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The effects of bimatoprost and unoprostone isopropyl on the intraocular pressure of normal cats

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Abstract

Objective To evaluate the effects on intraocular pressure (IOP), pupillary diameter (PD), blepharospasm score, conjunctival injection score, and aqueous humor flare score when either 0.03% bimatoprost solution is applied once daily or 0.15% unoprostone isopropyl solution is applied twice daily topically to the eyes of normal cats.

Materials and methods The aforementioned parameters were evaluated daily in each of 12 cats throughout the entirety of the study. During an initial 10-day treatment phase a single eye of six of the cats was treated with 0.03% bimatoprost solution while a single eye of the remaining six cats was treated with buffered saline solution (BSS) once daily. During a second 10-day treatment phase a single eye of six of the cats was treated with 0.15% unoprostone isopropyl solution while a single eye of the remaining six cats was treated with BSS twice daily. Contralateral eyes of all cats remained untreated at all time points.

Results Blepharospasm score, conjunctival injection score, and aqueous humor flare score never rose from a value of 0, for any eye of any cat during the study. The mean ± SD of IOP for eyes treated with 0.03% bimatoprost solution and BSS were 16.55 ± 3.06 mmHg and 18.02 ± 3.52 mmHg, respectively. The mean ± of PD for eyes treated with 0.03% bimatoprost solution and BSS were 5.7 ± 1.57 mm and 6.39 ± 1.78 mm, respectively. The mean ± SD of IOP for eyes treated with 0.15% unoprostone isopropyl solution and BSS were 15.7 ± 2.91 mmHg and 17.2 ± 2.9 mmHg, respectively. The mean ± SD of PD for eyes treated with 0.15% unoprostone isopropyl solution and BSS were 5.8 ± 1.43 mm and 6.9 ± 1.37 mm, respectively. There was no significant difference ($P \geq 0.05$) in IOP or PD between eyes treated with 0.03% bimatoprost solution vs. eyes treated with BSS. Similarly, there was no significant difference ($P \geq 0.05$) in IOP or PD between eyes treated with 0.15% unoprostone isopropyl solution vs. eyes treated with BSS.

Conclusion Neither once daily topical administration of 0.03% bimatoprost solution nor twice daily topical administration of 0.15% unoprostone isopropyl solution significantly affect the IOP of normal cats. Both 0.03% bimatoprost solution and 0.15% unoprostone isopropyl solution induced no significant ocular side effects in normal cats when dosed over a 10-day treatment period.

Key Words: bimatoprost, cat, glaucoma, intraocular pressure, prostaglandin, unoprostone isopropyl

INTRODUCTION

Glaucoma is a blanket term for a number of clinical syndromes characterized by progressive optic nerve and retinal damage, most commonly associated with elevation in intraocular pressure.[1] Glaucoma can be an insidious, blinding disease process in the cat.[2] Typically the underlying etiology is pre-existent intraocular neoplasia or uveitis; however, feline primary glaucoma has been described.[3–6] While undiagnosed glaucoma may be devastating to visual health, early and appropriate pharmacologic intervention can reduce ocular hypertension and potentially prolong functional vision in cats.[2]

Recently, a number of new drugs have become available in the United States for management of glaucoma. These

products, such as topical carbonic anhydrase inhibitors and the prostaglandin analogs, offer exciting potential for the long-term control of intraocular hypertension in numerous species.[7] Early work with the prostaglandin analog latanoprost (Xalatan®, Pfizer Inc., New York, NY, USA) has documented significant reduction of intraocular pressure (IOP) of normal and glaucomatous dogs.[8,9]

Topical application of prostaglandins, which are members of the prostanoid family, was originally shown to reduce the IOP of rabbits in 1977.[10] Since that time, extensive research has documented that prostaglandins produce sustainable IOP reductions in numerous mammalian species, including the domestic cat.[11–20] Initial documented ocular side effects of topical prostaglandin application included transient elevations in IOP, disruption of the blood aqueous barrier, and conjunctival irritation and hyperemia. Synthetic prostanoid analogs were successfully developed in an attempt to improve bioavailability while reducing these side effects.[21,22]

Prostaglandins and associated analogs reduce IOP by increasing uveoscleral and possibly trabeculoscleral outflow; however, the exact mechanism by which this occurs is unknown.[23–25] Recent studies suggest that numerous pathways may be involved, including ciliary muscular relaxation, alterations in cellular morphology, and extracellular matrix remodeling.[26–28] A majority of these mechanisms are probably activated through binding of drug to prostanoid receptors with subsequent alteration of gene expression.[27]

In cats, prostaglandin-induced changes in the ciliary muscle and associated decreases in IOP appear to be mediated thorough E and D prostanoid receptors.[29–31] This is in contrast to dogs and humans in whom ciliary body alteration and reduction in IOP are mediated by prostanoid F receptor agonists.[8,9,32] The difference probably explains why latanoprost (Xalatan®, Pfizer Inc.) {isopropyl-(Z)-7[(1R, 2R, 3R, 5S)3, 5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl] cyclopentyl]-5-heptenoate}, a highly selective prostanoid F receptor agonist, decreases IOP in dogs, but has no effect on IOP in cats.[8]

Recently, two additional prostanoid analog drugs have been approved in the United States for treatment of glaucoma. Bimatoprost (Lumigan®; Allergan Inc., Irvine, CA, USA) is a prostamide {(Z)-7-[(1 R,2 R,3 R,5 S)-3, 5-dihydroxy-2-[1 E,3 (S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide} and unoprostone isopropyl (Rescula®; Novartis Ophthalmics, Duluth, GA, USA) is a docosanoid compound {isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl) cyclopentyl]-5-heptenoate}.[33,34] Both of these compounds have been shown to safely reduce IOP in both dogs and humans.[35–38] However, clinical effectiveness of these drugs has not been assessed in cats.

Although the molecular mechanism of reduction in IOP has yet to be elucidated for bimatoprost and unoprostone isopropyl, studies have demonstrated that the action may be mediated through receptors other than the prostanoid F receptor.[34,39,40] Therefore, it remains possible that both of these drugs may decrease IOP in cats. The aim of this study was to evaluate the potential intraocular hypotensive effects of both bimatoprost and unoprostone isopropyl in normal cats.

MATERIALS AND METHODS

Animals

Twelve Domestic short- and medium-haired cats, six male and six female, of approximately 2 years of age were used throughout the course of the study. Cats were initially part of experiments evaluating the efficacy of topical flea products prior to participation in the current study and were adopted out to public households at the conclusion of this project. Routine physical examination and standard ophthalmic examination which included neuro-ophthalmic assessment, Schirmer tear testing, corneal fluorescein staining, applanation tonometry, slit-lamp biomicroscopy, and indirect ophthalmoscopy were performed on all animals prior to and upon completion of the study. This study was conducted in accordance with the ARVO statement on use of animals in ophthalmic and vision research and was approved by the institutional care and use committee.

Experimental protocol

IOP values were determined at 7 a.m. and 7 p.m., while pupillary diameter, blepharospasm score, conjunctival hyperemia score, and aqueous humor flare score were determined at 7 p.m. solely for each day of the study. Pretreatment values were documented for the initial 5 days (days 1–5). On day 6, six cats were randomly assigned to receive 30 μL of 0.03% bimatoprost solution (drug treatment 1) topically in a randomly selected eye (three right eyes and three left eyes were treated with drug solution). The additional six cats were randomly assigned to receive 30 μL of buffered saline solution (BSS®, Alcon Laboratories, Inc., Fort Worth, TX, USA) (control treatment 1) topically in a randomly selected eye (three right eyes and three left eyes were treated with control solution). The contralateral eye of each animal remained untreated (untreated control 1) at all time points. The eyes were treated at 7 a.m. for the subsequent 10 days (days 6–15). On day 16, all treatment was discontinued for a period of 5 days (days 16–20). On day 21, six cats were again randomly assigned to receive 30 μL of 0.15% unoprostone isopropyl solution (drug treatment 2) topically in a randomly selected eye. The remaining six cats were randomly assigned to receive 30 μL of BSS (control treatment 2) topically in a randomly selected eye. The contralateral eye of each animal again remained untreated (untreated control 2). Eyes were treated at both 7 a.m. and 7 p.m. for the subsequent 10 days (days 21–30). On day 31, all treatment was discontinued for the final 5 days of the study (days 31–35). Dosing frequency for each drug was based upon the manufacturer recommendations within the product inserts noted for lowering the intraocular pressure of affected eyes in humans afflicted with glaucoma. All investigators, with the exception of MTH who was only responsible for recording the primary data generated, remained blinded to treatment

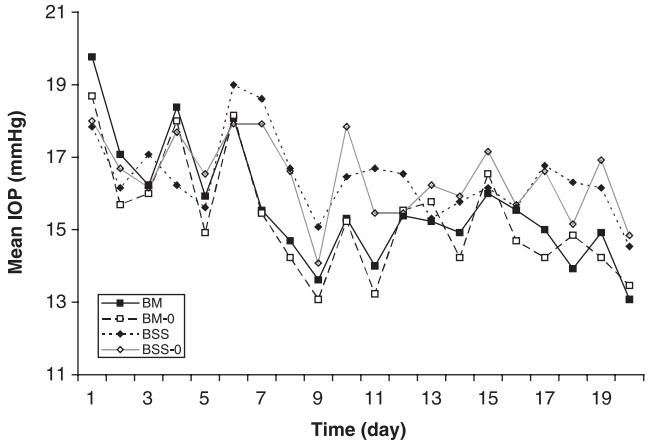

Figure 1. Mean intraocular pressure (IOP) in the eyes of cats treated with 30 μL 0.03% bimatoprost solution (BM) and the contralateral eyes remaining untreated (BM-0) vs. the eyes of cats treated with 30 μL buffered saline solution (BSS) and the contralateral eyes remaining untreated (BSS-0) over time.

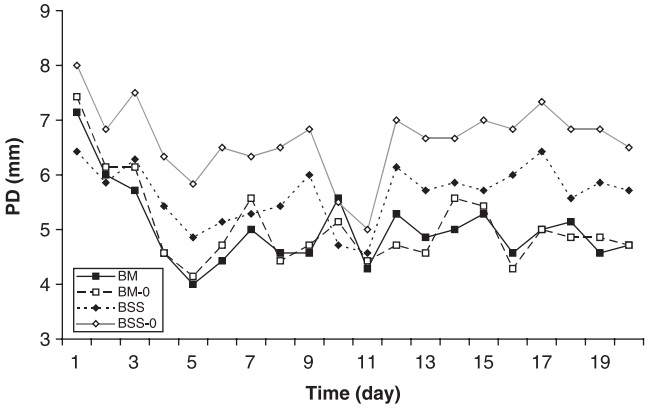

Figure 2. Mean pupillary diameter (PD) in the eyes of cats treated with 30 μL 0.03% bimatoprost solution (BM) and the contralateral eyes remaining untreated (BM-0) vs. the eyes of cats treated with 30 μL buffered saline solution (BSS) and the contralateral eyes remaining untreated (BSS-0) over time.

selection until the code was broken at completion of the study.

IOP determination

A single applanation tonometer (Tono-Pen® VET; Medtronic Solan, Jacksonville, FL, USA) was used throughout the duration of the study. The disposable tip cover was replaced and the instrument calibrated according to manufacturer's recommendations daily. Cats were minimally restrained without pharmacologic sedation and a single drop of 0.5% proparacaine hydrochloride ophthalmic solution (Bausch & Lomb Pharmaceuticals, Inc., Tampa, FL, USA) was instilled into each eye prior to tonometry. Tonometric values were determined and recorded if variance was < 5%.

Determination of pupillary diameter, blepharospasm score, conjunctival injection score, and aqueous humor flare score

Pupillary diameter (PD) was determined by measuring the horizontal distance between the axial medial and lateral edges of the iris using a Jameson caliper in standard room-light. Blepharospasm and conjunctival hyperemia were graded grossly on a scale of 0–3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Aqueous humor flare was evaluated with a slit-lamp biomicroscope (Kowa SL-14; Kowa Optimed Inc.,Torrance, CA USA) using a similar scale.

Statistical analysis

Changes in IOP and PD were analyzed using the *F*-test in repeated measure, three factorial design within: the bimatoprost treatment block, the unoprostone isopropyl treatment block and all nontreatment block periods individually. Differences in IOP and PD values between drug treatment vs. treatment control, drug treatment vs. nontreatment control, and treatment control vs. nontreatment control were evaluated. For all blocks assessed, significance was set at $P \leq 0.05$.

RESULTS

Physical examination revealed all animals to be in good general health prior to initiation and upon completion of the study. Routine ophthalmic examination detected no significant ocular lesions both at the start and end of the study.

At no time during the study did the mean values for IOP and PD calculated within treatment and nontreatment blocks for drug treated eyes, control treated eyes, and non-treated eyes depart from published reference ranges. The mean ± SD of IOP, over the 10-day treatment period, in cats administered 0.03% bimatoprost solution were 16.55 ± 3.06 mmHg for treated eyes and 16.41 ± 3.36 mmHg for untreated eyes. The mean ± SD of IOP in cats administered BSS were 18.02 ± 3.52 mmHg for treated eyes and 17.83 ± 3.03 mmHg for untreated eyes (Fig. 1).

The mean ± SD of PD for eyes treated with 0.03% bimatoprost solution were 5.7 ± 1.57 mm for treated eyes and 5.75 ± 1.61 mm for untreated eyes. The mean ± SD of PD for eyes treated with BSS were 6.39 ± 1.28 mm for treated eyes and 6.38 ± 1.45 mm for untreated eyes (Fig. 2).

The mean ± SD of IOP, over the 10-day treatment period, in cats administered 0.15% unoprostone isopropyl solution were 15.7 ± 2.91 mmHg for treated eyes and 15.48 ± 2.45 mmHg for untreated eyes. The mean ± SD of IOP in cats administered BSS were 17.20 ± 2.9 mmHg for treated eyes and 17.17 ± 2.86 mmHg for untreated eyes (Fig. 3).

While the mean ± SD of PD for eyes treated with 0.15% unoprostone isopropyl solution were 5.8 ± 1.43 mm for treated eyes and 5.24 ± 1.33 mm for untreated eyes. The mean ± SD of PD for eyes treated with BSS were 6.9 ± 1.27 mm for treated eyes and 6.87 ± 1.46 mm for untreated eyes. (Fig. 4)

No statistically significant difference was noted in the IOP or PD of cat eyes treated topically with 0.03% bimatoprost solution vs. eyes treated topically with BSS. Also, no significant difference in IOP or PD was observed between eyes treated

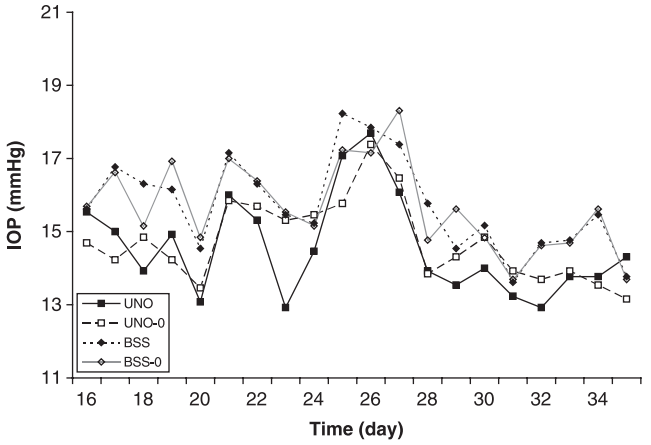

Figure 3. Mean intraocular pressure (IOP) in the eyes of cats treated with 30 μL 0.15% unoprostone isopropyl solution (UNO) and the contralateral eyes remaining untreated (UNO-0) vs. the eyes of cats treated with 30 μL buffered saline solution (BSS) and the contralateral eyes remaining untreated (BSS-0) over time.

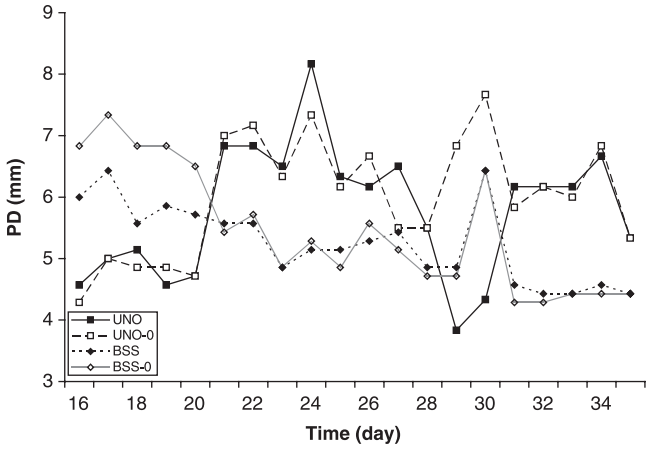

Figure 4. Mean pupillary diameter (PD) in the eyes of cats treated with 30 μL 0.15% unoprostone isopropyl solution (UNO) and the contralateral eyes remaining untreated (UNO-0) vs. the eyes of cats treated with 30 μL buffered saline solution (BSS) and the contralateral eyes remaining untreated (BSS-0) over time.

with bimatoprost solution vs. the contralateral untreated eye or eyes treated with BSS vs. the contralateral untreated eye.

Similarly, no statistically significant difference was noted in the IOP or PD of cat eyes treated topically with 0.15% unoprostone isopropyl solution vs. eyes treated with BSS, unoprostone isopropyl-treated eyes vs. the contralateral untreated eyes, and BSS-treated eyes vs. the contralateral untreated eyes. There was no significant difference in IOP or PD detected during any of the nontreatment blocks.

All cats commenced the study with values of 0 for blepharospasm score, conjunctival hyperemia score and aqueous humor flare score. At no time during the study was a deviation from this base-line value of 0 detected in any of the cats. Therefore, the individual scores were not analyzed for statistical difference.

DISCUSSION

The prostanoid receptor group is part of a larger family of rhodopsin-like G-protein-coupled receptors (GPCRs). Morphology of GPCRs consists of the characteristic seven putative transmembrane domains. The intracellular signaling cascades initiated by ligand binding to GPCRs occurs primarily through stimulation of phospholipase C or inhibition of adenylcyclase via inhibitory guanine nucleotide-binding regulatory protein.[41,42]

The prostanoid group includes five major receptor types with four subtypes designated: DP, FP, IP, TP, and EP_1, EP_2, EP_3, and EP_4. Each receptor is encoded by a separate gene. Interestingly, alternative splicing to produce messenger RNA isoforms, allowing variation in the intracellular C-terminal region of the receptor produced, is noted within the group. While differential splicing does not appear to significantly affect ligand-receptor interactions, it is thought to influence G-protein coupling specificity, constitutive activity level, and desensitization of the receptor.[41,42]

The ligand-binding specificity of each receptor is unique, with each preferentially recognizing a distinct type of prostanoid. However, there is considerable promiscuity between receptor classes, with each receptor binding different prostanoid agonists and antagonists with variable affinity.[41,42]

This affinity spill-over is thought to account for the putatively described side effects, such as conjunctival hyperemia, miosis and hyperpigmentation, associated with topical ocular application of prostaglandins.[22,43] Extensive structural manipulation of prostanoids by the pharmaceutical industry has subsequently ensued in an attempt to improve therapeutic indices. Countless synthetic prostaglandin analogs have been manufactured to separate the IOP hypotensive characteristics from the side effect-generating elements of the basic prostanoid backbone.[44]

Initial success in the United States culminated in approval by the Food and Drug Administration for use of latanoprost topically for the management of elevated intraocular pressure in 1996. Latanoprost is a potent $PGF_{2\alpha}$ analog with high specificity for the FP receptor.[45] This specificity is probably what accounts for the minimal ocular and systemic side effects noted with latanoprost application.[22]

However, this momentum in the direction of creating increased ligand-receptor selectivity is likely to significantly influence the ability of veterinarians to utilize current and future prostaglandin analog drugs for therapeutic intervention in the diverse species populations that they serve. It has been well documented that profound species differences exist both in tissue distribution of prostanoid receptors and response of those receptors to ligand binding.[41,42]

For example, while both the parent compound $PGF_{2\alpha}$ and latanoprost have significant effects on the pupillary diameter of cats, only $PGF_{2\alpha}$ reduces IOP when applied topically to cats.[8,19] The presumed explanation for this observed phenomenon is the presence of FP receptors in the iridies of cats, to which both $PGF_{2\alpha}$ and latanoprost bind and institute

receptor-mediated changes in intracellular levels of appropriate secondary messengers. However, the absence of FP receptors in the feline ciliary body eliminates facilitation of uveoscleral outflow by the highly selective FP agonist, latanoprost. The cross-reactivity of $PGF_{2\alpha}$ with multiple prostanoid receptors probably instigates increased uveoscleral outflow via the EP of DP receptors present in the ciliary body of the cat.[29–31]

The recent addition of bimatoprost and unoprostone isopropyl to the armoritarium of FDA-approved antiglaucoma drugs is exciting to veterinary medicine as it is proposed that these drugs mediate decreases in IOP through, as of yet, undescribed intraocular receptors.[39,40] This may be important for future treatment of species in which IOP reduction by prostanoid analogs does not require binding to the FP receptor.

This study failed to show a significant difference between the IOP of cat eyes treated with bimatoprost or unoprostone isopropyl solutions at any time point assessed. There are multiple possible explanations for our findings. First, the novel receptors through which bimatoprost and unoprostone isopropyl are purported to stimulate reduction in IOP *in vivo* may ultimately be isolated, cloned and described. An easy answer would arise from the presence of these receptors in the iridies with an absence in the ciliary body of cats, similar to the FP receptor.

Second, while a majority of the published data seem to support the intraocular hypotensive effects of bimatoprost induced through binding to an unreported class of prostamide receptors, this point is currently contentious. Separate data show that bimatoprost may directly and selectively bind the FP receptor or function as a prodrug that subsequently produces a selective FP receptor agonist upon exposure to biologic tissue. If either of these alternative theories were proven true, it would explain our results in that the domestic cat appears to lack ciliary FP receptors.

Third, as with a majority of glaucoma medications, the drug effects may be more pronounced in the diseased state. This obviously argues for additional controlled studies to evaluate the efficacy of bimatoprost and unoprostone isopropyl applied topically to cats diagnosed with glaucoma. With these studies the effects of differing concentrations of drug applied and increased treatment frequencies could also be investigated.

Interesting to note is the lack of grossly apparent side effects associated with topical instillation of bimatoprost and unoprostone isopropyl to normal cats. This suggests that pharmaceutical manipulation of the prostanoid backbone compounds to alleviate the side effects observed with application of the native prostaglandins is effective across species boundaries.

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REFERENCES

1. Brooks DE. Glaucoma in the dog and cat. *Veterinary Clinics of North America: Small Animal Practice* 1990; **20**: 775–797.
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.
3. Blocker T, Van Der Woredt A. The feline glaucomas: 82 cases (1995–1999). *Veterinary Ophthalmology* 2001; **4**: 81–85.
4. Ridgway MD, Brightman AH. Feline glaucoma: a retrospective study of 29 clinical cases. *Journal of the American Animal Hospital Association* 1989; **25**: 485–490.
5. Wilcock BP, Peiffer RL Jr, Davidson MG. The causes of glaucoma in cats. *Veterinary Pathology* 1990; **27**: 35–40.
6. Hampson EC, Smith RI, Bernays ME. Primary glaucoma in Burmese cats. *Australian Veterinary Journal* 2002; **80**: 672–680.
7. Willis AM, Diehl KA, Robbin TE. Advances in topical glaucoma therapy. *Veterinary Ophthalmology* 2002; **5**: 9–17.
8. 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.
9. 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.
10. Camras CB, Bito LZ, Eakins KE. Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. *Investigative Ophthalmology and Visual Science* 1977; **16**: 1125–1134.
11. Bito LZ, Srinivasan BD, Baroody RA *et al.* Noninvasive observations on eyes of cats after long-term maintenance of reduced intraocular pressure by topical application of prostaglandin E2. *Investigative Ophthalmology and Visual Science* 1983; **24**: 376–380.
12. Bito LZ, Draga A, Blanco J *et al.* Long-term maintenance of reduced intraocular pressure by daily or twice daily topical application of prostaglandins to cat or rhesus monkey eyes. *Investigative Ophthalmology and Visual Science*; **24**: 312–319.
13. Bito LZ. Comparison of the ocular hypotensive efficacy of eicosanoids and related compounds. *Experimental Eye Research* 1984; **38**: 181–194.
14. Bito LZ, Baroody RA, Miranda OC. Eicosanoids as a new class of ocular hypotensive agents. 1. The apparent therapeutic advantages of derived prostaglandins of the A and B type as compared with primary prostaglandins of the E, F and D type. *Experimental Eye Research* 1987; **44**: 825–837.
15. Bito LZ, Miranda OC, Tendler MR *et al.* Eicosanoids as a new class of ocular hypotensive agents. 3. Prostaglandin A2-1-isopropyl ester is the most potent reported hypotensive agent on feline eyes. *Experimental Eye Research* 1990; **50**: 419–428.
16. Hayashi M, Yablonski ME, Bito LZ. Eicosanoids as a new class of ocular hypotensive agents. 2. Comparison of the apparent mechanism of the ocular hypotensive effects of A and F type prostaglandins. *Investigative Ophthalmology and Visual Science* 1987; **28**: 1639–1643.
17. Lee PY, Podos SM, Severin C. Effect of prostaglandin F2 alpha on aqueous humor dynamics of rabbit, cat, and monkey. *Investigative Ophthalmology and Visual Science* 1984; **25**: 1087–1093.
18. Matsugi T, Kageyama M, Nishimura K *et al.* Selective prostaglandin D2 receptor stimulation elicits ocular hypotensive effects in rabbits and cats. *European Journal of Pharmacology* 1995; **275**: 245–250.
19. Stern FA, Bito LZ. Comparison of the hypotensive and other ocular effects of prostaglandins E2 and F2 alpha on cat and rhesus monkey eyes. *Investigative Ophthalmology and Visual Science* 1982; **22**: 588–598.
20. Yousufzai SY, Ye Z, Abdel-Latif AA. Prostaglandin F2 alpha and its analogs induce release of endogenous prostaglandins in iris and ciliary muscles isolated from cat and other mammalian species. *Experimental Eye Research* 1996; **63**: 305–310.

21. Camras CB, Alm A. Initial clinical studies with prostaglandins and their analogues. *Survey of Ophthalmology* 1997; **41** (Suppl. 2): S61–S68.
22. Stjernschantz JW. From PGF (2alpha)-isopropyl ester to latanoprost: a review of the development of xalatan: the Proctor Lecture. *Investigative Ophthalmology and Visual Science* 2001; **42**: 1134–1145.
23. Crawford K, Kaufman PL. Pilocarpine antagonizes prostaglandin F2 alpha-induced ocular hypotension in monkeys. Evidence for enhancement of uveoscleral outflow by prostaglandin F2 alpha. *Archives of Ophthalmology* 1987; **105**: 1112–1116.
24. Toris CB, Yablonski ME, Wang YL *et al.* Prostaglandin A2 increases uveoscleral outflow and trabecular outflow facility in the cat. *Experimental Eye Research* 1995; **61**: 649–657.
25. Lindsey JD, Kashiwagi K, Kashiwagi F *et al.* Prostaglandin action on ciliary smooth muscle extracellular matrix metabolism: implications for uveoscleral outflow. *Survey of Ophthalmology* 1997; **41** (Suppl. 2): S53–S59.
26. Anthony TL, Lindsey JD, Weinreb RN. Latanoprost's effects on TIMP-1 and TIMP-2 expression in human ciliary muscle cells. *Investigative Ophthalmology and Visual Science* 2002; **43**: 3705–3711.
27. Weinreb RN, Toris CB, Gabelt BT *et al.* Effects of prostaglandins on the aqueous humor outflow pathways. *Survey of Ophthalmology* 2002; **47** (Suppl. 1): S53–S64.
28. Ansari HR, Davis AM, Kaddour-Djebbar I *et al.* Effects of prostaglandin F2 alpha and latanoprost on phosphoinositide turnover, myosin light chain phosphorylation and contraction in cat iris sphincter. *Journal of Ocular Pharmacology and Therapeutics* 2003; **19**: 217–231.
29. Bhattacherjee P, Williams BS, Paterson CA. Responses of intraocular pressure and the pupil of feline eyes to prostaglandin EP1 and FP receptor agonists. *Investigative Ophthalmology and Visual Science* 1999; **40**: 3047–3053.
30. Woodward DF *et al.* Prostaglandin F2 alpha effects on intraocular pressure negatively correlate with FP-receptor stimulation. *Investigative Ophthalmology and Visual Science* 1989; **30**: 1838–1842.
31. Chen J, Woodward DF. Prostanoid-induced relaxation of precontracted cat ciliary muscle is mediated by EP2 and DP receptors. *Investigative Ophthalmology and Visual Science* 1992; **33**: 3195–3201.
32. Parrish RK, Palmberg P, Sheu WP. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. *American Journal of Ophthalmology* 2003; **135**: 688–703.
33. Yamamoto T, Kitazawa Y, Azuma I *et al.* Clinical evaluation of UF-021 (Rescula; isopropyl unoprostone). *Survey of Ophthalmology* 1997; **41** (Suppl. 2): S99–S103.
34. Woodward DF *et al.* The pharmacology of bimatoprost (Lumigan). *Survey of Ophthalmology* 2001; **45** (Suppl. 4): S337–S345.
35. Fellenbaum PS. Six-month randomized clinical trial comparing intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *American Journal of Ophthalmology* 2003; **136**: 392–393.
36. Gelatt KN, MacKay EO. Effect of different dose schedules of bimatoprost on intraocular pressure and pupil size in the glaucomatous Beagle. *Journal of Ocular Pharmacology and Therapeutics* 2002; **18**: 525–534.
37. Jampel HD *et al.* Randomized clinical trial of latanoprost and unoprostone in patients with elevated intraocular pressure. *American Journal of Ophthalmology* 2002; **134**: 863–871.
38. Ofri R, Raz D, Kass PH *et al.* The effect of 0.12% unoprostone isopropyl (rescula) on intraocular pressure in normotensive dogs. *Journal of Veterinary Medical Science* 2000; **62**: 1313–1315.
39. Bhattacherjee P, Paterson CA, Percicot C. Studies on receptor binding and signal transduction pathways of unoprostone isopropyl. *Journal of Ocular Pharmacology and Therapeutics* 2001; **17**: 433–441.
40. Woodward DF *et al.* Pharmacological characterization of a novel antiglaucoma agent, bimatoprost (AGN 192024). *Journal of Pharmacology and Experimental Therapeutics* 2003; **305**: 772–785.
41. Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. *Journal of the American Physiological Society* 1999; **79**: 1193–1223.
42. Breyer RM, Bagdassarian CK, Myers SA *et al.* Prostanoid receptors: subtypes and signaling. *Annual Review of Pharmacology and Toxicology* 2001; **41**: 661–690.
43. Schumer RA, Camras CB, Mandahl AK. Putative side effects of prostaglandin analogs. *Survey of Ophthalmology* 2002; **47** (Suppl. 1): S219–S230.
44. Resul B, Stjernschantz J, Selen G *et al.* Structure-activity relationships and receptor profiles of some ocular hypotensive prostanoids. *Survey of Ophthalmology* 1997; **41** (Suppl. 2): S47–S52.
45. Stjernschantz J, Selen G, Sjoquist B *et al.* Preclinical pharmacology of latanoprost, a phenyl-substituted PGF2 alpha analogue. *Advances in Prostaglandin, Thromboxane, and Leukotriene Research* 1995; **23**: 513–518.