Glaucoma medical treatment: philosophy, principles and practice

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ARTICLE

Abstract

There have been numerous recent advances in the management of glaucoma, not least the development of new drugs to help manage raised intraocular pressure. In addition, the concepts of improving blood flow to the optic nerve head and neuroprotection are currently provoking considerable interest. This article considers the aims and philosophy of glaucoma drug therapy, summarises some of the basic facts and principles of modern glaucoma medications, and suggests a practical approach to the choice of therapy.

Key words Blood flow, Intraocular pressure, Neuroprotection, Primary open angle glaucoma, Topical medications

Philosophy

Primary open-angle glaucoma is a complex disease for which a number of risk factors have been identified, including intraocular pressure, age, race and family history.[1,2] Due to our relatively limited understanding of the pathophysiology of glaucomatous optic neuropathy, therapy is currently limited to dealing with one parameter, namely intraocular pressure (IOP). All glaucoma therapies (medical, laser or surgery) are designed to lower IOP.

It has previously been shown that many patients on topical medications will not achieve a satisfactory IOP level and, with the passage of time, may lose visual field.[3,4] However, in recent years several new drugs have been developed to help manage elevated IOP. These medications consist of new compounds within classes of drugs already in use, combination products, or novel delivery systems. These have increased the options for the ophthalmologist.

In the past, the effectiveness of a medication in the treatment of glaucoma was measured by its ability to lower IOP. More recently, other factors have been considered, such as blood supply to the optic nerve and neuroprotection of the ganglia. The clinical importance of these variables has not yet been fully proven, but it is anticipated that future improvements in the efficacy of glaucoma treatment may include assessment of these parameters. Indeed compounds are under evaluation that affect the function of the optic nerve (via improved blood supply or improved neuronal cell physiology) but may or may not lower IOP. It may even be possible in the future to therapeutically alter the human genome, genetically deliver neuroprotective substances or aid regeneration of the optic nerve axons.

The main aim of glaucoma therapy must still be the preservation of visual function. At the same time, the therapy should not have adverse side effects and should not affect the quality of life of the patient (by causing either side effects or inconvenience and disruption of daily lifestyle). The cost of the therapy, both direct and indirect, must also be taken into consideration.[5]

Currently, typical glaucoma management consists of lowering the IOP to a satisfactory and safe target level.[6] To determine the success of this treatment, the patient must be followed long-term with routine assessment of IOP, discs and fields to exclude progressive damage. IOP, although a vital criterion in the management of the glaucoma patient, poses a number of problems, including the fact that some glaucoma patients continue to have progressive damage despite an apparently satisfactory IOP level, that others (i.e. with normal tension glaucoma) develop characteristic glaucomatous damage despite normal IOPs, that damage cannot be reversed, and that long-term follow-up is required before the success of therapy can be determined. Future glaucoma therapy will need to address these issues.

In this century it may become possible to investigate the stability of the optic nerve at the time of lowering the IOP. Such tests might be based on visual function or metabolism of the optic nerve *in vivo*. If, despite a lower IOP, no improvement in visual function occurs, or an abnormal metabolism is noted, this could suggest that a lower target IOP is required or that other factors, such as blood flow, might need to be addressed. It may be possible in the future to classify patients more accurately according to the factors that influence their disease, with therapy directed not only at IOP

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but also to the optic nerve directly. The success or otherwise of that therapy will also be determined in a shorter time.

Principles

This review will concentrate on the topical agents currently used to treat glaucoma, and will be restricted to the more commonly used agents.

Current glaucoma drugs alter cellular functions within the eye, either via interaction with receptors or via specific enzymes. Ion channels of the cells are probably important effectors of responses initiated by glaucoma drugs acting via receptors.[7] Signal transduction mediated by drug receptors is an important concept, with new developments occurring particularly in two areas: firstly, the discovery (via molecular biology techniques) of new subtypes of receptors (this includes new subtypes of receptors relevant to current glaucoma medications) and, secondly, the improved understanding of the biochemical events of signal tranduction initiated by receptor activation.[7]

In basic terms, glaucoma drugs reduce IOP by causing a decrease in aqueous production or by increasing outflow (either through conventional channels, i.e. the trabecular meshwork, or via uveoscleral outflow). The concepts of improvement of blood flow to the optic nerve head and neuroprotection have recently been raised as possible additional actions of certain drugs.

Specific agents

Beta blockers

Beta blockers have become the mainstay of glaucoma medical therapy. Receptor selectivity is important, with non-selective beta blockers affecting both beta-1 and beta-2 receptors, in contrast to beta-1-selective agents which are more selective for the beta-1 receptors. This selectivity affects both safety and efficacy.

Mechanism: Beta blockers reduce IOP by decreasing aqueous humour production by the ciliary body.[8]

Efficacy: Mean peak IOP is lowered by 25% and mean trough by 20% using non-selective agents.[9,10] IOP lowering is less with betaxolol, the beta-1-selective agent.[11] If beta blockers alone do not achieve adequate pressure lowering, then one of the other classes of agents can be used as adjunctive therapy. Beta blockers are generally administered twice daily. Levobunolol may be used once daily in some patients. Timolol XE is a once-daily formulation. If more than one concentration of the drug is available, the lower concentration should be used and is generally as effective in the majority of patients.

Side effects: Contraindications to beta blockers include severe chronic obstructive airways disease, asthma, heart block, bradycardia and congestive cardiac failure. Other systemic side effects are also common, including neurological symptoms such as depression and malaise. The elderly are more at risk of side effects. While selective beta blockers may lessen the incidence and severity of adverse events, they are not completely safe, and similar, if less severe, complications may occur. Topical beta blockers are effective and well tolerated by the majority of patients.[12] Rarely these agents have been linked with patient fatality. It is important that the ophthalmologist identify those patients in whom the product can safely be used and those in whom it is contraindicated, particularly as there are now adequate alternative choices.

Topical carbonic anhydrase inhibitors

Dorzolamide, a topical carbonic anhydrase inhibitor, differs in structure from the oral agents. It has increased aqueous solubility and lipid–water solubility, allowing corneal penetration. Dorzolamide 2.0% reduced aqueous flow by 38% (measured by fluorophotometry).[13]

Mechanism: Inhibition of the carbonic anhydrase enzyme lowers IOP due to a decreased production of aqueous. In order to inhibit the enzyme, carbonic anhydrase inhibitors must inhibit nearly 100% of the enzyme at all times. Topical carbonic anhydrase inhibitors act locally in the ciliary body, inhibiting aqueous production, but do not affect total body carbonic anhydrase, thus minimising systemic symptoms.

Efficacy: Dorzolamide 2% used three times daily resulted in a peak reduction of IOP of 22%, with a trough reduction of 18%.[14] In a 12 month study comparing dorzolamide thrice daily with timolol 0.5% b.d. and betaxolol 0.5% b.d., timolol was more effective than the other two drugs. No statistical difference was found between dorzolamide and betaxolol.[15]

Additivity: Dorzolamide has an additive effect with timolol, reducing the IOP by an additional 13–21%.[16] Comparing the additive effect of dorzolamide b.d. with pilocarpine 2% q.i.d., additional IOP reductions achieved were 13% and 10% respectively.[17] Dorzolamide thus appears to be a reasonable choice for adjuvant therapy.

Side effects: The only frequently reported systemic effect is a bitter taste after drop instillation, and the drug appears to be well tolerated, with only 5% discontinuing the drug due to an adverse event in controlled clinical trials. The majority of these side effects were ocular, and included topical discomfort and allergy.[15] Most patients tolerate the drug well.

Prostaglandin analogues

Prostaglandins are derived from arachidonic acid and display a wide range of biological functions.

Mechanism: Prostaglandins reduce IOP by increasing uveoscleral outflow,[18] possibly due to relaxation of the ciliary muscle and creating dilated spaces between ciliary muscle bundles, as well as due to alterations in the metabolism of the extracellular matrix that surrounds the ciliary muscle cells.[19] Since uveoscleral flow is independent of the episcleral venous system, it is possible to obtain particularly low IOPs (9–11 mmHg).[20]

Efficacy: Latanoprost reduces IOP by 25–34% and appears to be more effective than timolol 0.5%.[21–23] The drug is administered once daily, with evening instillation

proving more effective.[21] There appears to be good diurnal control of IOP, with no tachyphyllaxis over 12 months.

Additivity: Latanoprost is additive to timolol, reducing the IOP by an additional 13–35%.[24,25]

Side effects: Common side effects include conjunctival hyperaemia, discomfort and blurred vision. As prostaglandins mediate inflammation, they may precipitate intraocular inflammation in predisposed eyes. Increased iris pigmentation occurred in 11–23% of eyes on latanoprost.[21,22] This increased pigmentation occurs slowly and does not change after the cessation of the drug. Iris naevi do not appear to be affected. The long-term effects are not known, but the increased pigmentation appears to arise from the increased production of melanin within the iris melanocytes.[26] Few systemic side effects are reported, but include headache and upper respiratory tract symptoms.

Alpha agonists

Apraclonidine, a derivative of clonidine, was initially introduced, but is not recommended for chronic use. Brimonidine, a highly-selective alpha-2 agonist, with fewer systemic side effects, was developed more recently.

Mechanism: Brimonidine reduces IOP by a combination of aqueous reduction and increase in uveoscleral outflow.[27]

Efficacy: Compared with timolol 0.5%, brimonidine was equally effective at the 2 h peak, but less effective at trough (12 h). IOP is reduced by between 5.0 and 6.2 mmHg. No difference was found in the optic discs or fields in the two groups.[28] Brimonidine produces a statistically greater IOP reduction than betaxolol.[29] No adverse effect was noted on the ocular haemodynamics after the instillation of brimonidine.[30]

Additivity: Brimonidine has a good additive effect with the beta blockers.

Side effects: Brimonidine has no effect on pulmonary function, heart rate or blood pressure.[28] Possible adverse events include dry mouth and fatigue or drowsiness. Local effects include allergy (in 12% at 12 months) and discomfort.

Cholinergic agents

Although the use of cholinergics, such as pilocarpine, has declined since the introduction of the newer drugs mentioned above, which have less troublesome side effects, there is still a use for these drugs, which are relatively inexpensive and lower IOP well. Formulations such as pilocarpine gel and Ocuserts[31,32] may be more convenient for the patients.

Mechanism: Increase facility of outflow through the trabecular meshwork.

Efficacy: Reduce IOP by 20–30%.

Additivity: Additive to beta blockers, adrenergic agents and carbonic anhydrase inhibitors.

Side effects: Safe systemically, but cause local symptoms in the form of miosis, brow ache, myopic shift and exacerbation of the symptoms of cataract.

Combination therapies

Combination products of more than one agent have been developed, which have the same ocular hypotensive effect and safety profile of the individual components, with the added benefit of only one eyedrop to administer. An example of such a combination agent is Cosopt, which combines timolol maleate and dorzolamide. This product, given twice daily, demonstrated the same ocular hypotensive efficacy and safety as timolol b.d. and dorzolamide t.d.s. given separately but together.[33] The IOP is lowered by 21.6% with Cosopt and by 21.8% with concomitant dorzolamide and timolol.[16]

The glaucoma drugs discussed above are the commonly used preparations in the United Kingdom and do not constitute an exhaustive list.

Practice

In practice, each patient must be assessed individually in order to select the most appropriate therapy. Both the action and side effect profile of the drug need to be considered, as well as the indications or contraindications in the individual patient.

It is normal practice to commence treatment with a single agent and to assess the response to treatment before considering adding a further eyedrop. The ophthalmologist should be familiar with the actions, interactions and side effects of the individual preparations in order to choose the most appopriate drug or combination of drugs. It has been suggested that if the initial drug does not achieve a satisfactory response, this should be stopped before adding a second drop.[34] The concept of maximal medical therapy is now outmoded and, in the majority of cases, more than two topical medications are rarely indicated.

Currently, beta blockers, with long-term experience of their usage, are still the first line of therapy where no contraindication exists. If additional IOP lowering is required, one of the newer agents, or pilocarpine, may be added. Where a beta blocker is contraindicated, treatment can be commenced with one of the newer agents. Further long-term experience with the new drugs will enable us to assess whether, in the future, they should be used as the initial therapy.

Conclusion

Glaucoma medical therapy offers wide choice of options, with new medications available that act in a variety of ways to reduce IOP. It is possible that current research into the genetics of glaucoma may in the future allow for gene therapy, so that the effect of the glaucomatous gene on the trabecular meshwork or optic nerve can be

corrected. Problems with the concept of neuroprotection include how to deliver the product to the site of action without clinical side effects, and the limited knowledge of mechanisms of cell death in glaucoma. Another problem is how best to measure protection of physiological function. Problems with blood flow include the difficulties of measurement of haemodynamics in the relevant small and often anatomically variable retrolaminar blood vessels.

Future glaucoma therapy may indeed focus not only on IOP reduction but also on improved optic nerve head blood flow, neuroprotection, genetic therapy and optic nerve regeneration. However, before abandoning the concept of IOP reduction, the potential benefits of direct treatment of the optic nerve in glaucoma still need to be proven, as well as methods developed to deliver these medicines in a safe and effective manner to the target tissue.

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