Systemic Effects of Medications Used To Treat Glaucoma

Daniel E. Everitt, MD; and Jerry Avorn, MD

Medications used to treat glaucoma can have clinically important systemic effects in some patients; these effects may not be recognized in elderly patients who have chronic medical problems and who are taking several systemic medications. Beta-blocking ophthalmic agents are generally safe, but can be absorbed systemically to induce bronchospasm, worsen heart block, decompensate congestive heart failure, or create central nervous system effects in some patients. Reports of adverse systemic effects from miotics, such as pilocarpine, are rare, although cardiovascular decompensation has been seen in patients with acute angle closure who were given excessive doses before surgery. Topical sympathomimetic agents such as epinephrine may increase ventricular extrasystoles and have, on occasion, caused severe hypertensive reactions. Nearly 50% of patients taking carbonic anhydrase inhibitors must discontinue their use because of various adverse constitutional and central nervous system symptoms. Although these drugs are not usually part of internal medicine regimens, they can produce adverse effects that mimic primary disease in nonocular organ systems.

Annals of Internal Medicine. 1990;**112**:120-125.

From Beth Israel Hospital; Brockton-West Roxbury Veterans Affairs Medical Center; and Harvard Medical School, Boston, Massachusetts.

The clinical significance of medications used to treat eye diseases may be easily overlooked when evaluating patients. When a drug history is taken, many patients do not mention their eyedrops, assuming that this medication should not be considered in the same category as oral medicines. However, ophthalmic preparations used to treat glaucoma may have untoward effects that are not rare. Patients with glaucoma are likely to be older, have other chronic illnesses, take several medications, and have several caretakers. The internist must closely evaluate the adverse effects of ophthalmic drugs when treating these patients.

Glaucoma

Glaucoma is the second leading cause of blindness in the United States and is the third commonest reason for visits to ophthalmologists. The incidence increases with advancing age; glaucoma is found in 5% of persons over 75 years of age (1). Although glaucoma has various causes and pathologic findings, in general it tends to present with elevated intraocular pressure, which, if untreated, may produce some degree of optic atrophy with characteristic visual field loss. Normally, the production of aqueous humor in the posterior chamber, the passage of aqueous humor around the iris, and its absorption through the trabecular meshwork in the anterior chamber are delicately controlled to maintain an intraocular pressure of about 15 $\pm$ 3 mm Hg (2). In patients with primary open-angle glaucoma, this pressure is thought to be most often elevated because of a decrease in aqueous humor absorption, although the exact mechanism is not understood.

Primary open-angle glaucoma accounts for 75% of the cases of glaucoma. Its cause is unknown and, characteristically, it develops without symptoms. The common form of primary open-angle glaucoma occurs more frequently with advanced age, a positive family history, and in blacks (1, 3). Diabetes, systemic hypertension, and high myopia have been identified in some studies as risk factors for glaucoma, although these associations have been considered inconclusive (1). Similar clinical findings may be seen in secondary forms of chronic open-angle glaucoma, in which the flow of aqueous humor is impaired by congenital, metabolic, or neoplastic processes or drug toxicity.

Closed-angle glaucoma involves an elevation of intraocular pressure resulting from a mechanical or physical impairment of outflow of aqueous humor through the trabecular meshwork in the anterior chamber. This impairment, caused by a narrow angle between the iris and the cornea, may be inherited or may be the result of trauma, inflammatory diseases, or intraocular tumors. This form of glaucoma accounts for about 25% of all cases of glaucoma, and usually comes to the patient's attention during an episode of acute angle closure, which causes acute visual symptoms related to a rapid rise in intraocular pressure.

Most patients with glaucoma who are seen by internists have primary open-angle glaucoma and are followed chronically on medical therapy. The primary aim of therapy is to reduce intraocular pressure and, thus, to reduce the chance of optic nerve damage and consequent visual field loss (3-5). However, the criteria determining when therapy should be started are not always clear (6). Although physicians commonly treat patients with intraocular pressures greater than 30 mm Hg, physicians must make individual judgments when treating patients with pressures ranging from 20 to 29 mm Hg. In making these decisions, physicians must consider the appearance of the optic cup, visual field integrity, and risk factors for glaucoma (3-

5). In general, treatment begins with a single agent, and other agents with different modes of action are added as needed to lower the intraocular pressure. Commonly used agents are listed in Table 1. A surgical procedure may be used to lower intraocular pressure in patients refractory to medical therapy. The most commonly used procedure is laser trabeculoplasty, which achieves pressure control in 85% of patients. However, 75% of patients continue to require medical therapy after laser therapy, and control of pressure may decrease over time (2). Alternatively, filtering operations, which may include iridectomy or trabeculectomy, may be done.

Systemic Effects of Specific Agents

Although topical agents used to treat glaucoma are used for their local effect on the eye, considerable systemic absorption may occur with substantial consequent systemic effects. Entry into the systemic circulation occurs primarily by drainage into the lacrimal ducts, absorption through the highly vascular nasal mucosa, and direct drainage into the ophthalmic and facial veins (7). The drug thus avoids the first-pass hepatic metabolism that awaits oral medications. This effect of rapid absorption through the nasal mucosa is especially relevant for the beta-blockers, which may be 90% metabolized on a first-pass effect when taken orally. Systemic absorption and resultant blood levels vary widely. In part, these variances relate to topical administration technique. In one study (8), as much as 88% of the active drug was recovered outside the eye after spilling it over the lid. Absorption can be minimized by occluding the lacrimal puncta with gentle finger pressure for 5 minutes after application of eyedrops (4). Variable patient compliance may lead to the absorption of substantially larger quantities of drug than is intended in routine prescribing (9).

Beta-Adrenergic Blocking Agents

Since its introduction in 1978, topical timolol has rapidly become the most widely used agent for the treatment of glaucoma (10); premarketing trials reported that the drug was generally well tolerated (11, 12). The mechanism by which beta-blockers reduce intraocular pressure is not well understood, although beta-blockers are thought to decrease the production of aqueous humor in the eye through beta-2 receptor blockade (13, 14). Timolol blocks both beta-1 and beta-2 receptors and has no intrinsic sympathomimetic activity. In 1985, betaxolol, a relatively beta-1-selective blocking agent, was approved for marketing; like timolol, it is used twice a day. Late in 1985, levobunolol was introduced. A nonselective beta-blocker, levobunolol is used once daily. The beta-blocking effects of these drugs may cause adverse effects that fall primarily into three categories: pulmonary, cardiovascular, and central nervous system effects.

Table 1. *Agents Commonly Used to Treat Glaucoma*

Beta adrenergic blocking agents
Nonselective beta-blockers
timolol
levobunolol
Beta-1 selective beta-blockers
betaxolol
Miotics
Parasympathomimetic agents
pilocarpine
carbachol
Anticholinesterase agents (long-acting)
demecarium bromide
echothiophate iodide
isoflurophate
Sympathomimetic agents
epinephrine
dipivefrin
Carbonic anhydrase inhibitors
acetazolamide
methazolamide

Pulmonary Effects

Adequate beta-2 adrenergic tone is important for the maintenance of open airways in patients with reactive airway disease. Beta-2 receptor blockade may cause constriction of pulmonary bronchi and of some arterial vasculature. Although relatively few reports of pulmonary symptoms appeared in the early clinical trials of opthalmic timolol, these studies (11, 12) carefully screened out patients with asthma or obstructive pulmonary disease. Reports of pulmonary symptoms began to appear shortly after timolol became available for general ophthalmic use in 1979; by 1984, 16 fatal cases of status asthmaticus and more than 200 major pulmonary reactions had been reported to the National Registry of Drug-Induced Ocular Side Effects (15). Dyspnea and wheezing in patients with a history of pulmonary disease were commonly reported to the Registry.

Several prospective clinical trials (16, 17) have evaluated changes in pulmonary function when young patients with reactive airway disease started timolol or betaxolol therapy. Forced expiratory volume in 1 minute (FEV_1) fell by an average of 25% to 28% within 30 minutes of the administration of timolol, although a substantial number of subjects had no change in pulmonary function. Although formal clinical trials have generally shown betaxolol to be free of pulmonary effects, beta-1 selectivity is clearly not absolute and betaxolol may have some beta-2-blocking properties. Recently, six cases of elderly patients who developed dyspnea or wheezing shortly after beginning ophthalmic betaxolol therapy were reported (18, 19). Although three of these patients had histories of asthma, three patients had no known previous respiratory disease.

Thus, both ophthalmic timolol and betaxolol may cause respiratory distress in some patients. Patients with histories of reactive airway disease are at particular risk, although bronchospasm may occur in the absence of a history of respiratory disease. Many patients with some respiratory disease experience clearly have no untoward effects from ophthalmic beta-blocker drugs, and many of these patients continue to be treated with these agents. Patients at risk for broncho-

spasm might be given a first dose under surveillance in the office because most pulmonary effects from topical beta-blockers appear to develop within 30 minutes of administration.

Cardiovascular Effects

Systemic absorption of all three ophthalmic beta-blockers would be expected to affect the cardiovascular system through beta-1 receptor blockade. Such blockade may lower heart rate and blood pressure, slow cardiac conduction, and decrease cardiac contractility; these effects may lead to a decompensation of congestive heart failure. Clinical trials (12, 20) of ophthalmic timolol have indeed shown significant evidence of beta receptor blockade in the cardiovascular system, even in the absence of measurable serum levels. Although the commonly reported decrease in resting pulse in usually assymptomatic, case reports have described serious untoward cardiovascular effects, including decompensation of chronic congestive heart failure (21) and cardiac conduction abnormalities (12, 21, 22).

Only one prospective trial (23) has specifically examined cardiovascular effects of ophthalmic timolol in detail. Timolol significantly decreased heart rate and oxygen consumption at maximal exercise in young healthy subjects. Although these subjects displayed statistically significant changes in cardiovascular function without compromise, it is unclear how to generalize the findings from this trial to the elderly person with glaucoma (24).

Case reports, case collections from the National Registry, and randomized prospective trials indicate that measurable systemic beta-blockade occurs in many patients taking ophthalmic timolol; in an unknown proportion of these patients, serious adverse cardiovascular effects result. However, as is the case with pulmonary function, many patients with cardiovascular disease use timolol and betaxolol ophthalmic preparations and presumably have no untoward effects. Further research is needed to identify subgroups at particular risk for cardiovascular decompensation.

Central Nervous System Effects

Beta-adrenergic neurotransmission plays a major role in many aspects of central nervous system activity, and systemic beta-blockade has been linked with depression and other central nervous system dysfunction (25-29). The major categories of antidepressant medications enhance central adrenergic activity by increasing the availability of norepinephrine or serotonin at central synaptic junctions. Thus, there is a neurophysiologic basis for concern over the effect of beta-adrenergic blockade on central nervous system function.

Numerous reports have convincingly linked oral beta-blocker use with the development of central nervous system symptoms. However, only about five detailed case reports (30-32) of clear-cut central nervous system effects associated with timolol or betaxolol use have appeared in the literature, although one clinical trial (21) reported adverse central nervous system effects in 17 of 165 patients. Patients reported lightheadedness, mental depression, weakness, fatigue, tranquilization, disorientation, and memory loss. Currently, no evidence exists that selective beta-blockade affects the central nervous system differently than nonselective blockade. Clinical studies have not yet adequately evaluated the differential effects of timolol, betaxolol, or levobunolol on the central nervous system.

Miotics

The miotics, such as pilocarpine, stimulate parasympathetic receptors and cause constriction of the pupil and contraction of the ciliary muscle, resulting in a fall in intraocular pressure; this fall is thought to result from a decrease in resistance to the outflow of aqueous humor (4). These drugs are categorized as either parasympathomimetic agents or cholinesterase inhibitors. The anticholinesterase agents decrease the clearance of endogenous acetylcholine at effector sites and are categorized as either short-acting (physostigmine, rarely used in the treatment of glaucoma) or long-acting (demecarium bromide, echothiophate iodide, and isoflurophate).

Pilocarpine is the most widely used miotic and was the first line therapy of choice before the introduction of topical beta-blockers. It has several disadvantages, compared with beta-blockers, and is usually used as a second drug when intraocular pressure is not adequately controlled by a beta-blocker or in patients who do not tolerate beta-blockers. Pilocarpine must be given four times per day to consistently lower pressure, although a long-acting gel and a timed-release formulation are also available. The ciliary muscle contraction induced by pilocarpine may cause a bothersome fluctuating refractive error, and miosis can produce decreased vision at night and in patients with cataracts (4, 5). Younger patients may have a painful spasm of the ciliary muscle, and patients may complain of burning or irritation. Carbachol is a less commonly used parasympathomimetic agent that has a slightly longer duration of action than pilocarpine and a similar profile of ocular and systemic adverse effects (5).

Adverse systemic reactions to pilocarpine are thought to be rare, although the drug can cause a wide variety of symptoms through stimulation of the parasympathetic nervous system. Like muscarine, pilocarpine may stimulate smooth muscles of the gastrointestinal system, which can result in diarrhea, painful spasm, or anorexia (33, 34). Bronchial smooth muscles may be stimulated by pilocarpine, and bronchial secretions may increase.

Reports (34-37) of pilocarpine toxicity all involve elderly patients given repeated doses to treat acute angle closure before surgery. In these cases, doses representing two to five times the usual daily dose were given within a few hours. Symptoms included nausea, vomiting, profuse sweating, tremor (35), hypotension, sinus bradycardia (34), atrioventricular block (36), and mental status changes (37). Although such reports do not indicate the incidence of such toxic reac-

tions, hospital-based consultants should be aware of possible severe reactions with excessive preoperative use of pilocarpine. The literature includes little useful information on whether routine chronic use of pilocarpine or carbachol may cause more subtle systemic effects, such as nonspecific gastrointestinal symptoms or bronchospasm in patients who use excessive doses through either misunderstanding or cognitive deficits.

The long-acting miotics, including demecarium bromide, echothiophate iodide, and isoflurophate, are potent cholinesterase inhibitors that can be given twice daily. Because of the increased incidence of ocular and systemic side effects associated with the long-acting miotics, these drugs are usually reserved for patients refractory to the short-acting miotics (3, 5) or other agents. Some physicians suggest that surgery or laser trabeculoplasty should be undertaken before resorting to these drugs (4). However, recently published ophthalmology textbooks (2, 3, 5) consider these drugs to be useful, and internists, therefore, should be aware of these drugs' systemic effects.

Because the long-acting ophthalmic cholinesterase inhibitors cause an irreversible depletion of cholinesterase, they may be dangerous when used within several weeks before general anesthesia, if succinylcholine or procaine are to be used. The disposition of these anesthetic agents requires hydrolysis by plasma cholinesterase, and usual doses of succinylcholine may result in prolonged apnea if a long-acting cholinesterase inhibitor has been used within the past several weeks (38). Long-acting cholinesterase inhibitors may cause any of the systemic effects described for the short-acting miotics; however, with the use of long-acting inhibitors, anticholinesterase depletion is cumulative, and patients may gradually, and subclinically, develop toxic effects. Case reports and case collections (39) have noted gastrointestinal, respiratory, cardiovascular, and neurologic symptoms as well as life-threatening reactions (40) associated with chronic and routine use of these medications. Because effects on bronchial smooth muscle may be additive with effects from beta-blocking drugs, patients taking both of these agents should be closely observed for pulmonary symptoms.

Sympathomimetic Drugs

Topical epinephrine has been used for years for the treatment of primary open-angle glaucoma, and the pro-drug form of epinephrine, dipivefrin, is used increasingly often. Epinephrine and dipivefrin stimulate both alpha and beta adrenergic receptors and are thought to lower intraocular pressure primarily by enhancing outflow of aqueous humor through the trabecular meshwork, although the exact mechanism is obscure (33). These agents are usually used twice daily and are often used in combination with other drugs.

Systemically absorbed epinephrine may cause bronchodilation and an increased respiratory rate. In sufficient doses, it causes headache, tremor, restlessness, increased heart rate and blood pressure, and atrial and ventricular tachyarrhythmias (40). A single drop of 2% epinephrine (a common therapeutic dose) contains 0.1 to 2.0 mg of drug. Thus, systemic absorption could approach the systemic therapeutic dose of 0.1 to 0.5 mg.

As an agent to treat glaucoma, epinephrine has considerable ocular side effects. Up to 20% of patients must discontinue the drug because of these effects, which include headache, blurred vision, irritation, and lacrimation (40). Adverse systemic reactions to routine chronic use of topical epinephrine have been considered rare. An increased incidence of benign ventricular extrasystoles has been noted in patients taking topical epinephrine (40), and several cases of severe hypertensive reactions have been reported within minutes of instillation (41). It has been suggested that epinephrine be stopped before general anesthesia and that it be used with caution in patients with atherosclerotic cardiovascular disease, recent myocardial infarction, hypertension, dangerous cardiac arrhythmias, or hyperthyroidism (4, 5).

Carbonic Anhydrase Inhibitors

Acetazolamide, a sulfonamide that has been used to treat glaucoma for about 30 years, is a potent reversible inhibitor of carbonic anhydrase and blocks the hydration of carbon dioxide and the dehydration of carbonic acid (33). The primary therapeutic use of this drug, as well as of the newer carbonic anhydrase inhibitors methazolamide and dichlorphenamide, is as an adjunctive treatment of refractory primary open-angle glaucoma and to lower intraocular pressure in acute-angle closure. The carbonic anhydrase inhibitors lower intraocular pressure by suppressing the production of aqueous humor in the eye (5). However, these agents also inhibit carbonic anhydrase in the kidney and other tissues and cause a mild diuresis, a systemic acidosis, and alkalinization of the urine.

Acetazolamide commonly causes a range of adverse systemic effects that often require discontinuance of the drug (5, 42). Approximately 50% of 800 patients given a trial of long-term carbonic anhydrase therapy were unable to continue the drug because of side effects (43), often a symptom complex of malaise, fatigue, weight loss, anorexia, depression, and decreased libido; these symptoms resolve when the drug inhibitor is stopped (4, 44, 45). Patients with symptoms have systemic acidosis; in some cases, the administration of sodium bicarbonate also dramatically alleviates symptoms without diminishing the drug's effect on intraocular pressure.

Carbonic anhydrase inhibitors may frequently cause gastrointestinal symptoms of nausea, vomiting, and diarrhea. These symptoms are often independent of the malaise symptom complex and do not respond to bicarbonate therapy (45). Some patients report an alteration in the taste of carbonated beverages (4).

Other more serious adverse reactions to carbonic anhydrase inhibitors have also been reported. These agents may be dangerous to patients with severe chronic lung disease (FEV_1, less than 1 L) because these patients are unable to increase minute ventilation to compensate for the metabolic acidosis (45). This

inability to compensate can occasionally result in respiratory acidosis and failure in some patients on carbonic anhydrase inhibitors (45). Patients taking large doses of salicylates may be at particular risk for adverse effects (46). Acetazolamide has also been noted to accelerate the development of osteomalacia in patients taking phenytoin chronically (47).

Hematopoietic toxicity has also been attributed to carbonic anhydrase inhibitors; detailed case reports have linked both acetazolamide and methazolamide to the onset of aplastic anemia and agranulocytosis (46, 48). Sixty-eight percent of the adverse reactions occurred during the first 6 months of therapy. Carbonic anhydrase inhibitors are potent drugs that effectively lower intraocular pressure in difficult cases and may be added to other agents. However, use of these drugs is severely limited by intolerable symptoms that may occur in up to 50% of treated patients.

Summary

Medical therapy of glaucoma requires a careful evaluation of the need to lower intraocular pressure and an appropriate surveillance for unwanted effects of therapy. Deciding whether to treat glaucoma and how aggressively to lower intraocular pressure requires judging evidence that is often not clear-cut. Opinions vary on when patients who have pressures ranging from 20 to 29 mm Hg and normal optic discs and visual fields should be treated. As with any treatment, the relative benefits must be weighed against the potential or observed adverse effects in an individual patient. Increasingly, laser trabeculoplasty may be used earlier in patients whose pressure does not respond adequately to topical beta-blockers, the short-acting miotics, or sympathomimetic agents.

Internists should maintain a high index of suspicion concerning systemic effects of glaucoma medications, particularly in elderly patients. Such effects may be overlooked, present nonspecifically, and be misattributed to primary disease elsewhere. Internists should maintain an active dialogue with ophthalmologists and optometrists about patients who may have adverse effects of therapy for glaucoma.

Grant Support: By the National Eye Institute (EY-07715), the Medical Research Service of the Veterans Administration, the John A. Hartford Foundation, and the Food and Drug Administration (FD-0015D).

Requests for Reprints: Daniel E. Everitt, MD, Beth Israel Hospital, Program for the Analysis of Clinical Strategies, 333 Longwood Avenue, Boston, MA 02115.

Current Author Addresses: Drs. Everitt and Avorn: Beth Israel Hospital, Program for the Analysis of Clinical Strategies, 330 Brookline Avenue, Boston, MA 02215.

References

1. **Leske MC.** The epidemiology of open-angle glaucoma: a review. *Amer J Epidemiol.* 1983;**118:**166.
2. **Newell FW.** The glaucomas. In: *Ophthalmology: Principles and Concepts.* (6th ed.) St. Louis: The C.V. Mosby Company; 1986:378-98.
3. **Vaughan D, Asbury T.** *General Ophthalmology.* (11th ed.) Norwalk, Connecticut: Lange Medical Publications; 1986:184-99.
4. **American Medical Association.** Agents used to treat glaucoma. In: *Drug Evaluations.* (6th ed.) Chicago: American Medical Association; 1986:327-42.
5. **Mosteller MW, Zimmerman TJ.** The medical management of glaucoma. In: Spoor TC, ed. *Modern Management of Ocular Diseases.* Thorofare, New Jersey: Slack; 1985:179-88.
6. **Phelps CD.** The "no treatment" approach to ocular hypertension. *Surv Ophthalmol.* 1980;**25:**175-82.
7. **Chrai S, Patton TF, Mehta A, Robinson JR.** Lacrimal and instilled fluid dynamics in rabbit eyes. *J Pharm Sci.* 1973;**62:**1112-21.
8. **Alvan G, Calissendorff B, Seideman P, Widmark K, Widmark G.** Absorption of ocular timolol. *Clin Pharmacokinet.* 1980;**5:**95-100.
9. **Hayes LP, Stewart CJ, Kim I, Mohr JA.** Timolol side effects and inadvertent overdosing. *J Am Geriatr Soc.* 1989;**37:**261-2.
10. **Lewis RV, Lennard MS, Jackson PR, Tucker GT, Ramsay LE, Woods HF.** Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol.* 1985;**19:**826-8.
11. **LeBlanc RP, Kripp G.** Timolol. Canadian multicenter study. *Ophthalmology.* 1981;**88:**244-8.
12. **Boyer WP III, Puliafito CA, Steinert RF, Langston DP.** Long-term experience with timolol ophthalmic solution in patients with open-angle glaucoma. *Ophthalmology.* 1978;**85:**259-67.
13. **Novack GD.** Ophthalmic beta-blockers since timolol. *Surv Ophthalmol.* 1987;**31:**307-27.
14. **Tierny DW.** Betaxolol and levobunolol: new beta-blocking antiglaucoma agents. *J Am Optom Assoc.* 1987;**58:**722-7.
15. **Van Buskirk EM.** Adverse reactions from timolol administration. *Ophthalmology.* 1980;**87:**447-50.
16. **Schoene RB, Abuan T, Ward RL, Beasley CH.** Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. *Am J Ophthalmol.* 1984;**97:**86-92.
17. **Spiritus EM, Casciari R.** Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis [Letter]. *Am J Ophthalmol.* 1985;**100:**492-4.
18. **Harris LS, Greenstein SH, Bloom AF.** Respiratory difficulties with betaxolol. *Am J Ophthalmol.* 1986;**102:**274-5.
19. **Rohalt PC.** Betaxolol and restrictive airway disease. Case report. *Arch Ophthalmol.* 1987;**105:**1172.
20. **McMahon CD, Shaffer RN, Hoskins HD Jr, Hetherington J Jr.** Adverse effects experienced by patients taking timolol. *Am J Ophthalmol.* 1979;**88:**736-8.
21. **Nelson WP.** Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985. *Am J Ophthalmol.* 1987;**104:**97-8.
22. **Ahmad S.** Cardiopulmonary effects of topical timolol eyedrops [Letter]. *Lancet.* 1979;**2:**1028.
23. **Leier CV, Baker ND, Weber PA.** Cardiovascular effects of ophthalmic timolol. *Ann Intern Med.* 1986;**104:**197-9.
24. **Vestal RE, Wood AJ, Shand DG.** Reduced beta-adrenoreceptor sensitivity in the elderly. *Clin Pharmacol Ther.* 1979;**26:**181-6.
25. **Van Buskirk EM, Fraunfelder FT.** Ocular beta-blockers and systemic effects [Editorial]. *Am J Ophthalmol.* 1984;**98:**623-4.
26. **Fleminger R.** Visual hallucinations and illusions with propranolol. *Br Med J.* 1978;**1:**1182.
27. **Shore JH, Fraunfelder FT, Meyer SM.** Psychiatric side effects from topical ocular timolol, a beta-adrenergic blocker. *J Clin Psychopharmacol.* 1987;**7:**264-7.
28. **Petrie WM, Maffucci RJ, Woosley RL.** Propranolol and depression. *Am J Psychiatry.* 1982;**139:**92-4.
29. **Paykel ES, Fleminger R, Watson JP.** Psychiatric side effects of antihypertensive drugs other than reserpine. *J Clin Psychopharmacol.* 1982;**2:**14-39.
30. **Davidorf FH.** Did I tell you the story about Jim, the neurologist [Editorial]. *Contemporary Ophthalmic Forum.* 1987;**5:**4.
31. **Orlando RG.** Clinical depression associated with betaxolol. *Am J Ophthalmol.* 1986;**102:**275.
32. **Nolan BT.** Acute suicidal depression associated with use of timolon [Letter]. *JAMA.* 1982;**247:**1567.
33. **Goodman LS, Gilman AG, Rall TW, Murad F. eds.** *The Pharmacologic Basis of Therapeutics.* (7th ed.) New York: MacMillan Publishing Co.; 1985:105-8, 156-8, 890-2.
34. **Greco JJ, Kelman CD.** Systemic pilocarpine toxicity in the treatment of angle closure glaucoma. *Ann Ophthalmol.* 1973;**5:**57-9.
35. **Epstein E, Kaufman I.** Systemic pilocarpine toxicity from overdosage. *Am J Ophthalmol.* 1965;**59:**109-10.
36. **Littmann L, Kempler P, Rohla A, Fenyvesi T.** Severe symptomatic atrioventricular block induced by pilocarpine eye drops. *Arch Intern Med.* 1987;**147:**586-7.
37. **Reyes PF, Dwyer BA, Schwartzman RJ, Sacchetti T.** Mental status changes induced by eye drops in dementia of the Alzheimer type [Letter]. *J Neurol Neurosurg Psychiatry.* 1987;**50:**113-5.
38. **Humphreys JA, Holmes JH.** Systemic effects produced by echothiophate iodide in treatment of glaucoma. *Arch Ophthalmol.* 1963;**69:**737-43.
39. **Hiscox PE, McCulloch C.** Cardiac arrest occurring in a patient on echothiophate iodide therapy. *Am J Ophthalmol.* 1965;**60:**425-7.
40. **Ballin N, Becker B, Goldman ML.** Systemic effects of epinephrine

applied topically to the eye. *Invest. Ophthalmol Vis Sci.* 1966;**5**:125-9.
41. **Lansche RK.** Systemic reactions to topical epinephrine and phenylephrine. *Am J Ophthalmol.* 1966;**61**:95-8.
42. **Lichter PR, Newman LP, Wheeler NC, Beall OV.** Patient tolerance to carbonic anhydrase inhibitors. *Am J Ophthalmol.* 1978;**85**:495-502.
43. **Arrigg CA, Epstein DL, Giovanoni R, Grant WM.** The influence of supplemental sodium acetate on carbonic anhydrase inhibitor-induced side effects. *Arch Ophthalmol.* 1981;**99**:1969-72.
44. **Wallace TR, Fraunfelder FT, Petursson GJ, Epstein DL.** Decreased libido–a side effect of carbonic anhydrase inhibitor. *Ann Ophthalmol.* 1979;**11**:1563-6.
45. **Block ER, Rostand RA.** Carbonic anhydrase inhibition in glaucoma: hazard or benefit for the chronic lunger? *Surv Ophthalmol.* 1978;**23**:169-72.
46. **Fraunfelder FT.** Interim report: national registry of possible drug-induced ocular side effects. *Ophthalmology.* 1979;**86**:126-30.
47. **Mallette LE.** Acetazolamide-accelerated anticonvulsant osteomalacia. *Arch Intern Med.* 1977;**137**:1013-17.
48. **Werblin TP, Pollack IP, Liss RA.** Aplastic anemia and agranulocytosis in patients using methazolamide for glaucoma. *JAMA.* 1979;**241**:2817-8.