Clinical Ocular Pharmacology

Editor
JIMMY D. BARTLETT, O.D.

SIRET D. JAANUS, Ph.D.

Clinical Ocular Pharmacology

Editor
JIMMY D. BARTLETT, O.D.
Associate Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham; Director of Continuing Education, School of Optometry, University of Alabama in Birmingham; formerly, Chief, Optometry Section, Tampa VA Medical Center, Tampa, Florida; and Assistant Professor of Optometry, Department of Ophthalmology, University of South Florida College of Medicine, Tampa, Florida

Associate Editor
SIRET D. JAANUS, Ph.D.
Associate Professor, Department of Basic and Visual Sciences, Southern California College of Optometry, Fullerton, California; formerly, Chairperson, Department of Basic and Visual Sciences, Southern California College of Optometry, Fullerton; and Assistant Professor and Chairman, Department of Basic Sciences, State College of Optometry, State University of New York, New York City

BUTTERWORTH PUBLISHERS
Boston · London
Sydney · Wellington · Durban · Toronto

Every effort has been made to ensure that the drug dosage schedules within this text are accurate and conform to standards accepted at time of publication. However, as treatment recommendations vary in the light of continuing research and clinical experience, the reader is advised to verify drug dosage schedules herein with information found on product information sheets. This is especially true in cases of new or infrequently used drugs.

Library of Congress Cataloging in Publication Data
Main entry under title:

Clinical ocular pharmacology.

Includes index.
1. Ocular pharmacology. I. Bartlett, Jimmy D.
II. Jaanus, Siret D. [DNLM: 1. Eye — Drug effects.
2. Eye diseases — Drug therapy. WW 166 C641]
RE994.C55 1984 617.7'061 83-15273
ISBN 0-409-95041-6

Butterworth Publishers
80 Montvale Avenue
Stoneham, MA 02180

10 9 8 7 6 5 4 3 2

Printed in the United States of America.

CONTRIBUTORS

Larry J. Alexander, O.D.
Associate Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham; Assistant Dean of Student Affairs, School of Optometry, University of Alabama in Birmingham

David M. Amos, O.D.
Private Practice, Overland Park, Kansas; Consultant, Kansas City VA Medical Center, Kansas City, Missouri; formerly, Associate Professor of Ophthalmology, Department of Ophthalmology, University of Kansas Medical Center, Kansas City, Kansas

Jimmy D. Bartlett, O.D.
Associate Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham; Director of Continuing Education, School of Optometry, University of Alabama in Birmingham; formerly, Chief, Optometry Section, Tampa VA Medical Center, Tampa, Florida; and Assistant Professor of Optometry, Department of Ophthalmology, University of South Florida College of Medicine, Tampa, Florida

Talmage R. Bosin, Ph.D.
Professor and Chairman, Pharmacology Section, Medical Sciences Program, Indiana University School of Medicine, Bloomington

Louis J. Catania, O.D.
Associate Professor of Optometry, Pennsylvania College of Optometry, Philadelphia; Director of Continuing Education, Pennsylvania College of Optometry, Philadelphia; formerly, Chief, Eye Service, Genesee Valley Group Health Association, Rochester, New York

Freddy W. Chang, O.D., Ph.D.
Associate Professor of Optometry, Indiana University School of Optometry, Bloomington

Richard J. Clompus, O.D.
Private Practice, West Chester, Pennsylvania; Clinical Instructor, Pennsylvania College of Optometry, Philadelphia

Anthony P. Cullen, M.Sc., O.D., Ph.D., F.B.C.O.
Professor of Optometry, University of Waterloo School of Optometry, Waterloo, Ontario, Canada

Jess Boyd Eskridge, M.Opt., M.Sc., Ph.D.
Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham

Murray Fingeret, O.D.
Chief, Optometry Section, Brooklyn VA Medical Center, Brooklyn, New York; formerly, Chief, Optometry Section, Birmingham VA Medical

Center, Birmingham, Alabama; and Assistant Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham

Eduardo Gaitan, M.D.
Professor of Medicine, University of Mississippi School of Medicine, Jackson; Chief, Endocrinology Section, Jackson VA Medical Center, Jackson, Mississippi; Attending Physician, University Hospital, University of Mississippi Medical Center, Jackson

Steadman D. Harrison, Jr., Ph.D.
Associate Professor of Toxicology, Graduate Center for Toxicology, University of Kentucky, Lexington

Sally L. Hegeman, Ph.D.
Assistant Professor of Pharmacology, Pharmacology Section, Medical Sciences Program, Indiana University School of Medicine, Bloomington

Jeffrey A. Hiett, O.D., M.S.
Assistant Professor of Optometry, Department of Optometry, School of Optometry, University of Alabama in Birmingham; Staff Optometrist, Birmingham VA Medical Center, Birmingham, Alabama

Siret D. Jaanus, Ph.D.
Associate Professor, Department of Basic and Visual Sciences, Southern California College of Optometry, Fullerton, California; formerly, Chairperson, Department of Basic and Visual Sciences, Southern California College of Optometry, Fullerton; and Assistant Professor and Chairman, Department of Basic Sciences, State College of Optometry, State University of New York, New York City

William L. Jones, O.D.
Chief, Optometry Section, Albuquerque VA Medical Center, Albuquerque, New Mexico; Adjunct Assistant Professor, University of Houston College of Optometry, Houston, Texas

Gerald E. Lowther, O.D., M.Sc., Ph.D.
Professor of Optometry, College of Optometry, Ferris State College, Big Rapids, Michigan; Editor-in-Chief, International Contact Lens Clinic

Robert D. Newcomb, O.D., M.P.H.
Chief, Optometry Service, Columbus VA Outpatient Clinic, Columbus, Ohio; Clinical Assistant Professor, The Ohio State University College of Optometry, Columbus

Vincent T. Pagano, Ph.D.
Associate Professor of Pharmacology, Department of Biological Sciences, State College of Optometry, State University of New York, New York City; Adjunct Associate Professor, Department of Pharmacology, New York Medical College, Valhalla, New York

John W. Potter, O.D.
Chief, Optometry Service, Las Vegas VA Outpatient Clinic, Las Vegas, Nevada; Assistant Professor of Optometry, Southern California College of Optometry, Fullerton

Frederic G. Ransom, M.D.
Associate Professor of Medicine, Department of Medicine, School of Medicine, University of Alabama in Birmingham; Medical Director, Emergency Department, University Hospitals, University of Alabama in Birmingham

Jack E. Terry, O.D., M.S.
Chief, Optometry Section, Huntington VA Medical Center, Huntington, West Virginia; Clinical Assistant Professor of Optometry, Indiana University School of Optometry, Bloomington

William Wallace, O.D.
Director, Atlanta Educational and Diagnostic Center, Vision Educational Foundation, Atlanta, Georgia; Adjunct Assistant Professor, Indiana University School of Optometry, Bloomington; Adjunct Assistant Professor, University of Houston College of Optometry, Houston, Texas; Adjunct Assistant Professor, Southern College of Optometry, Memphis, Tennessee

David R. Whikehart, Ph.D.
Associate Professor of Physiological Optics, Department of Physiological Optics, School of Optometry, University of Alabama in Birmingham; Associate Professor of Biochemistry, Department of Biochemistry, School of Medicine, University of Alabama in Birmingham

FOREWORD

This excellent text, *Clinical Ocular Pharmacology,* would have been an unthinkable undertaking a generation ago and an unlikely one a decade ago. That it has been so carefully produced and edited is a tribute to its array of accomplished authors and to its dedicated editors. But more so, it is a milestone in the progressive development of the scholarship of the profession of optometry. For only those with a historical perspective will this book be unique. For all others, it will be simply a superb text.

The 1970s witnessed enactments, in one state after another, of legislation to alter the authority of doctors of optometry to utilize certain classes of pharmaceutical agents for diagnostic purposes. In a smaller number of states, drugs were authorized to be used by optometrists both for diagnosis and for the treatment of ocular diseases. This remarkable change in the practice of optometry has occurred in less than a half generation. It already has involved thirty-eight states at the time of this writing. Undoubtedly, the remaining states and the District of Columbia will have their practice acts amended in the near future to permit the use of drugs for diagnostic reasons. As well, a growing number of other states further will alter their practice laws to permit the treatment of ocular disease.

This dramatic shift in the practice modality of optometry could not have been accomplished were it not for a significant upgrading of standards and for substantive academic enhancements that occurred in the schools and colleges of optometry in the prior years. These were in no small way aided by "The Health Professions Educational Assistance Act of 1963" (and by subsequent amendments). Thus, curricular growth and academic development of the optometric educational enterprise formed the essential basis upon which was built the significant practice expansion of optometry.

Indeed, this is as it should be. The confidence of the public rests more securely upon those licensed practitioners whose knowledge base is formidable and whose scholarship is substantive. That essential fact, more than any other, in my respectful opinion, helped to convince legislative bodies throughout the nation that confidence could without concern be placed in optometry with respect to an expanded role responsibility of its qualified clinicians. I believe firmly that that confidence in the decades ahead will be proven not to have been misplaced.

As in any new understanding, the public's trust must be measured against generic mandates that the profession must bear. Simply stated, they are two-fold. Contribute to research and to the advancement of knowledge in the discipline; and enhance the intellectual skill of the clinician so that the public may benefit. These mandates are time-honored and responsive. Throughout the century of its growth and development, optometry has un-

derstood such mandates in the vision sciences and in the basic sciences upon which its applied knowledge depends. Now, these mandates institutionally have been broadened to relate to general and ocular pharmacology. Though crucial, it is not enough that the practicing optometrists learn about pharmacology and intelligently and responsibly use that discipline. It is, as well, of major importance that the profession, through its institutions, materially foster research and enhance the scholarship of general and ocular pharmacology. The carrying out of such mandates with regard to pharmacology cannot be diminished at the considerable risk of jeopardizing public trust and confidence.

The editors and authors wisely did not limit the orientation of this important text to optometry students, optometry residents, and to practicing optometrists. It is a carefully conceived volume which has major applicability to family practice physicians and to others in medicine. Indeed, the subject of responsibility "overlap" in the professions will undoubtedly become less of a substantive academic and professional issue as the scholarship and depth of knowledge increase among the members of the optometric community.

For many of the reasons stated above and for a host of others, *Clinical Ocular Pharmacology* represents an achievement of significant proportions and potential impact. My distinguished colleagues and friends, Professors Jimmy D. Bartlett and Siret D. Jaanus, have co-edited this fine and useful text with understanding and distinction. For this, all clinicians must express gratitude. But they have done an additional important service. They have directed our attention to the necessity for upgrading and enhancing the scholarship in a discipline area that is relatively new in optometry. For this, the public will benefit.

Alden N. Haffner, O.D., Ph.D.
Vice Chancellor for
Research, Graduate Studies,
and Professional Programs
State University of New York

PREFACE

The evolution of health care is measured, in part, by the development of clinical knowledge and by the specific clinical procedures that become salient features of contemporary health care practice. Recent advances in eye care technology serve as valid testimony that this evolution does indeed occur. Just as health care practices in general have become more sophisticated and specialized, the diagnosis and management of ocular disorders in particular reflects this trend to specialization with the proliferation of numerous secondary and tertiary level procedures and services.

With this emphasis on specialization and sophisticated technology, the generalist who serves the eye has become increasingly more frustrated with his or her apparent abandonment and isolation. The generalist is being called upon to care for a greater variety of eye problems, yet has not had an appropriate literature available that addresses his or her needs as a sophisticated primary care practitioner.

Clinical Ocular Pharmacology has been written for optometry students and residents, practicing optometrists, family practice physicians, pediatricians, and other primary care practitioners who are in need of a text that can be used as a practical guide for the clinical utilization of ophthalmic drugs. Ophthalmology residents and practitioners of ophthalmology will find the book useful as an updated source of information regarding the contemporary use of ophthalmic drugs for ocular conditions commonly encountered in office practice.

Our goal has been to produce a book that emphasizes the clinical uses of ophthalmic drugs in the diagnosis and management of those ocular disorders most commonly encountered in primary care practice. To achieve this goal we have felt it first necessary to discuss in Section I the basic pharmacologic principles that govern the various classes of ophthalmic drugs. The reader will find here a discussion of those pharmacologic agents that have been demonstrated by their longevity to be useful in the diagnosis and treatment of ocular disease. Drugs that have only recently been introduced into contemporary practice are also considered, including pimaricin, timolol maleate, dipivalyl epinephrine, cytosine arabinoside, trifluorothymidine, and others. In addition to those drugs normally used in the diagnosis and treatment of ocular disease, Chapter 12 considers the preparations utilized in contact lens practice. Throughout Section I, lists of commercially available drugs have been prepared to represent agents commonly employed in clinical practice.

Section II considers the pharmacologic diagnosis and management of ocular disorders according to tissue site or clinical problem. This format and approach should be of greatest value to the student, resident, or practitioner who uses the text as a reference in the clinic, hospital, or office. Emphasis has been placed on both the diagnostic as

well as the therapeutic uses of ophthalmic drugs in the context of total patient management and care. This approach allows the reader to better appreciate the utilization of ocular drugs as these drugs are used in clinical practice. Strong emphasis is therefore placed on etiology and differential diagnosis of those conditions discussed, for the effective and safe use of drugs for the treatment of ocular disease requires accurate and timely diagnostic skills as well as appreciation of the causes of those disorders. Where other, nonpharmacologic management modalities are employed, such as surgical or physical therapy, these have been mentioned so that the pharmacologic considerations are placed in proper perspective. The editors believe that this approach serves to better define and teach the relationship of ocular drug therapy to total patient care.

As more sophisticated methods are used in the clinical trials for ocular drugs, numerous side effects are being recognized. We consider in Section III important clinical aspects of drug toxicity. While Sections I and II discuss the important side effects of ocular drugs on the eye, Section III is designed to complement that discussion by considering adverse ocular effects of systemically administered drugs as well as the systemic side effects of drugs applied topically to the eye. The epidemiology and management of the latter group of side effects are considered in Chapter 30.

Throughout the text generic names of drugs are used, and these are occasionally followed in parentheses by proprietary names if a particular preparation is especially common or is the only preparation commercially available.

Because of the multiauthored nature of this text, some redundancy of material is inevitable. However, the editors have attempted to minimize redundancy by referring the reader, where appropriate, to other sections or chapters of the text. In this way completeness of individual discussions has been ensured while making the text as concise as possible.

The timely completion of this project would have been impossible without the able assistance, support, or encouragement from numerous individuals. We acknowledge the many hours of typing and preparation of the manuscript by Judy Bathstuebner, Doris Caldwell, Hazel Davis, Dorinda Finke, Richard Hawkins, Debbie Hicks, Kim Humphreys, Pat Humpres, Margo Jeffrey, and Ann Simpson. This laborious task was accomplished speedily and with great skill.

The accuracy of many of the bibliographic citations and other reference services were provided by Patricia Carlson and Nancy Clemmons.

Ronald Amaker, John Carswell, Richard Morrison, and Danny Musick provided much of the clinical photography, and the editors express special gratitude to Ken Norris, whose artistic pen created many of the line drawings and graphics.

Dr. JoAnn Graffeo, Dr. Dennis Matthews, Allison Hendrick, and Ann Honeycutt contributed expert technical assistance.

The editors owe deep gratitude to Drs. Robert F. Furchgott, Alden N. Haffner, Richard L. Hopping, and Ronald P. Rubin for their unfailing faith and support. A special appreciation is due to Dr. John F. Amos, who provided continuous encouragement and direction.

Finally, the individuals who brought this book from an idea to a reality deserve special acknowledgment — the contributing authors, whose work constitutes the essence of the final product; the numerous optometrists, pharmacologists, and physicians who reviewed portions of the manuscript and offered helpful comments and suggestions; our students and faculty colleagues, whose encouragement and patience created a supportive environment in which to work; our spouses, whom we asked to endure the preparation of this book; and the publisher, whose interest in, and constant support of this project led to an exciting and satisfying publishing experience.

Jimmy D. Bartlett
Siret D. Jaanus

CONTENTS

I PHARMACOLOGY OF OCULAR DRUGS

Drug therapy must be based upon correlation of effects of drugs with physiologic, biochemical and microbiologic kinetic aspects of diseases. Only through basic knowledge can we understand toxicology and limitations of drugs and how these can be overcome

—I. H. Leopold

1 FUNDAMENTAL CONCEPTS IN OCULAR PHARMACOLOGY

Sally L. Hegeman
Talmage R. Bosin
Steadman D. Harrison, Jr.

Ocular pharmacology is a branch of pharmacology that attempts to define and understand the interactions of chemicals and the eye. Knowledge borrowed from the disciplines of chemistry, botany, physiology, biochemistry, psychology, clinical medicine, and pathology, among others, is applied to this problem with the goal of providing safe and effective chemicals to be used for a variety of ocular conditions. Chemicals with diagnostically or therapeutically useful actions are called *drugs;* those that cause damage are termed *poisons* and are considered by the discipline of toxicology.

In order for a drug to produce an effect, a sufficient concentration of drug must reach its site of action in the eye, whether administered by the more usual topical route or by systemic administration. The factors that determine the concentration of drug at its site of action are the physical and chemical properties of the drug and the morphologic and pathologic state of the cell membranes. *Pharmacokinetics* deals with the role of these factors in controlling rates of absorption of drugs from the sites of administration, distribution within the body or eye, metabolism, and drug elimination. The effects of a drug, and where and how these effects are produced, is the study of *pharmacodynamics.* In pharmacodynamic studies, the actions of drugs are considered at many levels of biologic complexity — molecular, cellular tissue, organ, and organismal—with special attention paid to the relationship between useful and adverse drug actions and drug interactions.

The first section of this chapter is a discussion of general principles of pharmacodynamics and the factors that determine the concentration of drug at its site of action. Pharmacokinetics of topically and systemically administered agents is followed by a discussion of vehicles and delivery systems pertinent to topical administration of ophthalmic drugs.

PHARMACODYNAMICS

Both topically applied and systemically administered drugs produce a variety of effects when given for therapeutic or diagnostic purposes. A drug effect is usually initiated by the interaction of a drug with a macromolecule located in a cell or on a cell membrane. The interaction causes a series of reactions culminating in an observable functional change in the cell. Because a drug may interact with macromolecules located on many kinds of cells, many different effects can be expected from a single drug administration. Since only a few of these effects are important therapeutically, the rest are considered undesirable side effects. By understanding where the drug acts and how it interacts with cellular constituents, one might predict the therapeutic and adverse actions of a drug with presumable benefit to the patient. The mechanism of action of drugs as well as individual and population variation in the response to drug administration are considered in this section.

Drug Receptors

A drug receptor is thought to be a macromolecule, usually a protein, found in cell membranes or cytoplasm to which a drug may bind and cause a change in the functioning of the cell. The macromolecule, or drug receptor, is not made by the cell to specifically accommodate a drug, but rather to accommodate some endogenous chemical or process necessary for cell function. A drug may, for example, interact with the receptor for a hormone or a neurotransmitter, which are chemical messengers that allow communication among cells. If a drug is occupying the receptor for a neurotransmitter or a hormone, it may either wholly or partly block the interaction of the hormone or neurotransmitter with its receptor, or the drug may itself stimulate the receptor. In either case the normal communication among the cells has been altered. A drug does not provide a new function for a cell; it merely alters existing function.

Although most receptors are associated with the cell membrane, they may also be found in the cell cytoplasm or organelles where the drug-receptor interaction often produces changes in protein, hormone, or neurotransmitter synthesis. Often these receptors are enzymes involved in synthetic or energy-producing processes or are carrier molecules involved in the transmission of information from the cytoplasm to the nucleus.

Most drug-receptor interactions are reversible. Ionic bonds are important in attracting drug to the receptor while weak van der Waal interactions and hydrogen bonds are important in maintaining the interaction. The three-dimensional shape of the drug and receptor is especially important because the molecules have to be close together for the weak bonds to be effective. The weak bonds account for the reversible nature of a drug effect. A covalent bond between the drug and the receptor produces an effect with a long duration of action, and synthesis of new receptors is required before the drug effect is terminated.

Agonists and Antagonists

A drug that interacts with a receptor and produces a response is called an *agonist.* An agonist drug has *affinity* for the receptor (it binds to the receptor) and *intrinsic activity* or *efficacy* (potential for producing a biologic response). A pure *antagonist* interacts with the receptor but produces no biologic response; that is, it has affinity but no intrinsic activity. An antagonist, by occupying the receptor, will prevent an agonist from producing a biologic effect. If the antagonist can be displaced by increasing the concentration of the agonist, then the antagonism is called *competitive.* Noncompetitive antagonism occurs when the antagonist cannot be easily displaced by an agonist as, for example, when a covalent bond is formed between the receptor and the antagonist. A *partial agonist* is a drug that has some agonist properties yet is also an antagonist to other effective agonist molecules. Pentazocine, for example, is an effective narcotic