ORIGINAL RESEARCH

Distribution of ^{14}C-Latanoprost Following a Single Intracameral Administration Versus Repeated Topical Administration

Jie Shen · Rex A. Moats · Harvey A. Pollack · Michael R. Robinson ·
Mayssa Attar

ABSTRACT

Purpose: To qualitatively evaluate the ocular and periocular distribution of ^{14}C-latanoprost following a single intracameral administration or repeated topical ocular administration in beagle dogs and cynomolgus monkeys.
Methods: In the dog study, three animals received an intracameral dose of ^{14}C-latanoprost bilaterally and were euthanized at 1,

2, and 4 h post dose; three control animals received topical ^{14}C-latanoprost bilaterally once daily for 5 days and were euthanized at 1, 4, and 24 h post final dose. Sagittal 40-μm sections of eyes with surrounding tissues were collected and processed for autoradiography. Methods in the monkey study were similar; two animals received a unilateral intracameral dose of ^{14}C-latanoprost.
Results: After intracameral dosing in dogs, radioactivity was concentrated in the cornea, iris, ciliary body, and anterior chamber with no radioactivity detected in the eyelids or other periorbital tissues. After topical dosing, radioactivity was distributed in the bulbar conjunctiva, cornea, anterior chamber, iris, ciliary body, upper and lower eyelids, and periorbital tissues (fat/muscle). After intracameral dosing in monkeys, radioactivity was concentrated in the anterior chamber, cornea, iris, ciliary body, and posteriorly along the uveoscleral outflow pathway; there was no radioactivity in the eyelids or periorbital tissues aside from signal in the nasolacrimal duct, likely from reflux of ^{14}C-latanoprost into the tear film.
Conclusions: Intracameral delivery resulted in more selective target tissue drug exposure. Intracameral drug delivery has potential to reduce ocular surface and periocular adverse effects associated with topical administration of prostaglandin analogues, such as eyelash growth and periorbital fat atrophy.

J. Shen (✉) · M. R. Robinson · M. Attar
Allergan, An AbbVie Company, Irvine, CA, USA
e-mail: shen_jie@allergan.com

R. A. Moats · H. A. Pollack
Moats Laboratory at the Saban Research Institute,
Children's Hospital Los Angeles Research Imaging
Core, Department of Radiology, Keck School of
Medicine USC, Los Angeles, CA, USA

Key Summary Points

Topical administration is the most common mode of drug delivery for PGAs and other IOP-lowering medications, but poor adherence of patients to topical ocular hypotensive regimens is endemic.

Intracameral administration may be useful for delivery of PGAs to target tissues for IOP lowering in patients with glaucoma and ocular hypertension.

The objective of this study was to determine the ocular distribution of ^{14}C-latanoprost following a single intracameral administration or repeated topical ocular administration to beagle dogs and cynomolgus monkeys.

The results of these studies in dogs and monkeys demonstrate that intracameral PGA dosing delivers drug more selectively to intraocular target tissues compared with topical PGA dosing.

Intracameral PGA dosing can achieve targeted drug delivery because it bypasses the anatomic and precorneal barriers to drug penetration encountered by topical administration.

Delivery of PGA by intracameral injection may reduce the potential for side effects associated with topical PGA treatment by limiting PGA distribution to the conjunctiva, eyelids, and periocular tissues.

INTRODUCTION

Topical prostaglandin analogue (PGA) medications including latanoprost, tafluprost, travoprost, and the prostamide bimatoprost are widely used as first-line therapy for lowering intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT) [1]. These medications are well tolerated, systemically safe, and highly efficacious in lowering IOP [1–3]. The PGAs typically are administered by instillation of an eye drop once daily.

Topical administration is the most common mode of drug delivery for PGAs and other IOP-lowering medications, but poor adherence of patients to topical ocular hypotensive regimens is endemic [4,5]. Inconvenience, forgetfulness, difficulty in instilling eye drops, the frequency of required dosing, medication cost, and side effects are commonly reported reasons for patient nonadherence to IOP-lowering eye drops [6–8]. Furthermore, precorneal factors (tear film, tear turnover, blinking, lacrimal drainage, and induced lacrimation) as well as anatomical barriers (the cornea, conjunctiva, and sclera) limit the delivery of drugs applied topically to the eye to intraocular target tissues [9]. Drug that does not penetrate the eye has the potential to cause ocular surface and periocular side effects, and conjunctival hyperemia, eyelash growth, and iris, eyelid, and periocular skin pigmentation are common side effects of topical PGA treatment [10]. Prostaglandin-associated periorbitopathy (PAP), most likely resulting from periorbital fat atrophy [11], is now also recognized as a side effect of topical PGA treatment [12]. Clinical signs of PAP associated with chronic topical PGA treatment include deepening of the upper eyelid sulcus, enophthalmos, flattening of the lower eyelid bags, and inferior scleral show [13,14].

Intracameral administration of antibiotics and mydriatics is used routinely during cataract surgery [15–17], and this route of drug administration may also be useful for delivery of PGAs to target tissues for IOP lowering in patients with glaucoma and OHT. Intracameral injection of PGAs can potentially deliver drug to target intraocular tissues more efficiently than topical dosing and minimize side effects associated with topical PGA treatment by limiting drug exposure to the ocular surface and periocular tissues [18]. Studies in animal models have shown that an intracameral implant delivering bimatoprost [19–21] or another ocular

hypotensive medication [22–24] including a latanoprost analogue [25] can effectively reduce IOP. The intracameral sustained-release bimatoprost implant (Durysta™) has demonstrated efficacy and tolerability in patients with glaucoma [26] and is now approved by the US Food and Drug Administration for the treatment of OAG or OHT.

Drug distribution after administration can be expected to affect the IOP-lowering efficacy and safety of a PGA delivered intracamerally. The objective of this study was to determine the ocular distribution of ^{14}C-latanoprost following a single intracameral administration or repeated topical ocular administration to beagle dogs and cynomolgus monkeys.

METHODS

Animals

All animals were normal on ophthalmic examination. Animals were housed under controlled conditions and received a certified canine or primate diet and water ad libitum. The studies were conducted at Covance Laboratories Inc (Madison, WI, USA) in accordance with the Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research. All study procedures were performed in compliance with US Animal Welfare Act regulations.

Methods for Dog Study

Six male purebred treatment-naïve beagle dogs (Covance Research Products, Cumberland, VA or Covance Stock Colony), ages 6–7 months, weighing 9.7–12.1 kg, were used in the study.

Drug
The test compound was ^{14}C-latanoprost (178 mCi/mmol, 98.5% radiopurity). For intracameral injections, on the day of dosing, 30 μL of ^{14}C-latanoprost was dried under a stream of nitrogen and solubilized in 300 μL of vehicle containing 1% polysorbate 80, 0.75% sodium chloride, 0.16% sodium dihydrogen phosphate

monohydrate, 0.22% disodium hydrogen phosphate anhydrous, and sterile water. For topical dosing, ^{14}C-latanoprost was prepared in the same vehicle with the addition of 0.02% benzalkonium chloride. On the first day of topical dosing, 48.8 μL of ^{14}C-latanoprost was dried under a stream of nitrogen and solubilized in 2.4 mL of vehicle containing benzalkonium chloride. Aliquots of the solution were frozen at − 20 °C for use on the next 4 days. Drug stability was demonstrated by high-performance liquid chromatography.

Drug Administration
Animals were assigned to two study groups (n = 3 per group). Group 1 received a single bilateral intracameral dose of ^{14}C-latanoprost, and group 2 received a bilateral topical dose of ^{14}C-latanoprost once daily for 5 days. A similar topical dosing regimen of latanoprost has been shown to achieve steady state IOP lowering in glaucomatous beagle dogs [27]. The doses of latanoprost and radioactivity administered to the animals in each group are shown in Table 1.

Animals in the intracameral dosing group were anesthetized with a regimen of oxymorphone, glycopyrrolate, and midazolam, followed by dexmedetomidine. A topical anesthetic was applied to the eyes, and the eyes were then rinsed with an iodine solution followed by a saline rinse. A bilateral dose of ^{14}C-latanoprost was administered intracamerally by a board-certified veterinary ophthalmologist using a syringe and needle. For each administration, the eye was stabilized by grasping the conjunctiva with a fixation forceps, the needle was tunneled through the cornea near the limbus and advanced several millimeters toward the center of the anterior chamber, and a 10-μL dose was injected.

Animals in the topical dosing group received a topical 30-μL dose in both eyes once daily for 5 days at the same time each day. The dose was administered onto the cornea of the eye via a micropipette. After the dose was administered, the upper and lower eyelids were held together gently to distribute the dose across the eye.

Table 1 Dog study ^{14}C-latanoprost study groups

Study group	No. of animals	No. of treated eyes	Drug delivery mode	Target dose (µg latanoprost/dose)	Dose volume (µL/dose)	Total no. of doses per eye	Target dose radioactivity (µCi/dose)
Topical dosing	3	6	Topical ophthalmic drop once daily for 5 days in both eyes	1.50	30	5	0.61
Intracameral dosing	3	6	Single intracameral injection in both eyes	2.45	10	1	1.0

Sample Collection

Animals were euthanized with sodium pentobarbital at designated time points after drug administration. The three animals that received intracameral ^{14}C-latanoprost were euthanized at 1, 2, and 4 h after dosing; the three animals that received topical ^{14}C-latanoprost were euthanized at 1, 4, and 24 h after the last dose. Following euthanasia, the animals were exsanguinated, the head was shaved, and the eyelids on both eyes were sutured open such that the palpebral conjunctiva were visible and outward facing. Left eyes were enucleated, trimmed of excess tissue, rinsed with saline, blotted dry, and flash-frozen in liquid nitrogen for 15–20 s before storage at − 20 °C. Right eyes were kept in situ following euthanasia to ensure that periorbital tissues would be preserved for imaging drug distribution. Right eyes with surrounding structures were removed and frozen in a hexane/dry ice bath for 30–120 min, blotted dry, placed on dry ice or stored at − 70 °C for at least 12 h, stored at − 20 °C, and then were shipped on dry ice to QPS, LLC (Newark, DE, USA) for autoradiography.

The clinical dosing regimen for latanoprost eye drops is once-daily administration, and ocular samples from animals assigned to the group receiving 5 days of once-daily topical administration were collected at 1, 4, and 24 h post final dose to cover the entire dosing interval. The timing of tissue sampling after intracameral delivery differed because aqueous humor outflow in normal beagle dogs is estimated to be 4–6 µL/min [28], and with an estimated anterior chamber volume of 0.4–0.77 mL [28], the entire volume of aqueous humor is expected to be turned over within 3 h. Therefore, ocular samples from animals assigned to the intracameral dose group were collected at 1, 2, and 4 h post dose.

Autoradiography

Frozen samples containing right eyes and surrounding structures in situ were embedded in 2% carboxymethylcellulose, frozen into blocks, and sectioned on a cryomicrotome at − 20 °C. An aliquot of blood containing ^{14}C was injected into each block before sectioning as a marker to aid in the alignment of sections with autoradiographs. Serial 40-µm sections were taken in the sagittal plane at intervals of 0.5 mm through half of each eye (for eyes that had received intracameral ^{14}C-latanoprost administration, the half of the eye that included the injection site). Sections were selected that included the following areas/structures to be analyzed: ciliary body, lens, anterior and posterior chambers, sclera, anterior and posterior uvea, iris, cornea, and bulbar and palpebral conjunctiva. The sections were collected on adhesive tape (Scotch 8210; 3M, Maplewood, MN, USA) and were air-dried in the cryomicrotome for at least 48 h, then were mounted on a cardboard backing and wrapped with a thin plastic wrap to avoid contamination of the imaging plate.

The sections and calibration standards at 10 different concentrations (0.0003–5.3825 µCi/g) were then exposed to a ^{14}C-sensitive phosphor imaging plate (Fuji Biomedical, Stamford, CT) in light-tight cassettes for 4 days at room temperature. Quantification was performed by

image densitometry; a standard curve was constructed from nominal concentrations of ^{14}C-calibration standards. Concentrations of radioactivity were expressed as microcuries per gram (μCi/g) and converted to microgram equivalents of ^{14}C-latanoprost per gram sample (μg equiv/g). The lower limit of quantitation was 0.830 ng equiv/g.

Methods for Monkey Study

Two female drug-naïve cynomolgus monkeys (Covance Research Products, Cumberland, VA or Covance Stock Colony), ages 3–4 years, weighing 2.7–3.4 kg, were used in the study.

Drug and Drug Administration
For intracameral injections, the test compound and procedures used were similar to those described above for the dog study. A 204-μL aliquot of ^{14}C-latanoprost was dried and solubilized in 2.00 mL of vehicle. Two monkeys were anesthetized with a regimen of ketamine, glycopyrrolate, and dexmedetomidine. After application of a topical anesthetic to both eyes, the eyes were rinsed with an iodine solution followed by a saline rinse, and finally, additional drops of topical anesthetic were applied. A 10-μL dose of ^{14}C-latanoprost was administered intracamerally, to the right eye only, by a board-certified veterinary ophthalmologist using a syringe and needle, with the same procedure as described above in dogs.

Sample Collection and Autoradiography
Monkeys were euthanized with an overdose of sodium pentobarbital and exsanguination at 0.5 and 4 h post intracameral dose. Following euthanasia, both eyes were rinsed with saline, and the eyelids were sutured open. The head was removed from the body with the eyes in situ and was frozen in a hexane/dry ice bath for 15 min, then was drained, dried, placed in a labeled bag, and stored at − 70 °C for at least 12 h. The head was then embedded in chilled carboxymethylcellulose, frozen into a block, and stored at − 20 °C in preparation for autoradiographic analysis. Standards fortified with ^{14}C radioactivity were placed into the frozen block and used for monitoring the uniformity of section thickness.

Serial cross sections, collected up to 43 levels using the initial injection site as a reference, were collected on adhesive tape at 20-μm thickness using a Leica CM 3600 cryomicrotome. Sections were dried at − 20 °C. A representative section from each level of interest was mounted, tightly wrapped with plastic film, and exposed on a phosphor imaging screen with standards for calibration of the imaging analysis software. Screens were exposed for 7 days and scanned using the Storm system (Amersham Biosciences, Sunnyvale, CA, USA). InterFocus Imaging Ltd (Cambridge, England) MCID^{TM} Analysis software was used to create a calibrated standard curve and determine tissue concentrations, which were interpolated from each standard curve as nanocuries per gram and converted to μg equiv/g. The lower limit of quantitation was 2.36 ng equiv/g.

Three-Dimensional (3D) Rendering
The autoradiography images were rendered into 3D images/movies. A customized methodology was developed by the Moats Laboratory at The Saban Research Institute of Children's Hospital Los Angeles to accomplish the segmentation and alignment of the autoradiography images. The pre-processed stack images were exported to Amira Software (Thermo Fisher Scientific, Waltham, MA, USA) for 3D rendering to visualize the monkey images.

RESULTS

Dog Study

All animals appeared healthy after dosing. Both the intracameral and topical ocular doses of ^{14}C-latanoprost were well tolerated with no effects observed other than transient hyperemia.

Figure 1 shows representative sections and autoradiographs from in situ eyes of animals that received five daily topical doses of ^{14}C-latanoprost. Radioactivity appeared to be diffusely distributed throughout the anterior portion of the eye at 1, 4, and 24 h after the last
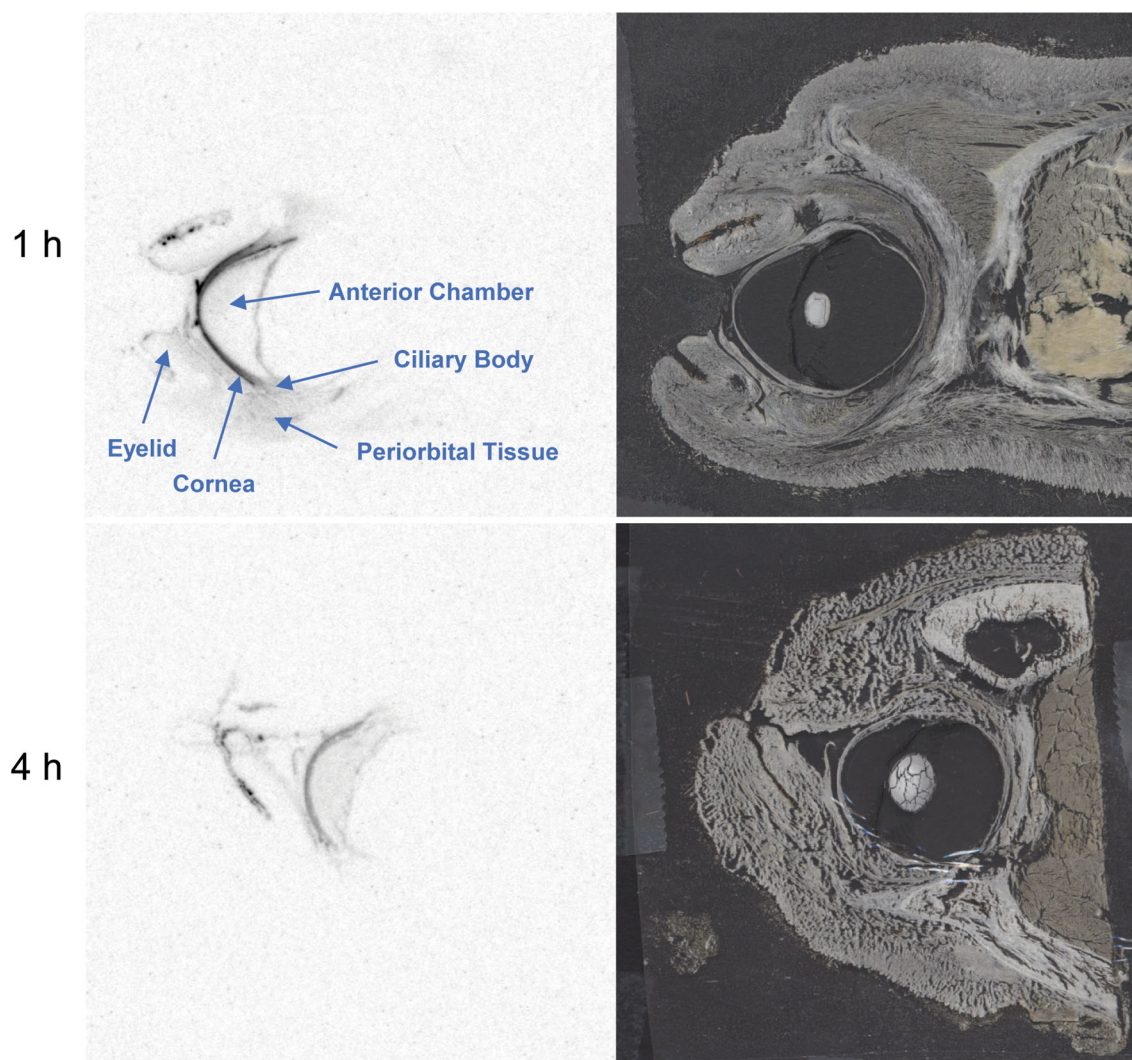
Fig. 1 Representative sections of fresh-frozen eyes in situ (right) and corresponding autoradiographs (left) from beagle dogs that received five daily topical ophthalmic bilateral administrations of ^{14}C-latanoprost. Eyes in situ were collected at 1 and 4 h after the last administration. Annotations identify tissues and areas of interest

dose. Radioactivity was present in the bulbar conjunctiva, cornea, anterior chamber, iris, ciliary body, upper and lower eyelids, and periorbital tissues (fat and muscle) after topical administration (Fig. 1).

Representative sections and autoradiographs from in situ eyes of animals that received a single intracameral dose of ^{14}C-latanoprost are shown in Fig. 2. Radioactivity was concentrated in ocular tissues including the cornea, iris, ciliary body, and anterior chamber after intracameral dosing. There was a diminution of

signal in the anterior segment from 1 to 4 h post intracameral dose. No radioactivity was detected in the eyelids or other periorbital tissues after intracameral dosing.

Radioactivity in anterior uvea and sclera was detected only sporadically on autoradiography with both dosing routes. Distribution of radioactivity to the posterior eye, including the retina, was negligible after both topical and intracameral dosing.
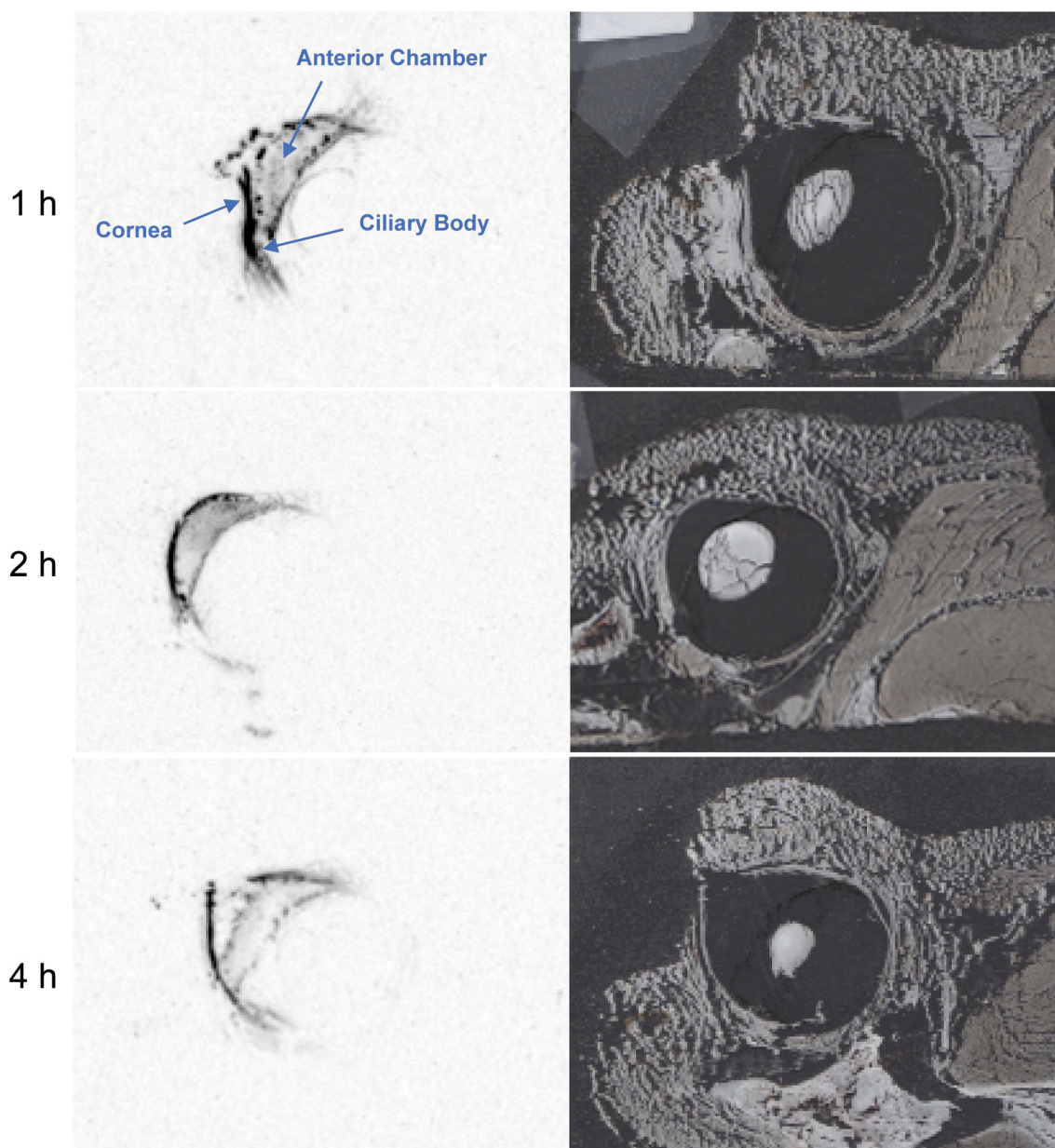
Fig. 2 Representative sections of fresh-frozen eyes in situ (right) and corresponding autoradiographs (left) from beagle dogs that received a single bilateral intracameral administration of ^{14}C-latanoprost. Eyes in situ were collected at 1, 2, and 4 h after the administration. Annotations identify tissues and areas of interest

Monkey Study

The 3D reconstruction of autoradiographs from sections taken at 0.5 h post single intracameral dose showed that radioactivity was concentrated in the anterior chamber, cornea, iris, and cilary body of the dosed eye (Fig. 3a). Radioactivity was also present in the uveoscleral outflow pathway, and in larger drainage pathways such as the superior ophthalmic vein (Fig. 3a). Some radioactivity was located in the nasolacrimal duct and nasal turbinates, and likely resulted from reflux of some of the injected dose into the tear film. However, no radioactivity was detected in the eyelids or other periorbital tissues. In the reconstruction
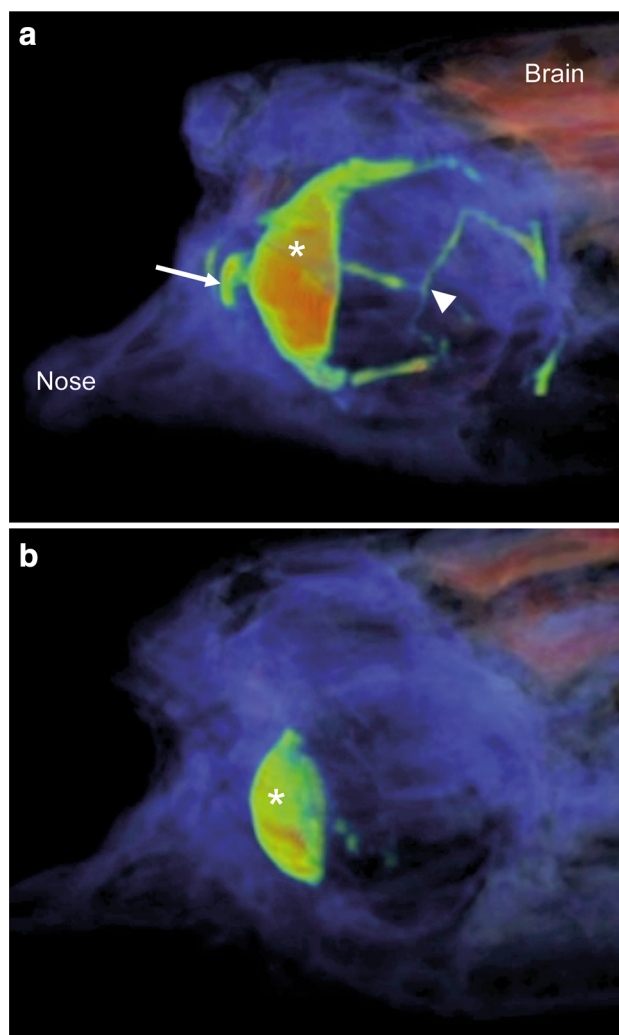
Fig. 3 Images of 3D reconstructions of the distribution of radioactivity in cynomolgus monkeys at **a** 0.5 h and **b** 4 h after a single intracameral administration of ^{14}C-latanoprost. Phosphor imaging autoradiographs of cross sections of the animal heads were used to develop the 3D reconstructions. *3D* 3-dimensional, *arrow* nasolacrimal duct, *arrowhead* superior ophthalmic vein, *asterisk* anterior chamber

of autoradiographs from sections taken at 4 h after the intracameral dose, radioactivity was concentrated in the anterior chamber of the dosed eye with less intensity compared with 0.5 h. Radioactivity was absent from the eyelids and periorbital tissues (Fig. 3b).

The full 3D reconstructions of the distribution of radioactivity at 0.5 h and 4 h after the intracameral dose are shown in Supplementary Video 1 and Supplementary Video 2, respectively.

DISCUSSION

Autoradiography was used in this study to qualitatively evaluate the distribution and concentration of radioactivity in dog eyes that were administered ^{14}C-latanoprost by a single intracameral injection or daily topical instillation. After the intracameral dose, radioactivity was concentrated in the cornea, iris, ciliary body, bulbar conjunctiva, and anterior chamber, whereas after 5 days of topical dosing, radioactivity was concentrated in the cornea and

bulbar conjunctiva, and was distributed more diffusely in other anterior ocular tissues. Radioactivity in the eyelids and periorbital tissue was detected only after topical dosing. Data in the monkey study were confirmatory with no signal detected in the eyelids or orbit after intracameral administration of ^{14}C-latanoprost.

The eyes of beagle dogs are similar to human eyes in anatomic and physiologic characteristics [28], and therefore, the beagle dog is a useful model for the evaluation of ocular drug distribution. Drug distribution to the ciliary body is important for the PGA class of topical ocular hypotensive medications, because these drugs decrease IOP by increasing uveoscleral outflow [29]. As the mechanism of action of topical PGAs may also involve an increase in aqueous outflow through the conventional pathway [29], distribution of drug to the anterior chamber adjacent to the trabecular meshwork is also relevant. The distribution of radioactivity seen in this study after intracameral and topical administration of ^{14}C-latanoprost to dogs shows that intracameral dosing can more selectively deliver PGA to target tissues for IOP lowering. Furthermore, the absence of radioactivity detected in the eyelids and periorbital tissues after intracameral dosing suggests that intracameral administration may be associated with a reduced incidence of some side effects associated with topical administration of PGAs, such as eyelash changes and PAP.

The delivery of therapeutic agents via topical administration may be influenced by the use of accompanying procedures such as punctal occlusion or eyelid closure, which could help increase the concentration and duration of stay of an agent in the anterior chamber and reduce either systemic or off-target exposure [30]. In the present dog study, the upper and lower eyelids of each treated eye were gently held together to distribute the dose across the eye and implement a form of eyelid closure after topical administration of the test compound. The marked presence of radioactivity in the eyelids and periocular tissues with these measures might reinforce the finding that intracameral delivery yields favorable localization of therapeutic agents compared with topical administration.

Although dogs are useful models for the evaluation of ocular drug distribution, their aqueous outflow systems differ from those in humans. In contrast, the orbital anatomy of cynomolgus monkeys and humans is very similar [31], and the aqueous drainage apparatus in cynomolgus monkeys is anatomically similar to that in humans [32]. To confirm that intracameral administration has a greater targeted tissue effect, cynomolgus monkeys were also used. As results from a previous study showed that drug is present in the eyelids of monkeys after topical PGA administration [33], we decided to only use intracameral administration in monkeys for this study. The results from the 3D rendition of the autoradiography in the monkey were very similar to the autoradiography results in the beagle dog. After intracameral administration, drug exposure was mainly limited to the anterior segment (the anterior chamber, cornea, iris, and ciliary body), as well as posterior drainage vessels, which was expected as the aqueous drains through the uveoscleral pathway and episcleral veins. Importantly, there was no eyelid or orbit exposure. These results indicate that there is a localized distribution of radioactivity when ^{14}C-latanoprost is administered intracamerally.

The results of our study are consistent with those of the recently reported drug distribution study of the intracameral sustained-release bimatoprost implant in beagle dogs [18]. In the bimatoprost implant study, the maximal concentration of bimatoprost in the iris-ciliary body was 4 log units higher after implant (15 μg bimatoprost) administration than after 7 days of once-daily topical administration of bimatoprost 0.03% [18]. In another study in beagle dogs, the intracameral bimatoprost implant was shown to cause selective dilation of episcleral aqueous outflow vessels [19], in contrast to the generalized vasodilation that causes ocular surface hyperemia after topical PGA administration in dogs [34], consistent with the suggestion that intracameral PGA dosing may be associated with reduced occurrence of ocular surface and periocular side effects.

An advantage of the use of autoradiography in this study is that drug distribution could be evaluated more precisely in discrete tissues

compared with drug distribution studies using isolated tissues. Radioactivity distribution in tissues including the eyelids and periorbital tissues was evaluated qualitatively. A limitation of the use of autoradiography to evaluate drug distribution in the present study is that the molecular identity of the radioactivity present in tissue sections (i.e., latanoprost, latanoprost acid, or other metabolite) could not be determined.

CONCLUSION

The results of these studies in dogs and monkeys demonstrate that intracameral PGA dosing delivers drug more selectively to intraocular target tissues compared with topical PGA dosing. Intracameral PGA dosing can achieve targeted drug delivery because it bypasses the anatomic and precorneal barriers to drug penetration encountered by topical administration. Delivery of PGA by intracameral injection may reduce the potential for side effects associated with topical PGA treatment by limiting PGA distribution to the conjunctiva, eyelids, and periocular tissues.

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Disclosure. Jie Shen, Michael R. Robinson, and Mayssa Attar are employees of AbbVie Inc. Rex A. Moats and Harvey A. Pollack declare that they have no conflict of interest.

Compliance with Ethics Guidelines. Animal procedures were carried out in accordance with the Association for Research in Vision and Ophthalmology (ARVO) statement for the Use of Animals in Ophthalmic and Vision Research. All animal procedures were performed in compliance with US Animal Welfare Act regulations.

Data Availability. The datasets generated during and/or analyzed during the current study are available from AbbVie Inc on reasonable request.

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