Drug-Induced Ocular Side Effects and Drug Interactions

F. T. FRAUNFELDER

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F. T. FRAUNFELDER, M.D.

Professor and Chairman
Department of Ophthalmology
University of Arkansas Medical Center
Little Rock Veterans Administration
Arkansas Children's Hospital
Little Rock, Arkansas

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To
Yvonne, Yvette, Helene Jean,
Nina, Ricky, and Nicholas

FOREWORD

This reference work will be a fitting companion for the clinical ophthalmologist in both office and hospital. With startling clarity, the author impresses the ophthalmologist with the importance of asking each patient: "What medicines are you taking?" Whatever the reply, the ophthalmologist can determine its significance by consulting this thoughtfully prepared book.

As Sir William Osler said: "To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all." Dr. Fraunfelder's book is a worthy follower of the Oslerian tradition, using the master word of Osler: "Work." The author has surveyed the literature extensively and has compiled huge amounts of data about the clinical significance of drugs, their side effects, and their cross reactions. This information is especially useful when a patient is taking drugs with which the ophthalmologist is not familiar.

However, I wish that the list could include, between the letter O and the letter Q, the word Physician. I believe that treating the patient with oneself, the physician, is the most important remedy that doctors have had or ever will have.

Robert P. Burns, M.D.
Professor
Department of Ophthalmology
University of Oregon Medical School

PREFACE

The clinician is overwhelmed by the volume of ocular toxicology in the medical literature and is in need of a reference book that "boils it down." It is for the busy practitioner that this book is designed. The subject of our work is the *probable* medication-induced ocular side effects and the *possible* interactions of drugs prescribed by the ophthalmologist with those the patient is already taking. These areas are of increasing importance to the clinician, and possibly only in presentations of this type can he efficiently make use of the volume of data available. If a patient receiving medication has ocular signs or symptoms, these are not necessarily drug-related. It is the physician's experience, his knowledge, and previous reports on the effects of a particular drug that will lead him to suspect a drug relationship. In a controlled experimental environment it is often difficult to prove that a sign or symptom is drug related; in clinical practice, with multiple variables, it may in many instances be impossible. The clinician, however, needs to remember that there is no active drug known which is without undesirable side actions. It is the intent of this book to compile and organize "previous reports" into a format useful to the physician. No animal data have been included, since ocular toxicologic studies, except in primates, have had limited clinical correlation. Owing to the nature of this book and the volume of material covered, errors, omissions, and misemphasis are inevitable. In the hope of improving future editions, I welcome suggestions or corrections.

Data in this book have been accumulated by innumerable physicians and scientists who have suspected adverse reactions secondary to drug therapy. My sincere thanks to Sir Duke-Elder and Dr. Calvin Hanna for their helpful comments and constructive suggestions, and to Professor Barrie Jones, Institute of Ophthalmology and Moorfields Eye Hospital, London, England, in whose department this book was completed. The enormous amount of library research and organization has been most ably done by Mrs. Martha Meyer and her assistant, Miss Robin Ross, without whom this text would not have been possible. Also, many thanks to Mrs. Lee Hallmark and Mrs. Margaret Casinger for hours of secretarial work expertly performed.

Little Rock, Arkansas

F. T. Fraunfelder, M.D.

INSTRUCTIONS TO USERS

The basic format used in each chapter for each drug or group of drugs in this book includes

Class: **The general category of the primary action of the drug is given.**

Generic Name: The United States National Formulary name of each drug is listed. A name in parenthesis following the National Formulary name is the international generic name if it differs from the one used in the United States.

Proprietary Name: The more common trade names are given. In a group of drugs, the number before a generic name corresponds to the number preceding the proprietary drug. This is true for both the systemic and ophthalmic forms of the drug. If a proprietary name differs from that of the United States, the country is given in parentheses after that particular proprietary name. Combination drugs are seldom included.

Primary Use: The type of drug and its current use in the management of various conditions are listed.

Ocular Side Effects:

A. Systemic Administration – Ocular side effects as reported from oral, intravenous, intramuscular, or intrathecal administration.
B. Local Ophthalmic Use or Exposure – Ocular side effects as reported from topical ocular application or subconjunctival, retrobulbar, or intracameral injection.
C. Inadvertent Ocular Exposure – Ocular side effects as reported due to accidental ocular exposure from any form of the drug.

The ocular side effects are listed in probable order of importance. The determination of importance is based on incidence of significance of the side effect. Side effects of inadequate documentation or current debate are followed by (?). The name of a drug in parenthesis adjacent to an adverse reaction indicates that this is the only agent in the group reported to have caused this side effect.

Clinical Significance: A concise overview of the general importance is given to the clinician of the ocular side effects produced.

Interactions with Other Drugs:

A. Effect of This Drug on Activity of Other Drugs
B. Effect of Other Drugs on Activity of This Drug
C. Synergistic Activity
D. Cross Sensitivity
E. Contraindications – specific

The amount of data in this area is voluminous. To make its use practical, only drugs which ophthalmologists might commonly prescribe are listed. If no interactions are listed, then none of major significance to the ophthalmologist have been reported. The symbol (↑) means enhanced or increased effect on the activity of a drug while (↓) means decreased effect on the activity of a drug. When (↑↓) is used, this means a variable response, in some cases increased, in others decreased.

References: References have been limited to either the best articles, the most current, or to those with the most complete bibliography. Since references for drug interactions are even more extensive, to save space they have not been included; however, a majority of the references are cited in Martin, E. W. (Ed.): *Hazards of Medication.* Philadelphia, J. B. Lippincott Co., 1971; Hansten, P. D.: *Drug Interactions.* 3rd Ed., Philadelphia, Lea & Febiger, 1975; and Garb, S.: *Clinical Guide to Undesirable Drug Interactions and Interferences.* New York, Springer Publishing Co., Inc., 1971.

Index of Side Effects: The lists of adverse ocular side effects due to drugs are intended in part to be indexes in themselves. The adverse ocular reactions are not separated in this index as to route of administration; however, this can be obtained by going to the text.

Index: The index includes both the drugs' generic and proprietary names. No indexing of drug interactions has been done, but this can be obtained by looking up the specific drug. The index is the primary source of entry into this book. This is a necessity since many drugs are in groups and would otherwise be missed.

In the following section, the services of the National Registry of Drug-Induced Ocular Side Effects are outlined. The intent of this registry is to make available data of possible drug-induced ocular side effects and to provide a central area where possible adverse ocular drug reactions can be reported.

* *

NATIONAL REGISTRY OF DRUG-INDUCED OCULAR SIDE EFFECTS

Rationale:

Collecting clinical data of drug-induced side effects for any organ system is still in its infancy. Reporting systems, registries, and surveys are currently being used along with costly prospective studies; however, none of these are being extensively used in ophthalmology. In a specialized area such as ophthalmology, seldom does a practitioner or even a group of practitioners see the patient volume necessary to make a correlation between possible cause and effect of drug-related or drug-induced ocular disease. A national registry to correlate this type of data may be of value, since this task would be difficult to carry out by any other method. If a number of these "possible" associations are found with a particular drug, then definitive controlled studies could be undertaken to obtain valid data. It is hoped that future editions of this book will present data with greater scientific significance, in part due to the reports of possible drug-induced ocular side effects which physicians will send to the registry.

Objectives:

To establish a national center where possible drug-induced ocular side effects can be accumulated.

To review possible drug-induced ocular side effect data collected through the FDA Forum 1639 and the FDA total community studies.

To compile the data in the world literature on reports of possible drug-induced ocular side effects.

To make available this data to physicians who feel they have a possible drug-induced ocular side effect.

Format:

The cases of primary interest are those adverse ocular reactions not previously recognized and those that are rare, severe, serious, or unusual. Data, to be of value, should be complete and follow the basic format as shown below.

Age:
Sex:
Suspected drug – trade name:
Suspected reaction – date of onset:
Route, dose and when drug started:
Improvement after suspected drug stopped – if restarted, did adverse reaction recur:
Other drugs taken at time of suspected adverse reaction:
Comments – optional: (Your opinion if drug-induced, probably related, possibly related, or unrelated.)
Your name and address – optional:

We would welcome, however, your impressions even without specific cases. To ensure confidentiality, no names of patients or physicians are used in any files or reports. This will protect you and the registry from legal interference.

Send to:

Ms. Martha Meyer, Associate Director
National Registry of Drug-Induced Ocular Side Effects
University of Arkansas for Medical Sciences
4301 W. Markham Street
Little Rock, Arkansas 72201

Phone: (501) 661-6011

Abbreviations

(↑) – Increase
(↓) – Decrease
(↑↓) – Variable response – increased or decreased
Arg. – Argentina
Austral. – Australia
Aust. – Austria
Belg. – Belgium
Braz. – Brazil
Canad. – Canada
Cz. – Czechoslovakia
Denm. – Denmark
Fr. – France
G.B. – Great Britain
Germ. – Germany
Ind. – India
Isr. – Israel
Ital. – Italy
Jap. – Japan
Neth. – Netherlands
Norw. – Norway
Pol. – Poland
Scand. – Scandinavian
Span. – Spanish
Swed. – Sweden
Switz. – Switzerland
U.S.S.R. – Union of Soviet Socialist Republics

CONTENTS

I. Anti-infectives

Class: Amebicides

Generic Name: 1. Amodiaquine; 2. Chloroquine; 3. Hydroxychloroquine. See under *Class: Antimalarial Agents.*

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Generic Name: 1. Diiodohydroxyquin (Diiodohydroxyquinoline); 2. Iodochlorhydroxyquin

Proprietary Name: 1. Diodoquin, Embequin (G.B.), Floroquin, Vaam-DHQ (Austral.), Yodoxin; 2. Enteroquin (Austral.), Entero-Vioform

Primary Use: These amebicidal agents are effective against *Entamoeba histolytica.*

Ocular Side Effects

A. Systemic Administration
   1. Decreased vision
   2. Optic atrophy
   3. Optic neuritis – subacute myelo-opticoneuropathy
   4. Nystagmus
   5. Blindness
   6. Macular edema
   7. Macular degeneration
   8. Diplopia
   9. Absence of foveal reflex
   10. Problems with color vision
      a. Dyschromatopsia
      b. Purple spots on white background
   11. Corneal opacities (?)

Clinical Significance: Major toxic ocular effects may occur with long-term oral administration of these amebicidal agents. Since they are given orally for *Entamoeba histolytica*, most reports are from the Far East. Data suggest that these amebicides may cause subacute myelo-opticoneuropathy (SMON). This neurologic disease has a 19 percent incidence of decreased vision and a 2.5 percent incidence of blindness. Possibly diiodohydroxyquin causes fewer side effects since less is absorbed through the gastrointestinal tract than with iodochlorhydroxyquin.

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Generic Name: Emetine

Proprietary Name: Emetine

Primary Use: This alkaloid is effective in the treatment of acute amebic dysentery, amebic hepatitis, and amebic abscesses.

Ocular Side Effects

A. Systemic Administration
   1. Nonspecific ocular irritation
      a. Lacrimation
      b. Hyperemia
      c. Photophobia
   2. Pupils
      a. Mydriasis
      b. Absence of reaction to light
   3. Paralysis of accommodation
   4. Decreased vision
   5. Blindness
   6. Visual fields
      a. Scotomas – central
      b. Constriction

B. Inadvertent Ocular Exposure
   1. Irritation
      a. Lacrimation
      b. Hyperemia
      c. Photophobia
   2. Eyelids or conjunctiva
      a. Allergic reactions
      b. Conjunctivitis – nonspecific
      c. Edema
      d. Blepharospasm
   3. Keratitis
   4. Corneal ulceration
   5. Iritis
   6. Corneal opacities