Intravitreal Sustained-Release Dexamethasone Device in the Treatment of Experimental Uveitis

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Purpose. Uveitis often runs a chronic course requiring long-term therapy. Topical treatment results in poor intravitreal penetration, and systemic therapy is associated with significant side effects. The authors investigated whether an intravitreal sustained-release dexamethasone device was effective in the treatment of severe panuveitis in a rabbit model.

Methods. Twenty New Zealand white rabbits were immunized twice subcutaneously with 10 mg of Mycobacterium tuberculosis H37Ra antigen. Twelve days later, sustained-release dexamethasone devices were implanted into the vitreous of the right eye of 10 rabbits. Ten control rabbits received a sham device. One day later, rabbits were challenged with an intravitreal injection of 33 μg of antigen. Three animals in each group were sacrificed on post-challenge days 7 and 13 for aqueous white blood cell (WBC) count, protein determination, and histologic examination. To simulate chronic inflammation with exacerbations, the eight remaining eyes were rechallenged with intravitreal antigen on day 15 and were observed for 3 1/2 months. Inflammation was graded clinically by two masked observers. Retinal function was evaluated by electroretinography (ERG). Light microscopy was used to evaluate the eyes histopathologically. The amount of residual drug in the devices was measured on day 13 and at the end of the experiment.

Results. By all clinical criteria measured—anterior chamber cells, flare, and vitreous opacity—treated eyes had significantly less inflammation than untreated eyes (P < 0.05). Clinical examination correlated well with objective data: Both protein concentration (P < 0.05) and aqueous WBCs (P < 0.02) were approximately 10-fold higher, and ERGs were significantly depressed (P < 0.05) in untreated eyes compared to treated eyes. Histopathologic examination showed marked inflammation and tissue disorganization in the untreated compared to the treated eyes. After antigen rechallenge, inflammation in experimental eyes was still less than in control eyes. Late complications such as corneal neovascularization, cataract, and hypotony were also less in the treated eyes than in the untreated eyes. At the end of the experiment (99 days after device implantation), approximately 30% of drug remained in the devices.

Conclusions. The intravitreal sustained-release dexamethasone device is highly effective in suppressing inflammation and preventing complications after two episodes of experimental uveitis in a rabbit model for at least 3 1/2 months. This device may be useful in the management of patients with severe chronic posterior uveitis who cannot tolerate systemic or periocular therapy. Invest Ophthalmol Vis Sci. 1995;36:442-453.


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Uveitis often runs a chronic course requiring long-term therapy. Current treatment for chronic uveitis usually includes topical, periocular, or systemic corticosteroids, but inflammation frequently recurs after the discontinuation of therapy. Complications of topical corticosteroid use include poor wound healing, toxicity to the corneal epithelium, and increased intraocular pressure. In addition, topical treatment re-
results in poor intravitreal penetration and is inadequate for the treatment of inflammatory conditions involving the posterior segment. Periocular corticosteroid injection often requires frequent repetition and is associated with risks of globe perforation, fibrosis of the extraocular muscles, and local toxic reactions to the vehicle in which the corticosteroid is delivered. Chronic systemic administration of corticosteroids is associated with many hazardous side effects, including hypertension, hyperglycemia, increased susceptibility to infection, peptic ulcers, and psychosis.

Optimal corticosteroid therapy would maintain therapeutic levels in the vitreous for a prolonged period. At present, these prolonged therapeutic levels can only be achieved by prohibitive high systemic dosing or frequent intraocular injections. An implantable sustained-release device has been used with success to deliver prolonged levels of ganciclovir intravitreally for the treatment of cytomegalovirus retinitis in patients with acquired immune deficiency syndrome. A similar device containing corticosteroid can maintain therapeutic intravitreal levels for prolonged periods with minimal systemic exposure and may prove useful in the clinical management of uveitis. Here, we investigate whether an intravitreal sustained-release device containing dexamethasone is effective in the treatment of severe panuveitis in a rabbit model.

**MATERIALS AND METHODS**

**Device Preparation**

Implantable sustained-release devices containing dexamethasone were prepared as previously described. Briefly, dexamethasone pellets 2.5 mm in diameter containing 5 mg of drug were prepared using a customized Parr Instrument (Moline, IL) pellet press. Each pellet was then coated with alternate layers of 10% polyvinyl alcohol (PVA, molecular weight 78,000; supplied by Polyscience, Warrington, PA) and ethylene vinyl acetate (EVA, grade 40w, DuPont, Wilmington, DE). A PVA suture tag was attached, and the completed device was heated at 120°C for 2 hours. The device was then sterilized using ethylene oxide at least 2 days before implantation.

**Preimmunization With Antigen**

All animal experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. A relatively severe, nonspecific experimental uveitis model was created according to a modification of previously published protocol. Twenty New Zealand White rabbits, each weighing 1.5 to 2.0 kg, were injected subcutaneously with 10 mg of Mycobacterium tuberculosis H37 RA antigen (Difco, Detroit, MI) suspended in 0.5 ml of mineral oil. One week later, a second injection of the same amount of subcutaneous antigen was given. In all animals, a firm, discrete nodule was identified at the injection site approximately 1 week after the second antigen injection, confirming the efficacy of immunization.

**Device Implantation**

Twelve days after the second immunization, the intravitreal sustained-release dexamethasone devices were surgically implanted into the right eyes of 10 rabbits (treated group) according to a previously described method. Briefly, animals were anesthetized with an intramuscular injection of 0.3 ml ketamine hydrochloride (100 mg/ml) and 0.1 ml xylazine hydrochloride (100 mg/ml) per kilogram body weight. A 5-mm peritomy was made at the superotemporal quadrant of the right eye. A 3-mm sclerotomy was created 2 to 3 mm from the limbus. The device was then inserted into the vitreous cavity through the sclerotomy and was secured at the sclerotomy site by a 6-0 dacron suture. The sclerotome wound and the peritomy were then closed with 7-0 vicryl sutures. In the untreated group, all 10 rabbits received surgical implantation of the polymer alone. One drop of topical 0.5% gentamicin solution was instilled into the eye after surgery for the prevention of infection.

**Uveitis Induction**

A microparticulate suspension of M. tuberculosis H37 RA antigen was prepared by ultrasonication of the crude extract in sterile balanced salt solution. One day after device implantation, 33 μg of antigen suspended in 0.1 ml of balanced salt solution was injected into the vitreous cavity of the right eye of all 20 rabbits under anesthesia (first challenge). To simulate chronic inflammation with exacerbations, four eyes in the treated group and four eyes in the untreated group were rechallenged with the same amount of intravitreal antigen on day 15 (second challenge). One drop of 1% atropine solution was then instilled into the eye to maintain postoperative cycloplegia.

**Clinical Observation**

All rabbits were examined by two masked observers on days 1, 3, 7, and 13 after the first challenge and on days 3, 10, 19, 25, and 75 after the second challenge. These time points were selected before the study was begun. Slit-lamp biomicroscopy and indirect ophthalmoscopy were used to evaluate the severity of conjunctival injection; corneal clarity, neovascularization and keratic precipitates; anterior chamber cells and flare; iris vessel congestion; posterior synechiae; cataract; and vitreous opacity. We chose anterior chamber cells, flare, and vitreous opacity as quantifi-
Aqueous Protein Measurement and Cell Count

Three animals in each group were randomly chosen 7 and 13 days after the first challenge for aqueous protein measurement and cell count. Animals were anesthetized, and 0.2 to 0.3 ml aqueous humor was aspirated from the right eye of each of three rabbits with a heparin-rinsed glass syringe connected to a 27-gauge needle. Aqueous cell count was measured by hemocytometer. One drop of aqueous was placed on a microscope slide and stained with Wright stain for differential cell count. The remaining aqueous was then centrifuged at 250g for 5 minutes, and the supernatant was used for protein measurement. The protein content of the aqueous humor was determined using a BioRad assay kit with bovine serum albumin as a standard dilution reference curve according to the manufacturer’s recommendation. After removal of aqueous, animals were killed by intravenous or intracardiac sodium pentobarbital, and the right eyes were enucleated for histologic study.

Electroretinographic Study

Retinal function was evaluated by scotopic and photopic electroretinography (ERG) using a Cadwell model 5200 unit with a Ganzfield flash (model VPA-10°; Kennewick, WA) on day 14 after first challenge and on days 4, 14, 28, and 80 after second challenge. Animals were anesthetized, and one drop of 2.5% phenylephrine hydrochloride solution and one drop of 0.25% scopolamine hydrobromide solution were instilled into both eyes of rabbits for mydriasis. Scotopic ERGs were performed after at least 30 minutes of dark adaptation at a frequency of 0.33 Hz, and the result was the average of 20 stimulus presentations. Photopic ERGs were performed at a frequency of 2.8 Hz after at least 5 minutes of light adaptation and were also the average of 20 stimuli. To minimize individual variability, the ratio of the b-wave amplitude of the antigen-challenged eyes to fellow eyes was used as an index of the retinal function.

Histopathologic Study

The right eyes of all rabbits were enucleated at various time periods. After enucleation, cuts were made at the equator, and the eyes were fixed in phosphate-buffered 10% formaldehyde (7 eyes) or coccylate-buffered 2% glutaraldehyde solution (12 eyes). Eyes were then rinsed with sodium cacodylate buffer and dissected into segments of interest including cornea, iris–ciliary body, device implantation sites, peripheral retina, and posterior retina. The formalin-fixed tissue samples were dehydrated with increasing concentrations of ethanol, cleared with xylene, and embedded in paraffin. Five-micron sections were cut and stained with hematoxylin and eosin. The glutaraldehyde-fixed tissue samples were similarly dehydrated, infiltrated, and embedded in Araldite 506 resin. One-micron sections were cut and stained with toluidine blue. Sections were then examined by light microscopy.

Measurement of Residual Dexamethasone in Devices

The implanted devices were removed from three rabbits 14 days after implantation and from three rabbits at the end of the experiment (day 99). Residual dexamethasone was then determined using a Hitachi (San Jose, CA) fully automated high pressure liquid chromatography unit with a reverse-phase C-18 column (supplied by Cole Scientific, Calabasas, CA). The mobile phase used a 35% acetonitrile, 65% sodium acetate buffer at pH 4.0 and a flow rate of 1.0 ml/minute. Detection was by ultraviolet absorption at 239 nm wavelength. The detection limit with this method was 0.5 μg/ml. The dexamethasone release rate from the device was then calculated by dividing the difference between the initial and the final drug amount by the duration.

Statistical Comparison

A Mann–Whitney nonparametric test was used to compare the grading of anterior chamber cells, anterior chamber flare, and vitreous opacity. An unpaired, two-tailed Student’s t-test was used to compare the ERG b-wave amplitude ratio between treated and untreated groups. A paired, two-tailed Student’s t-test was used to compare the intraocular pressure of the antigen-challenged eye to the unoperated fellow eye in both treated and untreated groups. Chi-square analysis with continuity correction was used to compare the frequency of corneal neovascularization, severe iris congestion, posterior synchiae, and cataract formation, respectively, between treated and untreated groups.
RESULTS

Clinical Observation

The results of the clinical grading of anterior chamber cells, flare, and vitreous opacity after initial intravitreal injection of antigen, and after the second antigen rechallenge, are depicted in Figure 1. On day 1 after the first intravitreal injection of antigen, all rabbit eyes in treated and untreated groups showed an immediate inflammatory reaction with marked cell and flare. By day 3, in the treated group the inflammation was suppressed, whereas in the untreated group the eyes remained inflamed for as long as to 2 weeks. In the untreated group, anterior chamber cells peaked at day 3 and subsided by day 7, but anterior chamber flare and vitreous opacity remained significantly greater than in the treated group through day 13.

To simulate chronic inflammation with exacerbations, the remaining eight rabbits (four in each group) were rechallenged with antigen on day 15. Three days after the second intravitreal injection of antigen, the untreated eyes showed an even more severe inflammatory reaction than that after first intravitreal antigen challenge (Fig. 1). All four untreated eyes had intense anterior chamber cell infiltration, dense plaquelike aqueous fibrin formation, marked corneal edema, and mutton-fat keratic precipitates (Fig. 2A). In contrast, the treated eyes were generally quiet (Fig. 2B), with minimal inflammation in the anterior chamber and vitreous cavity. Although the anterior chamber cells and flare subsided by the 19th day after the second challenge, the vitreous remained irreversibly opacified in all the untreated eyes until the end of the experiment (3V2 months). One rabbit in the treated group died on the fourth day after the second challenge. This rabbit never awakened from anesthesia on the third day after the second challenge, and its death was thought to be an anesthetic complication rather than a complication from the device. In the remaining three rabbits of the treated group, only one rabbit developed severe vitreous opacity.

Peripheral corneal neovascularization (Fig. 2C) was found in 6 of the 10 rabbits in the untreated group by day 7 after the first challenge, but in none of the treated group (P = 0.01). After the second challenge, all four of the untreated rabbits developed corneal neovascularization, whereas none of the three treated rabbits developed this complication (P = 0.06).

Severe iris congestion was found in 7 of the 10 rabbits by day 7 after the first challenge, but only in 3 of the 10 rabbits in the treated group. This difference was not statistically significant. After the second challenge, all four of the untreated rabbits developed severe iris congestion, whereas none of the three treated rabbits were found to have severe iris congestion (P = 0.06).

A small peripheral traumatic cataract was created in two of the treated rabbits and one of the control rabbits during device implantation. Of the remaining rabbits, posterior subcapsular opacity was found in 5 of the 7 (71%) untreated rabbits and in only 1 of the 6 (17%) treated rabbits by day 13 after the first challenge. After the second antigen injection, 3 of the...
The slit lamp biomicroscopic appearance of an untreated eye (A) and a treated eye (B) 3 days after the second antigen challenge. In the untreated eye, there is marked inflammation with corneal neovascularization and keratic precipitates in the lower portion of cornea (arrow points to the limbus). In contrast, the treated eye is quiet with a clear cornea and anterior chamber. (C) Extensive corneal neovascularization in an untreated eye on day 19 after the second antigen challenge.

4 untreated rabbits developed dense lenticular opacity that prohibited the observation of the posterior segment, whereas only 1 of the 3 treated rabbits developed dense cataract. These differences were not significant.

Posterior synechiae were seen in 60% of the untreated rabbits, but only in 10% of the treated rabbits, by day 3 after first antigen injection ($P = 0.06$). After the second antigen injection, all four untreated rabbits but none of the three treated rabbits had posterior synechiae ($P = 0.06$).

Intraocular pressure was measured on days 25 and 75 to assess the long-term effect of uveitis on the ciliary body, as well as the effect of dexamethasone on intraocular pressure. In the treated group, there was no statistically significant difference in intraocular pressure between the antigen-challenged eye and the fellow eye at either time point, whereas in the untreated group the intraocular pressure was significantly lower in the challenged eye than in the fellow eye at both time points ($P < 0.003$).

**Aqueous Protein Measurement and White Blood Cell Count**

The aqueous protein concentration and cell count confirmed the clinical observations (Fig. 3). In the treated eyes, the intravitreal dexamethasone device suppressed the mean aqueous protein concentration on both day 7 ($P = 0.05$) and day 13 ($P = 0.008$) compared to the untreated eyes. Similarly, in the treated eyes, the mean aqueous cell count was significantly lower on both day 7 ($P = 0.05$) and day 13 ($P = 0.008$) than in the untreated eyes.

**Microscopic Examination of Aqueous Smear**

The light microscopic examination of an aqueous smear of the untreated eyes stained by Wright's stain revealed numerous neutrophils and lymphocytes. In several smears, there were also some red blood cells that presumably resulted from the blood trapped in the needle while the anterior chamber paracenteses were performed. In contrast, there were no white blood cells seen in aqueous smears of the treated eyes.

**Electroretinography**

Both scotopic and photopic b-wave amplitude ratios (challenged eye/fellow eye) in the untreated group were markedly depressed compared to those in the treated eyes (Fig. 4). This depression was most marked after the second challenge; all four untreated eyes developed flat ERG waveforms by day 4 after the second challenge. Conversely, in the treated group, only one of the remaining three rabbits had a depression of the amplitude ratio (the same rabbit that developed a severe vitreous opacity). Differences between the two groups only approached marginal statistical significance at later time points, possibly due to the small sample size.

**Rate of Drug Release From Devices**

The device initially contained 5 mg of drug. The residual amount of dexamethasone in the three de-
Intravitreal Dexamethasone Device for Uveitis

FIGURE 3. The aqueous protein concentration (A) and cell count (B) on day 7 and day 13 after the first antigen challenge. Values represent mean ± SEM. Shaded box = experimental; diagonal box = control.

Histopathologic Study

Histology was performed for the purpose of illustrating the degree of inflammation in the experimental eyes compared to that of the control eyes. On histologic examination of the untreated eyes, there was a severe inflammatory cell infiltration that consisted of numerous polymorphonuclear leukocytes, lymphocytes, and macrophages. In the anterior segment, inflammatory cell infiltration was seen in the peripheral corneal stroma, limbus, and anterior chamber angle. Peripheral corneal neovascularization was frequently present (Fig. 6). The ciliary processes were markedly swollen with surrounding inflammatory cell infiltration and epithelial cell disorganization (Fig. 7A). In the posterior segment, inflammatory cells were also seen throughout the vitreous, retina, and choroid (Figs. 8A, 8B). Focal granulomatous chorioretinitis and vitritis were found in several sections (Fig. 8A). In most parts of the retina, the photoreceptor cell layer was necrotic or absent (Figs. 8A, 8B). A serous retinal detachment was present in some regions of the posterior retina, and there were numerous polymorphonuclear cells and lymphocytes in the subretinal fluid. Conversely, 8 out of 9 treated eyes showed minimal inflammation and preservation of normal intraocular architecture (Figs. 7B, 8C). There was no corneal neovascularization. Only one treated eye showed severe inflammation similar to the untreated eyes.

FIGURE 4. The b-wave amplitude ratios of scotopic (A) and photopic (B) ERGs versus time. Values represent mean ± SEM.
DISCUSSION

In this study, we demonstrate that an intravitreal sustained-release dexamethasone device is effective in suppressing the leukocyte infiltrate and protecting the blood ocular barriers in an experimental uveitis model induced by \textit{M. tuberculosis} antigen. Aqueous leukocyte count and protein measurement have been shown to be objective, quantifiable indicators of the severity of the anterior chamber inflammation and the integrity of blood aqueous barrier. In our study, the clinical grading of anterior chamber cells was confirmed by aqueous cell count and suggests that the intravitreal sustained-release dexamethasone device effectively inhibits the anterior chamber leukocyte infiltrate. Similarly, the clinical grading of anterior chamber flare was confirmed by aqueous protein determination and indicates that the dexamethasone device has a protective effect on the blood-aqueous barrier.

Currently available methods of delivering corticosteroids to the posterior segment are not optimal. Topical corticosteroids are effective in suppressing anterior chamber inflammation in various experimental uveitis models. However, they are often not adequate for the treatment of posterior inflammatory conditions. Systemic corticosteroids may provide therapeutic intravitreal levels. However, this form of therapy inevitably exposes the patient to many hazardous systemic side effects. Although periocular injection of corticosteroids provides another means to administer locally high doses of corticosteroid, the therapeutic effect on posterior inflammation is not reliable. Jennings et al have shown that in patients with uveitis and cystoid macular edema, posterior sub-Tenon’s injection of corticosteroid does not consistently affect blood-retinal barrier permeability. Similarly, by using Gd-DTPA magnetic resonance imaging, Wilson and associates have shown that intravitreal corticosteroid injection effectively protects the blood-aqueous barrier.
FIGURE 8. (A) The histopathologic appearance of an untreated eye. Note focal granulomatous inflammation involving vitreous, retina, and choroid. The photoreceptor layer is completely destroyed. Hematoxylin–eosin; original magnification, X250. (B) High-power view of sections of the retina in an untreated eye. There is marked inflammatory cell infiltration. Note the absence of outer segments and disorganization of the inner segments of the photoreceptor layer. Toluidine blue; original magnification, X625. (C) High-power view of sections of the retina in a treated eye. Inflammation is minimal, and the tissue integrity is preserved. Toluidine blue; original magnification, X625.

Intravitreal Dexamethasone Device for Uveitis

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retinal barrier from the detrimental effect of argon laser retinal photocoagulation; however, this protective effect was not seen after sub-Tenon's corticosteroid injection. In contrast, our results indicate that the dexamethasone device is effective in treating posterior uveitis. Treated eyes had clear vitreous, a normal appearing retina clinically and histopathologically, and a normal ERG. Untreated eyes, however, had an opaque vitreous by ophthalmoscopy, a severe vitreous and retinal inflammatory cell infiltrate, and disorganization of the retinal architecture on histopathologic examination. The sequelae of this inflammatory insult to the posterior segment was a loss of retinal function, as demonstrated by the flat ERG. Thus, by suppressing the posterior inflammatory reaction, the dexamethasone device preserves the retinal electrical activity.

The inflammatory reaction in the untreated eyes after the second challenge was even more severe than that after the first challenge, suggesting that there was a local immune sensitization after the first intraocular antigen challenge. In contrast, the treated eyes appeared to have a milder inflammatory reaction after the second intravitreal injection of antigen than that after the first challenge. Although the small number of animals undergoing rechallenge precluded definitive conclusions, we hypothesize that suppression of local immune sensitization by the dexamethasone or, alternatively, that higher tissue levels of dexamethasone at the time of the second challenge may provide a prolonged antiinflammatory effect during recurrent episodes of inflammation. Experiments to test this hypothesis are under way in our laboratory.

In addition to the therapeutic effect of the device on acute inflammation, the dexamethasone device was also effective in decreasing the incidence and the severity of chronic complications after experimental uveitis. The device prevented the development of corneal neovascularization, preserved the intraocular pressure, and lowered the incidence of cataract formation.

The absence of corneal neovascularization in all the treated eyes suggests that the dexamethasone device suppresses the angiogenic stimuli induced by the uveitis.20,21 On histologic examination of the cornea of the untreated eyes, corneal neovascularization was accompanied by inflammatory cell infiltration. Although the exact pathogenesis of corneal neovascularization is unknown,22 evidence suggests that leukocyte infiltration is a major contributing factor23–26 and that the inhibitory effect of corticosteroids on neovascularization is mediated by inhibition of leukocyte infiltration.31,32 Thus, although the device is located in the vitreous cavity, our results indicate that effective dexamethasone levels are established in the anterior segment, suppressing the inflammation in the cornea.
and consequently preventing the formation of neovascularization.

Intraocular pressure was sustained in all the treated eyes, whereas in the untreated eyes, the intraocular pressure was significantly lower compared to healthy fellow eyes. Clinically, uveitis can be associated with either increased, normal, or decreased intraocular pressure. In our study, the decrease in intraocular pressure in the untreated eyes may be a consequence of inflammatory infiltration of the ciliary body with epithelial destruction and tissue edema, as seen on histologic examination. The normal structure of the ciliary body with minimal leukocyte infiltration seen in the histologic examination of the treated eyes suggests that the dexamethasone device preserved the normal aqueous production by inhibition of the cyclitis.

Cataract formation is a common sequelae of chronic uveitis. In rabbits, cataract has been observed in several experimental uveitis models. By intravitreal injection of concanavalin A, Gwon and associates were able to induce a prolonged experimental uveitis with cataract formation in a rabbit model. Posterior subcapsular cataracts were initially observed as early as 2 weeks after intravitreal injection, some of which progressed to mature nuclear and cortical cataracts after 16 weeks. In their study, topical corticosteroids resulted in less severe anterior uveitis but had minimal effect on the posterior uveitis and the incidence of cataract formation. In our study, posterior subcapsular cataracts were observed on day 13 after the first intravitreal injection, and dense, mature nuclear and cortical cataracts were observed after the second intravitreal injection. In the treated group, the dexamethasone device seemed to lower the incidence of both types of cataract; however, because of the small sample size, these differences were not statistically significant. Although posterior subcapsular cataract formation can be caused by both corticosteroids and uveitis independently, mature dense cataracts are not usually caused by corticosteroids and are more likely sequelae of chronic inflammation. Our results suggest that by inhibiting the severity of posterior uveitis, the dexamethasone device may be beneficial in the prevention of uveitis-induced cataract.

Intravitreal corticosteroid injection has been shown to be effective in suppressing intraocular inflammation in a variety of infectious and noninfectious conditions. However, most previous studies involved a single intravitreal injection of dexamethasone in the treatment of intraocular inflammation. Dexamethasone is rapidly eliminated from the eye after direct intravitreal injection, with a half-life of less than 4 hours. The chronic and recurrent nature of endogenous uveitis usually necessitates sustained therapeutic tissue levels of corticosteroids. The intravitreal sustained-release dexamethasone device is designed to deliver a controlled amount of dexamethasone in the vitreous cavity for a prolonged time. Previous pharmacokinetic studies have shown that the devices release dexamethasone at 1.5 ± 0.2 μg/hour for more than 3 months and maintain drug levels of 2.5 ± 1.2 μg/ml when implanted into the vitreous of rabbit eyes. After 3 months, the devices release at a slightly slower rate of about 0.9 μg/hour and can maintain the vitreous drug level of 0.2 to 1.0 μg/ml for another 2 months. This concentration has been shown in vitro to be effective in suppressing several inflammatory processes, including the production and function of many cytokines, the synthesis of prostaglandins, and the migration and function of leukocytes. Our study shows that the intravitreal dexamethasone devices can exert their effect for at least two episodes of experimentally induced uveitis separated by 2 weeks. By the end of the experiment, 99 days after device implantation, approximately 30% of the drug remained in the devices. These results suggest that the device could continue to release dexamethasone for an even longer time.

The pharmacokinetics of dexamethasone device in the inflamed eye are not known. However, in the current study, analysis of the residual amount of dexamethasone in the devices taken from the treated rabbit eyes revealed a higher release rate of dexamethasone within 2 weeks of the first antigen challenge than at subsequent time points. In in vitro studies using a sustained-release device containing acyclovir and flurbiprofen, the drug release rate was 35 times faster in serum than in buffer solution. Together, these results suggest that during the active inflammatory episode, in which there may be breakdown of the blood ocular barriers and leakage of serum components into the eye, the device may have a higher release rate; as the eye quiets with restoration of the blood ocular barriers, the release rate decreases. If confirmed, these release kinetics would be another advantage of the sustained-delivery system, namely, that the drug is released in proportion to the severity of the active disease.

Corticosteroids have been shown to be relatively safe when administered as an intravitreal injection. In our studies, there was no toxicity that could be attributed to the intravitreal sustained-release dexamethasone device either by clinical observation, electroretinography, or histologic examination. A separate study performed in our laboratory also showed that the dexamethasone device did not cause any change in lens clarity, ERG, or retinal anatomy. Similarly, Kwak and colleagues found that an intravitreal injection of dexamethasone, up to 440 μg, is nontoxic to the retina, lens, and cornea in a rabbit model. Other long-acting corticosteroids, such as triamcinolone ace-
tonide, also have been shown to be nontoxic to various intracellular tissues.\(^{50}\) Although it is not possible to compare directly the toxicity of dexamethasone using these two delivery methods, our results suggest that the intravitreal sustained-release dexamethasone device is a safe method of administering a prolonged therapeutic level of corticosteroid to intraocular tissues. Systemic drug levels were not obtained in the rabbits given the device; however, these levels may be calculated using available pharmacokinetic data on the implant. The device is known to release dexamethasone at a rate of 2 \(\mu g\) per hour in vitro. Assuming a distribution volume of 1 (that is, all the drug is released into the systemic circulation) and a systemic half-life of less than 24 hours, the steady state systemic concentration of the drug would be below detectable limits (less than 0.2 ng/ml in a rabbit, and even lower in a human). Thus, a patient would be exposed to negligible levels of systemic corticosteroids, with a correspondingly low risk of adverse systemic side effects.

Our study shows that the dexamethasone device is effective in suppressing severe experimental panuveitis. However, one should be cautious in extrapolating the rabbit data directly to humans. There are at least three possible factors that must be considered further. First, dexamethasone, at the usual therapeutic level, is cytotoxic to rabbit lymphocytes.\(^{51,52}\) This effect is not observed in humans. Thus, the actual effectiveness of the dexamethasone device in humans may not be the same as that in rabbit study. Second, although the dexamethasone device did not appear to induce cataract formation in the current experiment, the follow-up may not be long enough for this effect to be observed. Cataract is a well-known side effect of long-term corticosteroid therapy.\(^{53}\) Because the sustained-release dexamethasone device is intended to be placed into the vitreous for a prolonged time, it is possible that cataract may develop as a side effect. Third, increased intraocular pressure is always a risk when corticosteroids are used chronically for the treatment of patients. Although we found no difference in the intraocular pressure between dexamethasone-treated eyes and fellow eyes, our sample size may have been too small to detect this effect. In addition, the ocular hypertensive effect of the intravitreal dexamethasone device may have been counterbalanced by the hypotonic effect of uveitis. Finally, it has been shown that rabbits are not reliably susceptible to a corticosteroid-induced elevation in intraocular pressure,\(^{54}\) whereas in humans a substantial percentage of the population may have such a response.

In conclusion, we have demonstrated that an intravitreal sustained-release dexamethasone device is highly effective in suppressing at least two episodes of induced inflammation in a rabbit model of severe panuveitis for more than 3 months. Devices with a longer release rate may prove useful in the management of uveitis in a selected patient population.

**Key Words**

Experimental uveitis, dexamethasone, intravitreal sustained-release device, corneal neovascularization, blood ocular barrier

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