Brimonidine in the treatment of glaucoma and ocular hypertension

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Abstract: Treatment in glaucoma aims to lower intraocular pressure (IOP) to reduce the risk of progression and vision loss. The alpha2-adrenergic receptor agonist brimonidine effectively lowers IOP and is useful as monotherapy, adjunctive therapy, and replacement therapy in open-angle glaucoma and ocular hypertension. A fixed combination of brimonidine and timolol, available in some countries, reduces IOP as effectively as concomitant therapy with brimonidine and timolol and offers the convenience of 2 drugs in a single eyedrop. Brimonidine is safe and well tolerated. Its most common side-effects are conjunctival hyperemia, allergic conjunctivitis, and ocular pruritus. The newest formulation of brimonidine, brimonidine-Purite 0.1%, has a higher pH to improve the ocular bioavailability of brimonidine. This formulation contains the lowest effective concentration of brimonidine and is preserved with Purite® to enhance ocular tolerability. Brimonidine-Purite 0.1% is as effective in reducing IOP as the original brimonidine 0.2% solution preserved with benzalkonium chloride. Recent results from preclinical and clinical studies suggest that brimonidine may protect retinal ganglion cells and their projections from damage and death independently of its effects on IOP. The potential for neuroprotection with brimonidine is an added benefit of its use in glaucoma and ocular hypertension.

Keywords: brimonidine, preservative, glaucoma, intraocular pressure, neuroprotection

Introduction

Glaucoma is an optic neuropathy characterized by acquired loss of retinal ganglion cells (RGCs) and atrophy of the optic nerve leading to vision loss. Elevated intraocular pressure (IOP) is a primary risk factor both for the development of glaucoma and for progression of optic nerve changes and visual field loss in the disease. Abundant evidence indicates that elevated IOP can cause the neuropathology of glaucoma. Clinical experience with angle-closure glaucoma and numerous preclinical studies in rats and primates have shown that acute and sustained increases in IOP can cause optic nerve damage (Morrison 2005; Rasmussen and Kaufman 2005). Primary open-angle glaucoma (POAG), the most common type of glaucoma in white populations, is characterized by chronically elevated IOP with no known cause for the elevated IOP or optic neuropathy. But many individuals with elevated IOP do not show signs of glaucomatous optic nerve damage, and conversely, many individuals with IOP consistently within the normal range (less than 21 mmHg) have glaucoma (Klein et al 1992). These findings suggest that factors beyond IOP have a role in the etiology of the disease (Drance 1997).

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IOP-lowering treatment

Regardless of the etiology of the disease, at present, the aim of treatment in glaucoma is to reduce IOP. Recent randomized, controlled clinical trials have shown that lowering IOP is effective in delaying or preventing the development of glaucoma in

patients with ocular hypertension (OHT) and in delaying or halting the progression of established glaucoma (Heijl et al 2002; Kass et al 2002). IOP reduction is beneficial in reducing the risk of progression of vision loss even when IOP is already within the normal range (Collaborative Normal-Tension Glaucoma Study Group 1998). Evidence suggests that very low IOP provides the best visual outcomes for patients (The AGIS Investigators 2000; Lichter et al 2001). Analysis of data from the Early Manifest Glaucoma Trial showed a 10% reduction in the risk of progression associated with each 1 mmHg of IOP reduction (Leske et al 2003).

IOP-lowering drugs are currently the only medical treatment approved for glaucoma management. The classes of ocular hypotensive drugs commonly used to reduce IOP in glaucoma and OHT include prostaglandin analogues, beta-adrenergic receptor antagonists, alpha-adrenergic receptor agonists, carbonic anhydrase inhibitors, and parasympathomimetics. The once-daily prostaglandin analogues (bimatoprost, latanoprost, travoprost) reduce IOP most effectively (Hedman and Alm 2000; Netland et al 2001; Higginbotham et al 2002) and are often used as initial monotherapy. Not all patients can use prostaglandin analogues, however. Further, for many patients the IOP lowering obtained with monotherapy is inadequate. Even patients with OHT or early glaucoma are likely to need more than 1 medication to reach sufficiently low pressures. For example, in the Ocular Hypertension Treatment Study (OHTS) by year 5 almost 40% of patients needed 2 or more medications to achieve their target IOP (Kass et al 2002), and in the Collaborative Initial Glaucoma Treatment Study (CIGTS) after year 2 more than 75% of patients needed 2 or more medications to reach their target IOP (Lichter et al 2001).

Brimonidine, the only selective alpha-adrenergic receptor agonist approved for chronic treatment in glaucoma, is indicated for reducing IOP in patients with open-angle glaucoma or OHT. Brimonidine is contraindicated in patients receiving monoamine oxidase inhibitor therapy, because antidepressants decrease the metabolism of circulating monoamines, leading to an increase in levels of endogenous monoamines that might inhibit the IOP-lowering effect of brimonidine. Brimonidine is also contraindicated in patients with hypersensitivity to any component of the medication, and it should not be used in children under the age of 2 because there have been reports of apnea, bradycardia, hypothermia, hypotonia, lethargy, and unresponsiveness in infants receiving brimonidine treatment (Berlin et al 2001; Prok and Hall 2003).

Pharmacology and mechanism of action of brimonidine

Brimonidine is a selective alpha2-adrenergic receptor agonist that shows up to 1780-fold selectivity for alpha2- over alpha1-adrenergic receptors (Cantor 2000). After topical instillation, brimonidine reduces IOP within 1 hour, and the peak effect occurs at 2–3 hours after dosing (Walters 1996). The trough effect occurs at 10–14 hours after dosing. Brimonidine is usually dosed twice daily, and no additional IOP lowering is provided at morning trough with tid versus bid dosing (Walters 1996). Brimonidine has a dual mechanism of IOP lowering: it both reduces aqueous humor production and stimulates aqueous humor outflow through the uveoscleral pathway (Toris et al 1995). The predominant effect of short-term brimonidine treatment is inhibition of aqueous production, whereas the predominant effect of chronic treatment is stimulation of aqueous humor outflow through the uveoscleral pathway (Toris et al 1999).

Pharmacokinetics of topical brimonidine

Pharmacokinetic studies in rabbits and monkeys have shown that topical brimonidine readily penetrates the eye and reaches pharmacologically active concentrations in the aqueous humor and ciliary body, the putative sites of its IOP-lowering activity (Acheampong et al 1995, 2002). The primary absorption route for brimonidine is via the cornea (Cantor 2000). Brimonidine that reaches the systemic circulation after topical administration in humans is rapidly metabolized and has a short plasma half-life of approximately 2 hours (Cantor 2000). The rapid metabolism and systemic clearance of brimonidine minimizes potential systemic effects of the drug, and twice- or thrice-daily dosing of brimonidine 0.2% is not associated with clinically significant cardiovascular or pulmonary systemic effects in adults (Cantor 2000).

Pharmacologically active concentrations of brimonidine are found in vitreous humor samples following topical administration of brimonidine 0.2% in rats, rabbits, monkeys, and humans (Kent et al 2001; Acheampong et al 2002). This is important because brimonidine may be present at the retina in concentrations sufficient for direct effects on RGCs.

Potential for neuroprotection

As it has become recognized that glaucoma is a multifactorial, progressive neuropathy that often occurs independently of elevated IOP, the diagnosis of glaucoma has changed from one based on IOP to one based on the optic nerve and visual field (Weinreb and Levin 1999). This paradigm shift has prompted investigation of a new approach to therapy in glaucoma called neuroprotection. The goal of neuroprotection is to slow or prevent death of neurons and maintain their physiological function (Weinreb and Levin 1999). One important advantage of a neuroprotective strategy is that treatment is possible even when the etiology of the disease is unknown or differs among patients (Weinreb and Levin 1999). A neuroprotective treatment in glaucoma might have no effect on IOP, but it would promote the survival of RGCs and their axons (the optic nerve fibers), and it could be effective regardless of the specific etiology of the disease (Weinreb and Levin 1999).

Neuroprotection has been investigated as a therapeutic approach for neurodegenerative conditions including stroke, spinal cord injury, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease. It may be difficult to achieve neuroprotection in acute conditions such as stroke, because treatment would probably have to begin at the time of the insult or soon after to prevent irreversible neuronal loss (Osborne et al 2004), but neuroprotection may be easier to achieve in chronic diseases characterized by progressive cell loss, such as open-angle glaucoma.

Preclinical studies have shown that brimonidine has neuroprotective effects in animal models of optic nerve injury relevant to glaucoma including partial optic nerve crush, chronic ocular hypertension induced by laser cautery of episcleral and limbal veins, and retinal ischemia induced either by transient elevation of IOP or ligature of ophthalmic vessels (Yoles et al 1999; Donello et al 2001; WoldeMussie et al 2001; Mayor-Torroglosa et al 2005). Brimonidine was shown to promote RGC survival in each of these models, and in most studies protection of visual function was also demonstrated through measurements of the compound action potential or the ERG b-wave. The effects of brimonidine are evident after topical administration of a 0.1% or 0.5% solution of drug (Vidal-Sanz et al 2001) and are mediated by activation of alpha2-adrenergic receptors (Donello et al 2001). Moreover, the effects appear to be independent of IOP lowering, because systemic administration of brimonidine, which does not reduce IOP, is also neuroprotective (Yoles et al 1999). Recent clinical studies of brimonidine, discussed later in this review, have suggested that topical brimonidine treatment may also protect RGCs in human glaucoma.

Brimonidine formulations

The original brimonidine 0.2% formulation (Alphagan®, Allergan, Inc, Irvine, CA, USA) has a pH of 6.4 and is preserved with benzalkonium chloride (BAK). BAK is the antimicrobial preservative most commonly used in ophthalmic solutions, but chronic exposure to solutions containing high concentrations of BAK has been associated with harmful effects on the corneal surface (Noecker 2001; Noecker et al 2004). Moreover, chronic treatment of glaucoma and OHT patients with IOP-lowering ophthalmic solutions preserved with BAK has been reported to result in subclinical inflammation evident by increased expression of HLA-DR on conjunctival epithelial cells (Cvenkel and Ihan 2002). This is a clinical concern, because chronic inflammation and fibrosis can decrease the success rate of trabeculectomy surgery (Skuta and Parrish 1987).

Brimonidine has been reformulated to improve its tolerability while maintaining its ocular bioavailability and IOP-lowering efficacy. The newer formulations of brimonidine are preserved with Purite®, a stabilized oxychloro complex and oxidative preservative that is converted to natural tear components (sodium and chloride ions, oxygen, and water) when exposed to light (Katz 2002). Purite is a microbicide and is non-toxic to mammalian cells (Grant et al 1996). The first reformulation of brimonidine that was introduced contains brimonidine 0.15% in a buffered solution of pH 7.2 preserved with Purite 0.005% (Alphagan® P 0.15%, Allergan Inc, Irvine, CA, USA). Although this formulation has a reduced concentration of brimonidine, it was shown in clinical trials to have the same IOP-lowering efficacy and better tolerability compared with the original brimonidine 0.2% formulation (Katz 2002) because the increase in pH provided better bioavailability (Dong et al 2004). More recently, a 0.1% formulation of brimonidine preserved with Purite at a pH of 7.7 was introduced (Alphagan® P 0.1%, Allergan Inc, Irvine, CA, USA). As discussed in detail below, the new brimonidine-Purite 0.1% formulation also shows efficacy equivalent to the original brimonidine 0.2% formulation. Animal studies have shown that aqueous humor levels of drug are the same with the newer formulations preserved with Purite and the old formulation preserved with BAK, despite the lower concentration of drug in the bottle, because at higher pH more brimonidine is non-ionized, and brimonidine is more

readily absorbed into the eye (Dong 2004; Allergan, data on file).

Clinical efficacy of brimonidine in reducing IOP

In its 1-year pivotal trials for drug approval, twice-daily brimonidine 0.2% reduced IOP as well as or better than timolol at peak effect (2 hours after dosing) but less effectively than timolol at morning trough (Schuman et al 1997; LeBlanc 1998; Katz 1999). The efficacy of brimonidine was sustained over long-term use, and after four years of treatment, brimonidine and timolol provided comparable IOP lowering at both peak and trough effect (David 2001). Brimonidine was well tolerated in the pivotal trials. Common side-effects of treatment included oral dryness, ocular hyperemia, and ocular allergy. The 1-year incidence of treatment-related ocular allergy to brimonidine was 11.5% (Katz 1999), but this incidence may have been overestimated because of the confusion of dry eye, seasonal allergic conjunctivitis, or bacterial conjunctivitis with drug-related ocular allergy (Melamed and David 2000).

Brimonidine has been compared with dorzolamide as monotherapy in glaucoma and OHT in 3 separate randomized, double-masked studies with a crossover design (Stewart et al 2000; Sharpe et al 2004; Whitson et al 2004). In each of these studies, brimonidine and dorzolamide showed comparable efficacy at trough effect, but at peak effect at 2 hours after dosing, brimonidine reduced IOP by 0.7–1.4 mmHg more than dorzolamide. There was no overall difference between drugs in the frequency of side-effects, but ocular stinging and burning were more often associated with dorzolamide treatment.

The versatility of brimonidine in reducing IOP was demonstrated in a large, open-label study involving 2335 patients. In this study, brimonidine effectively reduced IOP whether used as monotherapy, replacement therapy, or adjunctive therapy (Lee et al 2000). As adjunctive therapy, brimonidine provided significant mean additional IOP lowering when added to other ocular hypotensive medications including beta-blockers, carbonic anhydrase inhibitors, and the prostaglandin analogue latanoprost (Lee and Gornbein 2001). Several randomized controlled clinical studies in patients with glaucoma or OHT subsequently confirmed that brimonidine provides significant additional mean decreases in IOP when added to ongoing beta-blocker therapy (Simmons 2001; Simmons and Earl 2002; Sall et al 2003; Solish et al 2004). Other randomized controlled trials showed that brimonidine effectively reduces IOP when used adjunctively with a prostaglandin analogue (bimatoprost or latanoprost) (Netland et al 2003; Zabriskie and Netland 2003; Konstas et al 2005).

Brimonidine has been demonstrated to be more effective than dorzolamide when used as adjunctive therapy with a beta-blocker and at least as effective as dorzolamide when used as adjunctive therapy with latanoprost. In 2 randomized controlled trials that compared the efficacy and safety of brimonidine and dorzolamide as adjunctive therapy with beta-blockers, the reduction from baseline IOP (measured at peak effect) was significantly greater with adjunctive brimonidine than with adjunctive dorzolamide (Simmons 2001; Carrasco Font et al 2004). Brimonidine-Purite 0.15% was compared with dorzolamide as adjunctive therapy with latanoprost in a randomized, double-masked, crossover trial in 33 glaucoma patients who had uncontrolled IOP after at least a 3-week run-in on latanoprost monotherapy (Konstas et al 2005). Each study drug was given twice daily as adjunctive therapy with latanoprost for 6 weeks, with a 6-week washout between treatment periods. The primary outcome measure was circadian IOP, measured at 7 timepoints over 24 hours after 6 weeks of adjunctive therapy. The between-group differences in mean IOP reduction from baseline were not statistically significant. Of the 31 enrolled patients who had data available for analysis, 1 (3.2%) had the same circadian IOP (average of all 7 measurements) on both drugs, 19 (61.3%) had lower circadian IOP with brimonidine-Purite, and 11 (35.5%) had lower circadian IOP with dorzolamide, suggesting that brimonidine-Purite 0.15% is at least as effective as dorzolamide in providing 24-hour IOP control when added to latanoprost.

Clinical comparison of brimonidine-Purite 0.1% and brimonidine 0.2%

A prospective, randomized, double-masked, parallel-group clinical trial compared brimonidine-Purite 0.1% with brimonidine 0.2% for IOP-lowering efficacy and tolerability in patients with glaucoma or OHT (Allergan, data on file). The study was carried out at 27 centers across the United States. Patients with glaucoma or OHT in each eye were randomized to treatment with either brimonidine-Purite 0.1% (n=215) or brimonidine 0.2% (n=218) thrice daily for 12 months. Follow-up visits were scheduled at weeks 2 and 6 and months 3, 6, 9, and 12. IOP was measured at 8 AM (trough effect, immediately prior to the morning dose), 10 AM (morning peak effect), and 4 PM (afternoon peak effect,

2 hours after the afternoon dose) at all follow-up study visits except month 9, when it was measured at 8 AM and 10 AM only. The primary efficacy measure was mean IOP in the intent-to-treat patient population (all randomized patients) with last observation carried forward for missing values. All patients were treated bilaterally, and the average IOP from both eyes was used in the analyses.

Baseline demographic and ophthalmic characteristics of patients were similar between the 2 treatment groups. Mean IOP at baseline was also comparable between the 2 treatment groups at each hour. Throughout follow-up, mean IOP in each treatment group ranged from 17 to 22 mmHg and was significantly lower than at baseline ($p < 0.001$). The absolute values of the limits of the 95% confidence interval (CI) of the between-group difference in mean IOP were <1.0 mmHg at 12 of 17 timepoints and <1.5 mmHg at all 17 timepoints, demonstrating equivalent efficacy of the study formulations (Figure 1). Analysis of mean change from baseline IOP also showed equivalent efficacy of the study formulations, with the absolute values of the limits of the 95% CI of the between-group difference <1.0 mmHg at 9 of 17 timepoints and consistently <1.5 mmHg. The only significant differences in mean IOP reduction between treatment groups were at 4 PM at months 3 and 12, when the mean IOP reduction was significantly greater with brimonidine-Purite 0.1% than with brimonidine 0.2% ($p \leq 0.043$). Brimonidine-Purite 0.1% provided sustained IOP lowering over 12 months of treatment and was as effective as brimonidine 0.2% in reducing IOP at all timepoints. Figure 2 shows the mean change from baseline IOP with each formulation at the 10 AM timepoint of peak effect.

The percentage of patients with 1 or more treatment-related adverse events was lower in the brimonidine-Purite 0.1% group (41.4%) than in the brimonidine 0.2% group (53.2%, $p=0.014$). The only individual treatment-related adverse event with a significant difference in incidence between treatment groups was oral dryness, which was less frequent in the brimonidine-Purite 0.1% group (1.4% of patients) than in the brimonidine 0.2% group (5.5% of patients, $p=0.019$). Biomicroscopic findings of increased severity of lid erythema and lid edema were also less common in the brimonidine-Purite 0.1% group ($p=0.028$ and $p=0.006$, respectively).

The rate of discontinuations for adverse events was significantly lower in the brimonidine-Purite 0.1% group (21.4%) than in the brimonidine 0.2% group (33.5%, $p=0.005$). Only 1 patient in the brimonidine-Purite 0.1% group discontinued for a non-ocular, treatment-related adverse event (oral dryness). In contrast, patients in the brimonidine 0.2% group discontinued for several non-ocular treatment-related adverse events including asthenia, hypotension, somnolence, depression, and insomnia, as well as oral dryness.

In summary, the results of this trial showed that brimonidine-Purite 0.1% is statistically equivalent to

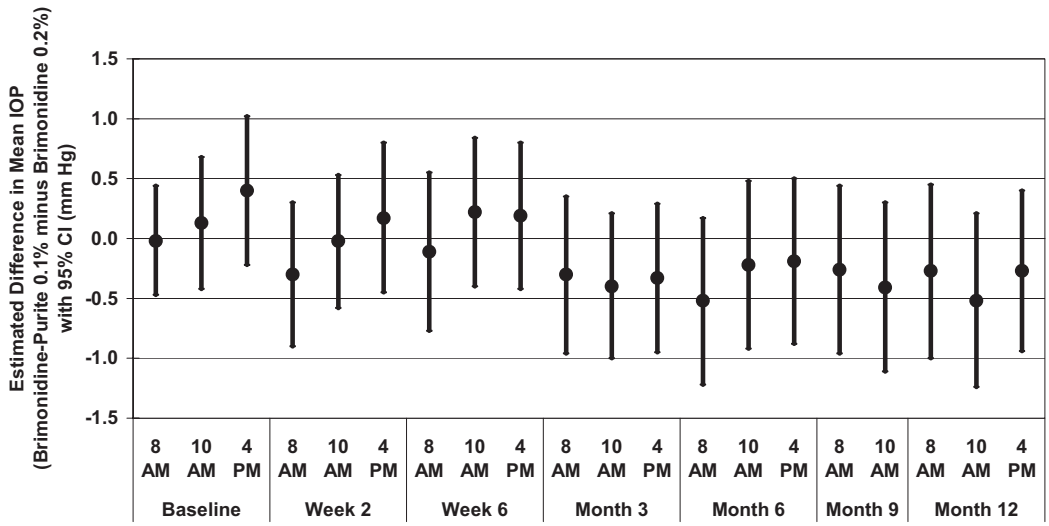

Figure 1 Equivalent IOP-lowering efficacy of brimonidine-Purite 0.1% and brimonidine 0.2%. In a 1-year clinical comparison study of the 2 formulations, the 95% CI of the difference in mean IOP between treatment groups (brimonidine-Purite 0.1% minus brimonidine 0.2%) was consistently within the range of –1.5 mmHg to 1.5 mmHg, demonstrating equivalent efficacy of the study formulations.
Abbreviations: CI, confidence interval; IOP, intraocular pressure.

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