REVIEW ARTICLE

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Pharmacological Therapy for Glaucoma
A Review

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Contents

Abstract

For some time the medical treatment of glaucoma has consisted of topical β-blockers, adrenergic agents, miotics and oral carbonic anhydrase inhibitors (CAIs). However, the therapeutic arsenal available for the medical treatment of glaucoma has recently extended with new classes of ocular hypotensive agents

i.e. prostaglandins, local CAIs and α_2-adrenergic agents. β-Blockers are still the mainstay in glaucoma treatment and are first line drugs. However, even if they are applied once daily, as with timolol in gel forming solution and levobunolol, the possible cardiopulmonary adverse effects of β-blockers remain a cause for concern.

When monotherapy with β-blockers is ineffective in reducing intraocular pressure (IOP) or is hampered by adverse effects, a change of monotherapy to prostaglandins, local CAIs, α_2-adrenergic agonists (brimonidine) or to dipivalyl epinephrine is advised.

Prostaglandins, local CAIs and α_2-adrenergic agonists, such as brimonidine, may in time become first line drugs because they reduce IOP effectively and until now systemic adverse effects have rarely been reported with these agents. The development of a pro-drug of either a local CAI or an α_2-adrenergic agonist with a sustained and continuous effect on IOP level, which could be applied once a day is suggested.

Because of these new developments, miotics, i.e. pilocarpine and carbachol, are recommended as second or third line drugs. The cholinesterase inhibitors are considered third line drugs as better agents with fewer local and systemic adverse effects have become available.

Oral CAIs may be used temporarily in patients with elevated IOPs e.g. post-surgery or post-laser, or continuously in patients with glaucoma resistant to other treatment.

Combining ocular hypotensive drugs is indicated when the target pressure for an individual patient cannot be reached with monotherapy. Combination therapy of β-blockers is additive with prostaglandins, topical CAIs and miotics. Prostaglandins such as latanoprost can be combined with β-blockers, adrenergic agents, local CAIs and miotics. Combinations with brimonidine or local CAIs need further investigation.

Treatment of glaucoma with the new ocular hypotensive agents, either in monotherapy or combination therapy, may provide lower IOPs and delay or postpone the need for surgery.

1. Definitions and Epidemiology

Glaucoma is a chronic progressive optic neuropathy characterised by excavation of the optic nerve head and visual field loss in the mid-periphery. Retinal ganglion cell death and consequent axon loss in the retinal nerve fibre layer result in cupping of the optic disc and visual field defects typical for glaucoma. The major risk factor in glaucoma is thought to be elevation of the intraocular pressure (IOP) beyond the statistical norm, i.e. 21mm Hg. The high IOP originates from an increased resistance to drainage of aqueous humour through the trabecular meshwork.[1-5]

Although different forms of glaucoma are known, the most common is adult onset open chamber angle glaucoma (OAG), which is age related[6] and characterised by an open angle, IOPs over 21mm Hg, a visual field defect typical for glaucoma and a pathologically excavated optic disc.

The estimated prevalence of OAG in the US, in the population over 30 years of age, is 1.3% in Caucasians and 3.5% in Blacks.[6] Worldwide, glaucoma accounts for approximately 15% of blindness,[7] and it is thought that by the year 2000 approximately 6.7 million people will have bilateral blindness secondary to glaucoma.[8] It should be noted that it is estimated that at any one time only one-half of patients with glaucoma are detected, leaving one-half of patients undetected and hence untreated.

Many patients with glaucoma have normal pres-

sure glaucoma (NPG) with similar pathologic characteristics to OAG, but without IOPs >21mm Hg. Relative to all open angle glaucomas, the prevalence of NPG is between 30 to 52% in Western countries[9] and up to 66% in Japan.[10]

Another group is patients with acute and chronic narrow angle glaucomas having a narrow or closed chamber angle instead of an open angle as in OAG. The main characteristic of the narrow angle glaucomas is a relative pupillary block with a forward bulging of the iris base thereby obstructing the aqueous humour flow at the chamber angle. The frequency among Caucasians is reported to be one-fifth of that of OAG.[11] A high incidence of angle closure glaucoma is found among Eskimos, affecting 2.65% of the population over 40 years of age.[12]

Patients with ocular hypertension have elevated IOPs and an open angle, but normal visual fields and normal optic discs.[13,14] They are also referred to as glaucoma suspects depending on additional risk factors.[15] The prevalence of ocular hypertension is approximately 10 times that of OAG.[16,17]

A special group are patients with secondary glaucomas wherein the IOP is elevated as a consequence of other pathological conditions such as uveitis, other forms of ocular inflammation, tumours, trauma, or following ocular surgery. The estimated prevalence of secondary glaucomas is one-fifth of OAG in Caucasians.[6]

2. Physiology of Intraocular Pressure (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. There is passive ultrafiltration in response to an osmotic gradient, hydrostatically influenced diffusion, and an active secretion by the nonpigmented layer of the ciliary body epithelium. The cell membranes of the nonpigmented ciliary epithelial cells contain α- and β-adrenoceptors, carbonic anhydrase, and sodium and potassium activated ATPases.[18] By stimulation or inhibition of these enzymes or receptors, the active transport of aqueous humour across the blood-aqueous barrier can be modulated.

The aqueous enters the posterior chamber via the ciliary processes, from there it flows through the pupil to the anterior chamber (fig. 1). From the anterior chamber, aqueous is either drained via the trabecular meshwork in the chamber angle, trabecular flow, or via the interstitial spaces between the ciliary muscle and iris root to the suprachoroidal spaces, uveoscleral flow.[20,21] In healthy individuals about 80% of the aqueous leaves the eye via the trabecular meshwork, while the remaining 20% is accounted for by the uveoscleral route.[22] Receptors for epinephrine, dopamine, prostanoids and biogenic amines are found at the endothelial cells of the trabecular meshwork and Schlemm's canal.[23,24] Stimulation of these receptors may result in facilitation of the flow through the trabecular meshwork to Schlemm's canal and consequently lower IOP.

The uveosceral pathway is known to drain aqueous humour, pressure independently,[24] to the suprachoroidal spaces and emisarial routes. It is not yet clear whether an increase of flow through the uveosceral channels is due to remodelling of extracellular matrix between the ciliary muscle cells or to relaxation of the ciliary muscle, thereby widening the spaces between muscle cells. Epinephrine[25] and prostaglandins[26] have an effect on

Table I. Site of action of the different classes of drugs used in the treatment of glaucoma

Class	Aqueous humour production	Trabecular outflow	Uveoscleral outflow
Adrenergic agonists	↑↓ (?)	↑	↑
α2-Adrenergic agonists	↓	–	↑ (?)
β-Blockers	↓	–	–
Carbonic anhydrase inhibitors	↓	–	–
Miotics	–	↑	–
Prostaglandins	–	↑ (?)	↑

↑ indicates agents increases this effect; ↓ indicates agents decreases this effect; **?** indicates probable effect; **–** indicates no effect

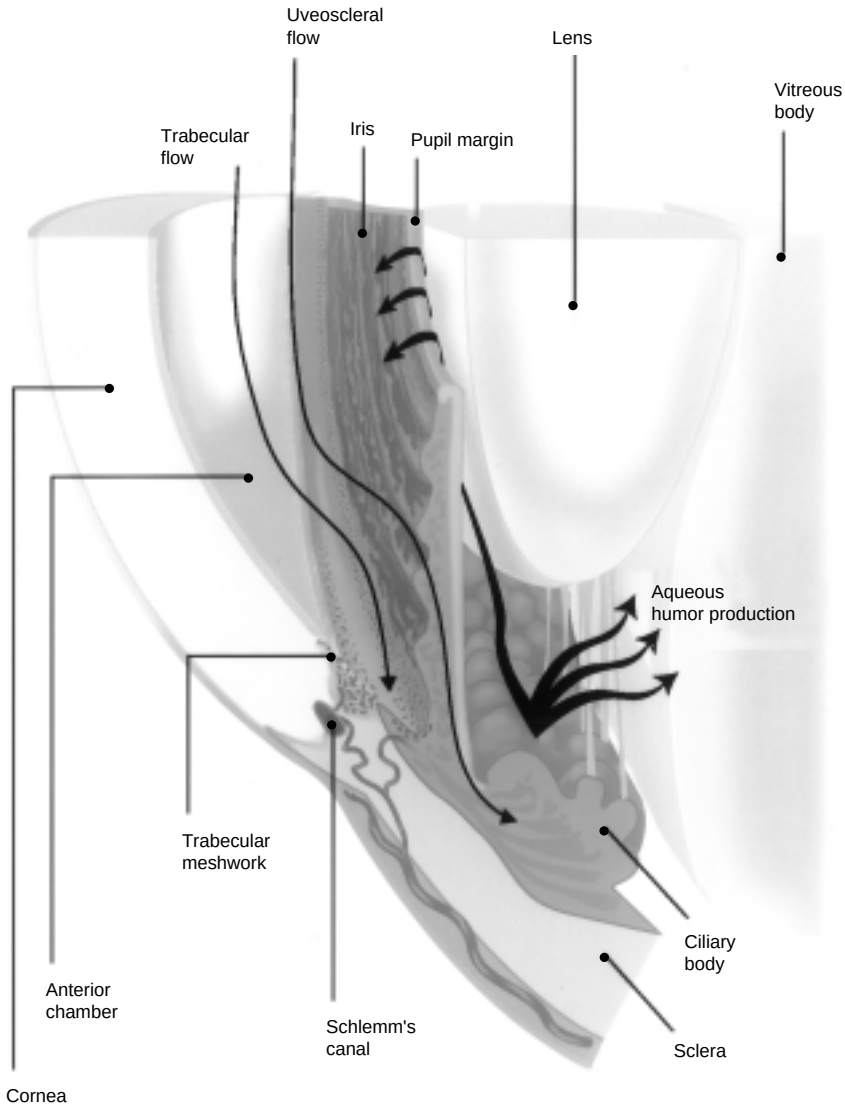

Fig. 1. Vertical section through the anterior segment of the eye. Indicated are trabecular and uveoscleral outflow pathways and production of aqueous humour in the ciliary body (reproduced from Hoyng and Rasker,[19] with permission).

uveoscleral flow leading to an increased drainage of aqueous humour (table I).

3. Effects of Elevated IOP

The elevated IOP is the main risk factor in glaucoma. The capillary perfusion pressure at the optic nerve head is the net result of the pressure in the ophthalmic artery (70mm Hg) and the IOP. When the IOP is raised or the pressure in the ophthalmic artery is lowered, the blood flow through the capillaries of the laminar and prelaminar part of the optic nerve head will diminish.

Two theories have been put forward to explain how the IOP damages the optic nerve head. The vascular theory hypothesises 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.[27-32] On the other hand the mechanical theory[33-35] 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 neurotrophins which may lead to apoptosis of the retinal ganglion cells. In common, both the mechanical and vascular theory suggest that for a certain patient, the IOP, elevated or not, is too high and compromises capillary blood flow, axonal flow or both at the optic nerve head. Although there is substantial evidence to support a relationship between the level of IOP and the development or progression of visual field defects,[36-38] other studies have shown progressive field loss in OAG in the absence of this relationship.[39,40] This may suggest a controversial role for IOP in the pathophysiology of glaucoma. However, in patients with visual field loss at normal or slightly supranormal IOP levels, a substantial lowering of IOP may slow down the decay of the visual field. Therefore, current glaucoma therapy is primarily directed towards lowering the IOP. A target pressure for each individual patient is chosen and visual field loss is expected to be halted at this target pressure.[41] From this it is clear that patients with glaucoma are not well controlled if the IOP during treatment is around 21mm Hg, as it was 2 decades ago.

4. Treatment Modalities

As mentioned in section 3, the treatment of glaucoma is primarily directed towards lowering IOP. This can be brought about by conservative medical treatment, laser therapy, or by surgery.

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 visual fields or increasing excavation of the optic disc, Argon laser trabeculoplasty (ALT) of the chamber angle around the scleral spur and trabecular meshwork is performed.[42,43] If, despite these treatment strategies, the glaucomatous process is not halted or the decay in visual fields is large compared with basal visual fields, then surgical intervention mostly by trabeculectomy, a filtering procedure with or without the use of antimetabolites, is performed.

Although certain authors advocate early surgical intervention[9] to control the glaucomatous process, this is not appropriate for everyday management of the patients with glaucoma. Surgery may provide patients with a safe target pressure which may lead to optimal preservation of visual fields, but it also requires surgical aftercare and may result in complications. The recent arrival of new, powerful ocular hypotensive drugs means that the decision for ocular surgery may be delayed because these drugs can sometimes provide patients with glaucoma with target pressures equal to those obtained after surgery. In addition, a substantial number of patients being operated on will eventually need additional ocular hypotensive agents because target pressure is not reached or maintained.

The treatment of patients with acute glaucoma or chronic narrow angle glaucoma with intermittent episodes of raised IOP, is primarily directed toward relieving the pupillary block and thus providing an unobstructed route for the aqueous to reach the chamber angle. Miotics can sometimes provide short term relief, but acute or recurrent episodes of angle closure can only be prevented by performing a peripheral iridotomy either by Argon laser, YAG laser or by surgery.[44]

4.1 Ocular Hypotensive Agents

Ocular hypotensive agents are the mainstay of glaucoma treatment (table II). Once the decision is made to treat a patient, it generally implies lifelong treatment. Most of the ocular hypotensive agents are given topically, although a few drugs are administered systemically. Topically applied ocular hypotensive agents reach lower blood concentrations than systemically administered ocular hypotensive agents, and consequently, topically applied drugs induce fewer systemic adverse effects. In

Table II. Brand and generic names of commonly used antiglaucoma medication

Class	Generic name	Brand name
β-Blockers	Timolol	Timoptic®, Timopol™, Loptomit™
	Timolol hemihydrate	Betimol®
	Levobunolol	Betagan®
	Betaxolol	Betoptic®
	Carteolol	Ocupress®, Teoptic®
	Metipranolol	OptiPranolol®, Beta-ophtiole®
Carbonic anhydrase inhibitors	Acetazolamide	Diamox®
	Methazolamide	Neptazane®
	Dorzolamide	Trusopt®
	Brinzolamide	Azopt®
Miotics	Carbachol	Isopto Carbachol®
	Pilocarpine	Isopto Carpine®
Prostaglandins	Latanoprost	Xalatan®
	Isopropyl unoprostone	
Sympathomimetics	Brimonidine	Alphagan®
	Apraclonidine	Iodipine®
	Epinephrine	Epifrin®
	Dipivefrine	Propine®, Diopine®

addition, higher intraocular concentrations are achieved when the drug is applied topically.

Once a topical formulation has been applied, it has to penetrate the cornea. The corneal epithelium and endothelium are lipid permeable, while the corneal stroma is water permeable. Therefore, an ocular drug should possess both water and lipid soluble properties. In addition, the pH of the topical formulation influences the penetration of compounds through the epithelium. Weak bases, weak acids or neutral pH are preferable since non-ionised compounds are more lipid permeable.

The vehicles used also determines the amount of drug that penetrates the cornea. For instance, the addition of hydroxypropylmethylcellulose or polyvinyl alcohol to topical formulations prolongs the contact time of the drug to the cornea. This results in a better penetration, allowing for a reduction of concentration or a less frequent administration of the eye drop, and thus improving the adverse effect profile. Other vehicles inducing a prolonged cornea contact time are soluble gels, suspensions and emulsions. Finally, compounds can be released from an ocular insert device which is placed in the conjunctival fornices. Usually, ocular inserts consist of 2 polymeric membranes, from which the drug slowly diffuses and exerts its effect over a period of one week.

Currently used ocular hypotensive agents consist of sympathomimetics, parasympathomimetics, sympatholytics, carbonic anhydrase inhibitors (CAIs) and prostaglandins.

The aim of medical treatment is to obtain a target pressure at which progression of visual field defects is halted. In our view, treatment should be started with topical β-blockers as monotherapy provided the patient has no cardiac or pulmonary disease. If the target pressure is not reached after 1 month of treatment or if unacceptable adverse effects occur, β-blockers should be stopped and another monotherapy initiated. Indicated drugs at this time are topical CAIs, prostaglandins, α_2-adrenergic agonists or dipivalyl epinephrine (DPE).

If treatment with one of these alternative agents also fails to induce or maintain target pressure or if there is progression of visual field defects, then combination therapy is needed. If despite combination therapy the progression of visual field defects continues or if target pressure cannot be maintained then ALT or ocular surgery is indicated.

5. Agents for Monotherapy

5.1 Parasympathomimetics

Parasympathomimetics or cholinergic agents, were introduced in 1877 by von Weber[45] and were

the first class of ocular hypotensive compounds used to treat glaucoma. Parasympathomimetics can act either directly or indirectly on the muscarinic receptors in the eye. Indirect parasympathomimetics inhibit the enzyme cholinesterase responsible for the degradation of acetylcholine.

5.1.1 Pilocarpine

Pilocarpine, an alkaloid, is the main representative of the miotics, so named for their constrictive effect on the pupil. Pilocarpine contracts also the ciliary muscle which leads to traction at the scleral spur, and this in turn reduces the outflow resistance of aqueous humour through the trabecular meshwork and Schlemm's canal. Disinsertion of the scleral spur inhibited the increase in outflow facility in monkeys after pilocarpine.[46,47] Furthermore, in monkeys but not in humans, pilocarpine has been shown to reduce flow through the uveoscleral channels.[20,48] Pilocarpine has hardly any effect on aqueous humour production.[20]

Pilocarpine is available in concentrations of 1, 2, 4, 6 and 8%, and since the effect of pilocarpine lasts about 6 hours, it has to be applied 4 times daily. To lower the application frequency, pilocarpine is also available in hydroxypropylmethylcellulose with 3 times daily application, in gel form for a once daily application and in an ocular delivery device which has to be replaced every week.

Pilocarpine reduces IOP by about 20 to 30%.[49] Maximal effect is reported with the 4% concentration[50] but may not be achieved in heavily pigmented eyes.

Adverse Effects

The ocular adverse effects of pilocarpine are mainly caused by its effect on the ciliary and sphincter muscle. Initially many patients, especially younger patients, complain of blurred vision. This is the result of the ciliary spasm which induces accommodation, causing myopia by forward displacement and thickening of the lens.[51,52] Ciliary spasm may also give rise to browache. Sphincter contraction results in miosis and accounts for dark vision. Other ocular adverse effects include conjunctival hyperaemia, lens opacities[53] and retinal detachments. Patients with especially bad myopia (≥ –6 diopters) are at risk for retinal detachments.[54,55] For this reason, strong miotics should be avoided in these patients.

Systemic adverse effects are more often observed when using higher concentrations of pilocarpine. These adverse effects include vomiting, nausea, diarrhoea, tachycardia, bronchospasm and sweating.

Recent advances in topical ocular therapy have placed pilocarpine as a third line drug. This is because of the frequency of application required and the ocular adverse effects.

5.1.2 Carbachol

Carbachol directly stimulates the muscarinic receptor site and also exerts an indirect effect by inhibiting cholinesterase.[56] Carbachol needs benzalkoniumchloride to promote penetration through the cornea to achieve effective concentrations in the anterior segment of the eye. The concentrations used are 0.75, 1.5 and 3% and the frequency of application is three times daily.[56,57] The effect on IOP is more marked than with pilocarpine.

Adverse Effects

The ocular adverse effects are similar but more serious than those seen with pilocarpine and may be reason to discontinue therapy.[57] A low grade anterior uveitis may be observed during therapy with carbachol. In addition, the systemic adverse effects are more frequently observed during therapy with carbachol than with pilocarpine.[57] Therefore, carbachol is not often currently used in glaucoma therapy.

5.1.3 Other Parasympathomimetics

The irreversible cholinesterase inhibitors as ecothiopate, demecarium bromide and diisopropyl fluorophosphate may be useful in certain patients with aphakia or pseudoaphakia, but in general they have little place in glaucoma therapy since new compounds with fewer ocular and systemic adverse effects have become available.

5.2 Sympathomimetics

5.2.1 Epinephrine

Epinephrine (adrenalin) is the main representative of this group of agents, stimulating α_1- and α_2–adrenoceptors, as well as β_2-adrenoceptors in the eye. The reduction of IOP during long term treatment is primarily due to an increase in flow through the trabecular meshwork[58-60] and the uveoscleral pathways.[25,58] The effect on aqueous humour production is a slight increase during the first hours after application. In patients with an open angle glaucoma and in patients with ocular hypertension it was observed that concentrations of epinephrine lower than 1% did not influence outflow facility.[61]

The concentrations used are 0.5 to 2% of the L-isomer or of the racemic mixture. Epinephrine is coupled to tartaric acid, citric acid or boric acid for stability. During prolonged treatment tolerance to epinephrine may develop.

The IOP reduction after epinephrine is about 15 to 25% with twice daily application.[62-64]

Adverse Effects

Intraocular epinephrine dilates the pupil via its α_1-adrenoceptor properties.[65] After instillation of epinephrine, vision may be blurred by a transient mydriasis. Because of the occasional mydriatic effect the drug should not be used in patients with narrow chamber angles but only in patients with proven open angles. In patients with aphakia or pseudophakia, it may induce cystoid macular oedema.[66-68] This effect on the macular area is reversible when the therapy is stopped. In particular, epinephrine should be avoided in patients undergoing complicated surgery since the aqueous may mix with the vitreous and epinephrine may reach the posterior pole of the eye.

Furthermore, epinephrine induces vasoconstriction of the conjunctival vessels followed by a vascular rebound with a reactive hyperaemia. Epinephrine can form adrenochrome deposits in the lower and upper palpebral conjunctiva.[69,70] Adrenochrome may also form in the cornea resulting in a black cornea,[71,72] and can obstruct the lacrimal punctum causing tearing of the eye.

Systemic adverse effects, especially observed in older patients, are tachycardia, arrhythmia, high blood pressure, anxiety and nervousness.

5.2.2 Dipivalyl Epinephrine (DPE)

To improve the therapeutic index and adverse effect profile of epinephrine, DPE has been developed. DPE is a pro-drug of epinephrine with 2 pyvalic groups added. DPE is more lipophilic than epinephrine and penetrates the cornea 17 times more easily. In the cornea, nonspecific esterases split off the pivalyl groups and epinephrine can exert its effect on IOP in the anterior segment.[73,74]

The IOP reduction with 0.1% DPE is comparable to the effect of 1 to 2% epinephrine, i.e. approximately 20 to 25%.[75,76] The systemic and ocular adverse effects occur less often than with epinephrine.

5.2.3 α_2-Adrenergic Agonists

Clonidine

Clonidine is a selective α_2-adrenergic agonist but it also has some α_1-adrenergic properties. α_2-Adrenoceptors are located prejunctionally and inhibit norepinephrine release at the nerve endings. α_1-Adrenoceptors are postjunctional and after stimulation induce vasoconstriction, among other effects. Because of its lipophilic properties, clonidine easily passes the blood brain barrier, which may result in systemic hypotension by stimulation of the vasomotor centres in the brain stem.

In patients, clonidine eye drops (0.125, 0.25 and 0.5%) induced systemic hypotension and lowered the pressure in the ophthalmic artery, and despite low IOPs, progression of visual field defects was suggested.[77-81] Therefore, new compounds were developed with less permeability of the blood brain barrier.

Apraclonidine

Apraclonidine or para-aminoclonidine hydrochloride has a higher polarity than clonidine, resulting in lower permeability of the blood brain barrier. Similar to clonidine, it reduces IOP mainly by decreasing aqueous humour production,[82,83] although a small increase in trabecular flow has also been reported.[84]

There is no difference in the effect on IOP between the 0.5 and 1% concentration.[83] The recommended therapy with apraclonidine 0.5% is 3 times daily. The effect on IOP is an approximate 20 to 27% reduction,[85,86] which is comparable to timolol at peak but at trough is less than timolol.[87-89]

The main indications for treatment with apraclonidine are post-laser and post-surgical pressure elevations. Apraclonidine reduces the spikes of IOP after laser trabeculoplasty, iridotomy,[90,91] after phacoemulsification with implantation of an intraocular lens,[92,93] and after Nd:YAG laser capsulotomies.[94]

Long term treatment of glaucoma can be achieved with apraclonidine as second line drug, but is often hampered by tachyphylaxis and its local adverse effects.[95]

Adverse Effects

Local adverse effects are the main problem with apraclonidine. During chronic treatment, 25 to 48% of patients developed allergic reactions including eye lid dermatitis, blepharoconjunctivitis and follicular conjunctivitis. Furthermore, hyperaemia, itching, tearing, and occasionally foreign body sensation were observed.[89,96-98] After instillation of apraclonidine, conjunctival blanching, mydriasis and eyelid retraction may occur, probably via α_1-adrenoceptor stimulation. The most common systemic adverse effects encountered in approximately 20% of the patients are dry nose and dry mouth[97] secondary to its vasoconstrictive properties. Nasolacrimal compression after topical administration may reduce the symptoms. Other systemic adverse effects are headache, fatigue and sedation, but these are not frequently observed.[96] Apraclonidine has no effects on blood pressure or pulse rate.[86,99,100]

Brimonidine

Brimonidine is a highly selective α_2-adrenoceptor agonist. It is more α_2-selective and more lipophilic than apraclonidine,[101] hence lower concentrations can be used. Brimonidine lowers IOP by decreasing aqueous humour production and possibly by increasing uveoscleral outflow.[102] It may also have a neuroprotective effect on retinal ganglion cell death as was observed in animal studies.[101,103] This neuroprotective effect is not yet demonstrated after topical administration in humans.

Brimonidine can be used for both short term treatment to prevent IOP spikes after laser trabeculoplasty, and for chronic treatment in patients with ocular hypertension or OAG.[104] The concentration available is 0.2% and this must be applied 3 times daily since the hypotensive effect on IOP may wear off after 6 hours.

Efficacy studies reported a fall in IOP of about 20 to 27% in patients with glaucoma or ocular hypertension.[104-108] This ocular hypotensive effect is comparable to timolol 0.5% at peak, however, timolol has a greater effect on IOP at trough than brimonidine.[106-109] Betaxolol 0.25% suspension has slightly less effect on IOP than brimonidine.[108]

Adverse Effects

Allergic reactions such as blepharitis, blepharoconjunctivitis or conjunctivitis were observed in about 9% of patients treated, conjunctival follicles in 7.8%, a mild hyperaemia in 26.3%, staining of the cornea in 8%, blurred vision in 17% and foreign body sensation in 17%.[106,107] These adverse effects can occur occasionally or chronically.[106,107] Furthermore, since brimonidine is far more selective for the α_2-receptors than for the α_1-receptors, α_1-adrenergic induced effects such as mydriasis, eyelid retraction or conjunctival vasoconstriction were less often observed. A dry mouth was reported in 33% of patients, fatigue in 16% and headache in 18.7%.[106,107] No effect on heart rate was reported, and occasionally a small but significant decrease of mean blood pressure without clinical symptoms was noted.[104,105] Brimonidine was found to lower diastolic blood pressure in one study.[106] In 18% of patients, brimonidine induced a significant decrease of the Schirmer tear test, indicating a decrease of tear production which was similar to that of timolol.[106]

5.3 Sympatholytics

β-Blockers are still the mainstay and first therapy of choice in glaucoma. The available β-blockers are either nonselective, inhibiting both β_1- and

β_2-adrenoceptors, or β_1-selective, which means that β_1-adrenoceptors are preferentially inhibited. β-blockers are lipophilic and should have no membrane stabilising activity since this induces corneal anaesthesia. β-blockers may exert some resting intrinsic sympathicomimetic activity (ISA) resulting in slight stimulation of the β-adrenoceptor site.

After the initial observation in 1967 that propranolol reduces IOP,[110] it was not until 1978 that the first topically administered β-blocker became available for glaucoma treatment.

5.3.1 Timolol

Timolol, a nonselective β-blocker, reduces IOP by inhibiting aqueous humour production[111] and not by increasing outflow facility.[112,113] In healthy individuals, timolol does not inhibit aqueous flow during sleep.[114] The precise mode of action of how timolol inhibits aqueous flow is not clear, but it is suggested that timolol down regulates the adenylate cyclase enzyme by inhibiting β_2-adrenoceptor sites at the ciliary processes.

Many studies have shown the efficacy of timolol in glaucoma.[115-128] 27 to 35% reductions in IOP are reported during long term treatment. Timolol is available in 0.1, 0.25 and 0.5% solutions and should be applied twice daily. A formulation with a gel as vehicle (Timoptic-XE®) permits once daily application.

Although one study reported timolol 0.25% to be as effective as timolol 0.5%,[129] in our opinion, patients with higher IOP levels (>30mm Hg) do better with timolol 0.5%. Also, patients with a dark iris need the higher concentration of timolol because timolol binds to the iris pigment and may lose some of its efficacy.[130,131]

Immediately after starting with timolol therapy there is a marked decrease of IOP that will stabilise at a slightly higher level in time.[125,126]

Adverse Effects

Shortly after the introduction of topical timolol it became clear that timolol caused fewer ocular adverse effects compared with the then available topical antiglaucoma agents (miotics and sympathomimetics). However, timolol may induce hyperaemia of the conjunctiva, burning, stinging or superficial punctate keratitis.[132,133] Timolol also reduces tear flow,[134,135] which may result in dry eye syndrome (keratoconjunctivitis sicca) or give problems for contact lens wearers. A possible vasoconstrictive effect of timolol at the posterior pole of the eye, thereby compromising flow through the peripapillary choroid capillaries, is a subject for current investigations.

Contrary to their beneficial ocular adverse effect profile, β-blockers may induce severe systemic adverse effects by blocking the β_1-adrenoceptors of the heart. Timolol may cause bradycardia, arrhythmia, congestive heart failure, and syncope by Adam-Stokes syndrome.[132,133,136,137] Furthermore, by blocking the β_2-adrenoceptors of the bronchioles, timolol can cause bronchospasm and status asthmaticus in patients with chronic obstructive pulmonary disease (COPD) or asthma.[132,133,136-139] Timolol should therefore be avoided in patients with a history of chronic obstructive lung diseases. In addition, timolol should not be used in patients with myasthenia gravis[140,141] or those with diabetic mellitus with hypoglycaemic attacks.[142] Often unnoticed, timolol may induce anxiety, depression, sexual impotence, fatigue, confusion, disorientation and hallucinations.[132,133,136]

All systemic adverse effects of timolol are caused by the immediate uptake of timolol in the blood via the epithelium of the nasopharynx. Plasma levels of timolol after instillation can be reduced up to 70% by compression of the nasolacrimal punctum at the time of application,[143] thereby minimising the unwanted systemic adverse effects.

5.3.2 Betaxolol

Betaxolol is a β_1-selective adrenoceptor antagonist. It exerts its effect on IOP by inhibiting aqueous humour flow.[144] Since the ciliary body contains hardly any β_1-adrenoceptors, it is thought that betaxolol may lower IOP by its weaker β_2-blocking properties. The effect on IOP is smaller than the effect of timolol and amounts to a fall of about 3.9 to 7.8mm Hg (18 to 26%).[145-148] Despite its smaller effect on IOP, betaxolol had a better effect on preservation of visual field than timolol in long term

studies.[149-151] This effect of betaxolol may be due to its calcium antagonistic effect.[152,153]

Betaxolol is available as a 0.25 and a 0.5% solution which should be applied twice daily. There is also a 0.25% suspension which, when given twice daily, is as effective as the 0.5% solution but produces fewer local adverse effects.

Adverse Effects

The most frequent ocular adverse effect of betaxolol is a short period of burning and stinging after topical administration. Furthermore, the ocular adverse effects are comparable to other β-blockers and their incidence are relatively low.

There is clinical evidence that betaxolol has less effect on cardiac and pulmonary function than nonselective β-blockers. In patients with asthma, no effect on forced expiratory volume has been observed,[154,155] which can be explained by the relative β_1-selective properties of betaxolol. However, in other studies betaxolol reduced pulmonary function in patients with asthma.[156,157] Therefore, special attention has to be given when betaxolol is prescribed to these patients.

In addition, the cardiovascular adverse effects as bradycardia, arrhythmias,[158] and congestive heart failure[159] occur less frequently with betaxolol than with nonselective β-blockers. The high binding capacity of betaxolol to plasma proteins and thus low free plasma concentration[160,161] may, in part, account for this. Betaxolol may induce adverse effects on the CNS such as depression, fatigue, impotence and confusion, but their incidence appears to be lower than with timolol.[162,163]

5.3.3 Levobunolol

Levobunolol is a nonselective β_1- and β_2-blocking agent. Its metabolite dihydrolevobunolol is also effective in lowering IOP. Levobunolol has no ISA nor local anaesthetic activity. Its ocular hypotensive effect is similar to timolol,[164-166] and is also caused by suppression of aqueous humour formation. Long term studies have demonstrated equal effectiveness of levobunolol and timolol in lowering IOP[167-169] and in preventing visual field deterioration.[167] The fall in IOP was about 27%.[167]

Levobunolol is available in 0.25 and 0.5% solutions and can be administered once[170-172] or twice daily.[164-169] Once daily application of levobunolol 0.25% induced a fall in IOP of 24%, and adequate IOPs were obtained in 72% of patients regulated with twice daily application.[171]

Adverse Effects

The adverse effect profile of levobunolol is similar to that of timolol. One study showed an incidence of allergic blepharoconjunctivitis of 4% after levobunolol treatment.[167]

5.3.4 Carteolol

Carteolol is a nonselective β-blocker with some ISA and no local anaesthetic activity.[173] The main metabolite, 8-hydroxycarteolol, was shown to be more effective in lowering IOP than carteolol in rabbits and monkeys.[174] Carteolol lowers IOP by reducing aqueous humour formation.[175] Aqueous humour formation was reduced by 20.4% with carteolol and by 39% with timolol in patients with ocular hypertension.[175]

Carteolol is available in 1 and 2% solutions and has to be applied twice daily. In randomised comparative studies, carteolol 1 and 2% were as effective as timolol 0.5% in lowering IOP.[176-180] The reported fall of IOP was 3.1 to 10mm Hg or 20 to 32%.

Adverse Effects

Ocular adverse effects such as irritation and pain occurring shortly after application, were observed less often during carteolol treatment than with timolol.[176,181]

Although carteolol reportedly possesses ISA, this property did not prevent β-blocking effects of carteolol on pulse rate, blood pressure and exercise induced dyspnea.[181,182] Therefore, carteolol should not be given to patients with cardiac or pulmonary insufficiency. After oral administration of carteolol, plasma high density lipoprotein (HDL) cholesterol levels are increased and plasma triglyceride levels are reduced,[183] thus producing a beneficial cardiovascular risk profile. This effect has been attributed to the ISA properties of carteolol. In contrast, carteolol 1% eye drops followed

by nasolacrimal compression decreased HDL cholesterol levels by 3.3%, in the timolol 0.5% treated group HDL cholesterol levels decreased by 8% which was significantly higher.[184] Hence, the effect of topical carteolol on plasma HDL cholesterol levels is not clear. It was suggested that the nasolacrimal compression may have been responsible for the decrease of HDL cholesterol levels in that study.

5.3.5 Metipranolol

Metipranolol is a nonselective β-blocker without ISA.[185] It has been reported to exert some corneal anaesthetic effect.[185] Metipranolol lowers IOP by inhibiting aqueous humour formation.[185-187] The effect on outflow facility is unclear. In one single drop study a significant increase in outflow facility was reported,[188] but with repeated doses of metipranolol no effect on outflow facility was observed.[186]

Metipranolol is available in 0.1, 0.3 and 0.6% solutions and should be administered twice daily. The fall in IOP approximates 25%[189,190] after metipranolol 0.1%, and 21 to 33%[191] after metipranolol 0.3%[191-194] and 0.6%.[191,193,195] In several studies, metipranolol induced a decrease of IOP similar to levobunolol[195] and timolol.[189,192]

Adverse Effects

Compared with timolol, instillation of metipranolol causes more stinging and burning for a short period of time.[191,192] It can induce mild conjunctival hyperaemia, similar to levobunolol.[195] Reports of 22 patients with anterior uveitis, attributed to metipranolol eye drops, have been published since 1991.[196-202] In these patients a granulomatous anterior uveitis developed after long term use of metipranolol. This reaction proved reversible after metipranolol was discontinued. The origin of this anterior uveitis remains unclear.

One long term multicentre study on the effects of topical metipranolol reported no effect on pulse rate or blood pressure.[191] However, other studies found a slight reduction in pulse rate and systolic blood pressure.[195] Therefore, metipranolol should be avoided in patients with cardiovascular or pulmonary diseases.

5.4 Carbonic Anhydrase Inhibitors (CAIs)

In the ciliary processes of the human eye, the enzyme carbonic anhydrase catalyses the conversion of H_2O and CO_2 to HCO_3- and H^+. Transport of sodium across the cell membrane is related to bicarbonate synthesis.[203]

Carbonic anhydrase isoenzyme II is the main representative in the human ciliary body.[204] Inhibition of carbonic anhydrase results in a decrease of aqueous humour production. To achieve adequate inhibition, the concentration of the inhibitor has to be approximately 10 times higher than the concentration of the enzyme.[205]

5.4.1 Systemic CAIs

Becker introduced the CAI acetazolamide to glaucoma treatment about 45 years ago.[206] Acetazolamide decreases aqueous humour production by approximately 27%.[207,208]

Acetazolamide is the most commonly used oral CAI. The maximum effect on IOP is reached with acetazolamide 250mg tablets 4 times daily or 500mg sustained release capsules twice daily. The reduction in IOP is about 20 to 30%[206] and dependent on the initial IOP. Acetazolamide is available as 125 and 250mg tablets, as 250 and 500mg sustained release capsules, and as a 500mg vial for intravenous injection. It is a second line drug and used in nonregulated glaucoma, post-surgically and post-laser therapy.

Methazolamide is another systemic CAI. The recommended dosage is 25, 50 or 100mg 3 times daily. The effect on IOP is somewhat smaller than that seen with acetazolamide, but it induces fewer adverse effects.[209]

Adverse Effects

Oral CAIs have hardly any ocular adverse effects. However, the systemic adverse effects hamper their use in glaucoma treatment. Well known adverse effects are paresthesia of the acra, fatigue, depression, renal stones, and gastrointestinal complaints such as nausea and diarrhoea.

Acetazolamide in higher doses induces metabolic acidosis especially in the elderly and is contraindicated in patients with renal failure, hepatic in-

sufficiency, lowered plasma potassium and sodium levels, and COPD. Treatment with methazolamide induces fewer renal calculi than treatment with acetazolamide but this may be attributed to the fact that methazolamide is used less frequently and that it is used in lower doses than acetazolamide.

Acetazolamide and methazolamide are sulfonamide derivatives. Because of this, they may induce agranulocytosis, aplastic anaemia, thrombocytopenia and neutropenia.[210] In addition, exfoliative dermatitis and Stevens-Johnson syndrome may occur during treatment with acetazolamide and methazolamide.

5.4.2 Dorzolamide

A major advance in the medical treatment of glaucoma is the recent development of topical CAIs. By local application the frequent systemic adverse effects of oral CAIs are avoided. Dorzolamide is a an inhibitor of human carbonic anhydrase isoenzyme II and also a weak inhibitor of isoenzyme IV. As with the oral CAIs, it also reduces IOP by inhibiting the formation of aqueous humour.[211] Because of its balanced lipid/aqueous solubilities, it penetrates the cornea well. Dorzolamide 0.1% applied on the cornea of rabbits induced a 100% inhibition of carbonic anhydrase activity in the iris and ciliary body.[212]

The recommended therapeutic regimen of dorzolamide is 3 times daily with a 2% solution. In a one-year multicentre study, dorzolamide as monotherapy lowered IOP by 23%, this was similar to betaxolol but slightly lower than the reduction of IOP achieved by timolol (26%).[213]

In a comparative study with timolol and either dorzolamide or acetazolamide as second line drug, dorzolamide 2% twice daily was slightly less effective than acetazolamide 4 times daily. However, the discontinuation rate in the acetazolamide group was 25% versus 2% in the dorzolamide group.[214]

Dorzolamide inhibits aqueous flow by about 17% while acetazolamide inhibits aqueous flow by about 30%.[214,215]

Adverse Effects

The local adverse effects of dorzolamide are stinging (12%), ocular burning (19%), temporarily blurred vision (9%), itching (12%) and tearing (7%). Eye lid oedema and conjunctivitis were seen in 4 and 4.5%, respectively, of treated patients.[213] Although CAIs may impair the corneal endothelial pump function, in several studies, dorzolamide did not increase corneal thickness.[216-218] However, some patients with endothelial compromise developed irreversible corneal decompensation after dorzolamide therapy.[219]

Up to 23% of the patients complained of bitter taste, other systemic adverse effects were not reported.[212,213]

5.4.3 Brinzolamide

Brinzolamide is a selective inhibitor of carbonic anhydrase isoenzyme II. In a multicentre study, twice daily application of brinzolamide had equivalent efficacy to 3 times daily dorzolamide and less efficacy than timolol. After a period of 3 months, patients with primary open angle glaucoma or ocular hypertension showed a reduction of IOP of 19.1% with twice daily treatment with brinzolamide 1% and 20.3% with 3 times daily application of brinzolamide. Twice daily timolol 0.5% resulted in an decrease of IOP of 22.8%.[220]

Adverse Effects

Brinzolamide caused slightly less ocular discomfort than dorzolamide. Stinging and burning after instillation of brinzolamide was seen in 1.8 and 3% of patients, respectively, for 2 and 3 times daily application, whereas dorzolamide 3 times daily gave ocular burning and stinging in 16.4% of patients. Other ocular adverse effects of brinzolamide were foreign body sensation 1.8%, itching 1.2%, tearing 1.2% and dry eyes 1.2%.[220]

Taste abnormalities were reported in 7.7% of the patients. Other systemic adverse effects were not observed after brinzolamide application.

5.5 Prostaglandins

Prostaglandins are mediators of the inflammatory response. In high doses they induce conjunctival hyperaemia, miosis, iris hyperaemia, and disruption of the blood-aqueous barrier leading to an

elevation of IOP in rabbits. However, in low doses it was shown that prostaglandins lower IOP.[221-223]

5.5.1 Latanoprost

Initial studies in patients with glaucoma were performed with the prostaglandin $F_2\alpha$ analogue PhXA34.[224,225] The D-enantiomer of PhXA34, PhXA41 (latanoprost) was found to be twice as potent as the racemic mixture, and was subsequently developed for glaucoma treatment.

In short term studies with latanoprost, a reduction in IOP of 25 to 36% was observed.[226,227] Twice daily application of latanoprost was less effective than once daily application.[228,229] Also, it was found that application of latanoprost in the evening was more effective than application in the morning.[230] In contrast to timolol, latanoprost reduced IOP as effectively during the night-time as during the daytime.[229,231]

Long term, multicentre studies comparing latanoprost with timolol revealed that latanoprost was more effective in lowering IOP in open angle glaucoma, ocular hypertension, exfoliative glaucoma and pigment dispersion syndrome.[232-234] The reported fall in IOP during latanoprost treatment is 27 to 35%. In a 12-month study, latanoprost as monotherapy lowered IOP by 32%.[235] In this study, no long term drift of IOP occurred. Only 3% of patients were withdrawn from the study because adequate control of IOP was not achieved.

Latanoprost was also effective in lowering IOP in patients with NPG. The reported reduction in IOP was 21.2%. In particular, if the initial IOPs were between 15 and 21mm Hg, latanoprost had a marked effect on IOP.[236]

The reduction of IOP by latanoprost is based on an increase in uveoscleral outflow.[231] Latanoprost has no effect on trabecular outflow or on aqueous humour production.

Latanoprost is available as a 0.005% solution and should be applied once daily, preferably in the evening.

Adverse Effects

Mild conjunctival hyperaemia after latanoprost treatment was noted in 3 to 15% of patients in long term studies.[232-234] Stinging, burning or tearing after application was observed in 20 to 40%. Punctate keratitis, blurred vision, eye pain and foreign body sensations were reported in 1 to 22% of patients.[232-234] After one year of treatment with latanoprost treatment, slight flare in the anterior chamber was observed in 2% and a few cells in the anterior chamber were occasionally seen in 5% of patients.[235] Anterior uveitis associated with the use of latanoprost was observed in 5 eyes, 4 of which had had prior intraocular inflammation or surgery.[237] Fluorescein angiography of latanoprost-treated patients with pseudophakia and a history of uneventful cataract surgery did not reveal cystoid macular oedema after one month of treatment.[238] However, recent case reports indicate that latanoprost can induce cystoid macular oedema in patients with pseudophakia after complicated surgery, with a history of retinal surgery, or pre-existent maculopathy.[239-244] Therefore, latanoprost should be avoided in these patients.

Latanoprost can increase iris pigmentation. Multicoloured irides are especially vulnerable to these changes in pigmentation. In one study, iris pigmentation increased in 12% of patients treated with latanoprost. All these eyes had multicoloured irides.[235] The increase in iris pigmentation was observed from 3 to 12 months after the start of the study. This increase in iris pigmentation is not due to proliferation of melanocytes but to an increase in melanosomes per melanocyte.[235,245,246] Unilateral treatment with latanoprost may induce a cosmetically undesirable effect. Hence, unilateral treatment is best avoided in multicoloured eyes. Furthermore, latanoprost may induce hypertrichosis and increased pigmentation of eyelashes.[247,248]

Long term studies with latanoprost have not revealed any cardiac or pulmonary effects.[230,235,249] After the application of latanoprost, heart rate, pulmonary function and blood pressure were not affected in patients with COPD.[250] Currently, no systemic adverse effects of topical latanoprost have been reported.

5.5.2 Isopropyl Unoprostone

Isopropyl unoprostone is an analogue of a prostaglandin metabolite and is used in glaucoma treat-

ment. It is available in concentrations of 0.06 and 0.12% and should be applied twice daily. Isopropyl unoprostone lowers IOP primarily by enhancing uveosceral flow, but also it has some effect on trabecular outflow in animals.[251-253]

The effect on IOP of the 0.12% solution is similar to that of timolol 0.5%.[254] In a 52-week study no upward drift of IOP was noted in patients treated with isopropyl unoprostone.

Adverse Effects

Local adverse effects consisted of conjunctival hyperaemia (7%), corneal erosion (2%) and blepharitis (1%).[254] In clinical studies, no effect of isopropyl unoprostone on iris colour has been observed. However one case report has appeared describing a patient who was treated in one eye and whose iris became darker, probably by the same mechanism that is responsible for iris darkening during latanoprost use.[255]

6. Combining Antiglaucoma Drugs

When the IOP is not adequately regulated with monotherapy, it is common practice to combine antiglaucoma drugs. Insufficient effect on IOP during monotherapy can be caused by initial insufficient effect of the drug, by the development of tolerance during long term therapy, or by progress of the disease. Especially if tolerance is suspected, it is advisable to try another monotherapy before combining several drugs.

When 2 agents are combined, an additional reduction of IOP of at least 15% is desirable. Drug combinations that act on different receptor sites or enzymes, and have a different mode of action, are preferred. When different drugs are combined in the treatment of glaucoma pure additivity is hardly ever reached, i.e. the effect of the combination on IOP will usually be less than the sum of both actions (table III).

6.1 Agents Used in Combination Therapy

β-blockers, which lower aqueous production, can be combined with miotics, which enhance aqueous trabecular outflow. The efficacy of combining β-blockers twice daily with pilocarpine 1 or 2% 4 times daily has been shown in various studies.[256,257] To increase patient compliance and for their convenience, fixed combinations were developed of timolol with pilocarpine 2% or with pilocarpine 4% and metipranolol 0.1% with pilocarpine 2%. The effect on IOP of these fixed combinations is similar to the effect when both agents are applied separately.[258-260]

The combination of a β-blocker with epinephrine, an agonist of α- and β-receptors, is less obvious since both drugs are partly counteracting. Combining timolol with epinephrine did not result in a clinical useful additional effect on IOP reduction.[261-263] In addition, the combination of levobunolol with dipivefrine resulted only in a modest additional IOP reduction.[263,264] In contrast, combining β_1-selective betaxolol with dipivefrine or epinephrine resulted in a significant additional reduction of IOP, due to an increase of conventional outflow facility.[265,266]

Combining β-blockers with oral CAIs, both inhibiting aqueous humour secretion, results in an additional IOP reduction of approximately 10 to 20%.[207,267,268] This can be explained by the different modes of action of β-blockers and CAIs, re-

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

Class	β-Blockers	Miotics	Adrenergic agonists	α_2-Adrenergic agonists	Prostaglandins
Miotics	+				
Adrenergic agonists	±	+			
α_2-Adrenergic agonists	+	?	?		
Prostaglandins	+	+	+	?	
Carbonic anhydrase inhibitors	+	+	+	?	+

+ indicates additive effect; ± indicates small effect; **?** indicates effect of combination not known.

Table IV. Fixed combinations available for the treatment of glaucoma

Brand name	Constituents	Dosage
Normoglaucon®	Metipranolol 0.1% Pilocarpine 2%	One drop 2-3 times daily
TP-2®,Timpilo-2® (TP-4®, Timpilo-4®)	Timolol 0.5% (0.5%) Pilocarpine 2% (4%)	One drop twice daily
Cosopt®	Timolol 0.5% Dorzolamide 2%	One drop twice daily

spectively, down-regulation of adenyl cyclase and inhibition of the carbonic anhydrase enzyme at the ciliary epithelium.

To avoid the systemic adverse effects of oral CAIs, a fixed combination is now available of timolol 0.5% and dorzolamide 2%. It has been shown that the fixed combination was as effective as the 2 agents applied concomitantly and results in an additional IOP reduction of 13 to 20% at peak and of 5 to 14% at trough, relative to timolol alone.[269-271] Similarly, in patients treated with once daily timolol maleate gel forming solution, the addition of dorzolamide once or twice daily resulted in an additional IOP reduction of approximately 13%.[272]

Another useful combination is timolol with latanoprost. Adding latanoprost to timolol treatment results in an additional IOP reduction of 13 to 37%. This reduction depends on the frequency of application of latanoprost and the IOP level during timolol treatment.[273-276] Once daily application of latanoprost combined with twice daily timolol proved more effective than twice daily application latanoprost.[276] A higher baseline IOP level resulted in relatively more reduction of IOP.[277]

The combination of latanoprost once daily with acetazolamide 250mg twice daily induced an additional IOP reduction of 21%.[275,277] Furthermore, combining latanoprost with dorzolamide resulted in an additional IOP reduction of 15%.[278] The addition of latanoprost to DPE induced a further hypotensive effect of 3.6mm Hg (20%) without an effect on the blood-aqueous barrier.[279]

Short term studies on the effect of combining latanoprost with pilocarpine 2% showed an additive effect on the fall of IOP.[280,281] This was surprising because, in monkeys, the hypotensive effect of prostaglandin $F_2\alpha$ was antagonised by high doses of pilocarpine.[48]

Combinations of topical CAIs with agents other than β-blockers are not known at this moment, but additional activity comparable to that seen with the combinations possible with oral CAIs could be expected.

Furthermore, information about combining other agents with brimonidine is not available. In theory, combining brimonidine with β-blockers is not advisable because both agents suppress the formation of cyclic AMP in the ciliary epithelium. Combining brimonidine with epinephrine or DPE is, again in theory not useful because epinephrine up-regulates the adenyl cyclase enzyme which brimonidine inhibits indirectly; brimonidine inhibits endogenous norepinephrine release (table IV).

7. Conclusion

When the decision to treat a patient with glaucoma or ocular hypertension has been made, in

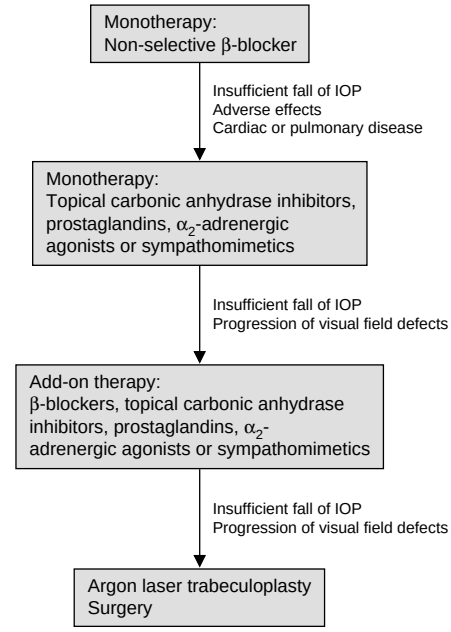

Fig. 2. Treatment algorithm for the management of primary open angle glaucoma. Note that these are only general guidelines. **IOP** = intraocular pressure.

general the IOP will be lowered with topical agents. The primary therapy of choice is monotherapy with a β-blocker, provided that β-blockers are not contraindicated as in patients with concomitant cardiac or pulmonary diseases (fig. 2).

If monotherapy with a β-blocker does not induce a useful target pressure, a change to monotherapy with topical prostaglandins, CAIs or α-agonists is instituted. Although the medical literature does not provide enough data to prefer one of these agents or another, it is clear that $PGF_{2\alpha}$ analogues induce a lower and more sustained IOP level than topical CAIs or α_2-agonists; in addition they lack a peak and trough effect on IOP.

Combination treatment (add-on) is needed when monotherapy with several agents does not lower IOP to target pressure or when visual fields deteriorate. β-blockers can be combined well with miotics, topical CAIs and prostaglandin analogues.

It is advisable that the add-on therapy should not exceed more than 3 agents in total, and to reduce treatment inconvenience it is preferable to use combined drug formulations such as timolol/pilocarpine or timolol/dorzolamide.

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