Managing refractory glaucoma with a fixed combination of bimatoprost (0.03%) and timolol (0.5%)

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Abstract: Glaucoma is a chronic progressive optic neuropathy characterized by progressive loss of retinal ganglion cells, which manifests clinically with loss of optic disc neuroretinal rim tissue, defects in the retinal nerve fiber layer, and deficits on functional visual field testing. The goal of glaucoma treatment is to reduce the intraocular pressure to a level that prevents or minimizes the progressive loss of vision. The current standard of management for the newly diagnosed primary open angle glaucoma (PAOG) patient is to start topical medication. Available topical medications include: beta-adrenergic antagonists, alpha-adrenergic agonists, carbonic anhydraze inhibitors, prostaglandin analogues and miotics. In some patients, IOP is not adequately controlled by monotherapy. In those refractory patients, where more efficacy is required, shifting to another medication or adding a second medication is indicated. The complimentary action between two drugs serves as the basis for combination medications. One avenue of delivering a second medication is through a fixed combination medication that has the advantage of providing two medicines within one drop. Bimatoprost/timolol represents a new fixed combination which is clinically and statistically more effective than either of its active constituents for patients with refractory glaucoma. As regard the safety of the combination, there were no signs or symptoms of intolerance and the incidence of conjunctival hyperemia was clinically and statistically significantly less than each of the two components separately. Bimatoprost/timolol fixed combination offers cost and time savings, which may enhance compliance; also reducing the amount of preservative applied to the eye, will improve tolerability and may also favorably improve eventual surgical outcomes in patients who might require filtering procedures.

Keywords: fixed combination, refractory glaucoma, timolol/bimatoprost

Glaucoma is a chronic progressive optic neuropathy characterised by progressive loss of retinal ganglion cells, which manifests clinically with loss of optic disc neuroretinal rim tissue, defects in the retinal nerve fiber layer, and deficits on functional visual field testing (Danesh-Meyer et al 2006).

In the United States, glaucoma is the second leading cause of blindness in the general population, and the leading cause of blindness in black patients. The pathogenesis of glaucomatous optic neuropathy remains incompletely understood. While elevated intraocular pressure (IOP) is a clear risk factor, vascular insufficiency and abnormal autoregulation of the optic nerve circulation have been hypothesized to play a significant role in the development and progression of glaucoma (Hayreh 1969; Ernest 1975; Sossi and Anderson 1983). Primary open-angle glaucoma (POAG) is the most common form of glaucoma in the United States. The number of people with POAG worldwide in the year 2000 has been estimated at nearly 66.8 million, with 6.7 million having bilateral blindness (Quigley 1996).

The goal of glaucoma treatment is to reduce the intraocular pressure to a level that prevents or minimizes the progressive loss of vision (Jay and Murray 1988; GLT 1990; Spaeth and Baez 1992; AGIS 1998; King and Migdal 2000).Three modalities

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of treatment are available including: medical therapy, laser surgery and conventional incisional surgery. Despite continued advances in laser and incisional surgery, medical therapy continues to be the primary means by which IOP is controlled (Schwartz and Bundez 2004).

The current standard of management for the newly diagnosed POAG patient is to start topical medication (Anderson 1989). Monotherapy with a single medication is usually tried first; however, many patients need more than one medication to lower IOP sufficiently to prevent progression. Available topical medications include: beta-adrenergic antagonists, alpha-adrenergic agonists, carbonic anhydrase inhibitors, prostaglandin analogues, and miotics.

Beta-blockers are highly effective in treating glaucoma (Zimmerman and Kaufman 1977a; Boger et al 1978; Radius et al 1978; Ritch et al 1978; Obstbaum et al 1978; Lin et al 1979) and were initially considered first line treatment. They reduce IOP by inhibiting aqueous humour production (Coakes and Brubaker 1978). Although they are usually well tolerated and are commonly used as monotherapy, they do have both local and systemic side effects. Local side effects include hyperemia of the conjunctiva, burning sensation, superficial punctuate keratitis and reduced tear flow (Van Buskirk 1980). Systemic side effects, which are of more concern, may be induced by blocking the β_1-adrenoceptors of the heart resulting in bradycardia, arrhythmia, congestive heart failure and syncope by Adam-stokes syndrom (Nelson et al 1986; McMahon et al 1979). Furthermore, blocking the β_2-adrenoceptors of the bronchioles may cause bronchospasm in patients with chronic obstructive pulmonary disease or asthma (Sadiq et al 1998).

Topical carbonic anhydrase inhibitors (CAIs) lower IOP by decreasing aqueous production (Maus et al 1997). The most frequent side effects of CAIs include burning sensation, ocular discomfort, superficial punctuate keratitis and allergic conjunctivitis (Strahlman et al 1995). CAIs also may impair the corneal endothelial pump function, thus causing corneal decompansation in predisposed patients (Konowal et al 1999).

Prostaglandin analogues are now considered the first line of treatment in POAG (Camras 1999). The reduction of IOP by prostaglandin analogues is based on an increase in trabecular and uveoscleral outflow (Mishima et al 1977). While no systemic side effects have been reported with prostaglandins, local side effects include conjunctival hyperemia, stinging, burning sensation, punctuate keratitis, increased iris pigmentation, as well as cystoid macular edema in pseudophakic patients (Camras 1996; Selen et al 1997; Ayyala et al 1998).

In some patients, IOP is not adequately controlled by monotherapy. In those refractory patients, where more efficacy is required, shifting to another medication or adding a second medication is indicated. The complimentary action between two drugs often serves as the basis for combination medications.

β-blockers can be combined well with miotics, topical CAIs, brominidine, and prostaglandin analogues. The efficacy of combining β-blockers with pilocarpine has been shown in various studies (Keates 1979; Kass 1983). The ocular side effects of pilocarpine include inducing myopia, headache, blurred vision, conjunctival hyperaemia, lens opacities and retinal detachments in predisposed patients (Levene 1975; Pape and Forbes 1978), limiting its usefulness.

One avenue of delivering a second medication is through a fixed combination medication that has the advantage of providing two medicines within one drop. Such a product potentially reduces confusion from multiple bottles, aids compliance, lowers patient costs, and helps eliminate potential washout effects (Fechtner and Realini 2004). In addition; safety might be theoretically increased by using a fixed combination product, which limits the exposure to benzalkonium chloride, a preservative in most eye drops that has demonstrated significant corneal epithelial toxicity that is dose dependent.

Topical CAIs are complimentary in ocular hypotensive efficacy when combined with β-blockers (Kass et al 1982). Dorzolamide/timolol fixed combination (DTFC) was found to be as effective as the concomitant administration of its components in reducing IOP and has also simplified the therapy for patients needing these two medications (Boyle et al 1991). DTFC twice daily provided better IOP control than prostaglandin analogues once daily (Parmaksiz et al 2006). For patients with pseudoexofoliation glaucoma (PXG), diurnal fluctuation of IOP is higher than in patients with POAG (Konstas et al 1997). Because damage to the optic nerve might be associated with fluctuations in IOP, a drug that consistently controls IOP throughout the diurnal curve may be an important choice for the medical treatment of refractory glaucomas such as PXG (Asrani et al 2000). In addition dorzolamide has been reported to increase blood flow in animal models and in healthy and glaucomatous patients (Harris et al 1999; Josefsson et al 2004). Several other studies have suggested that dorzolamide enhances ocular blood flow, including studies investigating the choroid (Harris et al 2003) and the retrobulbar vessels (Martinez et al 1999).

Fixed combination brimonidine/timolol provides a combination of a β-blocker that reduces IOP by inhibiting aqueous production (Coakes and Brubaker 1978) and brimonidine, an alpha-adrenergic receptor agonist that has a dual mechanism of action:increasing uveoscleral outflow and reducing aqueous production.

Another potentially useful fixed combination is β-blocker to prostaglandin analogue, which has proven to be effective in controlling IOP in refractory patients (Villumsen and Alm 1990). The mechanism of action of prostaglandin analogues is complimentary to the IOP lowering mechanism of β-blockers. Available lipid/timolol combinations (latanoprost/timolol and travoprost/timolol), have a similar complementary mechanism of action (Toris et al 1995).

The latanoprost/timolol fixed combination dosed in the evening demonstrated a lower absolute IOP level at each time point and for 24- hours curve. Also, the maximum, minimum, and range of pressure were lower with the latanoprost/timolol fixed combination than with either drug alone (Anastasios et al 2006). Adverse events included conjunctival hyperemia, ocular stinging and itching were observed frequently with the latanoprost/timolol fixed combination (Shen et al 2004).

Another new fixed combination is bimatoprost 0.03% or 0.3 mg/mL + timolol 0.5% or 5 mg/mL. Bimatoprost is a synthetic prostamide, structurally related to prostaglandin F (PGF) that does not act through any known prostaglandin receptors. It reduces intraocular pressure by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol maleate is a non-selective adreno-receptor antagonist that does not have significant intrinsic sympathomimetic activity or membrane stabilizing activies. Blocking the beta-adrenoreceptors results in reduction of the intracellular second messenger, cAMP, believed to be involved in aqueous humour dynamics. Timolol does not have any effect on the outflow mechanism and exerts its effect on IOP by reducing aqueous humour production (Yablonski et al 1978). Timolol 0.5% was selected as the preferred dose in the bimatoprost/timolol fixed combination product, as the 0.25% concentration is considered to be suboptimal in the poorly controlled patient. In addition, the use of timolol 0.5% once-daily has been shown to provide a beneficial effect on IOP over a 24-hour period, an effect that was less pronounced with 0.25% concentration (Zimmerman and Kaufman 1977b).

Studies have shown that bimatoprost/timolol fixed combination was rapidly absorbed and distributed into ocular tissues in close contact with the administration site. This concentration was highest in the iris and ciliary body which are the sites of pharmacological action. The pharmacokinetic parameters of bimatoprost/timolol fixed combination were similar with either single or combination treatment (EPAR 2007).

Systemic absorption of topical administration is well known. As expected, bimatoprost and timolol were detected systemically following ocular instillation. Systemic concentrations of bimatoprost and timolol are slightly lower when administered in combination versus single administration. Differences in metabolism of the two drugs suggest that they will not affect or alter one another (EPAR 2007).

For a fixed combination medication to be truly clinically advantageous, it must increase efficacy beyond each of its individual components given as monotherapy without decreasing safety (De Saint et al 2000). Brandt et al 2007, reported that the combination was effective, lowering mean IOP from baseline by up to 9.6 mmHg, and clinically and statistically superior to each constituent as judged by the overall criterion of $>$20% reduction in mean diurnal IOP, and maintaing the mean diurnal IOP below 18 mmHg at all visits. Also the reduction in IOP with the combination was numerically greater than for either active component and statically significant at most of the time points and visits.

As regards the safety of the combination, there were no signs or symptoms of intolerance and the incidence of conjunctival hyperemia was clinically and statistically less significant than each of the two components separately. The reason for the decreased incidence of conjunctival hyperemia is not clear. One possible explanation is that the α_1-adrenoceptor agonistic effects of endogenous catecholamines, now unopposed by β_2-adrenoceptor agonistic effects due to blockade by the timolol. Another explanation is that the antagonism of β_2-adrenoceptors by timolol could diminish the production of nitric oxide (Arai et al 2003), a mediator of bimatoprost-associated hyperemia (Chen et al 2005). Irrespective of the mechanism, the conjunctival hyperemia associated with bimatoprost is non-inflammatory (Leal et al 2004).

Actually the fixed combination of bimatoprost and timolol was clinically and statistically significantly more effective than either of its active constituents for patients with refractory glaucoma, for those patients requiring two or more ocular hypotensive medications, this single-bottle, fixed combination represents a convenient, therapeutic advantage over separate bottles. Also it represents a reduction in the number of drops per day that is required for the patient to instill. An established washout effect resulting from rapid sequence instillation of two medications requires that

patients wait approximately 5 minutes between eye drops (Chrai et al 1947). Bimatoprost/timolol fixed combination offers a reduced time commitment for drop instillation and the potential for greater efficacy by eliminating the washout effect. Bimatoprost/timolol fixed combination offers cost and time savings, which may enhance compliance; also reducing the amount of preservative applied to the eye, will improve tolerability and may also favorably improve eventual surgical outcomes in patients who might require filtering procedures (Lavin et al 1990; Broadway et al 1994).

Disclosures

The authors have no financial interest related to the article.

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