

New Developments in the Transscleral Delivery of Ophthalmic Agents

The profile of the drug being delivered is as important as the delivery method.

BY KARL G. CSAKY, MD, PhD

Multiple approaches have been used to deliver drugs to the posterior pole. Of these approaches (Table 1), the two that are used most commonly are intravitreal injections and the implantation of sustained delivery devices into the vitreous cavity.¹ Both of these approaches, however, can be associated with multiple serious complications including endophthalmitis, retinal detachment, vitreous hemorrhage, and ocular trauma. Additionally, drugs delivered into the vitreous have the disadvantage of poor access to the outer retina and choroid, the anatomic location of diseases such as age-related macular degeneration (AMD) (Figure 1).

Periocular delivery through a subconjunctival, suprachoroidal, or juxtasceral method offers the advantage

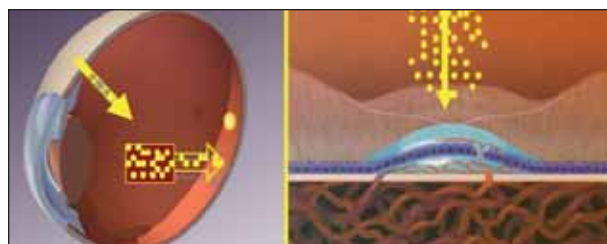


Figure 1. Drugs delivered into the vitreous have the disadvantage of poor access to the outer retina and choroid, the anatomic location of diseases such as AMD.

of a noninvasive approach. These methods may be especially suitable for the long-term treatment of disease such as diabetes, nonneovascular AMD, uveitis, and especially in prophylactic therapy to prevent progression and vision loss.

CURRENT STATE-OF-THE-ART METHOD?

Juxtasceral administration of anecortave acetate, for example, has been reported to result in therapeutic levels of the drug in the choroid and the retina for up to 4 to 6 months after administration. A subconjunctival injection of water-soluble dexamethasone appears to enter the eye and is detectable in the subretinal fluid up to 20 hours after a presurgical injection.²

TABLE 1. DRUG DELIVERY TO THE RETINA

• Eye Drops	• Juxtasceral Injection
• Scleral Plug	• Intravitreal Implant
• Subconjunctival Implant	• Intravitreal Injection
• Suprachoroidal Implant	• Oculex Products



Figure 2. Researchers have injected microspheres containing the antiangiogenic compound PKC 412 subconjunctivally in a porcine model of laser-induced choroidal neovascularization (B). Panel A shows the experimental CNV control lesion while Panel C shows the barely detectable lesion after therapy.

Researchers have injected microspheres containing the antiangiogenic compound PKC 412 subconjunctivally in a porcine model of laser-induced choroidal neovascularization (CNV) Figure 2.³ Panel A in Figure 2 shows the experimental CNV control lesion while panel C shows the barely detectable lesion after therapy.

In these experiments, the drug was detected in the retina 20 days after injection. For true long-term therapy, however, the use of a sustained delivery device may be essential. We have been exploring this technique and have studied the long-term safety of these devices in rabbits. For reservoir devices made of silicon or polyvinyl alcohol, indeed, these implants are highly tolerable for longer than 1 year.

TYPES OF SUBCONJUNCTIVAL IMPLANTS

There have been several studies on various types of subconjunctival implants. Of great importance are the limitations of this approach, which have been demonstrated. The release of lipophilic fluorescein in a subconjunctival implant shows that the drug penetrates a small anatomic area with subsequent poor levels in the retina (Figure 3). This tells us that the limitation of this approach might not be technical but scientific, namely understanding the question of why drugs do not enter the eye from an episcleral location.

To study this question we have been using MRI to examine drug distribution from a subconjunctival location. MRI has the advantage of allowing us to follow the

INTRAVITREAL DRUG DELIVERY DEVICE FOR AMD TREATMENT

REVIEWED BY HEATHER SHEARDOWN

An intravitreal device with a flexible, polydimethyl siloxane (PDMS)-based reservoir, coupled to an array of hollow glass microneedles, may offer an alternative for delivering targeted drugs to the posterior segment.

According to an abstract to be presented at the 2007 Association for Research in Vision and Ophthalmology meeting, this device was able to store, transport and eject liquid targeting the posterior eye segment. "Further benefits include ease of device fabrication, low manufacturing costs, and minimal use of expensive clean room facilities," wrote Heather Sheardown, McMaster University, Hamilton, Ontario, and colleagues.

An effective means of drug delivery to the posterior segment, especially in diseases such as age-related macular degeneration, has yet to be developed, the investigators wrote. In this study, they evaluated the feasibility of a drug-delivery device fabricated using photolithographic techniques to create a replica mold that could be repeatedly used to cast PDMS-based devices.

According to the abstract, the devices were coupled to hollow glass needles that could penetrate the sclera and vitreous. "We sought to determine if the resultant microfluidic system was capable of delivering liquid drug solution to the posterior eye segment of enucleated bovine eyes in a controlled and targeted fashion," the researchers wrote.

The device was placed onto the sclera of an enucleated bovine eye and inserted through the vitreous for infusion of a dye into the posterior segment. The device delivered a suspension of liquid dye into the ocular model at the targeted posterior delivery site. The investigators anticipate that tuning the device will permit the delivery of novel posterior segment drugs over a prolonged period of time. ■

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Mahadevan G, Jones K, Selvaganapathy P, Sheardown H. An intravitreal device for drug delivery to the posterior eye for the treatment of age related macular degeneration. To be presented at the 2007 Association for Research in Vision and Ophthalmology meeting, May 10, 2007. Fort Lauderdale, Fla.

drug in a live animal. In addition, MRI has the potential to allow us to extend our animal data and study ocular distribution in patients as well.

We placed subconjunctival implants containing the MRI contrast agent gadolinium in rabbits and studied drug distribution in both live animals and animals post-

euthanasia. Previous work had demonstrated that the sclera was not an important barrier to drug delivery. We found that no drug penetrated the posterior segment in the live animal (Figure 4), and a small amount of drug entered the anterior chamber. To our surprise, however, once the animal was euthanized, periocular drug

NONINVASIVE DRUG DELIVERY WITH THE VISULEX DEVICE FOR UVEITIS

REVIEWED BY JOHN W. HIGUCHI, MBA, MSIS

The Visulex (Aciont Inc., Salt Lake City) noninvasive, iontophoretic ocular delivery system for posterior eye diseases can deliver, noninvasively, a therapeutically relevant dose of triamcinolone acetonide.

According to an abstract to be presented at the Association for Research in Vision and Ophthalmology meeting in May, researchers performed iontophoresis of triamcinolone acetonide phosphate (TAP) on the eyes of healthy white New Zealand rabbits. They used an electrical current of 3.0 milliamps for 20 minutes using a Visulex sustained-release formulation of TAP, *in vivo*.

John W. Higuchi and colleagues from Aciont conducted an experiment to examine the amounts of triamcinolone acetonide and TAP delivered into the eye, whereby, the investigators dissected the eyes and used HPLC assay to determine drug distributions in the rabbit ocular tissues. An efficacy experiment study was also conducted to evaluate the Visulex transscleral drug delivery system in an endotoxin-induced posterior uveitis rabbit model using direct ophthalmologic examination. The investigators also visually tracked a contrast agent as part of a precipitating sustained-release depot (Figure 1) formed by the Visulex treatment at different time points with MRI to determine the distribution of the agent released from the depot.

"In the pharmacokinetics study, the amounts of TAP and triamcinolone acetonide delivered and formed as a depot immediately after treatment into the sclera and retina/choroid sections were approximately 0.30 mg and 0.03 mg, respectively, using the Visulex system," according to the abstract. Significant levels were also found in similar tissue samples dissected from other eyes at later time points. The results of the efficacy study showed a significant improvement in the uveitis score of the eyes treated by the Visulex/TAP sustained release formulation over the standard formulation and untreated controls. The MRI study showed noticeable distribution of the contrast agent from the precipitating drug depot toward the back of the eye.

Mr. Higuchi and colleagues concluded that the studies

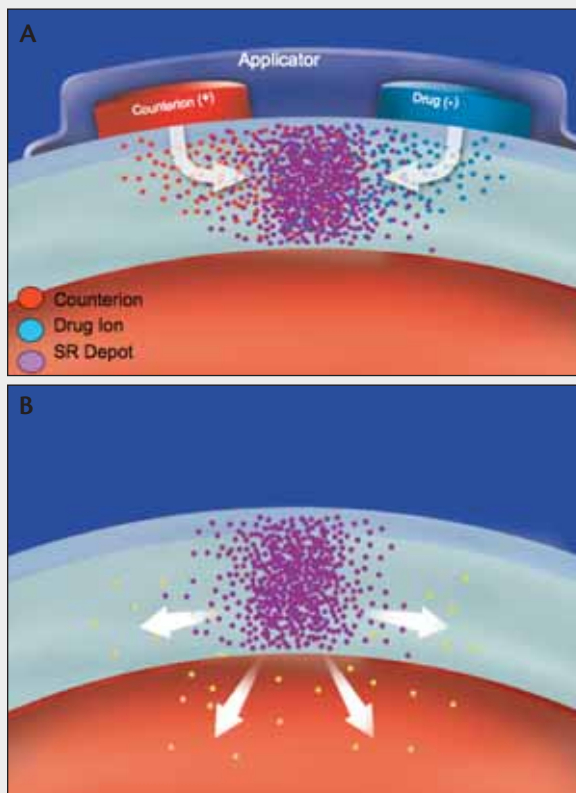


Figure 1. Visulex depot-forming methodology.

support that the Visulex sustained release system can deliver, in a noninvasive fashion, a dose of therapeutically relevant TAP/triamcinolone acetonide for the treatment of posterior eye diseases. Further studies need to be conducted to fully evaluate completely the distribution of drug released over time from the Visulex-created sustained release drug depots in the eye. ■

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Higuchi JW, Higuchi WI, Li SK, et al. Noninvasive delivery of a transscleral sustained release depot of triamcinolone acetonide using the Visulex device to treat posterior uveitis. To be presented at the Association for Research in Vision and Ophthalmology 2007 annual meeting. May 10, 2007. Fort Lauderdale, Fla.

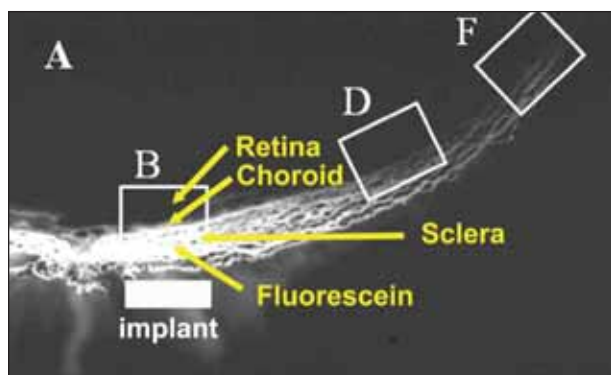


Figure 3. The release of lipophilic fluorescein in a subconjunctival implant shows that the drug penetrates a small anatomic area with subsequent poor levels in the retina.

appeared to pour into the eye. These results led us to the conclusion that the main barrier to drug delivery was actually physiologic and not anatomic in nature.

To verify this result we performed direct drug level detection in rabbits following subconjunctival injections of triamcinolone. The drug was not detected in the vitreous in the live animal, but following euthanasia the amount increased in the vitreous, confirming the importance of these physiologic barriers.

PHYSIOLOGIC BARRIERS

What are the main physiologic barriers to ocular drug penetration? There are three important ones: the episclera and conjunctival lymphatics and blood vessels, and the blood flow of the choroid. To understand more fully the relative contribution of these mechanisms, surgical elimination of each barrier was performed in rabbits. To eliminate the role of choroidal blood flow, cryotherapy was performed, and cuts in the conjunctiva and episclera were performed to negate the superficial elimination pathways.

Following each of these steps, triamcinolone was placed over the area and drug levels were measured in the vitreous. Only the animals undergoing the surface elimination of superficial lymphatics and conjunctival blood flow had a change in vitreous levels of triamcinolone, suggesting that this pathway—the episcleral lymphatic and blood flow pathway—may be playing a more important role than we had previously thought.

In fact, when we went back to our original gadolinium implant studies in the live animal to try to find out where the drug went when it did not go into the eye, we could localize the drug in the buccal lymph node, confirming the robust lymphatic clearance of drug from around the eye.

Do these observations have any clinical relevance as we

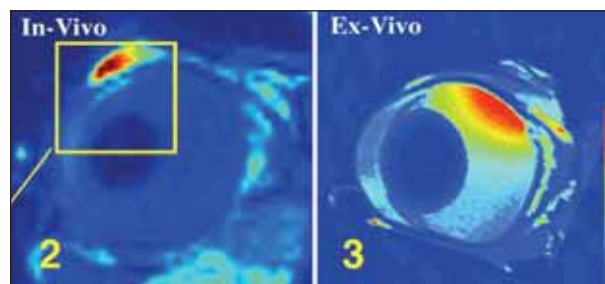


Figure 4. We placed subconjunctival implants containing the MRI contrast agent gadolinium in rabbits and studied drug distribution in both live animals and animals post euthanasia. No drug penetrated the posterior segment in the live animal, and a small amount of drug entered the anterior chamber. Once the animal was euthanized, periocular drug appeared to pour into the eye.

develop transcleral drug delivery modalities? While a trial in humans is still being planned, a trial in horses provides some potential clues. In a trial treating chronic equine uveitis, sustained drug delivery implants containing cyclosporine were initially placed in a subconjunctival location. Using this approach, however, no clinical response was noted.

To our surprise, when the same implant was placed into the suprachoroidal space, a dramatic response ensued, leading to an almost complete resolution of this disease. These results have important implications for future human trials.

It is important to note that a critical aspect of transcleral delivery is the drug compound itself. There are properties of a drug that lend themselves to transcleral delivery, including activity at low levels and lipophilicity. Newer polymer technologies, now under development, may allow for future transcleral delivery of peptides, aptamers, and indeed proteins.

The future of transcleral drug delivery is exciting and clearly represents one of the main important goals of treatment for our patients. ■

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