

CRC

HANDBOOK
of
CARDIOVASCULAR
and
ANTI-INFLAMMATORY
AGENTS

Matthew Verderame

CRC

PRESS

CRC Handbook of Cardiovascular and Anti-Inflammatory Agents

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DEDICATION

To my typist and companion and the mother of our four children — Fran.

PREFACE

The *CRC Handbook of Anti-Inflammatory and Cardiovascular Agents* is a companion to five other handbooks in this pharmaceutically related set published by CRC Press. The titles of the other five follow: *Handbook of Chemotherapeutic Agents* (Volumes I and II), *Handbook of CNS Agents and Local Anesthetics*, *Handbook of Autonomic Drugs and Autacoids*, and *Handbook of Hormones, Vitamins, and Radiopaques*.

The six handbooks represent a systematic collection of selective chemical and pharmacological reference data on drugs drawn from the major categories of therapeutically important agents. For the principal classes of drugs, or for individual drugs which do not belong to a particular class, the following topics were addressed: mechanism of action, structure-activity relationships, pharmacokinetics, uses and dosage, toxicity (including drug interactions), and physical-chemical and other data. Drug metabolism data were heavily emphasized in the pharmacokinetics sections. The term "toxicity" was used broadly to also include side effects. Generally included in the physical-chemical and other data sections was such information on the drug as the chemical name, formula, melting point, pKa value(s), solubility and stability data, physical description, salt forms, and any other property deemed worthy of inclusion.

Other topics generally considered included historical aspects leading to or associated with the development of the class of drugs, possible causes of the condition or disease state for which the drugs are used, life cycles of organisms against which the chemotherapeutic agents are used, testing methods employed in the screening of potentially useful compounds, and review articles covering the fields. Chemical syntheses were not emphasized. However, this topic received significant attention in a few sections. Figures were used appropriately to illustrate a point or concept, especially in the mechanism of action sections.

In this series of reviews, emphasis was placed on the most useful drugs associated with each physiological class or disease entity. The monograph format was used extensively, not only to denote the most useful members, but also to provide a close examination of these agents. Comparative pharmacological or therapeutic data on the principal drugs within the classes provide additional, practical information.

Monographs of drugs with useful multiple functions are appropriately placed in more than one section and cross-referenced. Though necessitating some repetition of data, these monographs generally complement each other and maintain a continuity of thought and application.

Newer and/or experimental drugs have also been included to round out the coverage and to present current knowledge and possible future trends.

This set of reference books should have appeal and utility for the practitioners and students of medicinal chemistry, pharmacology, pharmacy, and medicine. It should also be useful to researchers in the pharmaceutical industry and in other allied health professions.

A special debt of gratitude is extended to the many contributors who labored long and diligently to prepare their manuscripts for publication. Also, for their counsel and cooperation, the dedicated assistance of the Advisory Board is acknowledged with sincere appreciation.

The editorial assistance of the CRC staff and, in particular, the coordinating efforts of Ms. Amy Skallerup must not go unmentioned.

Finally, it is our hope that the reader will find these first edition handbooks interesting, useful, and valuable. Comments for improvement will be gratefully received.

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THE EDITOR

Matthew Verderame, Ph.D., is Professor of Medicinal Chemistry and Head of the Department of Chemical and Physical Sciences at the Albany College of Pharmacy, Union University. Dr. Verderame received his undergraduate education at the University of Connecticut, where he earned the Bachelor's degree in Chemistry in 1950. At the University of Wisconsin, he received an M.S. degree in Pharmacy in 1952 and the Ph.D. degree in 1955 in Pharmaceutical Chemistry. In 1954, he joined the faculty at the Albany College of Pharmacy as an Assistant Professor and moved through the ranks to his present position. Dr. Verderame's education was enhanced by his attendance of NSF-sponsored institutes at the University of North Carolina in 1962, Michigan State University in 1964, Duke University in 1969, and State University of New York in Albany in 1974. From 1955 through 1968, Dr. Verderame received consecutive year-long research grants from the Sterling-Winthrop Research Institute. In 1968 and again in 1973, he was cited for his contributions to teaching by receiving the Lederle Award. Courses which he regularly teaches include Medicinal Chemistry, Qualitative Organic Analysis, and Drug Analysis. The principal areas of synthetic research of Dr. Verderame include the preparation of various derivatives of cysteine, methionine, and piperazine as possible anti-infective agents. He also synthesized organo tin compounds and ether derivatives of cyclic hydrocarbons as possible anti-infective agents. He has authored several publications and has refereed technical papers. Dr. Verderame is a member of the American Chemical Society, Rho Chi, Sigma Xi, Phi Sigma, Rho Pi Phi, the American Association for the Advancement of Science, the New York Academy of Sciences, the American Association of University Professors, and Phi Lambda Upsilon.

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ANTI-INFLAMMATORY STEROIDS

Michael J. Green and Barry N. Lutsky

INTRODUCTION

The importance of glucocorticoids as therapeutic agents is generally appreciated. In fact, over the course of 33 years since the first report of the effectiveness of cortisone in the treatment of rheumatoid arthritis,¹ both natural and synthetic glucocorticoids have received wide clinical and experimental application as anti-inflammatory agents. This class of drugs has attracted such intense scrutiny because they have been regarded as the most effective type of agents which are capable of reversing all of the clinical manifestations of inflammation, namely, pain, erythema, heat, and swelling.²

Corticosterone was identified in 1937 by Reichstein et al.³ and Kendall and co-workers,⁴ and this work added impetus to the study of the physiological roles of adrenocorticotrophic hormone (ACTH) and adrenocortical steroids. Cortisone was isolated soon thereafter in Kendall's laboratory and a partial synthesis of cortisone, the forerunner of most presently available synthetic agents, was reported in 1946.⁵ In 1948, its usefulness in rheumatoid arthritis was described by Hench et al.¹ Large quantities of cortisone became available when the chemists at Merck succeeded in developing a workable synthesis from bile acids.⁶ The ensuing effort within the pharmaceutical industry has yielded much more potent glucocorticoids (such as betamethasone and dexamethasone) which lack at least one important adverse effect, that of sodium retention. This success spurred the search for synthetic corticoids with a better separation of anti-inflammatory from other major side effects, an effort which has thus far met with limited success. In fact, this may be a consequence of a direct relationship between anti-inflammatory activity and side effects. However, in the area of corticoids designed for local application, important dissociation of the local activity from the potential for systemic effect has been achieved. It appears that present world-wide emphasis in corticoid development involves extension of this effect to further dissociate local therapeutic effects from both systemic and local toxicity. It is to be hoped the decade of the 1980s will witness interesting developments in this regard.

MECHANISMS OF ACTION

In their control of steroid-responsive diseases, anti-inflammatory steroids are thought to exert three primary activities — anti-inflammatory, immunosuppressive, and antiproliferative. Despite their obvious widespread usefulness and the length of time that they have been subjects of research, the mechanisms of action of corticoids are still very poorly understood. In fact, since the etiologies of the various corticoid-responsive disease states differ, the effectiveness of this class of chemotherapeutic agents is testimony to their diversity of activities. This plethora of disparate effects, and the discussion of their relevance to physiological vs. pharmacological processes, has been the subject of fine recent reviews, and the reader is directed to these.^{2,7-11}

The naturally occurring adrenal steroids produce important effects on both electrolyte balance and glucose metabolism. The classical means of determining the ratios between these two effects, that of utilizing sodium retention in adrenalectomized animals and hepatic glycogen deposition, still serves as the basis for classification of corticosteroids into categories of mineralocorticoid and glucocorticoid, respectively. Only the natural and synthetic glucocorticoids which possess useful anti-inflammatory properties are discussed below.

Briefly, and as described in the references cited above, corticoids are thought to exert their biological effects by altering protein synthesis, presumably through interaction with

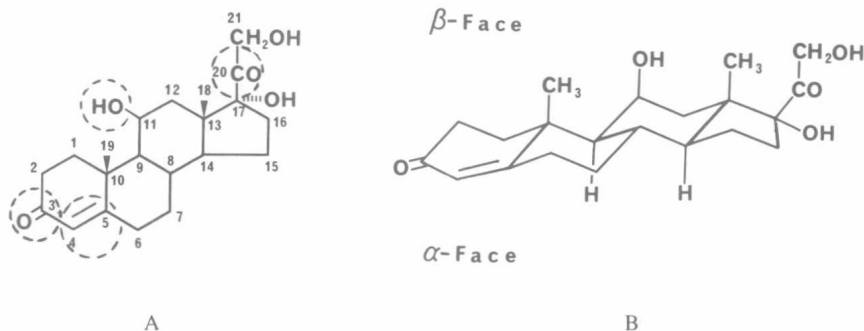


FIGURE 1. Hydrocortisone. (A) Structure and steroid numbering system; (B) perspective drawing.

specific glucocorticoid receptor proteins in the cytoplasm of corticoid-sensitive cells. These receptors, which have been identified in many tissues, become activated, enter the nucleus, and bind to chromatin, resulting in transcription and translation. The overall effect of glucocorticoids has been considered catabolic; thus, among other effects, these agents have been shown to generally decrease glucose (and other hexose) uptake and transport, protein, RNA and DNA synthesis, ATP levels, and the production of certain hormones (e.g., ACTH and prolactin). They also inhibit or stimulate growth hormone release, alter fatty acid metabolism and transport, alter cell structure, decrease cell viability, and increase cell death.

However, under certain circumstances, e.g., specific cell types and/or corticoid concentration, stimulatory effects may be observed, including enhanced secondary antibody response, liver enzyme and protein induction, stimulation of glycogen synthesis, enhanced growth of fibroblasts (under specific conditions) and viruses, and accumulation/induction of pancreatic amylase and chymotrypsin.

Within the last 4 years, increasing attention has focused on the possible role of glucocorticoids as inducers of the synthesis of inhibitory protein(s) which directly mediate catabolic and even anabolic events. In fact, Tsurufugi and co-workers¹² (among others) have proposed that the anti-inflammatory effects of corticoids occur through gene expression and the subsequent synthesis of specific proteins. Two laboratories have described corticoid-induced phospholipase A₂ inhibition where the inhibitory effects are attributable to an inhibitory protein called macrocortin¹³ or lipomodulin.¹⁴

Phospholipase A₂ is the major enzyme responsible for the release of arachidonic acid from membrane phospholipids. Hence, inhibition by these proteins would limit the amount of substrate available for the production of both cyclooxygenase (PG-E₂, PG-G₂, PG-H₂, thromboxanes) and lipoxygenase-derived (HPETEs, HETEs, leukotrienes) proinflammatory arachidonic acid metabolites. Nonsteroid anti-inflammatory agents, e.g., aspirin and indomethacin, act by inhibition of only the cyclooxygenase pathway.¹⁵ It is important, however, to note that glucocorticoids effectively inhibit the proinflammatory actions of a number of mediators, including histamine, serotonin, bradykinin, PG-E, LT-C, and LT-D.¹² Hence, ascribing the anti-inflammatory effects of glucocorticoids solely to the inhibition of phospholipase would be far too simplistic.

GENERAL STRUCTURE-ACTIVITY RELATIONSHIPS

Hydrocortisone is a C₂₁ steroid with a two-carbon side chain at C₁₇ of the typical tetracyclic steroid molecule. This structure, with the steroid numbering system, is shown in Figure 1A. The flat, lathe-like shape of the molecule, with clearly distinguishable α and β faces, is shown in Figure 1B. This shape is kept rigid by the system of trans fused rings and only the side chain has conformational mobility.

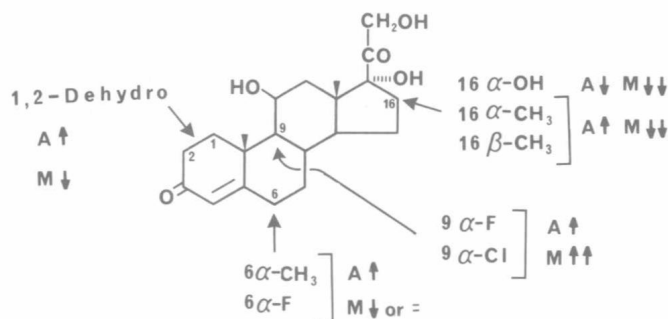


FIGURE 2. Structural modifications which alter anti-inflammatory (A) and mineralocorticoid (M) activity of hydrocortisone.

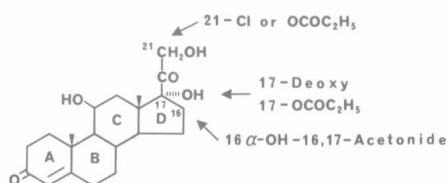


FIGURE 3. Structural modifications which increase topical activity of anti-inflammatory steroids.

Up until 15 years ago, it could be fairly stated that four of the functional groups of hydrocortisone (those circled in Figure 1) were essential for anti-inflammatory activity.¹⁶ However, such has been the ingenuity of medicinal chemists since then that apparently none of these positions can now be considered to be essential for activity, although their presence may be desirable for optimal potency.

The bulk of the structure-activity relationships¹⁷ that have been derived since the anti-inflammatory effects of hydrocortisone were discovered have involved the addition of further groups to the molecule. These additions changed both the desired anti-inflammatory properties and the side effects, principally the mineralocorticoid activity, of hydrocortisone. An analysis of these changes has led to a number of general "rules" relating structure with activity, which are shown schematically in Figure 2. To a large extent these effects are additive. For example, introduction of a fluorine atom at the 9 α -position dramatically increases not only the anti-inflammatory potency, but also the mineralocorticoid potency to the point where the product 9 α -fluorohydrocortisone is used clinically for the latter activity, e.g., in Addison's disease.¹⁸ This effect can, however, be largely eliminated by the further introduction of a 16-methyl group (either α or β) and a double bond between C₁ and C₂, both of which moderately increase anti-inflammatory activity while greatly reducing mineralocorticoid effects. These compounds are dealt with in the section entitled "Monographs".

Further structural changes can also be made to maximize the local effects of these steroids. These modifications are shown in Figure 3 and involve principally ring D and the side chain at C₁₇. Whether these changes minimize systemic absorption by increasing their solubility in fatty tissues or reduce systemic activity of the parent molecule is not clear, but the net effect is to minimize systemic side effects of the steroid when applied topically to either the skin, the lungs, or the nasal mucosa. Converting the polar hydroxyl groups to esters or acetonides increases the lipophilicity of the molecules, which enhances penetration of the steroid into the skin.⁵³ Whether the ester groups at C₁₇ and/or C₂₁ have to be hydrolyzed to the alcohols to be active has not been established. However, since there are highly active steroids in which one or the other of these hydroxyl groups are missing altogether, it would seem that such bioactivation is not obligatory.

For intraarticular therapy, insoluble, microcrystalline suspensions of corticoids are injected directly into the joint cavity. 6 α -Methylprednisolone 21-acetate is used for short-term therapy while triamcinolone hexacetonide is effective for up to 2 to 3 months.¹⁹ In the latter case, it seems reasonable to ascribe this long duration of action to the slow rate of hydrolysis of the highly hindered ester to the free alcohol in the synovial fluid.

In general, 11-keto steroids are not used as topical or intraarticular agents because they are much less active by these routes than the 11 β -hydroxy steroids. Since both forms are well absorbed by the skin,²⁰ this is ascribed to the inability of the skin (and synovial fluid) to be able to reduce the 11-ketone to the active 11 β -hydroxy form of the steroid. However, this can only be part of the reason since, at least in vitro, human skin has been shown to convert cortisone into hydrocortisone.²¹

The steroids that are used for topical and intraarticular therapy are covered in the tables of the section entitled "Monographs". Other corticoids for which at least some evidence of clinical activity has been obtained and which involve structural features not described above are also covered in these tables as well as in the section entitled "Infrequently Used and Newer Experimental Steroids".

METHODS FOR EVALUATING CORTICOSTEROIDS

An examination of the literature describing laboratory testing of new glucocorticosteroids reveals that the same basic screens that were described 20 years ago are still used today. Several of these were described in extensive reviews of standard laboratory assays such as that by Sarett et al.¹⁷ (and references cited therein). Briefly, these included

- Cotton pellet granuloma and croton oil granuloma pouch assays in rats for determination of anti-inflammatory/antiproliferative activities
- Thymolysis and adrenal suppression in rodents for effects on lymphatic tissues and hypothalamus-pituitary-adrenal axis
- Body weight depression and nitrogen excretion for general catabolic effects
- Eosinopenia in rodents for effects on cellular blood elements
- Liver glycogen for gluconeogenic effects
- Sodium retention for electrolyte effects

In addition, general anti-inflammatory screens such as carrageenan-induced rat paw edema,²² arthus reactions,²³ adjuvant arthritis induction in rats,²⁴ etc. have also been used to select corticosteroids on the basis of potency. More recently, research groups have evaluated corticosteroids at more fundamental levels such as determination of growth inhibition of cultured fibroblast²⁵ or binding to specific glucocorticoid receptors.²⁶

In the last decade, the synthesis of corticoids intended for topical/local use has appropriately resulted in proliferation of topical assays in animals and humans, designed to predict eventual topical efficacy in man. The earliest effects involved local rather than topical administration. For example, subcutaneously implanted cotton pellets result in granuloma formation, the extent of which is determined by removal and drying to constant weight.²⁷ By impregnating the pellet with the test steroid, one can determine the local anti-inflammatory potency. The croton oil pouch technique may be similarly utilized. In this test, croton oil as phlogistin is injected into an air pouch on the backs of rats, following which fluid and granulomatous tissue forms after several days.²⁸ Injection of corticoid directly into the inflammatory sites allows determination of local anti-inflammatory effects and, if desired, determination of systemic effects on other tissues and body weight.²⁹

One of the first topical tests was the croton oil induced edema of rat ears developed by Tonelli et al.³⁰ It allows facile evaluation of activity/potency by simple determination of ear

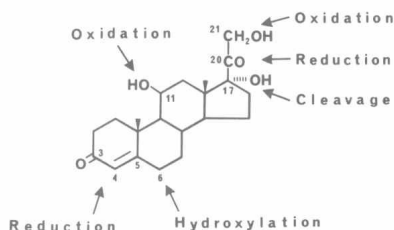


FIGURE 4. Sites of metabolism of systemic corticosteroids.

weight several hours following application. By the application of phlogistin and drug to one ear only, and croton oil alone to the contralateral ear, systemic anti-inflammatory effects may be measured. Many variations of the Tonelli test have evolved, including use of the procedure in mice³¹ and rabbits.³² Other topical assays include inflammation of ears or back skin provoked by mixtures of croton oil and sulfuric acid,³³ cantharidin,³⁴ tetrahydrofurfuryl alcohol,³⁵ and heat,³⁶ as well as contact sensitization reactions in rodents provoked by sensitizers such as oxazalone³⁷ and dinitrofluorobenzene.³⁸ Models for the evaluation of mitotic inhibition and/or DNA synthesis have also been established and include essential fatty acid-deficient rodents,³⁹ UV light-stimulated epidermis,⁴⁰ cellophane tape-stripped epidermis,⁴¹ and vaginal mucosa.⁴²

In humans, there is a fine parallelism between the topical efficacy of glucocorticoids in disease states such as psoriasis and eczema and their ability to produce cutaneous blanching. This test, called the vasoconstrictor assay,⁴³ has proved invaluable in allowing preclinical evaluation of new topical corticoids in humans. It has also proved useful in evaluating formulated corticoids. Other than certain conditions of experimental cutaneous inflammation in humans, the vasoconstriction test and its subtle modifications represent the only assay in humans which has had sustained utility.

METABOLISM

Corticosteroids are metabolized⁴⁴ chiefly in the liver, and the metabolites are excreted largely in the urine as conjugates with glucuronic acid. The chief sites of metabolism of the steroid structure for systemically administered corticosteroids are shown in Figure 4.⁴⁵ The relative importance of any one of these pathways varies with the structural modifications of the steroid nucleus.

C₁₁ Oxidation-reduction makes the 11 β -hydroxyl and the 11-ketone groups metabolically equivalent. Thus, clinically, oral cortisone and hydrocortisone are considered to be of almost equal therapeutic potency, yet only the 11 β -hydroxy compound hydrocortisone is actually active as an anti-inflammatory agent.⁴⁶ Ring A reduction occurs to give both 5 α - and 5 β -3 α -hydroxy-4,5-dihydro metabolites.⁴⁷ The importance of this pathway is reduced by the addition of a 1,2-double bond and is essentially blocked by a 9 α -F.⁴⁸

Metabolism of the side chain occurs by three pathways.⁴⁵ The most important of these is C₂₀ reduction, which gives both 20 α - and 20 β -hydroxy metabolites. Metabolism is largely shunted away from this pathway by substitution at C₁₆ of either a hydroxyl or methyl group. Another pathway involving oxidative cleavage of the side chain gives metabolites with a ketone group at C₁₇. Oxidation at C₂₁ to give a carboxylic acid also occurs, but usually to a minor extent.⁴⁵

6 β -Hydroxylation is a pathway for the metabolism of most anti-inflammatory steroids.⁴⁵ Its importance, however, is increased when Ring A reduction and side chain metabolism is blocked by structural modifications. This pathway even operates when a 6 α -F is present, in these cases with loss of the fluorine atom.⁴⁹

USES⁵⁰

As will be described in the monographs, the naturally occurring glucocorticoids hydrocortisone and cortisone, by virtue of their significant effects on electrolyte balance, are considered adequate replacement therapy in adrenocortical deficiency states due to structural or functional lesions of the adrenal cortex and/or anterior pituitary, e.g., in Addison's disease. The synthetic analogs, lacking mineralocorticoid activity, are used primarily for their anti-inflammatory/antiproliferative properties, although they may be used in conjunction with mineralocorticoids for the same conditions. The therapeutic uses of glucocorticoids in non-endocrine disease include

- Neoplastic diseases, including leukemias and lymphomas
- Rheumatic diseases, including rheumatoid and psoriatic arthritis, ankylosing spondylitis, bursitis, osteoarthritis, acute tendonitis
- Collagen diseases, such as systemic lupus erythematosus, polymyositis, mixed connective disease syndrome (not scleroderma, considered relatively unresponsive to corticoids)
- Dermatological disorders, including psoriasis, various eczematous conditions (e.g., atopic, contact, and seborrheic dermatitis), pemphigus, exfoliative dermatitis, mycosis fungoides
- Allergic diseases, including allergic rhinitis, bronchial asthma, drug hypersensitivity, and serum sickness reactions
- Ophthalmic diseases, including allergic conjunctivitis, keratitis, and other inflammatory states not masking bacterial, viral, or fungal infections or mechanical lacerations and abrasions of the eye
- Renal diseases such as nephrotic syndrome
- Hematologic disorders, including thrombocytopenia and hemolytic anemia
- GI disorders, including enteritis and chronic ulcerative colitis
- Liver diseases, such as alcoholic hepatitis, chronic active hepatitis, subacute hepatic necrosis, and nonalcoholic cirrhosis

Corticoids have also been found to be useful in treating cerebral edema and as immunosuppressives in transplantation; however, their use in shock remains controversial.

TOXICITY AND SIDE EFFECTS^{8,9,50}

Many of the general catabolic effects which may be responsible for producing anti-inflammatory, antiproliferative, and immunosuppressive effects can also lead to serious side effects following prolonged use of pharmacological doses. Such effects can include muscle weakness and degeneration, osteoporosis due to increased bone resorption and decreased bone formation, inhibition or arrest of growth in children, impaired wound healing, skin fragility and atrophy, negative nitrogen balance due to protein catabolism, susceptibility to infection, hyperglycemia, and glycosuria (if not controlled by diet or insulin), and cataracts. Corticoid effects on fat mobilization can lead to Cushingoid symptoms (e.g., "moon face", "buffalo hump", etc.). Hypothalamus-pituitary-adrenal suppression is sufficiently common to necessitate prolonged withdrawal from chronic therapy; failure to do so may result in characteristic withdrawal symptoms of fever, muscle and joint pain, malaise, and inadequate response to stress. Other potential consequences of prolonged glucocorticoid therapy include impaired fluid and electrolyte balance (much less with the new synthetic glucocorticoids) and behavioral disturbances ranging from nervousness, moodiness, insomnia, and euphoria to frank personality changes, including severe depression, psychosis, and suicidal tendencies.

The previous belief that corticoids caused or exacerbated peptic ulcers has been somewhat modified by suggestions of this relationship existing only in rheumatoid arthritis patients.

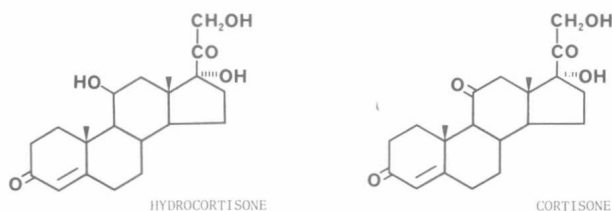
MONOGRAPHS

Included are monographs on the seven most widely used classes of corticosteroids and their derivatives:

- Hydrocortisone/cortisone
- Prednisolone/prednisone
- Triamcinolone
- Betamethasone
- Dexamethasone
- Corticosterone

Less widely distributed and newer experimental steroids are presented in the section entitled "Infrequently Used and Newer Experimental Steroids".

HYDROCORTISONE/CORTISONE



Mechanisms of Action

Both cortisone and hydrocortisone are naturally occurring hormones produced by the adrenal cortex and, in man, are the most important glucocorticosteroids. It is believed the 11-ketone in cortisone must be reduced to the 11 β -hydroxy moiety in hydrocortisone in order to exert biological effects.⁴⁶ One feature distinguishing these natural hormones from the synthetic corticosteroids is their specific binding to transcortin (corticosteroid binding globulin), whereas the synthetics bind to the albumin fraction of plasma.⁵¹ The mechanistic implications of differential binding can be surmised as influencing the kinetics of the steroid-induced response and/or steroid metabolism.

Structure-Activity Relationships

As discussed before, hydrocortisone and cortisone resulted from a systemic search for the active constituents of hog adrenal glands by Kendall at the Mayo Clinic.⁶ These two compounds formed the basis for 3 decades of analog synthesis and provided the parent structural units for six of the following semisynthetic glucocorticosteroids; details of these structural manipulations are given in the appropriate monographs.

The observation⁵² that 9 α -fluorination dramatically increased both glucocorticoid and mineralocorticoid potencies provided a key impetus to subsequent synthetic efforts. Similarly important was the understanding of the physicochemical interrelationships between the lipophilic steroidal drugs and the skin. Thus, increasing the lipophilic nature of these drugs by esterification at the 17- and/or 21-positions significantly increased topical corticosteroid potency, in comparison to hydrocortisone alcohol.⁵³

Pharmacokinetics

The metabolism of hydrocortisone has been more extensively studied than any other

corticosteroid. A total of 70% of an oral dose of hydrocortisone is metabolized by the liver to very weakly active or inactive substances.⁴⁵ These metabolites are mainly conjugated derivatives of Ring A reduced compounds (>85%) in which further metabolism via side chain reduction (25%) and cleavage (8%) has occurred to some extent. The reversible interconversion of the 11 β -hydroxy function occurs rapidly in the liver, but slowly in extrahepatic tissues (including the skin), probably accounting for the systemic biological equivalence of cortisone and hydrocortisone, but inactivity of topical cortisone in human dermatoses.

Hydrocortisone is normally bound to plasma proteins to the extent of 90% or greater and has a plasma half-life of about 90 min.⁹ A glycoprotein, corticosteroid-binding globulin (CBG), has high affinity for hydrocortisone, but low total binding capacity; however, this capacity is sufficient to account for binding of low to normal hydrocortisone concentrations of 20 to 25 $\mu\text{g/dl}$ plasma. Hydrocortisone levels greater than 25 $\mu\text{g/dl}$ will saturate CBG binding sites, resulting in increases in plasma albumin-bound hydrocortisone.⁵⁴

The other major site of corticosteroid application, the skin, has not been well characterized metabolically.⁵⁴ Qualitatively, the metabolism of hydrocortisone by the skin resembles hepatic modifications, although some anatomical differences have been demonstrated. For example, only 5 α -reduced metabolites are found in contrast to both 5 α - and 5 β -urinary metabolites which arise from systemic metabolism.⁴⁷

Specific epidermal binding sites (receptors) for corticosteroids have been demonstrated,⁵⁵ and depot accumulation has been shown, especially in the epidermis.⁵⁴ The uppermost layer of the skin, the stratum corneum, serves both as a barrier to penetration and as a functional reservoir for the steroid. The effects on penetration and efficacy by the presenting formulation may be profound and have been discussed in detail elsewhere.⁵³

Use and Dosage

The natural corticosteroids are predominantly marketed as hydrocortisone, although cortisone acetate (cortone acetate) is available in oral, injectable, and topical ophthalmic forms. Hydrocortisone is available as the free alcohol in oral tablet form and as the water-soluble 21-disodium phosphate and 21-sodium hemisuccinate esters for injectables. The oral forms are little used because compounds with reduced side effect potential (such as sodium retention) are available; however, injectables remain widely used for i.m. and joint injection. As the free alcohol or as the 21-acetate, hydrocortisone is formulated in ointment, cream, lotion, and spray and in combination with anti-infectives such as neomycin sulfate or polymixin B. The amount of corticosteroid in these products varies from 0.125 to 2.5%, and they are considered low-potency topical corticosteroid preparations, with comparably low potential for local or systemic side effects. Since 1980, 0.5% formulations have been available as OTC preparations for relief of minor eczemas, pruritus, etc.

Toxicities^{8,9,50}

Cortisone and hydrocortisone are capable of exerting typical corticosteroid side effects. These may be considered consequences of abrupt withdrawal following prolonged use or long-term treatment with large doses and include acute adrenal insufficiency, hyperglycemia, peptic ulceration, osteoporosis, Cushing's syndrome, increased susceptibility to infection, nitrogen loss, behavioral disturbances, acne, and hirsutism. Principal side effects of the natural hormones also include electrolyte and fluid disturbances.

Since the naturally occurring hormone is a relatively weak topical agent in the form of the free alcohol or the 21-acetate, it is thought that this corticosteroid does not provoke local toxicity such as skin atrophy, striae, perioral dermatitis, etc. However, the more potent 17-esters are purportedly capable of producing side effects typical of the fluorinated corticosteroids.