Brimonidine Tartrate

A One-month Dose Response Study

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Background: Brimonidine tartrate is a relatively selective alpha$_2$-agonist that effectively reduces mean intraocular pressure (IOP) and the incidence of IOP spikes after laser trabeculoplasty. The authors were interested in evaluating the dose response of brimonidine when applied topically for a longer duration in patients with elevated IOPs.

Methods: The authors conducted a 1-month, multicentered, double-masked, randomized, placebo-controlled, parallel clinical study in 194 patients with ocular hypertension or glaucoma (mean IOP, 25.6 ± 3.2 mmHg). The authors administered three concentrations of brimonidine (0.08%, 0.2%, and 0.5%) or placebo bilaterally every 12 hours for 1 month. The authors evaluated the following parameters: IOP, heart rate, blood pressure, visual acuity, pupil size, basal tear secretion as well as patient comfort at baseline, day 1, week 1, week 3, and week 4.

Results: All concentrations of brimonidine significantly reduced IOP, compared to baseline and placebo, at all follow-up visits. Maximum mean IOP decreases from baseline of 20.8%, 27.2%, and 30.1% were observed for the 0.08%, 0.20%, and 0.5% treatment groups, respectively. On days 1 and 21, the 0.2% and 0.5% treatment groups exhibited significantly greater IOP decreases than did the 0.08% group. After the initial steep decline in IOP, the effect decreased slightly and stabilized at day 14 at the level that was maintained throughout the study. The most frequent side effects reported were fatigue and dry mouth. No significant changes in heart rate were reported. Statistically significant decreases in mean blood pressure without clinical symptoms were observed within the 0.2% and 0.5% treatment groups.

Conclusion: Brimonidine 0.2% is well tolerated, efficacious, and shows potential as an agent in the long-term treatment of elevated IOP.

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Alpha$_2$-agonists are a relatively new class of glaucoma medication derived from clonidine that offer promise for the long-term therapy of glaucoma. Apraclonidine, the most widely used alpha$_2$-agonist, has been effective in lowering the intraocular pressure (IOP) in patients with ocular hypertension[1–4]; however, topical allergy[5–8] may limit its long-term potential in many eyes. Brimonidine

tartrate (AGN 190342-LF, UK 14,304-18) is a relatively selective alpha$_2$-agonist that, because of its distinct chemical structure, may have theoretical advantages over apraclonidine. Topically administered brimonidine lowers IOP in normotensive and ocular hypertensive monkeys, rabbits, and cats over a dose range of 0.001% to 1.0%.[9] In human subjects, the mechanism has been reported as being dual: a decrease in inflow and an increase in uveoscleral outflow.[10] Brimonidine is an effective agent in reducing elevations in IOP after argon laser trabeculoplasty and in patients with elevated IOP.[11,12]

Brimonidine, like apraclonidine, appears to have minimal effects on heart rate and systemic blood pressure.[13] Both agents, however, produce similar alpha$_1$ side effects, including dry mouth, fatigue, and conjunctival blanching. In this study, we attempted to determine the concentration of brimonidine that maximized IOP reduction and minimized side effects.

Methods

This study was a multicentered, double-masked, randomized, placebo-controlled, parallel, 1-month dose response evaluation of brimonidine 0.5%, 0.2%, and 0.08% in patients with open-angle glaucoma or ocular hypertension. We enrolled 194 chronic open-angle glaucoma or ocular hypertension patients with the following criteria:

1. All had untreated IOPs of at least 22 mmHg but not more than 35 mmHg in both eyes.
2. Neither eye could have marked optic nerve damage.
3. Patients were required to discontinue all topical glaucoma medications for up to 30 days before entry into the study.

We did not enroll patients into the study whose IOPs were greater than 21 mmHg requiring two or more medications. The following were not enrolled as patients in the study: patients who had glaucoma laser or filtration surgery within the past 3 months; women of childbearing potential or nursing mothers; patients with contraindications to alpha-adrenoceptor agonist therapy such as depression, coronary insufficiency, or Raynaud phenomenon; uncontrolled systemic disease or hypersensitivity to the study medication ingredients; patients using systemic adrenergic-agonist agents or whose therapy was changed during the study to agents that could have a substantial effect on IOP; patients with corticosteroid-induced, uveitic, or neovascular glaucoma; and patients with active ocular disease, corneal abnormalities, or contact lens-wearing patients. All institutional review boards approved the study, and we gave verbal explanation to all patients, and a written informed consent was signed by all study participants.

At the prestudy visit, we obtained a medical and ophthalmic history. An initial examination was performed at the baseline visit (day 0), which included Snellen visual acuity assessment; measurement of pupillary diameter using a millimeter ruler; slit-lamp evaluation of the anterior segment, including subjective determination of conjunctival blanching and erythema; ophthalmoscopic examination of the optic nerve; measurement of basal tear secretion using the Schirmer test; and an automated, static, central 24° threshold visual field if one had not been performed within the past 3 months. Intraocular pressure, resting heart rate, and blood pressure were measured in each patient between 7:30 AM and 9:30 AM (early morning) and 1, 2, 6, and 8 hours later.

After this baseline examination, we randomized the patients in a double-masked fashion into one of four treatment groups: brimonidine 0.5%, 0.2%, 0.08%, or placebo (brimonidine vehicle). We instructed patients to instill their medications into each eye at 12-hour intervals for a duration of 1 month, beginning the evening of the baseline examination. The patients did not receive instruction with regard to nasolacrimal occlusion. Patients returned 1, 7, 14, 21, and 28 days later for follow-up examinations. The patients were instructed not to use the study medication until after the early morning examination.

Patients returned for follow-up examinations in the morning on days 1, 7, 14, and 28 for assessment of the following variables: IOP (measured between 7:30 AM and 9:30 AM), visual acuity, pupil size, biomicroscopy, heart rate, systemic blood pressure, and general and ocular comfort. Diurnal IOP measurements (at hours 1, 2, 6, and 8) and ophthalmoscopy were performed only on the day 21 visit after the early morning examination and instillation of study medication. Efficacy was assessed by evaluating changes from baseline in IOP. Ocular safety was assessed by evaluating changes from baseline in visual acuity, biomicroscopy, ophthalmoscopy, and Schirmer testing. Systemic safety was assessed by evaluating changes from baseline in heart rate and blood pressure. Patients were questioned about specific ocular and systemic symptoms, including burning and stinging on instillation, blurred vision, dry mouth, and fatigue.

Numeric values are presented as mean ± standard deviation. For IOP, results from both eyes were averaged and treated as a unit. Mean changes from baseline were analyzed using an analysis of variance with Fisher protected Least significance procedure for between-group comparison and a paired t test for within-group analysis of changes from baseline. With respect to diurnal data, the diurnal time points of day 0 were used as baseline for the corresponding time points of day 21.

Results

The demographics of the 194 patients enrolled in the study are summarized in Table 1. Of the 194 patients enrolled in the study, 8 patients were disqualified because of improper entry or protocol violations. No significant pretreatment differences were noted between treatment groups. Mean pretreatment IOPs for the groups ranged from 25.3 ± 2.8 mmHg to 25.9 ± 3.4 mmHg. Most patients were white. There were slightly more women than men.

All concentrations of brimonidine significantly reduced IOP from baseline at all follow-up visits. Maximum

Table 1. Demographics

	0.08%	0.2%	0.5%	Vehicle	P*
No. of patients	45	48	48	45	
Age (yrs)	60 ± 12.4	58.9 ± 12.0	59.6 ± 12.9	57.2 ± 13.2	0.534
Sex					
Female	28 (62%)	25 (52%)	21 (44%)	18 (40%)	0.147
Male	17 (38%)	23 (48%)	27 (56%)	27 (60%)	
Race					
White	36 (80%)	38 (79%)	40 (83%)	31 (69%)	0.333
Black	5 (11%)	8 (17%)	6 (12%)	9 (20%)	
Hispanic	4 (9%)	2 (4%)	2 (4%)	5 (11%)	
Iris color					
Blue	17 (38%)	18 (37%)	12 (25%)	8 (18%)	0.956
Green	3 (7%)	2 (4%)	2 (4%)	2 (4%)	
Brown	24 (53%)	25 (52%)	27 (56%)	25 (56%)	
Hazel	1 (2%)	3 (6%)	7 (15%)	10 (22%)	
Intraocular pressure baseline	25.9 ± 3.3	25.7 ± 3.6	25.5 ± 3.4	25.3 ± 2.8	0.656

* Among-group comparisons.

mean IOP decreases from baseline of 16.1%, 22.4%, and 30.1% were observed for the 0.08%, 0.2%, and 0.5% treatment groups, respectively (Table 2). On the first day of therapy, brimonidine reduced IOP in a dose-related fashion. Brimonidine 0.2% and 0.5% decreased mean IOP significantly more than did brimonidine 0.08%, and the 0.5% group exhibited a greater percentage decrease in IOP than did the 0.2% group ($P < 0.05$). On day 14, all concentrations of brimonidine had statistically similar ocular hypotensive effects. Compared to the day 1 effect, there was a significant loss of effect for the 0.5% concentration ($P < 0.01$) but not for the 0.2% or 0.08% concentrations on days 7, 14, 21, and 28.

Analysis of diurnal IOP data (obtained at baseline and day 21) indicated that all treatment groups exhibited a significantly greater IOP decrease than did the vehicle control placebo group at hours 0, 1, 2, 6, and 8 (Fig 1). The 0.2% and 0.5% treatment groups had significantly greater decreases than did the 0.08% group during the first 2 hours. No clinically significant difference was observed between the 0.2% and 0.5% treatment groups. At hour 0 on day 21 (12 hours after the last dose of medication) the 0.08%, 0.2%, and 0.5% treatment groups exhibited a significantly greater decrease in IOP than did the vehicle control group ($P < 0.001$, −3.55 mmHg, −4.68 mmHg, and −4.41 mmHg, respectively). In all three treatment groups, peak ocular hypotensive efficacy occurred 2 hours after instillation. At hour 6, the 0.2% and 0.5% treatment groups had greater than 15% reduction in mean IOP. By the eighth hour, the percentage decrease had diminished to 14.5% and 12.0%, respectively.

The number of patients with at least a 20% IOP reduction is listed in Table 3. Overall, 23 (51%) of 45 patients in the 0.08% group, 39 (81%) of 48 patients in the 0.2% group, and 40 (83%) of 48 in the 0.5% group showed a reduction of 20% or more from baseline at one or more scheduled visits over the course of the study. The number of patients with a 20% reduction in IOP decreased over the course of the month, although this trend was significant only for the 0.5% concentration. At the final visit (day 28), 7 (16%) of 45 patients in the 0.08% group, 15 (31%) of 48 patients in the 0.2% group, and 10 (21%) of 48 in the 0.5% group showed a 20% IOP reduction from baseline.

The mean IOP decrease from baseline of 30.1% and 22.4% seen at day 1 in the 0.5% and 0.2% brimonidine groups, respectively, 12 hours after instillation diminished to just over 15% by day 14 in both groups and remained at this level for the remainder of the study (Fig 2).

Table 2. Intraocular Pressure Percent Changes from Baseline (Hour 0)

Day of Visit	0.08%	0.2%	0.5%	Vehicle	P*
1	−16.1 ± 11.1	−22.4 ± 14.3	−30.1 ± 13.3	−4.2 ± 14.4	<0.001
7	−16.5 ± 17.1	−18.6 ± 9.9	−21.6 ± 11.1	−4.3 ± 13.3	<0.001
14	−12.1 ± 10.3	−15.8 ± 10.2	−15.4 ± 12.0	−2.3 ± 10.6	<0.001
21	−13.8 ± 9.7	−18.3 ± 9.2	−16.9 ± 10.5	−6.2 ± 9.0	<0.001
28	−13.2 ± 8.9	−15.5 ± 11.8	−13.8 ± 11.2	−4.6 ± 10.5	<0.001

* Among-group comparisons.

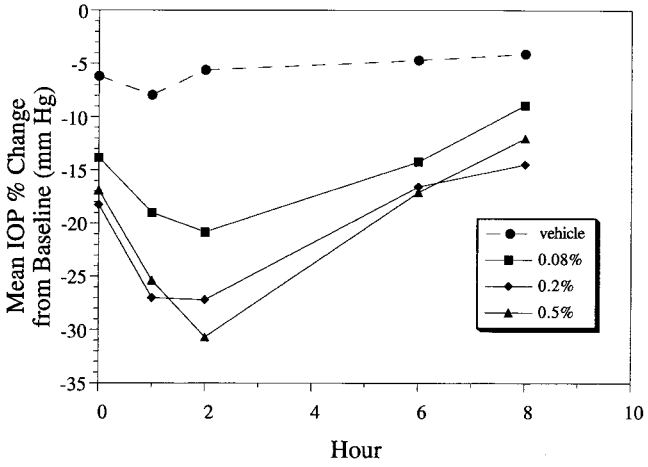

Figure 1. Percent reduction in intraocular pressure on day 21 relative to vehicle.

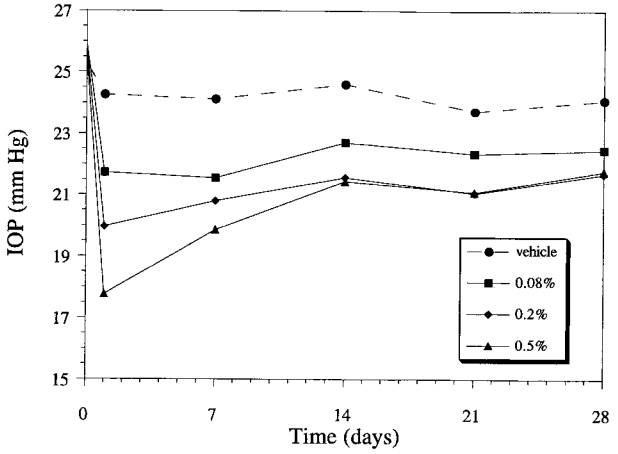

Figure 2. Mean intraoperative pressure readings before morning instillation of medication.

Conjunctival blanching appeared to be dose related; it was observed bilaterally in eight patients in both the 0.2% and 0.5% treatment groups, five patients in the 0.08% group, and four in the vehicle control group. Conjunctival erythema occurred more commonly with higher concentrations of brimonidine than with the lower concentration, occurring in 8 (17%) of 48 patients in the 0.5% group, 6 (12%) of 48 patients in the 0.2% group, and only 2 (4%) of 45 patients in the 0.08% group. However, we did observe conjunctival erythema in 8 (18%) of 45 patients who received only the drug vehicle. No clinically significant changes occurred in mean pupil size or basal tear secretion.

The only statistically significant change in mean heart rate occurred in treatment groups 0.2% (-4.5 ± 11.3 beats per minute, $P = 0.021$) and 0.5%(-3.1 ± 9.3 beats per minute, $P = 0.035$) at hour 6 on day 21. We noted statistically significant changes in mean systolic blood pressure on day 21; at hour 1 in the 0.08% treatment group (-6.0 ± 15.6 mm), hours 1, 2, 6, and 8 in the 0.2% treatment group (range, -5.7 ± 14.3 mm to -7.1 ± 10.2 mm) and hours 2, 6, and 8 in the 0.5% treatment group (range, -5.7 ± 14.6 mm to 9.1 ± 15.7 mm). At the day 21 follow-up diurnal examination, a total of 13 patients (29%) in the 0.08% treatment group, 20 patients (42%) in the 0.2% treatment group, 21 patients (44%) in the 0.5%, and 12 patients (27%) in the vehicle control group experienced decreases in systolic pressure of greater than 20 mmHg compared to the same time point at baseline. No patient experienced symptoms related to these changes in blood pressure.

Table 3. Subjects with an IOP Reduction of ≥20% from Baseline at Each Scheduled Visit: Number of Subjects

Visit	0.08%	0.2%	0.5%	Vehicle
No. of patients	45	48	48	45
Day 1	12	23	38	5
Day 7	15	21	24	5
Day 14	8	15	13	2
Day 21	10	15	13	2
Day 28	7	15	10	5
Overall*	23	39	40	11

IOP = intraocular pressure.

* Number of subjects with an IOP reduction of ≥20% from baseline at one or more scheduled visits over the study.

Mean changes in diurnal diastolic blood pressure ranged from -0.9 ± 12.9 mmHg to -4.1 ± 7.2 mmHg in the 0.08% treatment group, -0.3 ± 9.2 mmHg to -4.4 ± 9.0 mmHg in the 0.2% treatment group, -2.6 ± 10.2 mmHg to -7.0 ± 8.3 mmHg in the 0.5% treatment group, and -0.3 ± 7.4 mmHg to -2.1 ± 7.7 mmHg in the vehicle control group. The mean decrease in diastolic blood pressure was significantly greater in the 0.5% treatment group at hour 2 than in the 0.08%, 0.2%, and vehicle control groups ($P < 0.012$; -7.0 ± 8.3 mmHg, -3.7 ± 8.3, -3.8 ± 7.0, and -1.2 ± 10.0 for 0.5%, 0.08%, 0.2%, and vehicle control groups, respectively).

Burning and stinging and blurred vision were more frequently reported in the 0.5% treatment group than in either the 0.2%, 0.08%, or vehicle control group. Reports of burning or stinging on instillation ranged from 13% (0.08% group) to 27% (0.2% group) to 31% (0.5% group), and reports of transient blurred vision ranged from 16% (0.08% group) to 15% (0.2% group) to 35% (0.5% group). The vehicle control group also had a high reported incidence of burning and stinging (27%) and blurring (18%). Symptoms of general discomfort also were reported more frequently in the 0.5% treatment group. The most commonly reported symptoms included dry mouth (13.3%, 16.7%, 35.4%) and fatigue–drowsiness (6.7%, 10.4%, 29.2%) in the 0.08%, 0.2%, and 0.5% groups, respectively.

Discussion

This study shows that brimonidine effectively lowers IOP in patients with ocular hypertension in a dose-dependent

fashion. Important features in our study include its double-masked design and the monitoring of IOP for 12 hours after drug instillation. These help control nondrug-related variation in the parameters that we observed. By monitoring the IOP for several hours during the day at baseline and on day 21, we partially controlled for diurnal effects on the IOP. A maximum decrease in IOP of 25% attributable to brimonidine and relative to vehicle (30% relative to baseline) is similar to the decrease reported for apraclonidine.[14] The day 1 mean maximal IOP-lowering effect of brimonidine 0.5% was greater than either the 0.2% or 0.08% concentration. After the first day, both the 0.2% and 0.5% concentrations had similar efficacy and were more potent than was the 0.08% concentration. Apraclonidine has a similar dose response with the 0.25% concentration having a greater effect than the 0.125% concentration and no additional effect observed in either the 0.5% or 1.0% concentration.[1,15,16] At 3 weeks, all three concentrations of brimonidine had a similar duration of action of at least 12 hours. However, 8 hours after instillation, the IOP percentage decrease had diminished to 14.5% and 12.0% for the 0.2% and 0.5% groups, respectively.

In separate short-term studies, both brimonidine and apraclonidine appear to lose some potency over 1 to 2 weeks of use. In a 1-week dose response study of apraclonidine 0.5%, the average IOP reduction decreased from 20% to 14% from day 1 to day 8 after initiation of therapy.[1] We observed that brimonidine also has a more potent ocular hypotensive effect on day 1, which decreases and stabilizes by day 14 to the level maintained throughout the 4 weeks. The alpha$_2$-receptor may be most sensitive to brimonidine and other adrenergic medications acutely, then reach an equilibrium during chronic dosing at a slightly higher IOP.[17]

Not only was a dose response relation shown for the ocular hypotensive effects of brimonidine, but also for the effects on systolic blood pressure, conjunctival blanching, and ocular and systemic comfort.

At the day 21 follow-up diurnal examination, more patients treated with brimonidine 0.5% experienced decreases in systolic pressure of greater than 20 mmHg than any of the other treatment groups. Clonidine, another relatively selective alpha$_2$-agonist, has both ocular and systemic hypotensive action. In one study, clonidine 0.125% to 0.25% was as effective as pilocarpine 2% in lowering the IOP; however, 50% of patients experienced at least a 30 mmHg decrease in systolic blood pressure during the 1-week trial.[18] This adverse effect led to studies of other compounds that attempted to separate the systemic and ocular effects. Apraclonidine is similar to clonidine but has an amide group substituted on the para (C-4) position of the benzene ring. This chemical change increased the polarity of the compound, decreased its central nervous system absorption, and reduced its effects on blood pressure. In several studies of both healthy volunteers and patients with elevated IOPs, apraclonidine caused minimal effects on mean resting heart rate, mean arterial blood pressure, and exercise-induced tachycardia.[1,15,19] Similarly, brimonidine had little cardiopulmonary effect in healthy volunteers.[13] In a study evaluating the efficacy of brimonidine in limiting IOP elevation after laser trabeculoplasty, brimonidine 0.5% had minimal effects on systolic and diastolic blood pressure.[11] In this 1-month dose response study, brimonidine did produce, on the day 21 examinations, statistically significant effects on systemic blood pressure, but no adverse clinical effects were seen, and the magnitude of blood pressure effects was significantly lower than that observed with clonidine. The observed differences in the effects on blood pressure between brimonidine and apraclonidine may relate to differences in pharmacokinetics. Topical brimonidine may be more similar to clonidine than to apraclonidine in this regard. The systemic effects of brimonidine need to be evaluated in longer term studies, including comparison studies with apraclonidine.

Conjunctival blanching was observed to occur more frequently in both the 0.2% and 0.5% treatment groups than in the 0.08% group or the vehicle control group. This determination was made subjectively, with bilateral use of the medication, and without benefit of reference photographs. This effect is not unique to brimonidine, however, as conjunctival blanching is also seen commonly in patients using apraclonidine.[20]

Dry mouth appears to be a frequent symptom experienced by patients using topical alpha$_2$-agonists, and this effect may be dose related. Dry mouth was reported by approximately 13% and 17% of the patients in the 0.08% and 0.2% treatment groups, respectively. Approximately two-fold (35%) was this incidence of dry mouth reported by the 0.5%-treated patients. Dry mouth also was reported with studies on apraclonidine. Jampel et al[1] reported that, overall, 30% of patients experienced dry mouth or dry nose in a 1-week study evaluating apraclonidine 0.125%, 0.25%, and 0.5%.

The chronic use of apraclonidine appears to be associated with an allergic type of follicular conjunctivitis similar to the allergy produced by epinephrine compounds.[5] With apraclonidine 0.5%, this event is uncommon during the first month. The average time of onset was 1.5 months during a 3-month evaluation of patients already on maximum tolerated medical therapy.[4] Although the duration of this study was not long enough to fully evaluate the incidence of topical allergy after brimonidine use, there was only one report of redness and swelling that occurred (in the 0.08% treatment group) during the 1 month that brimonidine was used. Longer term studies may be needed to assess the incidence of topical allergy related to the use of brimonidine.

Because there appears to be no evidence to indicate that 0.5% is a more potent ocular hypotensive agent than is 0.2%, and because there are greater local and systemic side effects associated with the 0.5% concentration, brimonidine 0.2% appears to be the appropriate concentration for further long-term studies.

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