Published in final edited form as:

Vet Ophthalmol. 2016 July ; 19(Suppl 1): 91–96. doi:10.1111/vop.12376.

EFFECT OF TIMOLOL MALEATE GEL FORMING SOLUTION ON INTRAOCULAR PRESSURE, PUPIL DIAMETER, AND HEART RATE IN NORMAL AND GLAUCOMATOUS CATS

Julie A Kiland¹, Andrea M Voss¹, and Gillian J McLellan^{1,2,3,*}

¹Department of Ophthalmology & Visual Sciences, School of Medicine and Public Health, University of Wisconsin-Madison, WI, USA

²Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, WI, USA

³McPherson Eye Research Institute, University of Wisconsin-Madison, WI, USA

Abstract

Objective—Determine effects of once daily topical treatment with timolol maleate gel forming solution (GFS) on intraocular pressure (IOP), pupil diameter (PD), and heart rate (HR) in normal cats and cats with feline primary congenital glaucoma (FCG).

Animals studied and procedures—A single drop of timolol maleate 0.5% GFS was administered topically to one randomly assigned eye of 18 adult cats (8 normal, 10 FCG) at 8am for 8 days; the opposite eye served as the untreated control. IOP was measured in both eyes (OU) every 2h (PD and HR were measured every 4h), for 14h total, one day prior to and on days 1 and 8 of treatment. In a second treatment phase, a single drop of timolol was administered at 8pm for 3 nights and IOP, PD, and HR were measured, as above, beginning at 8am on day 4. Slit lamp examinations were done prior to and after treatment phases. Comparisons of mean IOP, PD and HR were made at each time point and between treated and untreated eyes by repeated measures ANOVA and Tukey-Kramer post-hoc test, with $p < 0.05$ considered significant.

Results—Timolol maleate 0.5% GFS had an inconsistent effect on IOP, with maximum IOP-lowering effect (mean = 5.6mmHg, 17.4%) observed 6h post-treatment in FCG. The drug caused significant miosis (from 4–8h post treatment), but had no effect on HR.

Conclusion—Once daily application of timolol maleate 0.5% GFS may be of limited clinical benefit in the management of feline congenital glaucoma.

Keywords

Glaucoma; Cat; Intraocular Pressure; Timolol; Pupil Diameter; Heart Rate

* corresponding author. Gillian J McLellan, Medical Sciences Center, 1300 University Avenue, Madison, WI 53706, Tel: +1 608 265 9848, gillian.mclellan@wisc.edu.

Introduction

Glaucoma is a disease that is characterized by progressive degeneration of the optic nerve¹ and is a leading cause of irreversible blindness in humans, dogs and cats. It is estimated that glaucoma may affect approximately 1% of cats older than 7 years of age². Of the many risk factors associated with the development of glaucoma, the most predictive of glaucomatous damage to the optic nerve is high intraocular pressure (IOP)³. The increased IOP associated with many forms of glaucoma is typically the result of impaired aqueous humor outflow, often at the level of the trabecular meshwork.^{4,5} In cats, as in humans, damage due to glaucoma is insidious and progresses gradually, and moderate elevations in IOP are not usually associated with obvious clinical signs⁵. Thus, glaucoma is often not diagnosed in cats until very late in the disease process when pupillary dilation, along with mild corneal edema and conjunctival hyperemia, may be observed.^{2, 6-9} Although glaucoma is not rare in cats, there are very few published studies that address the efficacy of conventional IOP-lowering drugs in glaucomatous cats, compared with the number of studies regarding treatment of primary glaucoma in other species, such as dogs. Many of the drugs commonly used clinically to treat high IOP and/or glaucoma in humans have been evaluated in normal cats, however their IOP-lowering efficacy has not been established in feline glaucoma patients. Most currently available treatments for glaucoma lower IOP by reducing the production of aqueous humor or increasing the outflow of aqueous humor from the eye. Topical and systemic carbonic anhydrase inhibitors reduce IOP by inhibiting the production of aqueous humor and have been shown to effectively lower IOP in both normal and glaucomatous cats, but often require topical application three times daily and are not always well-tolerated.⁹⁻¹¹ Topical prostaglandin analogs, such as latanoprost, reduce IOP primarily by increasing aqueous humor outflow via the uveoscleral route and have been shown to be effective in a number of species including humans, dogs,^{12,13} and monkeys.^{14,15} and is of questionable efficacy in horses.^{16,17} In a previous study, latanoprost was found to acutely lower IOP in cats with primary congenital glaucoma for up to 8 hours following a single treatment, however the IOP-lowering effect of the drug diminished after 3 weeks of twice-daily treatment,¹⁸ indicating that it may not be a suitable treatment for long-term IOP reduction in cats with glaucoma. The effects of topical cholinergic and adrenergic agents, such as pilocarpine and apraclonidine, have been examined in normal cats, but have been associated with local or systemic adverse effects.^{19,20}

Timolol maleate has been used widely and is often the first line of treatment to reduce IOP in humans with glaucoma. Timolol is a non-selective β -adrenergic antagonist that binds to the β -adrenergic receptors of the ciliary body, inhibiting synthesis of cyclic AMP and reducing aqueous humor production.²¹ Timolol can be applied topically either twice daily, or once daily when used as a gel-forming solution. Timolol maleate gel forming solution (GFS) is formulated with a gellan gum, which forms a gel when applied to the ocular surface, thus increasing the corneal contact time and ocular bioavailability.^{22,23} Once daily administration of timolol GFS has been shown to be as effective as twice daily application of timolol solution at lowering IOP in humans with ocular hypertension or open-angle glaucoma.²⁴ Therefore, timolol GFS may be a practical option for use in animals in a clinical or research setting since it could allow for a once daily administration of topical medication. In previous

studies, timolol, at concentrations from 0.5–4%, has been shown to lower IOP in normal cats.^{25,26} However, timolol has the potential to cause bradycardia and bronchoconstriction. Although clinically significant adverse effects are unlikely in otherwise healthy cats (i.e. those that do not suffer from asthma or cardiac disease), heart rate should be monitored in cats receiving topical treatment with timolol.⁵ To the best of our knowledge, no studies have previously been published that evaluate the efficacy and tolerability of topical timolol therapy in cats with glaucoma. A recessively inherited form of feline primary congenital glaucoma (FCG) has been identified and is studied in our laboratory as a valuable large-eyed translational research model for glaucoma. In this study the effect of topical 0.5% timolol GFS on IOP, pupil diameter and heart rate is examined in normal and FCG cats.

Materials and Methods

Animals

Eight normal adult cats (*Felis catus*) (median age= 3.92yr, range=3.83–8.08yr) and ten with FCG (median age= 4.54yr, range= 1.25–9.17yr) were studied. Cats were group-housed in a laboratory animal care facility, under standard, controlled environmental conditions, with a 12-hour light phase between 6am and 6pm. The cohort consisted of 2 intact males, 1 neutered male, 12 intact females, and 3 spayed females. Prior to the study, cats had been acclimated to IOP, pupil diameter (PD), and heart rate (HR) measurements at the same time of day and by the same personnel that participated in this study. Based on data obtained in an earlier study¹⁸, it was calculated that a sample size of 8 FCG cats would be required to detect a clinically important reduction of mean IOP (11mmHg; ~25%) in the treated relative to control eye with 90% power at a significance level (α) of 0.05. All animal procedures were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison and complied with the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Vision Research. Normal cats had not received any prior ocular medications and FCG had not received any topical ocular medications in the four weeks prior to the study. Procedures were conducted in conscious animals, which were lightly restrained in sternal recumbency or in a seated position.

Study Design

The study was separated into two phases that were designated as “AM phase” (comprising 8 days treatment) and “PM phase” (comprising 3 days treatment) with 3 days of recovery between the two phases. Baseline measurements were recorded for both eyes of all cats in both groups for a duration of 14 hours, one day prior to the initiation of the AM phase. Baseline IOPs were measured at 2-hour intervals and baseline PD and HR were measured at 4-hour intervals, with the initial measurements conducted at 8am. A schematic of the study design is shown in Figure 1.

Evaluation of ocular irritation

A slit-lamp biomicroscopic examination was done by a board-certified veterinary ophthalmologist (GJM) prior to treatment, after initiation of treatment and following the last dose in order to assess the tolerability of topical timolol ophthalmic gel forming solution

(GFS). Signs of ocular irritation were scored according to a modified Hackett-McDonald semi-quantitative scale.²⁷ The posterior segment was not evaluated during this study.

Measurement of Intraocular pressure, Pupil Diameter and Heart Rate

IOP measurements were obtained using a TonoVet® rebound tonometer (Icare Finland Oy, Helsinki, Finland) by the same trained, consistent observer throughout the study. IOP measurements at each time point represent the mean of triplicate TonoVet® readings, each of which were instrument-derived averages of multiple measurements with a standard deviation of 2.5 mmHg as indicated by “no bar” or “bar down” on the instrument display. Triplicate horizontal pupil diameter (PD) measurements were obtained using digital calipers (Fisher Science Education Traceable Digital Carbon Fiber Calipers, Fisher Scientific, Waltham, MA, USA) held 5mm from the corneal surface. Heart rates (HR) were measured by thoracic auscultation or palpation. Measurements were obtained under consistent luminance conditions as measured at the level of the examined eyes of the cats (i.e. “room lighting” or 200–220 foot candles; Sekonic Handy Lumi model 246, Sekonic Co., Ltd, Japan) with the exception of those conducted at the 12h time points, which were done under dim red light.

Drug Administration

AM Phase—A single drop of 0.5% timolol maleate ophthalmic gel forming solution (GFS) (Merck & Co., Inc., Whitehouse Station, NJ, USA) was administered topically to one randomly assigned eye of each cat. Drops were administered once daily, for 8 consecutive days, beginning at 8a.m.; the opposite eye served as the untreated control. A frequency of once daily treatment was chosen based on the dosing frequency for timolol GFS used clinically in human patients. On days 1 and 8 of this phase, IOP and PD was measured in both treated and untreated eyes and HR measurements were obtained in both groups, immediately prior to drug administration and were continued for 14 h at the same intervals as for the baseline measurements above.

PM Phase—After a three-day washout period during which no treatment was administered, cats received a single dose of timolol maleate 0.5% GFS administered topically to one randomly assigned eye at 8pm for 3 nights. On the fourth day of this phase, IOP, PD, and HR were measured, as above, for 14 h, beginning at 8am.

Statistical Analyses

Within each group (normal and FCG), mean IOP, PD and HR values at each time point were compared to baseline values, during each study phase, using repeated measures ANOVA with Tukey-Kramer multiple comparisons post hoc testing where appropriate. Data were tested for Gaussian distribution using the Kolmogorov-Smirnov test. Paired t-tests were used to compare treated and untreated control eyes for each time point in both normal and FCG cats. Pre-treatment day IOP values were compared to treatment day values using ANOVA and HR and PD values were also compared to baseline values using ANOVA (Instat, Graphpad Software Inc., San Diego, CA, USA). P-values < 0.05 were considered significant. Data are shown as mean ± s.e.m.

Results

Ocular Irritation

No signs of ocular irritation or adverse effects were identified during slit-lamp examination. No consistent effect on ocular irritation scores was observed due to treatment and all scores were 1, on a scale of 0–4,²⁸ in both the treated and control eyes during both phases of the study. No signs of ocular discomfort or adverse systemic effects were noted in any of the cats.

Intraocular pressure, Pupil Diameter, Heart Rate

Once daily timolol maleate GFS did not significantly or consistently lower IOP in normal cats or cats with FCG (Figures 2 & 3). IOP was a maximal 17.4% (5.6mmHg) lower in the treated vs. untreated eyes of FCG cats (26.5 ± 3.25 vs. 32.1 ± 2.97 mmHg, respectively) at 6h on day 1 of the AM phase, however the difference was not statistically significant ($p=0.10$) and this finding was not replicated at any other timepoint or on day 8 of the study. PD was significantly smaller in treated compared to untreated eyes of normal cats, at 4 and 8h post-treatment on day 1 (7.04 ± 0.93 vs. 9.88 ± 0.74 mm; $p=0.0482$ and 7.05 ± 0.86 vs. 10.06 ± 0.58 mm; $p=0.009$, respectively). PD was also significantly smaller compared to untreated eyes in FCG cats at 4 h post-treatment on day 1 (9.15 ± 1.09 vs. 11.35 ± 0.77 mm; $p=0.032$) (Figure 4). Timolol maleate GFS did not significantly alter HR in FCG or normal cats. The time at which treatment was administered did not significantly influence IOP, HR, or PD.

Discussion

No statistically significant reduction in IOP was observed in normal cats in contrast to previous published studies,^{25,26} and there was no statistically significant or clinically important reduction in IOP in cats with FCG. Although it is possible that significant differences in IOP may have been found had a larger sample size been evaluated, the sample size used in this study provided adequate power to identify a *clinically* important reduction in IOP (which we consider to be ~25% for cats in our FCG colony). A previous study of latanoprost treatment in 6 normal and 6 FCG cats was adequately powered to identify significant reduction in IOP in the FCG cats after latanoprost treatment and a statistically significant, though clinically unimportant, 1.5mmHg reduction in IOP in normal cats, despite the smaller sample size.¹⁸ It should also be noted that the glaucomatous cats in the present study were all affected by a single form of glaucoma. This provided a consistent and relatively homogeneous group of subjects. However, caution is warranted as the response in cats with congenital glaucoma may not be necessarily representative of the response that may be observed in other forms of feline glaucoma, particularly since secondary glaucoma is the most common form of the disease in cats.⁹

Similar to a previous study, we observed a significant reduction in PD in the timolol-treated eyes of both the normal and FCG cats.²⁵ The iris sphincter muscle of cats has been found to have a predominance of β -adrenergic nerve fibers^{28,29}. β -adrenergic nerve fibers are inhibitory to the iris sphincter muscle, thus the miosis in response to topically applied

timolol may be the result of its antagonism of inhibitory input to the iris sphincter muscle^{28,29}.

Although the cats were acclimated to IOP, PD and HR measurements prior to the study and tolerated the gentle restraint necessary for application of topical medication, they were not acclimated to the actual administration of the topical medication. This could potentially have led to stress, in turn influencing subsequent measurements. However, no signs suggestive of stress, ocular irritation or systemic adverse effects were observed in any cats. In a previous study, Wilkie et. al. observed a significant IOP reduction in both the treated and control eyes of normal cats after administration of one drop of timolol maleate to one eye, though PD was only reduced in the treated eye²⁵. However, in the current study, in addition to the reduction in PD being confined to the treated eye, IOP was not significantly lower in the treated or control eyes compared to baseline and no significant changes in HR were observed. Thus, failure to identify significant differences in IOP between the treated and control eyes could not be ascribed to a contralateral effect of unilateral treatment. The lack of a statistically significant effect of timolol treatment in the current study may have also been related to the type of tonometer used as applanation tonometry used in previous studies is less accurate than the TonoVet®, but provides readings with lower variability.^{30,31} Nevertheless the TonoVet® has been found to correlate strongly with manometric IOP and to provide accurate and reproducible IOP measurements in cats.³² Furthermore, as is common for pet cats in their home environment, the well-acclimated research cats in our colony have been observed to sleep for more than 20 hours per day, which can limit the IOP-lowering efficacy of β -blockers. Lack of sympathetic adrenergic tone has been shown experimentally to reduce the effects of timolol on IOP in cats,²⁶ and the IOP-lowering effects of timolol appear to be less in human subjects during sleep.^{33,34} Time of drug administration in our study appeared to have no effect on IOP regulation in cats with FCG. Although a short washout period was selected between treatment phases for practical reasons, it was considered to be adequate based on lack of response identified during the initial phase of the study. Further, no enhanced response to treatment was seen in the second (PM) treatment phase of the study.

Conclusion

Once daily treatment with 0.5% timolol maleate GFS does not substantially reduce IOP in FCG cats and may not represent a valuable treatment option for substantially reducing IOP in glaucomatous cats. However, as the present study was conducted using a single concentration of timolol, in a cohort of cats with a single type of glaucoma, the effect of timolol, and the efficacy of different dose frequencies and concentrations, in cats with feline open angle glaucoma or glaucoma secondary to other disease processes, warrants further investigation.

Acknowledgments

Supported by NIH Grants K08 EY018609 and P30 EY0016665 and by Research to Prevent Blindness. The authors would like to thank N. Matthew Ellinwood of Iowa State University for expert management of the feline glaucoma breeding colony at Iowa State University and Owen Bowie, Brandon Free, and Vincent Yaccarino for their technical support in the conduct of this study.

References

1. Ritch, R.; Shields, MB.; Krupin, T. The Glaucomas. 2nd. Mosby, St Louis: 1996.
2. Kroll MM, Miller PE, Rodan I. Intraocular pressure measurements obtained as part of a comprehensive geriatric health examination from cats seven years of age or older. *Journal of the American Veterinary Medical Association*. 2001; 219:1406–1410. [PubMed: 11724179]
3. Wilensky, JT. Epidemiology of open-angle glaucoma. In: Kaufman, PL.; Mittag, TW., editors. *Textbook of Ophthalmology 7 (Glaucoma)*. Mosby: St. Louis; 1994. p. 29–33.
4. Toris CB, Gabelt BT, Kaufman PL. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. *Survey of Ophthalmology*. 2008; 53(Suppl 1):S107–S120. [PubMed: 19038618]
5. McLellan GJ, Teixeira LBC. Feline Glaucoma. *Veterinary Clinics: Small Animal Practice*. 2015; 45:1307–1333. [PubMed: 26342763]
6. Blocker T, Van der Woerd A. The feline glaucomas: 82 cases (1995–1999). *Veterinary Ophthalmology*. 2001; 4:81–85. [PubMed: 11422987]
7. Ridgway M, Brightman A. Feline Glaucoma - A retrospective study of 29 clinical cases. *Journal of the American Animal Hospital Association*. 1989; 25:485–490.
8. Dietrich U. Feline Glaucomas. *Clinical Techniques in Small Animal Practice*. 2005; 20:108–116. [PubMed: 15948425]
9. McLellan GJ, Miller PE. Feline glaucoma--a comprehensive review. *Veterinary Ophthalmology*. 2011; 14(Suppl 1):15–29. [PubMed: 21923820]
10. Sigle KJ, Camano-Garcia G, Carriquiry AL, et al. The effect of dorzolamide 2% on circadian intraocular pressure in cats with primary congenital glaucoma. *Veterinary Ophthalmology*. 2011; 14:48–53. [PubMed: 21923823]
11. Dietrich UM, Chandler MJ, Cooper T, et al. Effects of topical 2% dorzolamide hydrochloride alone and in combination with 0.5% timolol maleate on intraocular pressure in normal feline eyes. *Veterinary Ophthalmology*. 2007; 10(Suppl 1):95–100. [PubMed: 17973840]
12. Gelatt KN, MacKay EO. Effect of different dose schedules of latanoprost on intraocular pressure and pupil size in the glaucomatous Beagle. *Veterinary Ophthalmology*. 2001; 4:283–288. [PubMed: 11906665]
13. Studer ME, Martin CL, Stiles J. Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats. *American Journal of Veterinary Research*. 2000; 61:1220–1224. [PubMed: 11039551]
14. Gabelt BT, Hennes EA, Bendel MA, et al. Prostaglandin subtype-selective and non-selective IOP-lowering comparison in monkeys. *Journal of Ocular Pharmacology and Therapeutics*. 2009; 25:1–8. [PubMed: 19232013]
15. Gagliuso DJ, Wang RF, Mittag TW, et al. Additivity of bimatoprost or travoprost to latanoprost in glaucomatous monkey eyes. *Archives of Ophthalmology*. 2004; 122:1342–1347. [PubMed: 15364714]
16. Willis AM, Diehl KA, Hoshaw-Woodard S, et al. Effects of topical administration of 0.005% latanoprost solution on eyes of clinically normal horses. *American Journal of Veterinary Research*. 2001; 62:1945–1951. [PubMed: 11763186]
17. Davidson HJ, Pinard CL, Keil SM, et al. Effect of topical ophthalmic latanoprost on intraocular pressure in normal horses. *Veterinary Therapeutics*. 2002; 3:72–80. [PubMed: 12050830]
18. McDonald JE, Kiland JA, Kaufman PL, et al. Effect of topical latanoprost 0.005% on intraocular pressure and pupil diameter in normal and glaucomatous cats. *Veterinary Ophthalmology*. 2015 epub ahead of print.
19. Wilkie DA, Latimer CA. Effects of topical administration of 2.0% percent pilocarpine on intraocular pressure and pupil size in cats. *American Journal of Veterinary Research*. 1991; 52:441–444. [PubMed: 2035919]
20. Miller PE, Nelson MJ, Rhaesa SL. Effects of topical administration of 0.5% apraclonidine on intraocular pressure, pupil size, and heart rate in clinically normal dogs. *American Journal of Veterinary Research*. 1996; 57:79–82. [PubMed: 8720243]

21. Liu HK, Chiou GC, Garg LC. Ocular hypotensive effects of timolol in cat eyes. *Archives of Ophthalmology*. 1980; 98:1467–1469. [PubMed: 6774702]
22. Greaves JL, Wilson CG, Rozier A, et al. Scintigraphic assessment of an ophthalmic gelling vehicle in man and rabbit. *Current Eye Research*. 1990; 9:415–420. [PubMed: 2166636]
23. Rozier A, Mazuel C, Grove J, et al. Gelrite: A novel ion-activated, in-situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *International Journal of Pharmacy*. 1989; 57:163–168.
24. Shedden A, Laurence J, Tipping R. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study. *Clinical Therapeutics*. 2001; 23:440–450. [PubMed: 11318078]
25. Wilkie DA, Latimer CA. Effects of topical administration of timolol maleate on intraocular pressure and pupil size in cats. *American Journal of Veterinary Research*. 1991; 52:436–440. [PubMed: 2035918]
26. Colasanti BK, Trotter RR. Effects of selective beta 1- and beta 2-adrenoreceptor agonists and antagonist on intraocular pressure in the cat. *Investigative Ophthalmology and Visual Science*. 1981; 20:69–76. [PubMed: 6108938]
27. Hackett, RB.; McDonald, TO. Ophthalmic toxicology and assessing ocular irritation. In: Marzulli, FN.; Maibach, HI., editors. *Dermatotoxicology*. 4th. Washington DC: Hemisphere Publishing Corp; 1996. p. 749-815.
28. Schaeppi U, Loelia WP. Adrenergic innervation of the cat iris. *American Journal of Physiology*. 1964; 207:273–278. [PubMed: 14205335]
29. Van Alphen GW, Kern R, Robinette SL. Adrenergic receptors of the intraocular muscles: comparison to cat, rabbit, and monkey. *Archives of Ophthalmology*. 1965; 74:541–545.
30. Miller PE, Pickett JP, Majors LJ, et al. Evaluation of two applanation tonometers in cats. *American Journal of Veterinary Research*. 1991; 52:1917–1921. [PubMed: 1785739]
31. Rusanen E, Florin, Hässig, et al. Evaluation of a rebound tonometer (Tonovet) in clinically normal cat eyes. *Veterinary Ophthalmology*. 2010; 13:31–36. [PubMed: 20149173]
32. McLellan GJ, Kemmerling JP, Kiland JA. Validation of the TonoVet® rebound tonometer in normal and glaucomatous cats. *Veterinary Ophthalmology*. 2013; 16:111–118. [PubMed: 22672669]
33. Topper JE, Brubaker RF. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. *Investigative Ophthalmology and Visual Science*. 1985; 26:1315–1319. [PubMed: 4044159]
34. Liu JHK, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. *American Journal of Ophthalmology*. 2004; 138:389–395. [PubMed: 15364220]

Study Design

Fig. 1. Schematic illustration of study Design

IOP, pupil diameter (PD) and HR were measured in 18 adult cats (8 normal, 10 FCG). AM Phase: IOP was measured in both eyes (OU) every 2h; PD and HR were measured every 4h, for a total of 14h, beginning at 8:00AM. Measurements were done one day prior to and on days 1 and 8 of treatment with 0.5% timolol maleate GFS to one eye; the opposite eye was untreated. PM Phase: after a 3-day washout period, a single drop of timolol was administered at 8pm for 3 nights and IOP, PD, and HR were measured, as above, beginning at 8am on day 4.

Fig. 2.

Composite plots of IOP vs time in 10 FCG cats at baseline (A) and on day 1 of the AM phase (B), day 8 of the AM phase (C), and day 4 of the PM phase (D). Data points and error bars represent mean $\pm$ s.e.m. for 10 cats each contributing one treated and one untreated eye.

Fig. 3. Composite plots of IOP vs time in 8 normal cats at baseline (A); on day 1 of the AM phase (B), day 8 of the AM phase (C) and day 4 of the PM phase (D). Data points and error bars represent mean $\pm$ s.e.m. for 8 cats each contributing one treated and one untreated eye.

Fig. 4.

Composite plots of pupil diameter (PD) vs time following application of timolol 0.5% GFS at 8am on day 1 in 8 normal (A) and 10 FCG cats (B). Significant reduction in PD was observed in the treated compared to the untreated eyes of both FCG and normal cats. Data points and error bars represent mean $\pm$ s.e.m. with each cat contributing one treated and one untreated eye; * $p=0.0032$, ** $p=0.0482$, *** $p=0.0099$.