with ACTH and cortisone in asthma were carried out at approximately the same time.

In 1950, Carryer et al. published the results of a study showing that asthma and hay fever symptoms were reduced when cortisone was administered [1] (Fig. 1).

These compounds were initially considered to be 'miracle' drugs and very high doses were administered. Nebulized cortisone was first used in the treat-

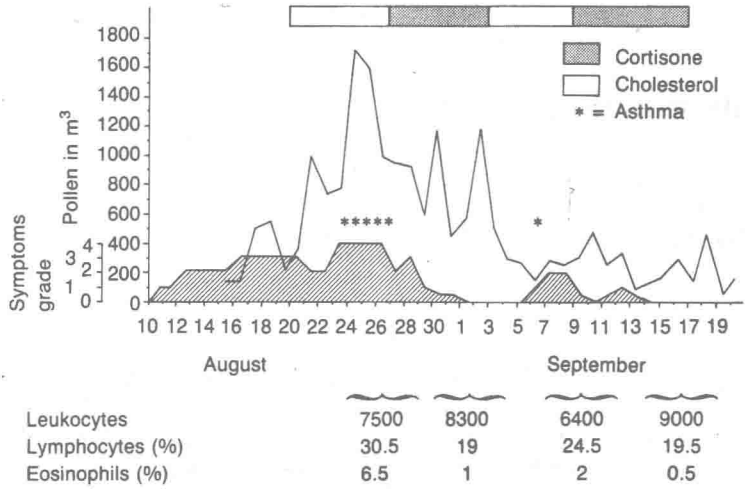


Fig. 1: The effect of cortisone on asthma and hay fever symptoms resulting from sensitivity to ragweed pollen in a single patient. (Reprinted from [1] with permission of the authors and publisher).

ment of pneumonia and asthma in the early 1950s [2, 3]. Clinicians rapidly became aware of significant side effects. This led to the synthesis of cortisone analogues such as prednisone and prednisolone.

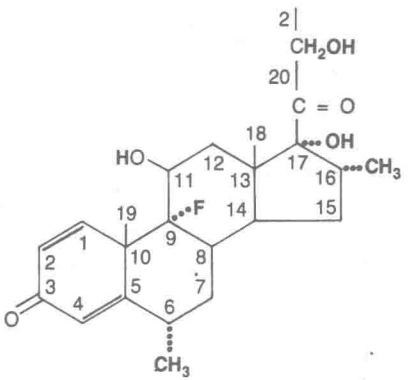
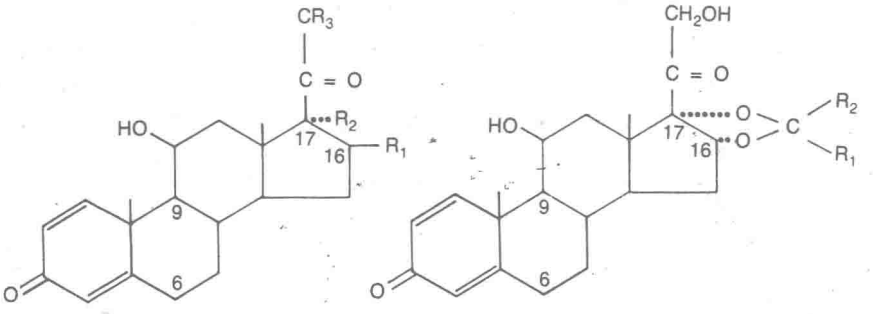


Fig. 2: Structure-activity relationship of adrenocorticosteroids. Light lines and letters indicate structural features common to compounds having anti-inflammatory action. Bold lines and letters indicate modifications that enhance or suppress characteristic activities. (Reprinted from [4] with permission of the authors and publisher.)

From 1960 onwards, researchers focused their attention on the development of topically active glucocorticoids for dermatological conditions. This led to the synthesis of lipid-soluble compounds which are absorbed less. The properties of these compounds were shown to be related to their vasoconstrictor action. A vast number of topical steroids were developed for dermatological purposes, and more than a 100 different topical steroids are currently in use.

Modification of several sites, i.e. nos. 6, 9, 16 and 17, can suppress or increase the anti-inflammatory properties of these compounds [4] (Fig. 2).



Esters Acetonides

Steroid	C-6	C-9	R_1	R_2	R_3	Vaso-constrictor score
Esters						
Fluocortin butyl ester	α-F	—	α-Me	H	$O_2C_4H_9$	+
Betamethasone valerate	—	α-F	β-Me	$OCOC_4H_9$	H_2OH	360
Beclomethasone dipropionate	—	α-C1	β-Me	$OCOC_2H_5$	$H_2OCOC_2H_5$	500
Clobetasol propionate	—	α-F	β-Me	$OCOC_2H_5$	H_2Cl	1870
Acetonides						
Flunisolide	α-F	—	Me	Me	—	+
Triamcinolone acetonide	—	α-F	Me	Me	—	75
Fluocinolone acetonide	α-F	α-F	Me	Me	—	100
Budesonide	—	—	H (isomeric)	C_3H_7	—	+

Fig. 3: Chemical structures of esters and acetonides and modifications of the chemical structures of various steroids in these two groups. (Reprinted from [5] with permission of the author and publisher.)

The first trials with betamethasone and beclomethasone were carried out in the UK in 1968. Since then, various steroid esters and acetonides have been developed. The topical anti-inflammatory activity of the compounds has been enhanced without increasing their systemic activity. Figure 3 shows the differences between esters and acetonides. Esters are represented primarily by betamethasone and beclomethasone and acetonides by flunisolide and budesonide [5].

Analogous to what happened in the field of dermatology a few years ago, there is no doubt that the next years will see the release of new inhaled steroid preparations which will have the advantages not only of causing fewer side effects and being less absorbed but which will also have heightened anti-inflammatory activity.

This symposium will focus on different aspects of asthma treatment with steroids. General topics on the mechanisms of asthma, the development of effective and safe inhaled glucocorticoids and a review of delivery systems will be covered. In addition, the acute and potentially chronic clinical benefits of glucocorticoids will be outlined. The present clinical attitude indeed favours the use of these preparations. This attitude is linked with recent emphasis on the central role of inflammation and airway hyperresponsiveness in asthma.

Finally, this symposium will honour an outstanding clinical research worker, Dr John Toogood (London, Canada). Dr Toogood is the author of numerous key publications and has made many important contributions to our knowledge of the use of oral and inhaled steroids including frequency of administration, dosing, side effects and comparisons of the efficacy and side effects of these preparations. I have always been particularly impressed by the remarkable quality not only of Dr Toogood's study designs but also of his data analysis.

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Mechanisms of asthma, bronchial hyperresponsiveness and action of glucocorticosteroids in asthma

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Introduction

Treatment with glucocorticosteroids (GCS), either by inhalation or by high oral dosing, has been shown not only to consistently reduce the symptoms of asthma but also to consistently reverse the exaggerated bronchoconstrictor response of asthmatics to inhaled spasmogens. This latter phenomenon, termed bronchial hyperresponsiveness (BHR), is thought to be a manifestation of the underlying pathophysiology of asthma [1]. This property of GCS, which is not seen with any other commonly used antiasthmatic therapy, has led to their use as first-line therapy in moderate to severe asthma in Europe and Australasia [2].

The mechanism and site of action of GCS in asthma are uncertain. Clarification is important for two reasons. First, it would be possible to design drugs which act directly at the site of action, thereby further reducing the side effect profile. Second, it may give an insight into the processes which are fundamental to the genesis or continuation of asthma.

Mechanism of asthma

Investigation of the mechanism of asthma has been simplified by the observation that asthmatic patients respond in an abnormal fashion to inhaled spasmogens [1]. The response is graded, with the patients with severe asthma [3] exhibiting the greatest sensitivity to the inhaled spasmogen. The