ANTI-INFLAMMATORY and ANTI-RHEUMATIC DRUGS

Volume III

K. D. Rainsford

CRC PRESS

Anti-Inflammatory and Anti-Rheumatic Drugs

Volume III: Anti-Rheumatic Drugs, Experimental Agents, and Clinical Aspects of Drug Use

Editor

K. D. Rainsford, Ph.D., M. R. C. Path.
Senior Research Associate
Department of Pharmacology
University of Cambridge
Cambridge, England

CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging inPublication Data
Main entry under title:

Anti-inflammatory and anti-rheumatic drugs.

Includes bibliographies and indexes.
Contents: v. 1. Inflammation mechanisms and actions of traditional drugs -- v. 2. Newer anti-inflammatory drugs -- v. 3. Anti-rheumatic drugs, experimental agents, and clinical aspects of drug use.
1. Anti-inflammatory agents. 2. Antirheumatic agents. I. Rainsford, K. D., 1941- . [DNLM: 1. Anti-Inflammatory Agents. 2. Arthritis, Rheumatoid--drug therapy. QV 247 A6292]
RM405.A58 1985 616'.0473 84-17651
ISBN 0-8493-6230-X (v. 1)

Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida, 33431.

International Standard Book Number 0-8493-6230-X
International Standard Book Number 0-8493-6231-8
International Standard Book Number 0-8493-6232-6

Library of Congress Card Number 84-17651
Printed in the United States

PREFACE

The past decade has seen the introduction of many new nonsteroidal anti-inflammatory and anti-rheumatic drugs, more than have ever been developed previously. With this has come the problem of an ever expanding literature on these drugs as well as that from newer understandings of the arthritic processes which they were designed to treat.

Many of these newer developments have centered on drugs which work by inhibiting production of inflammatory prostaglandins. These probably have the effect of controlling the symptoms (pain, swelling) of inflammation. While we have yet to appreciate the full implications of such prostaglandin-regulated controls, it became clear during the mid-1970s that inhibition of prostaglandin biosynthesis in some organs (e.g. gastric mucosa, kidney) could be responsible for some untoward side-effects. Though these actions *alone* do not account for the mechanism of development of these side-effects, they are in some respects fundamental, together with certain acidic properties of these agents.

It also became clear during this period that other mediators, most especially those from cells of the inflammatory and immunological system are important, together with their intrinsic cellular activities, in the chronic inflammatory processes underlying rheumatoid and certain other arthropathies. Thus, some programs were initiated to develop agents to specifically regulate these activities, which are considered more likely to control the fundamental arthritic disease processes especially those in rheumatoid arthritis. With this there have been some new problems, not only concerning what aspects of the inflammatory cell/immune system should ideally be manipulated in controlling arthritic diseases, but also the side-effects which may develop from such manipulations which we cannot yet predict or fully assess as to their clinical implications.

This book in an attempt to bring together the diverse information on (1) the basic processes underlying the clinically-observed and experimentally induced inflammatory processes, (2) the actions of traditional and new non-steroidal anti-inflammatory (NSAI) and anti-rheumatic drugs, and (3) the clinical uses and side-effects of the anti-inflammatory/anti-rheumatic drugs. Of the newer NSAI drugs selected for special discussion in the second section of this book some are in the clinical-experimental stage. Several drugs, among them benoxaprofen and clozic, have been recently suspended or restricted in their sale in some countries. The reason for the selection of a chapter on clozic as well as considering those in clinical development is quite deliberate. For instance the actions of benoxaprofen and clozic have been considered by many to illustrate what these new drugs have been able to achieve by controlling the manifestations of rheumatoid and some related arthropathies. They have also led to some problems, and these facts should be fully and openly discussed in order that the medico-scientific community should benefit from these lessons. It is possible that by more careful monitoring of prescription and use of these drugs, they may prove useful in their own right. It may be that by attacking some of the basic inflammatory/immune processes, unique problems of side-effects are revealed, and thus such drugs should in the future be more carefully restricted in their use and therapy with these agents more stringently monitored than at present. For the present the lessons are important for management of such novel agents at both the individual and community level.

Some of the newer NSAI anti-rheumatic drugs have effects of which some are incompletely understood as yet. The reviews here will help to focus on these problems as well as on those processes of chronic inflammation which can be usefully controlled by existing drugs, whether they be regarded as experimental agents or used clinically.

The chapters on the individual drugs have, where possible, included details of their chemistry, pharmacology, pharmacokinetics, and clincial uses. In this and in other

sections of this book, it is hoped the information will be of use to those involved in all aspects of drug development and the scientific understanding of their actions and clinical uses.

This book would not have been possible without the splendid efforts of its contributors, many of whom made a special effort to produce chapters in the face of official obligations which demanded their time. Also, I should like to specially thank Mrs. Janet Eastwell for her enthusiastic and most efficient secretarial help. I thank my wife for her support and encouragement.

Kim Rainsford

THE EDITOR

Kim D. Rainsford, Ph.D, M.R.C. Path., is Senior Research Associate, Department of Pharmacology, University of Cambridge, England and is also Visiting Reader in Pharmacology, Biochemistry Department, University of Surrey, Guildford, Surrey, and Honorary Lecturer in Chemical Pathology, King's College Hospital Medical School, University of London, London, England.

He graduated B.Sc. (Hons) at the Australian National University, Canberra, Australia, in 1968, and received his Ph.D. from the University of London in 1970. In 1982 he received an M.R.C.Path. from the Royal College of Pathologists (London). He also holds qualifications as M.I.Biol. (London), M.N.Z.I.C. (New Zealand), and M.A.C.E. (Australia).

Dr. Rainsford has held research and teaching positions in England, Australasia, Switzerland, and briefly in Zimbabwe. Among these he was a Senior Lecturer in Biochemistry at the University of Tasmania (until 1978), a Guest Professor at the Biozentrum, University of Basel, and a Visiting Scientist at the Lilly Research Centre, Windlesham, England.

Dr. Rainsford is a member of the Royal College of Pathologists, the British Pharmacological Society, the Biochemical Society, the Institute of Biology, the New York Academy of Sciences, the New Zealand Institute of Chemistry, the Australian Biochemical Society, and the Australasian Society for Clinical and Experimental Pharmacology. He has some 100 publications and 6 books in the field of the mode of actions of anti-inflammatory drugs in relation to their therapeutic actions and side-effects. He has lectured to over 40 international meetings and has taught in various subjects in the fields of pharmacology, biochemistry, and medicinal chemistry. His current interests are in the actions of drugs in preventing cartilage degradation in inflammatory conditions, the mechanisms of action of the non-sterodial anti-inflammatory drugs as they induce gastrointestinal side-effects, and the mode of actions of drugs in the control of granulomatous reactions in schistosomiasis.

CONTRIBUTORS

Neil R. Ackerman
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

R. L. Bell
Riker Laboratories, Inc.
3M Company
Saint Paul, Minnesota

Nicholas Bellamy
University of Western Ontario, London
and McMaster University
Hamilton, Ontario, Canada

W. Henry Betts
Rheumatology Unit
The Queen Elizabeth Hospital
Adelaide, South Australia

M. E. J. Billingham
I. C. I. plc.
Alderley Park, Cheshire, U.K.

Peter M. Brooks
University of Sydney
Royal North Shore Hospital
Sydney, New South Wales
Australia

W. Watson Buchanan
McMaster University
Hamilton, Ontario, Canada

Saul C. Cherkofsky
Du Pont Pharmaceutical
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Robert Clark
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

John M. Collier
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

P. F. D'Arcy
The Queen's University of Belfast
Medical Biology Centre
Belfast, Northern Ireland, U.K.

William Galbraith
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

I. Ross Garrett
Institute of Medical and Veterinary
Science, and University of Adelaide
Adelaide, South Australia

Steven C. Gilman
Wyeth Laboratories, Inc.
Philadelphia, Pennsylvania

Stephen B. Haber
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Walter E. Hewes
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Alan J. Lewis
Wyeth Laboratories, Inc.
Philadelphia, Pennsylvania

W. H. Lyle
Courtaulds plc.
London, U.K.

J. C. McElnay,
The Queen's University of Belfast
Medical Biology Centre
Belfast, Northern Ireland, U.K.

George G. I. Moore
3M Company
St. Paul, Minnesota

Dariel C. Rakestraw
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

David Rosenbloom
Chedoke-McMaster Hospitals,
and McMaster University
Hamilton, Ontario, Canada

A. R. Rushton
I.C.I.plc.
Alderley Park, Cheshire, U.K.

Gregory S. Shotzberger
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Thomas R. Sharpe
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

Karl F. Swingle
Riker Laboratories, Inc.
3M Company
Saint Paul, Minnesota

J. C. P. Weber
Medicines Division
Department of Health
London, U.K.

Michael W. Whitehouse
Department of Pathology
University of Adelaide
South Australia

Charles C. Whitney
Du Pont Pharmaceuticals
E. I. du Pont de Nemours & Co.
Wilmington, Delaware

VOLUME OUTLINES

Volume I: Inflammation Mechanisms and Actions of Traditional Drugs

Inflammation Mechanisms

Actions of Traditional Anti-Inflammatory Drugs

Volume II: Newer Anti-Inflammatory Drugs

Volume III: Anti-Rheumatic Drugs, Experimental Agents, and Clinical Aspects of Drug Use

Anti-Rheumatic Drugs, Experimental Agents, and Future Prospects

General Clinical Asepcts

TABLE OF CONTENTS

Volume III: Anti-Rheumatic Drugs, Experimental Agents, and Clinical Aspects of Drug Use

Anti-Rheumatic Drugs, Experimental Agents, and Future Prospects

General Clinical Aspects

Anti-Rheumatic Drugs, Experimental Agents, and Future Prospects

Chapter 1

PENICILLAMINE

W. H. Lyle

TABLE OF CONTENTS

I. INTRODUCTION

Penicillamine has an established therapeutic role in only one of the rheumatic diseases, and in this, as in some other respects, it resembles the gold (I) thiolates that have a much longer history as antirheumatoid (rather than antirheumatic) agents. Despite much effort aimed at the discovery of the way in which these drugs suppress rheumatoid activity, this problem remains unsolved. It is not clear whether penicillamine itself, a metabolite, or even a protein-bound complex of it constitutes the ''bullet'', neither has the system or tissue ''target'' been identified. Penicillamine continues to be prescribed for rheumatoid patients on the purely empirical basis that it quite frequently relieves their symptoms where better understood antiinflammatory drugs have proven inadequate. This beneficial activity develops slowly and is very often overshadowed by side effects that interrupt the treatment, at least temporarily. Some are potentially lethal so that examination of the patients must be frequent for as long as penicillamine is prescribed, a factor that discourages use of this drug until less demanding ones have been tried.

Many thousands of rheumatoid patients have been given penicillamine since Jaffe[1] first reported a good response to it in 1964, but it was initially introduced to therapeutics as a treatment for hepatolenticular degeneration (Wilson's Disease) in 1956 by Walshe.[2] It is the mainstay of treatment for that disease, for which it has life-saving properties. Walshe's[3] first female patient had completed 25 years of treatment by 1981 and had raised 3 healthy children of her own. In Wilson's disease and in cystinuria, lead intoxication, scleroderma, and some other disorders penicillamine has been prescribed on a basis of classical chemistry and biochemistry. Although the numbers of treated patients with all of these together are greatly outnumbered by the rheumatoid group some consideration of the performance of penicillamine in the nonrheumatoid ailments is relevant to its antirheumatoid role.

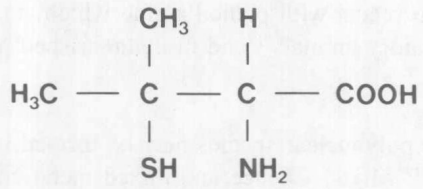

FIGURE 1. D(−)penicillamine

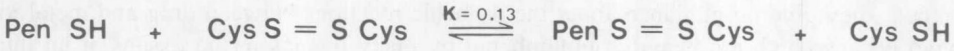

FIGURE 2. Formation of mixed disulfide from penicillamine (pen SH) and cystine (Cys S = S Cys).

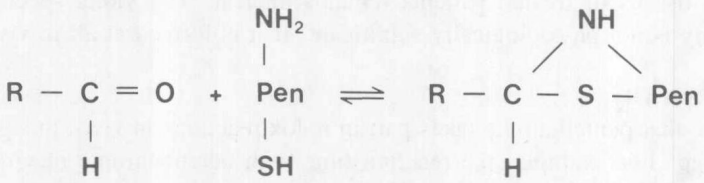

FIGURE 3. Thiazolidine formation by penicillamine (NH_2 Pen SH).

II. CHEMISTRY

Penicillamine, 3′,3″ dimethyl cysteine, is a naturally occurring metabolite of penicillin, appearing in the urine as the D(−)stereoisomer (Figure 1).[4] Soluble 1:9 in water, it is slowly oxidized to the internal dimer. A liquid preparation for oral use was formulated by reducing its pH to 3.4. When stored at 4°C for 14 days less than 5% was oxidized.[5] In the past the DL isomer and the hydrochloride, because of its greater stability, were used clinically.

A. Sulfydryl Activity

Penicillamine undergoes exchange reactions with disulfides. The reaction with cystine (Figure 2) is typical and is complete in about 15 min., being restricted by the methyl groups adjacent to the sulfhydryl moiety of penicillamine. Reaction of the mixed disulfide penicillamine-cysteine with additional penicillamine yields penicillamine disulfide; however, the equilibrium constant for this reaction is very low (0.01), therefore in biological fluids penicillamine tends to exist as a mixed disulfide.[6] This is the rationale for the use of penicillamine as a treatment for cystinuria, but it has also increased the difficulty of pharmacokinetic studies and of interpreting the results of experiments in which penicillamine is added to cell cultures. Similar interactions occur with the disulfide bonds of proteins.[7] An excess of protein with free sulfhydryl groups tends to reduce penicillamine disulfides to penicillamine, and any intracellular penicillamine is expected to be in a reduced state because of the presence of glutathione reductase.

B. Thiazolidine Formation

The sulfhydryl and amine groups of penicillamine enable it to react with carboxyl compounds to form stable thiazolidine derivatives (Figure 3). Their respective kinetics are such that penicillamine might compete successfully with cysteine in vivo in this type of reaction.[8] Both bind specifically to free aldehydes on collagen;[9] penicillamine is by this means able to inhibit cross-linking and to depolymerize incomplete cross-links of collagen so long as these linkages are of the aldimine type.[10] Thus, the effects of penicillamine are mainly upon skin collagen, giving rise to several side effects and some benefits (in scleroderma) as well.

Pyridoxal-5-phosphate also reacts with penicillamine which, in large doses, induces pyridoxine deficiency in laboratory animals[11] and in malnourished patients.[12]

C. Complexing of Metals

Binary, protonated, and polynuclear species may be formed in solutions containing penicillamine and metal ions.[13] Mixed valence and mixed metal complexes have been identified,[14] and the metals that form soluble complexes at neutral pH include mercury, lead, nickel, copper, silver, zinc, gold, cobalt, iron, cadmium, bismuth, antimony, chromium, and manganese. Although stability constants for many of these compounds have been determined, they give no guidance about the probable reactions between drug and metal ions in vivo because both are heavily outnumbered by many ligands in the tissues of an intact organism. The complexes formed with copper (II) ions have been studied the most because of the cupruretic action of penicillamine in Wilson's disease, but the nature of any complexes formed in the tissues of treated patients remains unclear. The violet species that is best known probably is not physiologically significant, if it is formed at all in vivo.[15]

D. Reducing Activity

It is possible that penicillamine takes part in redox reactions in vivo, though this has not been established. For example, the reaction time with adrenochrome in vitro is 30 times longer than between cysteine and adrenochrome, because of steric hindrance.[16] This factor, which probably prevents rapid binding and digestion in the gut and after absorption, is one of many that renders simple explantions of penicillamine activity, even as a treatment for lead poisoning, implausible.[8]

III. METABOLISM

A. Absorption

Patients with Wilson's disease rapidly absorb penicillamine given orally,[17] as do rheumatoid patients, peak absorption (t_{max}) varying from 1 to 3 hr for different individuals regardless of dose.[18] By means of intestinal perfusion preparations, Perrett[19] has shown that penicillamine (not as disulfide) was rapidly lost from the perfusate, probably binding to gut wall protein by disulfide bonds. Deficient absorption is inevitable if a given dose of penicillamine is oxidized early in transit through the gut, auto-oxidation therein being promoted by the alkaline conditions. Reduced penicillamine levels are also seen when the drug is taken simultaneously with an oral iron preparation[20] or with food or alkali, the greatest effect on plasma levels being by iron.[21] Nausea in response to the drug, presumably with delayed gastric emptying, was associated with the lowest plasma levels of penicillamine assayed in a group of normal subjects. The size of the reductions of absorption brought about by these agencies commonly exceeded 50%.[21,22] Reabsorption from the gut seems to be slight.[30]

B. Distribution

Studies of the pharmacokinetics of penicillamine have yielded an assortment of results that are reconciled only by taking into account the limitations of the assay methods used by different investigators. No simple quantitative system exists (or can really be envisaged) that might distinguish and measure simultaneously circulating penicillamine in its free (reduced) state, mixed disulfide, internal disulfide, 5-methyl moiety, metal and protein complexes, intra- and extracellularly distributed. The analytical techniques that have been used in studies of penicillamine kinetics have been critically reviewed by Lecavalier and Crawhall.[23]

1. Blood

High performance liquid chromatography (HPLC) enables penicillamine to be separated from its disulfides so that it may be assayed by means of an electrochemical detector. The

detection limit is 5×10^7 *M* penicillamine and the method is rapid.[24] Total (unbound) blood penicillamine concentrations, but not individual disulfides, can thus be determined.[25] Wiesner and colleagues[26] investigated the kinetics of (reduced) penicillamine by this method, giving intravenous and oral doses to normal subjects. After intravenous administration a rapid distribution phase was followed by a long elimination phase, the half-time of elimination ($t_{1/2}\beta$) being approximately 63 min. The volume of distribution was about 57.0 ℓ and plasma clearance was 560.7 mℓ/min with large individual variation, especially in the proportion of the dose that was detected in urine within 24 hr (22.2 to 67.7%). After an oral dose penicillamine was detected in the blood within 20 min, most subjects showing dual peak concentrations: a smaller one at 60 to 80 min and one larger at 110 to 140 min. The $t_{1/2}\beta$ was about 1 hr and the mean peak plasma concentration after a dose of 800 mg was approximately 4 μg/mℓ. The apparent fraction of absorption ranged from 27 to 61.8% (mean 41.2%). Peak urinary penicillamine (and copper) was at 4 hr. Others have obtained similar results in normal subjects[22] regardless of the source of penicillamine.[27] All failed to account for a large part of the administered doses and found such low concentrations in plasma after a few hours that a 6-hourly dosage schedule was suggested.[26] The same experiment done with patients who had responded well to penicillamine given for at least 3 months yielded a $t_{1/2}\beta$ ranging from 4.47 to 7.50 hr; this corresponded better with the ^{35}S studies in Wilson's disease.[17] The chief factor in this large discrepancy seems to be that in the single dose studies in normals, the $t_{1/2}\beta$ was calculated from observations collected over periods of 8 hr or less, and 24 hours in the rheumatoid patients. Nevertheless the long elimination phase in the latter and the relatively large V_d may indicate the existence of a ''deep compartment'' or ''slow pool'' of reversibly bound penicillamine.[28]

Penicillamine residues may, by other analytical methods, be detected in plasma 1 week or more after a single dose of 250 mg.[29] Acid oxidation of penicillamine and cysteine followed by anion exchange chromatography gives peak levels of about 5 μg/mℓ after a 250 mg oral dose. This may be compared with the approximate figure of 1 μg/mℓ obtained for reduced penicillamine.[22,27,28] Using this technique van der Korst's group[30] concluded that there were at least two ''pools'', one with a $t_{1/2}$ of 2 to 5 hr and one of about 6 days; at a constant dose of 750 mg accumulation occurs to give plasma concentrations of 20μg/mℓ or more.

Most of the penicillamine present in the blood is bound to plasma protein[17] and of the remainder in plasma Perrett[19] estimated that 7% is cysteine mixed disulfide, 5% is penicillamine disulfide, 6% is reduced penicillamine, and about 2% is not identified. Packed cell concentrations of 0.1 to 0.2 mg/100 mℓ after doses of 500 and 750 mg penicillamine have been recorded.[22,25] Fifty-two percent (52%) of large leukocytes (mostly monocytes) have been shown to bind penicillamine and perhaps ingest it as a complex with a soluble protein.[31]

2. Tissues

Perrett[32] recovered 85% of a single dose of ^{14}C-penicillamine from the excreta of a normal subject over a period of 72 hr. Direct evidence concerning tissue uptake is available only from animal experiments. Uptake is greatest in collagen-rich organs, notably the skin.[33] Using ^{3}H-D-penicillamine, Ruocco and others[34] showed that 4 hr after dosing the label was confined to the dermis, and was concentrated in the epidermis by 8 hr. Some 3% of an oral dose of ^{14}C-D-penicillamine per gram of dry tissue was detected in the skin at 4 hr, declining very slowly over the next 24 hr. The pattern was similar for the aorta, but with a peak value of 13%. Hepatic uptake declined from 5% to nil in about 8 hr. and in contrast to the L-isomer, bound only to immature collagen.[35] Only about 0.15% of ^{14}C-penicillamine was detected in expired air.[33]