Pharmacokinetic and Safety Evaluation of a Transscleral Sustained Unoprostone Release Device in Monkey Eyes

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Purpose. We evaluate the ocular tissue distribution and retinal toxicity of unoprostone (UNO) during 12 months, after transscleral sustained-UNO administration using a drug delivery device in monkey eyes.

Methods. The device consisted of a reservoir, controlled-release cover, and a drug formulation of photopolymerized polyethylene glycol dimethacrylate. Six mg UNO was loaded into the device (length, 17 mm; width, 4.4 mm; height, 1 mm). The concentrations of M1, a primary metabolite of UNO, in the retina, choroid, vitreous, lens, aqueous humor, iris, ciliary body, and plasma were determined by liquid chromatography-tandem mass spectrometry at 3, 6, and 12 months after implantation. Retinal toxicity was evaluated by electroretinography (ERG), optical coherence tomography (OCT), and IOP at preimplantation, and at 6, 9, and 12 months after implantation. Focal ERGs were performed at 9 and 12 months after implantation.

Results. M1 was detected in the choroid and retina with maximum peaks of 243.2 and 8.41 ng/g at 6 months, respectively. M1 in the ciliary body and iris was detected with maximum peaks of 7.66 and 10.4 ng/g at 6 and 12 months, respectively. Less than 1 ng/mL or ng/g of M1 was detected in the aqueous humor, vitreous, and lens. No changes were observed in retinal function as assessed by ERG, IOP or macula thickness and retinal histology by OCT examinations during the 12-month period. No differences in focal ERG amplitudes, especially in the macula, were observed.

Conclusions. The device provided intraocular sustained delivery of UNO for 12 months without producing severe retinal toxicity.

Keywords: drug delivery system, unoprostone, retina, polyethylene glycol dimethacrylate
electroretinography (ERG), histology by optical coherence tomography (OCT), and IOP, and the results were compared to those of fellow untreated right eyes before, and at 6, 9, and 12 months after implantation. Focal ERGs also were conducted at 9 and 12 months to evaluate local retinal function, especially in the macula. Intraocular UNO distribution was evaluated by liquid chromatography-tandem mass spectrometry (LC/MS/MS) at 3, 6, and 12 months after implantation.

METHODS

Device Fabrication

The URDs were designed as reported previously.7,9 Unoprostone isopropyl (UNO; molecular weight [MW], 424.64) was provided by Sucampo Pharmaceuticals (Rockville, MD, USA). Briefly, each device consisted of a reservoir that was loaded with a sustained release formulation of UNO and then sealed with a controlled release cover. Polyethylene glycol dimethacrylate (PEGDM; MW, 736; Shin-Nakamura Chemical, Tokyo, Japan) and triethylene glycol dimethacrylate (TEGDM; MW, 286, Shin-Nakamura Chemical) containing 1% 2-hydroxy-2-methylpropionic acid (Tokyo Chemical Industry, Fukaya City, Japan) as a photo-initiator, were used as starting materials. The curvature radius was 9 mm.

A concentrated mixture of 40% PEGDM/60% TEGDM (abbreviated as P40) at a concentration of 500 mg/mL, poured into the reservoir, and photo-polymerized for 40 seconds. After loading the drugs, a P40 mixture without UNO was applied to the reservoir, a PDMS mold was placed over the mixture, and UV cured for 4 minutes to provide a reservoir cover. The size of the URD was 17 mm long × 4.4 mm wide × 1 mm thick with a maximum drug loading volume of 12 μL. The curvature radius was 9 mm.

Animals

All animals were maintained and cared for in accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research, and after approval from the Institutional Animal Care and Use Committee of the Tohoku University Environmental & Safety Committee. Japanese macaque monkeys were provided by the National BioResource Project “Japanese monkeys” (National Institutes of Natural Science, Tokyo, Japan). Crab-eating monkeys were purchased from Hamri Co., Ltd. (Ibaraki, Japan). Six Japanese monkeys were used for measurement of M1 in the intraocular tissues, and four crab-eating monkeys were used for safety evaluation of 12-month implantation, using ERG, OCT, IOP determinations, and focal ERG analyses.

Implantations

The monkeys were anesthetized with ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg). Their ocular surfaces were anesthetized with a topical instillation of 0.4% oxybuprocaine hydrochloride. A 5 × 5 mm paralimbal conjunctival incision was made at the upper temporal limbus. The device was inserted between the conjunctiva and sclera and the front head of the device was placed just beside the optic nerve head. The device positions were confirmed after enucleation at the end of the experiments. The peripheral region was sutured onto the sclera with 7-0 silk to fix the devices tightly onto the sclera. The incision was closed with 9-0 silk and antibiotic ophthalmic ointment was inserted into the conjunctiva. For safety evaluations in crab-eating monkeys, the URDs were placed onto the left eyes and the right eyes remained untreated. For intraocular UNO distribution in Japanese monkeys, the URDs were placed onto both eyes. Four eyes from two Japanese monkeys were collected for the measurement of M1 in the eyes at 3, 6, and 12 months after implantation. The placebo devices were not treated to reduce the number of monkeys used, because there was no significant effect on eye functions and toxicity in rats and rabbits as shown by our previous studies.8,9

Measurement of M1

The concentration of M1, a primary metabolite of UNO, was measured using LC/MS/MS as reported previously.9 At 3, 6, and 12 months after URD implantation, the eyes were enucleated and frozen at −80°C. Plasma also was collected and frozen. The retina, choroid/RPE tissues, vitreous, lens, iris, ciliary body, and aqueous humor were separated. Except for plasma and aqueous humor, the tissues were diluted 10- or 5-fold, and homogenized on ice. Aliquots (25 μL) of the samples were mixed with 500 μL acetonitrile and internal standard. After centrifugation at 10,000g for 2 minutes at room temperature, the supernatants were mixed with 200 μL propylene glycol/ethanol (5:100, vol/vol) and dried under reduced pressure, followed by the addition of 200 μL methanol/water (20:80, vol/vol), and finally followed by centrifugal ultrafiltration at 3000g for 10 minutes at room temperature. The final filtrate was used for LC/MS/MS (Shimadzu 10A; Shimadzu, Tokyo, Japan). Chromatographic separation

Figure 1. Photograph (A) and schematic image (B) of the URD. The size of the URD was 17 mm long × 4.4 mm wide × 1 mm thick with a maximum drug loading volume of 12 μL. The curvature radius was 9 mm.
Transscleral Unoprostone Delivery in Monkey Eyes

was achieved by using a Develosil ODS-UG-3 (2.0 I.D. × 50 mm, 3 μm; Nomura Chemical, Aichi, Japan) analytical column and an Inertsil ODS-5 (3.0 I.D. × 10 mm, 3 μm; GL Science, Tokyo, Japan) precolumn with a gradient elution of two different mobile phases (mobile phase A: acetonitrile:water:acetic acid [20:80:1.0, vol/vol/vol]; and mobile phase B, acetonitrile:acetic acid [100:0.1, vol/vol]). The flow rate was 0.25 mL/min and the running time was 16.0 minutes. An AB SCIEX API5000; Applied Biosystems, Foster City, CA, USA) was used to perform the MS/MS. The peak area ratios of M1 to the internal standard were determined by interpolation from the calibration curve. The limit of quantification was <0.05 ng/mL for plasma and aqueous humor, and <0.5 ng/g at 3 and 6 months or <0.25 ng/g at 12 months for tissue.

Electroretinography

ERG (Mayo, Aichi, Japan) amplitudes were recorded before, and 6, 9, and 12 months after implantation. At 30 minutes before the recording, the animals were anesthetized with a mixture of ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg). The pupils were dilated with 1% tropicamide and 2.5% phenylephrine (Santen, Osaka, Japan). Scotopic ERG amplitudes were recorded in the dark-adapted eyes by placing a golden ring electrode (7.8 mm base curve; Mayo) in contact with the cornea. An identical reference electrode was placed in the mouth, and a ground electrode was attached to the ear. Stimuli were produced with a light-emitting diode stimulator (Mayo). Single white-flash stimuli of −3.523, −2.523, −1.523, −0.523, 0.477, and 1.477 log [cd/s/m²] were used. Photopic ERG amplitudes were recorded in the light-adapted eyes by the same methods as were used for scotopic ERGs. Single white-flash stimuli of −1.000, −0.050, 0.950, 1.477, and 2.000 log [cd/s/m²] were used. The amplitude of the a-wave was measured from the baseline to the maximum a-wave peak, and the b-wave was measured from the maximum a-wave peak to the maximum b-wave peak.

Optical Coherence Tomography

OCT images were recorded before, and 6, 9, and 12 months after implantation. The animals were anesthetized with a mixture of ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg). The pupils were dilated with 1% tropicamide and 2.5% phenylephrine (Santen). A contact lens (radius of curvature of the central optic zone, 8 mm; diameter, 12.8 mm; power = ±0 diopters [D]; center thickness [CT] = 0.2 mm; polymethyl methacrylate [PMMA]; Yunicon Co., Tokyo, Japan) was applied to the eyes. The RS-5000 Advance OCT system was used (Nideck, Aichi, Japan). The image quality of the real-time display was optimized by adjusting the ocular lens. Using the thickness-map mode, macula thickness was calculated automatically and presented as a color-coded topographic map. The map divided the macula into nine subfields, encircled by rings 1, 3, and 6 mm in diameter, and the central subfield (1 mm diameter) was evaluated. In addition, line-scan OCT images (scanning in the horizontal and vertical meridians through the fovea) were recorded.

IOP Measurement

IOP was measured before, and 6, 9, and 12 months after implantation using a tonometer (Tonovet M.E. Technica, Tokyo, Japan). The animals were anesthetized with a mixture of ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg).

Focal ERG

Focal ERG (ER-80; Kowa, Nagoya, Japan) amplitudes were recorded 9 and 12 months after implantation. The animals were anesthetized with a mixture of ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg). The pupils were dilated with 1% tropicamide and 2.5% phenylephrine (Santen). The system used to elicit the focal ERG basically was identical to that established by Kondo et al.,16 and consisted of an infrared fundus camera and a stimulator (Kowa). ERG amplitudes were recorded in the light-adapted eyes by placing a bipolar Burian-Allen electrode (7.5 mm base curve; Hansen Ophthalmic Development Laboratory, Coralville, IA, USA) in contact with the cornea. An identical reference electrode was placed in the mouth, and a ground electrode was attached to the ear. Stimuli were produced with a light-emitting diode stimulator (Mayo). A single white-flash stimulus of 30 cd/m² (duration, 100 msec) was used. The macula was stimulated with 5°, 10°, and 15° stimulus spots, and the upper temporal, lower temporal, upper nasal, and lower nasal sites were stimulated with 15° stimulus spots. The amplitude of the a-wave was measured from the baseline to the maximum a-wave peak, and the b-wave was measured from the maximum a-wave peak to the maximum b-wave peak.

Statistical Analysis

Experimental data are presented as the mean ± SD. Statistical significance was calculated with Eksusu-Toukei 2012 (Social Survey Research Information, Tokyo, Japan), using unpaired t-tests for normally distributed isolated pairs.

Results

URD Implantation

Figure 1 shows the URD used for the monkey experiments. The device was designed to fit within the curve of the monkey eyeball, and had grooves for sutures to fix it on the sclera. The curvature radius was 9 mm, which was close to the axial length of the monkey eyeball. The drug-releasing area was located at one end of the device, and it was placed so that the reservoir reached the posterior site. Figure 2 shows an eye 12 months after implantation. The device was seen under the conjunctiva during the course of the 12-month implantation (Fig. 2A). The device was fixed on the sclera at the implantation site 12 months after implantation and attached firmly to the sclera (Fig. 2B). There was no abnormal finding on the sclera related to long-term implantation after device removal (Fig. 2C).

Intraocular Distribution of UNO

The UNO distribution in the intraocular tissues and plasma was determined by measuring M1 using LC/MS/MS. The Table shows the M1 concentrations of intraocular tissues and plasma. The M1 amount in the aqueous humor was below the lower limit of quantification (<0.05 ng/mL) at 3 and 6 months, and was detected only in one in four samples at 12 months. Similarly, some samples from the vitreous and lens were below the lower limit of quantification, resulting in an M1 amount of less than 1 ng/g. However, M1 in the retina and choroid was detected in all samples during the 12-month implantation. The M1 concentrations reached maximum at 6 months, then decreased to 12 months. The M1 in the iris and ciliary body also was detected in all samples at 3 and 6 months; however, at 12 months, the M1 in some samples was below the detection level, and the average M1 concentration decreased. No M1 was detected in the plasma samples except at 3 months.
Transscleral Unoprostone Delivery in Monkey Eyes

Electroretinography

Figure 3 shows the time course of the photopic ERG spectra and average amplitudes. The spectrum shows that oscillatory potentials were observed clearly in the URD-treated group, like that in the nontreated group. There was no significant difference in amplitude and latent time between the URD- and nontreated groups at all of the different light stimulus intensities. In the scotopic ERG (Fig. 4), there was no significant difference in amplitude and latent time between the URD- and nontreated groups at all of the different light stimulus intensities.

Optical Coherence Tomography

There was no significant difference in the macula thickness in the central subfield (1 mm diameter) between the URD- and nontreated eyes during URD treatment for 12 months (Fig. 5). The average macula thickness was 265.0 ± 13.2 and 266.5 ± 13.9 μm, respectively, at 12 months after implantation (P = 0.881). In addition, the macula thickness did not change before, and 6, 9, and 12 months after URD treatments. Line-scan images showed that there was no abnormality in macular microstructure before and after URD treatment for 12 months.

Intraocular Pressure

Figure 6 shows the IOP during 12 months after URD treatments. There was no significant difference in IOP between the URD- and nontreated eyes during the 12-month implantation. The average IOP was 19.3 ± 1.97 and 19.0 ± 3.39 mm Hg, respectively, at 12 months after implantation (P = 0.878).

Discussion

We demonstrated long-term drug delivery to the retina using a nonbiodegradable polymeric device8 and determined its safety in terms of retinal function and histology. The device was intended to deliver a drug locally to the retina with less systemic circulation.17–19 No significant differences in IOP between the URD- and nontreated eyes, and almost no M1 detection in plasma and anterior chamber indicated that the URD could deliver UNO locally to the retina and choroid with less systemic distribution. Unidirectional release to the scleral side by the drug-permeable cover and impermeable reservoir could contribute to the localized distribution.8,9 Cuppoletti et al.20 reported that half maximal effective concentration (EC50) of UNO for stimulation of big potassium (BK) channel, related to retinal protection by UNO, was 0.6 ± 0.2 nm (0.254 ± 0.084 ng/mL) in a whole cell patch clamp assay. The M1

Table. Intraocular Concentrations of M1 in Tissue and Plasma

<table>
<thead>
<tr>
<th>Tissue/Parameter</th>
<th>3M</th>
<th>6M</th>
<th>12M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous humor, ng/mL</td>
<td>N.D.</td>
<td>N.D.</td>
<td>0.0380 ± 0.0760</td>
</tr>
<tr>
<td>Vitreous, ng/g</td>
<td>0.905 ± 1.35</td>
<td>0.797 ± 0.0756</td>
<td>0.147 ± 0.295</td>
</tr>
<tr>
<td>Retina, ng/g</td>
<td>4.61 ± 7.33</td>
<td>8.41 ± 4.48</td>
<td>4.00 ± 2.36</td>
</tr>
<tr>
<td>Choroid, ng/g</td>
<td>59.5 ± 65.2</td>
<td>243.2 ± 187.1</td>
<td>22.6 ± 6.18</td>
</tr>
<tr>
<td>Lens, ng/g</td>
<td>0.0960 ± 0.192</td>
<td>0.830 ± 1.43</td>
<td>N.D.</td>
</tr>
<tr>
<td>Ciliary body, ng/g</td>
<td>4.92 ± 3.48</td>
<td>7.66 ± 9.38</td>
<td>0.558 ± 0.747</td>
</tr>
<tr>
<td>Iris, ng/g</td>
<td>1.12 ± 0.587</td>
<td>3.12 ± 3.20</td>
<td>10.4 ± 20.3</td>
</tr>
<tr>
<td>Plasma, ng/mL</td>
<td>0.161 ± 0.228</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

The concentrations of M1 in tissue and plasma were measured by LC/MS/MS. The limit of quantification was <0.05 ng/mL for plasma and aqueous humor, <0.5 ng/g at 3M and 6M, and <0.25 ng/g at 12M for tissues. Values are the mean ± SD; n = 4 for 3M and 12M; n = 3 for 6M. M, months; N.D., not detectable.
concentration in the retina ranged from 4.00 ng/g at 12 months to 8.41 ng/g at 6 months, indicating the effective dose could be delivered for 12 months. On the other hand, our previously reported results in rabbits demonstrate that the M1 concentration in the retina ranged from 0.29 ng/g at 12 weeks to 2.86 ng/g at 1 week, which was approximately one-third of the present results. The difference in M1 level in the retina between monkeys and rabbits must be clarified so as to estimate the M1 levels in human ocular tissues for safety assessment. The release rate of UNO in the present study was almost the same as the URD used for humans and reported previously (approximately 10.7 μg/day for 12 months). The area of the drug-releasing surface, volume of the drug, and concentration of the drug were the same as those in URDs used for humans except for the device length (17 mm for monkeys and 19 mm for humans) and curvature radius (9 mm for monkeys and 11 mm for humans). In the case of URDs for rabbits, the size of the device (10 mm long × 3.6 mm wide × 0.7 mm thick) was smaller than that for monkeys (17 mm long × 4.4 mm wide × 1 mm thick) and the release rate (10.2 μg/day for 24 weeks) was slower than that for monkeys (12.2 μg/day for 24 weeks). Also, the physiologic properties, such as molecular permeability through the sclera and RPE, choroidal clearance rate, and retinal surface area, would differ among species. Nilsson et al. reported that the choroidal blood flow rate in rabbits was approximately two times higher than that in monkeys. This indicates that the elimination of drug via choroidal circulation could be larger in rabbits than in monkeys, resulting in less drug transport to the retina in rabbits. Kuhrt et al. reported that the mean retinal surface areas (in mm²) in adult rabbits and monkeys were 520 and 960, respectively. This indicates that the monkey retina could retain

**Figure 3.** Representative photopic ERG spectra (A) before and (B) 6, (C) 9, and (D) 12 months after implantation. The average ERG amplitudes of a- (E–I) and b- (J–N) waves in the groups treated with the URD. URD-treated (blue circles) and nontreated (red triangles) eyes at stimulus intensities of (E, J) 0.950, (F, K) 0.050, (G, L) 0.950, (H, M) 1.477, and (I, N) 2.000 log (cd × seconds/m²). Values are the mean ± SD; n = 4. Pre, before implantation; M, months.
much more drug than the rabbit retina. These findings might cause the difference in M1 level between monkeys and rabbits. In addition, the M1 level showed a maximum peak at 6 months, then decreased. The release rate decreased gradually when the remaining drug in the device decreased by approximately 50%.9 The decrease in the release rate may have caused a decrease of intraocular M1 concentration at 12 months; the similar decrease in M1 concentration was observed in rabbits.9 The peak of M1 level at 6 months might be related to the drug accumulation in tissues. As a separate study, we evaluated the toxicologic study using an URD without a cover as a burst-URD model (Supplementary Fig. S1). We found that there was no toxic effect of the burst-URD on retinal function (Supplementary Fig. S2), while the higher M1 level in the plasma over 3 ng/mL was detected for 4 weeks in burst-URD–treated eyes (Supplementary Fig. S3). Therefore, we concluded that the level of M1 in the choroid and retina at 6 months was under safety range because the M1 level in the plasma at 6 months was below the limit of quantification (0.05 ng/mL). The M1 detected in the iris and ciliary body could result from passage into the bloodstream through the choroid. The lack of M1 detection in the vitreous and lens might be due to the distance from the device and the controlled slower release of drug via the transscleral administration route. Thus, UNO was delivered to the retina at a therapeutic level under safety range for 12 months. Mechanisms of intraocular M1 distribution during long-term transscleral sustained drug delivery remain unknown and should be clarified in the future.

ERG is one method used to evaluate retinal function and toxicity after treatments. In this study, parameters, such as the

**Figure 4.** Representative scotopic ERG spectra (A) before and (B) 6, (C) 9, and (D) 12 months after implantation. The average ERG amplitudes of a- (E–I) and b- (J–N) waves in the groups treated with the URD (blue circles) and nontreated groups (red triangles) at stimulus intensities of (E, J) –2.523, (F, K) –1.523, (G, L) –0.523, (H, M) 0.477, and (I, N) 1.477 log (cd × seconds/m²). Values are the mean ± SD; n = 4. Pre, before implantation; M, months.
amplitudes of a- and b-waves, and implicit times did not differ between the URD- and nontreated eyes during the 12-month implantation. These findings confirmed that sustained transscleral administration of UNO was not toxic to retinal neurons and was biocompatible and safe enough for the delivery of drugs to the posterior segments of eyes. Focal ERG can evaluate localized retinal or macular area functions. There was no significant decrease in ERG amplitudes compared to nontreated eyes, indicating that long-term exposure to drug at local sites around the macula had no toxic effects on macula functions. The safety of long-term URD treatment also was supported by retinal histology and macula thickness as assessed from the OCT examinations. Although many types of transscleral drug delivery devices have been reported, to our knowledge there have been no reports regarding long-term safety assessment and intraocular drug distribution using primates. Furthermore, the ability of up to 1 year's long-term drug delivery shows a clear advantage over the previous reports, such as episcleral films releasing triamcinolone acetonide for 120 days and a capsular device releasing dexamethasone for 60 days.

Some intravitreal implants have been effective and safe for intraocular use. To date, two ocular drug delivery systems, Vitrasert and Retisert, which are intravitreal sustained-release implants of ganciclovir and fluocinolone acetonide, respectively, have been marketed. Although these devices release the drugs at relatively constant rates, they must be implanted surgically and later removed from the vitreous, which may cause complications and/or patient discomfort. The episcleral URD can be implanted and removed almost noninvasively by minor surgery (Supplementary Fig. S4, Supplementary Movie S1). Although scar formation around the device could be seen when the devices were removed at 12 months, the scars were stable and did not affect visual function as demonstrated by the lack of inflammatory cells or neovascularization. In a separate study, we performed URD replacement in the scar pocket where the first URD had already been transplanted for 6 months in rabbit eyes and evaluated the toxic effects for a further 6 months (totally 12 months).
months of implantation) based on Good Laboratory Practice. No toxic effects on retinal function based on ERG and histology, and on the anterior segment based on the scores of ocular irritation and corneal epithelium disorder (data not shown) were detected. Although we must perform the URD-replacement test in monkeys, the results indicated that the URD could be replaced in a safe manner. Studies of long-term transscleral drug delivery to the retina using primates are limited, so our results suggested novel clinical applications for transscleral drug delivery to the monkey and human eye.

A limitation of this study was the lack of a placebo URD group. We reported the pharmacologic effects of a URD in rats7 and rabbits.9 In these experiments, a placebo URD group was included, as well as URD- and nontreated groups. There was no difference in IOP, ERG amplitudes, and histologic evaluations as assessed by hematoxylin and eosin staining and OCT between the placebo URD- and nontreated groups, indicating no side effects of placebo URD treatment on retinal functions and histology. In addition, the reduction in the number of animals used was important. Therefore, we did not include a placebo URD-treated group. For clinical use, we reported the physicochemical properties and 2-year stability of URD for human use.15 In the future, we plan to examine the use of our URD in patients with RP.

In conclusion, the URD was an effective carrier for intraocular sustained delivery of UNO without producing severe retinal toxicity for 12 months. Some intravitreal implants have been effective and safe for intraocular use. However, they require replacement with new implants when the drug is depleted. The surgery to remove and replace the implant might be invasive and damaging to intraocular tissues. However, our episcleral URD is replaced easily with only minor surgery and is less invasive to intraocular tissue. Therefore, the transscleral drug delivery system, URD, could be a promising device for long-term treatment of posterior segment eye diseases.

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References


FIGURE 7. Average focal ERG amplitudes of a- (A, B) and b- (C, D) waves in the groups treated with the URD (blue) and nontreated groups (red) at (A, C) 9 and (B, D) 12 months after implantation. The macula was stimulated with 5° (5°M), 10° (10°M), and 15° (15°M) stimulus spots, and the upper temporal (15°UT), lower temporal (15°LT), upper nasal (15°UN), and lower nasal (15°LN) sites were stimulated with 15° stimulus spots. Values are the mean ± SD; n = 4. M, months.
Transscleral Unoprostone Delivery in Monkey Eyes


