

Glaucoma

— pharmacological treatment

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Leaf of the hemp or marijuana plant *Cannabis sativa*. Cannabis has been shown to lower intraocular pressure

Pharmacological treatment for glaucoma is directed at reducing intraocular pressure (IOP), the main risk factor for the disease. This article looks briefly at how IOP is regulated physiologically and outlines the range of drugs currently available to reduce it

There is more to glaucoma than a raised intraocular pressure (IOP). However, IOP remains the only factor in the disease that can currently be manipulated.

IOP is physiologically regulated by balancing the production and outflow of aqueous humour. In order to produce aqueous humour, plasma moves from the ciliary vasculature to the posterior chamber through the stroma (which mainly consists of connective tissue) and the pigmented and non-pigmented cells of the ciliary epithelium. This movement of plasma is based on the three processes of diffusion, ultrafiltration and active transport. Loss of aqueous humour occurs by two distinct pathways:

- Drainage through the trabecular meshwork (a sponge-like, porous network) and canal of Schlemm, ultimately to the episcleral vein and into the systemic circulation
- Drainage through uveoscleral tissue (ie,

through the ciliary muscle into the suprachoroidal space¹)

Drugs used to treat glaucoma therefore broadly work in one of two ways: either to reduce the production or to increase the drainage (ie, loss) of aqueous humour. Details about these drugs and their pharmacological actions are set out below.

— Parasympathomimetics

Parasympathomimetic drugs mimic the effects of stimulating the parasympathetic nervous system. In the eye, this results in the stimulation of the sphincter pupillae in the iris, which in turn stimulates the ciliary body and opens the trabecular meshwork, allowing an increased outflow of aqueous humour.

The main parasympathomimetic used to lower IOP is pilocarpine. Pilocarpine is an alkaloid derived from the South American shrub *Pilocarpus jaborandi*. It has been used in ophthalmology for over 100 years.

Stimulating the parasympathetic nervous system in the eye also causes pupil constriction, which reduces the amount of light entering the eye and also the overall field of vision. This can be a particular problem for glaucoma patients, who often have a signifi-

cant loss of visual field. This, together with the fact that it needs to be administered three to four times daily, contributes to poor patient compliance.¹ Systemic side effects of pilocarpine include hypersalivation, bronchoconstriction, nausea and vomiting, and diarrhoea. Patients with cardiovascular conduction system disease (ie, His-Purkinje conduction disorder) may be at risk of developing atrioventricular block if pilocarpine is used intensively.² Attempts have been made to limit systemic side effects and improve compliance with sustained release preparations of pilocarpine.³ For example, Ocusert-Pilo is a slow release ophthalmic delivery system of pilocarpine encapsulated in a semi-permeable membranous reservoir. The device is placed under the eyelid and left in place for seven days, releasing a dose of pilocarpine at 20 or 40 micrograms per hour.⁴ An alternative is a sustained release formulation gel formulation of pilocarpine.⁵ This is applied at bedtime to provide 24h control of the IOP and has been shown to reduce the incidence of the adverse effect of myopia.

— Sympathomimetics

Both non-selective (ie, stimulate both alpha- and beta-adrenergic receptors) and selective

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(ie, stimulate only beta-adrenergic receptors) sympathomimetics can be used to lower IOP.

Adrenaline Adrenaline is a non-selective sympathomimetic (although it has more effect on beta- than alpha-adrenoceptors) and was the first sympathomimetic drug to be used in the treatment of glaucoma. Stimulation of the various subtypes of alpha- and beta-adrenoceptors have opposing effects in the eye. For example, stimulating alpha-1-adrenoceptors in the ciliary body causes vasoconstriction, which results in a decrease in aqueous humour production, while stimulating beta-2-adrenoceptors in the ciliary epithelium increases aqueous humour production. Stimulating beta-2-adrenoceptors in the trabecular meshwork and alpha-2-adrenoceptors, which control uveoscleral outflow, increases the outflow of aqueous humour. These cumulative effects result in a reduction of IOP.

Adrenaline has a short half life and consequently its action is rapidly followed by vasodilation of conjunctival blood vessels in the eye, leading to redness. Systemic side effects have also been noted with the use of adrenaline eye drops.⁶ Adrenaline is photosensitive and administration of drops may lead to conjunctival pigmentation, which in extreme cases may accumulate as lachrymal stones.⁷ Adrenaline has also been reported to cause cystoid macular oedema (oedema in the macular area of the retina) in patients with aphakia (ie, without a natural or artificial lens).⁸ This is a reversible condition with symptoms of blurred vision, decreased visual acuity and haemorrhage.

Guanethidine Guanethidine increases and prolongs the sensitivity of the eye to adrenaline. This means that lower concentrations of adrenaline can be used which results in lower systemic absorption.⁹ One study has shown that a combination of guanethidine 1 per cent and 0.25 or 0.5 per cent adrenaline is as effective at lowering IOP as adrenaline 1 per cent alone.¹⁰ Guanethidine is available as a combined preparation with adrenaline (Ganda) in the respective strengths of 1 and 0.2 per cent, and 3 and 0.5 per cent. Higher strength combinations of guanethidine and adrenaline have been associated with corneal ulceration. This combination product is currently used rarely, because it causes hyperaemia and latanoprost achieves greater IOP reduction.

Dipivalyl adrenaline Dipivalyl adrenaline (dipivefrin) is a pro-drug of adrenaline which has improved lipophilicity, leading to better corneal penetration. The improved corneal penetration is reflected in the strengths of solutions used — 0.1 per cent dipivalyl adrenaline solutions achieve similar reductions in IOP as adrenaline 2 per cent solutions.¹¹ Dipivalyl adrenaline is not now

generally used because of the incidence of hyperaemia of the conjunctiva.

One study has shown that dipivalyl adrenaline is effective when used in combination with latanoprost.¹² The combination of the two drugs did not result in an “aqueous flare”, a side effect of adrenergic agonists that is believed to occur by a prostaglandin-mediated pathway.

Brimonidine Brimonidine is a highly selective alpha-2-adrenoceptor agonist. It is licensed as monotherapy in patients for whom topical beta-blocker therapy is contraindicated, and as adjunctive therapy to other IOP-lowering medicines when a target IOP is not achieved using a single agent.

Brimonidine causes a beta-adrenoceptor-mediated reduction in IOP by altering blood flow to the uvea (iris, the choroid and the ciliary body), creating a shift in the fluid dynamics within the uvea and the posterior and anterior chamber. This effect is reduced over the course of the first eight days of treatment, after which time an increase in uveoscleral outflow is observed. The increase in uveoscleral outflow is thought to result from an increase in prostaglandin production through the stimulation of beta-1-adrenoceptors which in turn affects the prostaglandin-F receptor, in a similar way to latanoprost (see later).¹³ In addition to this, beta-2-adrenoceptor stimulation relaxes the ciliary muscle and facilitates the percolation of aqueous humour.

Animal experiments also suggest that brimonidine has a neuroprotective effect on retinal ganglion cells.¹⁴ As will be discussed below, this effect has been shown with betaxolol and, possibly to a lesser extent, with other beta-blockers. This neuroprotective effect has yet to be demonstrated in the human eye.

Apraclonidine Apraclonidine is selective for alpha-adrenoceptors, but affects both main types (alpha-1 and alpha-2). Its use is restricted to delaying laser treatment or surgery in patients with glaucoma that is uncontrolled by drug treatment or in controlling IOP following anterior segment surgery (ie, short-term use). Its use has been superseded by brimonidine which has a more convenient dosing schedule and is less likely to cause tachyphylaxis and unpleasant local side effects (eg, eyelid swelling). Apraclonidine reduces IOP by inducing an increase in the trabecular outflow.

— Beta-blockers

Currently licensed beta-blockers include betaxolol (a selective beta-1-adrenoceptor antagonist), and timolol, carteolol, levobunolol and metipranolol (all non-selective beta-adrenoceptor antagonists). Timolol was the first agent to be marketed and continues to be the gold standard against which all new

glaucoma treatments are measured. Metipranolol use is restricted to the treatment of chronic open angle glaucoma in patients sensitive to preservatives, including patients who use soft contact lenses.

The mechanism of beta-blockers in reducing IOP is not fully understood, but is thought to include the blockade of beta-2-adrenoceptor-mediated active transport involved in the production of aqueous humour from the ciliary epithelium. In addition to this, there is a possibility that beta-blockers alter the blood flow within the ciliary processes, reducing the hydrostatic pressure within the ciliary vasculature.¹⁵ This reduces the rate of diffusion and ultrafiltration of fluid from the plasma to the posterior chamber of the eye. This theory is unconfirmed and some experimental work shows that beta-blockers cause little or no change in ocular blood flow.¹⁶

Betaxolol is a selective beta-1-adrenoceptor antagonist and blockade of beta-2-adrenoceptors cannot account for its effects. The exact mechanism of action is not known, but its IOP-lowering effect (which is less potent than that of the non-selective agents) is possibly mediated by a neuroprotective effect on retinal ganglion cells.¹⁷ Metipranolol and timolol are also thought to be retinal neuroprotectants, but to a lesser degree than betaxolol (although some studies have shown little difference in visual field performance between selective and non-selective beta-blockers).

The side effects of the various beta-blockers can be directly related to their pharmacological and physiological actions, a summary profile of which is set out in Panel 1. Beta-2-adrenoceptor blockade is associated with respiratory symptoms, such as bronchoconstriction, just as beta-1-adrenoceptor blockade is associated with cardiovascular effects, such as hypotension and bradycardia. Many of these side effects are ameliorated to a certain degree when the agent possesses some partial agonist activity often referred to as intrinsic sympathomimetic activity. Typical central nervous system side effects, such as nightmares and anxiety, are induced by drugs which cross into the central nervous system because of their lipophilicity. Such effects can be avoided by using a hydrophilic agent.

The Committee on Safety of Medicines has advised that beta-blockers, including those agents with apparent cardioselectivity, should be used with caution in patients with obstructive airways disease. The severity of systemic side effects is, however, reduced because of the fact that beta-blockers are used topically in glaucoma. Systemic absorption can be further reduced by the use of nasolacrimal occlusion (ie, patients placing their finger over the inner canthus [junction between upper and lower lid on the nasal side] when administering their drops). This technique has been shown to improve levels of drug in aqueous humour at lower administered concentrations.¹⁸

— Carbonic anhydrase inhibitors

The carbonic anhydrase (CA) enzymes are zinc-containing isoenzymes, of which there are 14 forms, each having different subcellular localisation (eg, membrane-bound [CA-IV, CA-IX, CA-XII and CA-XIV], cytosolic [CA-I, CA-II and CA-III], mitochondria-bound [CA-V] and secreted [CA-VI]). The isoenzymes relevant to the human eye are CA-I, CA-II and CA-IV.¹⁹

CA enzymes catalyse the interconversion between carbon dioxide and the bicarbonate ion. The bicarbonate ion is involved in the production of aqueous humour within the ciliary process of the eye and inhibition of carbonic anhydrase results in a decrease in production of aqueous humour.¹⁹

Acetazolamide has been used to treat primary open angle glaucoma for over 40 years.²³ Three other systemic sulphonamide-derived CA inhibitors have been used clinically: methazolamide, ethoxzolamide and dichlorophenamide.²⁰ All four of these agents reduce IOP markedly (by 25–30 per cent). However, they need to be given orally, because they do not penetrate easily into the eye. This means that they also inhibit the various CA isoenzymes present in tissues other than the eye, leading to a range of side effects.²¹ These include tingling of extremities, numbness, metallic taste, depression, fatigue, malaise, decreased libido, gastrointestinal irritation, weight loss, metabolic acidosis and renal calculi.²¹ Ocular side effects (transient myopia and blurred vision) are probably due to inhibition of CA

Panel 1: Summary of the pharmacological and physiological profiles of the various beta-blockers used to treat glaucoma

	Partial agonist activity	Beta-selective	Lipophilic/hydrophilic	Membrane stabilising effect
■ Betaxolol	No	Yes	Highly lipophilic	Yes
■ Levobunilol	No	No	Lipophilic	No
■ Timolol	No	No	Lipophilic	No
■ Carteolol	Yes	No	Hydrophilic	No
■ Metipranolol	No	No	Hydrophilic	Yes

isoenzyme I and II in the corneal endothelium and CA isoenzyme II in the lens.²²

Because acetazolamide needs to be given orally (and also frequently — four times a day), it is unsuitable for long-term use. Sustained release capsules and osmotic pump delivery systems²⁵ are available which reduce the frequency of administration, but still produce systemic effects.

CA inhibitors that can be used topically have also been developed — namely brinzolamide and dorzolamide. Dorzolamide, a non-bacteriostatic sulphonamide, is primarily metabolised to N-desethyl-dorzolamide. Both parent drug and metabolite inhibit CA-I, -II, and -IV.²² Dorzolamide penetrates the cornea on application and inhibits CA-II in the ciliary body, slowing the production of bicarbonates and thereby decreasing sodium and fluid transport, reducing the secretion of aqueous humour.²² Dorzolamide is licensed in the UK as a topically administered CA inhibitor for ocular hypertension, primary open angle glaucoma and pseudoexfoliative glaucoma (caused by plugging of the canals of the trabecular meshwork). It is licensed as an adjunct to beta-blockers, and is used twice daily in combination, and three times daily alone. A combination of dorzolamide plus timolol (Cosopt) is also available, which is also administered twice daily. CA-I, -II and -IV are also present in the cornea, and so there is concern about whether dorzolamide might be associated with corneal changes.

Brinzolamide is administered twice a day and has a more physiological pH — for these reasons it is often better tolerated than dorzolamide.

— Prostaglandin analogues

Three prostaglandin analogues are currently licensed in the UK for the treatment of raised IOP in open angle glaucoma and ocular hypertension — bimatoprost, latanoprost and travoprost.

Latanoprost and travoprost are structurally similar compounds, both being isopropyl ester prodrugs of the prostaglandin F receptor (FP) agonist, PGF₂.²³ Both drugs are rapidly hydrolysed by esterases in the cornea to their respective free acids, which have a high affinity for the FP receptor.

The stimulation of FP receptors by the free acids of latanoprost and travoprost increases the loss of aqueous humour by the uveoscleral route by up to 60 per cent.²⁴ The production of aqueous humour, and its drainage through the trabecular network, seems not to be affected.²⁵

The change in outflow through the uveoscleral pathway is mediated by cellular changes within the ciliary muscle. The ciliary muscle is composed of bundles of muscle fibres supported by an extracellular matrix (ECM). The major components of

the ECM are collagens I, III, IV and VI, laminin, fibronectin, hyaluran and elastin.²⁶ ECM undergoes regeneration and degradation on a cyclical basis, its breakdown being mediated by matrix metalloproteinases (MMPs). In patients treated with latanoprost and PGF₂, there is an increase in MMPs and in the breakdown of ECM,²⁶ resulting in a significant change in the structure of the ciliary muscle, making it less resistant to the flow of aqueous humour.

The mechanism of bimatoprost is unclear. There is controversy as to whether it is metabolised to its free acid, which is almost identical to the free acid of latanoprost, or whether it has an effect in its unmetabolised form. This is because its structure is similar to another FP-receptor agonist, prostamide F₂, which has a markedly different affinity for the FP receptor than the free acids of latanoprost and travoprost. Bimatoprost is reported as having an effect on both trabecular and uveoscleral drainage, with distinct structural changes being observed in the monkey eye trabecular meshwork at post mortem.²⁷

The adverse effects of all three drugs are similar:

- Conjunctival hyperaemia (bloodshot conjunctiva giving the appearance of red eye)
- Iridial pigmentation (alteration of the colour of the irises resulting in a darker more intense eye colour)
- Hypertrichosis (eyelashes grow in all dimensions and darken)
- Anterior uveitis (inflammation of the iris and the ciliary body)
- Cystoid macular oedema

The incidence and severity of side effects varies between the agents. Iridial pigmentation is dependent on eye colour, being more common in patients with heterochromic eyes (ie, blue-brown, green-brown) than in those with homochromic eye colour.²⁸ The effect appears to be secondary to increased levels of eumelanin (which is found in hair and skin and colours hair from brown to black) in the iridial melanocytes, rather than an increase in the number of melanocytes. Latanoprost has been shown to produce increased levels of prostaglandin E₂ in iridial melanocytes, which is potentially implicated in the cell signalling processes involved in the hyperpigmentation. One of the initial concerns about this side effect was that melanomas would develop, but as yet no pathological changes have been observed in iridial melanocytes as a result of treatment with prostaglandin analogues.²⁸

The hypertrichotic effect appears to be similar for all three agents.²⁹ The exact mechanism of action is unclear, but seems to be secondary to an FP receptor-mediated

stimulation of follicular melanocytes, which may then affect keratinocytes in the hair follicle.

Anterior uveitis and cystoid macular oedema are serious adverse effects and, although rare, must be taken into account when prescribing prostaglandin analogues. The incidence of both appears to be increased in pseudophakic (patients with an artificial lens following cataract surgery) and aphakic patients who already have a predisposition to the reactions. Agents should be used with caution in such patients.

— Cannabinoids

Cannabis sativa contains over 480 chemical constituents, of which 66 are known collectively as the cannabinoids,³⁰ the main psychoactive principle being Δ⁹-tetrahydrocannabinol.³¹ Cannabinoids exert their effects through cannabinoid receptors which are present in the brain, spinal cord and the eye, and in peripheral tissues, such as the lung, heart, and urogenital and gastrointestinal tracts.³¹

Cannabis, when smoked, has been shown in small studies to lower IOP by 25–30 per cent.³² Other ocular effects include a reduction in tear production and a change in pupil size.

How cannabinoids lower IOP is not fully understood. It was initially thought that a central nervous system-mediated mechanism was involved, but one study has shown that the topical application of cannabinoids can reduce IOP.³³ A reduction in aqueous humour production by 18 per cent has been demonstrated in primates using the synthetic cannabinoid WIN-55,212-2.³⁴ However, this is insufficient to reduce IOP, and therefore other mechanisms are likely to be involved. These potentially include:

- Decreasing the secretion of ciliary processes (ie, aqueous humour)³⁴
- Dilating the ocular blood vessels through a possible beta-adrenergic action³⁴
- Inhibiting calcium influx through presynaptic channels, which may in turn reduce noradrenaline release in the ciliary body, ultimately leading to a decrease in the production of aqueous humour³⁴
- An effect on prostaglandin pathways³⁴

In order that the systemic effects (eg, euphoria, deterioration in short-term memory, cognitive impairments) be reduced, topical application is the preferred route of administration. Unfortunately, cannabinoids have poor aqueous solubility, and vehicles used to solubilise them (ie, light mineral oil and sesame oil) have proved to be irritant to the human eye.³⁴ Cyclodextrins have also been used to improve solubility.

Future

The focus of the drug treatment of glaucoma is currently lowering IOP. Drugs are increasingly being investigated for their efficacy in treating glaucoma by other means, for example, by protecting retinal ganglion cells, but these will not be available for many years.

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