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A review of pharmacological therapy for glaucoma

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Abstract

Glaucoma is a chronic or acute disease in which optic nerve damage occurs in a characteristic way. In primary open angle glaucoma (POAG), the manifestations of the optic nerve damage include visible excavation that develops in the optic nerve head and regions of the retina lose ability to detect all the elements that go into the total sensory product called vision.[1, 2] When these regions worsen and enlarge to coalesce, the result is blindness.

The intraocular pressure (IOP) has a causative role in producing the damage. All eyes have an internal pressure to keep them inflated, perhaps 17 mmHg on the average, ± 5 mmHg standard deviation. In at least two thirds of the eyes that suffer glaucomatous damage, the intraocular pressure is high, at least a bit above the pressure found in 95% of the non-glaucomatous population. The cut-off is in the region of 20 to 22 mmHg used by most definitions.[2] However, a normal or even low intraocular pressure can be harmful to some eyes, and when it is, the person has normal or low tension glaucoma. The traditional treatment of glaucoma has logically been to lower the intraocular pressure, to prevent further damage to the optic nerve, though previous damage is not undone.

Key words: Glaucoma, intraocular pressure, optic nerve, visual field, anti-glaucoma medications

Introduction

The term glaucoma was first used by Aristotle when referring to blue-eyed patients with weakness of the eyes in daylight.[1] Al-Tabari is reported to be the first to associate the term glaucoma with an increased intraocular pressure.[2] In 1622, Banister discussed the detection of glaucoma using finger palpation to evaluate hardness of the eyeball.[2] Phenomenologically, glaucoma[1-4] is a syndrome of progressive optic neuropathy, characterized by optic nerve head excavation with consecutive defects in retinal sensitivity with visual field damage and other psychophysical alteration that is associated frequently but not invariably with raised IOP. Although the clinical picture of glaucoma is well described, the exact mechanism leading to this type of damage is not yet clear (Figure 1). The major risk factor in glaucoma is thought to be elevation of the IOP beyond the statistical norm of 21 mmHg. Glaucoma could perhaps be defined as a disorder of aqueous humour dynamics. There is evidence both from experimental studies and clinical observations that increased IOP alters structural and neural elements of the optic nerve head.[5, 6]

The purpose of this study is to review the pharmacological therapy for glaucoma and provide insight into pharmacologic mechanisms and the practical uses in the primary. If optometrists are to treat conditions such as POAG they will need to know the management and potential complications that they might encounter.

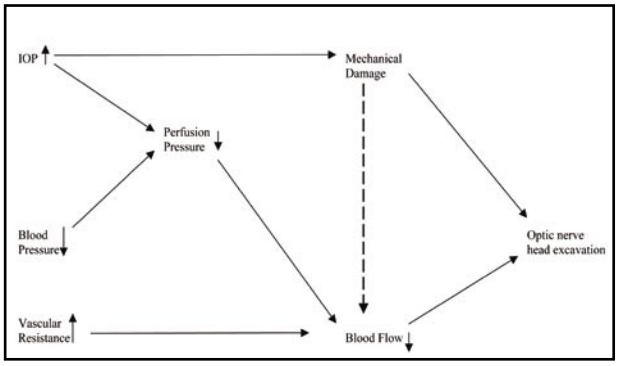

Figure 1: Concept for the possible pathogenesis of the glaucomatous damage. (Courtesy Prof AA Stulting)

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Physiology of IOP

IOP is the result of a homeostatic equilibrium between the formation and drainage of aqueous humour. Aqueous humour is produced by the ciliary body.[2, 3] There is passive ultra filtration in response to an osmotic gradient, hydrostatically influenced diffusion, and an active secretion by the non-pigmented layer of the ciliary body epithelium.[3] The cell membranes of the non-pigmented ciliary epithelial cells contain α- and β-adrenoceptors, carbonic anhydrase, and sodium and potassium activated ATPases.[2] By stimulation or inhibition of these enzymes or receptors, the active transport of aqueous humour across the blood-aqueous barrier can be modulated. Tight junctions between adjacent non-pigment epithelial cells constitute the blood-aqueous barrier.

The aqueous humour enters the posterior chamber via the ciliary processes. From there it flows through the pupil to the anterior chamber. From the anterior chamber, aqueous is either drained via the trabecular meshwork in the chamber angle, called the trabecular flow, or via the interstitial spaces between the ciliary muscle and iris root to the suprachoroidal spaces, called the uveoscleral flow.[3,8] In healthy individuals about 90% of aqueous leaves the eye via the trabecular (conventional) route.[3]

Receptors for the epinephrine, dopamine, prostanoids and biogenic amines are found at the endothelial cells of the trabecular meshwork and Schlemm's canal.[9] Stimulation of these receptors may result in facilitation of the flow through the trabecular meshwork of the Schlemm's canal and consequently lower IOP. The uveoscleral pathway is known to drain aqueous humour, pressure independently to the suprachoroidal spaces.[7] It is not clear whether an increase of the flow through the uveoscleral channels is due to remodeling of the extracellular matrix between the ciliary muscle or to relaxation of the ciliary muscle, thereby widening the spaces between muscle. Epinephrine and prostaglandins have an effect on uveoscleral flow leading to an increased drainage of aqueous humour[2] (Table 1).

Table 1: Site of action of the different classes of durgs used in the treatment of glaucoma.

Class of drug	Aqueous humour formation	Trabecular outflow	Uveoscleral outflow
Adrenergic agonist	Increases	Increases	Increases
α_2-adrenergic agonist	Decreases	No effect	Probably increases
β-blockers	Decreases	No effect	No effect
Carbonic anhydrase inhibitors	Decreases	No effect	No effect
Prostaglandins	No effect	Probably increases	Increases

Effects of elevated IOP

The mechanisms of glaucomatous damage are still not fully understood. But there is no doubt that increased IOP can lead to glaucomatous damage. Damage of the optic nerve head can be caused by increased IOP alone.[7] The capillary perfusion pressure at the optic nerve head is the net result of the pressure in the ophthalmic artery (70 mmHg) and the IOP.[10] When the IOP is raised or the pressure in the ophthalmic artery is lowered, the blood flow through the capillaries of the laminar and the prelaminar part of the optic nerve head will diminish.

Two theories have been put forward to explain how IOP damages the optic nerve head. The vascular theory hypothesizes that a high IOP may induce relative ischaemia in parts of the prelaminar region of the optic nerve head and result in retinal ganglion cell death and axon loss.[11-14] On the other hand, the mechanical theory[15-18] suggests compression of the axons at the optic nerve head and loss of supporting astroglia. Compression of the axons impedes axoplasm flow. Long-standing impaired axoplasm flow is thought to deprive ganglion cells of neutrophins which may lead to apoptosis of the retinal ganglion cells.[19-21] Both the mechanical and vascular theories suggest that for a certain individual, the IOP, elevated or not, is too high and compromises capillary blood flow, axonal flow or both at the optic nerve head.

The retinal nerve fibre layer (RNFL)

For many years, glaucoma was synonymous with visual field loss. It is evident now that RNFL defects precede the development of detectable optic disc and visual field changes.[22, 23] As retinal ganglion cells and their axons are lost in glaucoma, the nerve fibre layer thins. Thus glial cells, neurons and blood vessels all disappear. Thinning of the nerve fibre layer can be focal, diffuse or both. With focal thinning, a characteristic arcuate defect may be observed in a normal nerve fibre layer. With diffuse thinning, nerve fibre lay-

er striations are less visible and vessel margins are sharper. Conventional methods for observing the nerve fibre layer have utilized the ophthalmoscope (with a red-free filter) or high contrast, monochromatic, high resolution photographs.[3]

With a suitable nerve fibre layer photograph of a glaucomatous eye, one can recognize characteristic nerve fibre defects[24, 25] (subtle, thin, or darkened slit-like gaps). The appearance of focal defects conforms to topographic anatomy of nerve fibre layer. Diffuse nerve fibre layer defects are more difficult to observe and sometimes may only be recognized when blood vessel margins are sharp in comparison with the contralateral eye.[23] But the nerve fibre layer photography is not used widely in clinical practice because[23]:

- The RNFL is poorly observed in eyes with miotic pupils.
- Nerve fibre layer is poorly visualized in an eye with a lightly pigmented fundus, which is highly reflective.
- Nerve fibre layer is poorly visualized in the presence of a cataract.
- If the images are not obtained by an experienced photographer and developed correctly, the nerve fibre layer cannot be well visualized.
- If there is a considerable nerve fibre layer loss, it is difficult to detect changes in the nerve fibre layer.

Despite these limitations, the examination of the nerve fibre layer is quite helpful in glaucoma screening or management.

Several conventional optical instruments have been touted as being useful for diagnosing and managing glaucoma but they have not met the expectations of clinicians, and have not been adopted widely for use. During the past decade, several new instruments based on more advanced imaging technology have become available.[26-28] The confocal scanning laser ophthalmoscope (CSLO), allows layer by layer imaging of the optic nerve head and peripapillary retina.[26] This method appears useful for recognizing either local or diffuse defects. Another method for assessing the nerve fibre layer utilizes an instrument known as a scanning laser polarimeter (SLO) to measure nerve fibre layer thickness.[27] Optical coherence tomography (OCT) is a newer technology for obtaining high-resolution cross-sectional images of the retina. It is even useful in the diagnosis and staging of macular holes.[28]

Visual fields

Static threshold perimetry involves evaluation of the visual field. Although it is an essential part of the diagnostic evaluation for glaucoma, visual field testing is time-consuming, and the detection of glaucomatous visual field changes can be elusive. Sturmer[29] has shown that a relative scotoma or early visual field loss in glaucoma does not always consist of a sharply bordered area with a definite loss of sensitivity, but instead can be a region of increased scatter with poorly definable borders due to instability of threshold. In other instances, diffuse rather than localized areas of sensitivity losses are seen.

Frequency doubling perimetry is a simple and rapid test which shows considerable promise.[3] It is based on the frequency doubling illusion which is produced when a low spatial frequency sinusoidal grating undergoes high temporal frequency counter phase flicker. The rapid alterations in which the light bars become darker and vice versa, produces the illusion of the grating having doubled its frequency. Short-wave automated perimetry (SWAP) is another method that reflects the function of parvocellular cells by displaying a blue stimulus on yellow background.[30] It increases the detection of early visual field losses before they would be seen on standard white-on-white perimetry.

The autonomic nervous system

The autonomic nervous system of the efferent division is divided into the parasympathetic nervous system and the sympathetic nervous system.[22] The eye is an organ with multiple autonomic nervous system functions, controlled by several different autonomic receptors.[31] The anterior chamber is the site of several tissues controlled by the autonomic nervous system. These tissues include three different muscles (pupillary dilator and constrictor muscles in the iris and the ciliary muscle) and the secretory epithelium of the ciliary body.[31]

Treatment modalities

Since the elevated IOP is the main risk factor in glaucoma, therefore, the treatment of glaucoma is primarily directed towards lowering IOP. This medical treatment, laser therapy or by surgery.[3, 32-34] Initially, patients with glaucoma are treated with ocular hypotensive agents. If the IOP is not sufficiently lowered or the disease progresses, as estimated by decay of the visual fields or increasing excavation at the optic disc, argon laser trabeculoplasty of the anterior chamber angle around the scleral spur and the trabecular meshwork should be performed.[33, 34] If, despite these treatment strategies, the glaucomatous process is not halted or the decay of the visual fields is large compared with the basal visual fields, then surgical intervention mostly by trabeculectomy should be performed.[34] The arrival of the new ocular hypotensive drugs means that the decision for ocular surgery may be delayed because these drugs can provide patients with glaucoma with target pressure equal to those obtained after surgery.

Ocular hypotensive agents are the mainstay of glaucoma treatment. Most of the ocular hypotensive agents are given topically, although few are administered systematically.[35] Topically applied ocular hypotensive agents reach lower blood concentration than systematically administered, and consequently, topically applied drugs induce fewer systematic adverse effects.[36] In addition, higher intraocular concentrations are achieved when the drug is applied topically. Treatment should be started with topical β-blockers as monotherapy provided the patient has no cardiac or pulmonary disease (Table 2). If the target pressure is not reached after one month of treatment or if unacceptable adverse effects occur, β-blockers should be stopped and another monotherapy should be initiated, topical carbonic anhydrase inhibitors, prostaglandins, α_2-adrenergic agonists or dipivalyl epinephrine.[7]

The target IOP to attain would be the highest baseline IOP converted to a percentage, then the baseline IOP is reduced by this amount.[5] Say, the baseline IOP is 35 mmHg, (35)(0.35) = 12.25. The baseline IOP 35 mmHg minus 12.25 is 22.75 mmHg. This is the target IOP to attain.

Parasympathomimetics

Parasympathomimetics[37] also known as cholinomimetics are direct-acting cholinergic agonist (miotics). Parasympathomimetics can act either directly or indirectly on the muscarinic receptors in the eye. Indirectly, parasympathomimetics in-

Table 2: Class, generic and brand names, concentration in percentage (%) and cap or tablet colour of commonly used antiglaucoma medications. The concentration for oral medications is in milligrams (mg).

Class	Generic name	Brand or trade name	Concentration	Cap colour
β-Blockers	Timolol	Timoptic	0.25	Light blue
	Timolol	Timoptic	0.50	Yellow
	Levubunolol	Betagan	0.25	Light blue
	Levubunolol	Betagan	0.50	Yellow
	Betaxolol	Betoptic-S	0.25	Light blue
	Betaxolol	Betoptic	0.50	Dark blue
	Carteolol	Ocupress	1.00	White
Miotics	Carbachol	Isoptocarbachol	0.75	Green
	Carbachol	Isoptocarbachol	3.00	Green
	Pilocarpine	Isopto Carpine	0.50	Green
	Pilocarpine	Isopto Carpine	2.00	Green
	Pilocarpine	Isopto Carpine	4.00	Green
Sympathomimetics	Apraclonidine	Iodipine	0.50	White
	Dipivefrine	Propine	0.10	Purple
Carbonic anhydrase inhibitors	Acetazolamide	Diamox	250 mg	White tablets
	Acetazolamide	Diamox	500 mg	White tablets
	Dorzolamide	Trusopt	2.00	Orange
Prostaglandins	Latanoprost	Xalatan	0.005	Yellow

hibit the enzyme cholinesterase responsible for the degradation of acetylcholine. Pilocarpine is the main representative of the miotics, so named for their constructive effect on the pupil. It also constricts the ciliary muscle which leads to the traction at the scleral spur, and this in turn reduces the outflow resistance of aqueous humour through the trabecular meshwork and Schlemm's canal.[38] The ocular adverse effects of pilocarpine are mainly caused by its effect on the ciliary and sphincter muscle. Initially many patients, especially young patients, complain of blurred vision.[7, 38] This is the result of the ciliary spasm which induces accommodation, causing myopia. Other ocular adverse effects include conjunctival hyperemia, lens opacities and retinal detachment.[38] Carbachol directly stimulates the muscarinic receptor site and also exerts an indirect effect by inhibiting cholinesterase.[39] Carbachol is not currently used in glaucoma therapy because the ocular adverse effects are more serious than those seen with pilocarpine.[39] A low grade anterior uveitis may be observed during therapy.[7, 39]

Sympathomimetics

Sympathomimetics, also known as adrenergic agonists, mimic the action of norepinephrine.[37] They compete with norepinephrine to directly activate the receptors of the effector organ. The sympathomimetics lower IOP both by inhibiting aqueous humour production and by improving the outflow of the aqueous humour production through the ocular drainage network (the trabecular meshwork and Schlemm's canal).[37] Epinephrine (adrenalin) is the main representative, stimulating α_1- and α_2-adrenoceptors, as well as β_2-adrenoceptors in the eye.[31] The reduction of IOP is primarily due to an increase in flow through the trabecular meshwork[40] and the uveoscleral pathway.[41] Because of its occasional dilatation of the pupil via its α1-adrenoceptor properties, the drug should not be used in patients with narrow chamber angles but only in patients with proven open angles. Both apraclonide (iopidine)[42, 43] and brimonidine (alphagan)[44, 45] tend to lower IOP by the reduction of aqueous humour production. Brimonidine appears to also enhance the uveoscleral outflow.[45] The main indications for the treatment with apraclonide are post-laser and post-surgical pressure elevation. It reduces or prevents the spikes of the IOP after laser trabeculoplasty, iridotomy[46] after phacoemulsification with implantation of an intraocular lens[47] and after ND: YAG (neodymium: yttrium-aluminium-garnet) laser capsulotomies.[48]

Local adverse effects of apraclonide include eye lid dermatitis, blepharoconjunctivitis and follicular conjunctivitis.[3, 42-46] After instillation of apraclonide, conjunctival blanching, mydriasis and eyelid retraction may occur, probably via α_1-adrenoceptor stimulation. Since brimonidine is far more selective for the α_2-receptors than for the α1-receptors, α_1-adrenergic induced effects such as mydriasis, eyelid retraction or conjunctival vasoconstriction are less.[9, 45]

Sympatholytics

Sympatholytics, also known as adrenergic antagonists or β-blockers are the mainstay and first-line therapy for most glaucoma patients (Table 2). The typical β-blocker tends to exert its primary ocular hypotensive action through inhibition of aqueous humour formation while leaving the aqueous humour outflow unchanged. Timolol is a non-selective β-blocker. It reduces IOP by inhibiting aqueous humour formation[49], not by increasing outflow facility.[50] Timolol may cause bradycardia, arrhythemia, congested heart failure and bronchospasm or asthma.[51-53] All systemic adverse effects of timolol are caused by the immediate uptake of timolol in the blood via the epithelium of the nasopharynx.[52] Betaxolol is a β_1-selective adrenoceptor antagonist. It exerts its effect on IOP by inhibiting aqueous humour flow.[54] Since the ciliary body contains hardly any β_1-adrenoceptor, betaxolol lowers IOP by its weaker β_2-blocking properties. This effect may be due to its calcium antagonistic effect. It has a better effect on preservation of visual field than timolol.[55, 56] The most frequent ocular adverse effect of betaxolol is a short period of burning and stinging after topical application.[3] Levobunol is a non-selective β_1- and β_2-blocking agent.[31, 35] Its ocular hypotensive effect and adverse effect are similar to timolol.[57, 58] Carteolol is a non-selective β-blocker. It lowers IOP by reducing aqueous humour formation.[59]

Carbonic Anhydrase Inhibitors (CAIS)

When the IOP has to be lowered rapidly, as in angle closure glaucoma, the carbonic anhydrase inhibitors are the drugs of choice.[37] In the ciliary process the enzyme carbonic anhydrase catalyses the conversion of water and carbon dioxide to $HCO_3$and H^+. Inhibition of carbonic anhydrase results in a decrease of aqueous humour production.[60, 61] Dorzolamide is an inhibitor of human carbonic anhydrase isoenzyme II and also a weak inhibitor of isoenzyme IV. It reduces the IOP by inhibiting the formation of aqueous humour.[62] Other drugs used to lower IOP in this group are acetazolamide, brinzolamide and dichlorphenamide. Oral CAIs have hardly any ocular effects.[3, 9]

Prostagladins

Prostagladins are mediators of the inflammatory response.[63] In high doses they induce ocular adverse effects leading to an elevation of IOP. However, in low doses it was shown that they lower IOP.[64] The main mechanism of action of the prostaglandins is to reduce IOP by increasing the uveoscleral outflow of the aqueous humour.[65] Topical ocular prostaglandins is Latanoprost (Xalatan). Xalatan has no effect on trabecular outflow or on aqueous humour production.[65-67] Xalacom is another prostaglandin indicated for the reduction of IOP in patients who are not controlled on, or are intolerant to, monotherapy with compounds other than xalatan or timolol.[68] Mild stinging, conjunctival hyperemia, burning, tearing were reported after one year of treatment with latanoprost.[66]

Combining antiglaucoma drugs

When the IOP is not adequately regulated with monotherapy, it is common practice to combine anti-glaucoma medications. Insufficient effect on IOP during monotherapy may be caused by initial insufficient effect of drug, by the development of tolerance during long-term therapy, or by progress of the disease. Drug combinations that act on different receptor sites or enzymes, and have a different mode of action are preferred (Table 3). β-blockers, which lower aqueous humour production can be combined with miotics, which enhance aqueous trabecular outflow.[69, 70] The combination of timolol with epinephrine do not result in IOP reduction since both are partly counteracting.[61] Combining β_1-selective betaxolol with epinephrine or dipivefrin results in a significant IOP reduction due to an increase of the conventional outflow facility.[71, 72]

Surgical and laser therapy

Failure of medical therapy to prevent further optic disc and visual field changes necessitates re-evaluation and possibly laser or surgical intervention. Argon laser therapy (ALT) has been used to lower IOP in patients uncontrolled with maximum tolerated medical therapy.[73-75] Diode laser trabeculoplasty gives similar results to ALT with less disruption of blood-aqueous barrier. Goniotomy has been considered the safest and most effective treatment for control of infantile glaucoma.[76] Nd: YAG laser iridotomy is successful at lowering IOP in a limited number of patients with juvenile open-angle glaucoma.[76] Although not often used, this form of treatment might be considered before invasive goniotomy procedure.[76] Diode laser cycloablation lowers IOP by destroying part of the secretory ciliary epithelium,

Table 3: Combinations of antiglaucoma drugs that have an additive effect over the use of each agent alone.

Class	β- blockers	Miotics	Adrenergic agonist	α^2-adrenergic agonist	Prosta-glandins
Miotics	Additive effect	-	-	-	-
Adrenergic agonist	Small effect	Additive effect	-	-	-
α^2-adrenergic agonist	Additive effect	Unknown	Unknown	-	-
Prostaglandins	Additive effect	Additive effect	Additive effect	Unknown	-
Carbonic anhydrase inhibators	Additive effect	Additive effect	Additive effect	Unknown	Unknown

thereby reducing aqueous secretion.[3, 76] Trabeculectomy is the surgical procedure that lowers IOP by creating a fistula, which allows aqueous outflow from the anterior chamber to the sub-Tenon space.[3, 76]

Conclusion

Prior to initiating medication for glaucoma therapy, a target IOP should be determined. The primary therapy of choice is monotherapy with a β-blocker, provided that drug is not contraindicated as in patients with concomitant cardiac or pulmonary diseases. If monotherapy with β-blocker does not induce a useful target pressure, a change to monotherapy with topical prostaglandin, carbonic anhydrase inhibitor, miotics or α-adrenergic agonist should be instituted. If monotherapy with several agents do not lower IOP to target pressure or when visual fields deteriorate, combination treatment is needed. If all else fails, laser and/ or surgical procedures can be utilized.

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