

Glucocorticoids & Mechanisms of Asthma

Clinical & Experimental Aspects

一九九一年十月廿二日

一九九一年 二日



Glucocorticoids and Mechanisms of Asthma

Clinical and Experimental Aspects

**Proceedings of a symposium in Toronto,
18–19 November 1988**

Editors:

F.E. Hargreave, J.C. Hogg, J.-L. Malo, J.H. Toogood



1989

Excerpta Medica

Amsterdam, Hong Kong, Manila, Princeton, Sydney, Tokyo



© 1989 Elsevier Science Publishers B.V. (*Excerpta Medica*) and AB DRACO

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the copyright holder.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, the Publisher recommends that independent verification of diagnoses and drug dosages should be made.

Current Clinical Practice Series 52

ISBN (*Excerpta Medica*) 90 219 9818 1

ISBN (Elsevier Science Publishing Company, Inc.) 0 444 81102 8

Library of Congress Cataloging-in-Publication Data

Glucocorticoids and mechanisms of asthma.

(Current clinical practice series ; 52)

Symposium and proceedings dedicated to John H. Toogood.

Includes bibliographies.

1. Asthma--Hormone therapy--Congresses.
2. Glucocorticoids--Therapeutic use--Testing--Congresses.
3. Toogood, John H.--Congresses. I. Hargreave, Frederick E. II. Toogood, John H. III. Series. [DNLM: 1. Asthma--drug therapy--congresses. 2. Glucocorticoids --therapeutic use--congresses. W1 CU786M no. 52 / WF 553 G567 1988] RC591.G55 1989 616.2'38061 89-11675 ISBN 0-444-81102-8 (Elsevier Science Pub. Co.)

Sole distributors for the USA and Canada

Elsevier Science Publishing Company, Inc.
52 Vanderbilt Avenue
New York, NY 10017
USA

Published by

Excerpta Medica
P.O. Box 1126
1000 BC Amsterdam
The Netherlands

Printed in The Netherlands by Hooiberg, Epe

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 treatment of inhaled steroids and their impact on the inflammatory process of

Glucocorticoids and Mechanisms of Asthma

It is clear that the studies presented, it was clear that it is not only the patients, considered by experienced physicians to be optimally treated, who were treated with inhaled steroids, but also the patients who were treated with oral steroids. In the studies presented, the number of patients who were treated with oral steroids was small. In Dr Addicott's Swedish study, this resulted in a small number of patients who were treated with oral steroids. Studies of this type are not likely to convince physicians to advocate the use of inhaled steroids as the first line of treatment for all but the mildest asthmatic patients. This is not to say, however, that the studies are not of value. Further, this position is not correct.

Several presentations referred to the pathogenesis of asthma, and the role of hyperresponsiveness and airway inflammation. Mechanisms of hyperresponsiveness and airway inflammation are not yet fully understood. However, it is probable that the best method for evaluating the role of airway inflammation in asthma is to use a method which allows the measurement of airway inflammation in asthmatic subjects. We do not know if this method can be used in the way proposed by Elizabeth Jones.



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.

Glucocorticoids and
Mechanisms of Asthma



List of speakers

E. Ädelroth

Department of Pulmonary Medicine, University Hospital, 901 85 Umeå,
Sweden

R. Brattsand

Research and Development Department, AB Draco, Tunavägen 43,
Box 34, 22 100 Lund, Sweden

D.W. Cockcroft

Division of Respiratory Medicine, Department of Medicine, University of
Saskatchewan, Saskatoon, Sask. S7N 0X0, Canada

R. Dahl

Lungeklinikken & Lungemedicinsk Afdeling, Århus Kommunehospital,
8000 Århus C, Denmark

M. Dolovich

Department of Nuclear Medicine, St. Joseph's Hospital, McMaster
University, 50 Charlton Avenue East, Hamilton, Ont. L8N 4A6, Canada

L.M. Fabbri

Istituto di Medicina del Lavoro, Università di Padova, Via Facciolati, 71,
35127 Padova, Italy

C.W. Frankish

Department of Medicine, University of Western Ontario, London, Ont.
N6A 4G6 Canada

R.W. Fuller

Department of Clinical Pharmacology, Royal Postgraduate Medical
School, Du Cane Road, London W12 0HS, UK

List of speakers

F.E. Hargreave

Firestone Regional Chest and Allergy Clinic, St. Joseph's Hospital,
McMaster University, 50 Charlton Avenue East, Hamilton, Ont.
L8N 4A6, Canada

J.C. Hogg

University of British Columbia, Pulmonary Research Laboratory,
St. Paul's Hospital, 1081 Burrard Street, Vancouver, BC V6Z 1Y6,
Canada

H.M. Jansen

Afdeling Longziekten, Academisch Medisch Centrum, Meibergdreef 9,
1105 AZ Amsterdam Zuidoost, The Netherlands

E.F. Juniper

Department of Clinical Epidemiology & Biostatistics, McMaster
University, 1200 Main Street West, Hamilton, Ont. L8N 3Z5, Canada

G.H. Koëter

Afdeling Interne Geneeskunde, Academisch Ziekenhuis Groningen,
Oostersingel 59, 9715 EZ Groningen, The Netherlands

L.A. Laitinen

Research and Development Department, AB Draco, Tunavägen 43,
Box 34, 22 100 Lund, Sweden

G.F. MacDonald

Grey Nuns Hospital, 3015-62 Street, Edmonton, Alta. T6L 5X8, Canada

J.-L. Malo

Hôpital du Sacré-Cœur de Montréal, 5400, Boulevard Gouin Ouest,
Montréal, Qué. H4J 1C5, Canada

J. Molema

Medisch Centrum Dekkerswald, Universitair Longcentrum, Postbus 9001,
6560 GB Groesbeek, The Netherlands

P.M. O'Byrne

Department of Medicine, McMaster University, 1200 Main Street West,
Hamilton, Ont. L8N 3Z5, Canada

List of speakers

S. Pedersen

Department of Paediatrics, Kolding Sygehus, 6000 Kolding, Denmark

C.G.A. Persson

Research and Development Department, AB Draco, Tunavägen 43,
Box 34, 22 100 Lund, Sweden

J.H. Toogood

Department of Medicine, University of Western Ontario and Allergy
Clinic, Victoria Hospital, 375 South Street, London, Ont. N6A 4G5,
Canada

S.J. Williams

Stoke Mandeville Hospital, Mandeville Road, Aylesbury, Bucks
HP21 8AL, UK

Contents

List of speakers	IX
Introduction	1
<i>J.-L. Malo</i>	
Mechanisms of asthma, bronchial hyperresponsiveness and action of glucocorticosteroids in asthma	5
<i>R.W. Fuller and P.J. Barnes</i>	
Discussion	13
Development of glucocorticosteroids with lung selectivity	17
<i>R. Brattsand</i>	
Discussion	39
Safety of inhaled glucocorticosteroids	40
<i>S. Pedersen</i>	
Discussion	52
Therapeutic aerosol delivery systems	54
<i>M. Dolovich</i>	
Discussion	65
Side effects of inhaled steroids	68
<i>S.J. Williams</i>	
Discussion	86

Contents

Efficacy of oral vs inhaled glucocorticosteroids <i>J.H. Toogood, B.H. Jennings, S.A. Johansson and J.C. Baskerville</i>	87
Discussion	101
Mode of action of inhaled budesonide: topical or systemic? <i>J.H. Toogood, C.W. Frankish, J.C. Baskerville, S.A. Johansson and B.H. Jennings</i>	105
A comparison of budesonide and placebo in oral-steroid- dependent asthmatics: a preliminary analysis <i>G.F. MacDonald, A. Knight, J. Fleetham, B. Sproule and R. Dales</i>	111
Prednisolone-sparing effects of budesonide: European experiences and cost savings <i>E. Ädelroth</i>	125
Discussion	132
General discussion	134
Airway hyperresponsiveness: methodological aspects <i>D.W. Cockcroft</i>	135
Discussion	146
Corticosteroids in patients with asthma and chronic airflow obstruction <i>G.H. Koëter, T.E.J. Renkema, B. Auffarth, Th.W. van der Mark, J.G.R. de Monchy, D.S. Postma and H.F. Kauffman</i>	148
Discussion	155

Long-term effects of an inhaled steroid (budesonide) on airway responsiveness and clinical asthma severity: a double-blind randomized controlled trial	157
<i>E.F. Juniper, P.A. Kline, M.A. Vanzielegheem and F.E. Hargreave</i>	
Discussion	159
Pharmacological treatment of airway hyperresponsiveness in allergic asthma: a comparative study of inhaled cromoglycate vs inhaled budesonide	162
<i>J. Molema, C.L.A. van Herwaarden and H.Th.M. Folgering</i>	
Discussion	176
Effects of budesonide on early and late asthmatic reactions	178
<i>R. Dahl</i>	
Discussion	183
Antiasthma drugs in toluene diisocyanate-induced asthma	186
<i>C.E. Mapp, P. Chiesura Corona, M. Plebani and L.M. Fabbri</i>	
Discussion	194
The pathogenesis of airway hyperresponsiveness in asthma	197
<i>P.M. O'Byrne, E.E. Daniel, G.L. Jones and P.J. Manning</i>	
Discussion	213
Epithelial damage	215
<i>L.A. Laitinen</i>	
Discussion	230

Contents

Plasma leakage in inflamed airways. What glucocorticoids tell us about obstructive airway disease	232
<i>C.G.A. Persson</i>	
Discussion	240
Local immunopathologic studies using bronchoalveolar lavage in patients with asthma	243
<i>E.A. van de Graff, T.A. Out and H.M. Jansen</i>	
Discussion	260
New developments in the pathology of bronchial asthma	262
<i>J.C. Hogg, A.L. James and P.D. Pare</i>	
Discussion	269
General discussion	272
Conference summary	274
<i>P.M. O'Byrne</i>	

Introduction

J.-L. Malo

Hôpital du Sacré-Cœur, Montréal, Canada

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-

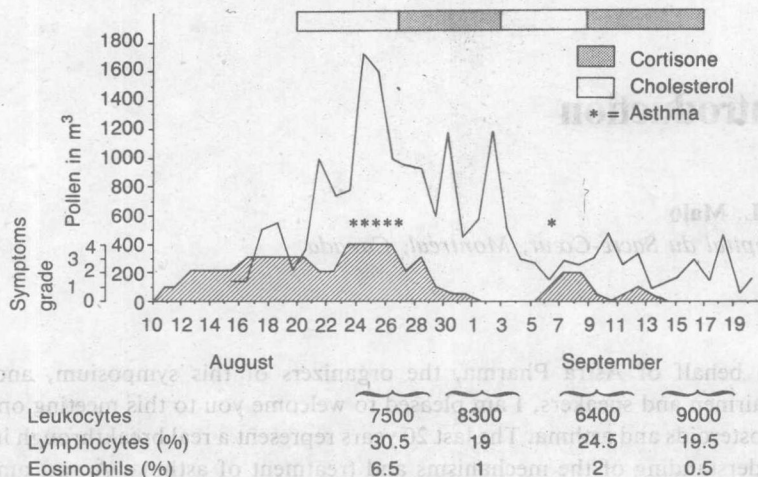


Fig. 1: The effect of cortisone on asthma and hay fever symptoms resulting from sensitivity to ragweed pollen in a single patient. (Reprinted from [1] with permission of the authors and publisher).

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.

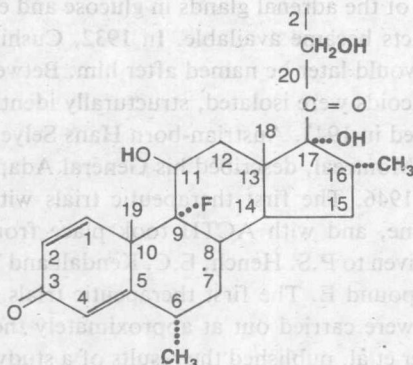
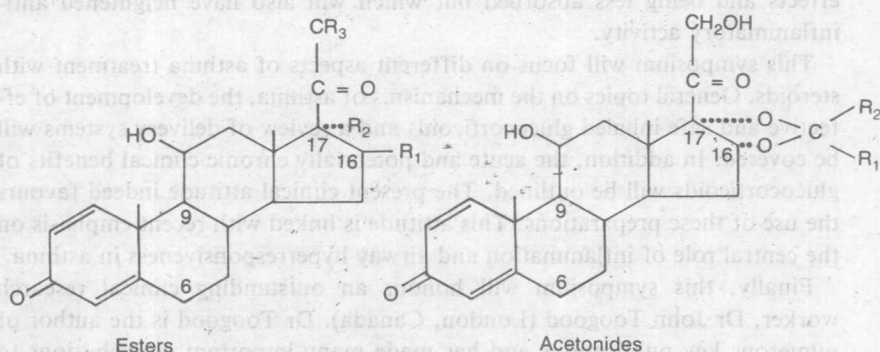


Fig. 2: Structure-activity relationship of adrenocorticosteroids. Light lines and letters indicate structural features common to compounds having anti-inflammatory action. Bold lines and letters indicate modifications that enhance or suppress characteristic activities. (Reprinted from [4] with permission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



Steroid	C-6	C-9	R ₁	R ₂	R ₃	Vaso-constrictor score
<i>Esters</i>						
Fluocortin butyl ester	α-F	—	α-Me	H	O ₂ C ₄ H ₉	+
Betamethasone valerate	—	α-F	β-Me	OCOC ₄ H ₉	H ₂ OH	360
Beclomethasone dipropionate	—	α-C1	β-Me	OCOC ₂ H ₅	H ₂ OCOC ₂ H ₅	500
Clobetasol propionate	—	α-F	β-Me	OCOC ₂ H ₅	H ₂ Cl	1870
<i>Acetonides</i>						
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 ₃ H 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.

References

1. Carrier HM, Koelsche GA, Prickman LE et al. The effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. *J Allergy* 1950; 21: 282-7.
2. Reeder WH, Mackey GS. Nebulized cortisone in bacterial pneumonia. *Dis Chest* 1950; 18: 528-34.
3. Gelfand ML. Administration of cortisone by the aerosol method in the treatment of bronchial asthma. *N Engl J Med* 1951; 245: 293-4.
4. Haynes RC, Murad F. Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis. In: Gillman A, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics*. 7th ed. New York: Macmillan, 1985; 1474.
5. Harding SM. Corticosteroids. In: Buckle DR, Smith H, eds. *Development of anti-asthma drugs*. London: Butterworths, 1984; 297-313.

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

R.W. Fuller¹ and P.J. Barnes²

¹ Department of Clinical Pharmacology, Royal Postgraduate Medical School and ² Department of Thoracic Medicine, National Heart and Lung Institute, London, UK

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