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Effect of single and multiple doses of 0.2% brimonidine tartrate in the glaucomatous Beagle

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Abstract

The objective of this study was to evaluate the changes in intraocular pressure (IOP) in glaucomatous dogs after instillations of 0.2% brimonidine once, twice and three times daily in single day studies, and after twice and three times daily for 4 days in multiple dose studies. We studied eight Beagles with inherited primary open angle glaucoma. Applanation tonometry (IOP), pupil size (PS) and heart rate (HR) measurements were obtained at 8 am, 10 am, 1 pm, 3 pm and 5 pm. The studies were divided into: eight glaucoma dogs and five of the eight dogs that demonstrated greater response to 0.2% brimonidine. Single-dose drug studies are divided into placebo (0.5% methylcellulose), 0.2% brimonidine administered once daily (8 am); twice daily (8 am and noon); and three times daily (8 am, noon and 5 pm). The 5-day multiple-dose studies included: day 1, no drug; and 4 days, 0.2% brimonidine instillations either twice daily (8 am and 2 pm) or three times daily (8 am, 2 pm and 9 pm). Statistical comparisons between drug groups included control (nondrug) and treated (placebo/0.2% brimonidine) eyes for both single- and multiple-dose studies. The mean ± SEM diurnal decrease in IOP in the eight glaucomatous Beagles for the control and placebo eyes were 3.4 ± 4.7 and 5.4 ± 2.8 mmHg, respectively. The mean ± SEM diurnal decrease in IOP after 0.2% brimonidine once, twice and three times daily was 6.4 ± 3.5, 8.0 ± 6.1 and 9.8 ± 8.1 mmHg, respectively; this trend was not significant statistically. Significant miosis occurred starting 2 h postinstillations, and the resultant mean ± SD pupil size was 2.7 ± 0.3 mm. A significant decrease in heart rate also occurred (12%). In the five most responsive dogs the changes in PS and HR during these studies were similar to the larger group, but significant decreases in IOP occurred at most measurement times. In the multiple-dose study with 0.2% brimonidine twice daily the mean ± SEM decrease in IOP for day 1 to day 4 was 5.0 ± 1.3, 5.7 ± 1.3, 1.4 ± 3.3 and 4.9 ± 1.3 mmHg, respectively. When 0.2% brimonidine was instilled three times daily the mean ± SEM diurnal IOP decrease was from day 1 to day 4 and was 0.75 ± 1.3, 2.4 ± 1.5, 1.2 ± 2.7 and 1.4 ± 1.8 mmHg, respectively. The mean change in pupil diameter was 1.3 ± 0.5 mm. Decrease in HR averaged 22%. In the same single-dose studies with the five most responsive dogs, PS and HR were similar, but the decreases in IOP were significant at more measurement intervals. We conclude that 0.2% brimonidine produces a decrease in IOP in dogs, a statistically significant miosis, and a reduced heart rate (12–22%). However, because of the limited drug-induced ocular hypotension, brimonidine should be combined with other drugs when used for the glaucomas in the dog.

Key Words: brimonidine, glaucoma, dog

INTRODUCTION

The adrenergics have been an important group of drugs for the clinical management of glaucoma in man and animals since 1978. Traditionally, the adrenergic drugs are divided into: α- and β-agonists, and α- and β-antagonists. Epinephrine, an α- and β-adrenergic agonist, lowers intraocular pressure (IOP) in normal and glaucomatous dogs by only a few mmHg, and must be combined with other drugs to result in clinically useful decreases in IOP.[1,2] Dipivalyl epinephrine, a epinephrine prodrug, results in similar decreases in IOP as 2% epinephrine in dogs.[1] Timolol, a nonselective β-adrenergic antagonist, also lowers IOP in normal and glaucomatous dogs,[3,4] but at the available commercial concentrations it must also be combined with other drugs that lower IOP further.[5]

Apraclonidine (0.5%), a selective α_2-adrenergic agonist, lowered IOP in normal dogs by ≈ 3 mmHg (16%), and produced 2.1 mm of mydriasis (29.7%). A 9–19.5% reduction in heart rate occurred in four of the nine test dogs.[6] In cats, this same drug resulted in greater decreases in IOP (4.8 mmHg or 24%), miosis and a decrease in heart rate (11.8%). Unfortunately, 0.5% apraclonidine also caused vomiting in eight of the nine test cats, and was not recommended for clinical use.[7]

Brimonidine tartate, a selective α_2-adrenergic agonist, has been introduced as a potential first-line therapy for primary open angle glaucoma in man.[8–11] Brimonidine is highly selective as an α_2-agonist, being 28 times more selective than apraclonidine and 10 times more selective than clonidine.[12,13] Ocular allergy, a frequent problem with apraclonidine, is less with brimonidine, perhaps because of its oxidative stability.[8] Brimonidine (0.2%) has been evaluated in normal, ocular hypotensive and glaucoma human patients, and the decrease in IOP appears similar to that associated with topical 0.5% timolol but without timolol's cardiopulmonary side effects.[14,15] The decrease in IOP after brimonidine instillations is caused by a reduction in the rate of aqueous humor formation, and an increase in the uveoscleral outflow.[16] A second mechanism for use of brimonidine for the therapy of the glaucomas may be neuroprotection of the optic nerve head and the retinal ganglion cells. In the optic nerve crush model in rats, systemic brimonidine promoted a dose-dependent reduction in injury-induced optic degeneration.[17]

This report presents the effects of single and multiple doses of 0.2% brimonidine on intraocular pressure, pupil size and heart rate in Beagles with primary open angle glaucoma.

MATERIALS AND METHODS

Eight glaucomatous Beagles were used [four males aged 30 (n = 2), 78 (n = 1) and 121 (n = 1) months; four females aged 31 (n = 1) and 78 (n = 3) months]. The single- and multiple-dose drugs were evaluated in random order and included: placebo (0.5% methylcellulose) and 0.5% brimonidine tartate (Alphagen, Allergan, Irvine, CA, USA). All dogs were examined using slit lamp biomicroscopy, gonioscopy and ophthalmoscopy, and exhibited primary open angle glaucoma in the moderate phases, and demonstrated clinical vision (positive menace and maze test).

Recorded measurements included: applanation tonometry (Model 30 pneumatonograph, Mentor O and O, Norwell, MA, USA), pupil size (Jameson calipers) and heart rate. The study times for the single-dose studies were 1 day and the following morning, followed by 14 days to allow for drug washout between each study. The multiple-dose studies consisted of the first day of all measurements without drug, followed by four complete days of testing and the following morning. The drug eye for each dog was selected at random, and all measurements were made at 8 am, 11 am, 2 pm and 5 pm, and 8 am on last day of each test. For the single-dose studies and first test week the placebo (0.5% methylcellulose) was instilled at 8 am and 5 pm. For the single-dose drug studies 0.5% brimonidine was instilled in the test/drug eye at 8 am (once daily), 8 am and 4 pm (twice daily), and 8 am, 2 pm and 5 pm (three times daily). For the multiple-dose studies, brimonidine was instilled in the test/drug eyes at 8 am and 4 pm (twice daily) or 8 am, 2 pm and 9 pm (three times daily).

Based on the initial studies with eight glaucomatous Beagles, five dogs that appeared most responsive to 0.2% brimonidine and exhibited less variability were analyzed separately. Drug comparisons were performed using SAS programs utilizing Tukey's HSD and ANOVA tests for repeated measurements.[18] Within each test week, the average measurements for IOP, pupil size and heart rate from baseline (8 am) for the each day were compared with subsequent measurements to detect significant changes ($P < 0.05$) using Tukey and ANOVA for repeated measurements. Between the nondrug or control and the drug (0.5% methylcellulose placebo or 0.5% brimonidine) eyes, the changes in IOP, pupil size and heart rate were compared for each measurement between the groups. Statistical significance was $P < 0.05$.

RESULTS

Single dose – Eight dogs: placebo

The mean ± SEM changes in pupil size (PS), heart rate (HR) and IOP for the control (nondrug) and placebo (drug) eyes are summarized in Fig. 1. Baseline (8 am) IOP for the control eye was 33.9 ± 4.4 mmHg with a diurnal decrease through the day. In the placebo and drug eyes similar IOP changes occurred, with baseline (8 am) IOP being 32.9 ± 4.2 mmHg. There were no significant differences between control and placebo eyes ($P = 0.88$) throughout the 9 h observation. Mean ± SEM pupil size (control, 3.1 ± 0.06 mm; placebo, 3.1 ± 0.07 mm) were also not significant ($P = 0.35$), and heart rate ranged from 98 ± 3 bpm to 101 ± 2 bpm with a minimum of 98 ± 3 bpm throughout the day.

Single dose – Eight dogs: 0.2% brimonidine once daily

Changes in PS, HR and IOP (mean ± SEM) after 0.2% brimonidine instillations in one eye of each dog once daily are

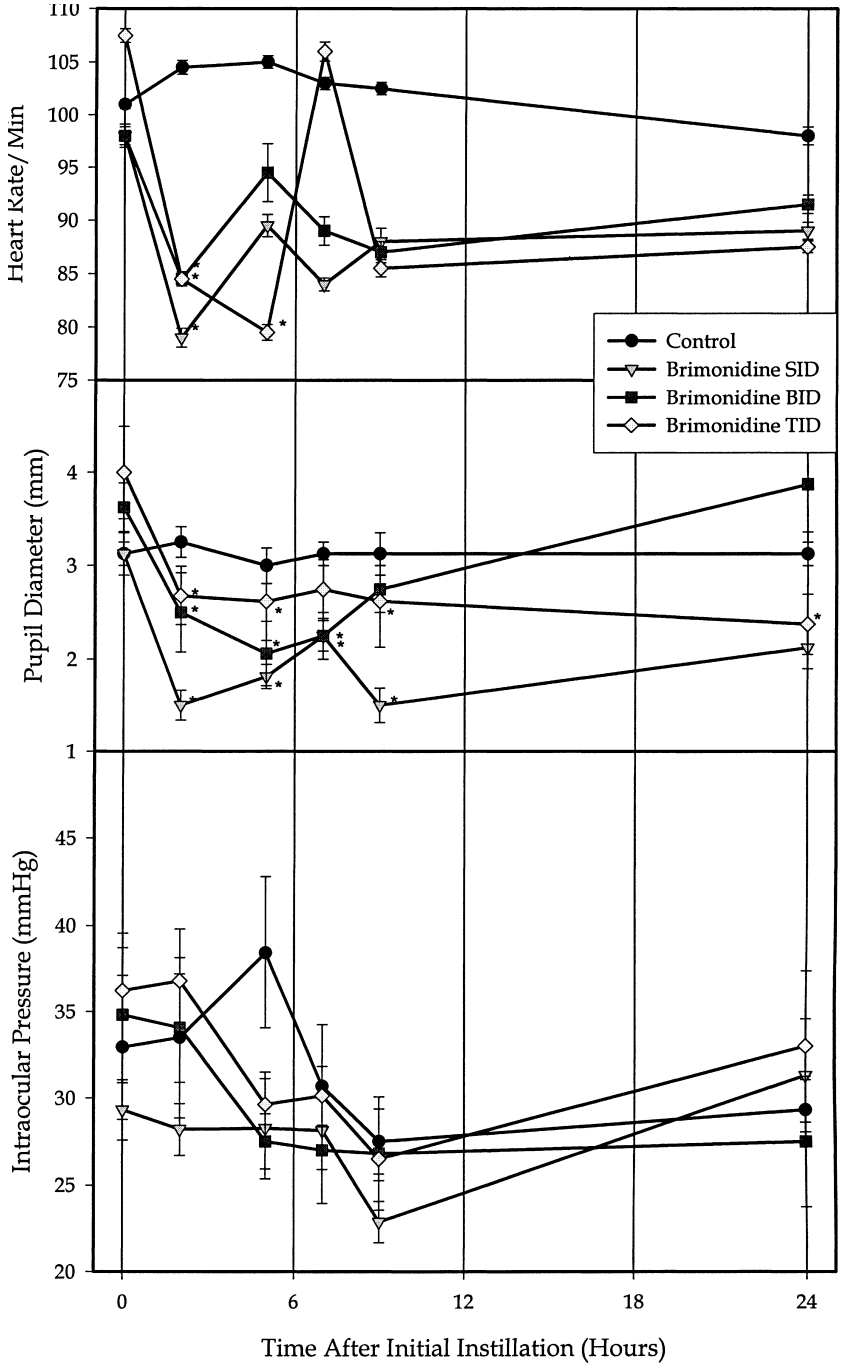

Figure 1. Single-dose study with unilateral one, two and three instillations of 0.2% brimonidine in eight glaucomatous Beagles, and the resultant mean ± SEM intraocular pressure, heart rate and pupil size. *Significantly different ($P < 0.05$) from control day.

summarized in Fig. 1. Comparisons of the nondrug and 0.2% brimonidine eyes indicated that the changes in IOP were not significantly different. Comparisons of these drug eyes with those of the placebo study indicated a trend in the decrease in IOP that was not quite significant ($P = 0.07$). Comparisons of IOP changes between the control eyes of the placebo study and these nondrug eyes indicated no significant changes ($P = 0.08$).

Miosis in the 0.2% brimonidine eyes was significantly different from the fellow control eye occurring at the 11 am measurements and lasting to the 5 pm measurements. The heart rate decrease was also significant changes starting at the 11 am measurements.

Single dose – Eight dogs: 0.2% brimonidine twice daily

PS, HR and IOP changes (mean ± SEM) after two 0.2% brimonidine instillations (8 am and 2 pm) in one eye of each dog are summarized in Fig. 1. The maximum IOP decrease in the control and drug eyes was 6.0 ± 1.9 and 8.0 ± 2.2 mmHg, respectively (at 2 and 5 pm, respectively). Comparisons of the nondrug and 0.2% brimonidine eyes indicated that the IOP changes were not significantly

different ($P = 0.08$) at 11 am, 2 pm and 5 pm, and the following morning (8 am). Comparisons of the IOP changes between the control eye (placebo study) and the nondrug eye in this study indicated no significant changes, but IOP comparisons between the placebo eyes and the 0.2% brimonidine eyes were significant.

Changes in PS and HR are summarized in Fig. 1. Significant changes in the pupil size in the 0.2% brimonidine eyes were first detected at 10 am and persisted until 4 pm. Miosis was limited to an ≈ 1.5-mm change in pupil size. Significant changes in HR were limited to only the 10 am measurements and represented a 12% decrease ($P = 0.0001$; 98 bpm to 85 bpm).

Single dose – Eight dogs: 0.2% brimonidine three times daily
PS, HR and IOP changes after three 0.2% brimonidine instillations (8 am, 2 pm and 5 pm) are summarized in Fig. 1. The maximum IOP decrease in the control and 0.2% brimonidine eyes was 8.5 ± 2.3 mmHg (5 pm) and 9.8 ± 2.3 mmHg, respectively. Comparison of placebo eyes with drug eyes indicated no significant differences.

PS and HR changes are summarized in Fig. 1. A slight, but significant, miosis (1.5–2.0 mm change) also occurred only in the drug eye, first detected at 10 am and persisting until 8 am on the second day. HR decreased at the 10 am measurement (from 103 bpm to 85 bpm; 18%) and persisted to the last measurement of the following day.

Single dose – Five dogs: placebo
PS, HR and IOP changes (mean ± SEM) of the five dogs in the control (nondrug) and placebo (drug) eyes are summarized in Fig. 2. The baseline 8 am IOP for the control eye was 38.5 ± 6.2 mmHg and for the placebo eye was 37.7 ± 5.7 mmHg. Both eyes demonstrated a diurnal decrease in IOP. There were no significant differences between the control and placebo eyes ($P = 0.65$) throughout the 9 h of observation. Changes in PS and HR throughout the day were also not significant ($P = 0.46$).

Single dose – Five dogs: 0.2% brimonidine once daily
PS, HR and IOP changes (mean ± SEM) after 0.2% brimonidine instillations in one eye of each dog once daily are summarized in Fig. 2. The maximum decrease in the control and drug eyes was 8.8 ± 3.3 and 7.2 ± 2.2 mmHg, respectively (at 2 and 5 pm, respectively). Comparisons of the nondrug and 0.2% brimonidine eyes indicated that the IOP changes were not significantly different. Comparisons of these drug eyes with those of the placebo study indicated a trend in the decrease in IOP that was not significant ($P = 0.25$). Comparisons of the IOP changes between the control eyes of the placebo study and these nondrug eyes indicated no significant changes.

Miosis in the 0.2% brimonidine eyes was significantly different to that in the fellow control eye occurring at 10 am and lasting to the second 8 am measurements. The decrease in HR was also significant starting at 10 am to the following 8 am measurements.

Single dose – Five dogs: 0.2% brimonidine two times daily
PS, HR and IOP changes (mean ± SEM) after two 0.2% brimonidine instillations (8 am and 2 pm) in one eye of each dog are summarized in Fig. 2. The maximum decrease in IOP in the control eye and drug eyes was 8.5 ± 2.3 and 11.4 ± 2.9 mmHg, respectively (at 5 and 2 pm, respectively). Comparisons of the nondrug and 0.2% brimonidine eyes indicated that the IOP changes were significantly different only at 11 am. Comparisons of the IOP changes between the control eye (placebo study) and the nondrug eye in this study indicated no significant changes ($P = 0.14$), but IOP comparisons of the placebo eyes with the 0.2% brimonidine eyes were significant ($P = 0.03$).

Significant changes in PS in the 0.2% brimonidine eyes were first detected at 11 am, 2 pm and 5 pm. Miosis was limited to an ≈ 1.5-mm change in PS. Significant changes in the HR occurred at 11 am, 2 pm and 5 pm and represented a 15% decrease.

Single dose – Five dogs: 0.2% brimonidine three times daily
PS, HR and IOP changes after three 0.2% brimonidine instillations (8 am, 2 pm and 5 pm) are summarized in Fig. 2. The maximum decrease in the control and 0.2% brimonidine eyes was 11.9 ± 2.8 mmHg (5 pm) and 11.5 ± 4.3 mmHg, respectively. Comparison of the placebo with the drug eyes indicated no significant differences at any IOP measurements.

A slight but significant miosis (1.4 mm change) also occurred only in the drug eye, first detected at 11 am and persisting until 8 am of the second day. HR decreased at 11 am (18%), and this lower HR persisted to the second 8 am measurement of the following day.

Multiple dose study – Eight dogs: 0.2% brimonidine two times daily
PS, HR and IOP changes after 0.2% brimonidine instillations at 8 am and 5 pm are summarized in Fig. 3. The daily maximum decrease in IOP in the control eyes over the 5 days were 3.9 ± 1.8, 4.8 ± 2.2, 8.1 ± 1.9, 1.6 ± 1.4 and 5.8 ± 1.9 mmHg. The daily maximum decreases in IOP in the drug eyes were 5.0 ± 1.3, 5.7 ± 1.3, 1.4 ± 3.3 and 4.9 ± 1.3 mmHg. IOP comparisons of the placebo eyes with the drug eyes were not significant different. The mean changes in PS and HR were significant.

Multiple dose study – Five dogs: 0.2% brimonidine twice daily
PS, HR and IOP changes after 0.2% brimonidine instillations at 8 am and 5 pm are summarized in Fig. 4. The daily maximum decreases in IOP in the control eyes were 4.9 ± 3.8 mmHg (no drug), 5.6 ± 2.6, 12.1 ± 1.8, 3.2 ± 2.2 and 4.1 ± 2.1 mmHg. The daily maximum decreases in IOP in the drug eyes were 6.8 ± 3.8, 6.3 ± 2.6, 13.6 ± 1.8, 2.1 ± 4.1 and 2.9 ± 2.1 mmHg. IOP changes of the placebo eyes compared with the drug eyes were not significant ($P = 0.53$). There were some significant changes in PS.

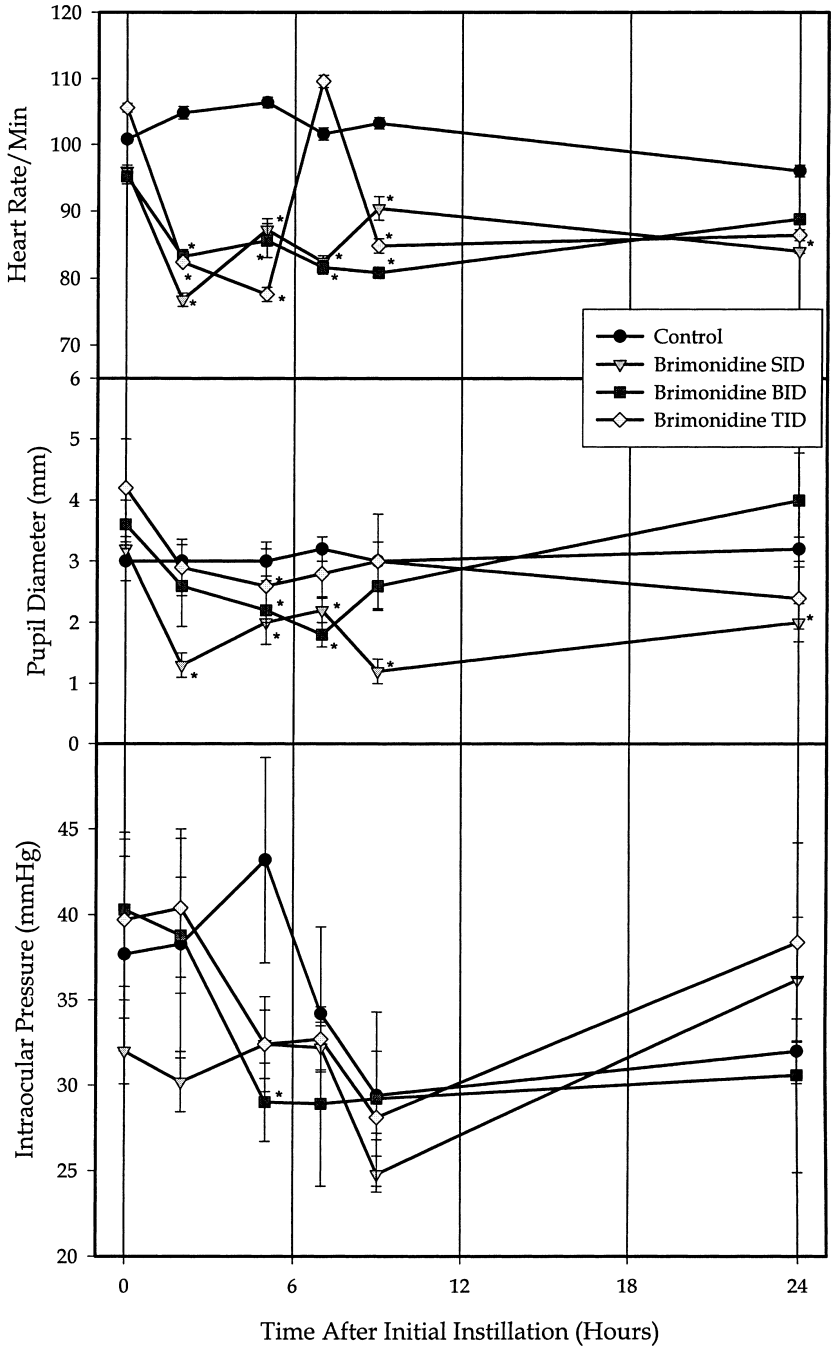

Figure 2. Single-dose study with unilateral one, two and three instillations of 0.2% brimonidine in five glaucomatous Beagles, and the resultant mean ± SEM intraocular pressure, heart rate and pupil size. *Significantly different ($P < 0.05$) from control day.

Multiple dose study – Eight dogs: 0.2% brimonidine three times daily

PS, HR and IOP changes are summarized in Fig. 5 after three daily 0.2% brimonidine instillations (8 am, noon and 5 pm). The daily maximum decreases in IOP in the control eyes were 3.2 ± 1.9, 3.1 ± 1.8, 3.7 ± 1.4, 1.4 ± 1.2 and 4.9 ± 2.2 mmHg. The daily maximum decreases in IOP in the drug eyes were 1.1 ± 1.0, 3.9 ± 2.1, 1.6 ± 1.2 and 3.1 ± 1.9 mmHg. IOP comparisons of the placebo eyes with the drug eyes were not significantly different ($P = 0.65$). The mean changes in PS and HR (average decrease 22%) were again significant.

Multiple dose study – Five dogs: 0.2% brimonidine three times daily

PS, HR and IOP changes are summarized in Fig. 6 after three daily 0.2% brimonidine instillations (8 am, noon and 5 pm). The daily maximum decrease in IOP in the control eyes were 4.9 ± 3.8 mmHg (nondrug), 2.5 ± 4.1, 7.8 ± 3.8, 2.1 ± 4.4 and 6.6 ± 3.2 mmHg. The daily maximum decreases in IOP in the drug eyes were 0.75 ± 1.3, 2.4 ± 2.7, 1.2 ± 1.8 and 1.4 ± 1.8 mmHg. IOP changes of the placebo eyes compared with the drug eyes were not significant ($P = 0.85$). The mean changes in PS were significant in approximately

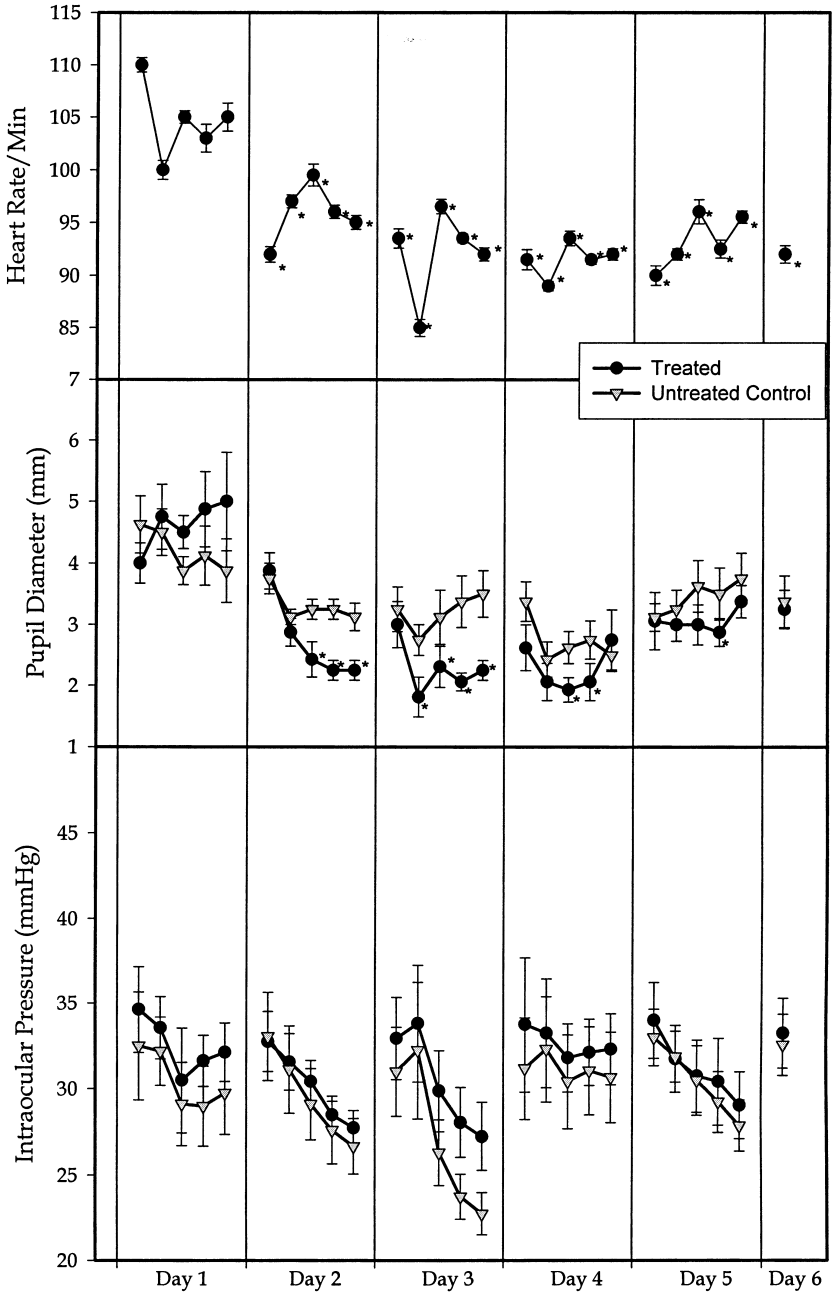

Figure 3. Multiple-dose study with unilateral 0.2% brimonidine instilled twice daily on intraocular pressure, pupil size and heart rate (mean ± SEM) in eight glaucomatous beagles instilled two times daily. *Significantly different ($P < 0.05$) from day 1 control.

one-half of the intervals, and the HR changes were significant only the 11 am measurements.

DISCUSSION

Past reports in both normal and glaucomatous dogs indicate that different adrenergics agents lower IOP and can influence PS and HR to variable degrees. IOP reductions after 1–2% epinephrine, 0.1–0.5% dipivalyl epinephrine, 0.5% timolol and 0.5% apraclonidine are statistically significant in the normal and glaucomatous dog, but of not sufficient magnitude (3–5 mmHg) to be used as sole agents for the treatment of canine primary glaucomas. As a result, adrenergics are combined clinically with other drugs to lower IOP in glaucomatous dogs. Based on this study, 0.2% brimonidine also demonstrates similar effects.

In this study, 0.2% brimonidine produced a decrease in IOP that was significant in the eight glaucomatous dogs at selected, but not all, IOP measurement intervals, but it demonstrated a statistically significant miosis and decrease in HR. Pupil changes signal drug penetration into the anterior segment, and the HR changes suggest systemic absorption. When instilled as either repeated daily instillations or for four consecutive days, a consistent, significant decrease in IOP

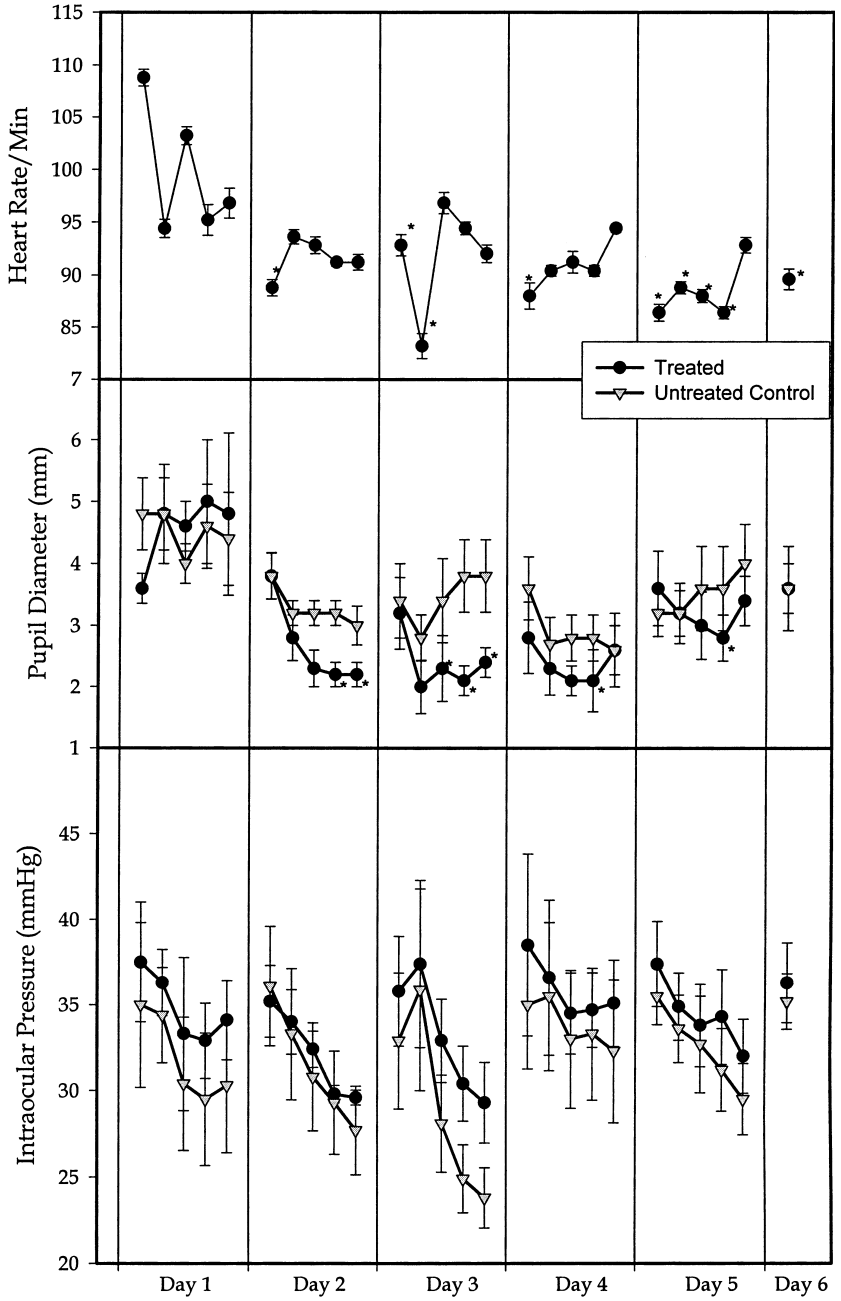

Figure 4. Multiple-dose study with unilateral 0.2% brimonidine instilled twice daily on intraocular pressure, pupil size and heart rate (mean ± SEM) in five glaucomatous Beagles. *Significantly different ($P < 0.05$) from day 1 control.

could not be shown, but occasional measurement intervals were significant.

As the single and multiple instillations of 0.2% brimonidine produced trends, but not statistically significant reductions, in IOP, higher concentrations of the drug may be necessary. As the anterior chamber volume is larger in the dog than in man, drug dilution may be a limiting factor. Another possibility may be the types and numbers of α- and β-adrenergic drug receptors available in the dog. Apraclonidine, another α_2-adrenergic agonist, induced mydriasis in normal dogs,[6] but in this study brimondine produced a small decrease in PS. *In vitro* studies of the canine iridal sphincter and dilator muscles suggest α_2-adrenergic innervation is inhibitory to the canine sphincter muscle.[19] Perhaps the different commercial concentrations of brimonidine (0.2%) vs. apraclonidine (0.5%) may be important.

As reported with topical 0.5% timolol in man, certain individuals respond to the drug favorably, whereas others exhibit no significant IOP changes. Based on the variability detected in this study, the IOP changes in each of the eight glaucomatous Beagles were plotted individually, and five dogs were determined to respond and analyzed collectively. The reduction in IOP, miosis and decrease in HR in these dogs were significant more often throughout the day. A reduced drug effect also seemed to develop as the study

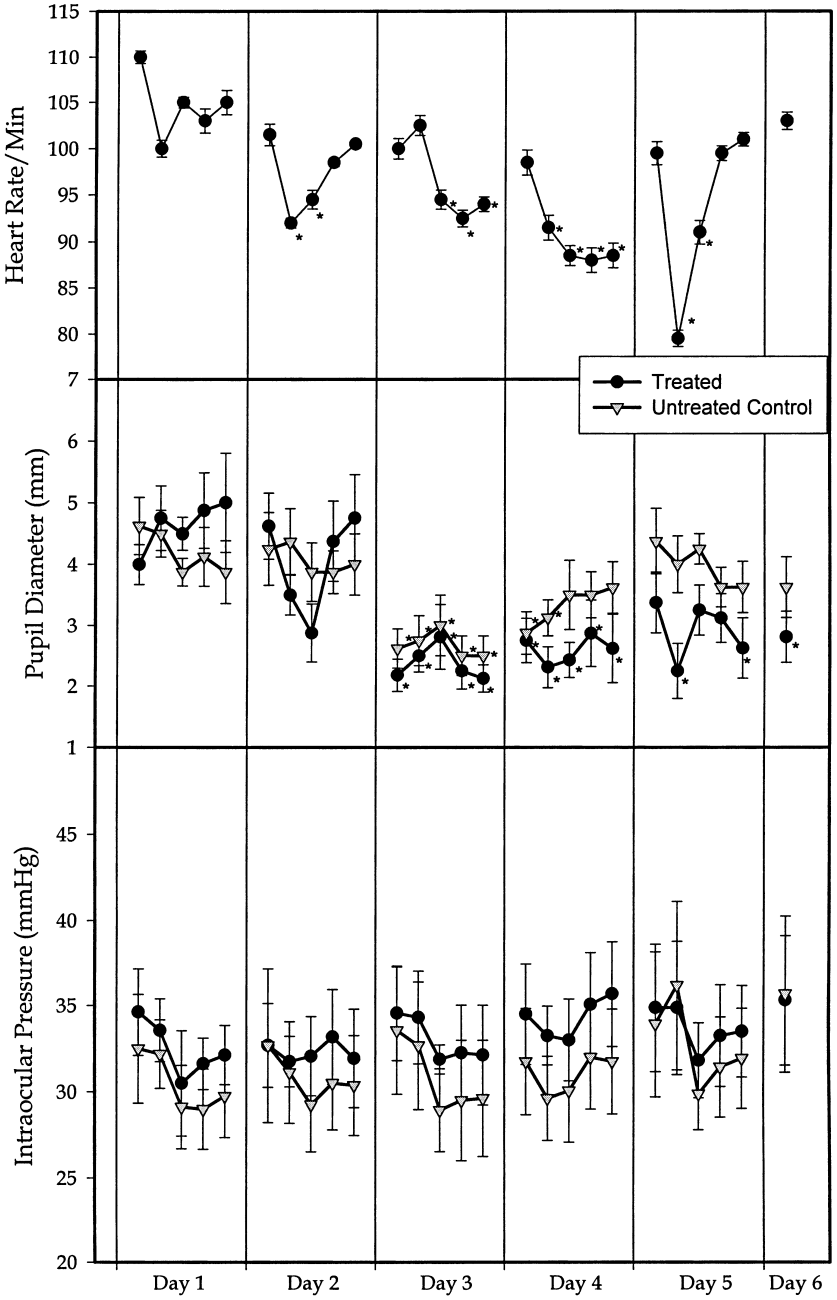

Figure 5. Multiple-dose study with unilateral 0.2% brimonidine instilled three times daily on intraocular pressure, pupil size and heart rate (mean ± SEM) in eight glaucomatous Beagles. *Significantly different ($P < 0.05$) from day 1 control.

progressed, suggesting a progressive tolerance to the drug and fewer PS, HR and IOP effects.

In man, 0.2% brimonidine, as an α_2-agonist, offers similar decreases in IOP as the standard, 0.5% timolol, a β-antagonist. In contrast to clonidine and apraclondine, 0.2% brimonidine offers lower possibilities of local ocular irritation and allergy, sedation (central nervous system effect) and systemic hypotension. Brimonidine also appears free of the cardiopulmonary side effects associated with the β-blocking ocular hypotensive agents.

Brimonidine's effect on IOP and PS has been investigated in cats, rabbits and monkeys.[20] Topical unilateral administration of brimonidine (0.0005–0.5 mg) produced dose-dependent decreases in IOP and PS. In general, reductions in IOP were ≈ 4–6 mmHg in the treated eye, and the contralateral (and nontreated) eye often showed greater reductions in IOP. These contralateral effects in cats indicated that the miosis and IOP reductions were of delayed onset and had a shorter duration. At a 0.5 mg dose of brimonidine in cats, sedation, nausea, salivation and diarrhea resulted.

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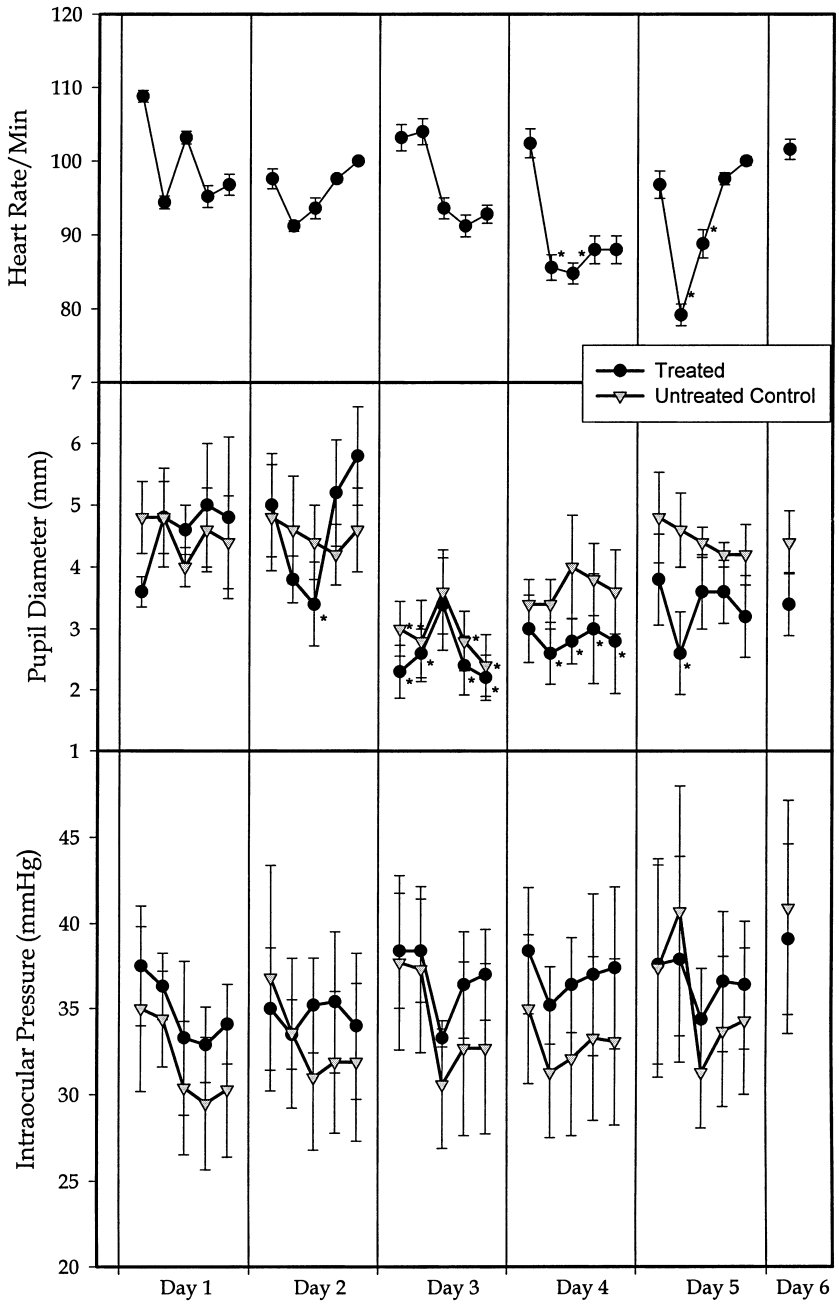

Figure 6. Multiple-dose study with unilateral 0.2% brimonidine instilled three times daily on intraocular pressure, pupil size and heart rate (mean ± SEM) in five glaucomatous Beagles. *Significantly different ($P < 0.05$) from day 1 control.

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