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Review

A new insight into the use of antihypertensives in glaucoma

Ashutosh Jani, Ramesh K Goyal and Anita A Mehta

Department of Pharmacology, L.M. College of Pharmacology, Ahmedabad. 380 009, India

SUMMARY

People with hypertension (high blood pressure) are at an increased risk of suffering from glaucoma, a condition in which the pressure within the eye increases. Its noted that several antihypertensive are found to be useful in lowering the intraocular pressure ,this review throws some light on the use of these antihypertensives as antiglaucoma drugs and about their probable mechanisms.

Key words: Antihypertensives; antiglaucoma drugs; ACEI; CCB

Measurement of intraocular pressure (IOP) has been the mainstay in the diagnosis and management of glaucoma for more than a century. However, in recent years importance of other factors like optic nerve damage, and disturbance in retrobulbular blood flow have also emerged. Various molecular mechanisms involved in these processes include apoptosis, increase in number of fibroblasts and extracellular matrix. Leighton *et al.* (1972) reported a correlation between degree of field loss in glaucoma and "Gradient" which takes into account the ophthalmic artery pressure and IOP. Dielmans *et al.* (1995) reported an association between systemic blood pressure and IOP. Accordingly there is a need to consider the treatment of glaucoma not only from the point of lowering IOP but also the prevention of optic nerve damage and correction of vascular dysregulation. This is a situation identical to the pharmacotherapy of hypertension wherein an ideal antihypertensive is the one that not only lowers the blood pressure but also prevents target organ damage like cardiomyopathy nephropathy etc. Coincidently, in recent years a number of antihypertensives have been shown to be useful in glaucoma. An antihypertensive drug is considered not only for its hemodynamic effects but also for metabotrophic effects i.e action on growth factors, apoptosis and cell proliferation.

Some patients with glaucomatous damage have an IOP within the normal range and in some cases of glaucoma reduction of IOP to normal values does not prevent the progression of the disease. This indicates that factors other than increased intraocular pressure also damage the neural tissue in glaucomatous optic neuropathy. The most prominent of these factors seems to be vascular dysregulation. Which may be of particular importance in normal pressure or low-tension glaucoma, which accounts for approximately one third of all glaucoma cases and in which IOP is normal.

Various studies suggest that impaired vascular responses like vasospasm, or altered systemic pressure

*Correspondence: Anita A Mehta, Department of Pharmacology, L. M. College of Pharmacology, Ahmedabad. 380 009, India. E-mail: dranitalmcp@rediffmail.com

like hypotension may reduce ocular blood supply (Flammer, 1996). This is supported by the observation that many of the glaucomatous patients have widespread cerebrovascular and cardiovascular disease (Drance, 1973; Goldberg, 1981) like migraine (Phelps *et al.*, 1985), Raynaud's-like peripheral circulation (Drance, 1987; Gasser *et al.*, 1991). Some patients of glaucoma are also reported to have an increase in both platelet adhesiveness and spontaneous platelet aggregation (Drance, 1973; Hoyng, 1992) and increase in plasma viscosity (Klaver, 1985).

Furthermore, an increased plasma level of endothelins has also been observed in some types of glaucoma (Kaiser, 1995; Sugiyama, 1995).

β Blockers

Topical β Blockers have been used for medical management of glaucoma for over past 15 - 20 years. They are potent hypotensive agents useful in all forms of glaucoma and are the first line agents in primary open angle glaucoma and ocular hypertension. However, a systemic side effect limits their use in the small proportion of glaucoma population.

Non-selective antagonists like timolol, levobunolol and carteolol or relatively β_1 selective betaxolol suppress aqueous humour secretion with minimal effect on outflow. They may gain access to the systemic circulation by adsorption through the conjunctiva, and mucosa of nasolacrimal system and nasal cavity. This may result in bradycardia, heart block and systemic hypotension. Topical nonselective beta- adrenergic blockers after systemic absorption may also decrease serum HDL and worsen the total cholesterol/HDL ratio. However, β Blockers with intrinsic sympathomimetic action appears to be lipid neutral (Stewart *et al.*, 1998).

Betaxolol, a β Blockers having affinity for L-type Ca^{+2} channels directly interacts with benzothiazepine binding sites and allosterically modulates the dihydropyridine binding site. Carteolol, propranolol and timolol were also reported to inhibit both specific [(3)H]diltiazem and [(3)H]nitrendipine binding to rat cortical membranes, but with less potency than betaxolol. Thus they may improve contrast sensitivity and prevent visual function loss through Ca^{+2} channel blockade which may be linked to ocular ischemia and thus reduces neuronal death as occurring in glaucoma (Melena *et al.*, 1999).

Vaninolol a selective β_1 adrenergic blocking agent, possesses an ocular hypotensive action. It improves the ocular blood flow in ciliary body and retina, but not in the iris and choroids. Further, it also improves the retinal functioning which appeared as a D-wave recovery in visual function testing carried out by Eleectroretinography and thus showing a therapeutic potential in ischemic retinopathy (Wu *et al.*, 1995).

Alpha and imidazole receptor agonists

Topical clonidine has a significant IOP lowering effect on an untreated fellow eye (Innemee *et al.*, 1979; Lee *et al.*, 1984). IOP lowering effect of clonidine appears to be due to decreased production of aqueous humour rather than an increase in aqueous humour outflow (Lee *et al.*, 1984). Further, clonidine also decreased the blood flow to the limbal blood vessels of the eye ball (Ralli, 1975), which would alter the episcleral venous pressure. Topical clonidine has been shown to prevent the IOP rise following Nd : YAG iridotomy. However, it causes serious decrease in pulse rate and blood pressure (Kitazawa *et al.*, 1989a).

Apraclonidine HCl and brimonidine are relatively more selective α_2 agonist they are not used as antihypertensives but decreases effectively the IOP (Abrams *et al.*, 1987) and have been recommended in glaucoma. The reason for their use in glaucoma is not just IOP lowering effect but they have been shown to produce miotic and neurotic effects. Brimonidine up regulates cellular and neuronal survival factors like bFGF, in response to the activation of α_2 receptors. It also alters the expression of bcl-2 and bcl-xl mRNA that inhibit apoptosis.

Moxonidine, a second generation centrally acting

Table 1. Mechanism of probable antiglaucoma drugs

Beta blockers	Supress the aqueous humor secretion and neuroprotection
Alpha agonist	Decrease formation/alter the episcleral venous pressure and neuroprotection
Ethacrynic acid	Increases the outflow facility by alteration in the cytoskeleton of out flow pathway of trabecular meshwork cells
Endothelins	Affect intracellular calcium and pH in meshwork cells and inhibit Na^+ K^+ ATPase pump
ANP	Activation of guanylate cyclase and increase in cyclic guanosine monophosphate (cGMP)
ACEI	Inhibit the formation of angiotension II, but also increase the level of bradykinin. Which activates the NO pathway, and reduced the formation of vasoconstrictor peptide, endothelin 1.
Calcium channel blocker	Calcium antagonist may also inhibit the synthesis of extracellular matrix collagen proteins.Also inhibit fibroblast attachment and proliferation and neuroprotection
Organic Nitrate	Relaxation of vascular smooth muscle, mediated by activation of soluble guanylate cyclase leading to an increase in intracellular cyclic guanosine monophosphate(cGMP) levels
Potassium channel opener	Affect the aqueous humor formation

antihypertensive drug that activates I_1 Imidazoline receptors in the rostoventrolateral medulla (RVLM) and lowers the IOP suggesting a possible benefit in glaucoma. Moxonidine, however, does not show neuroprotection (Ziegler *et al.*, 1995; Shan *et al.*, 1999).

Diuretics

Carbonic anhydrase (CA) inhibitors such as acetazolamide are among the most widely prescribed medications in the world today and rightly have a prominent place in glaucoma. Dorsolamide is the first carbonic anhydrase inhibitor to be used topically (Maren *et al.*, 1983).

Inhibitors of $Na^+/K^+/2Cl^-$

Kidney type Na bicarbonate (kNBC-1) and pancreatic type (pNBC-1) transporters are present in the corneal endothelium, trabecular meshwork, ciliary epithelium and lens epithelium. Proximal renal tubular acidosis associated with ocular abnormalities such as band keratopathy, glaucoma, and cataracts may be caused by mutations in the $Na+HCO_3^-$ Cotransporters (NBC-). However, the mechanism by which NBC-1 inactivation leads to such ocular abnormalities remains to be elucidated (Tomohiko *et al.*, 2001).

Neuman *et al.* (1992) reported occular hypotensive effect of loop diuretic ethacrynic acid in glaucomatous monkey eyes and patients. It has been shown to increase aqueous outflow when perfused into the anterior chamber of living monkey eyes and enucleated calf eye (Epstein *et al.*, 1987; Melamed *et al.*, 1992).

The mechanism of increased aqueous outflow with ethacrynic acid is uncertain, but appears to be related to alteration in the trabecular meshwork cells. Cultured cells from trabecular meshwork of human and bovine eyes showed reversible alteration in shape and in staining pattern of major cytoskeletal components including actin, alpha actin, vinculin and vimentin (Ericson *et al.*, 1992). In the same study, taxol which stabilized microtubules blocked the ethacrynic acid induced changes in the tubulin. Thus ethacrynic acid seems to increase the outflow facility by alteration in the cytoskeleton of outflow pathway of trabecular meshwork cells (Ericson *et al.*, 1992).

Spironolactone also produces significant IOP lowering in glaucoma patients, which can persist upto 2 weeks after termination of treatment.

Endothelins

The potent vasoconstrictor peptide endothelin-1 has been shown to participate in the control of peripheral vascular tone and in the regulation of ocular perfusion. The regulation of endothelin-1 release is disturbed in glaucoma patients (Kaiser *et al.*, 1995).

High concentration of ET-1 and ET-3 have been demonstrated in the iris and ciliary body of rabbit eyes (Mac Cumber *et al.*, 1991). When the ET-1 is injected intravitreally in rabbit eyes, there is a biphasic IOP response, with an initial rise followed by a reduction (Taniguchi *et al.* 1991). Endothelins increases the ANP level and also inhibits the Na+ K+ATPase.

Atrial natriuretic peptide (ANP)

ANP, a group of polypeptides synthesized by cardiac atrial myocytes have been shown to reduce IOP and aqueous flow in rabbits and monkeys, which may be mediated by activation of guanylate cyclase and an increase in cyclic guanosine monophosphate (cGMP) (Nathanson *et al.*, 1987).

Candoxatril, which increases endogenous ANP by inhibiting ANP metabolising enzyme neutral endopeptidase, has been shown to lower IOP significantly.

ACE inhibitors and angiotensin antagonist

Using reverse transcription polymerase chain reaction (RT-PCR) techniques, gene expression of components of the renin-angiotensin system has been demonstrated in the choroid and retina of human eyes, supporting the existence of intraocular synthesis of Angiotensin II. An activated renin-angiotensin system may, however, be involved in a number of diseases of the eye in which angiotensin II has been implicated as a possible mediator of optic nerve damage (Danser *et al.*, 1989).

Angiotensin II upregulates the expression of endothelin-1 messenger (m) RNA in cultured endothelial cells (Dzau, 1986; Lüscher, 1993). Inhibitors of ACE, therefore, not only inhibit the formation of Angiotensin II, but also increase the levels of bradykinin, which activates the nitric oxide pathway, and reduce the formation of the vasoconstrictor peptide, endothelin-1. Angiotensin II may also play a part in the regulation of aqueous outflow and therefore IOP since local application of ACE inhibitors lowers IOP (Constad *et al.*, 1988).

Angiotensin II is a growth factor for the heart and blood vessels (deGasparo *et al.*, 1995). Thus ACE Inhibitors can be helpful in preventing the vascularisation in the eye and could be useful in neovascular glaucoma in which there is neovascularisation over the different components of the eye specially the trabecular meshwork and thus impeding the aqueous humour outflow and leading to glaucoma.

Ischemia stimulates the synthesis and secretion of VEGF in retinal pericytes, endothelial cells, the retinal pigment epithelium, and possibly other cell types. Depending on the particular variant of mRNA splicing (Tischer *et al.*, 1991), secreted VEGF is either bound to cell-surface or basement-membrane proteoglycans containing heparin or is freely diffusible within the vitreous cavity (Houck *et al.*, 1992). Diffusible VEGF follows its concentration gradient from the vitreous to the anterior segment and is ultimately cleared through the trabecular meshwork. Neovascularization induced by the direct action of VEGF on endothelial cells can arise anywhere along this course, especially in areas of high exposure, such as the pupillary border and the trabecular meshwork. The angiogenic potential of VEGF is enhanced by the synergistic activity of fibroblast growth factor liberated by cellular disruption or death (Pepper *et al.*, 1992; Muthukrishnan *et al.*, 1991). The reduction in relative retinal ischemia as a result of reperfusion may reduce the production of VEGF and result in neovascular regression and quiescence.

Data from our lab also reveal the effectiveness of enalaprilat, ramiprilat and fosinopril in acute and chronic glaucoma models in rabbits (Shah *et al.*, 1999). Also losartan, an AT1 antagonist has been

reported to decrease IOP in rabbits (Costagolia *et al.*, 1999; Shah *et al.*, 2000).

Calcium channel blockers

Calcium flux could have several effects on aqueous humour dynamics, including a hydrostatic component caused by an effect on arterial blood pressure and ciliary body perfusion, and an osmotic component caused by an effect on the active secretion of sodium, calcium and other ions by ciliary epithelium (Brubaker, 1984). Calcium antagonists are potentially useful in the management of glaucoma (Netland *et al.*, 1995).

Verapamil was noted to have a minimal but consistent ocular hypotensive activity in normal subjects (Abelson *et al.*, 1988). One of the possible mechanism for ocular hypotensive effect of verapamil is local arterial and venous dilation. Verapamil inhibits the intracellular uptake of calcium by inactivating the inner phosphorylation-dependent calcium gate of the cellular membrane (Reaves *et al.*, 1983). The outflow of aqueous humour influenced by episcleral venous pressure may be directly affected by calcium inhibition (Brubaker, 1984).

Further Gap junctions, possibly regulated by calcium, exist between nonpigmented and pigmented ciliary epithelial cells, verapamil may interfere with these Gap junctions, altering cellular permeability of the ciliary epithelium and thus inhibiting normal aqueous humour formation (Green *et al.*, 1985).

Verapamil may also alter the cyclic adenosine monophosphate content in ciliary epithelium cells, thereby affecting intraocular pressure through a decrease in aqueous humour formation, or an increase in outflow facility (Sears *et al.*, 1984).

When verapamil was administered, the episodes of transient visual dimming ceased immediately. In addition, soon thereafter, visual acuity improved, the rubeosis partially regressed, and the hypotony reversed. This indicates that verapamil may be effective in treating cases of ocular ischemic syndrome, when vasospasm is a contributing cause (Winterkorn *et al.*, 1995).

Oral nifedipine was also found to have effect on ocular bloodflow and showed constant, sustained visual field improvement in patients with low-tension glaucoma (Kitazawa *et al.*, 1989). Results show that nifedipine does not increase optic nerve head blood flow during baseline conditions but reverses ET-1-induced constriction in ocular vasculature at doses that do not affect systemic hemodynamics. It also decreases the intraocular pressure in normal subjects (Kelly *et al.*, 1988). Moreover, the study provides a strong rationale for a study of low dose nifedipine as a supplementary medication in glaucoma patients (Geyer *et al.*, 1996).

Nilvadipine prevented progression of visual field defect in normal-tension glaucoma. Schnell (1975) found that a single 20 mg dose of nitrendipine sublingually caused an acute fall in IOP in glaucomatous patients. It reduces both IOP and systemic vascular resistance and increased choroidal perfusion in patients with essential hypertension and normal IOP (Lydtin *et al.*, 1976; Monica *et al.*, 1983).

Nicardine IV in monkeys caused an early decrease in optic nerve head blood flow followed by a slow rise to finally exceed the initial value (Harino *et al.*, 1992). A single dose of oral nimodipine in normal tension glaucoma patients and control subject was shown to improve contrast sensitivity (Kanellopoulos *et al.*, 1996). It is also possible that since lipophillic calcium channel blockers (CCB) (for example, nimodipine) more effectively penetrates the blood brain barrier they might posses greater bioactivity at the level of ocular arteries and arterioles. Indeed one study of nimodipine shows acute visual function effects in both patients and control subjects.

The topical administration of calcium ionophores A23187 and X573A has been shown to increase intraocular pressure (Podos, 1976). Calcium activates proteases, phospholipids and endonucleases etc. These degradative enzymes are activated in uncontrolled manner and may damage the cell ultimately leading to cell death (Trumpf *et al.*, 1995). Thus, calcium antagonist could prevent the cell

death and hence can be useful as neuroprotectants.

Calcium channel blockers following topical administration lower intraocular pressure and cause vasodilatation and reduce vascular resistance (Monica *et al.*, 1983; Abelson *et al.*, 1988). Variations in the content or function of collagen and other glycoproteins may alter the susceptibility to glaucoma injury (Tengroth *et al.*, 1985). For example, connective tissue is less dense at the upper and lower poles of the optic disk in precisely the areas that are most susceptible to glaucoma injury leading to hourglass-shaped atrophy (Quigley *et al.*, 1981; Dandona *et al.*, 1990). The optic-nerve head has been shown to contain many elastic fibers. Their appearance is dramatically altered in human eyes affected by glaucoma, suggesting a loss of elasticity as an effect of injury and possibly contributing to further damage (Hernandez *et al.*, 1990; Quigley *et al.*, 1991).

L-type (and T-type) calcium channels seem to have a role in cellular growth and proliferation in addition to their role in the acute changes in ion flux associated with changes in membrane potential. Several calcium antagonists, and possibly all, can inhibit the growth and proliferation of vascular smooth muscle and fibroblasts. The time and dose-related effects of five commonly used CCBs-verapamil, diltiazem, nicardipine, trifluoperazine, and dantrolene on human Tendon's fibroblast attachment and proliferation were studied. Fibroblasts were incubated with different concentrations of each drug. To evaluate the effect of each drug on fibroblast attachment, cell density was quantified by Coulter counter and hexosaminidase assays after 24 hours of incubation. All classes of calcium antagonists decrease the growth of vascular smooth-muscle cells in vitro and in animals, as measured by decreased uptake of uridine (RNA synthesis) and incorporation of leucine (protein synthesis) at drug concentrations associated with clinical effects (Andrawis *et al.*, 1992; Schmitt *et al.*, 1995). Calcium antagonists may also inhibit the synthesis of extracellular-matrix collagen proteins (Roth *et al.*, 1996).

Calcium channel blockers seem to inhibit fibroblast attachment and proliferation. Future clinical studies may show that these agents reduce collagen production, scar formation, and bleb failure following glaucoma filtration surgery (Kang *et al.*, 1997).

Organic nitrates

Organic nitrates such as intravenous nitroglycerine or oral isosorbide dinitrate have been reported to lower IOP in glaucoma and non-glaucoma patients (Hessemer *et al.*, 1997).

Nitric oxide is an important mediator of homeostatic processes in the eye, such as regulation of aqueous humor dynamics, retinal neurotransmission and phototransduction. Using immunohistochemical techniques, the presence of NOS containing neurons has been demonstrated in ocular tissues of rat, rabbit, and human origin (Yamamoto, 1993; Flügel, 1994). In the rat, NOS activity is localized in peripheral parasympathetic nerve fibers derived from the pterygopalatine ganglion and supplying mainly the choroid and limbal vessels as well as in a number of retinal cell types (Yamamoto, 1993). Studies using human eyes have also shown a wide distribution of NOS in the choroid (Flügel, 1994). Changes in its generation or actions could contribute to pathological states such as inflammatory diseases (uveitis, retinitis) or degenerative diseases (glaucoma, retinal degeneration).

After the administration of nitroglycerin, the end diastolic blood flow velocity was increased in the central retinal artery as well as the ophthalmic artery. Blood-flow velocity in the central retinal vein was also elevated (Gobel *et al.*, 1995).

A better understanding of the nitric oxide pathway will be the key to the development of new approaches to the management and treatment of various ocular diseases (Becquet *et al.*, 1997).

K^+ channel openers

Cromakalim significantly increases IOP during the initial period in normotensive and hypotensive

rabbits, by enhancing the formation of aqueous humor; but in the later time, reduced IOP in the chronic model possibly by relaxing the trabecular meshwork to reduce the outflow of aqueous humor (Chiang *et al.*, 1995). Nicorandil had a similar but less potent effect.

CONCLUSION

A new glaucoma therapeutic management paradigm, whereby clinical success is no longer simply measured by achieved level of intraocular pressure control but also by the long term preservation of visual function and patient quality of life is expected to dramatically change upon current concepts of ocular hypertension and glaucoma. Promising new focus on vision sparing and greater margins of safety and tolerability will provide improved treatment options and long term preservation of vision. Although monotherapy with effective ocular hypotensive agents may be sufficient for the preservation of visual function in many patients, a therapeutic 'cocktail' approach like antihypertensives must be tailored to each individual to best preserve visual function with available medicines will most likely represent the new paradigm for glaucoma management.

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