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GLAUCOMA AND BETA-BLOCKERS.

Dinesh Sachdeva*[1,2] Anil Bhandari[2]

1. Registrar, Rajasthan Pharmacy Council, Sardar Patel Marg, Jaipur, Rajasthan, India.
2. Dean, Faculty of Pharmaceutical Sciences, Jodhpur National University, Jodhpur, Rajasthan, India.

ABSTRACT

Beta-blockers are the first line drugs in lowering the elevated and normal intraocular pressure associated with neuropathy of glaucoma, but for many reasons the use of this group of drugs requires supportive medications. The systemic side effects due to overdose of these drugs leads to pathetic complications in patients suffering with cardiac and pulmonary diseases. This article provides necessary information for the safe use of beta-blockers with detailed information about the disease glaucoma. Recent advances in the glaucoma therapy with beta-blockers and novel drug delivery systems developed are reviewed in this study.

Key words: Glaucoma, beta-blockers, intraocular pressure, Timolol, Levobunolol

INTRODUCTION:

Glaucoma is the second major cause of blindness worldwide. Early diagnosis and latest medications for the management of glaucoma seems to be a good sign in preventing visual loss. Any how it depends on the comprehensive eye examination[1] by an expert physician to suspect glaucoma by slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, indirect ophthalmoscopy and stereoscopic examination of the optic disc and retinal nerve fiber layer (RNFL). To preserve the visual function and quality of life (QOL) of the sufferers, timely diagnosis and proper treatment is mandatory, however the primary open angle glaucoma is a

*Corresponding Author Email: dinesh.sachdeva@hotmail.com

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diagnosis of exclusion and the only treatable risk factor is intraocular pressure (IOP). By 2010, the prevalence of glaucoma[2] in India was about 11.9 millions and in the world about 60.5 millions and unfortunately the pathogenesis of the disorder is not fully explained. The main risk factor in the development and progression of glaucoma is the elevated IOP. So mostly the treatment of glaucoma commence with the topical application of drugs for the reduction of elevated IOP with drugs like beta-blockers, miotics, alpha-2 agonists, carbonic anhydrase inhibitors, prostaglandin analogues or hyperosmotic agents (Table1). Apart from the onset and duration of action, every drug has its systemic and local side effects profile in the topical administration. A detailed study about different types of glaucoma and the beta-blockers used in the treatment via diverse formulations are discussed in this article.

Etiology:

Glaucoma, translated meaning "Sea-Green eye" referred to a group of blinding diseases and by the 1700's, elevated IOP was considered as a distinct ocular disease. In 1854, with the introduction of ophthalmoscope, glaucoma was redefined as a disease of the eye with both optic nerve damage and elevated IOP. Till date increase in IOP is considered as the main pathogenic factor for the causation of glaucomatous optic atrophy.[3] Optic nerve damage caused by the different types of glaucoma is a result of a variety of initiating factors. Genetic predisposition, physical changes, systemic diseases, or medications may increase a person's risk of developing damage that may be broadly classified as intraocular pressure dependent or intraocular pressure independent. Increased intraocular pressure remains the major etiologic risk factor for the development of glaucoma. Myopia may be an additional risk factor, especially in younger patients.[4] Glaucoma can occur as a secondary manifestation of systemic disorders or trauma.

Pathogenesis [5]:

There are five stages in the pathogenesis of glaucoma: (1) a variety of initial events, causing (2) Changes in aqueous outflow, resulting in (3) Increased IOP, which leads to (4) Optic nerve atrophy, and finally, (5) Progressive loss of vision. This description highlights the importance of aqueous humor production and elimination in the progression of glaucoma and subsequent complications.

Open-Angle Glaucoma[6]:

In open-angle glaucoma, a physical blockage occurs within the trabecular meshwork that retards elimination of aqueous humor. The obstruction is presumed to be between the trabecular sheet and the episcleral veins, into which the aqueous humor ultimately flows. The impairment of

aqueous drainage elevates the intraocular pressure to between 25 and 35 mm Hg (normal intraocular pressure is 10 to 20 mm Hg), indicating that the obstruction is usually partial. This increase in intraocular pressure is sufficient to cause progressive cupping of the optic disk and eventually visual field defects.

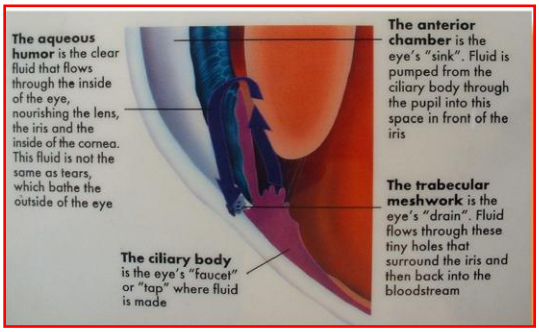

Figure 1; the flow of aqueous humor in to trabecular meshwork in normal eye maintain IOP and if blocked it leads to OAG or ACG accordingly.

Angle-Closure Glaucoma[7]:

In angle-closure glaucoma, increased intraocular pressure is caused by papillary blockage of aqueous humor outflow and is more severe. The basic requirements leading to an acute attack of angle closure are a papillary block, a narrowed anterior chamber angle and a convex iris. When a patient has a narrow anterior chamber or a pupil that dilates to a degree where the iris comes in greater contact with the lens, there is interference with the flow of aqueous humor from the posterior to the anterior chamber. Because aqueous humor is continually secreted, pressure from within the posterior chamber forces the iris to bulge forward. This may progress to complete blockage. The pathologic complications of angle closure and open angle glaucoma include the formation of cataracts, adhesion of the iris to the cornea, atrophy of the optic nerve and retina, complete blockage of aqueous outflow, and ultimately, blindness. Angle-closure glaucoma [8] is the disease of elders and only isolated cases in small series are reported in children and young adults.

Congenital Glaucoma[9]:

Congenital glaucoma is a rare disorder in which intraocular pressure is increased as a result of developmental abnormalities of the ocular structures in the newborn or infant. It may occur in association with other congenital abnormalities and anomalies such as homocystinuria and Marfan's syndrome. The optic nerve head and trabecular mesh work are the most involved structures in hereditary, congenital and juvenile glaucoma.

Normal-Tension Glaucoma[2]:

The etiology and pathogenesis of normal tension glaucoma remain to be completely understood. Normal tension glaucoma is though to be related, at least in part, to decreased blood flow to the optic nerve. This may eventually cause neuronal damage. In addition, these eyes appear to be more susceptible to pressure related damage within the normal or high normal range, and therefore a pressure lower than normal is often necessary to prevent further visual loss.

Drug-Induced Glaucoma[2]:

Several therapeutic classes of drugs, such as those with anti-cholinergic, adrenergic, or corticosteroid effects, have been implicated in inducing or worsening glaucoma. Medications affect open angle and closed angle glaucoma differently. Drugs that dilate the pupil, for instance, may precipitate an acute attack of angle closure glaucoma but usually do not produce harmful effects in those with open angle glaucoma. Dilation of the pupil in angle closure glaucoma may cause the peripheral iris to bulge forward, blocking the trabecular meshwork. The aqueous humor is prevented from reaching the outflow channels, which results in increased IOP. Because excessive resistance to outflow in open angle glaucoma is caused primarily by changes within the trabecular outflow channels, dilation of the pupil usually will not increase the intraocular pressure.

Aqueous Humor Production and Elimination[10]:

The relative production and elimination of aqueous humor physiologically determines intraocular pressure. Increased intraocular pressure usually is the result of decreased elimination, but may also be caused by increased production of aqueous humor or both. Aqueous humor is secreted by the ciliary process into the posterior chamber of the eye, where it flows to the trabecular meshwork and through the canal of Schlemm, owing to diurnal variability in aqueous humor production. Intraocular pressure measurements vary depending upon the time of day. Many patients with open-angle glaucoma have the greatest intraocular pressure in the morning and the lowest intraocular pressure during the sleeping hours. Because a decrease in the outflow facility of aqueous humor is the primary mechanism for producing an increase in intraocular pressure, anatomic changes associated with open angle and angle closure glaucoma are important.

Treatment:

Pharmacotherapy:

The goal of glaucoma therapy is the immediate and sustained reduction of intraocular pressure to prevent deterioration of the optic nerve and loss of vision. Medications used in the treatment of glaucoma may be classified as those that increase the elimination of aqueous humor and those

that decrease its formation. The five major classes of medications used for the management of glaucoma include beta-adrenergic blocking agents, miotics, adrenergic agonists, topical and oral carbonic anhydrase inhibitors, and prostaglandin analogs. Additionally, hyper-osmotic agents are used for the short-term rapid decrease of intraocular pressure necessary in the management of acute angle closure glaucoma. Table 1 summarizes these therapeutic classes of medications used in the treatment of glaucoma, differentiated by their mechanism of action.

Beta-blockers [11]:

Beta-blockers are the most widely prescribed drugs for the treatment of glaucoma and may be used alone or in combination with other agents. The ocular hypotensive effect caused by beta-blockers is probably due to suppression of aqueous humor formation by blockage of the beta-adrenoreceptors in the ciliary body. Beta-Blockers decrease aqueous humor production by approximately one-third. Beta-blockers reduce the rate of aqueous production from the base line of 2.5µl/min to 1.9µl/min and produce a decrease in IOP by 26%. All of the agents are available as solutions and are usually administered one to two times daily. Additionally, timolol maleate is available in a gel formulation, which may be given once daily. Commonly used beta-blockers for the treatment of open angle glaucoma includes timolol maleate, betaxolol HCl, levobunolol HCl, carteolol, and metipranolol.

Mechanism of action of beta-blockers:

Beta-blockers [4] act as adrenergic receptor blocking agents, when applied on the eye topically, reduce the elevated intraocular pressure by minimizing the formation of aqueous and to a little extent improve the outflow of the aqueous. These drugs reduce IOP by competing with catecholamine for b2-adrenocepters on the non-pigmented ciliary epithelium and thereby decreasing aqueous humor production. The onset of action of the beta-blockers commences within one-half hour after a single dose and significant lowering intraocular pressure extends up to 24 hours normally. Usually the beta-blockers are contraindicated to patients with bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, atrioventricular block as the systemic effects of this group of drugs have potency to interfere with pulmonary and cardiovascular systems. So, beta-blocker are used as first line drugs in the management of raised IOP in glaucoma, but invariably these drugs are needed to be combined with other ocular hypotensive drugs to provide adequate control of IOP. A beta-blocker can be combined with pilocarpine or topical carbonic anhydrase inhibitors (CAIs) or alpha-2-agonists to have an additive effect.

Novel formulations of beta-blockers:

The research is on to develop a topical ocular beta-blocker that matches all the criterion for an ideal and safe glaucoma therapy. An ideal ocular beta-blocker should have efficient IOP lowering efficacy with long duration of action and neuroprotective, but without membrane stabilizing activity, intrinsic sympathomimetic activity, local corneal toxicity, systemic effects, and systemic absorption.

Treatment of glaucoma with hydrogel formulation of Timolol Maleate [12] was reported that the hydrogel formulation using Polyacrylic acid as gelling agent and hydroxypropylmethylcellulose as viscolizer. The drug release data from this gel system was reported fitted to various kinetic studies.

Ocular films of Timolol maleate were prepared and characterized [11] for the treatment of glaucoma, for overcoming the reported problems with hydrogels and thick solutions. The stated problems of hydrogels like non-uniformity of dose of drug due to varying drop size of the formulation and blurred vision after the instillation of hydrogel and the presence of undesirable additives as polymers which are reported to have side effects. By using gelatin and glycerin biodegradable polymers, the ocular film of Timolol maleate was prepared and characterized for uniformity of thickness, drug content, water absorbing characteristics were studied and reported.

Ocuserts of Timolol maleate [13] using polymers like HPMC, EC, Eudragit RL100 and RS100 were formulated and evaluated for moisture absorption studies, thickness, uniformity of weight, content, folding endurance, in-vitro and in-vivo drug release.

Circular ophthalmic inserts of Timolol Maleate [14] were prepared by solvent casting technique using cellulose acetate as polymer and PEG600 with Diethyl phthalate as plasticizers. A new in-vitro drug release was also reported from this study.

The influence of drug release rate on the systemic timolol absorption from polymeric ocular inserts in rabbit was studied and reported [15].

Disc type of ophthalmic inserts [16] of beta-blockers with various polymers and drug release from the inserts were investigated. Tilisolol release from the poly (2-hydroxy propyl methacrylate) formulations showed different patterns in different pH and medium temperature.

Ocular drug delivery systems have some more recent advances[17] with listed current and future drugs in clinical trials for anterior and posterior drug delivery systems. Amongst six launched formulations reported, for anterior drug delivery systems, three dosage forms were indicated for glaucoma with beta-blockers. In addition the report included different novel formulations for

anterior drug delivery systems like Durasite® DDS based on polycarbophil aqueous solution. Polycarbophil is polyacrylic acid cross-linked with divinyl glycol, and forms hydrogen bonding with mucous, corneal, conjunctive epithelium which are negatively charged, to extend the effect of the drug to several hours. Rysmon® TG, a formulation from Wakamoto pharmaceuticals, Japan used combinations of MC, sodium citrate and polyethylene glycol, which act by lowering critical solution temperature of methyl cellulose. Gellan gum is an anionic deacetylated polysaccharide used in the formulation of timolol maleate and used for lowering IOP require once a day dose to be equally effective as equal concentration of simple eye drops.

Soft contact lens based drug delivery systems by (1) soak and absorption of drug solution, (2) piggyback contact lens combined with a drug plate, (3) surface-modification to immobilized drugs, (4) incorporation of drugs in colloidal structure dispersed in the lens, (5) ion ligand-containing polymeric hydrogel and (6) molecularly imprinting of drugs.

Cul-de sac inserts include the ocusert and Lacricert® for uniform controlled release of drugs. There was another new ophthalmic drug delivery system reported, Ocufit, a minidisc ocular therapeutic systems. Punctual plugs and sub-conjunctive implants are the other two anterior DDS for the controlled release of drugs and which are still in the trial state.

Conclusion:

Therapy for the glaucoma is now in a dynamic phase, evolving as the underlying disease pathology becomes more clearly understood and as new pharmacological agents and other treatment modalities become available. The medical therapy for glaucoma earlier period was limited to topical miotics and epinephrine; the carbonic anhydrase inhibitors (CAI's) were introduced about three decades before the introduction of beta-blockers and the introduction of a series of new drugs like alpha-2 agonists and prostaglandin analogs followed thereafter. Beta-blockers are a group of drugs used in the treatment of glaucoma by reducing the elevated and normal intraocular pressure by reducing the aqueous formation in the eye. There are numerous novel delivery systems were formulated for the controlled release of the beta-blockers in to the eye topically. There are so many formulations like ocular films, ocular inserts, hydrogels in addition to conventional dosage forms like eye drops, eye ointments, and suspensions. In future, site specific and targeted drug delivery systems with controlled release of the drugs with minimal systemic side effects of these beta-blockers are preferred. As found in the earlier studies Betaxolol is a safer drug when compared with Timolol and Levobunolol for those patients suffering also with chronic obstructive pulmonary disease (COPD), with lower efficacy in

minimizing intraocular pressure (IOP). Timolol and Levobunolol are non specific beta-blockers and are first line drugs of choice in lowering IOP associated with or without glaucoma; but require medical supervision during therapy for patients with cardiac and pulmonary diseases.

Table 1; Important drugs to control IOP as a measure in the treatment of glaucoma

Class	**Drug**	**Mechanism**	**Side effects**	
			Local	**Systemic**
Beta-blockers	Timolol, Levobunolol, Propranolol, carteolol, betaxolol	Aqueous humor production is decreased	Corneal anaesthesia, dryness of the eye, allergic conjunctivitis	Asthma, bradycardia, hypotension, insomnia, hypoglycemia, bronchospasm.
Miotics	Pilocarpine, Physostigmine, demecarium	Increase trabecular outflow of aqueous by contracting the ciliary body muscle	Miosis, accommodative spasm, lacrimation, iris cysts.	Increased sweating, salivation, bradycardia, tachycardia.
Alpha-2 agonists	Adrenaline, apraclonidine, dipivifrine	Decrease aqueous production and partially increase uveoscleral outflow	Allergic conjunctivitis	Drowsiness, dry mouth, headache, contraindicated in patients using MAO inhibitor
Carbonic anhydrase inhibitors	Acetazolamide, methazolamide, dorzolamide, rinzolamide	Decrease aqueous production	Conjunctive hyperemia, allergic reactions, burning/ stinging sensation	Fatigue, cramps, diarrhea, renal failure, acute leucopenia, anemia, agranulocytosis, hypokalemia, metabolic acidosis
Prostoglandin analogues	Bimatoprost, latanoprost, travoprost	Increase uveoscleral outflow	Reactivation of herpetic keratitis, cystoid macular edema in pseudophakic and aphakic patients.	Iris hyperchromia, skin rashes, skin pigmentation.
Hyperosmotic agents	Mannitol and oral glycerol	Increase osmololity of blood thus withdrawing aqueous from vitreous	Paratonic effect on conjunctive epithelium and other tissues.	Caution in patients with cardiac, renal and hepatic disorders. Pulmonary edema, dehydration, contraindicated in diabetic patients (Oral glycerol)

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