SAFETY AND PHARMACOKINETICS OF A PRESERVATIVE-FREE TRIAMCINOLONE ACETONIDE FORMULATION FOR INTRAVITREAL ADMINISTRATION

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Purpose: The safety and pharmacokinetics of a triamcinolone acetonide (TA) preservative-free (TA-PF) formulation were investigated after intravitreal administration in rabbits.

Methods: A TA-PF formulation was prepared as a sterile 40-mg/mL or 160-mg/mL suspension in single-use vials by adding TA powder to 0.5% hydroxypropyl methylcellulose in normal saline. TA-PF (4-mg and 16-mg doses) and Kenalog (Bristol-Myers-Squibb, Princeton, NJ) (4-mg dose) were injected into the vitreous of separate groups of rabbits, and drug levels were measured in the vitreous over time with HPLC. Ocular toxicology (clinical examination, serial electroretinography, and histopathologic analysis) was evaluated in a separate group of animals after intravitreal TA-PF injection.

Results: The half-lives of the injection amount in the vitreous, 4-mg TA-PF, 16-mg TA-PF, and 4-mg Kenalog, were found to be 24 days, 39 days, and 23 days, respectively. There were no signs of toxicities by clinical examination after TA-PF injection. Serial electroretinograms of rabbits receiving either 4-mg or 16-mg intravitreal TA-PF injections remained normal over time. Histopathologic analysis showed normal ocular tissues in animals receiving either 4-mg or 16-mg intravitreal TA-PF injections.

Conclusion: The half-life of TA in the vitreous after a 4-mg injection of either TA-PF or Kenalog was comparable. A 16-mg dose of TA-PF produced a long vitreous half-life, and this may be of clinical benefit in patients requiring 6 months of drug exposure in the eye for a chronic disease.

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Intravitreal administration of triamcinolone acetonide (TA) has been widely used for the treatment of eye diseases including diabetic retinopathy,[1,2] uveitis,[3,4] and choroidal neovascularization associated with age-related macular degeneration.[5,6] Kenalog (Bristol-Myers-Squibb, Princeton, NJ) is the most commonly used formulation for intravitreal use; unfortunately, there have been reports of sterile endophthalmitis[7–10] and vision loss thought to be related to the preservative and/or dispersion agent.[11,12] A TA preservative-free (TA-PF) formulation was prepared for use in National Eye Institute clinical trials. We report the results of the safety and pharmacokinetics of intravitreal injection of TA-PF in rabbit eyes.

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Materials and Methods

TA-PF Formulation

TA USP grade (Voight Global Distribution, LLC, Kansas City, MO) was prepared as a sterile 40-mg/mL or 160-mg/mL suspension in single-use vials by the Clinical Center Pharmacy Department at the National Institutes of Health. The suspending medium was normal saline USP (B. Braun Medical, Inc., Irvine, CA). Hydroxypropyl methylcellulose 0.5% USP grade (Dow Chemical Company, Midland, MI) was added to increase the viscosity of the formulation and enable the drug particles to stay in suspension for a minimum of 20 minutes after shaking the vial.

Ocular Pharmacokinetics

New Zealand white rabbits of either sex weighing 2 kg to 3 kg (Covance Laboratories, Inc., Vienna, VA) were used, and all procedures adhered to the guidelines from the Association for Research in Vision and Ophthalmology statement for the use of animals in ophthalmic and vision research. Animals were anesthetized with ketamine hydrochloride ([35 mg/kg] Fort Dodge, Inc., Fort Dodge, IN) intramuscularly and xylazine ([5 mg/kg] Phoenix Scientific, Inc., St. Joseph, MO) intramuscularly; 1% proparacaine ophthalmic drops (Allergan America, Hormigueros, PR) were used topically on the eye. The pupils were dilated with 1 drop each of 2.5% phenylephrine hydrochloride (Akorn, Inc., Decatur, IL) and 1% tropicamide (Alcon, Inc., Humacao, PR). A baseline eye examination including funduscopy with an indirect ophthalmoscope and intraocular pressure measurement were performed. After adequate anesthesia and akinesia were obtained, a lid speculum was placed, and the right eye was injected 4 mm behind the surgical limbus in the superotemporal quadrant with 0.1 mL of either TA-PF (4 mg or 16 mg) or Kenalog (4 mg). Anterior chamber paracentesis was performed to reduce the intraocular pressure in all rabbits. Rabbits receiving 4-mg and 16-mg doses were killed periodically over 4- and 8-month periods, respectively. Killing was performed with an intracardiac pentobarbital overdose (Beuthanasia-D Special; Schering-Plough Animal Health Corp., Kenilworth, NJ), and the right eye was enucleated and immediately frozen at −70°C for later drug extraction. The eyes were dissected while frozen, and the vitreous humor was isolated using previously described methods.[13] The TA was extracted by placing the vitreous in HPLC-grade acetonitrile (Fisher Scientific, Pittsburgh, PA) in sealed vials for 24 hours at room temperature. The contents were sonicated using a GEX 600 Ultrasonic processor (Daigger, Lincolnshire, IL) for 60 seconds and stored in sealed vials for another 24 hours at room temperature. The samples were spun down in a Centra C12 centrifuge (Thermo IEC, Needham Heights, MA) for 3 minutes at 3,500 rpm, and the supernatants were submitted for HPLC. The drug assays were performed using an Agilent HP1100 HPLC system (Agilent Technologies, Palo Alto, CA) equipped with a G1329A autosampler, a G1315A diode array detector, a G1312A binary pump, and a Dell workstation that controlled the operation of HPLC and analyzed the data. A Beckman Ultrasphere C-18 column (5 μm; 4.6 × 250 mm) (Beckman Coulter, Inc., Fullerton, CA) was used for separation, and detection was set at 254 nm. The flow rate used was 1.0 mL/min with a mobile phase of 60% of acetonitrile and 40% of water by volume. The retention time was 7.0 minutes, and the detection limit was 10 ng/mL.

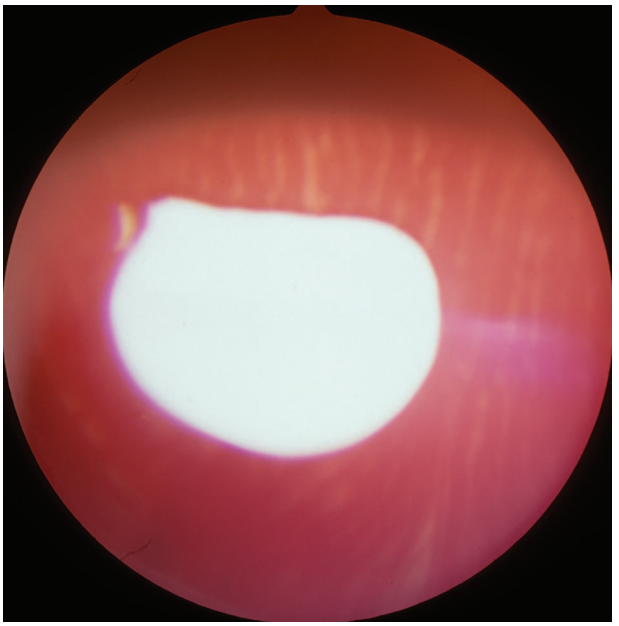

Fig. 1. The white drug depot is present in the vitreous 8 weeks after a 16-mg intravitreal injection of the triamcinolone acetonide preservative-free formulation.

TA injected into the vitreous aggregates to form an intravitreal globular depot (Fig. 1). On the assumptions that the amount of TA in the vitreous outside of the depot is negligible and that the rate of TA elimination from the vitreous at any specific time depends on the remaining amount in the depot, the experimental data were regressed with the following equation:

$$M = M_i \times \mathrm{Exp}(-k_i \times t), \qquad (1)$$

in which t is the time after injection, M represents the remaining amount of TA in the depot, M_i represents the initial injected amount, and k_i is the elimination

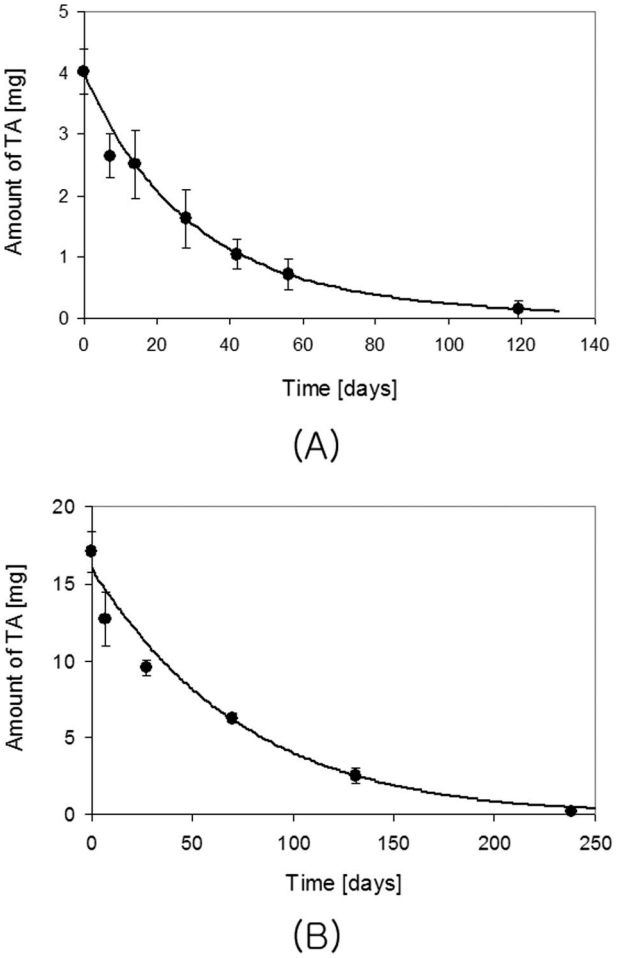

Fig. 2. Amount of triamcinolone acetonide (TA) remaining in the vitreous after intravitreal injection (**A,** 4-mg TA preservative-free [TA-PF] dose; **B,** 16-mg TA-PF dose). Single exponential regression results are represented by the solid lines.

rate constant that depends upon M_i. The elimination rate constants for 4-mg and 16-mg injections, k_4 and k_{16}, respectively, were found by regressing Equation (1) to the animal experimental data from the 4-mg and 16-mg injections using Microsoft Excel.

The elimination rate constants were assumed to be related to the initial amounts by the following relationship (see Appendix):

$$\frac{k_4}{k_{16}} = \left(\frac{M_4}{M_{16}}\right)^{n-1} \quad (2)$$

From the calculated k_4, k_{16}, and doses M_4 (4 mg) and M_{16} (16 mg), a value for n was determined. Equation (2) (see above) permitted estimation of the elimination for other intravitreal TA doses.

Ocular Toxicity

New Zealand white rabbits were anesthetized, and the right eye was injected in the same manner as

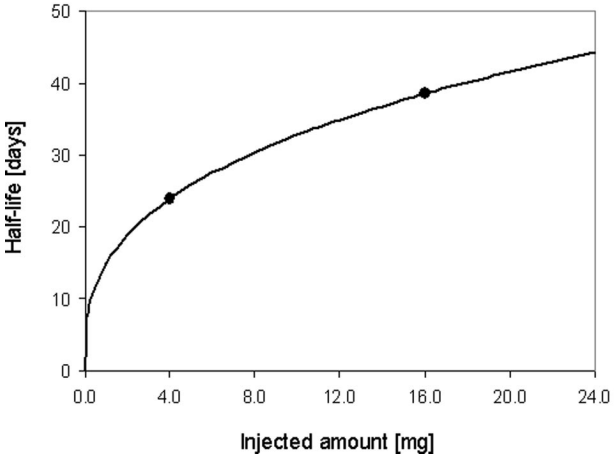

Fig. 3. The relationship between the injected amount of the triamcinolone acetonide preservative-free formulation and the estimated half-life. Measured half-lives of 4-mg and 16-mg doses are shown as dots, and the half-lives of other doses estimated from the pharmacokinetic model are shown as a solid line.

described above with 0.1 mL (4 mg or 16 mg) of TA-PF. Electroretinography (ERG) was performed at baseline (preinjection) and then periodically over 4-month and 7-month periods for the 4-mg and 16-mg doses, respectively. ERG findings were recorded during anesthesia with dilated pupils from each eye separately after 30 minutes of dark adaptation. A monopolar contact lens electrode (ERG-jet, La Chaux des Fonds, Switzerland) was placed on the cornea and served as a positive electrode. Subdermal needle electrodes inserted in the forehead area and near the outer canthus served as the ground and negative electrodes, respectively. ERGs were elicited by flash stimuli delivered with a Grass PS22 photostimulator (Grass Instruments, Quincy, MA) at 0.33 Hz. Responses were amplified, filtered, and averaged with a Nicolet Spirit Signal averager (Nicolet Instruments Corp, Madison, WI). The mean of 20 responses was measured to obtain amplitude values of a waves and b waves. Rabbits were killed, and both eyes were enucleated 2 weeks after the last ERG. Enucleated eyes were fixed in 10% formalin immediately after removal. Paraffin sections through the papillary/optic nerve head axis including the injection sites were stained with hematoxylin–eosin for light microscopic examination.

Statistical Analysis

The mean of the ERG amplitudes for all rabbits at each time point was calculated, and statistical analysis was performed separately for all right (treated) eyes and then all left (untreated) eyes. The differences in the mean ERG amplitudes at each recording from the baseline (preimplant) values were compared and

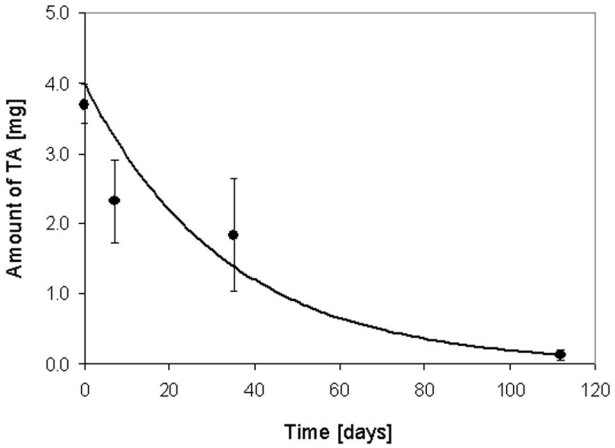

Fig. 4. The amount of triamcinolone acetonide extracted from the vitreous at each time after a 4-mg intravitreal Kenalog (Bristol-Meyers-Squibb, Princeton, NJ) injection is shown as dots, and the single exponential regression result is shown as a solid line.

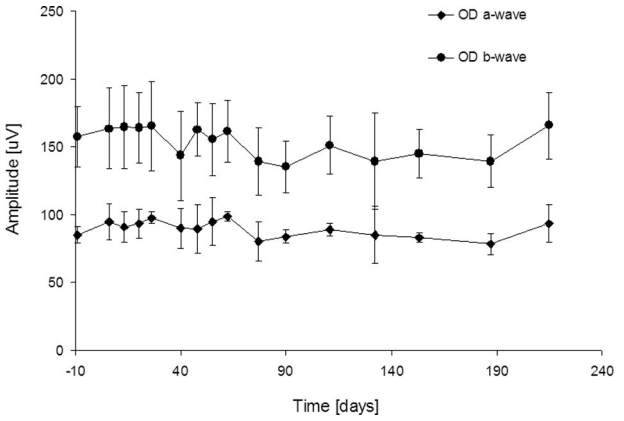

Fig. 5. Serial electroretinography a- and b-wave amplitudes after a 16-mg intravitreal triamcinolone acetonide preservative-free injection in the treated right eye.

tested by analysis of variance using PSI-Plot version 7.0 (Poly Software International, Inc., Pearl River, NY). Differences were considered likely to be clinically significant if $P < 0.05$.

Results

Ocular Pharmacokinetics

A total of 68 rabbits were injected with TA-PF or Kenalog, and 4 rabbits were killed at each time point. There were no detectable levels of TA in the aqueous humor of all rabbits. In the TA-PF groups, the amount of TA extracted from the vitreous at each time point is shown as dots in Figure 2. Both sets of data were regressed with Equation (1), and the results are shown as solid lines in Figure 2. The elimination rate constants for the 4-mg (k_4) and 16-mg (k_{16}) TA-PF injections were found to be 0.029 day^{-1} ($R^2 = 0.99$) and 0.018 day^{-1} ($R^2 = 0.97$), respectively. The relationship between the rate constants for the 4-mg and 16-mg TA-PF injections gives a value of $n = 0.66$ from Equation (2), which Equation (A-6) (see Appendix) indicates is a value consistent with an approximately spherical shape for the globular depot formed by aggregation of the injected particles. Equation (2) was generalized to Equation (3) to predict the rate constant value (k_i in day^{-1}) for any injection amount (M_i in milligrams):

$$k_i = 0.047 \times M_i^{-0.343}. \quad (3)$$

The half-life of each injected amount was calculated with Equation (4),[14] and the relationship between the initial injected amount (in milligrams) and the half-life is shown in Figure 3:

$$\text{half-life (days)} = 0.693/k_i. \quad (4)$$

The experimental data for the 4-mg intravitreal Kenalog injection were analyzed using the same methods as with the TA-PF injections, and k_4 was found to be 0.030 day^{-1} ($R^2 = 0.97$) (Fig. 4). With an assumption that injected TA stays in the vitreous for five times the half-life, "depot present in the vitreous" duration times were calculated (Table 1).

Ocular Toxicity

A total of 15 rabbits received 4-mg TA-PF ($N = 9$) and 16-mg TA-PF ($N = 6$) intravitreal injections. Rabbits are poor steroid responders; however, monthly intraocular pressure measurements were per-

Table 1. Pharmacokinetic Parameters for Intravitreal Injection of TA

Intravitreal Dose and Formulation	Elimination Rate Constant (k)	Half-life (d)	Drug Depot Present in the Vitreous, Estimated (d)
4-mg TA-PF	0.029	24	120
16-mg TA-PF	0.018	39	195
4-mg Kenalog*	0.030	23	115

* Bristol-Meyer-Squibb, Princeton, NJ.
TA, triamcinolone acetonide; TA-PF, TA preservative free.

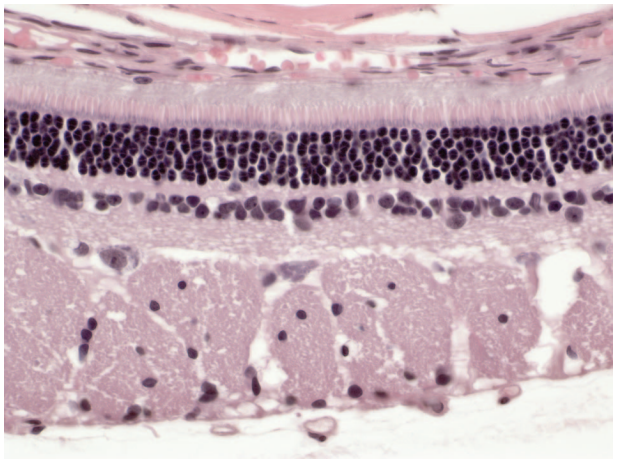

Fig. 6. Representative histopathologic section through the medullary ray region of the rabbit eye 38 weeks after intravitreal injection of 16-mg triamcinolone acetonide preservative-free formulation. The retina and choroid are normal with no inflammatory response or toxicity to the photoreceptors (stain, hematoxylin–eosin; original magnification, ×40).

formed and showed no increases over baseline in all groups. Clinical examination throughout the study period showed normal cornea, anterior chamber, lens, vitreous, and retina in both groups. ERGs for the treated eyes and untreated eyes with both the 4-mg and 16-mg TA-PF doses showed no significant changes in the a- or b-wave amplitudes during the study period (Fig. 5). Histopathologic analysis of the rabbit eyes receiving a 4-mg dose of TA-PF showed normal tissues by light microscopy at 10 weeks ($N = 4$) and 20 weeks ($N = 5$). Histopathologic analysis of the rabbit eyes receiving a 16-mg dose of TA-PF was normal at 38 weeks ($N = 12$) (Fig. 6).

Discussion

Although an intravitreal implant containing fluocinolone acetonide (Retisert; Bausch and Lomb, Rochester, NY) was approved in April 2005, there have been no injectable corticosteroid formulations sanctioned by the U.S. Food and Drug Administration for use in the eye. As a result, ophthalmologists have adapted commercial corticosteroid preparations to treat patients, initially with periocular administration. Experimental and clinical experience with commercial preparations of betamethasone and methylprednisolone acetate showed ocular toxicity.[12,15,16] With accidental injections in the vitreous cavity, the injury from the needle frequently resulted in a retinal detachment; however, the delayed effects, such as preretinal fibrosis, retinal pigment epithelial atrophy, and progressive optic atrophy, were thought to be related to the preservatives or detergents added to the corticosteroid formulation.[12] The recent cases of sterile endophthalmitis using Kenalog[7–10] may be related to the additives because pure TA has been shown to be safe in animal studies.[17] Kenalog, the only commercially available TA formulation in the United States, is approved for intraarticular and intramuscular uses only. When Kenalog was administered intravitreally, it was reported to be toxic to the retina.[18–20] Kenalog contains the preservative benzyl alcohol and the dispersion agent polysorbate 80. Both of these compounds have been associated with hypersensitivity and allergic reactions after intramuscular[21] and intraarticular[22] injections. Benzyl alcohol was linked in the early 1980s with numerous cases of anaphylaxis and death when used as a preservative in flush solutions for intravenous catheters.[23,24] Polysorbate 80 has been associated with hypersensitivity with intravenous formulations of multiple medications.[25–28] In addition, polysorbate 80 was used in an intravenous vitamin E preparation and associated with adverse events including liver failure.[29] The combination of polysorbate and benzyl alcohol was particularly ominous in the intravenous formulation of the antitumor agent etoposide, with hypersensitivities and anaphylaxis observed in 1% to 3% of patients.[28] When these two excipients were removed in a newer oral formulation of etoposide, hypersensitivities were not observed, even in patients with previous reaction to the intravenous formulation.[30]

The neurology and anesthesia communities were wary of preservatives and excipients in intrathecal and epidural preparations in the 1950s because of numerous cases of neurotoxicity in preclinical and clinical studies.[31–33] Because of several cases of aseptic meningitis in the 1960s with intrathecal preparations containing benzyl alcohol, modern intrathecal preparations of anesthetics and analgesics are prepared in single-use, preservative-free containers.[34] Because the retina and optic nerve are considered a peripheral extension of the central nervous system, avoidance of preservatives and excipients with intravitreal preparations is recommended, and we formulated a preservative- and dispersion agent–free TA suspension. Attempting to remove preservatives from Kenalog through bedside washing procedures is not recommended because this results in considerable variability in the degree of benzyl alcohol extraction and uncertain final drug concentrations in the vial.[35] For the current study, USP-grade hydroxypropyl methylcellulose was added to TA-PF in a low concentration to increase the viscosity for more reproducible aliquots of the suspension and delivery through 30-gauge hypodermic needles. No preservatives were necessary because TA-PF was provided in single-use vials. Hy-

droxypropyl methylcellulose was selected as the excipient in TA-PF for its long history of safety when used in the eye with significantly higher concentrations as a viscoelastic agent for ocular surgery.[36–39]

There are few studies in the literature examining the pharmacokinetics of TA injected in the vitreous cavity. Scholes et al[40] injected rabbits with a TA formulation containing the surfactant tyloxapol, a known cytotoxin in a variety of organ systems.[41,42] They estimated a vitreous half-life of 1.6 days with a 0.4-mg dose in rabbits; however, concomitant histopathology studies were not provided to verify that the ocular tissues were not damaged by the surfactant, which may have enhanced drug clearance. Furthermore, because most of their time points were before 7 days, the terminal elimination half-life may have been underestimated, suggesting that the mean elimination half-life was considerably longer than 1.6 days. One report estimated the vitreous half-life of TA in humans with serial drug measurements in the aqueous humor after a 4-mg intravitreal injection of Kenalog.[43] Using a two-compartment model with data for a limited number of patients ($N = 5$), they estimated the mean elimination half-life of 18.6 days in nonvitrectomized patients, similar to the 24-day half-life calculated in our study. As noted above, there have been recent reports of retinal toxicity after intravitreal injections of Kenalog in rabbits,[19,20] possibly related to the benzyl alcohol preservative.[18] These reports appeared after the data collection for the current study. Because we did not specifically examine the ocular toxicity of Kenalog, it is possible that toxic side effects could have influenced the pharmacokinetics.

There are differences in the anatomy and physiology of the rabbit eye that must be considered before extrapolating the results of this study to humans. Drug clearance may be enhanced by lensectomy and/or vitrectomy, and this was not specifically examined in our study.[44] In addition, the effect of vitreous syneresis and vitreous detachment on the pharmacokinetics of intravitreal TA was not examined. The vitreous in the young rabbit is well formed and may be more effective in keeping the injected drug in a consolidated depot compared with the liquefied vitreous observed in older patients. A less consolidated depot may have an increase in surface area for drug dissolution, and this may alter the pharmacokinetics of the drug. Because the animals used in this study were albino (New Zealand white) rabbits, the effect of ocular pigment on the ocular toxicity and pharmacokinetics of TA was not accessed. However, we previously reported that the vitreous half-life of a single 4-mg dose of TA-PF in pigmented Dutch-belted rabbits was 23 days,[45] similar to the 24-day half-life observed in the present study with New Zealand white rabbits. Last, the effect of the higher doses of TA leading to ocular hypertension could not be adequately evaluated in this study because rabbits are poor responders. The intraocular pressure needs to be carefully evaluated in the clinic with the TA-PF formulation, especially with the higher doses, because the experience with sustained-release ocular corticosteroid implants shows a considerable risk of ocular hypertension in humans when the drug is released for >6 months to 12 months.[46]

The half-life of the 16-mg injection of TA-PF in the vitreous of the rabbit was considerably longer than that of the 4-mg injection. Clinically, the longer duration of the higher doses of TA may be of benefit for patients that require up to 6 months of drug exposure for treating chronic eye diseases.[2] The observation of a longer vitreous half-life of a drug with higher intravitreal doses of small molecular weight lipophilic compounds has been attributable to "saturation" of elimination mechanisms.[47] In the Appendix, we propose as an alternative hypothesis that the dose dependence of half-life may be related to differences in the rate of dissolution arising from a dependence of depot superficial surface area on the initial mass of TA. If the drug clearance rate from the eye is limited by the rate of depot dissolution, the pharmacokinetics of TA in the vitreous would be independent of the vitreous volume. Consequently, these rabbit data would provide a reasonable approximation to the pharmacokinetics of TA in other species, such as humans.

Appendix

For each dose of TA administered, the amount of TA in the vitreous was found empirically to decrease exponentially with time after intravitreal injection as described by Equation (1) in the text. The rate of change in TA mass, M, remaining at time t is then given by

$$r = -\frac{dM}{dt} = k_i \times M, \qquad \text{(A-1)}$$

in which k_i is the elimination rate constant for the dose M_i. However, the magnitude of k_i varied inversely with M_i, the amount at time $t = 0$. To provide a simple quantitative relationship between k_i and M_i , we propose the following model for describing the processes that could plausibly dominate the clearance behavior. We begin with the observation that after injection into the midvitreous the particles of TA aggregate to form a globular depot. The aggregation may be promoted by colloidal interactions between the fine particles whose size distribution is narrow with a mean diameter of ≈ 4 μm. The depot is likely to be porous with

some entrained fluid. The depot eventually settles with gravity to a peripheral position, remains globular, and does not appear to come in contact with the retina. The aqueous solubility of TA is low so that dissolution is an important limiting step. Aggregation makes this more likely, because fluid trapped in the interior of the depot would become saturated with drug and further dissolution would only occur if free drug is removed by diffusion. Diffusion out of the mass is followed by diffusion of the free drug through the vitreous, permeation into the retina, and rapid clearance by the blood in the retinal and choroidal microvasculature. The distribution and clearance are thus driven by the saturation concentration C_S ($\approx$5 μg/mL in 0.9 N KCl at 37°C[48]), which is the maximum free concentration of TA in the vitreous. As a neutral lipophilic compound with a molecular weight of 434.5 Da, TA would be expected to readily permeate the retina. Consequently, the free concentration in the vicinity of the retina would remain much smaller than C_S. The magnitude of the overall driving force for elimination of TA is then of the order of C_S. An important consequence of aggregation is to change the surface area at which solubilization occurs from that of individual particles to an effective surface area of the depot, A. We postulate that the rate of elimination is proportional to the product of A and C_S with a proportionality coefficient representing an effective permeability, P,

$$r = P \times A \times C_s. \tag{A-2}$$

Equating Equations (A-1) and (A-2) gives

$$k_i \times M = P \times A \times C_s. \tag{A-3}$$

The formulation of Equation (A-3) implicitly assumes that the amount of TA in the vitreous outside of the depot is negligible based on the low aqueous solubility. Because k_i and C_S are constants for a given dose, Equation (A-3) suggests that the depot surface area at any time, t, is proportional to the mass of TA remaining in the depot,

$$A = A_i \times \left(\frac{M}{M_i}\right), \tag{A-4}$$

where A_i and M_i are the initial area and mass, respectively. Our interpretation of this result is that the observed dependence of k on dose arises because the initial depot area depends upon the initial depot mass by an empirical relationship of the form

$$A_i = K \times M_i^{\,n}, \tag{A-5}$$

where K and n are constant. A relevant illustrative example of a relationship of the form of Equation (A-5) is that for the surface area of a sphere of mass M and density ρ

$$A = \left(6\sqrt{\pi}\, M/\rho\right)^{2/3}, \tag{A-6}$$

for which $n = 2/3$. Combining Equations (A-3) through (A-5) gives for the 4-mg injection

$$k_4 = P \times K \times C_s \times M_4^{\,n-1} \tag{A-7}$$

and for the 16-mg injection

$$k_{16} = P \times K \times C_s \times M_{16}^{\,n-1}. \tag{A-8}$$

Taking the ratio of Equation (A-7) to Equation (A-8) gives

$$\frac{k_4}{k_{16}} = \left(\frac{M_4}{M_{16}}\right)^{n-1}. \tag{A-9}$$

Key words: intravitreal injection, ocular pharmacokinetics, ocular toxicity, retinal diseases, triamcinolone acetonide.

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