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Latanoprost-Eluting Contact Lenses in Glaucomatous Monkeys

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Purpose: To assess the ability of latanoprost-eluting contact lenses to lower the intraocular pressure (IOP) of glaucomatous eyes of cynomolgus monkeys.

Design: Preclinical efficacy study of 3 treatment arms in a crossover design.

Participants: Female cynomolgus monkeys with glaucoma induced in 1 eye by repeated argon laser trabeculoplasty.

Methods: Latanoprost-eluting low-dose contact lenses (CL_{LO}) and high-dose contact lenses (CL_{HI}) were produced by encapsulating a thin latanoprost-polymer film within the periphery of a methafilcon hydrogel, which was lathed into a contact lens. We assessed the IOP-lowering effect of CL_{LO}, CL_{HI}, or daily latanoprost ophthalmic solution in the same monkeys. Each monkey consecutively received 1 week of continuous-wear CL_{LO}, 3 weeks without treatment, 5 days of latanoprost drops, 3 weeks without treatment, and 1 week of continuous-wear CL_{HI}. On 2 consecutive days before initiation of each study arm, the IOP was measured hourly over 7 consecutive hours to establish the baseline IOP. Two-tailed Student *t* tests and repeated-measures analysis of variance were used for statistical analysis.

Main Outcome Measures: Intraocular pressure.

Results: Latanoprost ophthalmic solution resulted in IOP reduction of 5.4±1.0 mmHg on day 3 and peak IOP reduction of 6.6±1.3 mmHg on day 5. The CL_{LO} reduced IOP by 6.3±1.0, 6.7±0.3, and 6.7±0.3 mmHg on days 3, 5, and 8, respectively. The CL_{HI} lowered IOP by 10.5±1.4, 11.1±4.0, and 10.0±2.5 mmHg on days 3, 5, and 8, respectively. For the CL_{LO} and CL_{HI}, the IOP was statistically significantly reduced compared with the untreated baseline at most time points measured. The CL_{HI} demonstrated greater IOP reduction than latanoprost ophthalmic solution on day 3 ($P = 0.001$) and day 5 ($P = 0.015$), and at several time points on day 8 ($P < 0.05$).

Conclusions: Sustained delivery of latanoprost by contact lenses is at least as effective as delivery with daily latanoprost ophthalmic solution. More research is needed to determine the optimal continuous-release dose that would be well tolerated and maximally effective. Contact lens drug delivery may become an option for the treatment of glaucoma and a platform for ocular drug delivery. *Ophthalmology 2016;123:2085-2092 © 2016 by the American Academy of Ophthalmology.*

The first line of treatment for glaucoma in the United States is typically topical ophthalmic medications (eye drops) intended to reduce intraocular pressure (IOP); these ophthalmic solutions are associated with burning, stinging, and difficulty with self-administration.[1–4] Unfortunately, adherence with glaucoma eye drops is poor, and patients with lower adherence rates have worse outcomes.[5,6] Therefore, improving patient adherence with glaucoma medications has been described as a top public health priority.[7,8] Providing an effective method of sustained drug delivery has been identified as a major unmet need for the treatment of glaucoma.[7]

Since the introduction of contact lenses more than 50 years ago, they have been proposed as a method of ocular drug delivery. Historically, providing controlled and sustained drug release from a contact lens has proven problematic.[9,10] We have developed a drug-eluting contact lens that demonstrated the ability to provide sustained release of latanoprost, a prostaglandin analog glaucoma medication, for 1 month in rabbits.[11] As measured by aqueous humor drug concentrations, the latanoprost-eluting contact lenses delivered approximately the same amount of medication over the course of a day as a daily drop of 0.005% latanoprost solution. However, that study could not demonstrate whether the contact lenses could effectively lower IOP because latanoprost does not have that effect in rabbits.[12,13] It was particularly important to provide direct proof of the efficacy of the drug-eluting lens because its drug-release kinetics differed from that of drops and the effect of drug release kinetics on efficacy is not clear. Latanoprost ophthalmic solution demonstrated a large initial bolus followed by rapidly decreasing drug levels over 12 hours.[11] In contrast, the latanoprost-eluting contact lenses demonstrated an initial burst on day 1 followed by a sustained daily rate of delivery over the course of a month.[11] We examined the efficacy of sustained latanoprost delivery from drug-eluting contact lenses in glaucomatous cynomolgus monkeys.

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Methods

High molecular weight (119 kDa) 50:50 poly(lactic-co-glycolic) acid (PLGA; 50 glycolide: 50 L-Lactide) was obtained from DURECT Corporation (Birmingham, AL). Irgacure 2959 was purchased from Ciba Specialty Chemicals Corporation (Tarrytown, NY). For incorporation into the contact lenses, latanoprost was obtained in methyl acetate (10 mg/ml, Cayman Chemical, Ann Arbor, MI). Commercially available latanoprost aqueous solution (50 μg/ml) with benzalkonium preservatives was obtained from Sandoz Inc. (Princeton, NJ). Unpolymerized methafilcon was purchased in liquid form from Kontur Kontact Lens Company (Hercules, CA). Ethyl acetate and all the other reagents were purchased from Sigma Aldrich (St. Louis, MO). Phosphate-buffered saline (PBS, pH 7.4) was obtained from Invitrogen (Carlsbad, CA). Biopsy punches (2 mm and 3 mm) were obtained from Sklar Instruments (West Chester, PA).

Animals

The study protocol was approved by the Institutional Animal Care and Utilization Committee of The Icahn School of Medicine at Mount Sinai (New York, NY). All animals were treated according to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research (Association for Research in Vision and Ophthalmology Handbook, 1993). Four adult female cynomolgus monkeys, each weighing 3 to 5 kg, were included in this study. In 1 eye, elevated IOP and glaucoma had been previously induced by photocoagulation of the midtrabecular meshwork with an argon laser (65–120 spots, power 1.1–1.5 W, size 50 μm, duration 0.5 seconds) or diode laser (50–120 spots, power 1.2 W, size 75 μm, duration 0.5 seconds).[9,11,14] The contralateral eye remained untreated. Only the glaucomatous eye of each animal was studied.

Contact Lens Retention Study

To determine the shape of the contact lens that would be able to be worn on the glaucomatous eyes of monkeys, contact lenses were fabricated with a combination of back radius of curvatures (base curves) and diameters (Table 1) based on prior reports of the ocular dimensions of cynomolgus monkeys.[15,16] Contact lenses were lathed from cylinders of methafilicon, a co-polymer of poly(hydroxyethylmethacrylate) and methacrylic acid, which is one of the hydrogels that is approved for use as a contact lens in the United States and internationally; this hydrogel contains 55% water when hydrated. The trial set of contact lenses was composed of only methafilcon and lacked a drug-polymer film.

Before the initiation of the study to determine the best fit of lenses in the monkeys, the baseline IOP of their right glaucomatous eye was measured at 9:30AM on 2 consecutive days under anesthesia (ketamine hydrochloride 2–5 mg/kg of body weight administered intramuscularly). They were examined by slit-lamp biomicroscopy, and the corneal diameter was measured with vernier calipers. A contact lens was placed on the right glaucomatous eye and observed for proper fit while the animals were anesthetized. Once the monkeys recovered from anesthesia, they were observed for signs of discomfort, such as blepharospasm or eye rubbing. On day 3, the animals were anesthetized and the eyes underwent slit-lamp examination without removal of the contact lenses. On day 5, the contact lenses that remained in place were removed, and the eyes were examined with fluorescein to evaluate the corneal surface.

Table 1. Contact Lens Trial Set Parameters

Base Curve	Diameter
6.3	11.8
	12.5
	13.0
6.5	11.8
	12.5
	13.0
6.8	11.8
	12.5
	13.0

A contact lens trial set was manufactured with 3 different base curves, each with 3 different diameters. The lens underlined in bold was retained for 5 days and was therefore used in studies of drug effect.

Fabrication of Latanoprost-Eluting Contact Lenses

Pharmaceutical-grade latanoprost was supplied within a methyl acetate solution (10 mg/ml, Cayman Chemical). A total of 400 μl of the latanoprost solution and Good Manufacturing Practice–grade PLGA (60 mg, 50:50; DURECT corporation) were added to 600 μl of ethyl acetate. A total of 30 μl of the combined solution was then pipetted onto a concavity that had been lathed into a cylinder of dry polymerized methafilcon (Kontur Kontact Lens Company). A total of 40 μl of the drug-polymer solution was used to create a film with greater drug loading. After rotation on a spin coater (Model SC100B, Best Tools, LLC, St. Louis, MO) for 6 minutes, the ethyl acetate evaporated and only a drug-polymer film remained. A central aperture was cut from the film using a 3-mm biopsy punch for films created from the 30-μl drug-polymer solution (low-dose contact lenses [CL_{LO}]) and a 2-mm biopsy punch for films created from 40 μl of solution (high-dose contact lenses [CL_{HI}]) (Table 2). After desiccation for 1 day and lyophilization for 1 day, the drug-polymer film was encapsulated in methafilcon by ultraviolet photopolymerization (400 W metal halide bulb, Loctite Corporation, Rocky Hill, CT) to recreate a hydrogel cylinder. The methafilcon block was then lathed into a contact lens that consisted of the drug-PLGA film fully encapsulated in methafilcon. To remove any surface excipients, the contact lenses were placed in 5 ml sterile PBS solution and rotated at approximately 64 rpm at 37°C for 2 hours. The lenses were removed from PBS, dried at room temperature, and stored in airtight glass vials sealed with a sealed plastic screw top. Finally, the glass containers holding the lenses were placed in a temperature-controlled container and terminally sterilized by irradiation in a Gamma Cell 220E Cobalt 60 Irradiation Unit (Atomic Energy of Canada Ltd., Ottawa, Canada) with a total dose administration of 25 kGy.

Optical Coherence Topography of Contact Lenses

The morphologies of the contact lenses containing the drug-polymer films were imaged using anterior segment optical coherence tomography (OCT) (RTVue, Optovue, Fremont, CA). Dry contact lenses were positioned with the convex side of the lens facing the OCT camera. Raster scanning imaging was used in 4 segments for each contact lens to obtain cross-sectional images of