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REVIEW

Glaucoma therapy may take your breath away

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Abstract

Chronic simple glaucoma is a common disease in old age and lowering intraocular pressure is the treatment strategy. Although this can be achieved surgically, medical treatment with eye drops is more often prescribed. β-antagonists are the class of drug most often chosen, although other medical therapies are available. Systemic absorption of β-antagonist eye drops can cause unsuspected respiratory impairment. Physicians should be alert to the possibility of respiratory side-effects of topical therapy with β-antagonists and whenever such side-effects occur should use alternative treatments.

Keywords: *β-antagonists, glaucoma, respiratory impairment*

Introduction

Chronic simple glaucoma is a common disease in old age. Asymptomatic until visual field loss is noticed, it affects more than 5% of the population by 65 years [1]. The physical signs are of an enlarged optic disc cup, together with a visual field defect, reflecting the loss of optic nerve fibres. The exact mechanism by which the optic nerve head becomes damaged is unclear. Raised intraocular pressure (IOP) is the main risk factor for the development of glaucoma, and lowering of IOP the treatment. It is most important to identify people with glaucoma and lower their IOP.

Although lowering a raised pressure seems to slow progression of visual loss, this has never been tested by placebo-controlled studies. Epidemiological studies show that one-third of glaucoma suffers have recorded pressures within the normal range of 8–21 mmHg [2]. The effectiveness of ocular hypotensive treatment for those with normal pressure is unclear.

IOP reflects the balance between aqueous humour production and drainage. Production depends upon a combination of filtration and osmotic pressures, together with active ion transport, based upon a Na/K-ATPase. Drainage is mostly via the trabecular meshwork into the canal of Schlemm. A portion of the aqueous outflow is through the longitudinal fibres of the ciliary muscle into the supraciliary-suprachoroidal space and out through the sclera. (The sclera has perforations, surrounded by loose connective tissue spaces, to admit blood vessels and nerves.) This uveoscleral drainage may account for 10% (0.2 μl/min) of the total [3].

Surgical therapy

Treatment options for reducing IOP are surgery or medical therapy, the latter almost always in the form of eye drops. Surgery may be by argon laser trabeculoplasty or trabeculectomy. Trabeculoplasty involves administering laser burns to the trabecular meshwork which increases aqueous drainage. It is more effective in elderly people than in younger age groups. The effectiveness falls with time and after 5 years up to two-thirds will have failed [4]. Trabeculectomy is a technique whereby a drainage channel is fashioned superiorly between the anterior chamber and the subconjuctival space via a sclerostomy. This is the most effective primary treatment for reducing IOP and preserving visual fields [5]. Most ophthalmologists prefer initial medical therapy, reserving surgery for treatment failures.

Although very effective at lowering IOP, trabeculectomy is associated with cataract formation in up to one-third of eyes within 1 year. In addition, surgery may reduce corrected visual acuity by inducing astigmatism. Finally there is a significant failure rate—up to 10% in

the first year, with a proportion ceasing to function later due to the development of subconjunctival fibrosis. Antiproliferative agents applied at surgery (5-fluorouracil and mitomycin C) have improved the long-term success rate but at the cost of increased frequency of other surgical complications, such as too low an IOP and endophthalmitis. Because of the risk of causing visual damage to an eye with normal visual acuity, surgery is usually reserved for cases not responding to medical treatment or patients with advanced disease.

Improved surgical techniques and greater awareness of the problems of medical therapy mean that surgery is being used more often as a primary treatment or for failure of IOP control with a single agent.

Topical therapy

Most medical therapy for glaucoma is given as eye drops. Ocular cholinergic agents, such as pilocarpine, have been used since the latter half of the nineteenth century. Pilocarpine acts at parasympathetic muscarinic receptor site to cause ciliary muscle spasm and pupillary miosis. Contraction of the ciliary muscle produces traction on the trabecular meshwork, facilitating aqueous humour drainage and lowering IOP [6]. Local side-effects—such as headaches, due to ciliary muscle spasm, decreased vision in poor illumination, due to miosis, and accommodative myopia—cause the drug to be poorly tolerated. Compliance is poor in many cases [7], particularly as drops need to be put in four times a day.

β-receptors

β-adrenergic receptors are found on the ciliary body microvasculature and trabecular meshwork cells [8]. There is evidence that β-receptor stimulation increases aqueous formation by increased ciliary body perfusion secondary to arteriolar vasodilatation as well as increasing the permeability of ciliary capillaries [9].

Topical β-blockers transformed the management of glaucoma following their introduction in the 1970s and they remain the most commonly used form of treatment. Their principal action is to reduce aqueous formation [10], although their exact mechanism of action remains unclear. They are excellent ocular hypotensives and, because they have few local side-effects and are given only twice daily, are popular with doctor and patient alike. Several β-blockers—both selective and non-selective—reduce IOP. Pharmacodynamic factors seem more important than their β-1/β-2 selectivity or absolute receptor affinity. For example, the β-1 receptor antagonist betaxolol is an effective ocular hypotensive agent, yet the ciliary and trabecular receptors are predominantly of the β-2 subclass [11]. The relationship of β-receptors to control of IOP needs further elucidation. The effects of a topical β-antagonist on IOP are synergistic with pilocarpine, and the two drugs are often prescribed together. This means that the patient may have to administer six drops daily to each eye, bringing inevitable problems of compliance for many.

Systemic absorption

Drugs administered topically to the eye gain access to the systemic circulation via the nasolacrimal duct and the nasal mucosa. This avoids first-pass metabolism by the liver and significant amounts of topically administered drugs may be absorbed into the systemic circulation. For example, the standard topical dose of two drops of a 0.5% timolol solution, one to each eye, can approximate to the 10 mg oral dose given to treat systemic hypertension or angina [12].

Respiratory side-effects

Precipitation of asthma and exacerbation of chronic obstructive disease are recognized complications of topical β-blockers [13, 14], which should not be given to patients with a history of reversible airways obstruction. Many elderly people [15] have undiagnosed airways disease. This is partly because respiratory disease develops insidiously and partly because other medical conditions prevent breathlessness being noticed. In addition, elderly people have a reduced awareness of bronchoconstriction and may not notice symptoms when there is a fall of as much as 20% in forced expiratory volume in 1 s (FEV_1) [16]. This, coupled to an attitude that accepts reduced exercise tolerance and breathlessness as part of old age, results in elderly patients reporting fewer respiratory symptoms than younger ones. Recent work focusing specifically on elderly patients receiving topical timolol challenges the assumption that, in the absence of a history and symptoms of chest problems, topical β-antagonist therapy is safe.

In one randomized, double-masked, crossover study [17] 80 patients, aged over 60 years, without history of airways disease and using the non-selective β-antagonist timolol for at least 1 year were recruited. Therapy was changed to the cardio-selective betaxolol or the sympathomimetic agent dipivefrin. The study comprised two phases and all patients who completed both phases underwent a change in therapy. Spirometry was recorded on enrolment and at the end of each phase. There was a statistically significant ($P < 0.001$), effect of changing treatment to betaxolol or dipivefrin for mean peak flow (PF) and FEV_1. There was a significant ($P < 0.01$) improvement in the changes in mean FEV_1/force vital capacity ratio. Compared with timolol, mean PFs (95% CIs) using betaxolol and dipivefrin were greater by 39 l/min (27, 51) and 42 l/min (30, 54)

respectively. In addition, mean FEV_1 values (95% CIs) using betaxolol and dipivefrin were greater by 0.14 l (0.10, 0.18) and 0.20 l (0.16, 0.25). Of the 80 patients enrolled, 21 (26%) demonstrated clinically significant reversible airflow tract obstruction by improving both FEV_1 and PF by more than 15%. Recently the definition of 'clinically significant change in spirometry' has been changed to include an absolute improvement of 200 ml in FEV_1. Of the 21 improvers only four demonstrated changes less than 200 ml; they were in the range of 150–190 ml.

A second paper [18] reported an open study of changes in lung function tests. Fifty-two patients taking timolol had treatment changed to pilocarpine or betaxolol and 20 controls continued to take timolol. Spirometry was recorded at enrolment and repeated after 4 weeks. Changing from timolol to either pilocarpine or the betaxolol produced improvement in lung function tests. In the treatment change group, mean PF increased from 278 l/min to 328 l/min ($P < 0.001$) and mean FEV_1 from 1.66 l to 1.85 l ($P < 0.001$). Spirometry in a control group of 20 subjects was unchanged. Nineteen out of 47 patients completing the trial demonstrated clinically significant reversible airflow tract obstruction, defined as an increase of 15% or more in both PF and FEV_1.

Of particular concern are the high proportions of patients reported as demonstrating clinically significant reversible airflow tract obstruction (26% in the first study and 40% in the second). Such people are liable to develop severe bronchospasm, especially if they develop a respiratory tract infection. Therapy with β-antagonists is contra-indicated in such patients, even if they are asymptomatic. By using a standard symptom inquiry and the spirometric response to nebulized salbutamol, both studies attempted to identify, in advance of change in therapy, patients who would show reversible airflow tract obstruction. They found no reliable combination that would identify in advance all patients who would improve on changing therapy.

Two studies of elderly people starting β-antagonists have been reported. A US survey [19] of drugs given to a population receiving Medicaid found that, of 125 000 elderly patients commencing topical β-antagonists, 21 096 first prescriptions for bronchodilators were subsequently issued without stopping β-blockers. Of equal importance is the fact that in a further 3386 subjects previous therapy for airways disease was increased rather than eye drops being discontinued.

The second study [20] reports the results of 40 newly diagnosed glaucoma patients (mean age 74 years) recruited into a randomized, double-masked study. The enrolment criteria excluded those with a history of airflow tract obstruction and all subjects were mobile with no more than a single-point stick. Treatment groups received timolol or betaxolol to both eyes. Spirometry was performed before and after 4 weeks of therapy. There was no statistically significant change in mean spirometry between groups. However the mean PF and FEV_1 of those given timolol fell significantly ($P < 0.05$) from 336 to 309 l/min and from 2.02 to 1.93 l respectively. There was also a small, but not statistically significant, fall in PF and FEV_1 from 294 to 282 l/min and 1.69 to 1.65 l in the betaxolol group. At 1 year only 13 continued timolol and 12 betaxolol. Spirometric deterioration accounted for five timolol and two betaxolol changes and all were identified within the first 2 months of therapy.

Taken together, the studies suggest that elderly people, who are the majority of glaucoma sufferers, are especially vulnerable to the respiratory side-effects of topical β-antagonists. Although less effective ocular hypotensive agents, relatively cardio-selective preparations are safer.

Alternative medical therapy

Treatments free from the respiratory side-effects of β-antagonists include sympathomimetics. Topical adrenaline and the adrenaline precursor dipivefrin lower IOP. They probably act on pre-synaptic α-2 adrenoceptors on the ciliary body [21]. The selective α-2 agonist aproclonodine acts in a similar fashion to reduce IOP. They do not have the systemic respiratory side-effects of β-antagonists, but are less effective ocular hypotensive agents and have more local side-effects. Adrenaline and dipifevrin cause conjunctival hyperaemia in almost all patients, and this makes any subsequent surgical treatment likely to fail. In a minority of patients follicular conjunctivitis leads to cessation of therapy. Sympathomimetics therefore remain second-line therapy for glaucoma, reserved for patients intolerant to β-antagonists.

The carbonic anhydrase inhibitor dorzolamide has recently become available for topical administration. Inhibition of ciliary carbonic anhydrase reduces bicarbonate generation and aqueous production. In comparative studies dorzolamide is less effective than β-antagonists in controlling IOP. Systemic blood concentration of topically administered dorzolamide are low and are not associated with enzyme inhibition outside the eye. It is associated with more local side-effects than β-antagonists and has an unpleasant metallic taste for a quarter of patients [22]. Although free of respiratory side-effects, dorzolamide will not supplant topical β-blockers; it is, however, already widely used when β-antagonists are contra-indicated, as well as being an additional therapy in place of pilocarpine.

An exciting new topical therapy for glaucoma is the prostaglandin F2α (PgF2α) agonist latanoprost. It is at least as effective as β-antagonists at reducing IOP and is given only once daily [23]. Its action is to increase uveo-scleral outflow and it should act synergistically

with drugs that reduce aqueous production. Prostaglandins undergo little metabolism in the eye but are rapidly metabolized in the systemic circulation. Latanoprost causes some conjunctival irritation and hyperaemia—but less than some β-blockers—and is associated with fewer systemic side-effects, including respiratory symptoms. Latanoprost has one unusual side-effect. In almost half of those with mixed colour eyes it causes increased melanin formation by iridial melanocytes resulting in pigmentation of the iris. The pigmentation is thought to be irreversible. It has been licensed as second-line therapy in the US but because of the long-term risks of inducing iris tumours, is unlikely to be licensed as first-line therapy for glaucoma treatment in the UK until long-term data are available. Other PgF2α-agonists may be developed.

Conclusion

Despite the evidence of the effectiveness of surgery most ophthalmologists initially prefer a medical approach to IOP control so as to avoid the risks to sight of surgery. Because of their effectiveness, relative absence of local side-effects and the problems associated with topical therapy other than β-antagonists the latter are likely to remain the class of drug most often chosen. It would seem sensible advice to ophthalmologists to take a careful respiratory history and perform spirometry before commencing β-blockers. If spirometry were repeated at first review more asymptomatic respiratory impairment would probably be identified. Small, easy to use, low-cost electronic spirometers are available to measure PF, FEV_1 and FVC accurately [24]. Spirometry could be performed by nursing staff, who already record visual acuity, and in many clinics IOP, before the patient is reviewed by the ophthalmologist.

All doctors need remember that topical therapy is an essential part of the drug history. When an elderly patient is known to be receiving topical β-antagonists particular care needs to be taken to look for respiratory impairment. If detected, β-antagonists should be stopped immediately. Ophthalmologic advice should be sought and alternative treatment, with a topical sympathomimetic or carbonic anhydrase inhibitor, used while waiting for review by the eye surgeons.

Key points

- Enquiring about eye drops is an essential part of the drug history.
- Eye drops may have systemic side-effects.
- Asymptomatic respiratory impairment is common with topical β-antagonists.
- Topical β-antagonists should be ceased immediately if there is respiratory impairment.

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