Different Intravitreal Properties of Three Triamcinolone Formulations and Their Possible Impact on Retina Practice

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Purpose. We sought to better characterize the intravitreal profile of different triamcinolone formulations.

Methods. The study was performed in vitro and in vivo. Kenalog 40, Triesence, and Transton were characterized for ocular pharmacokinetics, particle size, crystallinity, and dissolving kinetics in vitreous following an intravitreal injection into 12 rabbit eyes. The relationship of free drug levels in the aqueous and vitreous was investigated through a dual probe microdialysis and liquid chromatography tandem mass spectrometry.

Results. Triesence had the most uniform particle size distribution (mean 11.51 μm) and Kenalog 40 had the largest particle sizes (mean 18.86 μm). Triesence and Kenalog 40 had 100% crystallinity, while Transton had 89% crystallinity. Triesence had a slower dissolution in vitreous than that of Kenalog 40, and Transton had the fastest dissolution, though their solubility was very similar. Following a 1.2 mg intravitreal injection in the rabbit eye, Triesence had a significantly lower ocular free drug level than Kenolog 40 ($P = 0.025$) and Transton ($P = 0.007$). Quantitative dual probe microdialysis revealed that the aqueous free triamcinolone (Kenolog 40) was less than 1% of the vitreous free triamcinolone during the first few hours, and this percentage increased to 26.8% at 2 weeks and was 11.7% at 3 weeks following an intravitreal injection.

Conclusions. Triesence demonstrated a significantly slower dissolution profile and lower free drug level in the vitreous than the other preserved triamcinolone, which may translate into a longer therapeutic duration and lower rate of drug associated complications. (*Invest Ophthalmol Vis Sci.* 2013; 54:2178 2185) DOI:10.1167/iovs.12 11460

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Triamcinolone acetonide (TA) is being used worldwide as a therapeutic agent for many chorioretinal diseases, such as diabetic macular edema, retinal vein occlusion, age related macular degeneration,[1] and uveitis.[2] Even with the advent of intravitreal antiangiogenesis agents, intravitreal TA remains an effective and low cost treatment modality when used alone or combined with other treatment options. Several commercially available TA formulations are being used for intravitreal injection either at a physician's discretion or due to the availability of the product.[3–5] Though TA intravitreal injections generally are effective, side effects, such as cataract formation and elevated IOP are common. Most recently, the preservative free TA formulations, Triesence and Trivaris, have been developed and are available on the market (Triesence; Alcon Pharmaceuticals, Ft. Worth, TX; and Trivaris; Allergan, Inc., Irvine, CA). The commercially available, preservative free TAs are likely different from preserved TAs in pH value, particle size,[6] crystallinity, solubility, and dissolution kinetics in the vitreous. All of these parameters are important for better gauging treatment effect and duration, as well as understanding adverse consequences following an intravitreal injection.[7] For example, the free TA concentration in vitreous fluid and aqueous fluid may be quite different following an intravitreal injection of different TA formulations, which will affect not only the therapeutic duration, but also the possibility of side effects, such as cataract formation and IOP elevation.

In the United States, preserved triamcinolone acetonide, such as Kenalog 40 (C24H31FO6 MW:434.50; Bristol Myers Squibb, Princeton, NJ) is the dominant TA formulation for intravitreal injection even after preservative free TAs have become available,[8] while Transton is the counterpart of Kenalog 40 in China (C24H31FO6 MW:434.50; Kunming Jida Pharmaceuticals Co., Ltd., Yunnan, China).[4,5,9–12] To the best of our knowledge, the difference of ocular free TA pharmacokinetics following an intravitreal injection of Kenalog 40 or Triesence is not yet well documented.[13] In our current study, we chose Kenalog 40 and Triesence (marketed in the United States), as well as Transton (marketed in China) to compare their ocular properties to better understand their implications in daily retina practice.

Materials and Methods

In Vitro Physicochemical Properties of the Three Different TA Formulations

Two types of commercially available preserved TA (Kenalog 40, C24H31FO6 MW:434.50; Bristol Myers Squibb; and Transton, C24H31FO6 MW:434.50, Triamcinolone Acetonide Injection; Kunming Jida Pharmaceuticals Co., Ltd.) and one preservative free TA (Triesence; Alcon Pharmaceuticals) were used for this study. The chemical grade triamcinolone acetonide was purchased from National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China, and used as a control.

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Osmolarity of the Supernatant from the Commercial Ampules. The commercial ampules of each TA formulation (Triesence, Kenalog 40, Transton) were centrifuged (Eppendorf 5810R; Eppendorf, Hamburg, Germany) at 3220*g* for 20 minutes and 0.5 mL of the supernatant from each ampule was collected using a 30 gauge needle attached to a 1 mL syringe. The osmolarity of the supernatant was measured using an auto freezing point osmometer (FM 8; Science Development Center at Shanghai Medical University, Shanghai, China). Three ampules each were studied from Kenalog 40 and Transton. For Triesence, 2 ampules were studied.

pH Value of the Supernatant from the Commercial Ampules. After the centrifugation specified above, 0.6 mL of the supernatant was sampled into a pH measuring cuvette and the pH value was determined using a pH meter (SG2 ELK; Mettler Toledo, Zurich, Switzerland).

TA Concentration in the Supernatant from the Commercial Ampules. After centrifugation of the TA ampule, 100 μL of the supernatant were sampled. Following filtration with a 0.45 μm filtering membrane, 50 μL of the filtered sample were mixed with 50 μL of high performance liquid chromatography (HPLC) mobile phase and 20 μL of the mixture was injected into HPLC (Agilent, Santa Clara, CA). The mobile phase consisted of methanol/water (52.5/47.5) and the flow rate was at 1 mL/min through a ZORBAX Eclipse XDB C18 (Agilent) (4.6 × 150 mm, 5 μm) column at 30°C. TA was detected by a diode array detector at (G1315B; Agilent) 240 nm. The TA concentration was determined from a standard 7 point curve with excellent linearity (R 0.999) between 0.5 and 20 μg/mL.

Particle Size Analysis of the Different TA Formulations. Two TA ampules of Triesence, Kenalog 40, and Transton were placed in an ultra low temperature freezer overnight. The crystal powder of the three types of TA then was collected by freeze dryer (2 4 LDplus; Christ Alpha, Munich, Germany). The particle size of each TA formulation was determined using a laser particle size analyzer (Mastersizer 2000; Malvern, Worcestershire, England).

Crystallinity of TA in the Different Formulations. TA ampules of Triesence, Kenalog 40, and Transton were placed in a 80°C temperature freezer overnight. Then, the crystal powder of three types of TA was collected by freeze dryer (2 4 LDplus; Christ Alpha). The powder was washed by deionized water once to remove the excipients. The crystal powder was recollected by lyophilization in the same way and then analyzed using an X ray diffractometer (X' Pert PRO; PANalytical, Eindhoven, Netherlands). The crystallinity was calculated by JADE5.0 software program used for crystal analysis (Materials Data, Inc., Livermore, CA).

Solubility of TA from the Different Formulations.

Solubility in PBS. The crystal powder of three types of TA was collected from the commercial ampules by lyophilization. In addition, a TA standard (purchased from National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China) was used as control. The 40 mg TA powder from Triesence, Kenalog 40, Transton, and the standard TA were placed into a dialysis bag (MD25 3.5; Viskase, Darien, IL) with a 3500 molecular weight cutoff (MWCO). The dialysis bag was placed in a polyethylene bottle with 150 mL PBS (pH 7.44). The polyethylene bottle then was placed in an orbital shaker (Thermo Fisher 481; Thermo Fisher, Marietta, GA) at 37°C with a speed of 25 revolutions per minute. At 2 , 4 , 8 , 16 , 24 , and 32 hour, and 2 , 4 , 5 , 7 , 10 , 15 , 21 , and 28 day time points, 1 mL of solution was sampled from the polyethylene bottle and 1 mL of fresh PBS was added back into the bottle. The TA concentration was determined by HPLC.

Solubility in Vitreous. As described above, 1.8 mg of TA powder from Triesence, Kenalog 40, Transton, and the standard TA were placed into a centrifuge tube containing 2 mL of blank rabbit vitreous. The tube was placed in the orbital shaker as described above, and centrifuged with 3220*g* for 10 minutes. A 20 μL supernatant then was sampled at 3 , 8 , 12 , 24 , and 36 hour, and 2 , 3 , 4 , and 5 day time points for HPLC analysis.

In Vivo Ocular Pharmacokinetics following a Single Intravitreal Injection

TA Pharmacokinetics in Aqueous Humor following Intravitreal TA Injection. The study was designed to characterize the free TA concentration profile in vitreous and in aqueous humor from an intravitreal injection of TA. To reduce the number of animals and minimize the variation between individual animals, we sampled the aqueous humor multiple times from the same animal at the designated time points. The aqueous humor was sampled, instead of vitreous, to avoid small TA particles being taken into samples, which would distort the free TA concentration profile to be studied. The assumption is that the free TA concentration in the vitreous and in the aqueous humor is proportional, and that their relationship can be defined in a separate dual probe microdialysis study.[14,15] For this study, 12 pigmented rabbits were used, 4 for each type of TA. Their mean body weight was 2.65 ± 0 28 kg. Handling of animals was in accordance with the Association for Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Visual Research. This study was approved by the Institutional Animal Care and Use Committee of Wenzhou Medical College. Only one eye was injected intravitreally with 1.2 mg of TA in 30 μL using a 27 gauge half inch needle attached to a 1 mL syringe. For the intravitreal injection procedure, the rabbits were anesthetized by an intramuscular injection of ketamine (21 mg/kg) and xylazine (5.25 mg/kg), and topical proparacaine 0.5% also was used locally. The vial of TA was shaken well before loading the syringe, in the same manner as a 4 mg TA intravitreal injection is performed in the clinic for a human eye. After the injection at postinjection days 1 and 5, and weeks 2, 3, 4, 6, and 8, a paracentesis was performed under anesthesia, using sterile technique, through a 31 gauge needle/0.3 mL syringe to sample 50 μL of aqueous humor under the direct view of a surgical microscope (F18; Leica, Wetzlar, Germany). The samples were stored under 80°C until LC MS/MS analysis. In addition, the vitreous TA aggregate was inspected using an indirect ophthalmoscope and noted at each aqueous humor sampling time point. At the eighth week, the rabbits were sacrificed and the whole vitreous was sampled using a snap freezing technique as described previously.[16] The whole vitreous samples were kept under 80°C until LC MS/MS analysis.

Microdialysis to Determine Quantitative Relationship between Free TA in Vitreous and Aqueous Humor. For this study, three rabbits were used. The dual probe microdialysis was performed immediately, and at weeks 2 and 3 following a 1.2 mg Kenalog 40 intravitreal injection. Only one eye of one rabbit was dual probe microdialyzed at each time point. For the procedure, the rabbit was anesthetized by an intramuscular injection of ketamine (35 mg/kg) and xylazine (6.25 mg/kg), and an anterior chamber probe (CMA 30, 4 mm custom made, molecular weight cutoff 6000 Da; CMA Microdialysis, North Chelmsford, MA) was installed before the vitreous probe (CMA 20, 4 mm probes, molecular weight cutoff 20,000 Da; CMA Micro dialysis) to avoid possible contamination of the aqueous probe by egressed vitreous fluid. In addition, aqueous probe installation causes some loss of aqueous; by installing the aqueous probe first, it allows time for the eye to recover. After the installation of the probes, bio glue (Vetbond1469SB; 3M Corp., St. Paul, MN) was applied around the probe entry at the globe surface to prevent ocular fluid leaks (Fig. 1). A minimum of 30 minutes was given to allow the eye to recover its fluid balance and IOP before the intravitreal TA injection (immediate microdialysis) or the first sample collection (weeks 2 and 3 time points). The probes were perfused at 1 μL (vitreous probe) or 2 μL (aqueous probe) per minute of 0.9% NaCl using a microsyringe pump (NE100; New Era Pump Systems, Inc., Farmingdale, NY). The vitreous and aqueous humor samples were collected every 20 minutes, and a minimum of 10 samples were collected for analysis. During the course of microdialysis, a boost of anesthesia was performed every 35 to 40 minutes using one half the volume of the first dose. Every other boost was ketamine only starting with the first boost because xylazine stays in the system longer.[17] The same type of probe was used for

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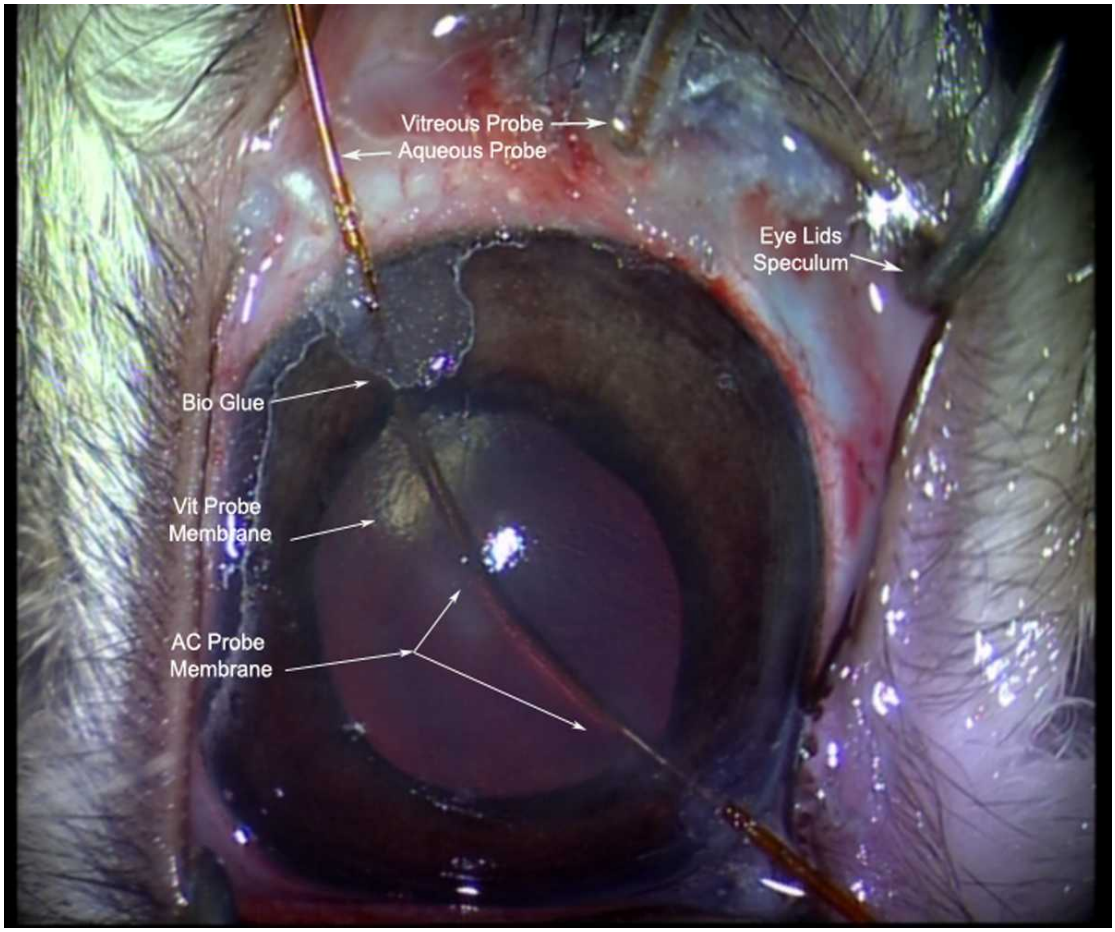

Figure 1. The photograph is taken from a dual probe microdialysis. The anterior eye globe was exposed using an eye lid speculum. The vitreous probe and aqueous probe are visible, as indicated in the photograph. Probes had a 4 mm dialysis membrane. The aqueous probe membrane is seen centered in the anterior chamber; the vitreous probe membrane is in the mid cavity of the vitreous, and looks whitish and distorted through the lens.

determining the rate of TA recovery at 37°C using 300 ng of TA per milliliter of 0.9% NaCl. The study was performed in the same manner as the microdialysis performed in the rabbit eye. In determining the TA recovery rate from the aqueous probe, 1 and 2 μL of infusion rates were used.

Ultra Performance Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) Analysis of TA Concentration in the Aqueous Humor and in the Vitreous

The measurement of TA concentrations in rabbit aqueous samples was performed using LC MS/MS as we described previously.[16,18]

Data Analysis

Data are expressed in mean ± SD. The mean dissolution rates in excised vitreous at the early time point among 3 different types of TA were compared for each pair using Student's *t* test. For in vivo aqueous pharmacokinetic data the difference among 3 types of TA was evaluated using paired *t* test by pairing data at each sampling time point. The pharmacokinetic parameters were extrapolated using Phoenix WinNonlin 6.2 (Pharsight, a Certara Company, St. Louis, MO) by fitting the aqueous TA concentration time data to the extravascular input model and the noncompartmental analysis. For in vivo dual probe microdialysis, the mean TA concentrations in vitreous or in aqueous humor were compared for each pair among 3 different times of microdialysis using nonparametric comparisons of Wilcoxon method.

Results

Physicochemical Properties of the Different TA Preparation

The physicochemical properties of the 3 different TA preparations are summarized into Table 1.

The free TA level in the commercial vial was the lowest for Triesence. The solubility of three TA formulations was similar and the solubility of TA in vitreous was higher than that in PBS. The particle size analysis demonstrated different particle size distributions (Fig. 2).

Triesence was the most uniformly distributed formulation with the narrowest bell shape of distribution. Kenalog 40 showed larger median size, and wider range of distribution than Triesence and Transton. The dissolution profiles of the different TA preparations in the excised vitreous are displayed in Figure 3. Though the solubility of Triesence, Kenalog 40, and Transton was similar after a 24 hour incubation period, the dissolution profile (a kinetic process) was quite different,

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Table 1. Physicochemical Characteristics of Different TA Formulations

TA Brand	Osmolarity*, mOsm/kg	pH*	TA*, μg/mL	Particle Size, μM	Crystallinity	Solubility in PBS, μg/mL	Solubility in Vitreous at 24 h, μg/mL
Kenalog 40	328.7 ± 1.7	5.76 ± 0.06	17.10 ± 0.68	18.86 ± 16.7	100%	12.91 ± 0.44	24.69 ± 0.82
Triesence	300.5 ± 3.5	6.90 ± 0.01	10.42 ± 0.59	11.51 ± 8.1	100%	13.42 ± 0.76	26.71 ± 3.42
Transton	309.3 ± 1.9	6.79 ± 0.1	18.28 ± 0.45	10.13 ± 7.6	88.79%	12.51 ± 0.59	23.91 ± 0.77
TA STD						12.31 ± 0.62	20.40 ± 1.13

STD, standard.
* Indicates the parameters was derived from measurement of the supernatant of the TA preparation.

especially at the earlier time points of 10, 20, and 30 minutes. Transton dissolved the fastest and Triesence the slowest among the 3 TA formulations (least square mean [LSmean] 18.23 > 12.39 > 9.95 ng/mL, $P < 0.05$ least square means Student's *t* test).

In Vivo Pharmacokinetics of Different Formulations of TA in Rabbit Aqueous

The aqueous samples were analyzed using LC MS/MS and the kinetics of each type of TA is demonstrated in Figure 4. In general, the aqueous TA concentration following a Transton intravitreal injection was significantly higher than following a Kenalog 40 injection ($P = 0.0225$, paired *t* test) and a Triesence injection ($P = 0.007$, paired *t* test). In addition, the TA level in the aqueous following a Triesence intravitreal injection was significantly lower than following a Kenalog 40 injection ($P = 0.025$). The TA in aqueous followed a first order elimination. The maximum concentration of TA in aqueous was 63.2 ng/mL for Transton, 21.1 ng/mL for Kenalog 40, and 7.2 ng/mL for Triesence. The time at which the highest TA concentration reached was postinjection 1 day for all three TAs. The area under the concentration time curve was 815.8 ng·d/mL for Transton, 277.1 ng·d/mL for Kenalog 40, and 83.9 ng·d/mL for Triesence.

During clinical observation, indirect ophthalmoscopy revealed that, in general, a smaller drug depot size was noted for Transton and Kenalog 40 (Fig. 5) when compared to Triesence at the fourth week or later post injection. On day 56 post injection, all rabbits were sacrificed, and the total mean vitreous TA and mean plasma TA concentrations are summarized in Table 2.

The Simultaneous Kinetics of Free Kenalog-40 in the Aqueous and Vitreous In Vivo, following an Intravitreal Injection of 1.2 mg Suspension

The vitreous probe TA recovery rate was 23.4 ± 2.7% at 37°C and under a perfusion rate of 1 μL per minute. In contrast, the aqueous probe TA recovery rate was 11.3 ± 1% at 37°C under a perfusion rate of 1 μL/min. With the perfusion rate of 2 μL/min, the recovery rate was only 6.6 ± 1.1%. The vitreous probe recovery rate was significantly higher than that of aqueous probe ($P < 0.0001$, *t* test). The aqueous probe recovery rate was significantly higher at 1 μL/min perfusion than that at 2 μL/min perfusion ($P < 0.0001$). Immediately following an intravitreal injection of triamcinolone, the free drug gradually increased in dialysate of vitreous and aqueous, and the level of free TA reached a near constant around 150 minutes post injection (Fig. 6, blue lines). It is clear that the

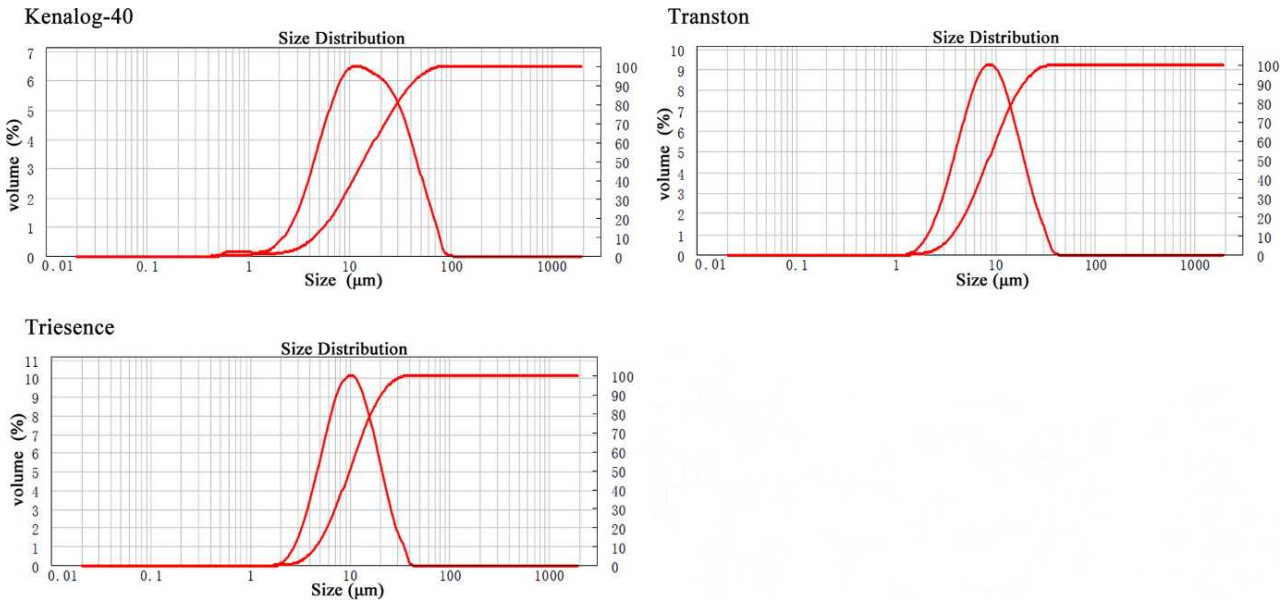

Figure 2. Particle size distribution of different formulations of triamcinolone. The *x* axis is in micrometers at a log scale. The *bell-shaped curve* indicates the range of particle size distribution at the corresponding sizes along the *x* axis, while the *left y* axis indicates the percent of sample having the size shown on the corresponding *x* axis. The *sigmoid curve* indicates the cumulative distribution of particle sizes and the cumulative percentage is shown on the *right y* axis.

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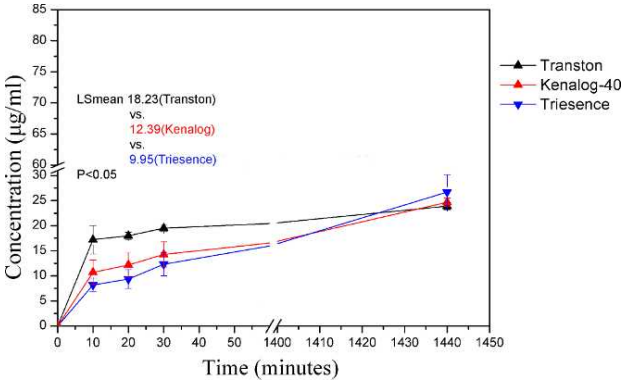

Figure 3. Dissolution kinetics for the different formulations of triamcinolone in excised rabbit vitreous. Within the first hour of dissolution, free TA from Transton consistently was the highest and free TA from Kenalog 40 was higher than that of Triesence. The higher free TA concentrations at the earlier time points indicate a faster dissolution.

changes in TA levels in vitreous and aqueous are proportional. For the microdialysis performed at two and three weeks post injection, the free TA in the aqueous and vitreous showed a near constant level during microdialysis. The mean TA concentrations were 0.21 ± 0.12, 6.03 ± 1.54, and 2.38 ± 0.96 ng/mL in the aqueous humor, and 137.72 ± 27.33, 46.57 ± 6.89, and 42.28 ± 12.6 ng/mL in the vitreous humor immediately after, and at 2 and 3 weeks post injection, respectively. Taking the probes' recovery rates, and the difference of the recovery rates between the vitreous probe and the aqueous humor probe, the calculated TA concentration in the aqueous humor at 2 weeks post injection was 26.8% of that in the vitreous and at 3 weeks post injection it was 11.7% that of free TA in the vitreous. The TA in the aqueous humor was less than 1% of the free TA in the vitreous within the first few hours following a 1.2 mg intravitreal injection.

Among the three time points, the free TA levels in the vitreous were significantly higher within the first few hours following the intravitreal injection ($P = 0.0127$ vs. 2 weeks post injection and 0.0101 vs. 3 weeks post injection; nonparametric comparisons for each pair using the Wilcoxon method), and the free TA levels in the vitreous at 2 and 3 weeks post injection were similar ($P = 0.218$). Free TA levels in the aqueous humor demonstrated a significant difference among the three time points, with the highest level at 2 weeks post injection, the second highest at 3 weeks post injection, and the lowest within the first few hours following the intravitreal injection (2 week vs. 3 week, $P = 0.0004$; 1 hour vs. 2 or 3 week, $P < 0.0001$).

Discussion

Triamcinolone is a crystal drug with limited solubility, causing it to form a drug depot following an intravitreal injection, and leading it to provide slow release and a long lasting therapeutic effect. It is important to note that only dissolved free triamcinolone has a therapeutic effect, and that the amount of free drug in ocular fluid can vary greatly due to the different formulation parameters and associated dissolution kinetics. To the best of our knowledge, our study is the most comprehensive study to date on the ocular pharmacokinetics following an intravitreal injection of different formulations of triamcinolone, preserved and preservative free.

It has been known that particle size, crystallinity, and dispersion profile all may affect the dissolution kinetics of a given drug. In our ex vivo vitreous dissolution study, we noted that the solubilities of Triesence, Kenalog 40, and Transton were comparable (26.71, 24.69, and 23.91 μg/mL, respectively), but the dissolution kinetics in the vitreous at 37°C were different. The preservative free Triesence dissolved much more slowly than Kenalog 40 and Transton, which dissolved the

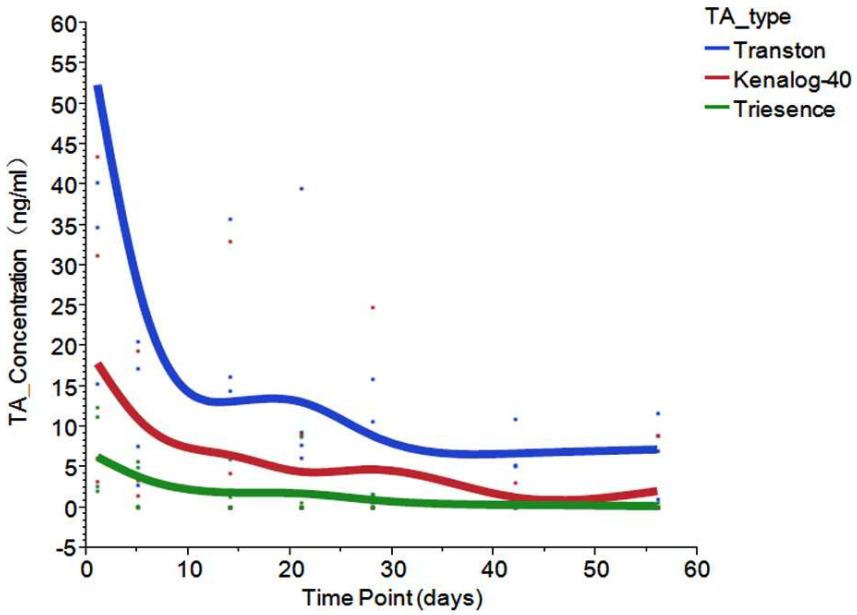

Figure 4. The pharmacokinetic profiles of free triamcinolone in aqueous following a 1.2 mg intravitreal injection. Transton, Kenalog 40, and Triesence demonstrated a similar elimination profile, but with very different maximum concentration (Cmax) values, which was the highest for Transton and the lowest for Triesence (statistical evaluation not available due to too small sample size, n 4). The paired t test of means at each time point for three curves revealed statistically significant difference of free TA levels among three types of TA (Transton versus Kenalog 40, P 0.023; Transton versus Triesence, P 0.007; Kenalog 40 versus Triesence, P 0.025).

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