

## CURRENT MANAGEMENT OF OPEN ANGLE GLAUCOMA

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**SUMMARY** – In recent years, a large number of drugs have been developed for treatment of glaucoma with the increasing choices of alternative medications.

A wide choice of newer local agents is now available for the treatment of glaucoma, each with differing efficacy and side effects. New treatment options for reducing IOP provide an opportunity to improve both compliance and therapeutic results while at the same reducing the level of side effects seen with multiple conventional drug regimens. This drug review considers the mode of action and properties of the various treatments, followed by practical advice to offer patients about their medication. Clinicians need to understand, synthesize and use data about medications that have specific benefits and risks for their glaucoma patients.

Glaucoma is a progressive optic neuropathy characterised by optic disc cupping and concomitant characteristic visual field defects. The term glaucoma describes a number of different disorders that affect the eye, all of which culminate in the death of the retinal ganglion cells of the optic nerve and visual field defects. Intraocular pressure (IOP) lowering is still the mainstay of treatment, the goal of which is to preserve visual function for the remainder of patients lifetime, whilst optimising the quality of life. Most of the drugs now used to treat glaucoma are primarily directed at lowering IOP. In sense they are like cholesterol lowering agents in that they are designed to manage the risk factors for the diseases which led to glaucoma, rather than its basic underlying cause.<sup>1</sup>

The concept of target IOP is worth considering. At the onset of treatment, it is helpful to establish a target IOP at which further damage to the optic nerve is deemed unlikely to occur. Commonly this is a 20 to 30 per cent reduction from the IOP at which damage occurred. If the glaucomatous optic neuropathy is worsening during the course of treatment, the target IOP may need to be adjusted. Compliance tends to fall off as the number of medications and dosing instructions increases and therefore, it is well worth reviewing a patient's list of medications to determine if some of the newer agents on the market may allow consolidation of treatments. This review deals with open angle glaucoma where medical therapy is commonly the initial form of management.<sup>2</sup>

### Topical ocular hypotensive agents

Intraocular pressure is maintained by balance between the production of aqueous humor by the nonpigmented epithelium of the ciliary body and escape of this fluid from the eye. Most of the drainage goes through the trabecular meshwork in the anterior chamber angle, the conventional route, which is a pressure dependent mechanism. About

10 per cent of aqueous outflow occurs more posteriorly through uveoscleral tissue.<sup>3</sup>

In recent years several new classes of topical medications have been developed so that we now have five classes of drugs commonly used for long term management of glaucoma. As these exert their effect at different sites, their IOP lowering effects are often additive. The various drugs also have different side effects profiles so that their suitability varies with different clinical situations.<sup>4</sup> This diversity enables us to customise treatment to each individual patient in a better way.

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All eye drops have the potential to cause both local and systemic unwanted effects. Systemic absorption of eye drops occurs through the nasal mucosa. Stinging or burning and transient blurring of vision at the time of drop application are frequently reported.<sup>5</sup>

More persistent local effects that are sometimes experienced are itching, hyperaemia, foreign body sensation, superficial punctate keratitis and dry eye. Many of these local effects may be caused by the preservative in the eye drop preparation.<sup>6</sup>

## Beta blockers

(*timolol* – *Timoptol*, *betaxolol* – *Betoptic*, *carteolol* *Teoptic*, *levobunolol* – *Betagan*, *metipranolol* – *Metipranolol*)

Beta blockers decrease the rate of aqueous humor formation by stimulating beta 2 receptors in the ciliary body. Betaxolol, a selective beta1 receptor antagonist, was developed in an attempt to eradicate the beta2 systemic side effects. However, IOP is lowered less effectively by selective beta blockers compared to nonselective agents.

The nonselective beta blockers *timolol*, *carteolol*, *levobunolol* and *metipranolol* are given twice a day. Most clinical studies have been performed using *timolol*, which has been available for the longest time and is considered to be the golden standard. *Timolol* lowers IOP by 25-27 per cent with an onset over two hours. The other nonselective beta blockers have a comparable efficacy.<sup>7</sup>

On the beta blocker front, Merck's *Timoptic XE* *timolol* maleate ophthalmic gel offers an old drug with a new delivery system. The rationale for the gel is that it will increase the contact time with the eye, reduce peripheral distribution, and with it any attendant systemic side effects. An added feature, the drug can be given once a day. The gel can cause transient blurring of vision, so patients should be warned of this possibility.

### Side effects

Ocular side effects are infrequent. It is the systemic effects of beta blockers that limit their use. Systemic beta 2 blockade can cause bronchospasm, bradycardia and worsening of heart failure. Betaxolol has better safety profile but its beta 1 selectivity is not absolute and it should not be the first line treatment in patients with respiratory disease.<sup>8,9</sup>

**Carteolol** is nonselective beta blocker with intrinsic sympathomimetic activity, which may reduce the cardiorespiratory side effects. Other side effects include depression, fatigue and sexual dysfunction.

Beta blockers have small adverse effect on lipid profile decrease in HDL lipoprotein and increase in triglycerides which is less marked with *carteolol*.<sup>7</sup>

Because of the potentially serious systemic side effects, newer agents are now being considered as possible replacements for beta blockers as the first line agent.

The IOP lowering effect of beta blockers is additive to all other agents, apart from the nonselective adrenergic agonists.<sup>6</sup>

## Selective adrenergic agonists

(*apraclonidin* – *Iopidin*, *brimonidin* – *Alphagan*)

The selective alpha2 agonists lower IOP by decreasing the rate of aqueous formation. They act by binding to alpha2 receptors in the ciliary body, thus preventing the sympathetic modulated increase in cyclic AMP.<sup>10</sup>

*Apraclonidin* (*Iopidin*) for a short term lowering of IOP 0,5 per cent-three times daily can be useful, but its effectiveness usually decreases after a few months due to tachyphylaxis.

*Brimonidin* (*Alphagan*) is used for long term control of IOP. And it also increases uveoscleral outflow. It is highly selective alpha2 agonist and thus does not cause the mydriasis and local vasoconstriction seen with *apraclonidine*.

### Side effects

Both drugs can cause eyelid retraction and follicular conjunctivitis. Ocular allergy is seen in up to a third of the patients. *Brimonidin* does not have any clinically significant cardiovascular effects but it can cause drowsiness and fatigue.<sup>11</sup>

*Brimonidin* has been observed to cause CNS depression in infants and thus should not be used in children. Its effect is additive to all other classes of IOP lowering agents, and *brimonidin* is frequently used in combination with beta blockers and increasingly as the first line agent.

## Nonselective adrenergic

agonists (*adrenaline* – *Eppy*, *dipivefrine* – *Propine*)

**Adrenaline** and **dipivefrine** are nonselective adrenergic agonists that lower by increasing outflow. They also have small effect on aqueous flow.<sup>8</sup>

Side effects: The major side-effects are ocular irritation due to reflex vasodilatation and palpebral conjunctival follicle formation. The chronic conjunctival hyperemia often seen with *adrenaline* and *dipivefrine* may

decrease the success rate of subsequent filtration surgery due to the increased conjunctival scarring. Systemic side-effects are rare but tachycardia and hypertension have been reported. This class is only minimally additive to nonselective beta-blockers.<sup>6</sup>

## Prostaglandin analogues

(*latanoprost-Xalatan*)

*Latanoprost* is a prostaglandin (PG) F2 alfa analogue that lowers IOP by increasing uveoscleral outflow. The evidence suggests that latanoprost activates specific prostaglandin receptors in the ciliary muscle. Latanoprost is a potent ocular hypotensive agent, achieving a 30-35 per cent lowering of IOP; however up to 20 per cent of patients may be nonresponders. Peak effect occurs at 8-12 hours after instillation and the response lasts for 20-23 hours. Studies have shown that a single dose in the evening is the most effective.<sup>12</sup>

### Side-effects

The side effects are largely ocular. Uveitis has been reported and PG analogues should not be used in inflammatory glaucomas. Cystoid macular edema has been observed in a few patients who had had previous cataract surgery. Latanoprost should be used with caution in patients with pseudophakia and avoided in those with aphakia.<sup>13</sup>

Iris pigmentation is observed in up to 18 per cent of the patients. The increase in number, thickness and pigmentation of eyelashes has also been reported.

Latanoprost can be added to all the other classes of agents. In normal tension glaucoma it may lower the IOP to the low normal range.<sup>14</sup>

## Topical carbonic anhydrase inhibitors

(*brinzolamid-Azopt, dorzolamide-Trusopt*)

Topical carbonic anhydrase inhibitors (CAIs) decrease aqueous production by reducing bicarbonate secretion into the posterior chamber by ciliary epithelial cells.

*Dorzolamide* per cent is given three times daily; the peak IOP-lowering effect of 23 per cent is observed after two hours and the effect lasts for 8-12 hours.<sup>15</sup>

Stinging on application, due to the low pH, is frequently reported with dorzolamide

*Brinzolamide* 1 per cent suspension is the latest arrival in the carbonic anhydrase inhibitor category. It has a similar IOP lowering ability and safety profile as Trusopt, but

has a pH closer to that of human tears, which may provide less ocular irritation.<sup>19</sup>

CAIs are additive to other glaucoma medications including beta-blockers, alpha agonists and latanoprost. *Cosopt* (Merck – dorzolamide hydrochloride- timolol maleate ophthalmic solution) takes the novel approach of combining two potent agents in one bottle. This product offers the convenience of the combination of two drugs, which should improve compliance. Adding a topical CAI to a systemic one result in no additional IOP lowering.<sup>20</sup>

## Miotics

(*carbachol-Isoptocarbchol 3%, pilocarpine hydrochloridi 0,5%, 1%, 2%, 3%, 4%, pilogel 4%*)

This class of drug has been used to treat glaucoma for over 100 years. The commonly used agents, *pilocarpine (Pilogel)* and *carbachol (IsoptCarbchol)*, are direct-acting acetylcholine-mimicking drugs.<sup>16</sup>

Pilocarpine drops are given up to four times daily and, typically, one starts with a weak strength, eg 1 per cent, to minimise initial side-effects and assess the IOP-lowering effect.<sup>12</sup>

### Side effects

The miosis and increased level of accommodation miotics cause account for many of the unwanted ocular effects. Headache is frequent but it is usually transitory. These drugs may worsen pre-existing inflammation and cause retinal tears in susceptible patients. Since the introduction of beta-blockers in the 1970s, pilocarpine has become a second-line agent. Its effect is additive to all other ocular hypotensive agents, and combined formulations with beta-blockers only require twice-daily dosage. With the new wave of topical ocular hypotensive drugs over the last decade, pilocarpine is being relegated to a third-line agent.<sup>11</sup>

## Systemic agents

### Carbonic anhydrase inhibitors

(*acetazolamid-Diamox*)

Oral CAIs are mainly reserved for acute management of raised IOP but can be used chronically as a last resort.

Acetazolamide (Diamox) is the most commonly used CAI, and is available in both oral and intravenous form. The maximal oral dose of 1g daily can lower the IOP dramatically.<sup>17</sup>

### Side effects

Long term therapy is most commonly discontinued due to a symptom complex of malaise, anorexia, weight loss, depression and a loss of libido. The dose of CAIs should be reduced in patients with renal impairment. Potassium supplements are recommended for patients who are taking thiazide diuretics concurrently. Renal stones can be precipitated by these drugs. Paraesthesias often occur for unknown reasons, but are innocuous and usually transient.<sup>16</sup>

### Treatment strategies

Drug therapy must be individualised according to each patient's clinical profile. In addition to heeding medical contraindications and possible side-effects there are practical issues to consider. Both the cost and a dosage frequen-

cy are important in terms of lifestyle and compliance. The newer agents (prostaglandins, alpha2 agonists) are more expensive and concerns regarding budgets may come into play.<sup>2</sup>

A suggested treatment strategy for primary open angle glaucoma is illustrated in Figure 1.

Initial treatment with beta-blocker is a common practice, although the above-mentioned newer agents are being increasingly used first-line.

Because monotherapy is preferable, if the first-line agent is ineffective the next step is often to switch to another agent.<sup>4</sup>

Combination therapy should always involve drugs from different classes. When prescribing multiple medications in the treatment of glaucoma, the clinician considers the mechanism of action of various drugs, the patient's general health, and the patient's lifestyle and ability to comply with medical therapy. When a second drop is added, pa-

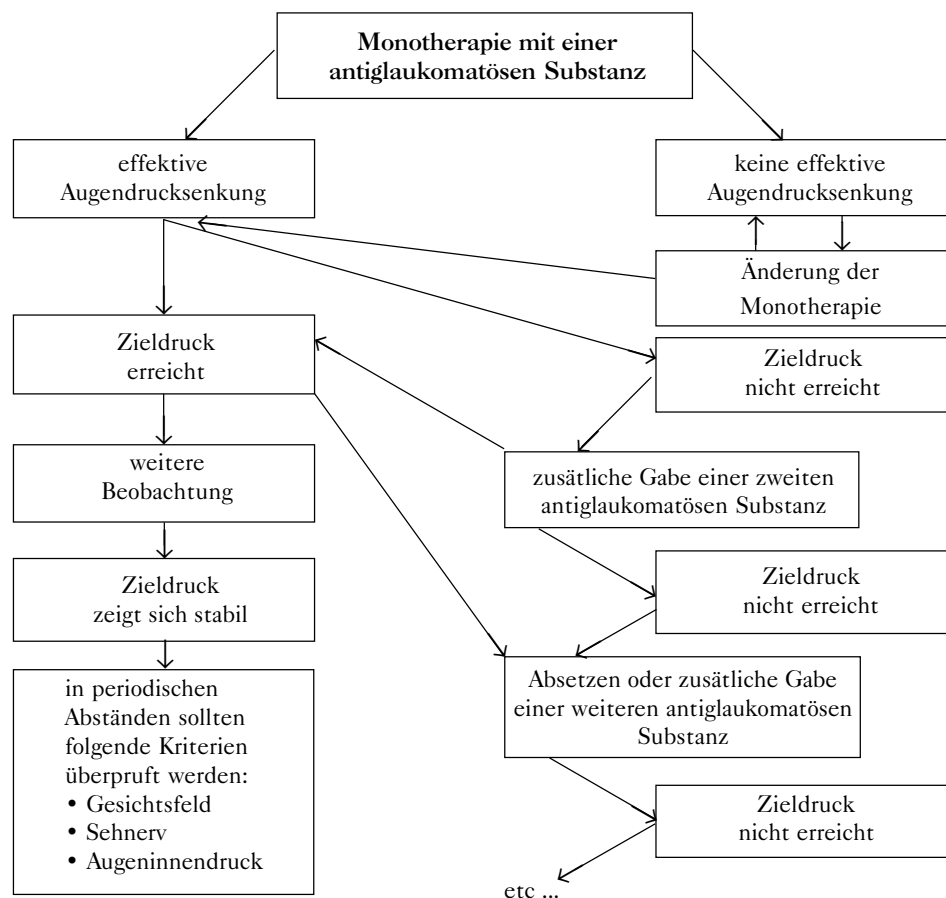


Figure 1. Treatment strategy for primary open angle glaucoma according to European Glaucoma Society (Reprinted from, Glaucoma, Norbert Pfeiffer, Thieme)

tients need to be instructed to wait at least five minutes between drops to minimise any dilution effect. Glaucoma medical therapy continues to evolve with several new preparations currently on the horizon.<sup>10</sup>

New approaches to management of the disease are aimed at treating possible causes of glaucoma which are located outside of the eye. For example, some investigators have already begun to study the use of calcium channel blocker or Ginkgo bilboa extract to treat ischaemia, while other modalities are used for the management of associated risk factors, such as arrhythmias, sleep apnoea and other haemodynamic alterations.<sup>12,13</sup> Many drugs have been reported to have neuroprotective effects (antioxidants, NMDA receptor antagonists, inhibitors of glutamate release, calcium channel blockers, cannabinoids, aspirin, melatonin, vitamin B-12).<sup>15</sup>

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## Sažetak

## SUVREMENO LIJEČENJE GLAUKOMA OTVORENOG KUTA

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U posljednjih nekoliko godina svjedoci smo razvoja velikog broja lijekova za liječenje glaukoma, sa sve većim izborom alternativnih medikacija.

Danas nam liječenje glaukoma stoji na raspolaganju širok izbor novih lijekova, svaki sa različitom efikasnošću i nuspojavama. Nove terapijske mogućnosti za sniženje intraokularnog tlaka omogućavaju nam da poboljšamo compliance i terapijske rezultate, a istovremeno se smanjuje broj lokalnih nuspojava koje se susreću kod konvencionalnih terapijskih shema. Ovaj pregledni članak bavi se načinom djelovanja i svojstvima različitih terapijskih mogućnosti, nakon čega slijede praktični savjeti o lijekovima. Kliničari bi, u liječenju glaukomskih bolesnika, trebali shvatiti, sintetizirati i upotrijebiti svoje znanje o lijekovima koji imaju posebne korisne i štetne strane.

Glaukom je progresivna optikoneuroterapija, karakterizirana ekskavacijom vidnog živca i popratnim oštećenjima vidnog živca i popratnim oštećenjima vidnog polja. Sam pojam glaukoma označava određen broj različitih poremećaja koji zahvaćaju oko, a koji svi kulminiraju smrću retinalnih ganglijskih stanica vidnog živca i oštećenjima vidnog polja. Okosnicu terapije i dalje čini sniženje intraokularnog tlaka, čiji je cilj očuvanje vidne funkcije uz istovremeno poboljšanje kvalitete života. Većina lijekova koji se danas koriste u liječenju glaukoma su prvenstveno usmjereni na sniženje intraokularnog tlaka. Oni se mogu usporediti sa lijekovima za sniženje kolesterola, jer su razvijeni da bi kontrolirali čimbenike rizika koji su doveli do glaukoma, a ne da bi liječili njegov osnovni uzrok.

Vrijedno je spomenuti i koncept ciljnog intraokularnog tlaka. Na samom početku terapije korisno je postaviti ciljni intraokularni tlak pri kojem će daljnja oštećenja vidnog živca biti malo vjerojatna. Obično je ta vrijednost manja za 20-30% od intraokularnog tlaka kod kojeg je došlo do oštećenja. Ako se oštećenje vidnog živca uzrokovano glaukomom pogoršava tijekom terapije, tada je potrebno postaviti novi ciljni intraokularni tlak. primijećeno je da se compliance pogoršava što se više povećava broj lijekova uključenih u terapiju i upute o njihovom uzimanju. Stoga je mudro provjeriti pacijentovu listu lijekova i utvrditi da li neki novi lijekovi na tržištu omogućavaju konsolidaciju terapije. Ovaj pregledni članak odnosi se na primarni glaukom otvorenog kuta gdje je medikamentozna terapija inicijalni način liječenja.