PHARMACOTHERAPY OF GLAUCOMA

ROHIT SAXENA*, JAI PRAKASH, PRIYA MATHUR, SURESH KUMAR GUPTA

*Dr. Rajendra Prasad Centre for Ophthalmic Sciences and Department of Pharmacology, All India Institute of Medical Sciences. Ansari Nagar, New Delhi-110 029.

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ABSTRACT
There has been a dramatic change in the medical therapy of glaucoma during the last two decades. Until the 1980s, miotics were the drugs of first choice for treating this disease but at present, β-blockers are regarded as the first choice drugs. Apart from β-blockers, a number of newer drugs which have fewer systemic and ocular side effects and act by different mechanisms have become commercially available for ophthalmic use. Important among these are latanoprost, unoprostone, brimonidine, apraclonidine, dorzolamide and brinzolamide. In addition, attempts have been made to enhance patient compliance and ocular delivery of already available antiglaucoma drugs like pilocarpine. Notable among the delivery systems are electronic devices, ocular inserts, transdermal and mechanical drug delivery systems and liposomes. Use of viscoelastic vehicles (soluble polymers to soluble gels) in ophthalmic formulations, emulsions and soluble ophthalmic drug inserts (SODI) have also enhanced the patient compliance and drug absorption by ocular tissues in patients on long term glaucoma therapy. The present review deals with various classes of β-blockers, prostaglandin analogs, carbonic anhydrase inhibitors, adrenergic agents, drugs affecting cholinergic pathway and hyperosmotic agents employed in the management of glaucoma. It also throws light on the role of neuroprotective agents and other drugs under investigation.

KEYWORDS
IOP           cholinomimetics           adrenergic-blockers             osmotics             prostaglandins
ocular drug delivery systems

Introduction

Glaucoma continues to be a major cause of irreversible visual disability all over the world. At present, there are approximately 7.5 million diagnosed cases of blindness, of which glaucoma accounts for 10-20%. It is estimated that there are about 2.47 million cases of primary open angle glaucoma in United States alone, the commonest type of glaucoma in the West1. A review of 15 population based glaucoma prevalence surveys in Western Europe, US, West Indies and Japan shows that the disease remains underdetected in nearly 50% of patients, the reasons for this being varied in nature2. Among Asians, the incidence of angle closure glaucoma is almost twice as high as that for caucasians. The true picture of the disease incidence in the Asian continent remains to be elucidated as yet. Glaucoma is characterized by progressive damage to the optic nerves resulting in increased cupping of the optic disc and subsequent loss of retinal nerve fibres. Current studies indicate the involvement of excitatory and inhibitory neurotransmitters viz. glutamate, gamma amino butyric acid (GABA) and glycine in the development of glaucoma. The excess supply of excitatory neurotransmitter glutamate is particularly linked to glaucoma3. Apoptosis or genetically programmed cell death has also been implicated as a mechanism for progression of glaucoma4.

Risk Factors

Elevated intraocular pressure (IOP) is accepted as the single most important risk factor for chronic open-angle glaucoma. A few other factors like eye trauma, concomitant use of drugs, presence of diabetes mellitus, hypothyroidism, cardiovascular and hematological abnormalities etc., are important as well5. Virtually every study that has examined the
relationship between age and chronic open angle glaucoma has confirmed that the older the individual, greater the risk of glaucoma. The Collaborative Glaucoma Study identified that visual field defects over a 13 year period were approximately 7 times higher in persons 60 years of age or older than in persons under 40 years of age. The hypothesis that race is a major risk factor for glaucoma is based on the data indicating a higher prevalence of the disease among blacks. Several ocular parameters associated with glaucoma are also known to be influenced by heredity and the presence of family history. Women of all races develop acute angle closure glaucoma 3 to 4 times as often as men. The global burden of glaucoma poses a challenge to the researchers, ophthalmologists and general practitioners to detect, prevent and effectively treat this visual disability and make safer drugs available to mankind at an affordable price.

**Pharmacotherapy of Glaucoma**

Prevention or modification of risk factors, particularly the raised intraocular pressure is the primary goal in the management of glaucoma. The disease needs to be managed medically, by laser therapy or by conventional surgery as the case may be.

**Classification of antiglaucoma agents**

Depending on their route of administration antiglaucoma agents may be classified as

**Topical drugs:**

1. Cholinergic agents *e.g.* pilocarpine, carbachol, demecarium bromide and echothiophate iodide.
2. Adrenergic agonists *e.g.* epinephrine, dipivefrin, brimonidine and apraclonidine.
3. Beta blockers *e.g.* timolol, carteolol, betaxolol, levobunolol and metoprolol
4. Prostaglandin analogs *e.g.* PGF$_2$α, latanoprost, unoprostone and PHXA-85.
5. Carbonic anhydrase inhibitors *e.g.* dorzolamide and brinzolamide.

**Systemic drugs:**

1. Carbonic anhydrase inhibitors *e.g.* acetazolamide and methazolamide.
2. Osmotic agents *e.g.* glycerine, mannitol and urea.

Miscellaneous drugs include forskolin, ethacrynic acid, steroid antagonists, cannabinoids, angiotensin converting enzyme inhibitors, atrial natriuretic peptide and neuroprotective agents.

**Mechanisms of action of antiglaucoma agents**

The antiglaucoma agents act on the aqueous humor dynamics to reduce the intraocular pressure mainly by three mechanisms.

- Decrease aqueous production in the ciliary body
- Increase aqueous humor outflow through the trabecular meshwork and
- Increase aqueous humor outflow via the uveoscleral pathway.

**Pharmacokinetics of topical drugs**

The availability of the drug at the receptor site is influenced by:

*a. Drug kinetics in the conjunctival cul-de-sac.*

Following topical instillation, the drug mixes with the tears in the cul-de-sac. Bulk of the drug is lost through the lacrimal drainage system while small amount mixes with the precorneal tear film and enters the cornea. The extent of precorneal film saturation governs the amount of drug crossing the cornea and the bioavailability of the drug. Newer developed vehicles have been employed to prolong the stay of the drug in the conjunctival cul-de-sac thereby increasing the precorneal film saturation. Some of these vehicles are soluble polymers (methylcellulose, polyvinyl alcohol), ointments, soluble gels (high viscosity acrylic vehicle), emulsions and suspensions.

*b. Corneal penetration*

The cornea is a lipid-water-lipid sandwich due to which drugs which are both lipid and water soluble are able to penetrate the intact cornea. This is called the differential solubility concept.

*c. Distribution and rate of drug elimination within the eye.*

**1. Cholinergic drugs**

In the past, miotics were the drugs of first choice for the management of most types of glaucoma but currently due to their high side-effects, their use has declined, especially in the West. Miotics are used as an adjunct to β-blockers or sympathomimetics because of their well
established additive effect to control IOP. Miotics can be divided into two groups: direct acting miotics and cholinesterase inhibitors. Pilocarpine is a direct acting miotic while carbachol is a dual action parasympathomimetic due to its weak anticholinesterase activity. Pure acetylcholinesterase inhibitors include physostigmine, ecolothiophate iodide and demecarium bromide.

**Pilocarpine**

Pilocarpine is the principal alkaloid of South American shrubs of the genus *Pilocarpus*. In angle closure glaucoma, the miotic action of the drug relieves the pupillary block and also pulls the iris away from the anterior chamber angle. It increases the trabecular outflow due to ciliary body contraction. This results in pull on the scleral spur and strengthening of the trabecular clamps. It is available in various concentrations ranging from 0.5 - 4% and is indicated in acute and chronic narrow angle glaucoma, open angle glaucoma and in secondary glaucoma resulting from pupillary block. Its onset of action is rapid, peak effect occurs between 30-60 minutes and lasts for 4-8 hours. Occasionally drug resistance can develop which is reversible. Ocular side effects are common with pilocarpine and can interfere with the patient's quality of life and compliance with recommended therapy. Superficial punctate keratitis is the most troublesome acute toxic effect of pilocarpine. Other side effects include ciliary muscle spasm which can lead to browache, induced myopia, miosis, possible retinal detachments, progression of cataract and corneal endothelial toxicity. Systemic toxicity is rare with the usual doses.

**Delivery systems for pilocarpine**

Drug delivery systems aim to achieve the desired pharmacological effect with the least amount of drug and to prolong the duration of therapeutic effect thereby decreasing the frequency of instillation and associated side effects.

a. **Soluble polymers** : Polymers like methylcellulose and polyvinyl alcohol increase the conjunctival sac retention time and increase corneal penetration.

b. **Pilocarpine gel** : The equivalent of 4% pilocarpine hydrochloride in a highly viscous acrylic vehicle when applied once daily at bed time has been reported to produce a significant reduction in IOP for 24 hours.

c. **Membrane-controlled delivery system** : This is an insert device placed in the cul-de-sac where it gradually releases pilocarpine at the rate of 20 µg/hour or 40 µg/hour, which is roughly equivalent to 2% and 4% eye drops respectively. This is effective for 7 days and the constant rate of release (zero order kinetics) provides good control of IOP throughout the day.

d. **Pilocarpine soaked soft contact lenses** : Not as yet recommended for general clinical use.

e. **Transdermal drug delivery system** : A new non ocular pharmaceutical device has been tested for pilocarpine. In this system pilocarpine was applied in two patches of 30 mg each over the supraclavicular skin of 24 patients. Substantial amount of pilocarpine was released from the patches to the dermis with detectable plasma drug levels at 12 hours and 24 hours after administration. The advantage of the system is that it avoids ocular side effects of eye drops.

f. **Electronic medication alarm device** : Another device which enhances the compliance in glaucoma patients taking pilocarpine is the electronic medication alarm device (Prescript TimeCap). A significant difference in patient compliance level was observed (95.8% compliance level with the alarm device versus 83.1% without it).

g. **Liposomal pilocarpine** : Liposome encapsulated pilocarpine has shown prolonged effect in normal and glaucomatous rabbits. However, clinically its effect remains to be substantiated.

**Cholinesterase inhibitors**

Cholinesterase inhibitors are another class of miotics which act by increasing the levels of endogenous acetylcholine by inhibiting the enzyme acetylcholinesterase. Physostigmine, neostigmine and demecarium are short acting cholinesterase inhibitors whereas ecolothiophate and isofluorophate are long acting cholinesterase inhibitors. Physostigmine and neostigmine are useful in angle closure and open angle glaucoma, though their use has declined due to the high incidence of allergic reactions. Ecolothiophate iodide and demecarium bromide are no longer used in glaucoma. Isofluorophate is more oculotoxic than ecolothiophate and demecarium. Cholinergic toxicities in the form of profound muscle weakness and cystoid macular edema have been reported with the use
of ecothiophate eye drops. These toxicities resolve spontaneously on discontinuation of the therapy. \cite{12,13}

Local ocular side effects of anticholinesterase agents similar to those of other miotics may be severe enough to warrant discontinuation of the drug e.g. iris cyst formation and cataract formation. In general, the use of anticholinesterase medications for the treatment of open angle glaucoma is reserved for cases in which the patient has become intolerant to pilocarpine or carbachol or when the pressure lowering effect of these agents is inadequate. Also these agents are more effective in secondary glaucoma like aphakic or pseudoaphakic glaucoma.

2. Adrenergic agonists

**Epinephrine**

It is a direct acting sympathomimetic amine and it acts by decreasing aqueous humor formation in the early phase presumably due to its $\alpha$-adrenergic effect. It also increases trabecular outflow probably by stimulating $\beta_2$-adrenergic receptors in the trabecular meshwork. Onset of action occurs at 1 hr with a peak effect at 4 hours and ocular hypotensive effect may last upto 72 hours. Long term epinephrine therapy achieves the same degree of IOP control as timolol.\cite{14}

Epinephrine is additive to pilocarpine and to oral carbonic anhydrase inhibitors. It is also partially additive to $\beta$-blockers. Epinephrine may be used as initial or adjunctive glaucoma therapy. It is available as hydrochloride, bitartarate and borate salt for topical ophthalmic use in concentration ranges varying from 0.25-2% to be administered twice daily. Topical instillation of epinephrine causes conjunctival decongestion and transient mydriasis. Systemic hypertension, stinging, browache, conjunctival hyperemia, adenochrome deposits and allergic lid reactions are reported with epinephrine. It needs to be administered topically with caution in patients of cardiovascular dysfunctions, hyperthyroidism or diabetes mellitus.

**Dipivefrin**

Dipivefrin is the prodrug which undergoes biotransformation to epinephrine within the cornea. Due to increased lipophilicity its penetration across the cornea is 17 times more than epinephrine, and lesser doses are needed to be administered as compared to epinephrine. It is better tolerated than epinephrine. The onset of its ocular hypotensive action is within 30 minutes and peak effect is observed in 1 hour. It exerts its action by decreasing aqueous production and enhancing the outflow facility. It is indicated for initial therapy or as an adjunct with other ocular hypotensive agents. It is available as 0.1% ophthalmic solution to be administered twice daily. This concentration represents a balance between efficacy and mydriasis. Used as a single agent dipivefrin produces a 20-24% reduction in IOP. Recently a multicentric study found dipivefrin equivalent to 0.5% betaxolol used twice daily as a single agent. It works well with pilocarpine and with oral carbonic anhydrase inhibitors. Its advantages over epinephrine are lower cardiovascular side effects. Like epinephrine it can be used in patients of asthma, in young patients intolerant to miotics and in those with cataracts. Dipivefrin does not easily discolor soft contact lenses and has a much lower incidence of adenochrome deposits than epinephrine. A common adverse effect of dipivefrin is follicular conjunctivitis.\cite{15}

**Apraclonidine**

Apraclonidine is an $\alpha_2$-adrenergic agonist which is basically a para amino derivative of clonidine. It acts by decreasing aqueous production, increasing trabecular meshwork outflow by reducing episcleral venous pressure and may also increase uveoscleral outflow by an increase in prostaglandin synthesis. It is now available commercially both as 1% and 0.5% ophthalmic solution and is mainly indicated to control the acute IOP rise after ocular laser therapy as longer treatment may lead to development of tolerance. Within one hour of instillation, apraclonidine 1% produces a rapid drop in intraocular pressure of at least 20% from baseline. The maximal effect is produced 3-5 hours after dosing. Single postoperative administration of 0.5% apraclonidine has been found to be equally effective to that of 1% apraclonidine in the prevention of immediate post-operative IOP rise in a prospective randomized study on 83 patients of trabecuoplasty, 62 patients of iridotomy and 52 patients of capsulotomy.\cite{16}

The ocular hypotensive effect of apraclonidine alone is equal to 0.5% timolol maleate up to 8 hours post dose but less than timolol maleate up to 12 hours post dose. It may be used concomitantly with other antiglaucoma agents and as many as 60% patients do not require additional therapy for up to 5 months, if
Brimonidine

Since its introduction in 1996, it has emerged as a new powerful first line agent for the treatment of elevated IOP. It is the drug of choice in chronic treatment of glaucoma and in patients with cardiopulmonary disease and who have contraindications to \( \beta \)-blockers. It is a highly selective \( \alpha_2 \)-adrenoceptor agonist. It is 7-12 fold and 23-32 fold more selective than clonidine and apraclonidine respectively. It has lower incidence of ocular side effects because of \( \alpha_2 \) selectivity. It reduces the intraocular pressure by suppressing the rate of aqueous humor flow and enhancing uveoscleral flow. It has good retinal bioavailability, ocular hypotensive and neuroprotective action in animal models\(^{19}\). Its peak IOP reduction efficacy is comparable to that of timolol and does not cause cardiopulmonary side effects as reported with timolol\(^\text{15}\). However, there are reports suggesting similar efficacy of brimonidine with that of timolol but with a greater incidence of adverse local reactions\(^{18}\). In a recent double blind clinical study brimonidine tartarate 0.2% twice daily provided sustained IOP lowering efficacy comparing to timolol 0.5% twice daily with no significant differences at trough or peak during 4 years of continuous use\(^\text{21}\).

3. Beta adrenergic antagonists

Drugs in this class have become the major therapeutic agents for most forms of glaucoma. Due to their almost universal efficacy and minimal ocular side effects, these drugs usually are the first line agents for the medical therapy of all kinds of glaucoma. They act solely by reducing the aqueous humor production by their action on ciliary body\(^{18}\). They block the \( \beta \)-receptors in the iris and ciliary body and thereby cause significant reduction in IOP. This class of drugs has several advantages over both cholinergic and adrenergic agonists. Majority of patients can be treated solely by \( \beta \)-blockers. Unlike miotics, \( \beta \)-blockers have little effect on pupil size or accommodadation, eliminating the problems of dim vision, decreased night vision and blurred vision. Unlike adrenergic agonists, \( \beta \)-blockers do not cause pupil size changes or hyperemia. \( \beta \)-blockers also have a significant additive action when combined with pilocarpine or other antiglaucoma agent.

Depending on their selective receptor inhibition, they are classified as \( \beta_1 \)-selective and non-selective \( \beta \)-blockers respectively. Betaxolol, atenolol and metoprolol are selective \( \beta_1 \)-blockers whereas timolol maleate, nadolol, befunolol, carteolol, penbutolol, labetalol, nipradilol are non-selective \( \beta \)-blockers. Currently the following five \( \beta \)-blockers are available for topical ophthalmic use - timolol, betaxolol, levobunolol, carteolol and metoprolol. The dosage regimens, duration of action and side effects of \( \beta \)-blockers and other selected antiglaucoma drugs are given in Table 1.

Timolol

The introduction of timolol in 1978 was a milestone in ocular pharmacology. It was the first topical \( \beta \)-adrenergic antagonist approved in US for the treatment of glaucoma and elevated IOP\(^{22}\). It is currently the prototype agent to which new antiglaucoma drugs are compared in clinical trials. Timolol inhibits both \( \beta_1 \) and \( \beta_2 \) adrenergic activity. It is being used extensively worldwide as a first line agent for the treatment of patients with open angle glaucoma and ocular hypertension. It is instilled as one drop of 0.25% or 0.5% solution twice a day and the duration of action exceeds 7 hours. At this dose timolol produces a significant reduction in IOP in most cases. Although numerous investigators have demonstrated the safety of timolol, significant local and systemic side effects have been documented, so this drug must be used with caution. Localized irritation of the corneal epithelium can result in blurred vision, conjunctival hyperemia, superficial punctate keratopathy and dry eye symptoms. Although several studies have confirmed the continued efficacy of chronic timolol therapy...
Table 1. Dosage regimens, duration of action and side effects of selected drugs used in the therapy of glaucoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Agent</th>
<th>Dosage regimen</th>
<th>Duration of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic agonists</td>
<td>Pilocarpine</td>
<td>0.5-4% eyedrops 2-4 times daily</td>
<td>8 hours</td>
<td>Ocular: miosis, follicular conjunctivitis, ciliary spasm, lacrimation. Systemic: salivation, urination.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ocuserts, applied once a week</td>
<td>7 days</td>
<td>Accidental loss, membrane break, tachyphylaxis, ciliary muscle changes.</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>Physostigmine</td>
<td>0.25-0.5% eyedrops or 1 cm ointment 4 times daily</td>
<td>12-36 hours</td>
<td>Pain, irritation, iris cysts.</td>
</tr>
<tr>
<td></td>
<td>Echotothiophate</td>
<td>0.125-0.06% eyedrops, once daily</td>
<td>12 hours</td>
<td>Ocular: corneal anaesthesia, uveitis, retinal detachment, ptosis, cataract. Systemic: headache, palpitation, bradycardia, memory disturbances.</td>
</tr>
<tr>
<td>Adrenergic agonists</td>
<td>Epinephrine</td>
<td>0.25-2% eyedrops twice daily</td>
<td>12 hours</td>
<td>Ocular: irritation, conjunctival hyperemia. Systemic: Headache, palpitation, sweating.</td>
</tr>
<tr>
<td></td>
<td>Apraclonidine</td>
<td>0.5-1% eyedrops twice daily</td>
<td>5-8 hours</td>
<td>Ocular: hyperemia, mydriasis, dryness. Systemic: diarrhoea, bradycardia, insomnia.</td>
</tr>
<tr>
<td></td>
<td>Dipivefrin</td>
<td>0.1% eyedrops 2-3 times daily</td>
<td>12 hours</td>
<td>Fewer side effects, minimum systemic absorption, less allergic reactions.</td>
</tr>
<tr>
<td>β-Adrenergic antagonists</td>
<td>Timolol</td>
<td>0.25-0.5% eyedrops twice daily</td>
<td>12-24 hours</td>
<td>Ocular: irritation, diplopia, ptosis. Systemic: headache, dizziness, bronchospasm, bradycardia, hypotension.</td>
</tr>
<tr>
<td></td>
<td>Betaxolol</td>
<td>0.5% eyedrops twice daily</td>
<td>12 hours</td>
<td>Stinging, bradycardia, hypotension.</td>
</tr>
<tr>
<td></td>
<td>Levobunolol</td>
<td>0.5% eyedrops 1-2 times daily</td>
<td>12-24 hours</td>
<td>Reduced side effects compared to timolol.</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>0.3% or 0.6% eyedrops twice daily</td>
<td>12-24 hours</td>
<td>Ocular: hyperemia of conjunctiva, blurred vision, photophobia. Systemic: potential cardiac, respiratory side effects, allergic reaction, headache, nausea, nervousness, rashes.</td>
</tr>
<tr>
<td></td>
<td>Carteolol</td>
<td>1% eyedrops 1-2 times daily</td>
<td>12 hours</td>
<td>Same as timolol.</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>Acetazolamide</td>
<td>250 mg tablets 2-4 times daily, p.o.</td>
<td>8-12 hours</td>
<td>Systemic: GIT upset, nausea, diuresis, renal calculi, aplastic anaemia. Ocular: transient myopia.</td>
</tr>
<tr>
<td></td>
<td>Methazolamide</td>
<td>50 mg tablets 2-3 times daily, p.o.</td>
<td>10-18 hours</td>
<td>Minor side effects, fatigue, malaise nausea, vertigo, paresthesia.</td>
</tr>
<tr>
<td></td>
<td>Dorzolamide</td>
<td>2% eyedrops 3 times daily</td>
<td>20-24 hours</td>
<td>Minimal side effects: burning, stinging in the eye.</td>
</tr>
<tr>
<td>Prostaglandin analogs</td>
<td>Latanoprost</td>
<td>0.005% solution 1 drop once daily at bed time</td>
<td>20-24 hours</td>
<td>Iris pigmentation, mild conjunctival hyperemia, local irritation, increased growth of eyelashes and cystoid macular edema.</td>
</tr>
</tbody>
</table>
in a significant number of cases, the pressure responsiveness decreases with continuous use. The timolol therapy is associated with the phenomenon of short term escape and long term drift. In short term escape, most patients experience a good IOP reduction after start of timolol therapy, but the pressure rises after a few days to finally level off by 3-4 weeks. One must therefore wait for at least one month after starting timolol to determine its efficacy. In long term drift, after around one year of timolol therapy, few patients show a slow decline in pressure responsiveness to timolol. Many of these will regain responsiveness to timolol after a washout period. The efficacy of timolol hemihydrate 0.5% solution given once a day has been found to be comparable to its IOP reducing efficacy to timolol gel 0.5% given once a day.25

Timolol has been shown to be more effective in lowering IOP than either epinephrine or pilocarpine. Systemic toxicity from topical timolol occurs more frequently than local toxicity and can affect the pulmonary, cardiac and central nervous system.24 These include bronchospasm, bradycardia, hypotension, arrhythmias, heart failure, myocardial infarction, depression, anxiety and confusion.

Timolol maleate (ophthalmic gel forming solution, Timoptic XE) is a new formulation of timolol. The vehicle is an anionic polysaccharide derived from gellan gum. Upon contact with the cations in the tear film, the product forms a gel allowing the drug to remain in contact with the eye for a longer period of time. Dosage is once daily and has the potential advantage of greater compliance, reduced cost and less systemic absorption.

**Carteolol**

Carteolol is the second most commonly prescribed topical β-blocker in the world. A multicentric trial comparing carteolol and timolol showed equivalent pressure lowering efficacy over three months to one year. The half life of its metabolite, the 8-hydroxycarteolol is 2-3 times that of the parent molecule and this may allow for the better bioavailability and increased duration of action compared with other β-adrenergic antagonists.

It is a non-selective β-blocker with intrinsic sympathomimetic activity and ability to partially activate β-receptors in the absence of catecholamines.25 Efficacy of carteolol is comparable to that of timolol and has been better tolerated as regards stinging and irritation.25-27 Since carteolol has fewer deleterious effects on lipid profile, some ophthalmologists prefer it in patients with hypercholesterolemia.

**Betaxolol**

Betaxolol hydrochloride was introduced in the early 1980s as the first topical, cardioselective β₁-adrenergic antagonist to be used in ophthalmology. Most clinical trials comparing betaxolol with timolol have shown betaxolol to be statistically less effective in both pressure lowering and reducing aqueous outflow. Onset of action is noted in 30 minutes, maximum effect occurs at 2 hours after topical administration and a single dose provides 12 hours of pressure reduction. The advantage of betaxolol over timolol is the absence of β₂-adrenergic inhibition which minimizes the risk of respiratory side effects. Betaxolol causes more burning and stinging than non-cardioselective β-blockers.

Marketed as 0.5% ophthalmic solution for all types of glaucomas, it requires to be instilled twice daily. It is reported to cause less impairment of respiratory and cardiovascular functions when compared to timolol particularly in the elderly. Betaxolol also has neuroprotective action on the eye and slows down the changes seen in retina after raised IOP induced ischemia/reperfusion.28,15,29

**Levobunolol**

It reduces intraocular pressure by reducing aqueous humor formation as well as by enhancing the outflow facility. It is as effective in reducing IOP as timolol maleate, metoprolol and carteolol.14 The potential advantage of levobunolol is once daily dosing due to longer duration of action. It is cost effective, causes less ocular discomfort and has better compliance.31 Topical levobunolol or timolol when instilled one drop for one week have been found to slightly increase the retinal blood flow in healthy volunteers.32 Levobunolol is contraindicated in patients predisposed to cardiac or respiratory disease. Caution is required in diabetics and those undergoing major surgery.33

**Metoprolol**

It is a cost effective, selective β₁ adrenergic antagonist similar to timolol in clinical efficacy. It reduces the intraocular pressure in normal eyes, chronic open
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angle glaucoma and ocular hypertensive patients. The recommended dose in glaucoma is one drop of 0.3% or 0.6% solution twice a day. IOP lowering effect is comparable to that of levobunolol and carteolol. It is associated with more eye burning, stinging and granulomatous anterior uveitis than other drugs. It also carries the risk of respiratory and cardiac toxicity.

4. Prostaglandin analogs

Latanoprost

It is a highly lipophilic 17-phenyl substituted PGF\( \beta_2 \) isopropyl ester prodrug having a novel mechanism of action. It undergoes enzymatic hydrolysis in cornea and gets activated to the acid of latanoprost. Its response seems to be mediated by prostanoid receptors. Latanoprost is more selective than PGF\( \beta_2 \) in this respect and thereby has superior therapeutic profile. It acts by enhancing uveoscleral outflow rather than altering the conventional trabeculo-canalicular aqueous outflow. It is available as 0.005% ophthalmic solution and requires to be instilled once at night.

A single dose of topical 0.005% latanoprost is equivalent to that of 0.5% timolol (bd dose) in patients suffering from primary open angle glaucoma and ocular hypertension and has a duration of action ranging from 20-24 hours. It is well tolerated with no detectable systemic side effects. Some 3-10% patients have shown iris pigmentation after 3-4.5 months treatment due to increased synthesis of melanin in the melanocytes of the iris stroma and cystoid macular edema. Other local side effects include mild conjunctival hyperemia, punctate corneal erosions and lengthening and thickening of eyelashes.

In a recent phase III clinical trial, latanoprost 0.005% once daily produced sustained reduction of IOP in ocular hypertension and primary open angle glaucoma patients to a greater extent than timolol. The efficacy of once a day 0.005% latanoprost is more than twice a day administration of 0.12% of unoprostone in patients of primary open angle glaucoma and ocular hypertension. Latanoprost can be administered as monotherapy and has good efficacy when combined with other drugs lowering IOP, including systemic acetazolamide. It can be used safely in patients of glaucoma with concomitant bronchial asthma.

Unoprostone

Unoprostone isopropylate is the first docosanoid derivative for glaucoma therapy. It acts by enhancing uveoscleral outflow without affecting aqueous humour production. It is available as 0.12% ophthalmic solution and requires twice a day instillation. Its oculohypotensive effect is similar to or slightly inferior to that of timolol 0.5%. It has also been seen in some studies to increase the optic nerve head blood flow. It has an additive efficacy with latanoprost and can safely improve the diurnal curve characteristics in patients who continue to have an elevated IOP on latanoprost 0.005% alone.

PhXA-85

11-Deoxy-PGE\(_1\) or PhXA-85 is another prostaglandin analog. It also acts by increasing uveoscleral outflow. It has also been shown to reduce the collagen turnover in the matrix surrounding the human ciliary smooth muscles in culture, in a dose dependent manner. The reduction in extracellular matrix components is suggested to lower the hydraulic resistance to aqueous flow thus contributing to pressure reduction.

5. Carbonic anhydrase inhibitors

Systemic carbonic anhydrase inhibitors have been an integral part of glaucoma medical therapy for the past 40 years. These are the reserved group of drugs and are given orally (with the exception of dorzolamide and brinzolamide which are available for topical administration) as an adjunct when IOP is not controlled adequately with topical medication. Approximately 50% patients have shown intolerable side effects with the use of systemic carbonic anhydrase inhibitors. Therefore these drugs are currently used to control IOP in patients waiting for surgery or till the time topical drugs become effective. Acetazolamide and methazolamide are the two potent systemically administered carbonic anhydrase inhibitors.

Acetazolamide

This is the most widely prescribed carbonic anhydrase inhibitor. However, approximately 50% patients stop treatment with acetazolamide as a consequence of intolerable side effects due to extraocular inhibition of carbonic anhydrase. It reversibly blocks the enzyme carbonic anhydrase in the ciliary body and thus suppresses aqueous humor production. The aqueous
fluid rich in sodium and bicarbonate ions is hyperosmotic as compared to plasma. Water is attracted to the posterior chamber as a result of osmosis and the high concentration of bicarbonate ions is diluted. When given orally, plasma levels attain a peak at 2 hours, persisting for 4-6 hours and then rapidly drop because of urinary excretion. Acetazolamide is available as tablets and as capsules. The usual oral dose is 125-250 mg four times daily. The effect of acetazolamide may be sustained by dispensing in 'coated granules form' and using an osmotic pump delivery system. Gastrointestinal upset is the most frequent symptom of acetazolamide intolerance. Severe side effects include myopia, pulmonary failure, renal stones, aplastic anaemia, metabolic acidosis, hypersensitivity reactions and peripheral neuropathy.

Methazolamide

It is more potent than acetazolamide and has structural similarity to it. It is indicated in patients of chronic open angle glaucoma where IOP is not controlled adequately with acetazolamide or topical medications. Its penetration across blood aqueous barriers is 50 times that of acetazolamide due to its good lipid solubility and low plasma protein binding. Its dose is 25-50 mg three times daily. Methazolamide is associated with drowsiness, fatigue, malaise and little gastrointestinal disturbances. Few incidences of phosphate renal stones have also been reported.

Dorzolamide

Dorzolamide is a non-bacteriostatic sulfonamide derivative devoid of systemic side effects as seen after oral administration of carbonic anhydrase inhibitors. It has become commercially available since 1995 for topical ophthalmic use. It is thought to reduce the raised IOP by the same mechanism as that the carbonic anhydrase inhibitors. It penetrates cornea, inhibits carbonic anhydrase-II in the ciliary body, slows the production of local bicarbonates and thus decreases sodium and fluid transport which in turn reduces the secretion of aqueous humor. It is available as 2% ophthalmic solution and the dose is one drop instilled twice daily alone or in conjunction with β blockers. The drug reduces the IOP by approximately 3.5-6.0 mm Hg in patients of primary open angle glaucoma or hypertension. It is of comparable efficacy to that of betaxolol, and slightly less than timolol. It is an effective second line agent for patients of open angle glaucoma and ocular hypertension who are unable to tolerate ophthalmic β blockers. When combined with timolol therapy, it shows efficacy similar to that of pilocarpine.

In lower concentrations it may be equally effective with better compliance which may further widen the therapeutic potential of this drug. It is associated with lower cardiovascular side effects than topical β blockers and less ocular side effects than pilocarpine. However, it can cause irreversible corneal edema in patients having a compromised endothelium.

Brinzolamide

It is also commercially available since 1998. Its 1% suspension is comparable to 2% dorzolamide in lowering IOP. It is administered three times daily. Though it has a lower incidence of burning and stinging, it elicits more blurred vision. 1% brinzolamide three times daily used adjunctively with timolol 0.5% twice daily produces a significantly additive IOP reduction in open angle glaucoma and ocular hypertensive patients with fewer side effects.

6. Osmotic agents

These agents act by enhancing the osmotic pressure of plasma with respect to intraocular structures thereby setting an osmotic gradient. Consequently the fluid moves from the eye to hyperosmotic plasma of ocular blood vessels, thereby reducing the vitreous volume which is responsible for lowering of IOP. Mannitol, glycerol, urea, isosorbide etc are the osmotic agents used for short term reduction of IOP. The use of these drugs is currently limited to short term emergency situations such as acute angle closure glaucoma or pre-operative control of raised IOP. The side effects of these drugs include nausea, vomiting, diuresis, headache, diarrhea, chills and fever. Rarely life-threatening problems such as cardiovascular overload, intracranial hemorrhage, pulmonary edema and acidemia may occur.

7. Miscellaneous agents

Forskolin

Forskolin is derived from methanolic extract of the roots of Coleus forskohlii. It has been shown to be an effective ocular hypotensive agent both experimentally and
GLAUCOMA THERAPY

Steroid antagonists

Animal studies of mifepristone (RU-486) and related compounds show the promise of these drugs as ocular hypotensive agents despite our poor understanding of the mechanism of the ocular hypotensive effect. Progression of the experimental work to human clinical trials is needed to ascertain their clinical usefulness. A more complete understanding of the physiological mechanism of steroid antagonists induced ocular hypotension may lead to improved or novel strategies for lowering IOP in patients of glaucoma.

Angiotensin converting enzyme inhibitors

Components of the renin angiotensin system are present in peripheral tissues, including the eye and may play a role in controlling aqueous humor production, retinal blood flow or retinovascular disease. Angiotensin II receptors of the retinal vasculature may play a significant role in the autoregulation of blood supply to the retina and optic nerve head. Topical angiotensin converting enzyme (ACE) inhibitors have been shown to lower IOP in rabbits, monkeys and humans. Experimental evidence suggests that ACE inhibitors might inhibit breakdown of bradykinin, promote formation of endogenous prostaglandins and also enhance uveoscleral outflow. Thus, inhibitors of ACE activity might be useful pharmacological agents in the medical therapy of glaucoma.

Atrial natriuretic peptide

The anterior uvea is also rich in atrial natriuretic peptide (ANP) and ANP receptors. Experimentally, ANP has been shown to reduce IOP via reduced secretion of aqueous humor by a direct effect on ciliary processes. An improved understanding of the physiological role of ANP and the elements of the renin angiotensin system present in the eye may lead to new and interesting treatment strategies for lowering IOP in glaucoma patients.

Cannabinoids

Marijuana or cannabis has been used as a herbal medication in many societies for centuries. Marijuana's ability to lower IOP in humans has spurred a great effort to identify not only the mechanism by
which this effect occurs but also to identify either members of this family, or a delivery system of these drugs to the eye, that can effectively reduce pressure without the well known psychotropic side effects.

**Ocular hypotensive lipids**

AGN-191129 and AGN-192024, are the two new antiglaucoma agents belonging to the class of compounds termed as ocular hypotensive lipids (OHL). These compounds contain a neutral substituent for the carboxylic acid group of PGF$_{2\alpha}$ and are not fatty acids. These are relatively metabolically stable unlike the prodrug latanoprost and the esterified PGF$_{2\alpha}$ analogue that is readily metabolized into active PGF$_{2\alpha}$.

These compounds do not interact with the FP or other known prostanoid receptors. These compounds have different pharmacological profiles yet are potent ocular hypotensive agents. Clinical trials were conducted on these OHL in open angle glaucoma and ocular hypertension cases. Twice daily dosing at concentration of 0.01% produced significant IOP lowering (26% decrease from baseline) and was certainly superior to that of timolol (0.5% bd). These new compounds continue to produce a significant IOP lowering effect upto 24 hours after the last drug instillation. These compounds are well tolerated and have a very favourable ocular and systemic safety profile with no patient drop out due to adverse events. These compounds will be an excellent alternative as a first and second line IOP lowering agent for the therapy of ocular hypertension and open angle glaucoma.

**Neuroprotective agents**

Neuroprotection has been projected as one of the important strategies for vision sparing through the promotion of retinal ganglion cell survival. Retinal cell death is initiated when pathological events like ischaemia, axonal injury and changes in the lamina cribrosa block the transport of growth factors from the brain to retinal ganglion cells. Blockade of these neurotrophins initiates a damaging cascade and the cell is unable to maintain its normal functions. When retinal ganglion cells undergo apoptosis and release oxygen free radicals, gene expression changes favourably, mitochondria alter and excitatory toxins are released during optic nerve injury.

Drugs which can affect this cell death pathway through differing mechanisms and provide effective neuroprotection are : brimonidine, latanoprost, N-methyl-D-aspartate (NMDA) antagonists (memantine and dizocilpine, eliprodil), calcium channel blockers (lomarizine), glutamate antagonists (riluzole), L-deprenyl, 5-HT$_{1A}$ agonists, nitric oxide synthase inhibitors, neurotrophic factors, free radical scavengers, antiapoptotic agents, naftidofuryl, polyamine antagonists, aspirin, melatonin, cannabinoids, and vitamin B$_{12}$.

**Monotherapy versus combination therapy**

β blockers are the most commonly prescribed first line therapy though the use of latanoprost and brimonidine as primary therapy is also increasing in the West. Latanoprost, brimonidine and topical carbonic anhydrase inhibitors are effective as early adjuective therapy in cases where a single drug alone is inadequate to control IOP. Adrenergic agonists and miotics are also useful as secondary or tertiary therapy but their use in the west is declining due to their significant topical and systemic side effects. It is thus evident that when therapy with a single agent is inadequate to control IOP, combination treatment is indicated. The additive benefit of two drugs depends to some extent on whether they reduce IOP by similar mechanisms. Miotics and carbonic anhydrase inhibitors in combination may be useful, perhaps because miotics increase aqueous outflow, whereas carbonic anhydrase inhibitors reduce inflow. It must be stressed that if the initial agent is only slightly effective at lowering IOP, it should be discontinued and other drugs tried individually before going on to combination therapy. The combination therapy in contrast to monotherapy has the possibility of delaying the need for surgery.

Timpilo, a new formulation combining pilocarpine hydrochloride (3%) and timolol maleate (0.5%) is useful in patients whose IOP is not controlled by monotherapy. Each of the two components reduces IOP by different but complementary mechanisms. While pilocarpine alone requires 4 times daily administration, twice daily administration of Timpilo is adequate. Dorzolamide 2%/timolol 0.5% is a well tolerated and effective fixed dose combination for
lowering IOP in the treatment of open angle glaucoma and may be used in those patients who do not respond adequately to first line monotherapy.

Conclusions and future directions

The wide variety of topically effective antiglaucoma drugs which are available today and few others in the developmental stage represent significant advancement in ocular therapeutics. Though, these topical ophthalmic preparations have reduced the risk of systemic toxicity to quite an extent, their long term use causes systemic as well as ocular toxicity, rarely leading to death. Ophthalmologists must select the drugs individually and replace them regularly in order to prevent habituation phenomenon and negative side effects.

A new futuristic glaucoma therapeutic management paradigm where clinical success is no longer simply measured by achieved level of intraocular pressure control but also long term preservation of visual function and patient's quality of life is expected to dramatically improve upon current treatment algorithms for ocular hypertension and glaucoma. Ideal drug candidates for this new combination therapy will offer better IOP lowering efficacy with fewer side effects and provide additional means of vision sparing through direct protection of optic nerve with currently available antiglaucoma agents.

A few but important problems need to be addressed in future from the point of view of glaucoma therapy. Acute studies with β blockers and adrenergic agents have shown that these agents reduce choroidal and optic disc blood flow. Timolol has a better influence on visual field and is considered as an outstanding agent for the management of glaucoma. Therefore newly developed antiglaucoma drugs must be compared with this agent. Such drugs must be designed which do not affect ocular hemodynamics, have better patient compliance and are cost effective.

Latanoprost and brimonidine represent a promising approach to IOP lowering with the potential of enhancing retinal ganglion cell survival. In addition, retinal ganglionic cell death elicited by the high levels of glutamate may be overcome by memantine or other compounds that effectively block this common secondary neuropathological pathway. Ideally neuroprotection in glaucoma shall be achieved by combining agents that effectively reduce IOP and directly protect the optic nerves (marginally damaged, undamaged but at risk) through the promotion of cellular survival or inhibition of cell death signals.

New and more sensitive procedures that are able to detect ganglion cell damage in humans before occurrence of visual field defects are developed and we shall be able to expedite the evaluation of neuroprotective efficacy of available and new drugs and new drug combinations in development.

Research into the basic pathophysiological mechanisms of glaucomatous optic neuropathy will eventually open new therapeutic pathways. Better understanding of the underlying genetic basis of heritable forms of glaucoma should provide new diagnostic tools and potential for new therapeutic avenues. There are reports on the involvement of an autoimmune component in certain types of glaucoma. Our understanding of these complex immune disorders is required and we may be able to tailor therapies to address this potential confounding issue. Promising new focus on vision sparing, greater patient safety and tolerability will provide improved treatment options and long term preservation of vision and quality of life.

A great deal of research is being directed towards applying new molecular and cellular techniques to induce regeneration of mammalian central nervous axons. This shall be an important step in therapy for glaucomatous optic nerve atrophy (which can lead to at least partial recovery of optic nerve function following atrophy from glaucoma).

Synthesis of cytokines and growth factors for reactive astrocytes and altered expression of cell surface adhesion molecules including neural cell adhesion molecule (N-CAM) hold promise. The search for pharmacological and neuroregenerative agents for the treatment of glaucoma promises to be most exciting pathways for the future treatment of glaucoma.
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