EIGHTH EDITION

Enhanced DIGITAL VERSION Included

DRUG-INDUCED OCULAR SIDE EFFECTS

Frederick T. **Fraunfelder**
Frederick W. **Fraunfelder**

ELSEVIER

Drug-Induced Ocular Side Effects

EIGHTH EDITION

FREDERICK "FRITZ" T. FRAUNFELDER, MD
Professor
Department of Ophthalmology
Oregon Health and Science University
Casey Eye Institute
Portland, OR, USA

FREDERICK "RICK" W. FRAUNFELDER, MD, MBA
Associate Dean of Faculty Affairs
Chair of Department of Ophthalmology
Roy E. Mason and Elizabeth Patee Mason Distinguished Professor of Ophthalmology
University of Missouri – Columbia School of Medicine
Mason Eye Institute
Columbia, MO, USA

Associate Editor:

BREE JENSVOLD-VETSCH, BS
National Registry of Drug-Induced Ocular Side Effects
Department of Ophthalmology
Oregon Health and Science University
Casey Eye Institute
Portland, OR, USA

For additional online content visit ExpertConsult.com

ELSEVIER London New York Oxford Philadelphia St Louis Sydney 2021

First edition 1976
Second edition 1982
Third edition 1989
Fourth edition 1996
Fifth edition 2000
Sixth edition 2008
Seventh edition 2015

Notices

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds or experiments described herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made. To the fullest extent of the law, no responsibility is assumed by Elsevier, authors, editors or contributors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-323-65375-6
e-Book ISBN: 978-0-323-67401-0
INK ISBN: 978-0-323-67402-7

Content Strategist: Kayla Wolfe
Content Development Specialist: Nani Clansey
Project Manager: Joanna Souch
Design: Patrick Ferguson
Illustration Manager: Theresa McBryan
Marketing Manager: Claire McKenzie

Printed in the USA

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Preface

This is the eighth edition of *Drug-Induced Ocular Side Effects*. This book is intended as a *guide* to help the busy clinician decide whether a visual problem is related to a medication. The clinician's past experience, the known natural course of the disease, the adverse effects of similarly structured compounds, and previous reports all help physicians make their decisions. Unfortunately, there have been only limited attempts to apply rigorous science to the clinical ocular toxicology of marketed products. There are many variables, and there is a paucity of research dollars available to assess cause-and-effect relationships between drugs and visual adverse events. The clinician needs to keep in mind the marked variability of how each human metabolizes or reacts to the drug or its metabolites. A change in the expected course of a disease after starting a drug should heighten the physician's suspicion of a drug-related event. Peer-review journals have difficulty in accepting papers on potential visual side effects of drugs because causation, once the drug is marketed, is usually difficult to prove by scientific parameters. Clinical ocular toxicology primarily relies on case reports, case series, and spontaneous reporting systems. Although we have attempted to classify a suspected adverse event with our impression as to causality (i.e. *certain, probable, possible, unlikely, conditional/unclassified*), one needs to remember that this is based on less powerful scientific evidence. We continue to review spontaneous reports from the US Food and Drug Administration (Bethesda, Maryland), World Health Organization (Uppsala, Sweden), and the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health & Science University, Portland, Oregon). The classification system categories are meant to be "signals," and any intended causality may be unsubstantiated. Our rationale is there may be a pattern in a subset of the user population that we feel the clinician should consider in possible patient adverse drug reactions. This is only a guide for the busy clinician and will always be a work in progress. We welcome your input.

F.T. Fraunfelder, MD
F.W. Fraunfelder, MD, MBA

List of Contributors

Wiley A. Chambers, MD
Clinical Professor of Ophthalmology
Adjunct Assistant Professor of Computer Medicine
George Washington University School of Medicine
Washington, DC, USA

Michael F. Marmor, MD
Professor of Ophthalmology, Emeritus
Byers Eye Institute at Stanford
Stanford University School of Medicine
Palo Alto, CA, USA

Instructions to Users

The basic format used in each section of ocular side effects is:

Class: The general category of the primary action of the drug, chemical, or herb is given.

Generic Name: The recommended International Nonproprietary Name (rINN) for each drug is listed, which is designated by the World Health Organization. In parentheses is the United States National Formulary name or other commonly accepted names.

Proprietary Name: The United States trade names are given, but this is not an all-inclusive listing. In a group of drugs, the number before a generic name for both the systemic and ophthalmic forms corresponds to the number preceding the proprietary drug. International trade names and multi-ingredient preparations are not listed unless indicated.

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

OCULAR SIDE EFFECTS:

Systemic Administration: Ocular side effects are reported from articular, auricular, cutaneous, epidural, implant, infiltration, intradermal, inhalation, intra-arterial, intracarotid, intramuscular, intrapleural, intraspinal, intrathecal, intratympanic, intrauterine, intravenous, nasal, oral, percutaneous, perineural, rectal, subcutaneous, sublingual, topical, transdermal, urethral, or vaginal administration or environmental exposure.

Local Ophthalmic Use or Exposure: Ocular side effects are reported from topical ocular application or eyelid, intracameral, intralesional, intraocular, intravitreal, parabulbar, periocular, retrobulbar, subconjunctival, or subtenon injection.

Inadvertent Ocular Exposure: Ocular side effects are reported due to accidental ocular exposure.

Inadvertent Systemic Exposure: Ocular side effects are reported due to accidental systemic exposure from topical ophthalmic medications.

The ocular side effects are listed as *certain, probable, possible, unlikely,* and *conditional/unclassified*. This classification is based, in part, on the system established by the World Health Organization. There are debatable scientific bases for our opinions. They are only intended as guides for the clinician and are the results of "educated" conjectures from the authors, F. T. Fraunfelder and F. W. Fraunfelder. The name of the preparation in the parentheses adjacent to an adverse reaction indicates that this is the only drug in the group reported to have caused this side effect.

SYSTEMIC SIDE EFFECTS:

Systemic Administration: Systemic side effects are reported from ophthalmic medications administered by an intramuscular, intravenous, or oral route.

Local Ophthalmic Use or Exposure: Systemic side effects are reported from topical ocular application or intracameral, intraocular, periocular, retrobulbar, or subconjunctival injection.

The listing as to certainty of causality is the same as that used by systemic medications.

WHO CLASSIFICATION SYSTEM

Where data are available (i.e. published or submitted for publication), we have classified medication adverse reactions, in part, according to the following World Health Organization Causality Assessment of Suspected Adverse Reactions Guide.

Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but that could also be

explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction about which more data are essential for a proper assessment, or the additional data are under examination.

Clinical Significance: A concise overview of the general importance of the ocular side effects produced is given. Not all side effects listed are reported for each drug and are only a guide for ocular side effects for the class of drugs.

References: References have been limited to the most informative articles, the most current, or those with the most complete bibliography.

Further Reading: Other publications that are useful.

Recommendations: For specific medications, we make recommendations on following patients for probable related effects on the visual system. This was often done in consultation with other coworkers interested in the specific drug; however, this is only intended as a possible guide.

Index of Side Effects: The lists of adverse ocular side effects due to preparations are intended in part to be indexes in themselves. The adverse ocular reactions are not separated in this index as to route of administration.

CHAPTER 1

National Registry of Drug-Induced Ocular Side Effects

FREDERICK W. FRAUNFELDER, MD • FREDERICK T. FRAUNFELDER, MD

RATIONALE

In a specialized area such as ophthalmology, it is not common for a practitioner to see the patient volume necessary to make a correlation between possible cause and effect of medication-related ocular disease. Postmarketing observational studies from multiple sources permit the evaluation of drug safety in a real-world setting where off-label use and various practice patterns occur. There is no question that this has limited ability to determine causation, but it can detect signals that alert the clinician as to adverse drug events. In subspecialty areas of medicine with comparatively limited markets, sometimes this is all that we have. A national registry specifically interested in a specialized area of medicine has filled a need, as shown by the more than three decades of the National Registry of Drug-Induced Ocular Side Effects (NRDIOSE).

The NRDIOSE, which is based at the Casey Eye Institute in Portland, Oregon, USA (www.eyedrugregistry.com), is a clearinghouse of spontaneous reports collected mostly from ophthalmologists from around the world. It is the only database that collects only eye-related adverse drug reactions (ADRs). The MedWatch program run by the US Food and Drug Administration (FDA) (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) collects ADRs on all organ systems in the United States and is another source for reporting data and requesting data. The Uppsala Monitoring Center, a branch of the World Health Organization (WHO) in Uppsala, Sweden (www.who-umc.org), collects spontaneous reports on all organ systems from around the world and has more than 70 national centers that report to them, including the FDA. Finally, clinicians and patients frequently report an ADR directly to the drug company, who in turn periodically submits these spontaneous reports to the FDA.

Regardless of where an ADR is submitted, the various organizations mentioned here can be contacted with questions about an ADR or how many types of reports exist for specific drug–ADR combinations. The NRDIOSE provides this information free of charge to ophthalmologists, and the FDA is required to provide this information to the public through the Freedom of Information Act. The WHO may charge a fee, depending on the type of information requested. The information from pharmaceutical companies should eventually end up in the FDAs MedWatch database.

Spontaneous reporting databases have adopted statistical analyses methods of interpreting ADRs. At the Uppsala Monitoring Center, for instance, a quantitative method for data mining the WHO database is part of the signal detection strategy. Their method is called the Bayesian Confidence Propagation Neural Network (BCPNN). An Information Component (IC) number is calculated based on a statistical dependency between a drug and an ADR calculated on the frequency of reporting. The IC value does not give evidence of causality between a drug and an ADR; it is only an indication or signal that it may be necessary to study the individual case reports in the WHO database. The IC value calculation is a tool that can guide the WHO to create a hypothesis of association between drugs and ADRs among the over 3 million case reports in the WHO database.

This method of analysis is also being adopted within the pharmaceutical industry and at the FDA. The NRDIOSE is also able to use the IC values because its staff are consultants to the WHO. If a clinician suspects an ADR, especially if it may be a new drug-induced ocular side effect, he or she is encouraged to report this to the NRDIOSE. Access to the website is free.

OBJECTIVES OF THE NATIONAL REGISTRY OF DRUG-INDUCED OCULAR SIDE EFFECTS

The Registry

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

- To review possible drug-induced ocular side-effects data collected through the FDA, WHO Monitoring Center, and our registry.
- To compile data in the world literature on reports of possible drug-, chemical-, or herbal-induced ocular side effects.
- To make available these data to physicians who feel they have a possible drug-induced ocular side effect.

HOW TO REPORT A SUSPECTED REACTION

The cases of primary interest are those adverse ocular reactions not previously recognized or those that are rare, severe, serious, or unusual. To be of value, data should be complete and follow the basic format shown here:

Age:
Gender:
Suspected drug:
Suspected reaction date of onset:
Route, dose, and when drug started:
Improvement after suspected drug stopped. If restarted, did adverse reaction recur?:
Other drug(s) taken at time of suspected adverse reaction:
Other disease(s) or diagnosis(es) present:
Comments optional (your opinion if drug induced, probably related, possibly related, or unrelated):
Your name and address (optional):
Send to:
Frederick T. Fraunfelder, Co-Director
National Registry of Drug-Induced Ocular Side Effects, Casey Eye Institute, Oregon Health Sciences University, 515 SW Campus Drive, Portland, Oregon 97239-4197
http://www.eyedrugregistry.com
E-mail: eyedrug@ohsu.edu

FURTHER READING

Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol*. 1998;54:315–321.

Bate A, Lindquist M, Edwards IR, et al. A data mining approach for signal detection and analysis. *Drug Saf*. 2002;25:393–397.

Bate A, Lindquist M, Orre R, et al. Data mining analyses of pharmacovigilance signals in relation to relevant comparison drugs. *Eur J Clin Pharmacol*. 2002;58:483–490.

Bate A, Orre R, Lindquist M, et al. Explanation of data mining methods. *BMJ*. http://www.bmj.com/cgi/content/full/322/7296/1207/DC1.html.

Coulter DM, Bate A, Meyboom RH, et al. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: a data mining study. *BMJ*. 2001;322:1207–1209.

Lindquist M, Stahl M, Bate A, et al. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. *Drug Saf*. 2000;23:533–542.

Orre R, Lansener A, Bate A, et al. Bayesian neural networks with confidence estimations applied to data mining. *Comput Stat Data Anal*. 2000;34:473–493.

Spigset O, Hagg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. *Int Clin Psychopharmacol*. 2003;18:157–161.

Van Puijenbroek EM, Bate A, Leufkens HG, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reaction. *Pharmacoepidemiol Drug Saf*. 2002;11:3–10.

CHAPTER 2

Ocular Drug Delivery and Toxicology

FREDERICK T. FRAUNFELDER, MD

Drug delivery to the eye is a complex process. The eye is unique in the body in many ways that affect its pharmacology and toxicology. It includes several different cell types and functions basically as a self-contained system. The rate and efficacy of drug delivery differ in healthy and diseased eyes. Variables affecting delivery include age, genetic ancestry, and route of administration. The complexities of delivery, toxicology, or both are greatly influenced by patient compliance, especially in the management of glaucoma, which requires multiple topical ocular medications to be given at one sitting each day, often multiple times daily. Each time and method of drug delivery modify the therapeutic and toxicologic response.

Ocular toxicology is dependent on the concentration of the drug, frequency of application, speed of removal, and whether the drug reaches sensitive cells such as the corneal endothelium, lens epithelium, or macula in toxic concentrations. Of equal importance is the vehicle for delivery and the pH, buffering systems, and preservatives necessary for optimum drug delivery. Each adds its own potentially toxic effect to this complex picture. Originally, much of ocular pharmacology and toxicology was conducted by trial and error, often with local corner pharmacies compounding medications. Today, the ocular pharmaceutical industry is acutely aware of potential problems and is continuously researching and producing medications, usually with fewer side effects and delivered by better medications.

TOPICAL OCULAR ADMINISTRATION

This is by far the most commonly used method of drug delivery to the eye. Topically administered medications are convenient, easy to reapply, and relatively inexpensive. This method concentrates the pharmacologic activity of the drug on/in the eye while limiting systemic reactions. Local toxic responses are increased, however, especially with lifelong use, as with glaucoma medications. Unlike medication given orally, topical ocular medications reach systemic circulation while avoiding the first-order pass effect through the liver. A drug absorbed through the nasal mucosa or conjunctiva "drains" to the right atrium and ventricle. The blood containing the drug is then pumped to the head before returning to the left atrium and ventricle. The second passage is through the liver, where the primary detoxification occurs before going to the right atrium. When medications are orally administered, the first pass includes absorption from the gut through the liver, where, depending on the drug, up to 90% of the agent is detoxified before going to the right atrium. Thus oral medications are metabolized during the first pass, whereas ocularly or nasally administered drugs are not metabolized until the second pass. This is the reason why therapeutic blood levels, and accompanying systemic side effects, may occur from topical ocular medications. Other factors include racial differences in metabolism, as with timolol. One percent of people with Japanese or Chinese genetic ancestry, 2.4% of African Americans, and 8% of those with European ancestry do not have the p450 enzyme CYP2D6 that is necessary to metabolize this drug. The lack of this enzyme significantly enhances systemic blood levels of timolol.[1]

BASIC PHARMACOLOGY AND TOXICOLOGY OF TOPICAL MEDICATIONS

Ocular toxicology is based on pharmacokinetics – how the drug is absorbed, including its distribution, metabolism, and elimination – as well as pharmacodynamics, the action of the drug on the body. This bioavailability is influenced by age, body weight, sex, and eye pigmentation. It is also affected by the disease process, interactions with other drugs, and mode of delivery. Only a small percentage of any topically applied drug enters the eye. At best, 1–10% of topical ocular solutions are absorbed by ocular tissues.[2] This absorption is governed by ocular contact time, drug concentration, tissue permeability, and characteristics of the cornea and pericorneal tissue. Nearly all solutions will leave the conjunctival sac, or cul-de-sac, within 15–30 seconds

of application.[3] The average volume of the cul-de-sac is 7 μL, with 1 additional μL in the precorneal tear film.[4] The cul-de-sac may hold 25–30 μL of an eye drop; however, blinking will decrease this volume markedly and rapidly, so that, at most, only 10 μL remain for longer than a few seconds. The drop size of commercial drugs varies from 25 μL to more than 56 μL.[4] In a healthy eye, one not affected by disease, lid manipulation to instill the drug will double or triple the normal basal tear flow exchange rate of 16% per minute, thereby decreasing ocular contact time via dilution.[4]

The cornea is the primary site of intraocular drug absorption from topical drug application. This is a complex process that favors small, moderately lipophilic drugs that are partially nonionized under physiologic conditions. Although the cornea is a five-layer structure, it has significant barriers to absorption into the eye. It can be visualized as three layers, like a sandwich, with a hydrophilic stroma flanked by lipophilic epithelium and endothelial layers.[4]

Topically administered drugs are also absorbed via the conjunctiva, sclera, and lacrimal system. The total surface area of the conjunctiva is 17 times the corneal surface area.[4] The conjunctiva allows absorption of lipophilic agents to a lesser degree than the cornea, but it is relatively permeable to hydrophilic drugs. The sclera is porous via nerve and blood vessel tracts, but otherwise fairly resistant to penetration. Hydrophilic agents may pass through it 80 times faster than through the cornea; however, the lacrimal system can remove the drug 100 times faster than the cornea and conjunctiva can absorb it.[4,5]

Clearly, overflow from every administration of eye drops occurs not only over the eyelid but also in the lacrimal outflow system. Lynch et al showed that 2.5% phenylephrine topically applied to the eyes of newborn babies in 8-μL or 30-μL aliquots produced no difference in pupillary response.[6] However, neonates who received the 30-μL dosage had double the plasma concentrations of phenylephrine of those who received 8 μL, increasing the potential for systemic complications.

INTRAOCULAR DISTRIBUTION

Once a drug reaches the inside of the eye, anatomic barriers play a major role in where it ends up. Drugs that enter primarily through the cornea seldom penetrate behind the lens. The pattern of aqueous humor flow and the physical barriers of the iris and ciliary body help keep the drug anterior. It is not uncommon for a drug to be more concentrated in the ciliary body than in the aqueous humor due to scleral absorption directly into the ciliary body, with less fluid exchange than in the aqueous humor. In addition, pigmented tissue reacts differently to different drugs. For example, lipid-soluble mydriatics that are more slowly absorbed by pigmented cells will dilate dark pupils more slowly, resulting in longer duration but a decrease in maximum dilation.[7]

Drug distribution is markedly affected by eye inflammation. Tissue permeability is increased, allowing greater drug availability. However, as Mikkelson et al have demonstrated, protein binding may decrease drug availability 75–100% in inflamed eyes.[8] The protein–drug complex decreases bioavailability. Increases in aqueous or tear protein, such as mucus, are also factors in bioavailability, as is the increased tearing that may wash away a drug before it can be absorbed.[8]

PRESERVATIVES

Preservatives are important parts of topical ocular medications, not only to prolong shelf life but also to disrupt the corneal and conjunctival epithelium to allow greater drug penetration.

Preservatives such as benzalkonium have been shown to have antibacterial properties almost as great as those of topical ocular antibiotics. Even in exceedingly low concentrations, benzalkonium causes significant cell damage by emulsification of the cell-wall lipids. De Saint Jean et al report cell-growth arrest and death at concentrations as low as 0.0001%.[9] Short-term use seldom causes clinically significant damage to healthy corneas and conjunctiva other than superficial epithelial changes. However, with long-term use, e.g. in patients with glaucoma and dry eye, preservatives in topical eye medication may cause adverse effects. Hong et al have shown induction of squamous metaplasia by chronic application of glaucoma medications containing preservatives.[10] This may progress to more severe side effects, as shown in Table 2.1.

VEHICLES FOR TOPICAL OCULAR MEDICATION DELIVERY

Aqueous solutions: With aqueous solutions, ingredients are fully dissolved within a solution. Benefits include easy application and few visual side effects. The main drawback is a short ocular contact time, which leads to poor absorption and limited bioavailability. Nevertheless, this is still the most commonly used means of delivering topical ocular medications. Solutions may congregate in the lacrimal sac (Fig. 2.1).

TABLE 2.1
Preservative Ocular Side Effects

Eyelids and Conjunctiva	Cornea
Allergic reactions	Punctate keratitis
Hyperemia	Edema
Erythema	Pseudomembrane formation
Blepharitis	Decreased epithelial microvilli
Conjunctiva, papillary	Vascularization
Edema	Scarring
Pemphigoid lesion with	Delayed wound-healing symblepharon
Squamous metaplasia	Increased transcorneal permeability
Contact allergies	Decreased stability of tear film Squamous metaplasia

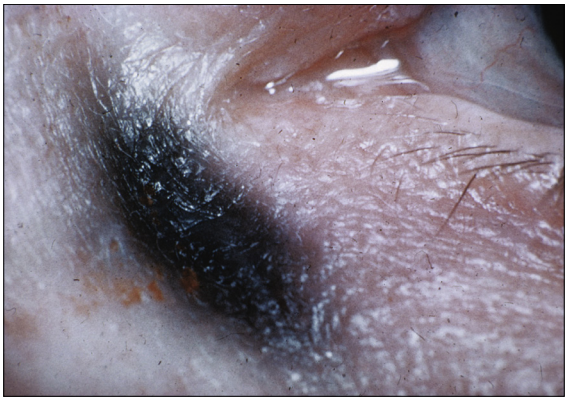

FIG. 2.1 Chronic use of silver nitrate solutions causes staining of the lacrimal sac and surrounding tissue[18].

Suspensions: With this vehicle, the active ingredient is in a fine particulate form suspended in a saturated solution of the same medication. This method allows for longer contact time with greater bioavailability. Its drawbacks include the necessity of vigorously shaking the container before application and a possible increase in foreign-body sensation after application because of the deposition of particles in the corneal tear film.

Ointments: These consist of semisolid lipoid preparations containing lipid-soluble drugs. They are designed to melt at body temperature and are dispersed by the shearing action of blinking. Ointments are frequently entrapped in lashes, fornices, and canthal areas, which are capable of acting as reservoirs. They can also become entrapped in corneal defects (Fig. 2.2); e.g. ointment at the base of the lashes comes in contact with the skin. Because ointment will melt when it comes in contact with the skin, the ointment at the base of the lashes reaches the eye in a continuous process of becoming entrapped in the lashes and remelting into the eye. Ointments have high bioavailability and require less frequent dosing than other methods but suffer by being difficult to administer. Other problems include variable dosing (it is difficult to control the amount applied) and possible unacceptability to patients due to blurred vision and cosmetic disfigurement.

Pledgets: Pledgets (small absorbent pads saturated with medication) may be used to deliver high concentrations of drugs directly to the ocular surface for relatively prolonged periods. This method of drug delivery to the eye is not approved by the US Food and Drug Administration. Pledgets of vasoconstrictors to limit bleeding in keratorefractive surgery have been shown to cause significant systemic reactions, including hypertension, cardiac arrest, subarachnoid hemorrhage, convulsions, and death.[11]

Injections: Subconjunctival injections allow medication to be concentrated locally, with high bioavailability and limited systemic side effects. Wine et al suggested that the mechanism of drug delivery may be in part simple leakage of the drug through the needle-puncture site with subsequent absorption through the cornea.[12] McCartney et al showed that subconjunctival injections of hydrocortisone did penetrate the overlying sclera and that the injection site should be located directly over the area of pathology.[13]

Intracameral injections are administered directly to the anterior chamber of the eye and are most frequently used to place viscoelastics. Although small amounts of antibiotics may also be administered, some of these drugs pose risks to the corneal endothelium, and cataracts, corneal opacities, anterior uveitis, and neovascularization are possible.

Intravitreal injections have become increasingly popular due to their efficacy against macular degeneration, bacterial and fungal endophthalmitis, and viral retinitis. Each drug has its own toxicity profile; however, these injections are so commonly done that the volumes, concentrations, and vehicles are well tested, and complications are within an acceptable risk–benefit ratio.

Other delivery devices: Ocuserts (small plastic membranes impregnated with medication); collagen corneal shields (biodegradable contact-lens–shaped clear

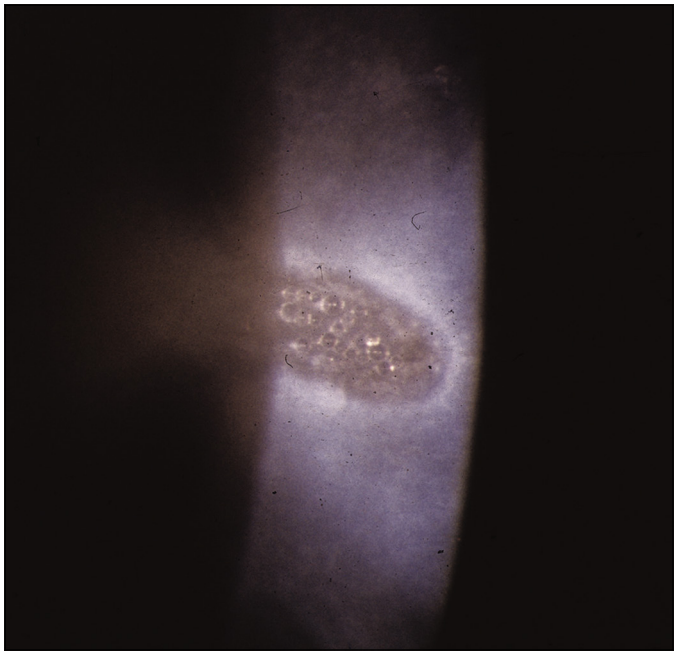

FIG. 2.2 Corneal defects may entrap ointment on the surface, creating ointment globules[18].

films made to dissolve within 12–72 hours); contact lenses; and various other delivery systems, including nanoparticles, liposomes, emulsions, and gels, have either made it to market with limited success or are still in the research pipeline.

TOXICITY RESPONSES

Anterior segment: Toxicity produces an inflammatory response without prior exposure to the host, whereas hypersensitivity responses require prior exposure. In general, allergic reactions involve repeated exposure to the antigen and sufficiently elapsed time to allow the immune system to react. Depending on the potency of the sensitizing agent or the strength of the immune system, this may vary from a few days to years.[14] The clinical diagnosis of a toxic response is usually presumptive, whereas in allergic reactions conjunctival scraping may reveal eosinophils or basophils. One of the most common signs of ocular toxicity from topical medication is hyperemia. This reaction includes burning and irritation, usually without itching, occurring after starting an offending agent, with classic symptoms of intracanthal eyelid edema and erythema (Fig. 2.3). There are no definitive confirmatory tests. In more severe cases, a papillary hyperemia with a watery mucoid type of discharge is evident. If the cornea is involved, this may present as a superficial punctate keratitis, usually more severe inferiorly or inferior nasally. Occasionally, intraepithelial microcysts may be seen, although these are more commonly seen with chemical toxicity. If the reaction is severe enough or goes unrecognized, it may become full blown with corneal ulceration, limbal neovascularization, anterior uveitis, cataracts, and damage to the lacrimal outflow system. The diagnosis is confirmed if clearing occurs after stopping the offending drug and the eye and adnexa improve markedly.

Drugs can induce a condition such as ocular pemphigoid, a syndrome of nonprogressive toxic reactions, which are self-limiting once the drug is discontinued. This condition is clinically and histologically identical to idiopathic ocular pemphigoid and includes a conjunctival cicatricial process with scarring of the fornix and tarsal conjunctiva, corneal and conjunctival keratinization, corneal vascularization, and lacrimal outflow scarring with occlusion.

Almost any type of pathology can be seen as a result of a toxic response in the anterior segment. Systemic medications affect the anterior segment and occur via secretion of the drug into the tears with secondary changes due to the drug or its metabolites on ocular structures (Fig. 2.4). If the drug is secreted in the tears

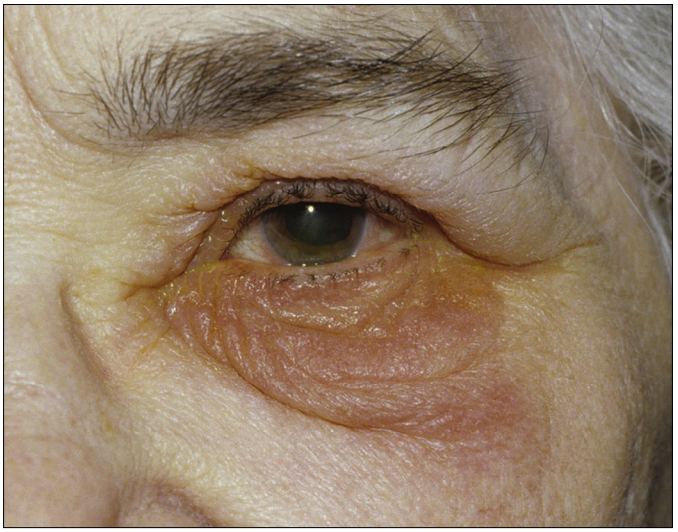

FIG. 2.3 Allergic reaction[18].

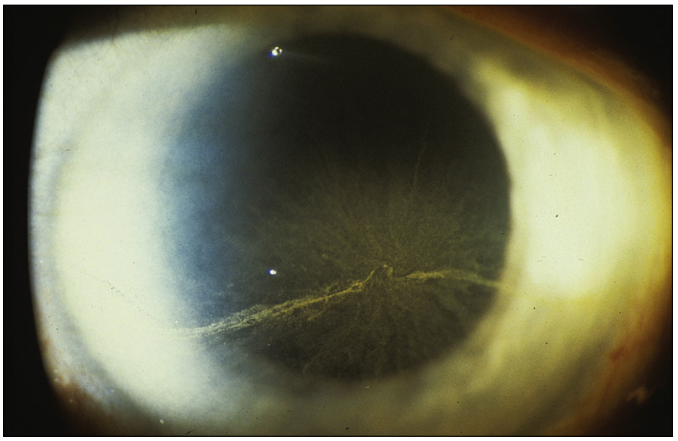

FIG. 2.4 Amiodarone keratopathy secondary to the drug being secreted in the tears[18].

and deposited in the conjunctiva or cornea, it may produce changes in color vision or visual changes. The key to recognizing a toxic response is a high degree of suspicion that the pattern of symptoms and signs is not characteristic for the clinician's differential diagnosis. A toxic effect is due to a pharmacologic effect from a drug that damages a structure or disturbs its function. An irritation is an inflammatory effect unrelated to sensitization or cellular immunity.

Ciliary body: Ciliary body ultrasound has shown bilateral choroidal effusions caused by various systemic drugs that may cause bilateral narrow-angle glaucoma.

Lens: It is difficult to identify which drugs are weak cataractogenic agents because these studies often require large numbers of patients. Findings are also difficult to confirm because instrumentation or classification systems are often cumbersome and costly. Some drugs used in the past, such as MER-29 (tiaparanol), caused acute lens changes, but cataractogenic drugs in current use are slow to cause lens changes, which may take many years to develop. In general, a drug-induced lens change is fairly specific for that drug. For example, both topical and systemic corticosteroid medications produce posterior subcapsular

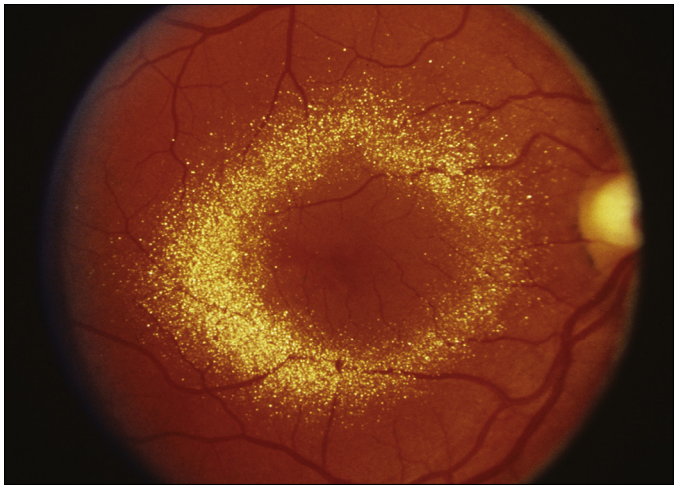

FIG. 2.5 Canthaxanthine perimacular deposition[18].

opacities. Early recognition may in some cases reverse these changes, but this is rare for almost all drug-induced cataracts.

Posterior segment: As newer classes of drugs are introduced, we are seeing more adverse retinal and optic nerve abnormalities. Whereas in the past visual acuity, color vision testing, and ophthalmoscopy were our primary tools for investigating retinal and optic nerve changes, electrophysiology testing is now being used with improved instrumentation and better standardization of methodology. Drugs can cause blood vessels to narrow, dilate, leak, swell, and hemorrhage. They can also cause pigmentary changes, photoreceptor damage, or inflammation. There can be deposition of the drug or its metabolites into the retina, as well as lipidosis. A drug can cause edema of the choroid, exudative detachment, or retinal detachment (Fig. 2.5).

Elevation of intraocular pressure: Adverse ocular effects may cause acute glaucoma by dilation of the pupil or ciliary body effusions, by vasodilatation, by affecting the mucopolysaccharides in the trabecula (secondary to uveitis), or by means of a substance that interferes with aqueous outflow. Drugs or preservatives may, on chronic exposure, deposit in the ocular outflow system causing ocular pressure elevation.

Neurologic disorders: Multiple drugs can affect the extraocular muscles, causing weakness or paralysis, which in turn leads to ptosis, nystagmus, oculogyric crisis, or lid retraction. Direct neurotoxicity to the retina or optic nerve can occur, as can secondary optic nerve edema from benign intracranial hypertension.

Miscellaneous: Eyelash, eyebrow, and orbital disturbance reactions such as poliosis, madarosis, and exophthalmos or enophthalmos can also occur.

Newer methods of delivery and new drugs have brought on side effects and toxicities not seen or recognized previously. The various metabolic pathways of patients and multiple variables such as drug, food, or disease interactions make recognition more difficult. Also, the basic incidence is often small, which makes an association difficult to prove.

HOW TO APPLY TOPICAL OCULAR MEDICATION

Applying Medication to Someone Else[15]

1. Tilt the person's head back so he or she is looking up toward the ceiling. Grasp the lower eyelid below the lashes and gently pull it away from the eye (Fig. 2.6A).
2. Apply one drop of solution or a match-head–sized amount of ointment into the pocket between the lid and the eye (Fig. 2.6B). The external eye holds only about one quarter to one half of a drop, so don't waste medicine by applying two drops.
3. As the person looks down, gently lift the lower eyelid to make contact with the upper lid (Fig. 2.6C). The person should keep their eyelid closed for 3 minutes.

Applying Your Own Medication[15]

1. Tilt your head back. Rest your hand on your cheek and grasp your lower eyelid below the lashes. Gently lift the lid away from your eye. Next, hold the

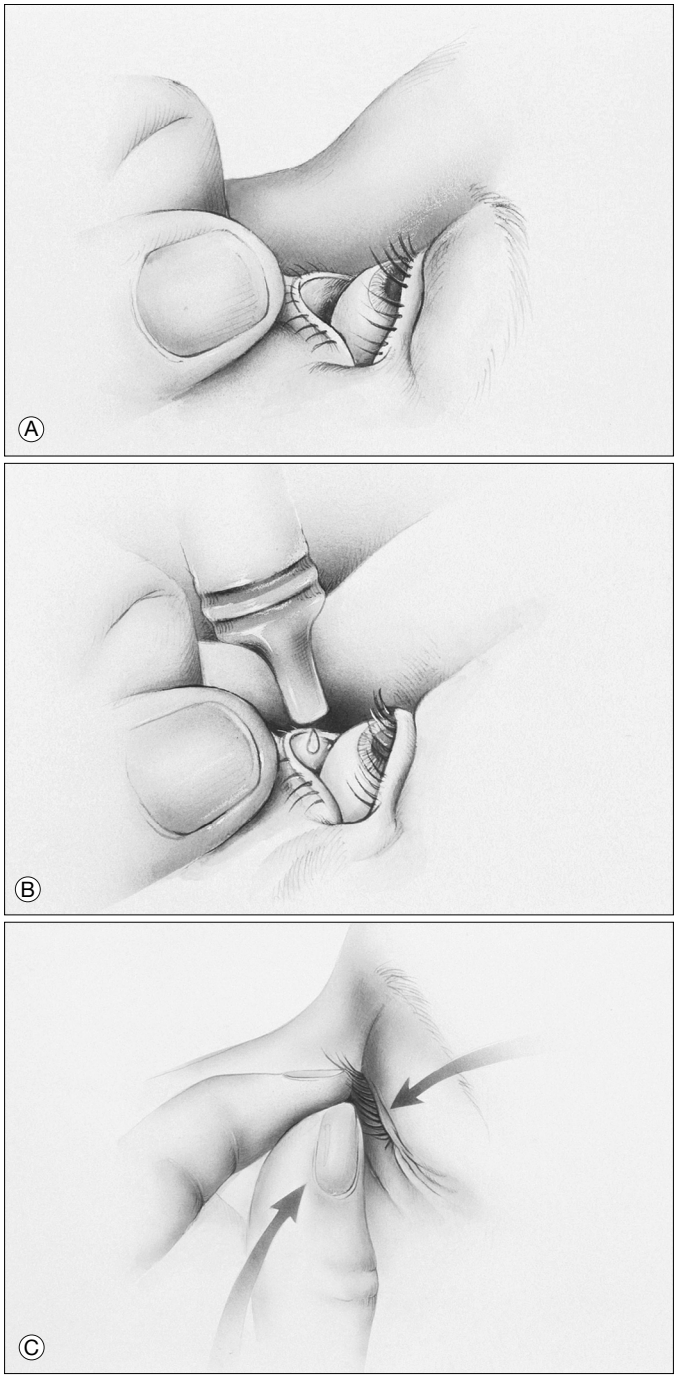

FIG. 2.6 (A–C)[15]

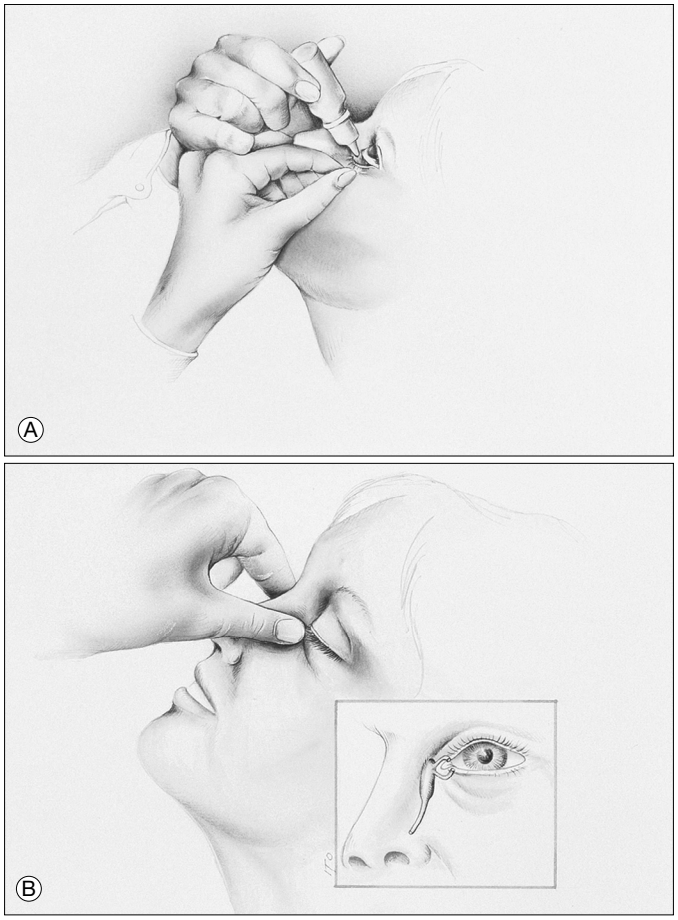

FIG. 2.7 (A and B)[15]

dropper over and as near to your eye as you feel is safe, resting the hand holding the dropper on the hand holding your eyelid (Fig. 2.7A).

2. Look up and apply one drop of the medication into the pocket between the lid and the eye. Close the eyelid and keep it closed for 3 minutes. Blot away any excess medication before opening your eye.

When applying eye medications, it is best to ask someone else to apply them for you. It is very important to wash your hands before applying eye medication. The person receiving medication should keep their eyes closed for 3 minutes after application. Blot excess fluid from the inner corner of the lids before opening the eyes. This is especially important with glaucoma medication. Wait 5–10 minutes between drug applications when applying more than one eye medication. All medications should be kept at room temperature because cool solutions stimulate tearing. This causes the drug to be diluted and may cause epiphora.

Lid closure has been well documented as dramatically increasing ocular contact time and decreasing lacrimal drainage.[16] Zimmerman et al demonstrated that merely closing the eyelids for 3 minutes can decrease plasma concentrations of timolol by 65% when measured 60 minutes after topical application.[17] Likewise, the therapeutic benefits of nasolacrimal occlusion are substantial, particularly for drugs absorbed from nonconjunctival routes. Pressure over the lacrimal sac can allow for a decrease in both the frequency and dose of topical ocular agents (Fig. 2.7B). It may be difficult for patients to perform nasolacrimal occlusion routinely, so this technique is not used as frequently as it should be.

REFERENCES

1. Edeki T, He H, Wood AJ. Pharmacogenetic explanation for excessive beta-blockage following timolol eye drops. Potential for oral ophthalmic drug interaction. *JAMA*. 1995;274:1611–1613.
2. Schoenwald RD. The control of drug bioavailability from ophthalmic dosage forms. In: Smolen VF, Ball VA, eds. *Controlled Drug Bioavailability. Bioavailability Control by Drug Delivery System Design*. Vol 3. New York: John Wiley; 1985:257–306.
3. Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. *Surv Ophthalmol*. 1982;26:207–218.
4. Mishima S, Gasset A, Klyce Jr SD, et al. Determination of tear volume and tear flow. *Invest Ophthalmol*. 1966;5:264–276.
5. Van Ootegham MM. Factors influencing the retention of ophthalmic solutions on the eye surface. In: Saettone MF, Bucci M, Speiser P, eds. *Ophthalmic Drug Delivery. Fidia Research Series*. Vol. 11. Berlin: Springer Verlag; 1987:7–18.
6. Lynch MG, Brown RH, Goode SM, et al. Reduction of phenylephrine drop size in infants achieves equal dilation with decreased systemic absorption. *Arch Ophthalmol*. 1987;105:1364–1365.
7. Harris LS, Galin MA. Effect of ocular pigmentation on hypotensive response to pilocarpine. *Am J Ophthalmol*. 1971;72:923–925.
8. Mikkelson TJ, Charai S, Robinson JR. Altered bioavailability of drugs in the system due to drug protein interaction. *J Pharmacol Sci*. 1973;62:1648–1653.
9. De Saint Jean M, Brignole F, Bringuier AF, et al. Effects of benzalkonium chloride on growth and survival of Chang conjunctival cells. *Invest Ophthalmol Vis Sci*. 1999;40:619–630.
10. Hong S, Lee CS, Seo KY, et al. Effects of topical antiglaucoma application on conjunctival impression cytology specimens. *Am J Ophthalmol*. 2006;142:185–186.
11. Fraunfelder FW, Fraunfelder FT, Jensvold B. Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol*. 2002;134:624–625.
12. Wine NA, Gornall AG, Basu PK. The ocular uptake of subconjunctivally injected C14 hydrocortisone. Part 1. Time and major route of penetration in a normal eye. *Am J Ophthalmol*. 1964;58:362–366.
13. McCartney HJ, Drysdale IO, Gornall AG, et al. An autoradiographic study of the penetration of subconjunctivally injected hydrocortisone into the normal and inflamed rabbit eye. *Invest Ophthalmol*. 1965;4:297–302.
14. Abelson MB, Torkildsen G, Shapiro A. Thinking outside the eye dropper. *Rev Ophthalmol*. 2005;12:78–80.
15. Fraunfelder FT. Ways to diminish systemic side effects. In: Vaughan D, Asbury T, eds. *General Ophthalmology*. 15th ed. Norwalk, CT: Appleton and Lange; 1999:68–73.
16. Fraunfelder FT. Extraocular fluid dynamics: how best to apply topical ocular medication. *Tran Am Ophthalmol Soc*. 1976;74:457–487.
17. Zimmerman TJ, Sharir M, Nardin GF, et al. Therapeutic index of epinephrine and dipivefrin with nasolacrimal occlusion. *Am J Ophthalmol*. 1992;114:8–13.
18. Fraunfelder FT. *Chronic use of silver nitrate solutions causes staining of the lacrimal sac and surrounding tissue; Corneal defects may entrap ointment on the surface, creating ointment globules; Allergic reaction; Amiodarone keratopathy, secondary to the drug being secreted in the tears; Canthaxanthine perimacular deposition [photographs]*. Portland (OR): Casey Eye Institute, Oregon Health & Science University; ©1990. 5 photographs: color.