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Ocular Hypotensive Efficacy of Brimonidine 0.15% as Adjunctive Therapy With Latanoprost 0.005% in Patients With Open-Angle Glaucoma or Ocular Hypertension

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ABSTRACT

This study was undertaken to evaluate the ocular hypotensive efficacy of brimonidine Purite® 0.15% (Alphagan® P 0.15%; Allergan, Inc., Irvine, Calif) given as adjunctive therapy with latanoprost 0.005% (Xalatan®; Pfizer Inc., New York, NY) to patients with open-angle glaucoma or ocular hypertension. In this multicenter, open-label, prospective evaluation, the intraocular pressure (IOP) of the 43 enrolled patients was ≥18 mm Hg after at least 6 wk of latanoprost monotherapy. The primary outcome measure was IOP at peak drug effect (10 AM, or approximately 2 h after the morning dose of brimonidine 0.15%). IOP at trough drug effect (8 AM, or approximately 12 h after the evening dose of brimonidine) was also measured. Baseline IOP was 21.9 (±2.3) mm Hg. After 1 mo of treatment, additional mean IOP reductions from latanoprost-treated baseline values were 5.8 mm Hg (26%) at peak drug effect ($P<.001$) and 3.3 mm Hg (15%) at trough ($P<.001$). At the month 2 visit, additional mean IOP reductions from latanoprost-treated baseline values were 5.1 mm Hg (23%) at peak drug effect ($P<.001$) and 2.0 mm Hg (9%) at trough ($P=.002$). Brimonidine Purite 0.15% provided statistically significant additional reductions in IOP from latanoprost-

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treated baseline values. These findings suggest that brimonidine Purite 0.15% is an efficacious adjunctive therapy in patients given latanoprost who require additional lowering of IOP.

Keywords: brimonidine; Alphagan P; latanoprost; Xalatan; glaucoma

INTRODUCTION

The current treatment paradigm for glaucoma management is focused on lowering intraocular pressure (IOP) to a target pressure at which the progression of glaucoma is halted or slowed. The higher a patient's IOP remains, the greater is the likelihood that optic nerve damage and visual field loss will occur.[1-3] Ideally, adequate IOP reduction is achieved with the use of a single ocular hypotensive agent, but in reality, most patients require more than monotherapy to maintain adequate IOP control.

Several large, controlled studies have shown that patients with glaucoma and ocular hypertension often require adjunctive therapy to reach low target IOPs and sometimes to prevent the progression of glaucomatous damage. More than 75% of patients who were assessed in the Collaborative Initial Glaucoma Treatment Study required at least 2 medications to reach their target pressure at the month 60 visit.[4] Similarly, in the Ocular Hypertension Treatment Study, 49% of patients required 2 or more medications to achieve their target IOP after 2 y of therapy.[5] When selecting an agent for adjunctive therapy, clinicians should consider efficacy, safety, and complementary mechanisms of action of selected medications.

Brimonidine Purite® 0.15% (Alphagan® P 0.15%; Allergan Inc., Irvine, Calif) is a highly selective and potent α_2-adrenergic agonist whose peak ocular hypotensive effects occur at 2 h post dosing. Fluorophotometric studies in animals and humans have suggested that brimonidine tartrate has a dual mechanism of action—it reduces aqueous humor production and enhances uveoscleral outflow.[6] The commercial preparation is preserved with Purite (a stabilized oxychloro compound that is more benign to the ocular surface than benzalkonium chloride, which is used to preserve the original formulation of brimonidine 0.2%). In addition, compared with the original 0.2% brimonidine formulation, this formulation contains 25% less of the active drug that improves ocular tolerability and enhances systemic safety. A pooled analysis of 2 identically designed trials showed that brimonidine Purite 0.15% provided clinically relevant IOP lowering that was comparable with that of brimonidine 0.2%, as well as a better overall adverse event profile (41% less allergic conjunctivitis and 80% less fatigue).[7]

Brimonidine has been shown to be a highly effective adjunctive agent to a variety of ocular hypotensive medications, including topical lipids and β-blockers. For example, Simmons and Earl[8] reported that brimonidine 0.2% and latanoprost each provided comparable IOP lowering when used adjunctively with topical β-blockers. In a large open-label study, Lee and Gornbein[9] reported that substantially more IOP lowering occurred when brimonidine 0.2% was added to latanoprost alone or to regimens that included latanoprost. Zabriskie et al[10] reported that the combination of brimonidine and latanoprost provided IOP lowering that was superior to that produced by the fixed combination of timolol and dorzolamide. These trials, however, evaluated the original brimonidine 0.2% formulation and, although the equivalence of the 2 for-

mulations has been demonstrated when used as monotherapy, additional studies are needed to conclude that brimonidine Purite 0.15% is effective as adjunctive therapy.

The purpose of this study was to evaluate the efficacy of brimonidine Purite 0.15% as an adjunctive agent to latanoprost.

METHODS

This study was a multicenter, open-label, prospective evaluation of 43 patients in whom open-angle glaucoma or ocular hypertension had been diagnosed. At baseline, all patients were being treated with latanoprost monotherapy and had an IOP ≥18 mm Hg after at least 6 wk of treatment. Brimonidine Purite 0.15% twice daily was then added to the treatment regimen. Patients were assessed at 1 and 2 mo after brimonidine Purite was added to the treatment regimen. Primary outcome measures consisted of IOP at peak drug effect (10 AM, or about 2 h after the morning dose) and at trough drug effect (8 AM, or about 12 h after the evening dose of brimonidine Purite 0.15%).

Patients were excluded from the study if they had previously used brimonidine 0.2% or brimonidine Purite 0.15%. They were also excluded if they had corneal abnormalities, a history of intraocular surgery over the previous 3 mo, or concomitant use of another ocular medication (with the exception of the occasional use of artificial tears). Other exclusion criteria included active ocular disease, functionally significant visual field loss, and evidence of progressive visual field loss within the previous year.

Before they were enrolled, all patients underwent a complete ophthalmic examination that consisted of biomicroscopy, visual acuity, and external examination. Patients were instructed to wait 15 min after they had instilled latanoprost before instilling brimonidine Purite 0.15%. They were further instructed not to instill their morning dose of brimonidine on the morning of follow-up visits, but to instill the normal dose of latanoprost the evening before. In the morning on the days of follow-up visits, IOP was measured at 8 AM (+/–1 h) for trough drug effect. Adjunctive therapy was then administered by office personnel, and the patient returned 2 h later for another measurement of IOP at peak drug effect.

RESULTS

The mean age of study patients was 65.4 y. Men accounted for 53% of the study population; 63% of patients had been diagnosed with open-angle glaucoma and 37% with ocular hypertension. Thirty-five of the patients were white, 6 were black, and 2 were Hispanic.

IOP

At the baseline study visit, mean IOP was 21.9 mm Hg after at least 6 wk of latanoprost monotherapy. After patients began brimonidine Purite 0.15% twice daily as adjunctive therapy to ongoing latanoprost treatment, mean IOP at peak drug effect was 16.1 mm Hg at month 1 and 16.8 mm Hg at month 2 (Fig 1). The addition of brimonidine Purite 0.15% provided a statistically significant mean IOP reduction from latanoprost-treated baseline values at both follow-up visits (mean IOP reduction of 5.8 mm Hg [26%] at month 1, and 5.1 mm Hg [23%] at month 2) (Fig 2).

Fig 1. Mean IOP at peak drug effect.

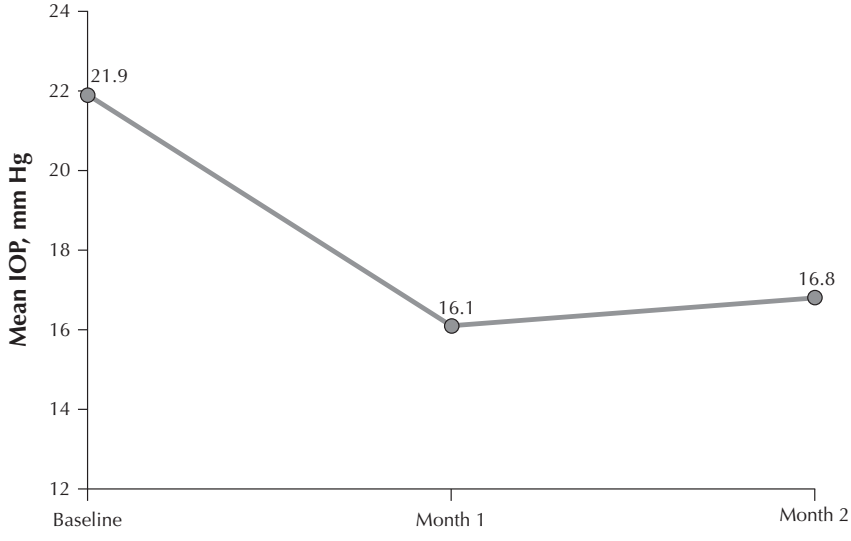
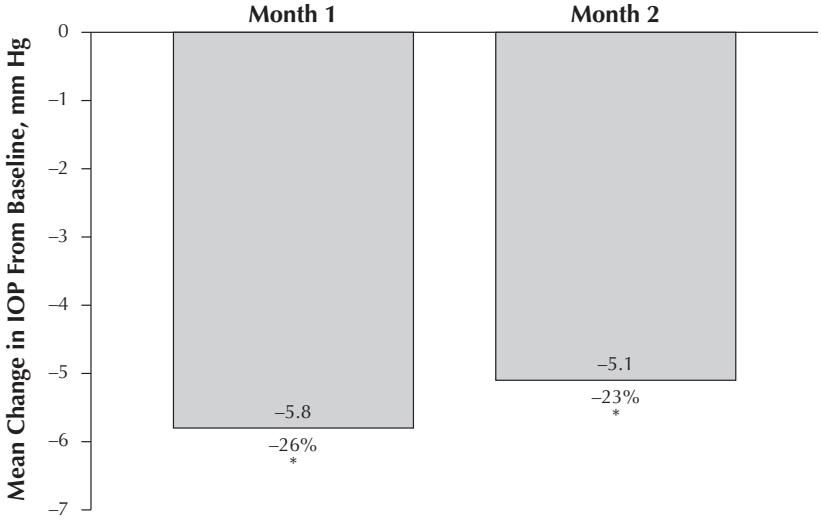


Fig 2. Mean change in IOP from latanoprost-treated baseline values at peak drug effect.



*P<.001.

At both follow-up study visits, brimonidine Purite® 0.15% provided a statistically significant additional IOP reduction from latanoprost-treated baseline levels (P<.001).

Fig 3. Mean IOP at trough drug effect.

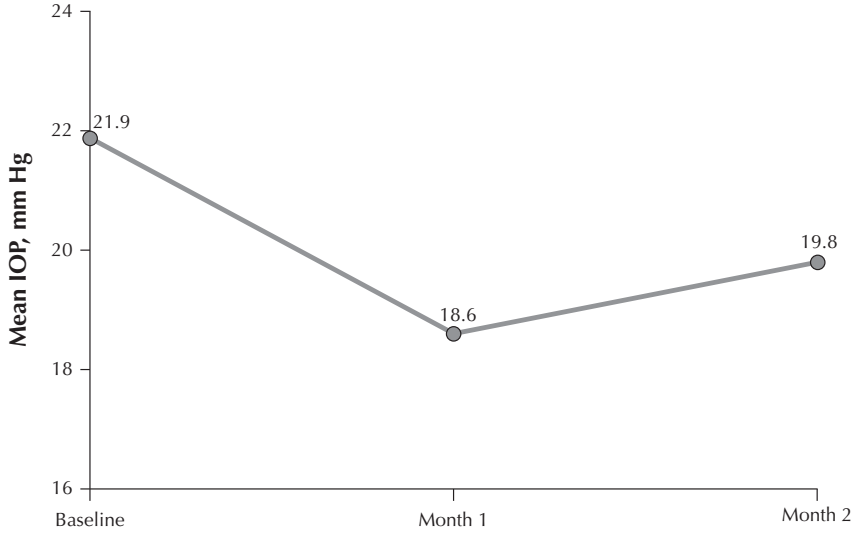
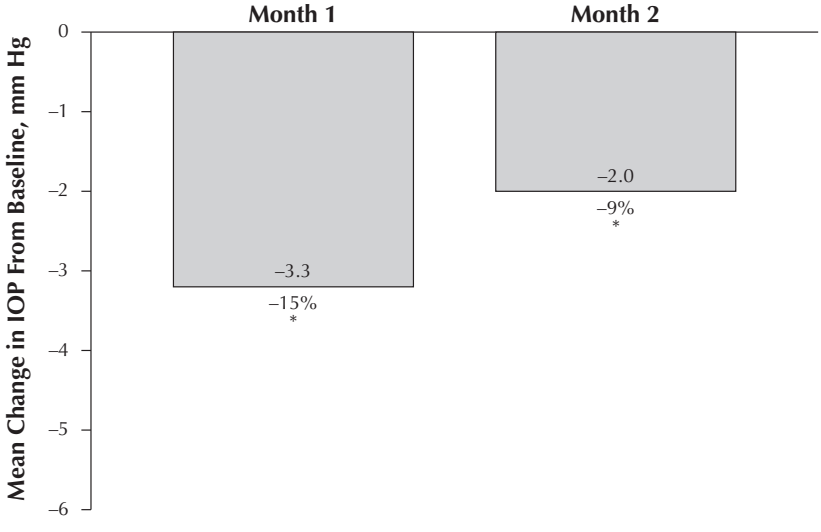


Fig 4. Mean change in IOP from latanoprost-treated baseline values at trough drug effect.



*P=.002.

At the month 1 follow-up, brimonidine Purite 0.15% provided an additional mean IOP reduction of 15% from latanoprost-treated baseline values in trough drug effect (P<.001). At month 2, the additional mean IOP reduction was 9% (P=.002).

Use of brimonidine Purite 0.15% as adjunctive therapy to latanoprost significantly reduced mean IOP at trough drug effect ($P \leq .002$). At month 1, mean IOP at trough drug effect was 18.6 mm Hg; by month 2, mean IOP was 19.8 mm Hg (Fig 3). The addition of brimonidine Purite 0.15% provided a statistically significant mean IOP reduction from latanoprost-treated baseline values at both follow-up visits (Fig 4). Mean IOP reduction at trough drug effect was 3.3 mm Hg (15%) at month 1 and 2.0 mm Hg (9%) at month 2 ($P \leq .002$).

Safety and Tolerability

Brimonidine Purite 0.15% was a safe and well-tolerated adjunct to latanoprost treatment. No study patients discontinued adjunctive therapy, and no serious adverse events were reported. The most common adverse events were ocular allergy (n=2; 4.7%) and foreign body sensation (n=2; 4.7%).

DISCUSSION

The findings of the present study suggest that brimonidine Purite 0.15% is an effective adjunctive agent when administered with latanoprost. Brimonidine 0.2% has already been established as an effective adjunctive agent to β-blockers in reducing IOP. Over 3 y, the Brimonidine Study Group found that brimonidine 0.2% given twice daily provided sustained IOP-lowering efficacy and visual field preservation that was equal to that attained with timolol 0.5% given twice daily.[11] An earlier study from the Chronic Brimonidine Study Group established that brimonidine provides a sustained long-term ocular hypotensive effect, is well tolerated, and has a low rate of allergic response.[12]

In this open-label study, 43 patients with IOP that was uncontrolled by latanoprost monotherapy were treated with brimonidine Purite 0.15%; investigators evaluated the safety and efficacy of brimonidine Purite 0.15% given as an adjunct with latanoprost. After 2 mo of therapy, at peak drug effect, brimonidine Purite 0.15% provided an additional IOP reduction of 23% from latanoprost-treated baseline values.

Large prospective trials have reported that the risk of glaucomatous progression is substantially reduced when IOP is lowered. In the Early Manifest Glaucoma Trial, each millimeter of mercury reduction in IOP was associated with an approximate 10% decrease in the risk of progression.[13] In addition, the Early Manifest Glaucoma Trial group found that the lower IOP was at follow-up, the lower the risk for progression. The enhanced efficacy observed when brimonidine 0.15% was added to latanoprost suggests that patients may be able to further reduce their risk of glaucomatous progression and visual field loss with combination therapy rather than monotherapy.

Brimonidine Purite 0.15% was safe and well tolerated, and only minor adverse events were reported. The most frequently reported adverse events associated with brimonidine Purite therapy included allergic conjunctivitis, conjunctival hyperemia, and eye pruritus.[14] In this study, ocular allergy and foreign body sensation were each reported by 2 (4.7%) patients.

The demonstrated efficacy of brimonidine Purite 0.15% as an adjunctive agent to latanoprost may be due to complementary mechanisms of action: latanoprost is a lipid receptor agonist that lowers IOP predominantly by increasing uveoscleral outflow.[15] It promotes the flow of aqueous fluid through the ciliary muscle and through the sclera into the orbit, thereby enhancing uveoscleral or "unconventional" outflow.[16] Brimonidine is an α_2 agonist that lowers IOP through dual mechanisms, thereby enhancing uveoscleral outflow and reducing aqueous production.[17] It reduces IOP by inhibiting aqueous production. Brimonidine also facilitates uveoscleral outflow, which is especially desirable throughout long-term treatment.[14]

In addition to providing a complementary method of action, the addition of brimonidine Purite 0.15% to latanoprost reduces exposure of the ocular surface to benzalkonium chloride in patients who require more than a single medication for the lowering of IOP. The preservative in brimonidine Purite 0.15% is Purite, which is the preservative used in Refresh Tears® Lubricant Eye Drops (Allergan, Inc., Irvine, Calif). It is a microbicide with a broad spectrum of antimicrobial activity and very low toxicity to mammalian cells.[16] Purite has been used safely and effectively in Europe and the United States for longer than 20 y.

Brimonidine Purite 0.15% has a recommended dosing of 1 drop 3 times daily, taken about 8 h apart. This study evaluated the IOP-lowering efficacy of brimonidine Purite 0.15% given twice daily because in clinical practice, this is the dosing schedule most commonly used. Investigators sought to make the findings of this study clinically relevant and true to life by generating data that replicate usual clinical practice outcomes.

Limitations of this study include the small sample size and the short study duration. Additionally, this study was not double-blinded. It is recommended that longer-term, larger studies be conducted to confirm the findings presented here.

CONCLUSIONS

Brimonidine Purite 0.15% provided statistically significant additional reductions in IOP from latanoprost-treated baseline values in terms of peak and trough effects. These findings suggest that brimonidine Purite 0.15% is an effective adjunctive therapy in patients using latanoprost who require additional IOP lowering.

FINANCIAL DISCLOSURE

This study was supported by an unrestricted research grant from Allergan, Inc.

A poster that reported these study findings was presented at the Annual Meeting of the Association for Research and Vision in Ophthalmology, held in Fort Lauderdale, Florida, from April 30 to May 4, 2006.

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