

by Kaysi McGhie, PharmD

Column Editor: Lee Vermeulen, MS, RPh,  
Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

## Brimonidine

### *An alpha-2 adrenergic agonist for glaucoma*

#### Summary

**Indication:** Brimonidine is indicated for the treatment of ocular hypertension, glaucoma and the reduction of elevated intraocular pressure following laser trabeculoplasty.

**Monitoring Parameters:** Patients should be monitored for changes in intraocular pressure and visual acuity. The most common adverse effects are dry mouth (33%), fatigue (16%), headache (18.7%), mild hyperemia (26.3%), blurred vision (17%) and foreign body sensation (17%). Blood pressure and heart rate should be monitored during the first few hours after argon laser trabeculoplasty and periodically during chronic glaucoma therapy.

**Dose:** The recommended dose of brimonidine 0.2% is one drop in the affected eye(s) three times daily, approximately three hours apart.

**Pregnancy Category:** B

**Breastfeeding:** Brimonidine has been shown to be excreted in breast milk in animal studies but it is not known whether it is excreted in human milk.

**Pediatrics:** Safety and efficacy in children have not been established. There have been a number of case reports of serious adverse effects including bradycardia, hypotension, hypothermia, hypotonia, respiratory depression, and apnea in infants treated with brimonidine.

**Geriatrics:** No dosing alterations are required for geriatric patients.

**Cost:** Brimonidine 0.2% ophthalmic solution is supplied in 5 mL, 10 mL and 15 mL multidose containers. The average wholesale prices for 5 mL, 10 mL, and 15 mL are \$30.53, \$61.01, and \$ 91.58, respectively.

#### Introduction

Glaucoma accounts for approximately 15% of blindness worldwide and is the leading cause of irreversible blindness.<sup>1</sup> It is defined as an optic neuropathy that leads to optic nerve tissue loss and the cupping or excavation of the nerve head.<sup>2</sup> This slowly progresses to loss of peripheral and subsequent central vision. Ocular hypertension differs in that it is not associated with optic nerve damage. There are a number of factors believed to contribute to the development of glaucoma including intraocular pressure, age, race, and family history.<sup>3</sup> The major and only modifiable risk factor in glaucoma is the elevation of intraocular pressure (IOP). Elevations of IOP is primarily due to decreased drainage of aqueous humour through the trabecular meshwork.<sup>1</sup> There are several classes of glaucoma based on the reason for poor aqueous outflow: congenital, open-angle, and closed-angle. These categories are further subdivided into primary and secondary subtypes. Adult onset open angle glaucoma, for example, is age related and associated with IOPs greater than 21 mmHg. Due to the lack of direct treatment for optic neuropathy, all currently approved glaucoma medications are directed at reducing the IOP.

Numerous pharmacological agents are used to counteract the progression of glaucoma. These include beta-adrenergic antagonists, alpha-2 agonists, prostaglandin antagonists, carbonic anhydrase inhibitors, sympathomimetics, and miotics.<sup>1,2,3</sup> Table 1 lists the available agents for glaucoma. Timolol, a

nonselective topical beta-adrenergic antagonist, is presently the agent of choice. The utility of timolol is limited by its cardiovascular, pulmonary and central nervous system side effects. In addition, it is contraindicated in patients with or at high risk for cardiopulmonary disease.

The alpha-2 agonists are indicated as second- or third-line agents for glaucoma in (1) patients with uncontrolled glaucoma as adjunctive or replacement therapy and (2) patients where beta-blockers are contraindicated. An ophthalmic formulation of clonidine, the first drug in this class, was found to be effective for the management of intraocular pressure but was associated with significant hypotension. Apraclonidine and brimonidine are Food and Drug Administration-approved alpha-2 agonists for the treatment of glaucoma. Unlike clonidine, apraclonidine does not significantly affect blood pressure, but it is associated with a high incidence of ocular allergy. Brimonidine was developed in an attempt to improve on the intraocular pressure lowering effects of apraclonidine while decreasing the side effect profile.<sup>1,2</sup> Brimonidine produces less ocular irritation and allergy than apraclonidine.<sup>1</sup>

#### Pharmacology/Pharmacokinetics

Brimonidine is a selective alpha-2 adrenergic agonist.<sup>4</sup> It is structurally similar to clonidine and apraclonidine. It is more lipophilic and alpha -2 selective than apraclonidine. The intraocular pressure lowering effects are mediated via reduc-

*The information given and views expressed herein do not necessarily reflect the opinions of PSW, its Board or members.*

tions in uveoscleral outflow, aqueous humor production and flow. In animal studies, brimonidine has shown some neuroprotective effects resulting in reduced retinal ganglion cell death but this has not been demonstrated in humans.

The peak response following ocular instillation of brimonidine is two hours.<sup>4</sup> The duration of intraocular pressure-lowering effect is 12 hours. Brimonidine is absorbed systemically to a limited extent following ophthalmic administration as demonstrated by reductions in blood pressure. Peak serum concentrations are reached within one to four hours. Brimonidine undergoes extensive hepatic metabolism. The active drug and its metabolites are primarily eliminated via renal excretion. Approximately 87% of an oral dose of oral brimonidine is eliminated within 120 hours with 74% found in the urine.

### Clinical trials

A multi-center, double-masked, randomized, placebo-controlled study conducted by Derick et al evaluated brimonidine 0.08%, 0.2%, and 0.5% in 194 patients with open angle glaucoma or ocular hypertension.<sup>5</sup> Patients were randomized to receive placebo or one of the three brimonidine formulations twice daily for one month. Intraocular pressure, visual acuity, pupil size, heart rate, systemic blood pressure and general and ocular symptoms were assessed at follow-up visits. Pretreatment IOP for all groups ranged from  $25.3 \pm 2.8$  mmHg to  $25.9 \pm 3.4$  mmHg. Patients in the active treatment groups experienced a significantly greater reduction in IOP than those receiving placebo ( $p < 0.001$ ). Mean IOP reductions of  $16.1 \pm 11.1\%$ ,  $22.4 \pm 14.3\%$  and  $30.1 \pm 13.3\%$  were seen after the first visit with the brimonidine 0.08%, 0.2% and 0.5% formulations respectively. In contrast, IOP was only reduced by  $4.2 \pm 14.4\%$  in the placebo group. At the end of the study, IOPs in the 0.08%, 0.2% and 0.5% patients groups were reduced by  $13.2 \pm 8.9\%$ ,  $15.5 \pm 11.8\%$ , and  $13.8 \pm 11.2\%$ , respectively. A significant loss of effectiveness was seen in the brimonidine 0.5% from baseline ( $p < 0.01$ ). Statistically significant decreases in heart rate were noted in the 0.2% ( $-4.5 \pm 11.3$  beats per minute;  $p = 0.021$ ) and 0.5% brimonidine ( $-3.1 \pm 9.3$  beats per minute;  $p = 0.035$ ) groups on day 21. Reductions in blood pressure were also seen but patients did not experience symptoms associated with hypotension. Increased incidence of burning, stinging, blurred vision, conjunctival blanching, fatigue and dry mouth were reported with higher doses of brimonidine compared to lower doses.

Schulman et al performed a one-year study to evaluate the safety and efficacy of brimonidine three times daily versus timolol twice daily in 374 patients with ocular hypertension and glaucoma.<sup>6</sup> This was a multicenter, double-masked, randomized, parallel group trial. The primary efficacy variable was IOP; cup:disc ratios and visual fields were secondary

variables. Patients were also evaluated for ocular and systemic adverse effects. Eligible patients were required to have untreated IOP between 23 mmHg and 35 mmHg in each eye and a best-corrected visual acuity of 20/100 or better. Examinations were performed at baseline, week 1, and months 2, 3, 6, 9 and 12. The mean baseline IOP was 24.8 mmHg in the brimonidine group and 24.6 mmHg in the timolol group following a four-week washout period. The overall mean peak intraocular pressure measured 2 hours after the morning dose were 18.3 mmHg (range, 17.8 - 18.9) and 18.5 mmHg (range, 18.3 - 19.4) in the brimonidine and timolol groups, respectively. The reduction in mean peak IOP from baseline was statistically significant in both treatment groups at all follow-up visits ( $p < 0.001$ ). The overall trough IOPs measured 12 hours after the evening dose were 20.5 mmHg (range, 19.5 - 21.1) in the brimonidine group and 18.3 mmHg (range, 17.8 - 18.8) in the timolol group ( $p < 0.001$ ). The trough IOP data gives a better understanding of the ocular hypotensive efficacy of the agent. Both drugs sustained their therapeutic effect throughout the year. No significant changes were seen in cup:disc ratio, visual fields, visual acuity, or pupil size. Patients in the timolol group experienced a significantly greater mean reduction in heart rate (1.7 - 3.0 beats per minute) than those in the brimonidine group at most visits ( $p$  not reported). Patients in both groups experienced hypotension, but this was not considered to be clinically significant.

Javitt et al conducted a study to compare the clinical success rates and quality of life scores of brimonidine 0.2% or timolol 0.5% twice daily in newly diagnosed patients naïve to glaucoma therapy.<sup>7</sup> This was a four-month, multicenter, randomized, double-masked, trial: 111 patients in the brimonidine group and 109 in the timolol group. Clinical success was defined as whether the investigator would recommend that the patient remain on his or her medication after evaluating IOP reduction and adverse events. Quality of life was determined by the SF-36 Health Survey and Glaucoma Disability Index questionnaires. Patients were randomized to receive either brimonidine or timolol. If treatment failure occurred after one month, patients were crossed over to the alternate therapy. If the patient still did not respond after one month on the second agent, they were treated with both agents. Clinical success was reported in 70.8% (75/106) of brimonidine patients and 69.5% (73/105) of timolol patients ( $p = 0.083$ ). Nineteen patients in each group were changed to alternative therapy. Clinical success was seen in 15 of the 19 (78.9%) patients who switched to timolol and 10 of 15 (52.6%) who switched to brimonidine ( $p = 0.17$ ). The IOP decreased from 25.3 mmHg and 25.4 mmHg at baseline to 18.8 (range, 18.7 - 19.1) mmHg and 19.2 (range, 19.4 - 19.6) mmHg in the brimonidine and timolol groups, respectively. No clinical or statistically significant changes in quality of life from baseline were seen in either

group. At baseline the mean score for the physical and mental component of the health survey for brimonidine was 52.4 (range, 23.5–64.7) and 63.1 (range, 38.7–74.8), respectively. In comparison, patients in the timolol group had baseline mean physical and mental component scores of 53.8 (range, 21.4–64.0) and 62.9 (range, 32.2–73.8). Throughout the study, the mean scores for both groups varied by less than one unit. There were also no changes noted in the glaucoma disability score between each group at baseline and one year.

A study conducted by LeBlanc et al compared the long term safety and ocular hypotensive effects of brimonidine 0.2% and timolol 0.5% in patients with glaucoma or ocular hypertension.<sup>8</sup> This was a double masked, parallel-group, multicenter trial in which 483 patients were randomized to receive either brimonidine or timolol twice daily for one year. Intraocular pressure, the primary efficacy variable, was measured at baseline and at each visit. Cup:disc ratio, visual fields, visual acuity, and adverse events were also monitored. Statistically significant reductions in peak (hour 2) and trough (hour 0) IOPs were seen in both groups ( $p < 0.001$  vs baseline). The overall mean IOP reduction from baseline at peak were 6.8 mmHg (range, 6.4–7.6 mmHg) and 5.9 mmHg (range, 5.5–6.6 mmHg) in the brimonidine and timolol group, respectively. In contrast, timolol produced a significantly greater IOP reduction at trough than brimonidine throughout the study ( $p < 0.001$ ). The overall decrease in IOP from baseline was 3.9 (range, 3.8–4.8) mmHg in the brimonidine group and 6.0 mmHg (range, 5.7–6.4 mmHg) in the timolol group. The average of the peak and trough IOP reductions for both groups was not significantly different. Statistically significant differences were not seen in cup:disc ratios, visual acuity, Schimer tear test, or visual fields. Patients in the timolol group experienced increases in heart rate which were not considered clinically significant. Dry mouth, conjunctival follicles, and ocular allergic reactions were seen more frequently in the brimonidine group than in the timolol group ( $p \leq 0.036$ ) while timolol produced more stinging and burning ( $p < 0.001$ ). Tachyphylaxis was not noted in either group. Forty patients discontinued the study due to lack of efficacy: 10.3% in the brimonidine group and 5.2% in the timolol group. In addition, 85 patients discontinued the study secondary to adverse events: 26% (76/292) and 5% (9/191) in the brimonidine and timolol groups, respectively. Ocular allergic reaction associated with brimonidine accounted for 14.7% (43 of 292) of patients discontinuing the study.

Melamed et al conducted a multicenter, interventional, double-masked trial in which 94 eligible patients from the Brimonidine Study Group 2 initially studied by LeBlanc et al were followed for three years. Patients were randomized to receive brimonidine 0.2% or timolol 0.5% twice daily.<sup>9</sup> Mean reduction from baseline IOP at trough was the primary efficacy variable. Visual acuity, visible fields, and safety variables

including adverse events, ocular symptoms, heart rate, blood pressure and laboratory results were also monitored. Baseline IOP was measured on the first visit of year three and IOP at trough every three months thereafter. During the first year, timolol produced a greater IOP reduction at trough ( $p < 0.001$ ) than brimonidine. Both agents produced sustained and significant reductions in IOP throughout the third year ( $p < 0.001$ ). Throughout the third year, the overall mean IOP reductions were 5.02 (range, 4.64–5.21) mmHg and 5.57 (4.75–6.11) mmHg for the brimonidine and timolol groups, respectively ( $p = 0.383$ ). Brimonidine produced higher IOP reductions than timolol at the end of the third year but the difference was not statistically significant. There were also no significant differences in the secondary variables: visual fields, visual acuity, other ocular safety variables, and systemic adverse effects. No tachyphylaxis was noted in either group.

Stewart et al evaluated the safety and efficacy of brimonidine 0.2% compared to dorzolamide 2%, a carbonic anhydrase inhibitor, administered three times daily in 40 patients with ocular hypertension or primary ocular glaucoma.<sup>10</sup> The primary efficacy variable was the IOP difference at trough between visit 4 and 7, and peak IOP. Ocular and systemic adverse effects were also monitored. Patients underwent a two-week washout period. The study was a double masked, multicenter, crossover study over a 6 to 12 week period. The baseline IOP for 40 patients (76 eyes) was  $24.1 \pm 20$  mmHg. The trough IOP after a six week treatment were  $20.7 \pm 3.1$  mmHg and  $20.8 \pm 3.2$  mmHg for dorzolamide and brimonidine, respectively ( $p = 0.99$ ). The peak IOPs were  $18.6 \pm 3.4$  mmHg and  $17.8 \pm 2.7$  mmHg for dorzolamide and brimonidine, respectively. Dorzolamide produced more stinging/burning (35%) than brimonidine (2%) ( $p < 0.01$ ). No significant differences in terms of fatigue, dizziness, taste perversion, dry mouth or depression were seen between brimonidine and dorzolamide.

Javitt et al compared the clinical efficacy of brimonidine 0.2% and betaxolol 0.25% administered twice daily in 188 patients with ocular hypertension or open angle glaucoma<sup>11</sup>. This was a prospective, double-masked, randomized, multicenter trial. Therapy naive patients required no washout period while those with prior use of glaucoma medications had to undergo a specific washout period. Examinations were done at baseline, one month and four months. Clinical success rate was the primary outcome variable. IOP and quality of life were also measured. Patients were switched to the alternative regimen if at one month, clinical success was not reached and subsequently remained on that regimen for the next four months. The only demographic difference existed in race and medical history but the authors concluded neither had a significant influence on the clinical success. Baseline IOPs were 23.55 mmHg and 23.29 mmHg in the brimonidine and betaxolol group, respectively. Approximately 74% (65/88) of brimonidine

patients and 57% (51/89) of betaxolol patients experienced clinical success at their initial treatment ( $p < 0.027$ ). Eight (72.7%) of the 11 brimonidine patients and 13 (54.2%) of the 25 betaxolol patients who switched to the alternative therapy achieved clinical success ( $p = 0.461$ ). The overall mean IOP reduction from baseline was 5.9 mmHg and 3.8 mmHg in the brimonidine and betaxolol group, respectively. Ocular burning was the most commonly experienced side effect (7.4%) in the betaxolol group while oral dryness was seen most in the brimonidine group (6.5%). There were no significant differences in heart rate, blood pressure and quality of life between groups. A significant increase from baseline glaucoma disability index score was noted in the brimonidine group ( $+ 1.52 \pm 5.43$ ,  $p = 0.021$ ) but not in the betaxolol group ( $+ 1.03 \pm 5.52$ ,  $p = 0.164$ ). The changes were not considered to be clinically significant.

### Adverse effects

The most common side effects associated with brimonidine therapy are dry mouth (33%), fatigue (16%), headache (18.7%), mild hyperemia (26.3%), blurred vision (17%) and foreign body sensation (17%).<sup>1</sup>

### Cardiovascular effects

Hypertension, palpitations and syncope have been reported in less than 3% of brimonidine treated patients in clinical trials.<sup>4</sup>

Nordlund et al compared the cardiovascular, pulmonary and ocular hypotensive effects of brimonidine 0.2%, timolol 0.5%, betaxolol 0.25% ophthalmic solutions and a brimonidine vehicle in 24 healthy volunteers.<sup>12</sup> This was a single center, double masked, randomized, crossover study. The reduction in resting (5.3 to -6.5 beats per min;  $p \leq 0.004$ ) and exercise-induced heart rate (4.3 to -13.6 beats per min;  $p \leq 0.022$ ) were greater in the timolol treated subjects than in other treatment groups. Brimonidine 0.2% solution produced a slight reduction in systolic blood pressure upon recovery from exercise and at 4 hours (5.2 to -7.3 mmHg;  $p \leq 0.024$ ) compared to other study medications. Mean resting heart rates at hours 0, 2, and 4 hours did not differ from baseline examination.

### Central nervous system effects

Brimonidine has been reported to potentiate headache or fatigue/drowsiness in 10 - 30 % of patients.<sup>4</sup> Carlsen et al reported two cases of central nervous system depression in infants.<sup>13</sup> An 11-year-old infant became lethargic and apneic after one drop of brimonidine following a congenital cataract removal. The symptoms were reproduced after the second administration. The second infant, a 5 month old, was lethargic and poorly responsive within a half-hour of receiving a drop in each eye. Symptoms resolved in both patients upon discontinuation of brimonidine.

### Ocular effects

Adverse ocular effects occurring in 10 to 30 % of patients receiving brimonidine are ocular hyperemia, burning and stinging, blurring, foreign body sensation, conjunctival follicles, ocular allergic reactions, and ocular pruritus.<sup>5</sup> Three to 9 % of patients reported corneal staining/erosion, photophobia, eyelid erythema, ocular aching/pain, xerophthalmia, tearing, eyelid edema, conjunctival edema, blepharitis, ocular irritation, conjunctival blanching and abnormal vision.<sup>4</sup>

### Tachyphylaxis

Tachyphylaxis has been reported with long term use of brimonidine.<sup>4</sup> This phenomenon was not noted in the evaluated trials.<sup>8,9,11</sup>

### Cost, dose, and how supplied

The recommended dose of brimonidine 0.2% is one drop in the affected eye(s) three times daily, approximately three hours apart. Walters et al found that there is no clinical advantage to three times daily dosing over twice daily dosing. Both regimens were equally effective in reducing IOP during trough levels.<sup>14</sup>

Brimonidine 0.2% ophthalmic solution is supplied in 5 mL, 10 ml and 15 ml multidose containers.<sup>4</sup> The average wholesale prices for 5 ml, 10 ml, and 15 ml are \$30.53, \$61.01, and \$91.58, respectively. In contrast, the average wholesale prices for 5 ml of apraclonidine 0.5%, timolol 0.25% and timolol 0.5% are \$53.91, \$14.02 and \$16.58, respectively.

### Conclusion

Brimonidine has established itself as an effective agent in the treatment of glaucoma. Presently, there are no comparative trials comparing brimonidine and apraclonidine in glaucoma. Comparative studies have found no significant difference between brimonidine and timolol in reducing IOP in patients with glaucoma. Brimonidine provides an effective alternative to timolol in patients with a cardiac or pulmonary dysfunction or unable to tolerate in those using systemic beta-blockers. However, it should not replace timolol as first line agent due to its cost, ocular side effect profile and labeled three-times-a-day dosing. ■

---

References available on request.