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DRUG-INDUCED OCULAR SIDE EFFECTS

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ELSEVIER

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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.

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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
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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

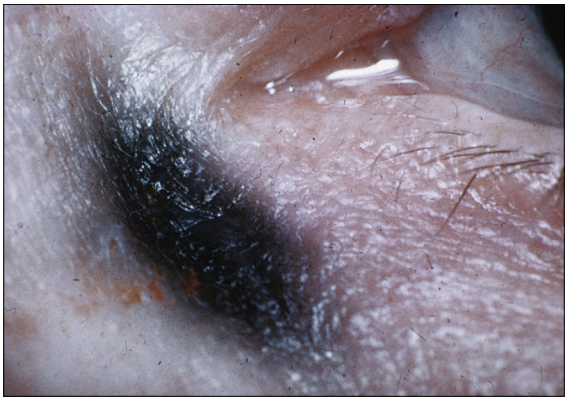

FIG. 2.1 Chronic use of silver nitrate solutions causes staining of the lacrimal sac and surrounding tissue[18].

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

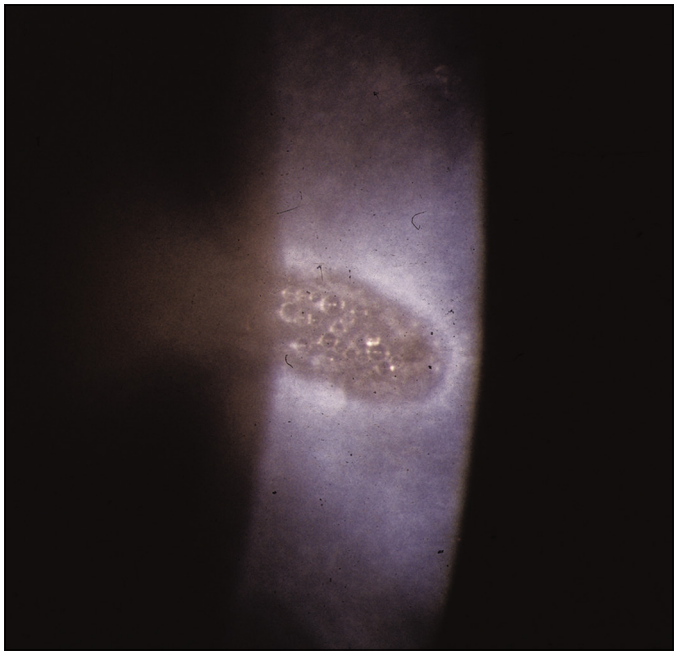

FIG. 2.2 Corneal defects may entrap ointment on the surface, creating ointment globules[18].

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

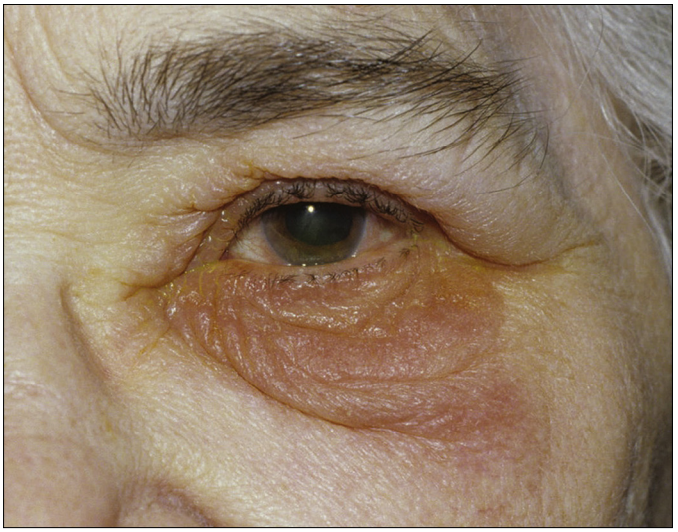

FIG. 2.3 Allergic reaction[18].

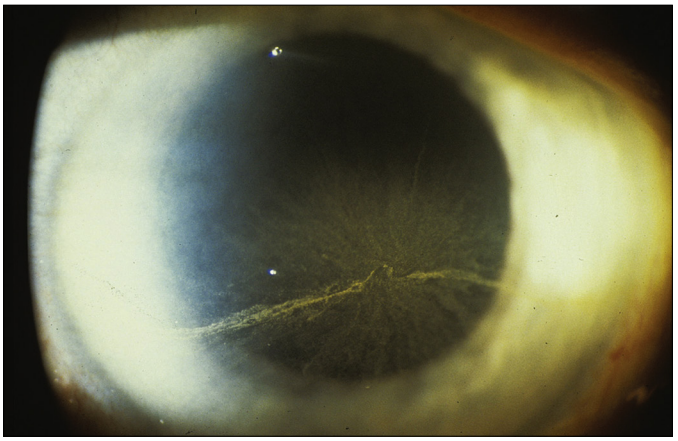

FIG. 2.4 Amiodarone keratopathy secondary to the drug being secreted in the tears[18].

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

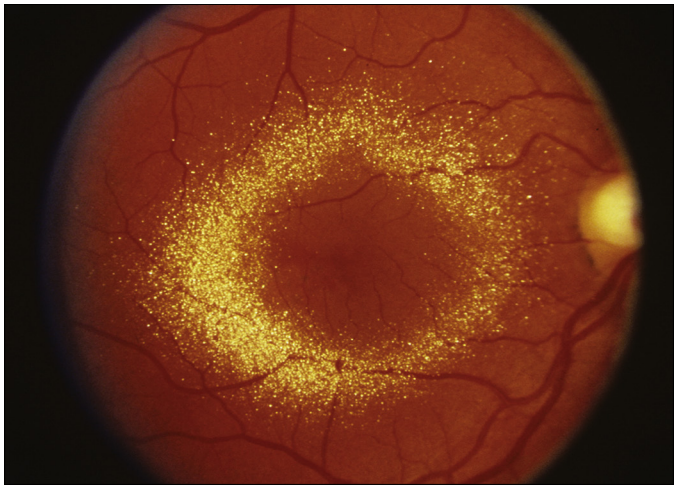

FIG. 2.5 Canthaxanthine perimacular deposition[18].

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

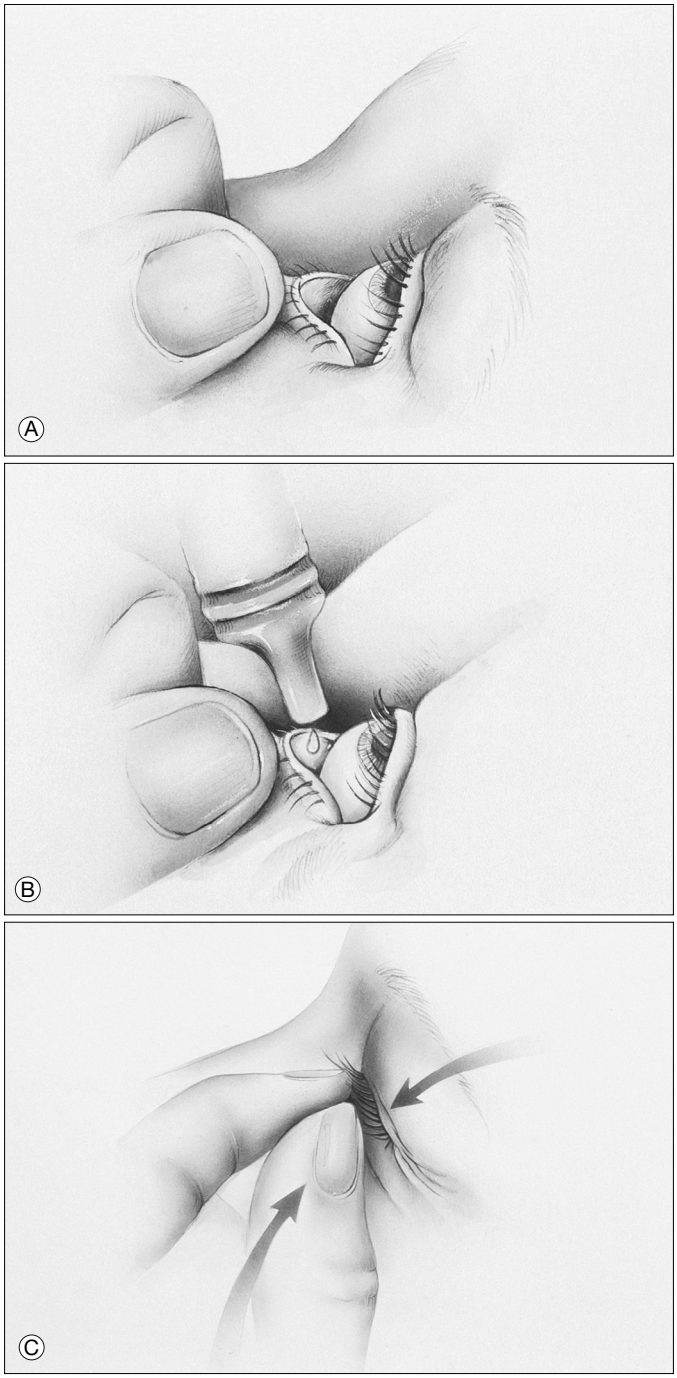

FIG. 2.6 (A–C)[15]

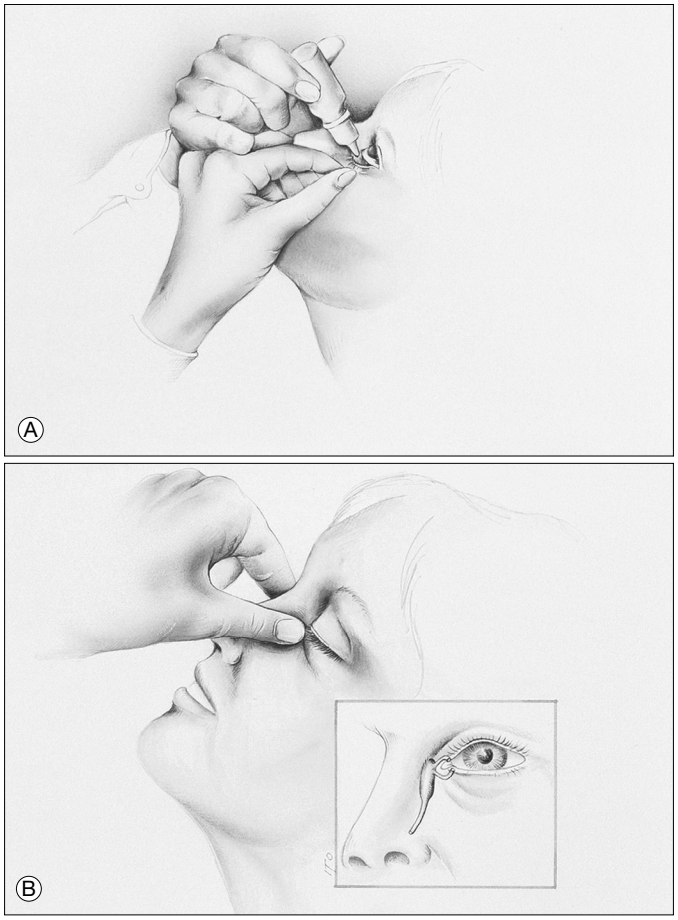

FIG. 2.7 (A and B)[15]

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.

CHAPTER 3

Methods for Evaluating Drug-Induced Visual Side Effects

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This chapter reflects the views of the author and should not be construed to represent the US Food and Drug Administration's (FDA's) views or policies.

RISK

All drug products have some risk. If there is pharmacologic activity due to the drug product, there is also a risk of adverse events from the pharmacologic activity. Risk is generally best assessed in controlled clinical studies. Unfortunately, in the case of low-incident events, this is not always possible. A risk may not be identified until after the drug product has been commercially marketed. At that time, it is often difficult to determine the number of people who have been exposed to the drug product. If the number of people exposed cannot be accurately determined, the exact frequency or likelihood of a side effect cannot be accurately determined.

The assessment of risk generally improves as more individuals receive the drug product. Although it would be extremely helpful to know the full risk profile of every drug product before release into commercial marketing, usually the full risk profile is not completely known until after the drug product has been marketed, and sometimes not until years later.

SELECTING DIAGNOSTIC TESTS

A wide variety of diagnostic testing modalities may be used to detect and evaluate a suspected ocular toxicity. Although it is theoretically possible to perform each of these tests on any individual who is suspected to have an abnormality, the time, expense, resources, and ability of the patient to cooperate must be taken into consideration. In broad terms, these tests may be divided into two main categories. The first covers methods capable of detecting objective anatomic changes, and the second covers methods capable of detecting functional changes. The former category of tests is not necessarily better than the latter; they simply measure different things.

The number of tests needed to characterize an abnormality (or deviation) will vary with the abnormality being evaluated and the extent to which it needs to be characterized. Screening tests may be used to superficially scan for irregularities without fully quantitating the extent of the anomaly, but there should be a justified reason for the selection of each test. Each test should be appropriate for the type of potential event in question.

As noted earlier, it may be theoretically possible to perform many tests, but consideration of the following questions can help narrow the choice:

1. What are the findings from any nonclinical toxicology studies in nonhuman animals?
2. What abnormalities are expected based on the known pharmacologic action of the drug?
3. What is the route of administration of the drug?
4. How widely is the drug distributed throughout the human body?
5. How serious is the potential abnormality?
6. How likely is the test to detect an abnormality?
7. How invasive is the test?

When possible, it is recommended that nonclinical toxicology studies be conducted before conducting human toxicology studies. Ideally, nonclinical studies should be conducted using higher multiples (2×, 10×, 100×) of the doses proposed for humans (based on concentration and/or frequency of administration). The duration of dosing should be at least as long as planned in humans (up to 9 months). It is helpful to compare multiple different dose levels in these studies. The findings of the nonclinical toxicology studies should then be used to help guide the initial tests to be conducted in humans. Although the events observed in nonhuman studies may not be duplicated in human studies, there is frequently some overlap. It is therefore important to assess the potential for these events.

For example, an important characteristic that may be determined in nonclinical studies is whether or not a drug product binds to melanin. Melanin is found widely in the

eye, and products that bind to it may cause ocular toxicities. If a drug product has been found to bind to melanin, it would be important to know whether the nonclinical studies demonstrated abnormalities in electroretinograms (ERGs). If a drug product is found to bind to melanin and demonstrates ERG abnormalities in animals, it would be prudent to monitor best corrected distance visual acuity, color vision, automated threshold static visual fields, ocular coherence tomography (OCT), and dilated fundus photographs of subjects in clinical studies.

Histopathology in the nonclinical studies can be important. If in nonclinical studies, a retinal lesion or retinal drug deposit is observed in animals, best corrected distance visual acuity, color vision, threshold static visual field, OCT, and fundus photographs should be monitored in clinical studies of humans. Drug products that cause retinal lesions and ERG changes in nonhuman animals often cause toxicity in humans as well.

If in nonclinical studies, lens opacity is observed in animals, then best corrected distance visual acuity and lens photography or the use of a standardized lens grading system should be included in clinical studies of humans.

The structure of the drug, nonclinical pharmacology studies, and clinical pharmacology studies may be helpful in identifying the expected pharmacologic actions of the drug. To the extent that the pharmacologic action potentiates or interferes with ocular functions, ocular tests may be planned to quantitate the enhancement or interference of the function. For example, drug products that affect the sympathomimetic system are likely to affect intraocular pressure (IOP) and pupil size. It is therefore important to perform tonometry and pupil size measurements to quantitate the expected changes. Drug products that affect the cholinergic system are likely to affect IOP, pupil size, tear production, and the corneal surface. Tests such as tonometry, pupil size measures, Schirmer tear tests, and rose bengal or lissamine green corneal staining may be useful.

The seriousness of a potential adverse event should influence the effort spent on characterizing the likelihood of the event to occur and any factors that may mitigate or enhance its occurrence. It is most helpful to be able to predict events that can cause irreversible changes and in particular events that can lead to irreversible blindness. To the extent that these events are associated with warning signs or symptoms, some of these events may be preventable.

FREQUENCY

The frequency of a potential adverse event occurring will influence the methods used to characterize the event. For the reasons discussed later, the likelihood of detecting rare events (such as those that occur in fewer than 1 per 10,000 subjects) in controlled clinical studies is rare. Other methods must be used to study the events. In cases where the frequency of events is dose dependent and increases with increasing dose, it may be possible to study in a clinical trial the potential for the event in patients by administering artificially high doses in study subjects.

The frequency of a potential event occurring in the general population, and more importantly, in the population of patients likely to take a particular drug product, may make recognizing an association with that particular drug product difficult. Ocular events, such as nonarteritic ischemic optic neuropathy (NAION), occur very rarely. NAION events occur most frequently in patients with known risk factors for them, such as crowded optic discs, coronary artery disease, diabetes, hyperlipidemia, hypertension, older age, and smoking. If patients who have any of these conditions take a drug product and then have a NAION event, it is extremely difficult to determine whether the drug product, the other risk factors, or both contributed to the event.

It should also be recognized that some serious events may occur too infrequently to be able to be adequately studied. Taken at the extreme, if an event is so rare that it is expected to occur in 1 in 7 billion patients, even if it results in total blindness, the frequency is so low that no one would expect to ever see another case.

TOPICAL ADMINISTRATION

The route of administration will affect the particular areas of the eye that are exposed to the drug product. Direct application of a drug product to the eye increases the likelihood that significant concentrations of the drug reach the eye. As a general rule, the following tests are recommended for all subjects of all drug products administered topically to the eye:

1. Best corrected distance visual acuity
2. Dilated slit lamp of anterior segment
3. Dilated indirect fundoscopy or photography
4. Pupil diameter
5. Applanation tonometry
6. Assessment of symptoms in the first minute after topical application

Additionally, a subset of patients receiving a drug product topically administered to the eye should have corneal endothelial cell counts.

ORDER OF TESTING

The order of conducting the tests is important. A number of tests are capable of producing temporary ocular

abnormalities or temporarily masking ocular abnormalities. If the order of the tests is not chosen carefully, some of the temporary ocular abnormalities caused by earlier tests will be detected by later tests and incorrectly attributed to the drug product. For example, applanation tonometry requires the use of an anesthetic agent. The anesthetic's effect may last up to 30 minutes and may mask ocular discomfort produced by the test product.

TIMING OF TESTING

Whenever possible, the inclusion of a baseline test before exposure to a drug product is extremely helpful in the interpretation of any suspected abnormalities. It is also helpful to have a post drug-exposure test to determine whether any abnormality is reversible or permanent. Besides these two time points, additional testing is dependent on the drug and the particular test.

FUNCTIONAL TESTS

Visual Acuity

Visual acuity is the most commonly used and universally understood measure of visual function. It is important to measure visual acuity because it provides a simultaneous measurement of central corneal clarity, central lens clarity, central macular function, and optic nerve conduction. If it is normal, it provides a quick assessment of this central ocular pathway. If it is abnormal, however, it does not distinguish between the many causes of an abnormality.

Visual acuity should be measured as best corrected distance visual acuity. A recent refraction is required to obtain the best corrected visual acuity. Although the traditional distance used to measure visual acuity was 20 feet or 6 meters, distance vision can be measured at any distance from 3 feet or greater. The closer the subject is to the target, the more important it is to limit potential movement of the head and prevent the subject from moving closer to the test object, artificially increasing the visual angle. The use of a 4-meter distance for refractions has the advantage of being one quarter of a diopter in lens power from a theoretical infinite distance. Each eye should be tested separately. The test should be conducted using a high-contrast chart with an equal number of letters per line and equal spacing between lines. The stroke width of the letters should be smaller on each succeeding line so that the visual angle needed to identify the letters is reduced by two-thirds per line.

The result of a visual acuity test should be reported as a log-MAR value (log of the minimum angle of resolution). Normal visual acuity for most adults is approximately −0.1 on this scale, which is equivalent to 20/16 on a Snellen visual acuity chart. A two-line or greater change from one visit to the next in a single patient should suggest additional investigation. A three-line or greater change in a single individual is usually considered clinically significant. In the evaluation of a group of subjects, changes in the mean logMAR score and in shift tables created by categorizing subjects by gains and losses in zero, one, two, three, or more lines of visual acuity are often helpful in recognizing changes in visual acuity.

Additional measures of visual acuity, such as best corrected near visual acuity, uncorrected distance visual acuity, and uncorrected near visual acuity, are rarely necessary unless it is not possible to perform a best corrected distance visual acuity. Although abnormalities may occur that alter near visual acuity without affecting best corrected distance visual acuity, these abnormalities are better characterized by measuring the accommodative amplitude together with any observed changes in refractive power in association with the best corrected distance visual acuity. Refractive power can be measured by either a manifest refraction or a cycloplegic refraction. When evaluating the effect of a drug product on refractive power, it is usually best not to perform a cycloplegic refraction, as the pharmacologic action of the cycloplegic agent may alter the results.

Color Vision

Color vision is a test of macular function because there are relatively few cones outside the macular area. There is a large variety of color vision tests with different degrees of sensitivity and specificity. The different color tests are most commonly distinguished by their ability to screen for color vision defects versus quantitating color defects, as well as their ability to detect common congenital defects in color vision (red-green confusion) versus typical acquired defects in color vision (blue-yellow confusion). Each eye should be tested separately. The gold-standard test of color vision is the Farnsworth Munsell (FM) 100 hue color test. The FM 100 hue color test can be used to detect both red-green and blue-yellow confusion, and to some degree it can quantitate the extent of the confusion. The FM 100 hue color test consists of four trays of color caps that are arranged in sequential hue. The test is scored on the basis of caps that are placed out of order and, when plotted, can provide both the magnitude and type of deviation. However, the FM 100 hue color test has a learning curve associated with improvements in scores during the first few test administrations.

Subsets of the FM 100 hue color test can also be used to screen for color vision abnormalities. These subsets include 40 and 28 hue tests. The sensitivity of these tests progressively decreases as fewer caps are tested. These tests are also known as the *Lanthony 40 hue, Lanthony 28 hue, Roth 28 hue*, or *FM 28 hue desaturated tests*.

Another subset of the FM 100, the 15 hue test, including the desaturated versions of the 15 hue (Farnsworth D15 and Lanthony D15), is not always sensitive enough to detect mild losses in color vision. This test, the Hardy Rand and Rittler (HRR) color vision test, and the SPP2 color vision test are useful as screening tests for color vision defects.

The following tests are generally not useful in testing acquired color vision defects because they do not evaluate blue-yellow confusion: Ishihara test, SPP1, and Dvorine color vision tests. These tests predominantly provide an evaluation of red-green confusion.

Visual Fields

Visual field tests can be broadly divided into several categories. These categories include manual versus automated perimetry tests, static versus kinetic perimetry tests, threshold versus suprathreshold perimetry tests, white light target versus colored targets, and central field versus peripheral field perimetry tests. When automated, threshold perimetry tests are generally the preferred methods for evaluating drug-induced visual field defects; the use of static versus kinetic, central versus peripheral, and white versus color filtered light is dependent on the particular abnormality being investigated. For most drug-induced visual field defects, automated threshold, static, central 24-degree, white object perimetry testing is adequate to detect potential defects. Perimetry programs that meet these criteria include the Humphrey 30-1, 30-2, 24-1, 24-2, SITA Fast and SITA Standard Visual Field Tests, and the Octopus 30-1 and 30-2 Visual Field Tests.

Reporting of visual fields should always include the actual thresholds determined for each field point and the number of false positives, false negatives, and fixation losses. A significant learning curve is demonstrated by most subjects who take a visual field test. This learning curve should be expected to take place over at least the first three tests completed in each eye. The learning curve most commonly results in a significant increase in mean threshold values for normal individuals.

In cases where there is an expectation that rods will be affected more than cones, an automated peripheral white object perimeter testing program is preferred, e.g. the Humphrey P-60 and FF-120 visual field tests. In cases where there is an expectation that the cones will be affected more than the rods, an automated color filtered, central visual field test is preferred.

The most widely used kinetic test can be performed with a Goldmann perimeter. It is important that the same technician performs the testing with a Goldmann perimeter from visit to visit to reduce the chances of variability in the field due to operator differences.

The Amsler grid test may help identify central macular changes. It is occasionally useful as a screening test in assessing drug toxicity when there are drug deposits in the macular area.

Contrast Sensitivity Testing

Contrast sensitivity testing has often not been included in toxicity testing because it was assumed that the measurements would overlap with other tests already included. When performed using standardized methodologies, contrast sensitivity testing is capable of measuring aspects of visual function that may not otherwise typically be measured by visual acuity, color vision, or visual field tests. When testing for toxicity purposes, multiple different levels of contrast should be included.

Electroretinography

International standards of electroretinography testing are set by the International Society for Clinical Electrophysiology of Vision (ISCEV). These standards provide complete details on the conduct of the testing parameters, including the light stimuli. If ISCEV standards are not followed, an explanation for why they were not followed should be included. For interpretation purposes, it is important to report full numerical results and graphs when reporting electroretinography findings.

Testing is expected to measure both rod and cone functions in a variety of stimuli. From a toxicology standpoint, amplitudes and/or latent times must usually change by at least 40% to be considered clinically significant. Electroretinography testing is often the most informative method available for assessing retinal function in nonhuman animals. It is a mainstay in testing drug products that bind to melanin and/or produce retinal lesions (seen by ophthalmoscopy, OCT, or histology). Development of a particular drug product is often stopped if it is shown to cause both retinal lesions and decreased amplitudes on electroretinography testing. Electroretinography abnormalities in nonhuman animal studies alone are not necessarily predictive of human injury.

Photostress Tests

Retinal damage may sometimes be manifested in delays in recovery time. Photostress tests may be helpful in identifying this type of injury if the effect is widespread

throughout the retina. There is considerable subject-to-subject variability in photostress test evaluations, and therefore it is usually difficult to detect an abnormality unless the injury is great or the number of subjects tested is very large.

Double Vision and Ocular Motility

Complaints of double vision must first be assessed to determine if the double vision is uniocular or binocular. The Worth 4 DOT test can be used to assess this. If the double vision is binocular, assessments of ocular motility in nine fields of gaze should be conducted and cover/uncover tests should be conducted to assess phorias and tropias. This is one of the few times when both eyes should be tested simultaneously.

Pupil Measurements

Pupillary measurements provide an opportunity to test responses to ocular stimuli. It is important that pupillary diameters be measured under reproducible controlled settings of light and accommodation. Pupillary responses to light stimuli and to accommodation should be measured separately. Pupillary responses in one eye due to a light stimulus in the other eye should also be measured separately from the pupillary response to a light stimulus in the same eye. Pupillary measurements may be made in a variety of ways. It is rarely necessary to measure pupil responses to a sensitivity of more than a tenth of a millimeter.

Corneal Sensitivity

There are relatively few methods to quantitatively measure corneal sensitivity. The most commonly used instrument is the Cochet-Bonnet esthesiometer. This instrument can discriminate between fairly large changes in corneal sensitivity.

Corneal Thickness

The corneal endothelial cells provide an effective pump system that, when functioning properly, keeps the cornea thin. Corneal thickness, therefore, although an anatomic measurement, can be a surrogate for corneal endothelial cell function. There are two common corneal pachymetry methods – optical and ultrasonic. For the purposes of assessing corneal endothelial cell function, either can be useful as long as the same instrument is used consistently in a subject.

OBJECTIVE ANATOMIC METHODS

For most ocular tissues, electronic digital images provide the best method for recording anatomic findings. These electronic photographs generally provide opportunities for more complete analysis and characterization. A large number of different areas of the eye can be well imaged. These areas include all five layers of the corneal surface, corneal surface topography, corneal thickness, corneal clarity, anterior chamber depth, anterior chamber inflammation, lens thickness, lens clarity, nerve fiber thickness, vitreous inflammation, vitreous traction, retinal surface irregularities, retinal vasculature, optic nerve size, and optic cup size and contour.

Cornea and Conjunctiva

As external, relatively clear structures, the cornea and conjunctiva can be evaluated by direct observation. Direct observation can be aided by the magnification provided by a slit lamp or a confocal microscope. The application of different stains such as fluorescein, lissamine green, or rose bengal can help by differentially staining various cells or tissues. Fluorescein stain is incorporated when epithelial cells are dead or missing; lissamine green and rose bengal stains are incorporated when epithelial cells are injured and have lost some of their functionality. These stains are useful in assessing corneal or conjunctival epithelial damage.

Corneal endothelial cells, if exposed to a toxic substance, are among the most sensitive in the eye to ocular damage, and because they are not regenerated in humans, they provide a permanent marker of damage. Endothelial cell counts measure damage to the corneal endothelium.

The best method for recording corneal or conjunctival changes is with electronic images by digitalized photography. This method is generally most useful for future analysis and characterization. When this is not possible, predefined scales may be used to capture a description of any findings.

Tear Film

The production of tears may be affected by different pharmacologic agents in terms of both the quantity and quality of the tears produced. The effects on tear quantity may be evaluated by Schirmer tear test (anesthetized and nonanesthetized conditions). The effects on tear quality may be evaluated by tear breakup time.

Lens

Any evaluation of a lens change should include the type of lens change, as well as the size and the location of the change. Digital photography remains the gold standard for evaluating lens clarity, although a single photograph is rarely capable of capturing all aspects of the lens. Multiple photographs taken on and off

the central axis, and including but not limited to retroillumination, are useful in assessing lens clarity and therefore cataract development. If this is not available, a predefined scale system with reference photographs for each point on the scale is useful. It is extremely useful to grade posterior subcapsular changes, cortical changes, and nuclear changes separately because often they may be independent of one another.

Lens opacities tend to occur slowly. Whereas direct trauma to the lens can cause opacities to develop within minutes, hours, or days, most milder injuries take weeks to months or years to develop. Corticosteroid drug products, which are well known to cause cataracts even when administered intraocularly, may take up to 2 years to cause clinically recognizable lens changes. It is recommended that when a drug product is to be administered for a period of 6 weeks or more, lens changes be monitored at 6-month intervals for at least 2 years.

At least as important as the size of an opacity in the lens is the location of that opacity in the lens. Although all opacities in a lens are important and may spread to other areas of the lens, the initial location may have more impact on the immediate clinical consequences and help characterize a particular toxicity. Opacities that occur in the posterior portion of the lens generally cause more interference with sight than opacities that occur in the anterior portion of the lens. Opacities that occur in the center of the visual axis cause the most interference with sight. Drug-induced toxicities tend to first occur more commonly in the posterior portion of the lens.

It is not always possible to directly appreciate the impact of a lens change on an individual patient's visual acuity. In some of these cases, visual acuity will change before any lens opacity becomes noticeable. Visual acuity should therefore always be measured when evaluating patients for lens changes.

Anterior Chamber

The position of the lens and consequently the size and shape of the anterior chamber can be affected by pharmacologic agents. This is best assessed by slit lamp examinations and diagnostic ultrasound measurements. Pharmacologically induced angle closure may be first identified by cases of elevated IOP in association with refractive changes.

Retina

Both color digital photography and OCT are the current gold standards for evaluating the retinal surface. Fluorescein angiography (FA) and indocyanine green (ICG) angiography provide separate and additional information on the retinal vasculature. Direct fundoscopy and indirect fundoscopy, although capable of detecting retinal abnormalities, often provide more limited views with less magnification. Direct fundoscopy may include the use of a direct ophthalmoscope or the use of a slit lamp with an additional 78D or 90D lens. The ability to follow fundus photographs and OCT images over time makes these methods superior to direct or indirect fundoscopy.

Intraocular Pressure

The measurement of IOP for the purposes of toxicology assessments can be adequately made by applanation tonometry. The invasiveness of more accurate measures is usually not warranted. In the rare cases where a more exact estimate of aqueous production is needed, tonography can be performed.

NUMBER OF PATIENTS TO TEST

Common events are easier to identify and characterize than more unusual ones. It is customary to attempt to identify events that occur at a frequency of 1% or higher before the commercial distribution of a drug product. Mathematical principles of probability dictate that when the true event incidence is 1% or higher, to have a 95% chance of observing at least one event, 300 subjects must be monitored. This is often referred to as the rule of three.[1]

The rule of three states that to detect events that would occur at X% or more, you need Y patients, where 3 / Y = X. Applying this rule suggests that if a true incidence rate of 10% is to be identified, at least 30 patients need to be studied. If an incidence rate of 5% is to be detected, 60 patients must be studied. If an incidence rate of 0.1% is to be detected, 3000 patients must be studied.

SUMMARY

Many potential ocular toxicities can occur as the result of administering a pharmacologic agent. Ocular toxicity tests should be used to investigate potential adverse events that might be either frequent or serious. There should be a justified reason for the selection of each test, and each test should be appropriate for the event in question.

REFERENCE

1. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*. 1983;249:1743–1745.

CHAPTER 4

Anti-Infectives

CLASS: AMEBICIDES

Generic Names:

1. Broxyquinoline; 2. diiodohydroxyquinoline (iodoquinol).

Proprietary Names:

1. Starogyn; 2. Sebaquin, Yodoxin.

Primary Use

These amebicidal drugs are effective against *Entamoeba histolytica*.

Ocular Side Effects

Systemic administration – oral

Certain

1. Decreased vision
2. Optic atrophy
3. Optic neuritis – subacute myelo-optic neuropathy (SMON)
4. Nystagmus
5. Toxic amblyopia
6. Macular edema
7. Macular degeneration
8. Diplopia
9. Absence of foveal reflex
10. Color vision defect – purple spots on white background

Clinical Significance

Major toxic ocular effects may occur with long-term oral administration of these amebicidal drugs, especially in children. Since they are given orally for *E. histolytica*, most reports come from the Far East. Data suggest that these amebicides may cause SMON. This neurologic disease has a 19% incidence of decreased vision and a 2.5% incidence of toxic amblyopia. It has been suggested that in patients being treated for acrodermatitis enteropathica, which is a disease of inherited zinc deficiency, optic atrophy may be secondary to zinc deficiency instead of diiodohydroxyquinoline. Because long-term quinolone exposure has been shown to result in accumulation of the drug in pigmented tissues, retinal degenerative changes may be observed. The best overall review of this subject is in Grant et al.[1]

Generic Name:

Emetine hydrochloride.

Proprietary Name:

Multi-ingredient preparations only.

Primary Use

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

Ocular Side Effects

Systemic administration – subcutaneous or intramuscular injection near toxic levels

Certain

1. Irritation
   a. Lacrimation
   b. Hyperemia
   c. Photophobia
   d. Foreign body sensation
2. Eyelids or conjunctiva
   a. Hyperemia
   b. Edema
   c. Urticaria
   d. Purpura
   e. Eczema
3. Cornea
   a. Superficial punctate keratitis
   b. Erosions
4. Pupils
   a. Mydriasis
   b. Absence of reaction to light
5. Decreased accommodation
6. Decreased vision
7. Visual fields
   a. Scotomas – central
   b. Constriction
8. Retinal and optic nerve
   a. Ischemia
   b. Hyperemia optic nerve

Inadvertent ocular exposure

Certain

1. Irritation
   a. Lacrimation