β-Blockers as Glaucoma Therapy

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Introduction

In ancient times the term 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 (1,2). In 1854, with the introduction of ophthalmoscope, glaucoma was redefined as a disease of the eye with both optic nerve damage and elevated IOP (1). Till date raised IOP is considered as the main pathogenic factor for the causation of glaucomatous optic atrophy. WHO estimated the global population with high IOP (>21mm Hg) as 104.65 million and the number with chronic open angle glaucoma at 13.5 million (3). As only 10% of glaucoma patients in the world are blind; thus the recognition of those at greatest risk of blindness i.e. with raised IOP, would allow identification of those who would be helped (4).

Pharmacological strategies for the glaucoma:

Therapy for the glaucomas 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 glaucomas in the early 1950's, was limited to topical miotics and epinephrine; the carbonic anhydrase inhibitors (CAI's) were introduced through the work of Bernard Becker and Thomas Maren about another quarter century before the introduction of beta - blockers and the introduction of a series of new drugs like alpha-2 agonists and prostaglandin analogs followed there after (5).

β-adrenergic antagonists: In spite of a series of available drug options, β-adrenergic antagonists account for approximately 70% of all prescriptions for glaucoma medications (6). These drugs reduce IOP by competing with catecholamines for b2-adrenoepters on the non-pigmented ciliary epithelium and there by decreasing aqueous humor production (6,7). These have several advantages over cholinergic and adrenergic agonists, as these have little effect on pupil size or accommodation and do not cause mydriasis or reactive hyperemia unlike cholinergic and adrenergic drugs respectively. All antiglaucoma drugs may affect the physiologic function of corneal endothelial cells through change of [Ca2+ ]i mobility (8). It has been reported that cellular proliferation in human corneal keratocytes is inhibited by only a 1/10 dilution of various drugs including timolol, betaxolol, carteolol, levobunolol, etc which could be linked to the benzalkonium chloride preservative contained in these drugs (9).

Timolol (10-13): It is a moderately lipophilic, non-selective b-blocker without partial agonist or membrane stabilizing activity. It is an asymmetric molecule with active l-isomer and less active d-isomer. The l-isomer is one available commercially. It has a half life of 5 hours, volume of distribution of 1.74 to 3.64 L/kg and is 5 to 10 times more potent than propranolol. It is extensively metabolised in liver with 20% excretion (unchanged) by the kidney. It reduces the rate of aqueous production from the base line of 2.5 µl/min to 1.9 µl/min and produces a decrease in IOP by 26 %. It is less efficacious during nocturnal hours, as the rate of flow of aqueous humor during the day is twice as high as that during night (10). Both the phenomenon of "short term escape", due to increase in the number of b receptors and "long term drift" due to desensitization of the β-receptors have been demonstrated in most of the patients treated with topical timolol therapy. However, topical timolol has good corneal tolerability, no pseudoallergic property and no substantial haemodynamic effect on retina-bulbar vessels in therapeutic concentrations (0.25 to 0.50 % twice a day). However, various systemic adverse effects have been reported with its topical use including CVS, Respiratory and CNS effects like bradycardia, hypotention, syncope, cardiac vascular accidents.


Levobunolol (14) : Levobunolol is a potent longer acting, non-cardio selective β-blocker without ISA(intrinsic sympathomimetic activity). Bunolol contains equal proportions of l-isomer and d-isomer; l-isomer has greater b blocking activity. Majority of it is metabolised in the liver and RBCs. into an active metabolite dihydrolevobunolol, which undergoes renal excretion with a small fraction being excreted in stools and urine unchanged. It is used clinically in a concentration of 0.5% to 1% twice or once a day. Its efficacy is comparable to timolol and has no associated long term drift. A mean plasma levels of 0.1 to 0.3 micro gram per litre and 0.3 to 0.6 micro gram per litre can be achieved following topical instillation of 0.5% and 1.0% levobunolol respectively, but systemic effects have been rarely (approximately 0.0000273%) reported with its use. However, various systemic adverse effects seen with its use are headache, lethargy, transient ataxia, urticaria, pruritis, respiratory difficulties, A.V. blocks, syncope, decreased heart rate and blood pressure. It has an advantage over timolol in having favourable effects on retinal blood flow.

Betaxolol (7,15,16) : Betaxolol a cardio selective, b1-adrenoceptor antagonist (70:1 :: b1 : b2) has an advantage of sparing b2 blockade and can be given safely in patients with pulmonary diseases. It has a weak membrane stabilizing activity, ISA (in high doses) and little 5 HT agonist activity. It has an oral bioavailability of 90%, plasma protein binding of 50%, volume of distribution of 6.12±.044 litre/kg and gets metabolized in the liver with 10 to 17% renal excretion. It is less efficacious than timolol; as it is available as a racemic mixture of l-and d- isomers and timolol as a pure solution of active l-isomer. Reduction in IOP produced by it is due to β2-blockade produced with its relatively high concentration in ocular tissue or due to the actual involvement of β1-receptors in aqueous production or because of some unknown mechanism. Its concentration in aqueous humor is twice as high as that of timolol, with much lower plasma levels, because of its better corneal penetration as it has an excellent lipid - aqueous solubility. It has an advantage of favourable effects on ocular circulation and neuro- protective effect on visual fields, because of its b2 sparing and calcium- ion influx inhibiting properties. It has a tendency to aggravate nocturnal arterial hypotension and to produce reduction in HR (heart rate) with a potential risk of anterior ischemic optic neuropathy (17). It has pseudo -allergic property, which is responsible for various ocular side effects like itching and hyperemia associated with its use.

Carteolol (18) : It is a non-selective b- blocker with (ISA) intrinsic sympathomimetic activity. It has plasma half life of 3.4-7.2 hrs, plasma protein binding of 15% and volume of distribution of 4.05 Kg -1 . 1% solution of carteolol is used 12 hourly in glaucoma .Systemic metabolic effects with its use are not seen.

Metoprolol (19) : It is a cardio-selective, b-adrenoceptor antagonist used in concentration of 0.3 % or 0.6% twice a day. Its IOP lowering efficacy is comparable to that of levobunolol and carteolol.However it is associated with more eye burning, stinging and granulomatous anterior uveitis than other drugs.

Nipradilol (20,21) : Another non- selective b-blocker, nipradilol with a blocking and nitro glycerine like vasodilating activities is under investigation for its efficacy in lowering IOP. Its invitro b-blockering activity is twice that of timolol ,alpha-1 blocking activity is one-fifth of phentolamine and nitro-glycerine like vasodilatory activity is approximately one-fifth of nitro-glycerine. Its alpha blocking activity meight adds to its IOP lowering capacity by increasing uveo-scleral out flow inadition to its ocular antihypertensive activity due to β-blockering activity. Moreover, it has potential positive effect on ocular circulation due to its a blocking and nitro glycerine like vasodilating action. It also causes beneficial effects on NMDA-induced retinal damage.

Concomitant Therapy (10) : β-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 b- blocker can be combined with pilocarpine or topical CAI's or alpha 2 gonists to have an additive effect. However, when a drop of medication is instilled into the eye, approximately 10 µl of it is retained by the conjunctival sac and used to leave the eye by tear formation, blinking and lacrimal drainage.
at the rate of 15% per minute. Hence, to maximize absorption a patient should instill a second drug at least 5 to 7 minutes after the first drug.

**Long Term Complications**: Patients with glaucoma may have to continue ocular β-blocker therapy during several decades of adult life and are thereby exposed to the systemic and metabolic effects of the therapy for many years. Advance age, diabetes mellitus, hypertension, positive family history and obesity are known risk factors for both CHD (coronary heart disease) and increased IOP (22,23). Serum lipids are additionally related to the risk of atherosclerosis (24). However, no association has been established so far between lipid levels and IOP. Still serum lipid fractions may be important in the chronic therapy of glaucoma, as topical β-blockers have been shown to qualitatively mirror the effects of oral β-blockers on serum lipids (25). Various studies demonstrated significant increase in triglycerides, total cholesterol : HDL (high density lipoprotein) ratio and decrease in HDL after topical 0.5% timolol instillation (25-28). A few studies demonstrated no adverse effect on HDL and TC/HDL ratio with 1% carteolol (25,26). However, a study demonstrated fall in HDL after topical carteolol instillation (26). As POAG and atherosclerosis both are fairly common diseases of elderly, so any adverse change in serum lipids as a result of glaucoma therapy can increase the risk of CHD many folds. It has been seen that as low as 1% fall in cholesterol results into 2 to 3% fall in the rate of CHD (29,30). Again LDL is highly atherogenic as a result of its low binding affinity for the LDL-receptors, prolonged t½ and long resistance to oxidation (31,32). A 10% reduction in LDL can decrease the rate of CHD by 50% over 5 years and a 10% increase in LDL can increase the risk of CHD by 20% (33,34). However, every 1mg/dl increase in LDL can reduce the risk of CHD by 2 to 3% (35). Moreover, the ratio of LDL to HDL cholesterol provides a composite marker of risk, with ratio below 3 indicating lower risk and ratio above 5 indicating a higher risk of CHD (36).

**Conclusion**

Many β-blockers of differing structure reduce IOP, but for the most effective drug pharmacodynamic factors are more important than their B2/B1-selectivity ratio or absolute receptor affinity. Nonetheless, reasonable concern remains that lipid changes induced by topical β-blockers may be detrimental and could reduce the therapeutic benefits of these drugs; as seen with the use of diuretics and β-blockers in hypertensive patients to reduce incidence of CHD (25). Moreover, this potentially atherogenic effect of ocular β-blockers may influence the choice of the glaucoma therapy, especially in younger patients, who may require treatment for longer period of time (26). However, a lower drug concentration, smaller drop size, once a daily dosing and the practice of nasolacrimal occlusion or eye closure may markedly reduce systemic absorption of topical β-adrenergic antagonists and thus reduce any effect on plasma lipids, cardiovascular system and respiratory systems.

**References**


Erratum

Please read Rajinder S. Deswal correctly as Randhir S. Deswal in Article entitled “Safety and Efficacy of Duloxetine Versus Venlafaxine in Major Depression in Indian Patients” published in JK Science 2006 ; 8(4) : 195-99