Assessment of Subconjunctival and Intrascleral Drug Delivery to the Posterior Segment Using Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Stephanie H. Kim, Craig J. Galbán, Robert J. Lutz, Robert L. Dedrick, Karl G. Csaky, Martin J. Lizak, Nam Sun Wang, Ginger Tansey, and Michael R. Robinson

PURPOSE. Sustained-release intravitreal drug implants for posterior segment diseases are associated with significant complications. As an alternative, subconjunctival infusions of drug to the episclera of the back of the eye have been performed, but results in clinical trials for macular diseases showed mixed results. To improve understanding of transscleral drug delivery to the posterior segment, the distribution and clearance of gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA) infused in the subconjunctival or intrascleral space was investigated by means of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

METHODS. In anesthetized rabbits, catheters were placed anteriorly in the subconjunctival or intrascleral space and infused with Gd-DTPA at 1 and 10 μL/min. Distribution and clearance of Gd-DTPA were measured using DCE-MRI. Histologic examination was performed to assess ocular toxicity of the delivery system.

RESULTS. Subconjunctival infusions failed to produce detectable levels of Gd-DTPA in the back of the eye. In contrast, intrascleral infusions expanded the suprachoroidal layer and delivered Gd-DTPA to the posterior segment. Suprachoroidal clearance of Gd-DTPA followed first-order kinetics with an average half-life of 5.4 and 11.8 minutes after intrascleral infusions at 1 and 10 μL/min, respectively. Histologic examination demonstrated expansion of the tissues in the suprachoroidal space that normalized after infusion termination.

CONCLUSIONS. An intrascleral infusion was successful in transporting Gd-DTPA to the posterior segment from an anterior infusion site with limited anterior segment exposure. The suprachoroidal space appears to be an expandible conduit for drug transport to the posterior segment. Further studies are indicated to explore the feasibility of clinical applications.

From the 1Department of Chemical and Biomolecular Engineering, University of Maryland, College Park, Maryland; the 2Division of Bioengineering and Physical Science, Office of Research Services, National Eye Institute, and the 3MRI Research Facility, National Institute of Neurological Disease and Stroke, National Institutes of Health, Bethesda, MD.

Sustained-release polymeric implants have been shown to be effective in delivering drugs from the anterior vitreous to the posterior segment to treat macular diseases. However, ocular drug distribution studies have demonstrated significant drug concentrations in the anterior segment leading to complications including cataract and glaucoma. In addition, surgical entry through the pars plana to access the anterior vitreous has been associated with implant extrusion, vitreous hemorrhage, and retinal detachment. To improve the efficacy and safety of drug delivery to the macula, temporary cannulas have been placed in the subconjunctival space on the episclera behind the macula, followed by drug infusions. The safety profile appears excellent; however, the drug concentrations in the macula may not have been optimal, given the marginal results in clinical trials for macular disease. To improve our understanding of transscleral drug delivery to the posterior segment, we examined the distribution and clearance of a model drug, gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA), infused in the subconjunctival space using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Because our previous work had suggested that the blood vessels and lymphatic circulation in the conjunctiva may be a barrier to transscleral delivery, we also evaluated infusion in the intrascleral space.

MATERIALS AND METHODS

Infusion Procedure

Female New Zealand White rabbits weighing 3 to 3.5 kg were purchased from Covance Laboratories, Inc. (Vienna, VA) and were used according to the guidelines set forth in the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Rabbits were monitored under general anesthesia during the magnetic resonance imaging (MRI) scan period. Placement of subconjunctival catheters behind the globe has been reported to deliver drugs to the macular region. However, access to the back of the globe is difficult, and intrascleral catheter placement may result in an inadvertent perforation. As a result, we placed catheters anteriorly, with the axis parallel to the limbus, for easier access. A 90° vycryl suture was placed at the limbus and the eye was rotated downward to expose the superonasal quadrant. A 24-gauge × 4-inch-long intravenous catheter (Terumo Medical Corp., Somerset, NJ) was prepared by removing the plastic tubing and hub from the needle and cutting off the tubing from the hub. The tube and hub were threaded back onto the needle and then inserted either subconjunctivally or intrasclerally 3 to 4 mm from the limbus. For intrascleral insertions, incisions were made in the conjunctiva and Tenon’s fascia with Wescott scissors to reveal bare sclera, to ensure that the tubing was placed intrasclerally. The catheter was inserted superonasally and was advanced into the eye at least 5 mm for subconjunctival infusions and 3 mm for intrascleral infusions. The needle was then carefully withdrawn, leaving the catheter in the tissue. The eyelids were sutured closed to prevent corneal and sclera desiccation during the scan, and the distal portion of the catheter was left pro-
truding between the eyelids. The catheter was connected to 7 m of PE-10 tubing (BD Biosciences, Franklin Lakes, NJ) by a 10-cm length of silicone tubing (0.025 in. inner diameter × 0.047 in. outer diameter, RensSil; Braintree Scientific, Inc., Braintree, MA). The silicone tubing was glued on one end to the PE-10 tubing and prefilled with Gd-DTPA solution (Magnevist; Berlex, Inc., Montville, NJ) before connecting to the catheter by a friction fit. The Gd-DTPA solution was prepared by diluting the stock concentration 100-fold in phosphate-buffered saline (PBS; pH 7.4) to 5 mM. The solution was administered through the entire tubing by using a programmable infusion syringe pump (Stoelting Co., Wood Dale, IL) located outside the scan room. A three-way stopcock was used to connect the syringe and the PE-10 tubing to prevent leakage of solution from the catheter before and after the infusion. The Gd-DTPA solution was faintly colored with 100 mg/mL sodium fluorescein (Akorn, Inc., Decatur, IL) to a final concentration of 0.5 mg/mL to enhance visibility of the fluid in the tubing.

MRI Experiment

Experiments were performed using a 4.7-T MRI system (Bruker Instruments, Billerica, MA). After placement of the catheter, a 4-cm passively decoupled receive-only surface coil was placed over the rabbit’s eye. The rabbit was placed on a cradle and inserted in a transmit-only volume coil. TR/TE = 400/16 ms, field of view (FOV) = 4.7 × 4.7 cm², matrix = 256 × 256, and averages = 2. Each scan lasted 3.5 minutes. Three contiguous 1.5 mm slices were acquired by using two different orientations (Fig. 1). Slices in orientation 1 (O1) were aligned parallel to the cornea and placed near the posterior edge of the lens. Slices in orientation 2 (O2) were orthogonal to O1 and cut through the major axis and the infusion site. One set of scans (O1 and O2) was acquired before the start of infusion. The infusion was then started at either 1 or 10 μL/min, and the eye was scanned continuously for 20 to 30 minutes. For rabbits infused intrasclerally, the infusion was then halted, and scanning continued until Gd-DTPA signal had cleared completely from the suprachoroidal space. All rabbits were euthanatized by pentobarbital overdose (200–250 mg/kg) at the end of each MRI experiment. All experiments were repeated at least in duplicate.

Image Analysis

MR images were analyzed using ImageJ (ver 1.33a; available by ftp at zippy.nimh.nih.gov/ or at http://rsb.info.nih.gov/nih-image; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD). Signal intensities from MR images were normalized to an average signal intensity from a region-of-interest (ROI) determined within the vitreous for each scan. We assumed that the concentration of Gd-DTPA within the vitreous was negligible during the time course of all experiments. Temporal analysis of the signal intensities from the vitreous region starting from the preinjection scan to the end of the experiment indicated that its signal intensity value was relatively constant with values that were 5 to 10 times lower than the average signal intensity values from the suprachoroidal region. The signal intensities in the vitreous had a mean fluctuation of ±15% during the entire course of each experiment. Further support for the assumption of negligible vitreous concentration is derived on the basis of the low Gd-DTPA permeability of the ocular tissues (see the Discussion section).

To perform quantitative calculations of clearance rates for clearance from the suprachoroidal space, the normalized signal intensities for each pixel in an ROI were recorded and converted into Gd-DTPA concentration by using a calibration curve determined from various concentrations of Gd-DTPA (pH 7.4) in 2% hydroxypropyl methylcellulose (HPMC) samples in PBS. The calibration curve was constructed by scanning the HPMC samples with the same MR imaging parameters used for the rabbit infusion experiments. The peak signal intensity of the calibration curve occurred at 5 mM, which was chosen as the calibration concentration. A similar calibration curve has been reported. The detection limit of our technique was 0.1 mM.

The circumferential distribution and clearance rate of Gd-DTPA in the suprachoroidal space was determined from the three image slices acquired in O2 during intrascleral infusion experiments. The mass clearance rate of Gd-DTPA from the suprachoroidal space was calculated from the normalized signal intensity converted to concentration in each image by the following procedure: an ROI was established in each of the three slices from the last scan obtained before halting infusion, to monitor the clearance of Gd-DTPA from the suprachoroidal space. The ROI consisted of a curved line that was drawn through the hypointense suprachoroidal band. The ROIs were saved and superimposed onto the images of successive scans acquired during Gd-DTPA clearance. Normalized signal intensities for each pixel in an ROI were recorded and pixels with values near background intensity were discarded. The remaining pixels of the ROI were used to calculate a mean signal intensity which was converted into the average Gd-DTPA concentration of the suprachoroidal space.

The mass of Gd-DTPA for each image was determined by multiplying the average concentration of Gd-DTPA by the volume of the corresponding suprachoroidal space (number of pixels remaining in the ROI × pixel volume). The average mass of Gd-DTPA in the suprachoroidal space was computed by using the mass values of the three slices. The average mass clearance of Gd-DTPA was fitted to an exponential function, \( M = Ae^{-kt} \), where \( M \) is the mass of Gd-DTPA in the ROI at time \( t \), \( A \) is a constant, and \( k \) is the rate constant for clearance. The half-life was derived from the rate constant \( (t_{1/2} = 0.693/k) \). Regressions were also performed on semilog plots of \( M \) versus time and probabilities of the goodness-of-fit of the exponential curve were computed.

Histology Study

Six rabbits under anesthesia were infused at 10 μL/min intrasclerally with 5 mM Gd-DTPA for 1 hour to examine the eye histologically for toxicity. Two rabbits were euthanatized, and the infused eyes were enucleated immediately upon death. The four remaining rabbits were recovered from anesthesia; two rabbits were euthanatized after 24 hours and the remaining two after 3 weeks. Rabbit eyes were enucleated immediately upon death. To limit the potential for fixation artifacts and to maintain the spatial relationship of the choroid and retina, enucleated eyes were immediately placed in plastic molds filled with embedding medium (Tissue-Tek OCT Compound; Sakura Finetek, Torrance, CA) and flash frozen at −80°C. Frozen eyes were sectioned coronally in 10-μm slices on a cryostat at −20°C and fixed in 4%
paraformaldehyde after sectioning. Dried sections were stained with hematoxylin-eosin for light microscopy. Histologic sections were also acquired from rabbits without prior infusion to serve as control images.

RESULTS
Subconjunctival Infusion
Most of the Gd-DTPA infused subconjunctivally appeared to remain in the bleb formed by the conjunctival tissue. Increasing the infusion rate from 1 to 10 μL/min only increased the bleb size and did not contribute to any noticeable penetration of Gd-DTPA into the underlying tissues (Figs. 2A–C). Additional experiments were performed with 10 μL/min subconjunctival infusions lasting up to 2 hours (data not shown). However, a comparison of the scans to those acquired before infusion revealed that levels of Gd-DTPA were below the detection limit in the choroid/retina during the entire scan period.

Intrascleral Infusion
During intrascleral infusions, Gd-DTPA was seen to appear in the suprachoroidal space, indicated by the inner hyperintense band (Figs. 2D, 2E). Due to limited resolution, the distribution of Gd-DTPA in the inner choroid and retina was not discriminated. There was no Gd-DTPA detected in the anterior chamber, with a small increase in signal intensity present in the ciliary body region near the catheter tip.

Gd-DTPA was detected in the suprachoroid immediately after the start of infusion at 1 and 10 μL/min. Gd-DTPA began to spread posteriorly in the suprachoroid from the infusion site. Figure 3 represents the distance traveled from the infusion site by the leading edge of the Gd-DTPA signal. After 7 minutes of a 1 μL/min infusion, the posterior spread of Gd-DTPA in the suprachoroid reached a steady state and covered an average circumferential distance of 7 mm (Fig. 3). Prolonged infusion produced only a minimal increase in Gd-DTPA distribution. Figure 4 shows the spread of the Gd-DTPA signal in the O1 and O2 planes during a 10 μL/min intrascleral infusion. Increasing the infusion rate to 10 μL/min caused Gd-DTPA to travel farther into the suprachoroidal space. This distance is shown in Figure 3 (squares). After 14 minutes of infusion Gd-DTPA had reached the optic nerve (Fig. 4F). Continued infusion increased the amount of Gd-DTPA in the suprachoroidal space. Gd-DTPA was also detected in the conjunctiva near the infusion site. This suggests that intrascleral catheters may also allow Gd-DTPA to partially infuse the overlying conjunctiva.

A comparison of images taken in O1 (Figs. 4A–D) and O2 (Figs. 4E–H) shows that Gd-DTPA traveled slightly farther by moving parallel to the limbus rather than in the posterior direction toward the optic nerve. This movement may be due to the transport and mechanical properties of the involved tissues but could also be influenced by the orientation of the catheter, which was placed parallel to the limbus rather than pointing toward the posterior pole of the eye.

**FIGURE 2.** (A) T1-weighted image (O2) before infusion; after 42 minutes of subconjunctival infusion (B) at 1 μL/min and (C) at 10 μL/min; and after 31.5 minutes of intrascleral infusion (D) at 1 μL/min and (E) at 10 μL/min. Arrows: catheter tubing; arrowheads: Gd-DTPA in suprachoroidal space. In T1-weighted images the conjunctiva and choroid/retina appear hyperintense, whereas the sclera appears hypointense. The color scale bar on the left indicates the signal intensity converted to concentration in molar units.

**FIGURE 3.** Spread of Gd-DTPA measured in the suprachoroidal space in images (O2) during intrascleral infusion at 1 μL/min (▲) and 10 μL/min (■).
Suprachoroidal Clearance

Qualitatively, the MR images in Figure 5 show that the concentration of Gd-DTPA in the suprachoroidal space decreases uniformly after halting intrascleral infusion. Images shown in Figure 5 were positioned more obliquely than those shown in Figures 4E–H.

The clearance rate of Gd-DTPA from the suprachoroidal space was determined from a quantitative analysis of the Gd-DTPA mass at sequential time points, as described in the Methods section. The rates of suprachoroidal clearance for 1 and 10 L/min infusions are plotted in Figure 6 by using the average mass from the three slices acquired in O2 for each scan. The clearance data show a good fit to exponential equations (probability in Fig. 6 caption). This suggests that the mass clearance from the suprachoroidal space can be modeled as first-order for both 1 and 10 L/min infusions, with half-lives of 5.4 and 11.8 minutes, respectively. Complete Gd-DTPA clearance from the suprachoroidal space after intrascleral infusion at the 1 and 10 L/min required approximately 20 and 60 minutes, respectively.

Histologic Examination

Eyes enucleated immediately after 1 hour of a 10 L/min intrascleral infusion showed an expansion of the suprachoroidal space (Fig. 7). This indicated that much of the infused Gd-DTPA solution accumulated in the suprachoroidal space. In eyes enucleated 24 hours after infusion, the suprachoroidal space had normalized, and tissue structures were no different from control images taken before infusion (Fig. 7A). Eyes enucleated 3 weeks after infusion also showed normal ocular tissues by light microscopy.

DISCUSSION

Subconjunctival catheter infusions demonstrated no levels of Gd-DTPA in the choroid/retina detectable by dynamic MRI, possibly because of clearance by conjunctival blood vessels and lymphatics and by rapid removal of any agent that does diffuse to the choroid. Although sustained delivery methods have been proposed as a method to enhance delivery to the choroid and retina, the results from this study show that the concentration of Gd-DTPA in the choroid/retina was under the MRI detection limit after sustained subconjunctival infusion.

In contrast, intrascleral catheter infusions expanded the suprachoroidal layer and rapidly delivered Gd-DTPA circumferentially and posteriorly with very limited anterior segment exposure. Our results indicate that higher infusion rates allow greater distribution of Gd-DTPA in the suprachoroidal space. Whereas intrascleral infusions of 10 L/min achieved Gd-DTPA delivery to the optic nerve after 15 minutes, infusions of 1 L/min localized the spread of Gd-DTPA near the infusion site. The rate of infusion and clearance may have reached equilibrium during 1 L/min infusions, and this may account for the steady state in spatial distribution of Gd-DTPA in the suprachoroidal space.
Suprachoroidal clearance (mean ± SD of three slices) after 1 and 10 µL/min intrascleral infusion. Triangles: rabbit 1; squares: rabbit 2. Open symbols: 1 µL/min; filled symbols: 10 µL/min. Dashed lines: exponential curve fit for rabbit 1; solid: rabbit 2. Average half-life: 5.4 minutes (1 µL/min), 11.8 minutes (10 µL/min). The goodness-of-fit probabilities for all experiments were <0.0001 except for rabbit 1, 1 µL/min, which was 0.001.

The suprachoroidal space is a virtual space and is avascular, consisting of loose connective tissue. It was assumed that, after intrascleral infusion, the suprachoroidal space consisted mostly of Gd-DTPA solution (as shown by histology), and that this could be adequately modeled using a polymer solution. Gd-DTPA calibrations were not made for other ocular tissues (sclera, choroid, retina), since quantitative calculations were only performed for the Gd-DTPA signal present in the suprachoroidal space.

Although the suprachoroidal clearance data from this study was obtained from a portion of the globe, an estimate of the amount of Gd-DTPA present in the entire suprachoroidal space after 30 minutes of infusion at 10 µL/min can be calculated by multiplying the average suprachoroidal Gd-DTPA concentration by the volume of the suprachoroidal space. Adapting a methodology for the calculation of the scleral surface area, the surface area of the suprachoroid was approximated as 8 cm². The suprachoroidal space is included within a volume of 8 cm³ multiplied by the pixel width (0.184 mm). This calculation yields an approximate apparent volume of 150 mm³. Because the average concentration of Gd-DTPA after 30 minutes of infusion is approximately 0.001 M, the estimated mass of Gd-DTPA in the suprachoroidal space is approximately 0.14 mg. This value represents approximately 10% of the total infused amount of Gd-DTPA.

The suprachoroidal clearance of Gd-DTPA was rapid, and the agent was undetectable in the eye after approximately 1 hour after a 10 µL/min infusion. Clearance of Gd-DTPA followed first-order kinetics and the average half-life after a 30-minute 10 µL/min infusion was approximately double that of a 1 µL/min infusion. Although the higher infusion rate increased the half-life, the fast elimination of Gd-DTPA from the suprachoroidal space suggests that infusions may have to be maintained for a defined period, to deliver the desired amounts successfully. The actual mechanisms responsible for the decrease in Gd-DTPA are not known but could include diffusion and convection through the sclera, uptake by the chorio-capillaris, and movement of tracer laterally out of the plane of the image slices. The pressure created by the solution infused into the eye may also contribute to the elimination of Gd-DTPA.

In calculating the suprachoroidal mass clearance of Gd-DTPA, the number of pixels in the ROI that were above background signal intensity decreased with time, and this may reflect the volume decrease of the suprachoroidal space after halting infusion. Although the data from this study are insufficient to determine whether the decrease in Gd-DTPA mass is due to the decrease in volume, the normalization of the suprachoroidal space over time indicates that fluid may also be cleared from the suprachoroidal layer.

Limitations in sensitivity and resolution prevented the detection of low levels of Gd-DTPA in the choroid/retina and vitreous and the delineation of the plane between the neurosensory retina and choroid. The resolution used in this study also could not clearly separate the Gd-DTPA solution filled suprachoroidal space from the choroid/retina. Partial volume averaging may contribute to error in calculation of the Gd-DTPA mass clearance rate. There have been recent reports demonstrating high resolution in ocular MRI. However, we were unable to use these scanning methods in this study due to limitations in temporal resolution. The dynamics of suprachoroidal Gd-DTPA distribution during and after infusion are rapid, and fast scan times were necessary to acquire a sufficient number of images for clearance rate determination.

DCE-MRI has shown to be useful in determining pharmacokinetic and physiologic properties. Studies involving ocular pharmacokinetics with MRI have been previously reported. MRI pharmacokinetics is an emerging field, and the improved resolution with newer generation scanners will allow for noninvasive pharmacokinetic analysis in preclinical evaluation of ocular drug delivery systems.

The expandable capabilities of the suprachoroidal layer have been demonstrated clinically where large choroidal effusions after glaucoma filtering procedures can resolve without sequelae. Previous animal studies with deliberate expansion of the suprachoroidal space with volumes of hyaluronate more than 300 µL have shown that expansion is associated with choroidal engorgement and an increase in choroidal thickness.

Figure 7. Hematoxylin-eosin stained light microscopy images. (A) Without infusion. (B) After a 10-µL/min infusion for 1 hour. Scale bar, 50 µm.
show complete resolution without toxicities.55,56 Our histologic studies with rabbits that were infused intrascleral at 10 μL/min for 1 hour showed that the suprachoroidal layer could expand and contract without affecting tissue morphology and structure. This suggests that intrascleral infusions at rates of up to 10 μL/min for 1 hour can be safely performed in rabbits.

Technological advances with programmable implantable pumps across many specialties can potentially be applied to deliver drugs in the sclera for an extended period.57–59 Because there are no implantable infusion pumps approved for ocular drug delivery, a 15-minute intrascleral infusion using an external pump may be feasible to deliver a sustained-release formulation into the suprachoroidal space over the macular region.60–63 The suprachoroidal space would serve as a reservoir for a sustained-release formulation that establishes a steep concentration gradient for drug diffusion into the choroid and retina. Investigators have directly accessed the posterior segment through the suprachoroidal space by using either a rigid10 or flexible (Olsen TW et al. IOVS 2006;47:ARVO E Abstract 3882) cannula. After placement of a cannula behind the porcine eye via the suprachoroidal space and injection of a triamcinolone acetonide depot posteriorly, pharmacokinetic studies showed high local drug concentrations in the choroid and retina in the macular region for at least 4 months. The flow-assisted delivery system used in our study may be a safer alternative, since mechanical damage from the catheter tip, such as choroidal tears and optic nerve injury, would be avoided (Olsen TW et al. IOVS 2006;47:ARVO E Abstract 3882). Diffusion-based implants have also been used for drug delivery to the retina through the suprachoroidal space, requiring surgical incisions for placement of the implant.11–12 However, the implant insertions, necessitating incisions through the sclera and dissection to the suprachoroidal space, are invasive and may have a greater potential for adverse events.

In vitro methods using perfusion apparatuses with isolated sclera with or without choroid tissue mounted between two chambers, have traditionally been used to study transscleral drug delivery (Cheruva NPS et al. IOVS 2005:46:ARVO E Abstract 5390).14,43–46 However, the barriers to transscleral delivery are complex and involve intact physiologic systems to evaluate properly.12,47 The barriers to transscleral drug delivery leading to subtherapeutic drug levels in the choroid and retina are (1) the sclera acting as a physical diffusion barrier19,44,48; (2) drug clearance via conjunctival lymphatics and blood vessels5; (3) drug clearance via the choroidal blood vessels6; (4) counterdirectional fluid currents from uveoscleral flow50,51 hydrostatic,52,53 and osmotic pressure54 differences, all resulting in bulk flow from the vitreous to the choroid and episcleral region; (5) the tight junctions and cellular barriers of the retinal pigment epithelium55; and (6) the retina.56,57 Specific drug characteristics, such as molecular weight, charge, and lipophilicity can also impact drug tran-
sit.13,14,19,46 Further in vivo imaging and pharmacokinetic studies are warranted to improve our understanding of the barriers to transscleral drug delivery and optimize the design and placement location of systems for drug delivery to the choroid and retina.

In addition to the questions of MRI spatial and temporal resolution, there were several other limitations in this study. One has to be cautious in extrapolating ocular imaging data from rabbits to humans, given the relative differences in the size of the eye, scleral thickness, choroidal flow velocities, and degree of retinal vascularization.58,59 In addition, the results of the ocular distribution and clearance of Gd-DTPA cannot be generalized to all drugs because of differences in properties relevant to drug transport.13,14,19,45 The effect of pigment binding in the uvea can influence drug transport, but this is not studied appropriately in albino rabbits.

We anticipate future studies that include examining changes in Gd-DTPA ocular distribution with different catherer tip orientation and using higher infusion concentrations of Gd-DTPA to monitor its penetration into the vitreous, to estimate tissue permeability values. In this study, the concentration of Gd-DTPA in the vitreous was assumed to be below the detection limit of 0.1 mM at all times for all experiments. We normalized all signal intensity values to the vitreous signal intensity which we assumed to have negligible concentrations Gd-DTPA. We feel that this assumption is justified on the basis of the low infusion concentration (5 mM), the limited time course of our image acquisitions, and low the permeability of the retina-choroid-sclera membrane (2.0 × 10^-6 cm/s)10 to Gd-DTPA. Using higher concentrations of Gd-DTPA may produce lower signal intensities near the infusion site due to T2-shortening effects, but the concentration of Gd-DTPA in the vitreous may rise above detection limits and allow measurement of Gd-DTPA concentration levels. As mentioned in the Methods section, the average signal intensity of the vitreous did not significantly change during the duration of the experiments of our study. Longer scan times may allow greater amounts of Gd-DTPA to accumulate in the vitreous, producing higher signal intensities.

In summary, Gd-DTPA could not be detected in the choroid retina with subconjunctival infusions. In contrast, an intrascleral catheter was successful in transporting Gd-DTPA to the posterior segment, and there was limited drug exposure of the anterior segment. The suprachoroidal space appears to be an expandable conduit to transport drugs from the front to the back of the eye, and further studies are in progress to explore its potential for clinical applications.

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