Treatment of Intralocular Diseases with Poly(ortho ester)-Based Drug Delivery Systems

Suzanne Einmahl*[1], Francine Behar-Cohen[2], Cyrus Tabatabay[1], Robert Gurny[1]

[1] Department of Pharmaceutics and Biopharmaceutics, School of Pharmacy, University of Geneva, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland

[2] Department of Ophthalmology, Hôtel-Dieu Hospital, Place du Parvis de Notre-Dame 1, F-75004 Paris, France

SUMMARY: A poly(ortho ester) (POE) has been investigated as a carrier for controlled delivery in intraocular therapy. The intraocular biocompatibility of POE was assessed in the rabbit after intravitreal as well as suprachoroidal injections. In both cases, the injection was feasible and reproducible, and the tolerance of POE was good, with no clinical or cellular signs of inflammation. The polymer degraded slowly within 2 to 3 weeks, with total bioresorption. POE allowed to sustain the release of an antifibroblastic agent in a model of glaucoma filtering surgery in the rabbit. A formulation based on POE and 5-fluorouracil was administered to prevent the failure of the surgery. This POE formulation was effective in inhibiting the fibrotic response, allowing a local and controlled release of a small amount of the antiproliferative drug, while reducing its toxicity. Based on these results, POE appears to be a promising carrier for sustained drug delivery in treatment of intraocular affections.

Introduction

The treatment of many intraocular disorders is hampered by poor penetration into the eye of many topically or systemically administered drugs. To circumvent these barriers, different routes of intraocular drug delivery, such as subconjunctival, intravitreal or subretinal administration, have been investigated. Unfortunately, successful treatment of most intraocular diseases requires multiple intraocular injections to maintain therapeutically effective drug concentrations for a desired period of time. However, repeated intraocular injections cause several complications. Moreover, initial peak levels of drug after bolus injection result in toxicity to ocular tissues and severe side effects. Researchers have thus been encouraged to develop new systems of intraocular drug delivery that would sustain therapeutic levels of the drug over an extended period of time[1)]. A modern treatment modality would be to perform one single administration of a sustained delivery system that would release the drug over a period of 2 to 4 weeks. Among diseases particularly adequate for such

 CCC 1022-1360/00/$ 17.50+.50/0

therapeutic systems, are glaucoma filtering surgery, proliferative vitreoretinopathy (PVR) and age-related macular degeneration (AMD).

Glaucoma filtering surgery entails the construction of a fistula between the anterior chamber and the subconjunctival space as an alternative to or enhanced passage for the drainage of the aqueous humor from the eye, in order to reduce the intraocular pressure and preserve vision in severe cases of glaucoma patients. The outcome of filtering surgery is affected by wound healing, which leads to the obstruction of the filtration site due to fibroblast proliferation. Pharmacological treatment aims at the inhibition of the fibrotic response by frequent subconjunctival injections of anti-inflammatory and/or antiproliferative agents[2]. A sustained delivery system allows to reduce the frequency of these post-operative injections[3].

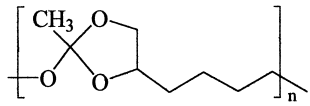
PVR is a pathologic condition occurring in part as a complication of retinal detachment, in which cells, originating from the retina, proliferate, inducing the formation of retractile membranes which re-detach the retina[4]. The aim of the pharmacological treatment of PVR is to target several stages of the disease with intravitreal injections of anti-inflammatory steroids and antifibroblastic drugs. A controlled delivery system offering a concomitant release of both types of drugs can prevent the development of PVR in high-risk eyes after retinal detachment surgery and hinder PVR recurrence while minimizing toxic side effects and improving the comfort of the patient[1].

AMD is the leading cause of irreversible visual loss in the elderly people in the world, due to degenerative changes in the retinal pigment epithelium (RPE) cells. The disease can appear as a localized degeneration without further complications, or in more severe cases, retinal cells are destroyed by the disruptive effects of choroidal neovascularization[5]. Laser photocoagulation of choroidal neovascular membranes is currently the only well-studied and widely accepted treatment modality. Consequently, investigators have attempted to develop new approaches for treating AMD. Pharmacological therapy has focused on interfering with inflammation, oxidative changes, and angiogenesis[6]. Notably, antiangiogenic drugs may be useful in treating the neovascular phase of AMD. A direct, slow-release suprachoroidal administration of drugs would allow to target choroidal neovascularization over a prolonged period of time[7].

Systems which control and prolong the action of therapeutic agents have grown in importance during the recent years with the development of bioerodible polymers. They are particularly advantageous for intraocular therapy, since there is no need to remove them after the drug has been released[8].

Poly(ortho ester)s (POE) are a new family of hydrophobic, biocompatible[9] and bioerodible

polymers presenting particularly interesting characteristics[10]. An example of third-generation poly(ortho ester) is



Due to their hydrophobic characteristics and lability of the ortho ester linkage, POE undergo surface erosion. Hence, drug release from POE is almost constant, following zero-order kinetics, without any burst effect. It can be controlled by factors such as polymer molecular weight and physicochemical properties of the incorporated substances[11,12]. Indeed, ortho ester linkages are sensitive to acid catalysis. Notably, the incorporation of basic additives, such as sodium acetate or magnesium hydroxide, allows to stabilize the polymeric backbone and hence prolong the lifetime of the polymer. Also drugs with base characteristics, such as dexamethasone sodium phosphate, possess this stabilizing property[12].

The viscous, ointment-like consistency of POE allows the incorporation of drugs by simple mixing at room temperature, without the use of solvents. POE-based formulations can be injected using a conventional syringe with an appropriate needle, which is a significant advantage when compared to solid devices that must be placed through a complex surgical procedure.

This paper presents results related to the intraocular application of the poly(ortho ester) in various tissues of the eye. First of all, their intraocular biocompatibility has been assessed in various parts of the rabbit eye, i.e. after intravitreal[9] and suprachoroidal injections. Polymer alone has been tested, but also POE formulations containing drugs or additives as degradation modulators. This study has also allowed to determine the lifetime of the polymer within the eye and to check if it is compatible with a sustained drug delivery over 2 to 4 weeks.

Then, an animal model of glaucoma filtering surgery has been developed in the rabbit. POE subconjunctival biocompatibility has been demonstrated[13,14]; thus, a formulation based on POE and containing an antiproliferative drug has been applied during the surgery to prevent the failure of the operation. Post-operative observations allowed to determine the efficacy of the POE formulation in this animal model.

Methods

Polymer synthesis

As previously described by Merkli et al.[10], the above POE is synthesized by a transesterification reaction between hexane-1,2,6-triol and trimethyl orthoacetate under

anhydrous conditions. The reaction is carried out in cyclohexane, with 4-methylbenzene-1-sulfonic acid as a catalyst. The formed methanol is removed by azeotropic distillation. Excess solvent is then poured off and the polymer is thoroughly dried under vacuum. The POE purification procedure consists of a precipitation in methanol, which removes all impurities such as residual monomers and oligomers. To further eliminate residual solvents, the polymer is dried under vacuum (1 Pa) at room temperature. The structure of the POE and intermediate hydrolysis products was characterized by ^{1}H and ^{13}C NMR spectroscopy[10]. The average molecular weight of the POE was determined by size exclusion chromatography, with tetrahydrofuran as eluent[10].

Preparation of POE-based formulations

The POE-based formulations were prepared under a laminar air-flow hood. The added substances were previously sterilized by γ–radiation at 2.0 Mrad and mixed with the aseptically prepared polymer under sterile conditions at room temperature[15]. The final concentration of incorporated substance was 1% w/w. Several formulations were tested:

- POE alone (MW 9000, 10000, 14000)
- POE loaded with magnesium hydroxide (MG), a basic additive which modulates POE degradation and prolongs its lifetime,
- POE loaded with drugs: an antimetabolite, 5-fluorouracil (5-FU), or an anti-inflammatory dexamethasone disodium phosphate (DEX). This derivative has been preferred (to other dexamethasone species, dexamethasone alcohol or dexamethasone acetate) due to its basic properties which stabilize the polymer[12].

Animals

Pigmented Fauve de Bourgogne female rabbits were used, and all experiments were conducted in accordance with the ARVO (Association for Research in Vision and Ophthalmology) statements on the use of animals in ophthalmic and vision research.

The rabbits were sedated with 2 mg/kg intramuscular nidazolam, and then anesthetized with 60 mg/kg intramuscular ketamine. If needed, pupils were dilated with topical 10% neosynephrine and tropicamide. Local anesthetic (oxybuprocain 0.4%) was applied before surgery.

Intravitreal biocompatibility

Intravitreal tolerance was evaluated in eyes (n=6) receiving 100 µL of each formulation. A lid speculum was placed and a transconjunctival incision of the sclera was made in the temporo-superior quadrant of the eye at 3 mm off the limbus under a surgical microscope, using a 45°

surgical knife. Then, an 0.9 mm needle was inserted in the vitreous cavity, with a glass slide over the cornea to allow visual control of the needle, and polymer formulation was slowly injected (Fig. 1).

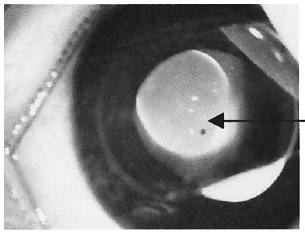


Figure 1: Intravitreal POE at the time of injection

Slit-lamp observations and photographs of the anterior chamber were regularly performed post-operatively during two weeks. The posterior segment was also periodically observed with a Volk Superfield lens. Eventually, rabbits were sacrificed by injection of a lethal dose of pentobarbital, their eyes enucleated and fixed to be studied histologically by conventional optical microscopy.

Suprachoroidal biocompatibility

The conjunctiva and Tenon's capsule were opened in the upper temporal quadrant as appropriate for the extent of the procedure. A small (2 mm), limbus-parallel full-thickness scleral incision was performed 5 mm from the limbus. Then, a 5-6 mm long tunnelization of the sclera was made with microsurgical scissors in order to separate the sclera from the choroid and reach the suprachoroidal space. A curved cannula with an olivary tip (0.6 mm ID) was introduced into the suprachoroidal space and advanced to the posterior pole (Fig. 2).

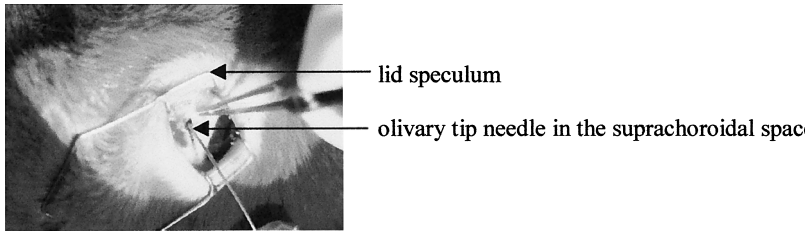


Figure 2: Suprachoroidal POE injection

Each formulation was injected with an injection volume of 100 µL (n=6). The needle tip was apposed to the inner wall of the sclera to avoid contact with choroid. No reflux of material was observed through the sclerotomy. The scleral incision was sutured by 8/0 silk sutures. The conjunctiva was finally sutured and topical antibiotic ointment was instilled to minimize

the risk of postoperative infection. The whole operation was followed under the operation microscope. The location of the injection was noted with indirect ophthalmoscopy.

Rabbits were examined at regular intervals after operation up to 20 days. Slit-lamp observations were performed in order to assess the inflammatory state of the eye. The fundus was observed by indirect ophthalmoscopy. Pictures of the fundus were taken with a retinograph specially designed for small animals (Kowa). Intraocular pressure was measured by Goldmann aplanation tonometry to detect any hypertony. Ultrasound echography (Alcon) was performed at regular intervals before and after operation to visualize POE in the suprachoroidal space. Fluorescein angiography was also performed at fixed times after operation to assess the presence of the polymer in the suprachoroidal space. A 10% fluorescein solution was injected intravenously with an injection volume of 0.5 mL. Fluorescein angiograms were performed with a fundus camera (Topcon). Rabbits were sacrificed as described above and histology study was performed.

Clinical application in an animal model of glaucoma filtering surgery

A lid speculum was inserted to expose the bulb. A limbus-based conjunctival flap was reflected. Tenonectomy was performed to expose the underlying sclera, followed by careful conjunctival dissection anteriorly to the limbus. Hemostasis was carefully maintained with cautery. At this point, a group of rabbits (n=6) received an intraoperative tamponade of 5-FU: a 4 x 1 mm dry section of a Weck cell sponge was soaked in a 50 mg/mL 5-FU solution, and the sponge was placed between the conjunctiva and the sclera, over the planned filtration site, for 5 min. The treated area was thoroughly irrigated with 20 mL of balanced salt solution. A half-thickness, limbal-based, 4 x 4 mm scleral flap was made extending just anterior to the limbus. A 3-mm limbal incision was made with a 45° blade which entered the anterior chamber. A block of tissue containing inner sclera, trabeculum and peripheral cornea, measuring about 3 mm x 1 mm, was excised at the limbus (Fig. 3a). A peripheral iridectomy was then performed. The scleral flap was approximated with two 8/0 nylon sutures. The conjunctiva was repositioned and the wound closed with 10/0 vicryl suture in a continuous fashion. Just before the last point, a 0.9 mm needle was inserted in the created subconjunctival pocket and 200 µL of polymer alone or loaded with 1% 5-FU was injected adjacent to the trabeculectomy (n=6) (Fig. 3b). The suture was tightly closed and a topical antibiotic ophthalmic ointment was applied.

Slit-lamp observations were regularly performed during 30 days after operation to assess the filtering bleb status and the overall inflammatory state of the eye. Intraocular pressure was measured at regular times using Goldmann aplanation tonometry and compared with the

preoperative intraocular pressure. The persistence of the POE bleb was assessed. 5-FU was quantified in the anterior chamber by an HPLC method in order to determine the amount of drug which penetrates into the eye. 5-FU must act locally, at the trabeculectomy site; if it goes into the anterior chamber, it could trigger major corneal toxicity. Eventually, rabbits were sacrificed as described above and histology study was performed.

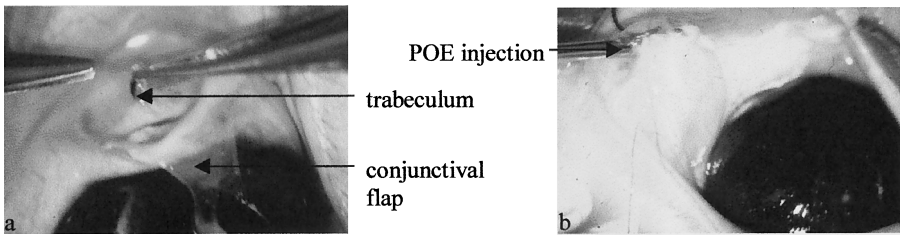


Figure 3: (a) Removal of the trabeculum during filtering surgery; (b) subconjunctival POE injection.

Results and Discussion

Intravitreal biocompatibility

In the first hours after intravitreal injection, POE appeared as a round bulk lying on the retina but moving in the vitreous cavity concomitantly with the eye movement. No inflammatory reaction could be observed clinically in any of the groups tested. The anterior chamber, as well as the vitreous cavity, were clear and the retina seemed unaffected by the presence of the polymer.

At day five, POE alone was markedly degraded and almost disappeared from the vitreous cavity, whereas the presence of the basic substances MG or DEX significantly prolonged the polymer lifetime in the vitreous cavity up to two weeks due to stabilization of the ortho ester bonds in the polymer backbone. POE containing 1% MG appeared noticeably as a round, whitish and opaque bleb in the vitreous cavity (Fig. 4).

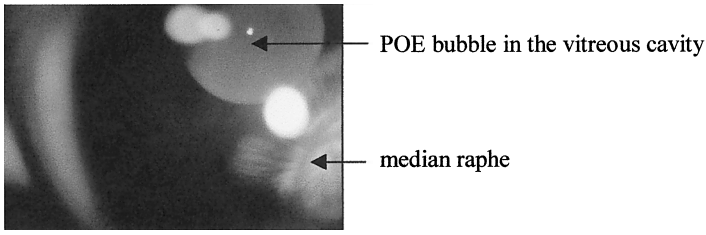


Figure 4: Indirect ophthalmoscopy of POE + MG in the vitreous cavity 5 days after operation.

No inflammatory reaction developed, as noted by clinical observation. At the time of

sacrifice, two weeks after operation, the polymer completely disappeared from all eyes, which appeared as clinically normal. Semithin histological sections showed no anomalies of ocular tissues, and, notably, normal anatomy of the retina. In some cases, rare inflammatory cells were found in the vitreous gel and at the optic nerve head. Table 1 summarizes the lifetime of the polymer bubble within the vitreous cavity, as well as the frequency of the presence of inflammatory cells in the vitreous cavity found by histological analysis. Here again, stabilizing MG or anti-inflammatory DEX improve POE biocompatibility; moreover, they prolong the polymer persistence in the eye.

Table 1: Intravitreal injection of loaded or non-loaded POE: persistence of the polymer and infiltration of inflammatory cells in the vitreous humor (n=6).

Formulation	Persistence in the eye (days)	Inflammatory cells in the vitreous cavity (no. of eyes)
POE	7	3
POE + $Mg(OH)_2$	14	0
POE + DEX	14	0

Suprachoroidal biocompatibility

Just after injection, the polymer spread in the suprachoroidal pocket created by the tunnelization, triggering no visible elevation of the retina and choroid as observed clinically. The only mild change noted in the appearance of the fundus was a minimal alteration of the retinal pigmentation in the region of the injected polymer (Fig. 5). These irregularities seem to be due rather to a pigment redistribution in the choroid than to an alteration of the RPE cells, as later confirmed by angiography.

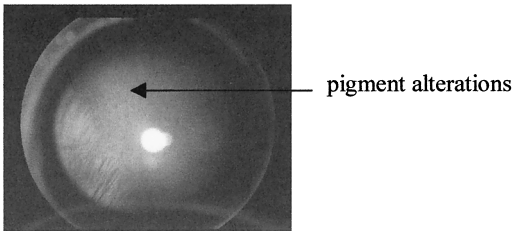


Figure 5: Fundus showing minimal alterations of pigmentation after suprachoroidal POE injection.

All eyes were quiet, with no evidence of immediate or delayed intraocular inflammation of the anterior or posterior segment, other than that associated with a conjunctival incision. No significant tendency of postoperative intraocular pressure or shallowing of the anterior chamber was noted. The polymer remained present with the same aspect for about 1 week,

then it progressively disappeared over 2 to 3 weeks. No significant differences could be noted clinically between different POEs obtained, which were all well tolerated. By ultrasound echography, POE was clearly observed as a hypoechogenic substance in the suprachoroidal space at the site where it has been injected, with a limited spreading, without triggering any retinal or choroidal detachment, nor hematoma (Fig. 6).

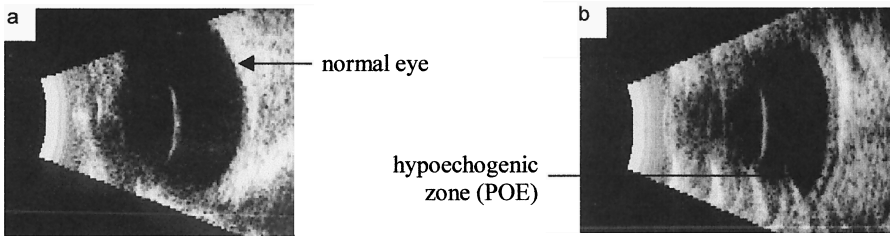


Figure 6: (a) Echography of rabbit eye before operation; (b) a hypoechogenic zone corresponding to POE in the suprachoroidal space after operation.

This shows that a local drug release can be potentially achieved by this delivery system. Echographic examinations allowed to notice that polymer was still present at the end of the experiment, i.e. 20 days after operation. However, the dark zone corresponding to the polymer in the suprachoroidal space passably thinned.

In the angiogram, the choroidal filling showed a limited alteration of choroidal pigment where POE was localized (Fig. 7) but no destruction or detachment of the RPE which would have caused a window effect or a subretinal leakage of the dye.

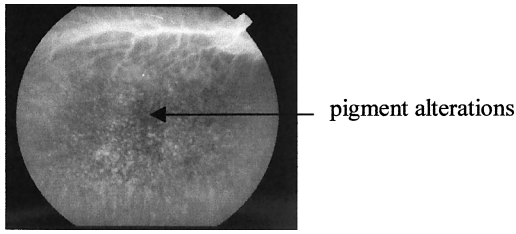


Figure 7: Fluorescein angiogram showing choroidal pigment alterations at the site of polymer injection on day 5 after operation.

The arterial and venous phases appeared normal and no late hyperfluorescence was observed, showing that the retinal vasculature permeability was not altered. The choroidal pigment alterations remained stable during the angiographic sequence. These minimal changes noticed at the angiographic level showed that no retinal damages resulted from the suprachoroidal presence of POE or of its degradation products.

In eyes receiving POE formulations, histological examination of the tissues in the injection region showed the polymer in small or large vacuoles in the choroid, involving the external layers for large vacuoles and the inner layers for small vacuoles, next to Bruch's membrane. These vacuoles mostly appeared to be phagocytosed by giant melanophages whose pigment presented a degree of redistribution. Overlying this, a thinned choroid, intact but somewhat depigmented RPE and normal neuroretina were observed, without any obvious inflammatory reaction. No major disorganization of the main inner membranes of the eye could be found.

Clinical application in an animal model of glaucoma filtering surgery

Eyes were observed clinically for 30 days after operation with a special attention to conjunctival hyperemia and corneal edema; the results are summarized in Fig. 8. Conjunctival hyperemia was scored according to a modified Draize test[13]: grade 0, normal vessels; grade 1, definitely injected vessels; grade 2, diffuse crimson red, individual vessels not easily discernable; grade 3, diffuse beefy red. Corneal edema was also scored as follows: grade 0, normal cornea; grade 1, slight corneal edema present at the surgical site; grade 2, diffuse corneal edema extending to half of the surface of the cornea; grade 3, opaque cornea with neovascularization.

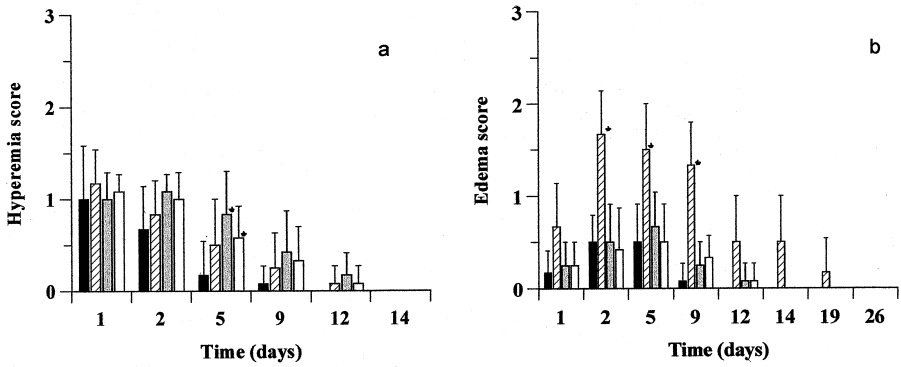


Figure 8: Evaluation of (a) the conjunctival hyperemia and (b) corneal edema. Eyes undergoing trabeculectomy alone (■), eyes with intraoperative 5-FU tamponade (▨), eyes receiving POE alone (▧) and eyes receiving POE containing 5-FU (⊔) (n=6, mean ± SD). Asterisks indicate significant difference from the group undergoing trabeculectomy alone ($p < 0.05$).

Trabeculectomy triggered a slight hyperemia of the conjunctiva which resolved after about 1 week. When 5-FU was applied as a tamponade, no significant increase in the hyperemia occurred. Hyperemia triggered by the presence of POE, with or without 5-FU, was slightly more pronounced, with a significant difference on day 5. Eventually, hyperemia resolved two

weeks after operation. Trabeculectomy also triggered a reversible edema of the cornea at the site of surgery, culminating on day 5. The presence of POE triggered an edema of the same intensity, which was also reversible. On the other hand, 5-FU applied intraoperatively as a tamponade triggered a more severe edema, extending to half of the cornea. The frequency and the severity of corneal edema in the 5-FU tamponade group was significantly higher than in any other group. Superficial punctuate keratitis occurred in 2 eyes. The group receiving POE and 5-FU showed also some edema, but it remained localized at the surgical site and was not significantly different from the control group. The incorporation of 5-FU into a polymeric matrix allowed its slow and continuous release.

POE could be observed at the subconjunctival site for 12 days (Fig. 9). On the other hand, the incorporation of the slightly acidic 5-FU reduced its presence to 10 days due to an accelerated acid-catalyzed degradation. After that time, POE seemed to disappear from the eye by bioresorption; actually some POE could still be present under the conjunctiva but not visibly as the viscous POE was able to spread.

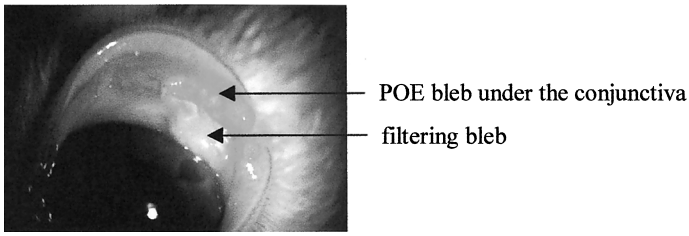


Figure 9: Filtering and POE blebs in a rabbit eye having received POE and 5-FU (day 5 after operation).

Intraocular pressure (IOP) was measured after operation and the results were correlated with filtering bleb persistence, which is actually a more trustful parameter to observe since intraocular pressure is subject to marked inter- and intraindividual variations (Fig. 10).

In the eyes undergoing trabeculectomy alone, the mean IOP returned to preoperative levels on day 9. When eyes received polymer alone, IOP also returned to baseline values but with some delay. This delay could be explained by the physical presence of POE at the surgical site, which might delay the occlusion of the fistula. Moreover, the existence of various chemical residues at the trabeculectomy site, i.e. the polymer and its degradation by-products, might alter the inflammatory reaction. There was no statistical difference between these two control groups at any time. Eyes treated with 5-FU either as a tamponade or incorporated in POE had significantly lower IOP than control groups from day 9 to the end of the experiment. However, no statistical difference was found between these two 5-FU groups.

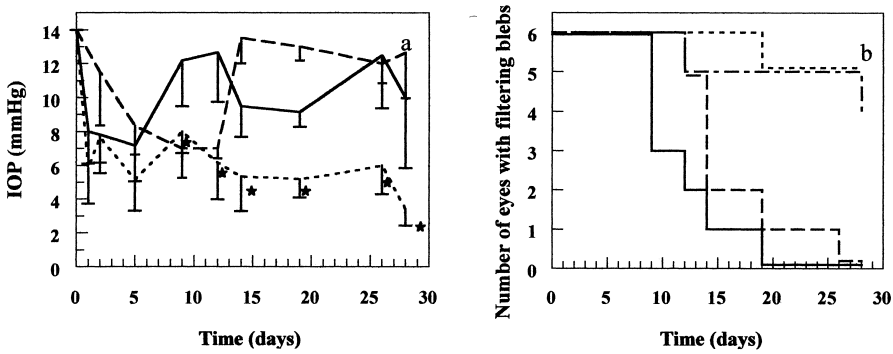


Figure 10: (a) Postoperative intraocular pressure (IOP); (b) filtering bleb persistence in rabbits. Eyes undergoing trabeculectomy alone (—), eyes with intraoperative 5-FU tamponade (–·–), eyes receiving POE alone (- - -) and POE containing 5-FU (---). (n=6, mean ± SD). Asterisks indicate significant difference from the control ($p < 0.05$).

The determination of 5-FU in the aqueous humor is particularly important to ensure that its concentrations in the anterior chamber are nontoxic to the corneal endothelium. Such corneal toxicity includes corneal opacification and neovascularization. For all samples, determination of 5-FU in the aqueous humor exhibited detectable amounts of 5-FU, below 0.5 μg/mL. Particularly, no burst release of 5-FU was observed in the early post-operative period. Thus, every time, minimal amounts of 5-FU were present in the anterior chamber corresponding at least to three orders of magnitude below the threshold concentration for 5-FU toxicity to the corneal endothelium (1 - 10 mg/mL) reported by Mannis et al.[16].

After histological analysis, following observations could be made. Bleb failure occurred on day 10 in eyes undergoing trabeculectomy alone. Eyes showed evidence of inflammatory cell infiltration and fibrovascular tissue at the surgical site. The trabeculectomy and bleb closed due to the bulk filling by granulation tissue and fibroblasts. Until the end of the experiment, eyes receiving 5-FU, either as a tamponade or incorporated in POE, showed no signs of fibrosis of the filtration fistula. The scleral flap margins were empty from any fibrotic subconjunctival fibroblasts. Eyes were also observed to detect any inflammatory reaction triggered by POE. A transient acute pseudo-eosinophilic inflammatory reaction was observed around POE on day 5, as previously described[13]. This inflammatory reaction resolved on day 7, without recurrence or encapsulation of the biomaterial. No histological evidence of chronic inflammation was found after ulterior analysis.

Conclusion

Drug delivery to the intraocular tissues remains a major challenge in ophthalmology. Many conditions necessitate repeated intraocular injections in order to maintain therapeutic levels of drugs within the eye. Such an uncomfortable and dangerous treatment regimen could be circumvented by single administration of a sustained drug delivery system, which would release the therapeutic agent over an extended period of time. Of various polymers which have been recently developed as carriers for sustained drug release, a viscous poly(ortho ester), bioerodible and hydrophobic, shows interesting characteristics and promising applications in ophthalmology.

The overall intraocular biocompatibility has been studied. When injected intravitreally, POE is well tolerated, as observed by indirect ophthalmoscopy, and the degradation rate can be modulated by the appropriate choice of drugs and/or excipients. The presence of magnesium hydroxide or dexamethasone sodium phosphate prolongs polymer lifetime up to 2 weeks, compared with POE alone which degrades within 1 week. Moreover, polymer biocompatibility is increased by their presence, both improving polymer tolerance within the eye.

Suprachoroidal injections were also investigated as a potential new route of administration to deliver drugs to the choroid. A suprachoroidal injection is easy to perform and safe because there is no penetration inside the vitreous cavity; therefore, the risk of infection is limited, and POE biocompatibility in the suprachoroidal space is excellent. A sustained release of drugs to the choroid, which is of great interest in the case of age-related macular degeneration, where new vessels sprout from the choroid, is currently under investigation.

The newly developed drug delivery system based on bioerodible POE and 5-FU has potentially significant clinical applications for glaucoma filtering surgery in patients who are at high risk of failure. Scarring at the filtration site can be inhibited by a localized and sustained release of the antifibroblastic agent, 5-fluorouracil, thus avoiding the need for frequent subconjunctival injections and decreasing toxic ocular side effects caused by intraoperative topical administration. POE combines the advantage of a hydrophobic polymer allowing a slow release of the hydrophilic drug 5-FU with a relatively fast biodegradability, disappearing in about two weeks when all the drug has been released. Its proved biocompatibility makes it a biomaterial of choice for delivering drugs in a sustained, controllable way. POE biodegradability is a major advantage since there is no need to remove the device once it is depleted of drugs, and it is possible to incorporate sensitive drugs such as thermolabile compounds or oligonucleotides.

As a conclusion, one can affirm that POE has tremendous potential for intravitreal or suprachoroidal drug delivery for the treatment of proliferative vitreoretinopathy or age-related macular degeneration, respectively. On the other hand, the excellent results obtained in the animal model of glaucoma filtering surgery make its potential use in humans very promising.

Acknowledgement

This work was supported by a Swiss National Science Foundation grant No. 3200-056750.99/1.

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