OCULAR THERAPEUTICS AND PHARMACOLOGY

Philip P. Ellis

FIFTH EDITION

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OCULAR THERAPEUTICS AND PHARMACOLOGY

PREFACE to fifth edition

In this edition an effort has been made to continue the fundamental purpose of the book, that is, to present in a concise form the basic considerations of current ocular therapy and pharmacology.

Extensive revisions have been made in this edition. Two new chapters have been added: one on carbonic anhydrase inhibitors and osmotherapeutic agents and another on anesthetic agents. Many sections have been rewritten entirely. New therapeutic agents, including various antibiotics, anti-inflammatory drugs, enzyme inhibitors, autonomic nervous system agents, and antiglaucoma medications, have been added. Newly reported side reactions to local and systemic ocular therapy are described. Consideration of new techniques of therapy and drug delivery is presented. The pediatric dosage tables have been expanded.

The second section on therapeutic agents has been condensed so that groups of drugs are described together. This avoids the needless repetition that occurred with the previous system of alphabetical listing. Referral to the index will provide the reader with the location of individual drug descriptions.

It is impossible to give recognition to all those who contributed to the preparation of this revised text. I particularly wish to thank Dr. S. Lance Forstot for his help in revisions of the chapters on therapy of diseases of the conjunctiva and therapy of the diseases of the cornea, Dr. Richard Deitrich for review of the chapter on autonomic nervous system agents, Dr. Theodore Eickhoff for his help with antibiotic medications, Dr. Merritt Rudolph for his assistance on the chapter on principles of cortisone and ACTH therapy, Dr. Jerry Meislik for his assistance on the chapter on glaucoma medications, Dr. Stuart Frankel for his help on the chapter on therapy of diseases of the eyelids, Dr. W. Bruce Wilson for his assistance on the chapter on therapy of optic neuritis, Dr. Dale Johnson for his help with the pediatric dosage tables, Dr. William Roberts for his assistance with the chapter on medical agents in surgical care, and Dr. Charles Van Way for his help with the fluid and electrolyte medications. I am extremely grateful to Mrs. Toma Wilson for her considerable efforts in manuscript editing, and I am especially thankful to Miss Kit Skiby for her many secretarial activities in preparation of this edition.

Dr. Donn L. Smith, who was a coauthor of the first four editions, has withdrawn in this edition. His past contributions are most appreciated.

Philip P. Ellis

PREFACE to first edition

All books have purposes; some are realized, but probably more are not. Besides the obvious desires to satisfy an ego and to impress the medical school administration, this handbook has been compiled for very definite reasons. It was written to serve as a quick reference for the busy practicing ophthalmologist who may have forgotten a specific dose or side reaction of a certain medication. It will also serve as a guide in therapy for beginning residents in ophthalmology and for nonspecialists who are treating ocular disorders. In general, it was designed to present in a concise form the basic considerations of current ocular therapy and pharmacology. It is not intended to be a textbook of therapeutics and pharmacology, nor is it meant to serve as a review of all types of treatment and ocular medications.

When any handbook is compiled, it becomes necessary to be somewhat arbitrary in presentation of material. One must take the license of deciding what are the most significant, practical, and effective forms of current therapy, realizing quite well that what he presents at any particular time may rapidly become outdated. The reader will find that some rare ocular conditions have been considered in detail, whereas other rather common ocular disorders have been dealt with in a very general fashion. This variation in approach has usually been based on the assumption that the reader has a basic knowledge of therapeutics and pharmacology and is acquainted in a general sense with the use of common medications. The reader will further observe that there is frequently a duplication of the rationale and methods of administration of a certain drug for treating the same disorders in various parts of the eye. This duplication is necessary because the book was designed for quick reference to treatment of a specific condition without it being necessary to read through the entire text.

The handbook is divided into two sections. The first section, on therapeutics, is designed to present some basic considerations of treatment and also to summarize the present medical therapy of most ocular disorders. The second section, on pharmacology, presents the most commonly used medications that a practicing ophthalmologist would have occasion to administer. The actions, uses, side reactions and contraindications, preparations, and dosages of these drugs are presented. The basic pharmacology is outlined, but the emphasis has been on the clinical use of drugs in ophthalmology. Attention is directed to the fact that the

dosage schedule is for adults unless otherwise stated. Methods of determining pediatric doses are given at the beginning of the section.

It is impossible to give complete recognition to all those people who contributed to the development of this book. The therapeutic approaches have been evolved from the teachings and opinions expressed by many authorities in ocular therapeutics, and listing the sources of all these references is obviously impossible. Furthermore, some of the therapeutic ideas expressed have resulted from several years of teaching ocular therapeutics to eye residents.

We would particularly like to thank Dr. George Tyner of the Division of Ophthalmology, University of Colorado Medical Center, for his contributions to the organization and preparation of the chapters on the therapy of glaucoma and the therapy of uveitis.

Dr. Herbert P. Jacobi of the Department of Biochemistry, University of Nebraska College of Medicine, and Mr. Herbert Carlin, Chief of the Hospital Pharmacy at the University of Colorado Medical Center, have been most helpful in the preparation of the section on basic considerations. We are indebted to Dr. Ralph Druckman, Division of Neurology, University of Colorado Medical Center, for his constructive criticism during the preparation of the manuscript. Finally, we should like to thank Miss Barbra Pehrson and Mrs. Janet Kelley for their valuable help in typing the manuscript.

Philip P. Ellis
Donn L. Smith

CONTENTS

SECTION ONE
OCULAR THERAPEUTICS

1 Basic considerations, 3

2 Principles of cortisone and ACTH therapy, 19

3 Principles of antibiotic therapy, 32

4 Autonomic nervous system agents, 47

5 Carbonic anhydrase inhibitors and osmotherapeutic agents, 56

6 Local anesthetics, 64

7 Medical agents in surgical care, 72

8 Therapy of diseases of the eyelids, 86

9 Therapy of diseases of the conjunctiva, 98

10 Therapy of diseases of the lacrimal apparatus, 108

11 Therapy of diseases of the cornea, 111

12 Therapy of diseases of the sclera, 125

13 Therapy of glaucomas, 128

14 Therapy of intraocular infections, 141

15 Therapy of diseases of the retina, 150

16 Therapy of uveitis, 162

17 Therapy of optic neuritis, 176

18 Therapy of diseases of the orbit, 181

19 Therapy of miscellaneous ophthalmic diseases, 186

SECTION TWO

THERAPEUTIC AGENTS

Analgesics, 195

Anesthetics, 198

Antianxiety drugs, 205

Anticoagulants, 209

Antihistamines, 212

Anti-infective chemotherapeutic agents, 216

Antifungal agents, 220

Antiviral agents, 223

Anti-inflammatory agents, 224

Immunosuppressive (antineoplastic) agents, 227

Chelating and epitheliolytic agents, 231

Enzymes, 233

Miotics, 234

Mydriatics and cycloplegics, 238

Preservative-antiseptics, 244

Sedatives and hypnotics, 246

Vaccines, 249

Vasodilators, 250

Vitamins, 251

Miscellaneous, 252

Pediatric dosage determination, 254

Standard pediatric dosages, 255

SECTION ONE

OCULAR THERAPEUTICS

CHAPTER 1

Basic considerations

MECHANISMS OF DRUG ACTION

Drug receptor interactions

In order for a drug to produce a pharmacological action, it must interact with a receptor and in addition induce some change in that receptor. Compounds such as acetylcholine, which do both, are called agonists. Drugs such as atropine, which interact only with the receptor but do not induce a physiological change, are called pharmacological antagonists. The term "potency" refers to how tightly the compound is bound to the receptor. A compound that is very avidly taken up by the receptor will be a very potent compound, either as an agonist or antagonist. The strength of this binding, and therefore potency, is determined by how well the molecular and electronic configuration of the drug fits into that of the receptor site. The example often used is that of a lock and key. Although definite proof is lacking, receptors probably are mainly proteins and may have enzymatic activity. For example, the adenyl cyclase receptor system is located on the cell membrane. The combination of epinephrine with this receptor system leads to activation of adenyl cyclase, which in turn catalyzes the formation of cyclic AMP (cAMP). The effect of cAMP on the cell is dependent on the cell type.

Once an agonist is bound to the receptor, it must produce a change in the receptor, which is then amplified many times to bring about an observable reaction in the system. The ability of a compound to bring about this change is referred to as the power of the drug. The most powerful compound in a group of drugs is usually taken as the standard against which all others are compared. It is not necessarily true that the most powerful drug is also the most potent one. A drug that does not produce a maximum effect is referred to as a partial agonist. Obviously it is also a partial antagonist because it diminishes the action by blocking access of more powerful drugs to receptor sites. Pilocarpine is an example of a partial agonist.

Drug interactions

The interactions between drugs are extremely important. We have already referred to one such interaction, pharmacological antagonism, in which two drugs are competing for the same receptor site. Another interaction is physiological antagonism, in which two antagonists react with their respective recep-

tors but produce opposite end results, for example, antagonistic effects of acetylcholine and norepinephrine on pupil size. A third type of antagonism is simple chemical antagonism. Two compounds may react chemically either within or outside the body to effectively neutralize their pharmacological action much as an acid neutralizes a base. An example is chelation of calcium by ethylenediamine tetra-acetate (EDTA). Much more complicated drug interactions are possible.

One drug may stimulate the metabolism of another, thus decreasing its effectiveness or shortening the duration of its action. Barbiturates are classic examples of compounds capable of inducing drug-metabolizing enzymes and thus of increasing the metabolism of many other drugs. The metabolic pathway of one drug may be suppressed by another drug, and therefore a prolonged effect occurs. As an example, prolonged action of succinylcholine occurs in patients receiving echothiophate iodide drops for treatment of glaucoma. Pseudocholinesterase hydrolyzes succinylcholine, and the plasma concentration of this enzyme decreases with systemic absorption of echothiophate iodide.

Additive or synergistic drug actions occur by a variety of mechanisms. If two equally powerful drugs are given at the same relative dose and act on the same receptor, their effects will simply be additive provided that the system is not reacting maximally already. An example would be increased miosis occurring with the concurrent administration of pilocarpine and carbachol. On the other hand, if the two drugs act on different receptors to bring about the same end results, a combination may produce a greater than additive, or synergistic, effect. An example of this phenomenon is the increased improvement in aqueous humor outflow with the combined use of pilocarpine and epinephrine.

Since patients are frequently treated with multiple drugs by different physicians, the possibility of adverse drug interactions becomes of great clinical importance. For example, when aspirin is given to a patient who is taking anticoagulants orally, an increased effect of the anticoagulants occurs. It is also important to recognize that drug therapy may alter the results of clinical laboratory tests. It is beyond the scope of this book to list such reactions, but an indication of these effects may be appreciated by the following examples. Acetazolamide therapy results in elevated blood levels of ammonia, bilirubin, glucose, sodium, and uric acid and in decreased levels of potassium and decreased blood pH. Corticosteroid therapy produces elevated blood levels of glucose, sodium, and amylase and decreased levels of potassium, uric acid, and protein bound iodine. Corticosteroids may also elevate the levels of urinary glucose and proteins.

It is impossible for any physician to memorize all the potential drug interactions. Nonetheless, it is important for him to be aware of other drugs the patient is receiving and to consider the possibilities of significant drug interactions to medications he is prescribing. Some drug interactions of importance to the ophthalmologist are cited in sections related to specific uses of drugs for

treatment of various ocular disorders and in the discussion of therapeutic agents in the second section of this book.

PREPARATION OF OPHTHALMIC SOLUTIONS

At the present time most of the routinely prescribed ophthalmic medications are prepared by pharmaceutical manufacturers. Although it may be argued that the physician has thus been forced to standardize his dosage, the advantages of commercial ophthalmic preparations seem to outweigh their disadvantages. Stability, uniformity, and sterility characterize these products. It is no longer necessary for the physician to be concerned with the pharmacist's knowledge of proper pH and correct buffering for ophthalmic collyria or to fear that any patient will be unable to duplicate his prescription in any part of the country. Nonetheless, since all students of ophthalmology should be aware of basic pharmacological and pharmaceutical principles in the preparation of ophthalmic medications and since all preparations are not commercially available, a brief summary is given here.

Preparation of ophthalmic solutions is largely a problem of tonicity, pH, stability, and sterility. Of these, sterility is the most important but often the most neglected. These problems have been reviewed by Riegelman and Vaughan.

Tonicity

For many years pharmacists gave considerable attention to the matter of making ophthalmic solutions isotonic with tears (initially, 1.4% sodium chloride equivalent; later, 0.9% sodium chloride equivalent). Sodium chloride equivalents of most aqueous solutions of water-soluble drugs were determined, and buffers and salts were then added as required for isotonicity. Many buffers were employed; phosphate buffer is the most commonly used.

It is now recognized that the eye easily tolerates solutions with sodium chloride equivalents ranging from 0.7% to 2%. Therefore if the ophthalmic solution has about a 0.9% sodium equivalent, as in 2% boric acid or 4% pilocarpine, no adjustment to effect isotonicity is required. In cases in which the further concentration of the drug exceeds 5%, sterile water should be used as the diluent, since the solution is already hypertonic. Although hypertonic drops are rapidly diluted by tears, it is probably desirable to achieve isotonicity in a physiologically buffered solution for certain drugs in order to reduce discomfort caused by instillation. This is true notably of pilocarpine.

pH

In most instances the pH of ophthalmic solutions is of little importance. Since the tears rapidly neutralize the small effect of the unbuffered drug, the use of buffered solutions is generally unnecessary to control pH. It should be pointed out that increasing the pH of alkaloid drugs favors penetration of the lipid barrier of the cornea but that increasing the pH decreases solubility and stability of

the alkaloid substances. Certain other drug solutions, such as the sulfonamides and fluorescein sodium, remain stable only at a pH slightly above 7. (See discussions of stability and drug penetration.)

Most ophthalmic solutions with pH values varying from 3.5 to 10.5 are well tolerated by the eye. However, unbuffered solutions of pilocarpine hydrochloride, 2% and higher, are quite irritating to the eye because of their acidity. Consequently, they are usually buffered to a pH of about 6.8

Stability

The stability of ophthalmic drugs in solution is largely dependent on the temperature and pH of the solutions and on the degree of dissociation of the drug. Alkaloids and other weak bases are much more stable at a pH of 5 than at a pH of 7. This is related to the proportion of the drug that exists in the less stable undissociated form at a given pH. With decreasing pH, dissociation of the drug increases, and therefore stability increases. Decomposition of the drug occurs much more rapidly at the elevated temperatures encountered in autoclaving than at room temperature. The rate of decomposition with autoclaving is much less if the pH is 5 than if it is 6.8. Therefore the general use of 2% boric acid solution (pH 4.7) as the vehicle, slightly modified by an added drug, is desirable to ensure stability, particularly if the solution is to be autoclaved. The exception to this rule is the preparation of fluorescein sodium and sulfonamide eye solutions, since these drugs are unstable at a pH of 5 (Table 1).

Chemical deterioration producing pharmacological inactivity is characteristic of certain ophthalmic preparations. Epinephrine solutions and, to a lesser extent, phenylephrine hydrochloride (Neo-Synephrine) oxidize in the presence of air, with resultant loss of activity. Solutions of most antibiotics lose their antimicrobial effect at room temperature within a few days after preparation. Isoflurophate (DFP), which is dispensed in anhydrous peanut oil, rapidly hydrolyzes

Table 1. Stability of selected ophthalmic drugs (time for 50% decomposition)*

Drug	*pH 5.0*		*pH 6.8*	
	25° C	*120° C*	*25° C*	*120° C*
Procaine and tetracaine	19 yr	36 hr	—	10 min
Atropine	130 yr	60 hr	2 yr	1 yr
Pilocarpine	S†	>24 hr	66 days	34 min
Physostigmine	S	~1 hr‡	6 mo	<10 min
Phenylephrine	S	>2 hr	?	?
Chlorobutanol	40 yr	~2.5 hr	1 yr	<5 min
Homatropine	14 yr	10 hr	0.4 yr	<10 min

*From Riegelman, S., and Sorby, D. L.: EENT preparations. In Martin, E. W., editor: Husa's pharmaceutical dispensing, ed. 6, Easton, Pa., 1966, Mack Publishing Co.

†S, several years.

‡When properly buffered, methylamine is formed during the hydrolysis. It shifts the pH to more alkaline values and thereby increases the rate of hydrolysis.

on exposure to water and becomes inactive. Physostigmine solutions undergo partial oxidizations and develop a pink color. However, this partial breakdown to rubreserine does not materially interfere with the pharmacological action of physostigmine. The addition of sodium bisulfite will inhibit the formation of the "pink" rubreserine.

Sterility

Complete sterility of ophthalmic medications can be achieved by autoclaving. Whenever possible, drugs to be placed in a traumatized or "surgical" eye should be so treated. Filtration to remove bacteria is another effective method of sterilizing ophthalmic solutions. Although widely advocated in the past, this method is now less popular because the technique is time consuming and subject to chemical contamination.

Once the dispensing container is opened, the entire contents may become contaminated. Therefore single-dose dispensers are recommended for use in the "surgical" or traumatized eye. The ever-present danger of contamination of fluorescein sodium solutions with *Pseudomonas* may be avoided by the use of fluorescein-impregnated filter paper strips.

Preservatives should not be used for single-dose solutions because they may cause severe irritation. They should be employed only in multiple-dose solutions, which tend to become contaminated in time. Among the widely used preservatives are benzalkonium (Zephiran) chloride, chlorobutanol, polymyxin B sulfate, organic mercurials, phenols, and substituted alcohols.

PREPARATION OF OPHTHALMIC OINTMENTS

Preparation of ophthalmic ointment does not present the same problems as does preparation of ophthalmic solutions.

The active ingredient for an ophthalmic ointment is mixed in a bland, nonirritating base. In such a medium the drug does not ionize readily, and consequently, tonicity and pH are not factors in stability. A petrolatum base is most commonly used. Water-soluble bases are suitable for preparing some medications, but they cannot be used for any of the antibiotics, since these drugs rapidly lose their effect in an aqueous medium.

In past years little attention was given to the problem of sterility in the preparation of ophthalmic ointments. Although microorganisms do not multiply significantly or spread in ointments, they can survive. Several studies have demonstrated a significant incidence of contamination of ophthalmic ointments. In the past few years considerably more attention has been given to the sterile preparation of ophthalmic ointments. Additionally, techniques of formulation with preservatives compatible with ointment preparation have been developed.

Ophthalmic ointments in general are much more stable than are ophthalmic solutions.

METHODS OF APPLICATION

Solutions for topical application

Solutions are the most commonly used preparations in the local treatment of eye disease. They have several advantages: They are easily instilled; they do not cause interference with vision; they cause few skin reactions; and they do not interfere with the mitosis of the corneal epithelium. Their chief disadvantage is that they do not remain in contact long with the eye; 90% of aqueous solutions are eliminated from the eye within the first minute or two of application. The contact time of drops with the external surface of the eye is dependent on several factors: the amount of tearing and blinking, degree of conjunctival injection, intactness of corneal surface, and viscosity of the medication. More rapid elimination of the medication occurs with increased tearing and blinking. Conjunctival hyperemia increases the absorption of the drug. The medication may be retained longer if surface defects are present.

Aqueous solutions are still commonly used, particularly as presurgical preparations and in the dispensing of topical anesthetics. Aqueous methylcellulose solutions are now commonly prescribed. The addition of methylcellulose to water increases the viscosity of the solution and, consequently, the contact time of the drug with the eye. Methylcellulose solutions can be autoclaved. Although the methylcellulose becomes solidified at high temperatures, the mass can be dispersed by agitation as the solution approaches room temperature. Polyvinyl alcohol in a 1.4% concentration, also now employed as an ophthalmic vehicle, increases contact time of the ophthalmic medication and is easily sterilized. Agents such as polyvinylpyrrolidone, gelatin, and dextrans have been employed in ophthalmic solutions to simulate the physiological effects of mucins usually found in the tear film. It is now believed that mucus adsorbs on the epithelium of the cornea, forming a hydrophilic surface and permitting even spread of the tear film on the corneal surface.

Oily solutions are sometimes used. In the case of DFP, a hygroscopic drug, an oily solution is necessary to prevent inactivation of the drug by hydrolysis.

Ointments for topical application

Ointments have several advantages over solutions: They remain in contact with the eye much longer and thereby give a prolonged effect; they are usually quite comfortable upon initial instillation; there is less absorption into lacrimal passages; and ointments, particularly antibiotic carriers, are more stable than solutions. Disadvantages are that they produce a film in front of the eye and obstruct vision, they more frequently cause contact dermatitis reactions, and they may inhibit mitosis of the corneal epithelial cells.

Packs

Packs are sometimes used to give prolonged contact of a solution with the eye. A cotton pledget is saturated with an ophthalmic solution, and this pledget