Improving patient compliance can increase the effectiveness of medical therapy.

BY RENGARAJ VENKATESH, MD

Glaucoma is a chief cause of blindness worldwide. Several large randomized clinical trials have shown that adequate control of IOP can reduce the risk of functional progression of glaucoma by as much as 10% to 19%.1–3 Currently, the only modifiable risk factor for glaucoma is raised IOP. Globally, antiglaucoma medications are often the first choice of treatment. The role of these medications in the treatment of different types of glaucoma has become increasingly important with time as more medications with fewer side effects have been introduced, especially during the past 2 decades.

Antiglaucomatous medications can be broadly classified into those that decrease aqueous production and those that increase aqueous outflow. The drugs that cause decreased aqueous production include beta-blockers, alpha-adrenergic agonists, and carbonic anhydrase inhibitors (CAIs). Those that increase aqueous outflow include miotics, prostaglandin analogues (PGAs), and hyperosmotics (Table 1).

PROSTAGLANDIN ANALOGUES
Also known as hypotensive lipids, PGAs are the first drugs of choice in the medical management of glaucoma. Currently, four PGAs are in clinical use: latanoprost, travoprost, bimatoprost, and unoprostone isopropyl.

Mechanism. PGAs increase uveoscleral outflow and have both pressure-dependent and pressure-independent IOP-reducing mechanisms. PGAs act by relaxing the ciliary body muscles, thereby increasing the spaces between ciliary muscle bundles, facilitating aqueous outflow through the uveoscleral pathway. They also act by causing remodelling of extracellular matrix that surrounds the ciliary muscle cells.

Latanoprost and travoprost reduce IOP by 25% to 32%, and bimatoprost reduces it by 27% to 33%. Unoprostone is less effective, lowering IOP by 13% to 18%.

Dosage. Dosages for the PGAs are as follows: latanoprost 0.005% once daily; travoprost 0.004% once daily; bimatoprost 0.03% once daily; and unoprostone 0.12% twice daily.

Side effects. Side effects reported in association with topical PGAs include increased iris pigmentation, conjunctival hyperemia, hypertrichosis, trichiasis, distichiasis, hyperpigmentation of the eyelid skin, and hair growth around the eyes. Potential for exacerbations of underlying herpes keratitis, cystoid macular edema, and uveitis are the main contraindications for the use of these agents.

BETA-BLOCKERS
Beta-blockers were the mainstay of medical glaucoma management and the first drug class of choice before the introduction of PGAs. They are still important in the armamentarium of glaucoma medications.

Mechanism. Beta-blockers lower IOP by inhibiting cyclic adenosine monophosphate production in the ciliary epithelium, thereby reducing aqueous humor secretion by 20% to 30%.
50% (2.5 μL/min to 1.9 μL/min), with a corresponding IOP reduction of 20% to 30%.

Beta-blockers act mainly during the daytime, thus presenting the risk of potential progression of optic disc damage during the night. Beta-blockers are helpful as an additive to other classes of agents, such as miotics, PGAs, and CAIs; however, extended use may reduce their effectiveness because the response of beta receptors is affected by constant exposure to an agonist (long-term drift, tachyphylaxis). Similarly, receptor saturation (drug-induced up-regulation of beta receptors) may occur within a few weeks, with loss of effectiveness (short-term escape).

Beta-blockers can be grouped as cardioselective and nonselective depending on the selectivity of the receptor they antagonize. There are six beta-blockers in clinical use for lowering IOP: betaxolol, carteolol, levobunolol, metipranolol, timolol maleate, and timolol hemihydrate. All except betaxolol are nonselective β1 and β2 antagonists. Betaxolol selectively acts on the β1 receptor and, hence, is safe in cardiac and asthmatic patients; however, it provides less IOP control compared with nonselective blockers.

**Side effects.** Beta-blockers can have both ocular and systemic side effects, including bronchospasm, bradycardia, increased heart block, lowered blood pressure, reduced exercise tolerance, central nervous system depression, lethargy, mood changes, depression, altered mentation, light-headedness, syncope, allergy, impotence, reduced libido, and alteration of serum lipids. In diabetic patients, beta-blockers can mask the symptoms of hypoglycemia because of their sympathetic blockade. They can also aggravate myasthenia symptoms. Ocular side effects include punctate keratitis, allergy, corneal anesthesia, and visual disturbances.

**Dosage.** Timolol maleate is formulated at 0.25% and 0.5%, betaxolol HCl at 0.25%, levobunolol HCl at 0.25 and 0.5%, carteolol HCl at 1%, and metipranolol at 0.3%.

**PARASYMPATHOMIMETIC AGENTS**

Also called miotics, parasympathomimetic agents can be grouped as directly acting cholinergic agonists and indirectly acting anticholinesterase agents.

**Mechanism.** The direct-acting cholinergic agonists function similarly to acetylcholine and act directly on motor endplates, whereas the indirect-acting drugs inhibit cholinesterase, prolonging and enhancing the action of naturally secreted acetylcholine. Pilocarpine is the most commonly prescribed direct agonist. Carbachol has both direct and indirect actions, whereas ecotiohphate iodide acts as an indirect agent only.

Both direct- and indirect-acting agents reduce IOP by causing contraction of the longitudinal ciliary muscle, which pulls the scleral spur to tighten the trabecular meshwork, increasing aqueous humor outflow. These agents can reduce IOP by 15% to 25%. The only remaining indication for this group of drugs, however, is in long-term management of IOP in eyes with some degree of open filtering angle, in the acute treatment of an angle closure attack, and as prophylaxis in angle-closure glaucoma before iridotomy. Parasympathomimetic agents may act as additives to beta-blockers, adrenergic agents, and CAIs.

**Side effects.** Parasympathomimetic agents are associated with ocular and systemic side effects. Ocular side effects include induced myopia due to ciliary spasm, browache, cataract formation, iris pigment epithelial cysts in children, epiphora due to lacrimation or punctal stenosis, increased inflammation in uveitic patients, and increased bleeding during surgery and breakage of the blood-aqueous barrier. Systemic side effects, which are mainly due to the indirect-acting agents, include diarrhea, abdominal cramps, increased salivation, bronchospasm, and even enuresis.

**CARBONIC ANHYDRASE INHIBITORS**

CAIs are the only group of drugs used in glaucoma medical therapy that contains orally administered agents.

**Mechanism.** These drugs act by inhibiting the carbonic anhydrase enzyme located on the ciliary epithelium, thereby decreasing the secretion of aqueous by more than 50%. CAIs must block at least 90% of the enzyme in order to achieve the desired effect. They can be administered either topically or systemically.

Acetazolamide and methazolamide are the most commonly used oral CAI agents. Dichlorphenamide is another agent in this group. Oral CAIs begin to act within 1 hour of administration, with maximal effect within 2 to 4 hours. Sustained-release acetazolamide can reach peak effect within 3 to 6 hours of administration. Oral drugs are mainly reserved for the acute control of IOP rise and are not intended for long-term management due to potential side effects.

Dorzolamide 2%, a topical CAI, is different in structure from the oral agents. It has increased aqueous solubility and suitable lipid-water solubility for corneal penetration, which allows effective topical application. Brinzolamide is another topical CAI formulation, available in a 1% concentration.

**Side effects.** The main contraindication for CAI use is sulphur allergy. Adverse effects are mainly dose dependent and include paresthesia of fingers and toes, abdominal discomfort, weight loss, decreased libido, depression, and a rare idiosyncratic reaction of aplastic anemia. Oral CAIs should be carefully administered in combination with other potassium-lowering agents, as severe hypokalemia may result. Common adverse effects of topical CAIs include bitter taste, blurred vision, and punctate keratopathy. Dorzolamide is more acidic than brinzolamide and therefore causes greater ocular surface irritation. These drugs should be carefully used in eyes with compromised corneas, as they can aggravate endothelial dysfunction.

**ADRENERGIC AGONISTS**

The α2-adrenergic agonists mainly include apraclonidine and brimonidine. Apraclonidine decreases aqueous production but is associated with an increase in outflow facility and a decrease in episcleral venous pressure. Brimonidine is 23 times more α2-selective than apraclonidine and 12 times more selective than clonidine.
Mechanism. Apraclonidine HCl (para-aminoclonidine) is an α2-adrenergic agonist and a clonidine derivative that prevents the release of norepinephrine at nerve terminals. It decreases aqueous production and increases trabecular outflow. Apraclonidine is mainly used to prevent an acute spike of IOP following anterior segment laser surgery (argon laser iridotomy, argon laser trabeculoplasty, Nd:YAG laser capsulotomy). Brimonidine has a similar IOP-lowering effect and the additional function of neuroprotection.

Side effects. Long-term use of apraclonidine is limited due to its potential to cause allergic reactions such as follicular conjunctivitis and contact blepharitis-dermatitis. Development of tachyphylaxis is also seen with this drug. Brimonidine has a similar side effect profile but lower incidence compared with apraclonidine. Brimonidine 0.15% (preserved with Purite) has been shown to cause fewer side effects but achieve a similar therapeutic effect. Systemic side effects include dry mouth and lethargy. The use of brimonidine in infants and young children should be avoided because of an increased risk of somnolence, hypotension, seizures, and apnea.
Fixed combinations incorporate two or more agents in a single bottle. Most currently available fixed combinations for the treatment of open-angle glaucoma consist of a beta-blocker combined with a PGA, an alpha-agonist, or a CAI. Fixed combinations provide a convenient option for avoiding the poor adherence associated with complex therapeutic regimens. A regimen consisting of one drop, once daily, from one bottle means fewer instillations and less opportunity for patient error. A single instillation also avoids the washout effect, whereby the premature addition of a second drop can reduce the effect of the first.

Convenience is an important factor for patients, and eliminating the need for a waiting period between instillations of multiple therapies is likely to improve compliance. Other advantages of fixed combinations include reduced exposure to excipients and preservatives, improved tolerability compared with unfixed combinations, and the potential for reduced costs. A systematic review found that fixed combinations generally offer efficacy and safety equivalent to unfixed combinations.\(^4,5\)

Given all of these considerations, fixed combinations are important additions to the management of glaucoma. They are of particular value in patients at high risk of visual disability, such as those who present with high IOP, pseudoexfoliative glaucoma, or severe visual field defects or those who subsequently exhibit a rate of functional disease progression that will lead to visual impairment during their expected lifetime.

Compliance

Compliance is an important factor influencing the outcome of medical therapy. Understanding and improving patient compliance can increase the effectiveness of medical therapy. The therapeutic benefit from these medications is maximized when administered correctly. However, patients’ eye drop administration techniques can be highly variable and unpredictable.

Maximizing patient adherence to medication has the potential to reduce the number of surgical interventions required to treat glaucoma, prevent unnecessary vision loss, and save the health care system money in the long run.\(^6\)


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