Pharmacokinetics and Pharmacodynamics of a Sustained-Release Dexamethasone Intravitreal Implant

Joan-En Chang-Lin,1 Mayssa Attar,1 Andrew A. Acheampong,1 Michael R. Robinson,1 Scott M. Whitcup,1 Baruch D. Kuppermann,2 and Devin Welty1

PURPOSE. To determine the pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone (DEX) intravitreal implant (Ozurdex; Allergan, Inc.).

METHODS. Thirty-four male monkeys (Macaca fascicularis) received bilateral 0.7-mg DEX implants. Blood, vitreous humor, and retina samples were collected at predetermined intervals up to 270 days after administration. DEX was quantified by liquid chromatography–tandem mass spectrometry, and cytochrome P450 3A8 (CYP3A48) gene expression was analyzed by real-time reverse transcription-polymerase chain reaction.

RESULTS. DEX was detected in the retina and vitreous humor for 6 months, with peak concentrations during the first 2 months. After 6 months, DEX was below the limit of quantitation. The Cmax (Tmax) and AUC for the retina were 1110 ng/g (day 60) and 47,200 ng · d/g, and for the vitreous humor were 213 ng/mL (day 60) and 11,300 ng · d/mL, respectively. The Cmax (Tmax) of DEX in plasma was 1.11 ng/mL (day 60). Compared with the level in the control eyes (no DEX implant), CYP3A48 expression in the retina was upregulated threefold up to 6 months after injection of the implant (0.969 ± 0.0565 vs. 3.07 ± 0.438; P < 0.05 up to 2-month samples).

CONCLUSIONS. The in vivo release profile of the DEX implant in an animal eye was similar to the pharmacokinetics achieved with pulse administration of corticosteroids (high initial drug concentration, followed by a prolonged period of low concentration). These results are consistent with those in clinical studies supporting the use of the DEX implant for the extended management of posterior segment diseases. (Invest Ophthalmol Vis Sci. 2011;52:80–86) DOI:10.1167/iovs.10-5285

The synthetic glucocorticoid, dexamethasone (DEX), is widely used for the treatment of serious inflammatory diseases, such as systemic lupus erythematosus,1 allograft rejection,2 and cerebral edema.3 More recently, DEX has been used for the treatment of retinal diseases such as macular edema.4 Topical and systemic deliveries of DEX are relatively ineffective for treatment of ocular disease because the high concentrations of drug needed to deliver adequate quantities across the tight cellular junctions at the ocular surface or through the blood-retinal barrier can cause significant toxicity.4–6 Therefore, direct intravitreal injection is the most widely used route of administration.4,7,8 The disadvantage of this mode of administration is the need for frequent injections, as DEX is a small molecule that is rapidly cleared from the vitreous, with an estimated vitreal half-life of 5.5 hours in humans.9 To overcome this limitation, sustained-release preparations for intravitreal use are being developed and evaluated.4,8,10–16

The DEX implant (Ozurdex; Allergan, Inc., Irvine, CA) is a novel approach approved by the United States Food and Drug Administration (FDA) for the intravitreal treatment of macular edema after branch or central retinal vein occlusion and for the treatment of noninfectious uveitis affecting the posterior segment of the eye.17 Key features of the drug delivery system are the sustained-release formulation of the poly(lactic acid-co-glycolic acid) (PLGA) matrix material, which dissolves completely in vivo, and the single-use applicator for intravitreal placement.18 Findings in clinical trials of patients with persistent macular edema have shown the DEX implant to be effective and well tolerated, with improvements in visual acuity that increase up to 60 days and persist for up to 180 days after administration.19–21 However, there is a paucity of published data to confirm the sustained-release profile of the DEX implant in vivo and explain the long-term biological responses that are observed after administration.

In this study, we assessed the pharmacokinetics of the DEX implant for 9 months after administration. The pharmacodynamics of the drug released from the implant was assessed by using expression of the DEX-sensitive gene cytochrome P450 A38 (CYP3A48) as a marker of biological activity.22

METHODS

Animal Model and Study Design

This study complied with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and was conducted in accordance with the FDA Good Laboratory Practice Regulations and the Animal Welfare Act. Young adult, male cynomolgus monkeys (Macaca fascicularis; n = 37) weighing 2.2 to 3.1 kg from Covance Research Products Inc. (Alice, TX) and the Covance Laboratories Inc. (Madison, WI) stock colonies were provided with food (Global Animal Diet; Harlan Teklad, Inc., Madison, WI) supplemented with appropriate fruits and fresh water ad libitum. Animal health was monitored by clinical observations and ophthalmic examinations.

The monkeys were assigned to four groups for pharmacokinetic and genetic analyses with at least one animal per time point for each group. On day 0, 34 monkeys received a 0.7-mg DEX implant in each eye, and 3 monkeys remained without the implant as control subjects. Tissue samples were collected after the monkeys were euthanatized on days 7, 30, 60, 90, 120, 150, 180, 210, 240, and 270. For eyes that received an implant, at each time point, blood, vitreous humor (6 eyes per time point, except 14 eyes at day 270), and retina (4 eyes per time point, except 8 eyes at day 270) samples were collected for pharma-
cokinetic analyses, and retina samples (2 eyes per time point, except 6 eyes at day 270) were collected for gene expression analyses. Retina samples (6 eyes) were collected from eyes of the control monkeys.

A Comparative Ophthalmic Research Laboratory board-certified veterinary ophthalmologist conducted external and internal ophthalmic examinations before intravitreal administration, immediately after administration, and before euthanatization. The adnexa and anterior portion of each eye were examined using slit lamp biomicroscopy, and the ocular fundus was examined with an indirect ophthalmoscope. Ophthalmic examinations and color fundus photography (TRC-50EX; Topcon, Tokyo, Japan) were conducted on day 1 or 2 after intravitreal administration and before euthanatization, to document the implant position.

**Intravitreal Administration Procedure**

Fasted monkeys were lightly anesthetized with an intramuscular injection of ketamine hydrochloride (10 mg/kg; Ketaset; Fort Dodge Animal Health, Fort Dodge, IA) followed by desmethyl metabolite hydrochloride (0.025 mg/kg; Dexamethasone; Orion Pharma, Orion Corp., Espoo, Finland). The eyes were prepared for administration of the DEX implant, with iodine solutions (2.5%)—povidone (Triad Disposables, Hartland, WI) or povidone iodine (Betadine; Purdue Products LP, Stamford, CT)—and 0.9% sodium chloride for the injection and preoperative hydrochloride 0.5% ophthalic drops (Falcon Pharmaceuticals, Ltd., Fort Worth, TX, and Bausch and Lomb, Inc., Tampa, FL).

A 22-gauge needle of a preloaded DEX implant applicator was introduced through the dorsotemporal quadrant of each eye, approximaterly 3- to 5-mm posterior to the limbus (through the pars plana). The implant was deployed just behind the ciliary body in the superior pars plana. The orientation of the implant was determined after surgery and at necropsy.

**Tissue Collection and Handling**

After blood collection by cardiac puncture under pentobarbital sodium anesthesia (Eutha-6; Western Medical Supply, Arcadia, CA), the animals were euthanatized via an overdose of intravenous pentobarbital sodium. Blood, collected into tubes containing K$_2$ EDTA, was centrifuged to obtain plasma before freezing. The position of the implant was documented, and a suture was placed at the 12 o’clock position through the bulbar conjunctiva to ensure that each eye was oriented appropriately during dissection. Both globes were enucleated and cleaned of extraocular muscle tissue before they were snap-frozen in liquid nitrogen. After the cornea, iris, ciliary body, and lens were excised, the vitreous humor was collected. As the implant was difficult to separate from the vitreous humor, the globes were bisected transversely into two hemispheres with and without the DEX implant. The eye was oriented so that the hemisphere containing the remnant was collected in a consistent manner. Care was taken to ensure that the hemisphere without the implant not be contaminated with implant remnants during dissection, and instruments were cleaned between samples to ensure that there was no cross contamination. The retina was dissected from both hemispheres (i.e., with and without the implant) and analyzed separately. Samples were stored at or below -70°C until analyzed.

**Pharmacokinetic Analysis**

**Ocular Tissue and Plasma Sample Preparation and Analysis.** The concentration of DEX in the total retina (in nanograms/gram) was calculated by dividing the total amount of DEX from retinal samples dissected from both hemispheres by the total tissue weight. The concentration of DEX was analyzed and reported separately for the vitreous humor from each of the dissected hemispheres (i.e., with and without the implant).

Liquid-liquid extraction was used to extract DEX from the samples. Beclomethasone was used as the internal standard for the assay of vitreous humor and retina samples with high DEX concentrations, and tetradeteruterated dexamethasone (DEX-d4) was used as the internal standard for the assay of samples with low DEX concentrations. The organic solvents used for extraction were methyl tert-butyl ether for vitreous humor, 95% methanol and 5% water for retina, and ethyl acetate for plasma. For sample preparation, internal standard and organic solvent were added to vitreous and plasma samples, the mixture was centrifuged, and the organic layer was transferred to another tube and dried. Retina samples were soaked overnight in 95% methanol and 5% water for 24 hours at 4°C. After the 24-hour incubation, the supernatant was transferred to another tube; the internal standard was added; and the mixture was dried. Dried residues from the vitreous and retina extractions were reconstituted with 70% methanol and 30% water with 0.1% acetic acid (internal standard, beclomethasone) or 40% acetonitrile and 60% water containing 0.2% formic acid and 2 mM ammonium formate (internal standard, DEX-d4) for liquid chromatography-tandem mass spectrometry (LC/MS/MS) injections. The dried residues from the plasma extraction were reconstituted with 40% methanol and 60% water containing 0.2% formic acid and 2 mM ammonium formate.

DEX concentrations were determined by LC/MS/MS using triplicate quadrupole mass spectrometers (models API 3000 and API 5000; Applied Biosystems [ABI]/Sciex, Concord, ON, Canada, for high and low concentrations, respectively). The mass spectrometers were interfaced with an HPLC system (Shimadzu, Columbia, MD) and an autosampler (Leap Technologies, Carboro, NC). HPLC for vitreous and retina samples containing the internal standard beclomethasone was performed on a C18 column (3.9 × 150 mm, 4 μm; Novapak; Waters Corp., Milford, MA) using 85% methanol and 15% water with 0.1% acetic acid as the mobile phase at a flow rate of 0.8 mL/min. HPLC for vitreous and retina samples containing DEX-d4 was performed on another column (2.1 × 100 mm, 5 μm; Zorbax Eclipse XDB-C18; Agilent Technologies, Inc., Santa Clara, CA), using gradient elution with 0.2% formic acid and 2 mM ammonium formate in both solvent A (water) and solvent B (acetonitrile) at a flow rate of 0.25 mL/min. HPLC for the plasma sample analysis was performed on another C18 column (2.1 × 50 mm, 5 μm; Zorbax Eclipse XDB-C18; Agilent Technologies, Inc., Santa Clara, CA), using gradient elution with 0.2% formic acid and 2 mM ammonium formate in both solvent A (water) and solvent B (methanol) at a flow rate of 0.25 mL/min. Mass spectrometric detection was accomplished by using positive ionization with either ESI or APCI (heated nebulizer) sources and scanning in the multiple reaction monitoring mode. The specific precursor product ion pairs used were m/z 393→m/z 373 (DEX), m/z 397→m/z 377 (DEX-d4), and m/z 409→m/z 391 (beclomethasone). The LC/MS/MS retention time was approximately 1.5 minutes for DEX and beclomethasone (model API 3000) and approximately 2.5 minutes for DEX and DEX-d4 (model API 5000; both ABI/Sciex).

The vitreous, retina, and plasma assays were validated according to industry standards. The methods showed acceptable accuracy and precision for quality-control samples, with precision less than 15% and accuracy within ±15% of the nominal value. Assay linearity was demonstrated over the concentration ranges of 0.001 to 1.00 ng/mL (low DEX concentrations) and 500 to 750,000 ng/mL (high DEX concentrations) for vitreous humor, 0.001 to 1.00 ng/retina (low DEX concentrations) and 0.100 to 100 ng/retina (high DEX concentrations) for retina, and 0.200 to 20.0 ng/mL for plasma.

**Data Analysis.** Pharmacokinetic data analysis was conducted by using noncompartmental methods (Laboratory Information System, ver. 7.3; Watson, Waltham, MA). The maximum mean concentration (C$_{max}$), the time to reach maximum concentration (T$_{max}$), mean concentration at the last detectable time (C$_{LDT}$), and the time to reach the last detectable concentration (T$_{LDT}$) were determined by visual inspection of the data. All area under the curve (AUC) calculations were based on the area of the last observable concentration (AUC$_{0→T_{obs}}$) and were calculated using the log-linear trapezoidal method.

**Gene Expression Analysis**

**Ocular Tissue Sample Preparation and Analysis.** Total RNA was isolated and purified from retina samples (RNeasy Mini Kit;
Table 1. Primers and probes used for real-time reverse transcriptase polymerase chain reaction

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer and Probe Sequences</th>
<th>GenBank Accession Number</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A8</td>
<td>F: 5'-ACACCGATGTTCTTCTCTGTTATAT-3'</td>
<td>S55047</td>
<td>Uno et al.22</td>
</tr>
<tr>
<td></td>
<td>R: 5'-TTGTTGCTTTGTTGTTTGAATCTGTA-3'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 5'-ATGTCAGGAAACT-3'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td>F: 5'-CAACTGGGACGACATGGAGAA-3'</td>
<td>DQ464112</td>
<td>Wood et al.25</td>
</tr>
<tr>
<td></td>
<td>R: 5'-GCCACACGACGTCTATTGTA-3'</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P: 5'-ATCCTGACAGACACACT-3'</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, forward primer; R, reverse primer; P, probe.

Pharmacokinetic Profile

DEX concentrations in the retina were characterized by two distinct phases (Fig. 2), which corresponded to the observed fragmentation of the implant. From days 7 to 60, high concentrations of DEX were present, with a C_{max} of 1110 ± 284 ng/g recorded on day 60 (T_{max}; Table 2). From days 90 to 210, low concentrations of DEX were present: C_{last} was 0.0167 ± 0.0193 ng/g at day 210 (T_{last}) with an AUC_{0-Tlast} of 47,200 ± 4,900 ng·d/g. From day 240 to 270, DEX was below the limit of quantitation (0.001 ng/retina).

DEX concentrations in the vitreous humor (with and without the implant) were also characterized by two distinct phases (Fig. 2). For the vitreous humor without the implant (soluble drug released from the implant), from days 7 to 60, high concentrations of DEX were detected, with the mean peak DEX concentration (C_{max} = 213 ± 49 ng/mL) recorded at day 60 (T_{max}; Table 2). At days 90 to 180, DEX release was sustained at low concentrations, decreasing to 0.00131 ± 0.00194 ng/mL (C_{last}) at day 180 (T_{last}). From days 210 to 270, DEX was below the limit of quantitation (0.001 ng/mL). The AUC_{0-Tlast} was 11,300 ± 1,500 ng·d/mL.

DEX was present at low concentrations in plasma (Fig. 2). Although the concentration had decreased from 0.585 ± 0.115 ng/mL on day 7 to 0.380 ± 0.042 ng/mL on day 30, the C_{max} was 1.11 ± 0.11 ng/mL on day 60 (T_{max}; Table 2). From day 90, DEX was below the limit of quantitation (0.200 ng/mL).

Pharmacodynamic Profile

In the eyes that received the DEX implant, the pattern of CYP3A4 expression in the retina paralleled the concentrations of DEX in the retina (Fig. 3). Compared with CYP3A4 expression in the control eyes (mean relative quantity = 0.969 ± 0.0565), CYP3A4 expression in the eyes that received the implant increased more than threefold (3.07 ± 0.438; P < 0.05) in the high-DEX group (i.e., day 7–60), remained high (2.88 ± 0.328; not significant) in the low-DEX group (i.e., day 90–210), and decreased to control levels (0.933 ± 0.0783; not...
The sustained targeted delivery of DEX was supported by the release of DEX, extending the therapeutic period to 6 months. The first phase provided high concentrations of DEX followed by a second phase in which low concentrations of DEX were released, extending the therapeutic period to 6 months. Compared with conventional drug delivery strategies, these data provide a sound rationale for the use of the DEX implant for the chronic treatment of posterior segment eye disease, such as macular edema.

**DISCUSSION**

This study demonstrates targeted delivery of DEX in the retina and vitreous with two phases of drug release after implant administration. The first phase provided high concentrations of DEX followed by a second phase in which low concentrations of DEX were released, extending the therapeutic period to 6 months. The sustained targeted delivery of DEX was supported by the increased expression of CYP3A48 (a marker of DEX biological activity) in the retina, which was maintained for 6 months. Compared with conventional drug delivery strategies, these data provide a sound rationale for the use of the DEX implant for the chronic treatment of posterior segment eye disease, such as macular edema.

In our study, DEX concentrations in the retina and vitreous humor reached a plateau within days of administration and were maintained at high levels for 2 months before declining over subsequent months. The considerable variation in the concentration of DEX at various time points is unlikely to be a result of variation between animals and was most likely due to the distribution of small implant remnants in the no-implant fractions or a small remnant in the retinal tissue in some samples. Although biodegradable implants generally undergo a triphasic drug release pattern, characterized by an initial drug burst, sustained release, and final drug burst, variation in the degradation rates and drug release kinetics can be achieved by modification of the physicochemical properties of the implant matrices. In this study, the maximum concentrations of DEX in the retina and vitreous were observed at day 60, when most of the DEX implant had fragmented. After day 60, the remaining implant fragments continued to degrade to the base constituents, slowly releasing DEX from the remnant material, without a final drug burst. Although this study was conducted in monkey eyes, the steady state concentrations of DEX achieved in the monkey eye are expected to be similar to those in humans and compare well with the sustained therapeutic benefit of the DEX implant that has been observed in human eyes. In clinical studies of patients with macular edema, significant and continued improvement in mean visual acuity was observed for up to 60 to 90 days and was sustained for up to 180 days after administration of the DEX implant. In addition, the low rate of adverse events in this study confirm the favorable safety and tolerability profile of the DEX implant after administration in human eyes.

The pharmacokinetic drug profile of the DEX implant in this study is similar to the pharmacokinetics achieved with pulse administration of systemic corticosteroids, during which a short, initial, high-dose period (e.g., with intravenous methylprednisolone) is followed by a longer, low-dose period (e.g., with oral prednisone). The high concentrations of corticosteroid that are achieved in serum after pulse administration have been shown to exert immunologic effects, such as T-cell apoptosis. These immunologic effects are thought to account for the prolonged immunosuppression that is observed with pulse application compared with low-dose therapy. The concentrations of DEX in the retina during the first 2 months after implantation in this study were within the equivalent

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**Table 2. Pharmacokinetic Parameters of DEX in the Vitreous Humor, Retina, and Plasma after Intravitreal Administration of the 0.7 mg DEX Implant in Test Animal Eyes**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vitreous Humor</th>
<th>Retina</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>213 ± 49 ng/mL</td>
<td>1110 ± 284 ng/g</td>
<td>1.11 ± 0.11 ng/mL</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>60 d</td>
<td>60 d</td>
<td>60 d</td>
</tr>
<tr>
<td>$C_{\text{last}}$</td>
<td>0.00131 ± 0.00194 ng/mL</td>
<td>0.0167 ± 0.0193 ng/g</td>
<td>0.11 ± 0.11 ng/mL</td>
</tr>
<tr>
<td>$T_{\text{last}}$</td>
<td>180 d</td>
<td>210 d</td>
<td>60 d</td>
</tr>
<tr>
<td>AUC$_{0-\text{last}}$</td>
<td>11,300 ± 1,500 ng · d/mL</td>
<td>47,200 ± 4,900 ng · d/g</td>
<td>33.4 ± 1.4 ng · d/mL</td>
</tr>
<tr>
<td>AUC interval</td>
<td>0–180 days</td>
<td>0–210 d</td>
<td>0–60 d</td>
</tr>
</tbody>
</table>

Data are the mean ± SD for $C_{\text{max}}$ and the mean ± SEM for AUC$_{0-\text{last}}$.
concentration range that has been estimated to be required to induce T-cell apoptosis after pulse administration of intravenous methylprednisolone. This finding suggests that the DEX implant may benefit patients with retinal diseases, such as uveitis, in which T cells play a central role in pathogenesis.

To our knowledge, this is the first study to describe basal gene expression of CYP3A8 in monkey retina. Consistent with sustained DEX concentrations in the retina, DEX biological activity in the retina, as measured by CYP3A8 expression, was maintained for 6 months. After 6 months, when DEX concentrations decreased below the limit of detection, CYP3A8 expression decreased to control levels. DEX has been shown to increase the expression of CYP3A8 in hepatocytes in a concentration-dependent manner and, when applied topically as an ophthalmic treatment, to increase the expression of CYP3A8 in the lacrimal glands. Given the importance of the CYP3A subfamily of enzymes in the oxidative metabolism of drugs in monkeys and humans, it is possible that an increase in CYP3A8 expression has the potential to offset the biological activity of DEX. Although we found no evidence of such an effect in this study, inclusion of a sham control arm such an effect in this study, inclusion of a sham control arm would be expected to achieve subtherapeutic levels of DEX that may or may not be sustained over several months.

In conclusion, the DEX implant resulted in sustained levels of DEX in both the vitreous and the retina in this study suggest that other routes of administration would be expected to achieve subtherapeutic levels of DEX that may or may not be sustained over several months.

In addition to the DEX implant, a nonbiodegradable, fluocinolone acetonide (FA) implant, Retisert (Control Delivery Systems, Watertown, MA), is FDA approved for human use, and a variety of other biodegradable, slow-release drug delivery systems are currently being evaluated. Although DEX and FA implants have similar drug loads, administration of the DEX implant resulted in initial intravitreal concentrations that were up to five times higher than those reported for the FA implant (100 to 200 ng/mL vs. 17 ng/mL, respectively), which is comparable to the concentrations achieved with DEX-loaded poly(e-caprolactone) (PCL) intravitreal implants and intravitreally administered PLGA nanoparticles. Both PCL implants and PLGA nanoparticles have been shown to provide sustained release of DEX into the vitreous at therapeutic levels (0.15 – 4 μg/mL) over approximately 50 days. Given that DEX and FA have similar potency, the higher concentrations of DEX with these biodegradable drug delivery systems are likely to be clinically relevant.

In conclusion, the DEX implant resulted in sustained levels of DEX and biological activity for 6 months, with peak levels of drug over the first 2 months. This drug-release profile is consistent with the need for frequent intravitreal injections for the treatment of chronic conditions. Although the concentration of DEX was lower in the vitreous than is achieved immediately after a standard 0.4-mg intravitreal dose in humans (~100,000 ng/mL assuming a 4-mL vitreous humor volume), higher concentrations of DEX were sustained in the vitreous for up to 2 months with the DEX implant, compared with a single intravitreal injection (Table 3). Last, our data demonstrated that the sustained-release DEX implant achieves higher and more stable levels of DEX in the vitreous during the initial delivery phase than subconjunctival, topical, or oral administration of DEX in human eyes (Table 3). Given that intravitreal administration is the most direct route for targeted delivery to the retina, the high concentrations of DEX in both the vitreous and the retina in this study suggest that other routes of administration would be expected to achieve subtherapeutic levels of DEX that may or may not be sustained over several months.

**Table 3.** C<sub>max</sub> (ng/mL) of DEX Achieved with the DEX Implant in Test Animal Eyes Compared with Published Data of Other Routes of Administration in Human Eyes

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dose (mg)</th>
<th>Mean C&lt;sub&gt;max&lt;/sub&gt; (min, max)</th>
<th>Time from Last Administration</th>
<th>Mean C&lt;sub&gt;max&lt;/sub&gt; (min, max)</th>
<th>Time from Last Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitreous Humor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Topical ocular</td>
<td>0.55†</td>
<td>1.1 (BLQ, 1.6)</td>
<td>21–128 min</td>
<td>0.7 (BLQ, 1.2)</td>
<td>3–101 min</td>
</tr>
<tr>
<td>Oral</td>
<td>7.50</td>
<td>5.2 (1.7, 25.4)</td>
<td>4–10 h</td>
<td>61.6 (2.5, 98.1)</td>
<td>1–3 h</td>
</tr>
<tr>
<td>Peribulbar</td>
<td>0.50</td>
<td>13 (4.4, 208)</td>
<td>4–8 h</td>
<td>60 (NR)</td>
<td>30 min</td>
</tr>
<tr>
<td>Subconjunctival</td>
<td>2.50</td>
<td>72.5 (NR)</td>
<td>3 h</td>
<td>32.4 (NR)</td>
<td>0 min</td>
</tr>
<tr>
<td>Intravitreal</td>
<td>0.40</td>
<td>67.4 (13.9, 392)</td>
<td>60–73 h</td>
<td>1.11 (0.998, 1.22)‡</td>
<td>7–60 days</td>
</tr>
<tr>
<td>DEX implant</td>
<td>0.70</td>
<td>213 (124, 252)</td>
<td>7–60 days</td>
<td></td>
<td></td>
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<tr>
<td><strong>Plasma</strong></td>
<td></td>
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<td>DEX implant</td>
<td>0.70</td>
<td>213 (124, 252)</td>
<td>7–60 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>7.50</td>
<td>5.2 (1.7, 25.4)</td>
<td>4–10 h</td>
<td>61.6 (2.5, 98.1)</td>
<td>1–3 h</td>
</tr>
<tr>
<td>Peribulbar</td>
<td>0.50</td>
<td>13 (4.4, 208)</td>
<td>4–8 h</td>
<td>60 (NR)</td>
<td>30 min</td>
</tr>
<tr>
<td>Subconjunctival</td>
<td>2.50</td>
<td>72.5 (NR)</td>
<td>3 h</td>
<td>32.4 (NR)</td>
<td>0 min</td>
</tr>
<tr>
<td>Intravitreal</td>
<td>0.40</td>
<td>67.4 (13.9, 392)</td>
<td>60–73 h</td>
<td>1.11 (0.998, 1.22)‡</td>
<td>7–60 days</td>
</tr>
<tr>
<td>DEX implant</td>
<td>0.70</td>
<td>213 (124, 252)</td>
<td>7–60 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BLQ, below the limit of quantitation; ND, not determined; NR, not reported.

† Cumulative dose of 10–11 drops of 0.1% DEX administered over 15 hours.
‡ Dose of DEX 1.40 mg, as the 0.7-mg DEX implant was placed in both eyes.
sistent with clinical studies supporting the use of the DEX implant for the extended management of posterior segment diseases, such as macula edema.8,20

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References


6. Lee V, Pince K, Frambach D, Martini B. Drug delivery to the vitreous humor and retina samples; Mary Ghebrial, Cristina Johnson, and Lisa Borbridge (Allergan, Inc.) for the validation and analysis of the low level retina, vitreous, and plasma samples; Moon Kim (Allergan, Inc.) for technical assistance in the gene expression analysis; and Serina Stretton, PhD (ProScribe Medical Communications) for independent medical writing assistance, funded by Allergan, Inc.


