Intraocular Nanoparticle Drug Delivery: A Pilot Study Using an Aerosol during Pars Plana Vitrectomy

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PURPOSE. To describe a method of drug delivery to the retina via aerosolized nanoparticles in the gas phase during the gas-exchange stage of vitrectomy in a porcine model.

METHODS. An ultrasonically atomized and dried sodium fluorescein aerosol was produced with a concentration of 12 ng/mL and a mass median particle size of 407 nm. Eighteen porcine eyes were randomly divided into six groups and subjected to standard three-port pars plana vitrectomy. After the air-fluid exchange and during the gas exchange, the eyes were exposed to the aerosol, either as a steady flow through the chamber (3.6 μg/min) or as a single fill (50 ng) at three exposure times (three eyes/time point).

RESULTS. The flow-through delivery mode provided a relatively uniform deposition of aerosol on the inner surface of the retina, and longer delivery time led to an increase in the quantity deposited, with greater than 40 ng total deposition by 10 minutes. The single-fill method had uniform deposition but lower total delivery, approximately 10 ng by 60 minutes. Modeling of the data suggests that deposition in the flow-through mode is successful if the vitreous chamber contents are well mixed. The single-fill delivery was described by diffusion in a quiescent state.

CONCLUSIONS. This study demonstrates a novel method of drug delivery to the posterior pole by using aerosolized nanoparticles that may be used in the gas phase of vitrectomy. Therapeutic applications include antimitabolites for modulation of proliferative vitreoretinopathy, antimicrobial agents for endophthalmitis, antiangiogenic compounds for vasoproliferative disorders, corticosteroid delivery, and other pharmacotherapies directed at the retina and choroid. (Invest Ophthalmol Vis Sci. 2007;48:5243–5249) DOI:10.1167/iovs.07-0523

PROLIFERATIVE VITREORETINOPTHY (PVR) is the leading cause of retinal redetachment and requires aggressive surgical means to correct the anatomic abnormalities.1–6 Ryan postulated that mechanical intervention (surgical treatment) will be necessary until pharmacologic intervention can be used to control the cellular processes.2 To date, limited therapeutic options are available to modify the healing response that occurs after retinal detachment.

Many authors have reported on the long and varied risk factors for PVR that include: preoperative PVR, larger or multiple retinal breaks (i.e., giant retinal tears), duration of the detachment, associated choroidal detachment, vitreous hemorrhage, recent complicated cataract surgery (i.e., vitreous involvement with cataract surgery), multiple surgeries, low preoperative intraocular pressure, more than two quadrants involved, anterior proliferation, inferior detachment, complex cytokine interactions (possibly cytokine gene polymorphism), myopia, uveitis, endophthalmitis, trauma, intraocular foreign bodies, use of extensive cryotherapy, and younger age.3,7–33 Nagasaki et al.22,24 conclude that the events responsible are those that lead to a “breakdown of the blood–ocular barrier.”

Proliferation of dispersed retinal pigment epithelial (RPE) cells or glial cells from the neurosensory retina leads to preretinal fibrosis, contraction, and PVR with detachment of the retina. Currently, the standard of treatment of PVR is surgical and involves scleral buckling surgery, pars plana vitrectomy, membrane dissection, and the use of postoperative gas-phase tamponade with agents such as perfluoropropane (C3F8) or sulfur hexafluoride (SF6). Alternatively, silicone oil is commonly used as a permanent tamponade but requires a second surgery for removal. Asaria et al.34 demonstrated in a randomized, prospective clinical trial that 5-FU and heparin in the infusion bottle during the fluid phase of vitrectomy in humans decreases the rate of PVR and redetachment. However, the technique described has not gained widespread acceptance for a variety of reasons. First, the infusion solution has adverse effects on external ocular tissues. Management and containment of the fluid after the infusion exits the eye is challenging and can interfere with proper wound healing, especially in cases in which sutureless closures are used. In addition, logistic constraints involved in formulation and compounding off-label agents into vitrectomy fluids limit the ease of use.

A necessary stage of the surgical procedure is the air fluid, followed by a gas exchange. During this phase, the retina is reapposed to the RPE and underlying choroid by the intraocular tamponade and high surface tension properties of air. We believe that this phase of the surgery provides an opportunity for drug delivery. Recent technology has allowed the aerosolization of drug into nanoparticles that can be suspended in air and delivered into the gas phase of the retinal tamponade. This novel method of drug delivery could be optimized in animal models of PVR to study the effects in vivo. Delivery in the air phase allows for the maintenance of air or gas tamponade, while still allowing for delivery of drugs, a unique advantage. Although other methodologies are available for the fluid phase of delivery, such as intravitreal injections, implants, or pellets, the pharmacokinetics from these methods are less optimal in gas-filled eyes. The proposed technology would also have applications for treating other retinal disorders during vitrectomy, including infectious retinitis, proliferative disorders such as diabetic retinopathy with tractional detachments, and im-

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mune modulation such as the treatment of uveitis, or even cystoid macular edema with corticosteroids.

In this study, we describe a methodology for the delivery of aerosolized nanoparticles by using a tracer dye in the porcine model. In the future, diverse types of drugs could be delivered with this technology, including antimetabolites such as 5-FU or mitomycin, corticosteroids, peptides, lipophilic agents, combinations of drugs, and numerous other therapeutic agents. Herein, the aerosol deposition was determined with two types of delivery: either flow through or single fill of the vitreous chamber.

METHODS

Materials

Sodium fluorescein (Sigma-Aldrich, St. Louis, MO) and 2',7'-dichlorofluorescein (Eastman Organic Chemicals, Rochester, NY). All organic solvents were HPLC grade, and the water was deionized and distilled in an all-glass apparatus.

Aerosol Generation and Characterization

For particle generation, a Pyrex glass baffle was constructed (University of Minnesota, Department of Chemistry Glass Shop) and placed in the water bath directly over the ultrasonic transducer. The 2.55-MHz transducer was custom built (Boston Piezo-Optics, Boston, MA) and used to generate the initial droplets of a sodium fluorescein solution (0.1 mg/mL) that were subsequently dried on a silica column. The transducer was driven with a frequency generator (WaveTek; BK Precision 4040A; B&K Precision Corp., Yorba Linda, CA), and the signal was amplified with an EIN RF power amplifier (model 350L, B&K Precision Corp.). Air was directed into the baffle and adjusted to a flow rate of 300 mL/min, measured by an inline flow meter. The air entrained the aerosol droplets containing sodium fluorescein and carried the particles into the silica drying column.

The particle size distribution of the dry particles was determined after isokinetic dilution of the aerosol particles with an electromobility analyzer coupled with a scattered-light detection system (model 1000XP WPS; MSP Corp., Minneapolis, MN). The mass output of the aerosol was determined by collecting the particles on a filter at reduced pressure. The filters were extracted with a basic aqueous solution, and the fluorescence intensity was measured with a microplate reader (model FL600; Bio-Tek Inc., Winooski, VT).

Animals and Surgery

All animals were handled in accordance with both the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the University of Minnesota Institutional Animal Care and Use Committee guidelines. Telazol (Fort Dodge Animal Health, Fort Dodge, IA)/xylazine (2-10 mg/kg IM) was given as a preanesthetic, and general anesthesia was induced intravenously with a triple-drip solution containing ketamine 2 mg/mL and xylazine 1 mg/mL, and 5% guaifenesin. The solution was titrated to effect, and oxygen was delivered via nasal cannula with intubation equipment available. The pupil was pharmacologically dilated using 2.5% phenylephrine along with 1% tropicamide and 1% atropine eye drops. The eye was prepared and draped, and a lid speculum was inserted into the eyelid. An infusion cannula with intubation equipment available. The pupil was pharmacologically dilated using 2.5% phenylephrine along with 1% tropicamide and 1% atropine eye drops. The eye was prepared and draped, and a lid speculum was inserted into the eyelid. An infusion cannula was injected onto a 250-mm² chamber. The infusion cannula was connected to a high-efficiency filter to prevent contamination of the outer surface of the eye as well as the atmospheric air of the operating room. The eye was passaged through the chamber for 20 seconds to remove the remaining particles before kill/dissection. The aerosol was vented from the eye by an infusion tube that was connected to a high-efficiency filter to prevent contamination of the outer surface of the eye as well as the atmospheric air of the operating room. For the single-fill delivery group, the vitreous chamber was filled with the fluorescein aerosol at 300 mL/min for 20 seconds (i.e., a brief flow through) followed by removal of the tubes and sealing the holes. We refer to this method as single fill. The aerosol was allowed to deposit onto the inner surface for 30, 45, or 60 minutes, and then the animal was euthanized and the eye immediately enucleated. In these experiments, the enucleation time ranged from 8 to 10 minutes. The uvea (retina and choroid) and sclera were divided in half to assess the uniformity of deposition on the inflow and outflow sides (inflow half on one side, outflow half on the other). After dissection, the tissues were frozen in liquid nitrogen and stored in a freezer.

Tissue Analysis

Fluorescein was assayed by HPLC with an adaptation of the procedure of Knudsen et al. The tissues were weighed, and 10 mM phosphate buffer (pH 10) along with 20 μL of a 10-mg/mL solution of 2',7'-dichlorofluorescein as internal standard was added to glass vials that were vortexed and refrigerated overnight. After centrifuging at 13,000 rpm for 10 minutes, the supernatant was transferred to a clean centrifuge tube. The extraction was repeated, the combined supernatants were diluted with phosphate buffer, and 20 μL of supernatant was injected onto a 250-mm × 4-mm, 5-μm column (Asahipak ODP-50; Agilent, Santa Clara, CA). The other HPLC components consisted of a solvent delivery module (model LC-10AT) an auto injector (model SIL-10AD), fluorescence detector (model RF-10A XL), and integrator (C-R5A Chromatopac; all from Shimadzu Corp., Kyoto, Japan). The extraction efficiency of sodium fluorescein ranged from 60% to 95%, depending on the tissue.

RESULTS

The average output rate of sodium fluorescein from the ultrasonic generator/drying system was 5.73 ± 0.68 μg/min, and the mass median particle size and associated geometric stan-
As with the significant difference between the means (paired at 3, 5, and 10 minutes. At each time, there was no significant difference between the means (P < 0.05) and thus the data from the two sides were pooled.

The mass of fluorescein at the inflow side and outflow side in the uvea and sclera as a function of time for the flow-through delivery model of aerosol exposure was compared at 3, 5, and 10 minutes. Each at time, there was no significant difference between the means (P < 0.05) and thus the data from the two sides were pooled.

The pooled mass of fluorescein in the tissues increased with longer delivery time and was highest in the retina/choroid or uvea (Fig. 2). The mass of fluorescein deposited on the uvea appeared to reach a peak at 45 minutes, whereas the lens and sclera never exceeded 8 ng on the uvea, with much less detected in the sclera and lens. The mass on the sclera was similar to that on the lens. The corresponding concentrations are provided in Table 1, where the concentration of fluorescein (mass of fluorescein/weight of tissue, ng/g) in uvea is seen to be higher than that in the sclera at each interval.

The results for the single-fill delivery are shown in Figure 3. As with the flow-through delivery mode, there was no difference in the distribution of fluorescein between the inflow and outflow sides. Thus, the data were pooled. The total mass never exceeded 8 ng on the uvea, with much less detected in the lens and sclera. In addition, the change in mass with time in the uvea appeared to reach a peak at 45 minutes, whereas the mass in the sclera and lens increased with exposure time.

To compare the two different delivery modalities, the total mass of fluorescein (the sum of the fluorescein in the uvea, sclera, and lens) as a function of time is shown in Figure 4. For the flow-through method, the mass observed at 3 minutes of flow was near 25 ng and rose to nearly 45 ng as the time of flow increased to 10 minutes. For the single-fill delivery mode, the observed mass was lower, with only approximately 5 ng at 30 minutes. The mass deposited remained relatively static at 60 minutes, with none of the values significantly different (P = 0.05).

The delivery efficiency was determined by expressing the percent fluorescein deposited relative to that delivered. For the flow-through mode, the deposition rate, in terms of mass per unit time, was divided by the mass inflow rate of fluorescein, also given as mass/time, and then expressed as a percentage. In Figure 5, the percent deposited was initially approximately 0.2%, and it fell with time to a little over 0.1%.

Figure 6 shows the corresponding deposition efficiency for the single-fill delivery mode. In this case, the deposited mass was calculated as a fraction of the total mass of aerosolized fluorescein that was introduced into the eye. The deposition efficiency was much higher than the flow-through delivery mode and reached a maximum value near 20% at 45 minutes.

### DISCUSSION

We have described a novel method of drug delivery to posterior segment tissues, using aerosolized particles during the gas exchange phase of vitrectomy surgery. This new method has broad implications for pharmacotherapies delivered to an air- or gas-filled eye. Furthermore, we have investigated the kinetics of drug deposition with two variants of this methodology: the single-fill and the flow-through modes.

Pharmacologic management of retinal disorders, such as PVR, requires a measured and reliable method of delivery.

### Table 1. Concentration of Fluorescein in Eye Tissues

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Delivery Mode</th>
<th>Uvea (ng/g)</th>
<th>Sclera (ng/g)</th>
<th>Lens (ng/g)</th>
<th>Uvea/Sclera Concentration Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Flow</td>
<td>36.6 ± 26.8</td>
<td>12.6 ± 11.2</td>
<td>24.1 ± 15.1</td>
<td>2.90</td>
</tr>
<tr>
<td>5</td>
<td>Flow</td>
<td>26.4 ± 15.7</td>
<td>8.32 ± 3.12</td>
<td>55.2 ± 25.8</td>
<td>6.82</td>
</tr>
<tr>
<td>10</td>
<td>Flow</td>
<td>50.9 ± 31.5</td>
<td>26.5 ± 26.9</td>
<td>66.2 ± 90.6</td>
<td>1.92</td>
</tr>
<tr>
<td>30</td>
<td>Fill</td>
<td>4.90 ± 4.91</td>
<td>1.07 ± 1.20</td>
<td>—</td>
<td>4.58</td>
</tr>
<tr>
<td>45</td>
<td>Fill</td>
<td>11.9 ± 10.5</td>
<td>0.99 ± 1.23</td>
<td>2.73 ± 4.73</td>
<td>12.0</td>
</tr>
<tr>
<td>60</td>
<td>Fill</td>
<td>10.1 ± 2.1</td>
<td>2.04 ± 0.93</td>
<td>6.58 ± 11.4</td>
<td>4.95</td>
</tr>
</tbody>
</table>

Data are expressed as mean nanograms per gram ± SD.
Management of drug delivery in the gas phase of surgery creates a unique opportunity for intervention at a critical stage in the complex cascade of cytokine expression and cellular proliferation. Gas-phase pharmacotherapy could allow for manipulation of the healing response that leads to severe vision loss from PVR. Careful and measured drug delivery is critical. For this reason, it is necessary to quantify the aerosol concentration of sample agents, expressed as the mass of drug in a given volume of air as well as the total mass, which is the product of the aerosol concentration and the volume. Such measures will help ensure more predictability with delivery.

Our results suggest that the flow-through delivery method has optimal tissue kinetics, with greater quantities of drug delivered in a short period, yet at lower efficiency. The single-fill method had lower quantities of drug delivered and required a significant additional amount of time, yet at higher efficiencies. By using the flow-through delivery mode, we were able to maintain a constant aerosol concentration of 12.4 ± 2.3 ng/mL in the globe. Using this value, we estimate that approximately 50 ng of fluorescein was suspended as an aerosol in a 4-mL vitreous chamber. In the single-fill delivery method, the globe (~4 mL) initially contained 50 ng of fluorescein aerosol, and the aerosol concentration decreased with time as deposition occurred. This method could be incorporated into either surgical or nonsurgical situations, such as office-based air-fluid gas exchanges or even pneumatic retinopexy, with predictable, albeit lower, quantitative delivery.

There are three main mechanisms by which aerosol particles can deposit at a surface: inertial impaction, sedimentation, and diffusion. Inertial impaction and sedimentation are more efficient, with larger particle size, whereas, diffusion is more efficient with smaller particle size. Moreover, both of these mechanisms would lead to a nonuniform deposition pattern. In both the flow-through and single-fill modes of delivery, the failure to detect a difference in the assayed mass of fluorescein on the inflow and outflow sides of the uvea at any time point is consistent with a mechanism of diffusional deposition, although data with greater reproducibility are needed to strengthen the argument.

If deposition occurred by random diffusion, the relative mass in the retina and choroid in comparison to the lens would be proportional to the exposed surface area. The retina/choroid-to-lens area ratio is estimated to be ~20, much higher than the observed mass ratio. Of note, a significant mass of fluorescein was measured in the sclera even at 3 minutes, suggesting that the solid particles of fluorescein were deposited within the surface fluid (probably a thin layer of residual vitreous), diffused into the retina/choroid and subsequently diffused into the sclera. By accounting for the 10-minute dissection time, the correction for the mass in the uvea to the mass of fluorescein that diffused into the sclera, the mass ratio is closer to the expected area ratio.

The time dependence of drug distribution is also important in delivery efficiency. Given the small number of animals used in this study, time-dependence data should be cautiously interpreted. Moreover, fluorescein is a small molecule, and the use of larger molecules or even peptides will change the kinetics. In the flow-through delivery, the concentration of fluorescein in the retina-choroid was two to three times higher than that in the sclera for all three delivery durations (Table 1). This concentration difference most likely provided the driving force for the transport of fluorescein from the uvea to the sclera. In addition, the uvea-to-sclera concentration ratio did not change with time. Therefore, transport of fluorescein from the uvea to sclera is likely to be more rapid than the transport into the orbit, with the sclera serving as a diffusion barrier, as previously suggested. Potential toxicities and variability of this methodology due to changes in the internal limiting membrane have not been specifically assessed. Finally, these estimates...
may underestimate actual tissue delivery due to loss into the retinal and choroidal vasculature.

In the single-fill delivery mode, the mass measured in the retina/choroid and sclera did not increase between the latter two time points (45 and 60 minutes). The concentration and rate of deposition of aerosol particles in the posterior segment decreased with time as deposition occurred. At 45 minutes, the tissue concentration appeared to reach a maximum, which would indicate that the rate of mass deposition in the uvea becomes smaller than the rate of mass transfer from the retina and choroid to the sclera. The single-fill method would be useful in intraocular gas–fluid exchanges, pneumatic retinopexy, or simply to supplement delivery from the flow-through method (i.e., leave the eye filled at the end of the air–fluid gas exchange). Intravitreal fluorescein kinetics have been studied in the fluid phase. Macha and Mitra\(^3\) studied the transport of fluorescein from the vitreous by using microdialysis. After intravitreal injection, fluorescein in the vitreous humor fell by first-order kinetics with a half-life of 3 hours, the rate was sensitive to the integrity of the blood–aqueous barrier, and there was no resistance by the vitreous. Fluorescein most likely enters the blood stream through the choroidal vessels, known to be permeable to fluorescein dye. Knudsen et al.\(^3\) observed that vitrectomized porcine eyes had an altered blood–retinal barrier with more rapid kinetic fluorescein transport and is transported or diffuses to other tissues or into the circulation. Deposition efficiency is the percentage of the fluorescein deposition that occurs by diffusion through the diffusional boundary layer (stagnant layer) was used. Based on the extensive work involving lung deposition (data not shown), the small particle size will lead to a slow sedimentation rate as well as a short stopping distance, which minimizes the role of sedimentation and inertial impaction in particle deposition. The rate of mass deposition, \(\Delta m/\Delta t\), would be calculated by: \(\Delta m/\Delta t = DAC/b\).

Where \(D\) is the diffusion coefficient of the aerosol particle, \(A\) is the area of the chamber, \(C\) is the aerosol concentration, and \(b\) is the boundary layer thickness. The value of the deposition rate was estimated from the slope of the total mass deposited as a function of time (ng/min; Figs. 4, 6). Using estimates for the parameters as given in Table 2, the diffusional boundary layer thickness is estimated to be 10 \(\mu\)m.

### Modeling Flow-Through Delivery

For flow-through, a model of aerosol particles of uniform concentration and the assumption that the deposition occurs by diffusion through the diffusional boundary layer (stagnant layer) was used. Based on the extensive work involving lung deposition (data not shown), the small particle size will lead to a slow sedimentation rate as well as a short stopping distance, which minimizes the role of sedimentation and inertial impaction in particle deposition. The rate of mass deposition, \(\Delta m/\Delta t\), would be calculated by: \(\Delta m/\Delta t = DAC/b\).

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### Modeling Single-Fill Mode Delivery

For single-fill delivery, two models estimate the deposited mass: a pure diffusion model and a stirred settling model. The diffusion model has an expression for the mass deposited with time that provides a solution for the diffusion equation with spherical coordinates:\(^3\)

\[
M(t) = M_0 \left[ 1 - \frac{6}{\pi^2} \sum_{n=1}^{R} \frac{1}{n^2} \exp \left( -\frac{n^2 a^2}{R^2} \frac{t}{D} \right) \right],
\]

where \(M_0\) is the initial mass of aerosol in a hollow sphere of radius \(R\), \(M(t)\) is the mass deposited in time \(t\), and \(D\) is the molecular diffusivity. For deposition by settling, two limiting cases of sedimentation are quiescent settling and stirred settling.\(^3\) In our application, we assumed stirred settling more applicable with an exponential decay in the aerosol population. Deposition can be represented as

\[
M(t) = M_0 [1 - \exp(-\beta t)],
\]

where the deposition rate coefficient \(\beta\) is expressed as the terminal velocity of sedimentation divided by the length scale of the enclosure. For the spherical geometry,\(^4\) the following after expression for \(\beta\) applies:

\[
\beta = \frac{3\nu}{4R}
\]
where \( v \) denotes the settling velocity. The corresponding deposition curve is shown in Figure 7 and represents a deposition rate much faster than that observed in porcine eyes. The stirred-settling model lacks an adequate representation of the movement of the gas phase. As particles move downward, they pull the surrounding gas down and a compensatory upward drift of gas fills the void, inhibiting particle deposition. At higher particle concentrations, this effect is more significant. The observed values are closer to the simulated values from the diffusion model that is not corrected for losses due to clearance. Nevertheless, the diffusion model seems more appropriate than the settling model.

Optimizing Aerosol Delivery

As discussed, the administration of the drug to the retina by aerosol should be optimized to attain the maximal mass. We suggest that using the flow-through mode for a specified time, followed by diffusional deposition, offers maximal delivery. Figure 8 simulates this combined method and is based on the measured deposition rates of flow-through mode for 10 minutes followed by single fill.

With discontinuation of the flow, mass is still deposited by diffusion, which can maintain the high concentration of fluorescein for more than 1 hour. If the particle size is reduced, the diffusional deposition time may be extended to several hours or even several days.

In summary, aerosol delivery of drug nanoparticles is a novel method for delivery of therapeutic agents to the posterior segment during an air or gas phase. Herein, we have characterized deposition with aerosolized fluorescein in a pig model of drug delivery and generated a model-based prediction for maximizing delivery. The flow-through delivery mode provided an increase in deposition with increasing flow time and would allow the effective concentration of therapeutic agents to be established quickly. Filtering the aerosol as it exits the eye decreases secondary external toxicities. The fill mode provides a means of sustaining delivery after the globe has been closed. Of clinical importance, the mass of drug deposited by a diffusion mechanism is distributed uniformly on the inner surface of the ocular chamber, providing an even layer of drug on the retinal/choroid tissue. The data are consistent with preliminary modeling efforts that suggest deposition occurs primarily by diffusion in both cases; however, greater reproducibility is needed along with a more careful examination of time-dependent distribution. Careful design of the aerosol generation and delivery parameters (aerosol particle size, delivery mode, and exposure time) and the formulation composition will lead to controlled and sustained release of the therapeutic agents. Aerosolized delivery of drugs to the posterior segment is a novel methodology for pharmacologic management of posterior segment disorders and takes advantage of the gas phase of vitrectomy to treat conditions such as PVR after retinal detachment in high-risk eyes. Additional uses could include antibiotics for endophthalmitis, antiviral for infectious retinitis, antiangiogenic compounds for proliferative disorders, or immunomodulation.

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References