



Article scientifique

Article

2001

Published version

Public access

This is the published version of the publication, made available in accordance with the publisher's policy.

A new poly(ortho ester)-based drug delivery system as an adjunct
treatment in filtering surgery

Einmahl, Suzanne; Behar-Cohen, Francine; D'Hermies, François; Rudaz, Serge; Tabatabay, Cyrus A.;
Renard, Gilles; Gurny, Robert

How to cite

EINMAHL, Suzanne et al. A new poly(ortho ester)-based drug delivery system as an adjunct treatment in filtering surgery. In: Investigative Ophthalmology & Visual Science, 2001, vol. 42, n° 3, p. 695–700.

This publication URL: <https://archive-ouverte.unige.ch/unige:127643>

© This document is protected by copyright. Please refer to copyright holder(s) for terms of use.

Last deposit update in Archive ouverte UNIGE on 15.03.2023 19:32

A New Poly(Ortho Ester)-Based Drug Delivery System as an Adjunct Treatment in Filtering Surgery

Suzanne Einmahl,¹ Francine Behar-Cohen,² François D'Hermies,² Serge Rudaz,³ Cyrus Tabatabay,¹ Gilles Renard,² and Robert Gurny¹

PURPOSE. Pharmacologic modulation of wound healing after glaucoma filtering surgery remains a major clinical challenge in ophthalmology. Poly(ortho ester) (POE) is a bioerodible and biocompatible viscous polymer potentially useful as a sustained drug delivery system that allows the frequency of intraocular injections to be reduced. The purpose of this study was to determine the efficacy of POE containing a precise amount of 5-fluorouracil (5-FU) in an experimental model of filtering surgery in the rabbit.

METHODS. Trabeculectomy was performed in pigmented rabbit eyes. An ointmentlike formulation of POE containing 1% wt/wt 5-FU was injected subconjunctivally at the site of surgery, during the procedure. Intraocular pressure (IOP), bleb persistence, and ocular inflammatory reaction were monitored until postoperative day 30. Quantitative analysis of 5-FU was performed in the anterior chamber. Histologic analysis was used to assess the appearance of the filtering fistula and the polymer's biocompatibility.

RESULTS. The decrease in IOP from baseline and the persistence of the filtering bleb were significantly more marked in the 5-FU-treated eyes during postoperative days 9 through 28. Corneal toxicity triggered by 5-FU was significantly lower in the group that received 5-FU in POE compared with a 5-FU tamponade. Histopathologic evaluation showed that POE was well tolerated, and no fibrosis occurred in eyes treated with POE containing 5-FU.

CONCLUSIONS. In this rabbit model of trabeculectomy, the formulation based on POE and containing a precise amount of 5-FU reduced IOP and prolonged bleb persistence in a way similar to the conventional method of a 5-FU tamponade, while significantly reducing 5-FU toxicity. (*Invest Ophthalmol Vis Sci.* 2001;42:695-700)

Glaucoma filtering surgery involves producing a filtration fistula to allow controlled escape of aqueous humor from the surgical trabeculectomy into the subconjunctival space. The body's natural tendency to heal, however, can seal the surgical site and result in failure of the operation.^{1,2} The use of drugs that interfere with early postoperative wound healing by inhibiting fibroblast proliferation and preventing closure of the filtration fistula has become increasingly important in improving the success rate of glaucoma filtering surgery in patients at

high risk of surgical failure. Drugs with proven efficacy include 5-fluorouracil (5-FU)³ and mitomycin C.⁴⁻⁷

The antimetabolite 5-FU is a fluorinated pyrimidine analogue that competitively inhibits thymidylate synthetase, resulting in thymidine deficiency and decreased DNA synthesis. Currently, 5-FU is administered by frequent subconjunctival injections away from the surgical site. Such frequent 5-FU injections are inconvenient for the surgeon and uncomfortable for the patient. Furthermore, therapeutic drug levels are only transiently achieved, necessitating frequent injections and administration of large amounts of drug. Toxic effects on the surrounding ocular tissues are a predictable consequence of this dosage regimen. Toxicity on the conjunctival and corneal epithelium, wound dehiscence, and wound leaks have been reported after repeated subconjunctival administration of 5-FU.³ Topical intraoperative administration of 5-FU with a sponge soaked in a concentrated drug solution has also been used and is associated with adverse side effects, some of which are vision threatening.⁸ Another disadvantage of this mode of administration is the high drug concentration to which the tissues are exposed during the tamponade as well as the imprecision of the amount of 5-FU delivered to the tissues.

These complications may be reduced by using subconjunctivally implanted drug delivery systems that would provide a localized and sustained release of antiproliferative drugs over an extended period (approximately 2 weeks) and then would disappear, leaving a patent fistula after glaucoma filtering surgery. This 2-week period is critical with respect to inflammatory and fibrotic reactions.⁹ Drug delivery systems investigated to date include collagen implants,^{10,11} bioerodible polymers,¹²⁻¹⁵ nonbioerodible polymers,¹⁶ liposomes,¹⁷ and microspheres.¹⁸

Poly(ortho esters) (POE) are a new family of hydrophobic, biocompatible,^{19,20} and bioerodible polymers possessing particularly interesting characteristics. Biodegradability represents a significant advantage over other drug delivery systems, because there is no need to remove the device surgically once all the drug has been released. Kinetics of drug release from POE, as well as polymer degradation rate, are almost constant, without any burst effect, and can be controlled by factors such as polymer molecular weight and the physicochemical properties of the incorporated substances.^{21,22} The viscous, ointmentlike consistency of the polymeric material allows the incorporation of drugs into the carrier by simple mixing at room temperature, without the use of solvents. POE can be injected using a conventional syringe with an appropriate needle, which is a significant advantage when compared with solid devices that must be placed either with a trocar or through a more complex surgical procedure. Moreover, the viscous properties of POE make its presence within the eye smooth and nontraumatic, because it spreads in the space.

The purpose of this study was to evaluate a sustained drug delivery system based on POE and 5-FU as an adjunct treatment to filtering surgery in rabbits.

From the Department of ¹Pharmaceutical Technology and Biopharmaceutics and the Department of ³Pharmaceutical Analytical Chemistry, School of Pharmacy, University of Geneva, Switzerland; and the ²Department of Ophthalmology, Hôtel-Dieu Hospital, Paris, France.

Supported by Swiss National Science Foundation Grant 32.46795.96 and Fondation pour l'Avenir, France.

Submitted for publication June 9, 2000; revised November 20, 2000; accepted December 5, 2000.

Commercial relationships policy: N.

Corresponding author: Robert Gurny, Department of Pharmaceutical Technology and Biopharmaceutics, School of Pharmacy, University of Geneva, 30 quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland. robert.gurny@pharm.unige.ch

MATERIALS AND METHODS

Polymer Synthesis

As described earlier,²³ POE is synthesized by a transesterification reaction between 1,2,6-hexanetriol and trimethyl orthoacetate (Aldrich Chemie, Steinheim, Germany) under anhydrous and aseptic conditions. POE is further purified by a precipitation procedure in methanol to remove impurities such as residual monomers and oligomers.

The polymer was characterized by infrared spectroscopy, nuclear magnetic resonance and size exclusion chromatography.²² The average molecular weight of the polymer used in this study is 9.3 kDa, with a polydispersity of 1.4. POE is a viscous material, with Newtonian behavior. It is transparent, with a refractive index of 1.47 and is gel-like in appearance.

Preparation of the Formulations

Formulations were prepared under a laminar air-flow hood. The added drug, 5-FU (Sigma, Buchs, Switzerland), had been γ -sterilized at 2.0 MRad and homogeneously dispersed in the aseptically prepared semi-solid polymer under aseptic conditions at a concentration of 1% wt/wt.²⁴ The viscous mixture was conditioned into a 1.0-ml syringe, each sample being 200 μ l (240 mg).

Animals

Pigmented Fauve de Bourgogne female rabbits weighing from 2 to 3 kg, 10 to 12 weeks of age, were used (Jean-Pierre Ravaut; Institut de la Recherche Agronomique, Nouzilly, France), and experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Six eyes were used in each experimental group.

Filtering Surgery

General anesthesia was induced with intramuscular injection of 50 mg/kg ketamine and 15 mg/kg xylazine. With rabbits under local anesthesia with oxybuprocaine 0.4% (Novesine; Ciba Vision, Basel, Switzerland), a lid speculum was inserted to expose the globe. A limbus-based conjunctival flap was reflected. Tenonectomy was performed to expose the underlying sclera, followed by careful conjunctival dissection anterior to the limbus. Hemostasis was carefully maintained with cautery. A half-thickness, limbal-based, 4 \times 4-mm scleral flap was made that extended just anterior to the limbus. At this point, one group of rabbits received an intraoperative tamponade of 5-FU. A 4 \times 1-mm dry section of a Weck-Cel sponge (Edward Weck, Research Triangle Park, NC) was soaked in a 50-mg/ml 5-FU solution (Fluorouracil; Teva, Mijdrecht, The Netherlands). The sponge was placed between the conjunctiva and the sclera over the planned filtration site for 5 minutes. The corneal epithelium was protected by applying a wet sponge over the cornea. The treated area was thoroughly irrigated with 20 ml of balanced salt solution. A 3-mm limbal incision was made with a 45° blade that entered the anterior chamber. A block of tissue containing inner sclera, trabeculum and peripheral cornea, measuring approximately 3 \times 1 mm, was excised at the limbus. A peripheral iridectomy was then performed. The scleral flap was approximated with two 10-0 nylon sutures. The conjunctiva was repositioned and the wound closed with 8-0 Vicryl suture (Ethicon, Piscataway, NJ) in a continuous fashion. Just before the last step, a 0.9-mm needle (20-gauge) was inserted in the subconjunctival space, and 200 μ l of polymer mixture was injected adjacent to the trabeculectomy. The suture was closed tightly, and topical neomycin ophthalmic ointment was applied.

Four different groups were tested ($n = 6$): group I, eyes that underwent trabeculectomy alone; group II, eyes that received 5-FU as an intraoperative tamponade; group III, eyes that received POE alone; and group IV, eyes that received POE containing 1% wt/wt 5-FU.

Clinical Observations

Slit-lamp observations were performed approximately every 2 days for 30 days after surgery to assess the filtering bleb status and the overall inflammatory state of the eye. Intraocular pressure (IOP) was measured at the same time intervals using Goldmann applantation tonometry, with rabbits under local anesthesia, and was compared with the preoperative IOP.

Statistical analysis was performed to compare experimental data with data from control eyes, using a nonparametric Mann-Whitney test. The following variables were analyzed: IOP, time to bleb failure, conjunctival hyperemia, and corneal edema. $P < 0.05$ was considered significant.

Quantitative Determination of 5-FU

Concentrations of 5-FU were determined by liquid chromatography (LC) using a high-performance liquid chromatography (HPLC) system (LC module I plus; Waters, Milford, MA), consisting of a power line controller pump (model 600^B) an autoinjector (715 Ultra WISPTM), a tunable absorbance UV detector set at 268 nm, and a software integrator (Millennium) all from Waters. Separation was performed with a C18 HPLC column (Nucleosil 100-5; Macherey Nagel, Düren, Germany; 250 \times 4.0 mm; internal diameter, 5 μ m). The mobile phase consisted of ammonium phosphate buffer (50 mM; pH 6.0) delivered at 1.0 ml/min. Before use, the mobile phase was filtered through a 0.45- μ m membrane filter (Millipore, Molsheim, France) and degassed 10 minutes by sonication.

At postoperative days 1, 2, 5, 7, and 14, a paracentesis was made with rabbits under local anesthesia, and 100 μ l of aqueous humor was collected for quantitative analysis. Samples and quantitative standards were homogenized and directly injected into the HPLC system, with an injection volume of 20 μ l.

Histologic Analysis

Rabbits were killed at different time points ranging from 5 to 30 days after surgery by intracardiac injection of a lethal dose of pentobarbital, and their eyes were enucleated and fixed to be studied histologically by conventional optical microscopy. Anteroposterior sections were stained with hematoxylin-eosin to examine the conjunctiva, the irido-corneal angle, and the appearance of the site of the bleb. Every sample was treated simultaneously to reduce variations among fixation procedures.

RESULTS

Clinical Findings

Clinical Appearance of the Eyes. Eyes were observed clinically for 30 days with special attention to conjunctival hyperemia and corneal edema. Results are summarized in Figure 1. Conjunctival hyperemia was scored according to a modified Draize test¹⁹: grade 0, normal vessels; grade 1, definitely injected vessels; grade 2, diffuse crimson red, individual vessels not easily discernible; and grade 3, diffuse beefy red. Corneal edema was 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 the surface of the cornea; and grade 3, opaque cornea with neovascularization.

Trabeculectomy triggered slight hyperemia of the conjunctiva that resolved after approximately 1 week. When 5-FU was applied as a tamponade, no significant increase of the hyperemia occurred. Hyperemia triggered by the presence of POE, with or without 5-FU (groups III and IV), had a score approximately 0.25 higher than in group I, with a significant difference at day 5. Eventually, hyperemia disappeared as the polymer degraded, by 2 weeks after surgery.¹⁹

At the site of surgery, trabeculectomy also triggered reversible edema of the cornea, which reached its apex at day 5. The

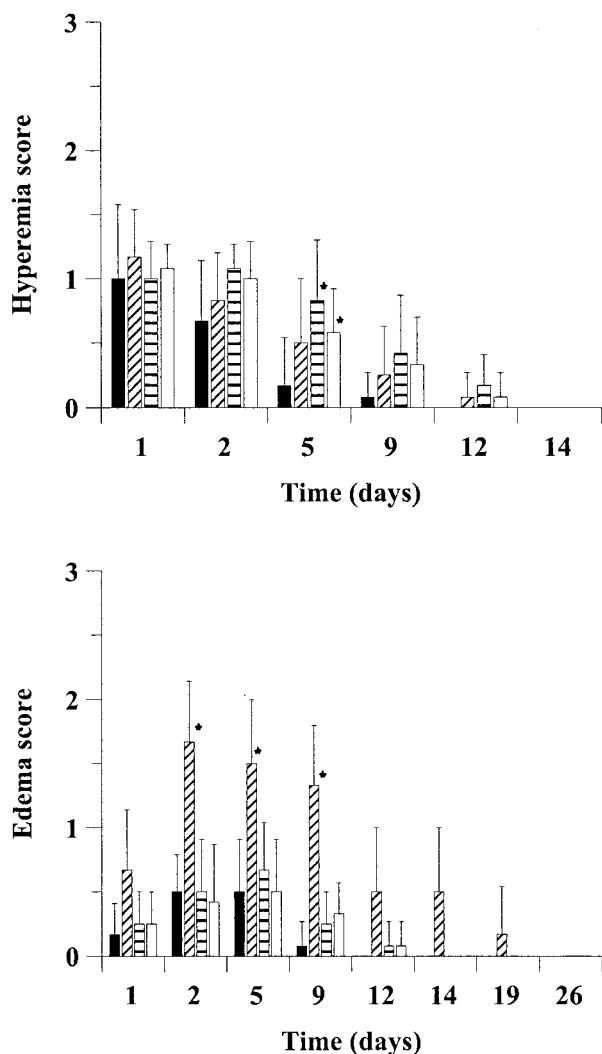


FIGURE 1. Evaluation of conjunctival hyperemia and corneal edema. Group I (■), group II (▨), group III (▤), and group IV (□). *n* = 6, mean ± SD. *Significant difference from group I (*P* < 0.05).

presence of POE triggered edema of the same intensity, which was also reversible. In contrast, 5-FU applied during surgery as a tamponade triggered more severe edema, extending to half the cornea (Fig. 2, II). The frequency and the severity of corneal edema in the 5-FU tamponade group was significantly higher than in any other group. Superficial punctate keratitis occurred in two eyes. The group that received POE+5-FU also showed some edema, but it remained localized at the surgical site and was not significantly different from that in the control group (Fig. 2, IV).

POE could be observed at the subconjunctival site for 12 days, but the incorporation of the acidic 5-FU into the POE active formulation reduced its presence to 10 days because of accelerated, acid-catalyzed, degradation.^{21,22} After that time, POE seemed to disappear from the eye after bioresorption. It is possible that some POE may still have been present under the conjunctiva, but not visibly so, with the viscous POE spreading in the subconjunctival space. Moreover, it was sometimes difficult to distinguish a POE bubble from the filtering bleb.

Bleb Appearance and Survival Curves. In group I (control eyes that underwent trabeculectomy alone), all blebs were elevated and typically had sharply demarcated edges a few days after surgery. Fifty percent of blebs had collapsed by 9 days and 100% by 19 days. In group II (eyes that received an intraoperative 5-FU tamponade), the blebs were significantly more persistent, lasting from day 12 until the end of the experiment (day 29). Group III, which received POE alone, showed delayed persistence of the bleb compared with group I (Fig. 2, I and III), but eventually all blebs failed. All blebs in group IV (POE containing 5-FU) survived until postoperative day 19, and 83% survived after 1 month. There were no significant differences between group IV and group II. Bleb survival curves for the four groups are displayed in Figure 3.

Intraocular Pressure. In group I, the mean IOP returned to preoperative levels by day 9 (Fig. 4). In eyes that received polymer alone (group III), IOP also returned to baseline values, but with some delay. There was no statistical difference between these two control groups at any time.

Eyes treated with 5-FU either as a tamponade (group II) or incorporated in POE (group IV), had significantly lower IOP than control groups from day 9 until the end of the experi-

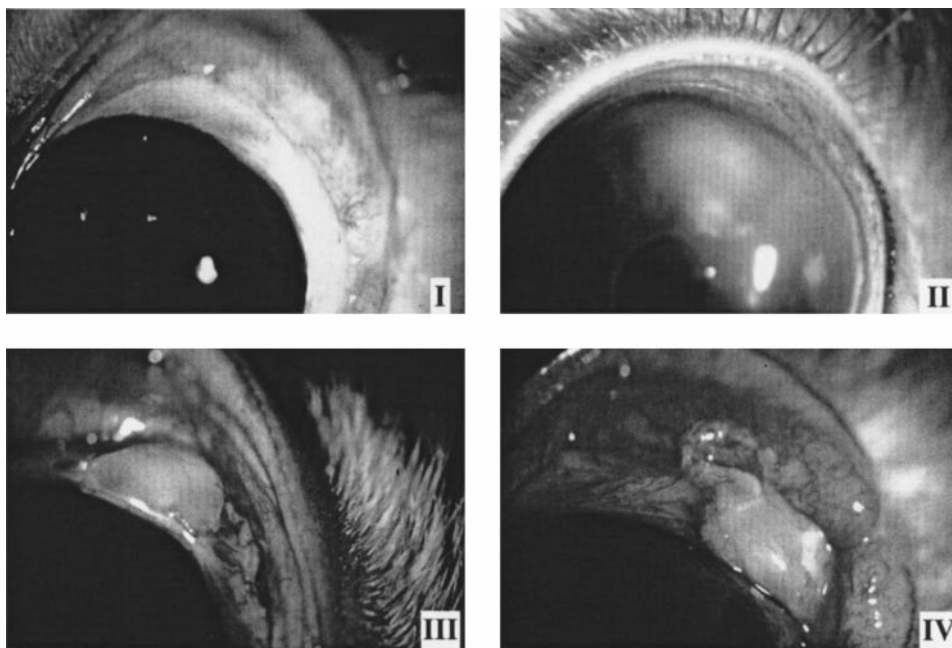


FIGURE 2. Eye status in each group at postoperative day 7.

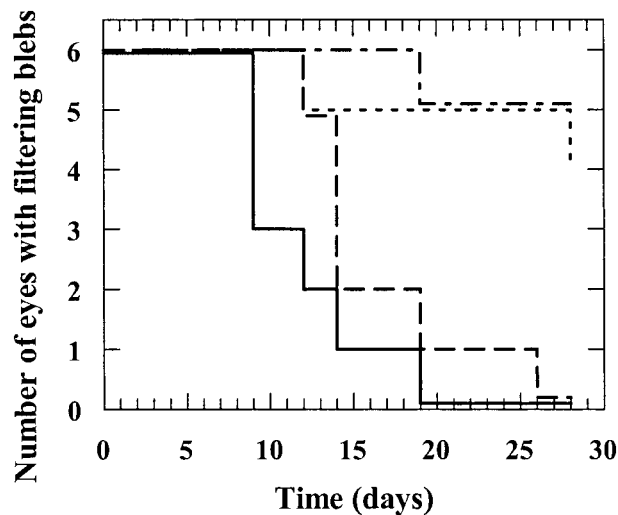


FIGURE 3. A Kaplan-Meier graph of the duration of blebs in rabbits: group I (solid line), group II (long-short dashes), group III (long dashes), and group IV (short dashes). $n = 6$; mean \pm SD.

ment. However, no statistical difference was found between these two 5-FU groups (Fig. 5).

Quantitative Determination of 5-FU

The quantitative determination of 5-FU concentration in the aqueous humor is particularly important to ensure that the levels reached are not toxic to the corneal endothelium. Corneal toxicity includes epithelial defects, corneal opacification, and vascularization.

In all eyes that received POE+5-FU, quantitative determination of 5-FU in the aqueous humor showed detectable amounts of 5-FU (below $0.5 \mu\text{g/ml}$) for 2 weeks, which shows that POE was still present in the subconjunctival space for that period and released 5-FU in a continuous fashion. In particular, no burst release of 5-FU was observed in the early postoperative period, according to observations for in vitro 5-FU release.²² Thus, at each time point, a minimal amount of 5-FU was present in the anterior chamber, corresponding at least to 3 orders of magnitude below the threshold concentration for 5-FU toxicity to the corneal endothelium (1–10 mg/ml) reported by Mannis et al.²⁵

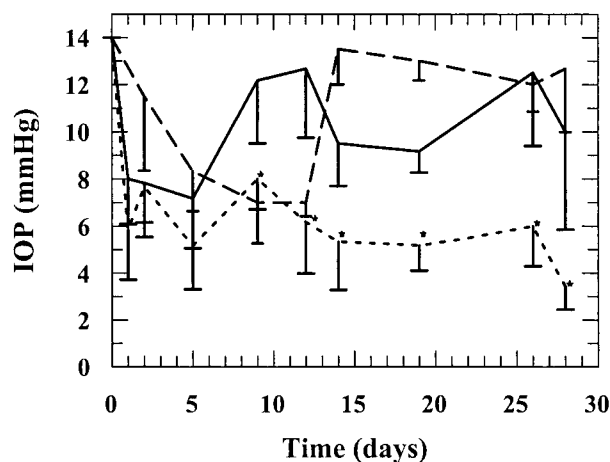


FIGURE 4. Postoperative IOP of rabbits that received POE with 1% 5-FU versus control animals. Group I (solid), group III (long dashes), and group IV (short dashes). $n = 6$; mean \pm SD. *Significant difference from group I ($P < 0.05$).

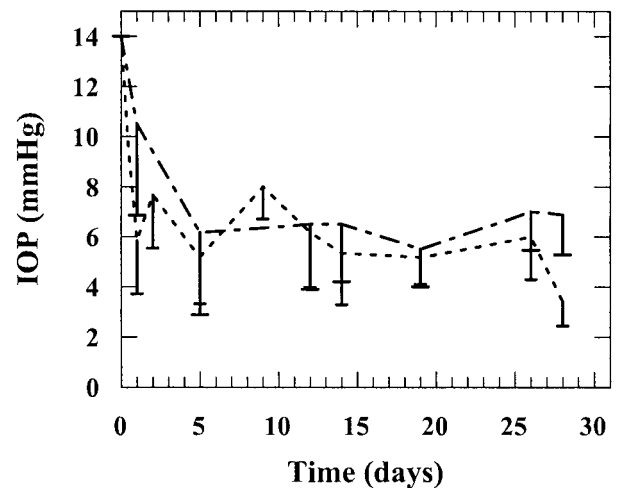


FIGURE 5. Postoperative IOP of rabbits having received POE with 1% 5-FU versus 5-FU as a tamponade: group II (long-short dashes) and group IV (short dashes). $n = 6$, mean \pm SD.

5-Fluorouracil was not quantified in the anterior chamber of eyes that received an intraoperative tamponade for several reasons: 5-FU is applied and rinsed off before opening the anterior chamber, and therefore no 5-FU should penetrate into the eye; 5-FU soaks the surrounding tissues and does not diffuse into the anterior chamber; moreover the flux direction is opposite to the direction of the possible 5-FU intracameral penetration; and last, in all the published literature concerning 5-FU intraoperative tamponade,^{4,6,8,26,27} none of the authors ever measured the 5-FU concentrations in the anterior chamber.

Histology

In control animals killed at 5 days after surgery, a bleb was present, and the trabeculectomy was patent. Some inflammatory cell (polymorphonuclear cells) infiltration was observed around the margins of the scleral flap. The edges of the iris around the iridectomy had partially prolapsed into the fistula in some specimens, although they did not completely block it. No evidence of any conjunctival filtration could be seen.

Bleb failure occurred at 10 days in eyes that underwent trabeculectomy alone (group I). Eyes showed evidence of inflammatory cell infiltration and fibrovascular tissue at the surgical site. The trabeculectomy and bleb closed due to bulk filling by granulation tissue and fibroblasts.

Until the end of the experiment, eyes that received 5-FU, either as a tamponade or incorporated in POE, showed no signs of fibrosis of the filtration fistula. The scleral flap margins were absent from any fibrotic subconjunctival fibroblasts (Fig. 6). The conjunctival filtration was efficient, visible as a small cavity surrounded by fibrin and cells. Some slight modifications of the iris were observed, notably pigment redistribution. These modifications of the uvea were more marked in the 5-FU tamponade group in which significant pigment alterations and pigment migration into the external tunica were observed.

Eyes were also observed to detect any inflammatory reaction triggered by POE. A transient acute inflammatory reaction was observed in the subconjunctival space, with granulated neutrophils around POE by day 5, as previously described.¹⁹ This inflammatory reaction was resolved within 2 weeks, with neither recurrence nor encapsulation of the biomaterial. In some eyes, giant multinucleated cells were found around cavities that were empty or filled with some grayish material, probably POE. No histologic evidence of chronic inflammation

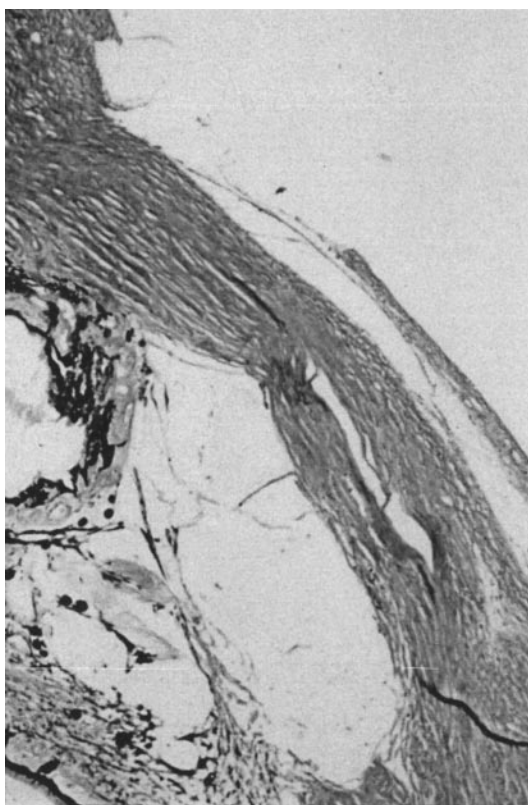


FIGURE 6. Histologic section through the iridocorneal angle after trabeculectomy and subconjunctival injection of 200 μ l POE+5-FU.

was found after 4 weeks after surgery. These results confirm the previously described biocompatibility of POE.^{19,20}

DISCUSSION

The surgical technique, a half-thickness trabeculectomy, used in this study produced a lowering of the IOP, which returned to normal values within 7 to 10 days after surgery, as observed in the control groups. Closure and fibrosis of the trabeculectomy followed the general pattern of acute inflammation and repair. Fibrosis can be equated to the disappearance of the filtering bleb, as well as to the return to normal, preoperative IOP values. When POE alone was injected subconjunctivally, IOP rose after approximately 15 days. The delay could be explained by the physical presence of POE at the surgical site, which may have delayed the occlusion of the fistula. Moreover, the existence of different chemical entities at the trabeculectomy site (i.e., the polymer and its degradation by-products) may have altered the inflammatory reaction.

Intraoperative 5-FU had a marked effect on IOP that lasted longer than is reported in the literature. Khaw et al.²⁶ reported a significant difference from the control from day 5 to day 18 for the same dosage regimen in rabbits. In our model, filtering blebs lasted at least 1 month. However, intraoperative application of 5-FU triggered severe complications, such as corneal edema and epithelial defects.

The administration of POE containing 5-FU promoted the success of glaucoma filtering surgery in rabbit eyes. Eyes that received POE and 5-FU after trabeculectomy had lower IOP for at least 1 month, and they showed filtration blebs and patent fistulas, as supported by the histopathologic findings. This improvement in the duration of lowered IOP in the experimental eyes was due to the slow and continuous release of 5-FU

from the polymeric matrix, inducing facilitated outflow. In both groups that received 5-FU, no abnormal morphologic changes were seen in the ciliary body epithelium and trabecular meshwork when compared by light microscopy with control eyes. When incorporated in POE, 5-FU also appeared to trigger less toxic reactions, such as corneal edema than when administered during surgery.²⁷ The slow release of 5-FU from POE prevented the focal attainment of high and toxic drug levels. Clinical observations showed that eyes that received POE with 5-FU had reactions similar to those in control eyes. There was some conjunctival hyperemia and corneal edema, but the intensity was comparable to that in control eyes.

POE is a new biomaterial with potential as a controlled release system for drugs as an adjunct treatment in glaucoma filtering surgery. Sustained release of an antiproliferative drug such as 5-FU from a POE carrier means that only one subconjunctival injection must be performed at the time of surgery and enables a precise and small amount of drug to be administered. In contrast, during an intraoperative tamponade, tissues are exposed to a high concentration of antiproliferative drug that is potentially toxic to the corneal epithelium,²⁸ and they are soaked with a very variable, uncontrolled, and unpredictable amount of drug that diffuses rapidly from the sponge. Moreover, the 5-FU solution is basic (pH 9.0) to increase drug solubility, which can also trigger a more acute inflammatory response. We showed that both techniques—that is, the incorporation of a low amount of 5-FU (2.4 mg) in POE or an intraoperative tamponade with a 50-mg/ml 5-FU solution—showed comparable results in IOP and bleb persistence. The incorporation of 5-FU in POE also reduced the toxicity of the drug, because lower amounts had to be used.

Although the results described in previous studies with other biomaterials are very encouraging,¹³ our system provides several additional intrinsic advantages. Regarding physical properties, the viscous consistency of POE makes it slightly traumatic to ocular structures, compared with solid devices.¹³ After injection, POE spreads under the conjunctiva and assumes the curve of the ocular globe. Concerning chemical characteristics, the hydrophobic backbone of the polymer allows surface erosion and thus a linear and almost constant release of drugs.²² Burst release, which is often encountered with poly(DL lactic-co-glycolic acid) PLGA-based systems,²⁹ is avoided. The burst release of a drug such as 5-FU with its associated toxicity could have dramatic effects on tissue tolerance. Also, POE has shown excellent biocompatibility in several parts of the eye,²⁰ notably under the conjunctiva.¹⁹ Compared with reported results with collagen¹¹ or PLGA,³⁰ POE is better tolerated. Another advantage is that POE does not become encapsulated, because it is progressively resorbed in approximately 2 weeks, in contrast to PLGA-based systems, which degrade more slowly than the drug is released and thus present a risk of encapsulation.¹³

All animal models of glaucoma filtering surgery have advantages and disadvantages. This study demonstrates a consistent and predictable response of the tissues in the normal rabbit, with the trabeculectomy closing and the bleb collapsing within a short and convenient time period. The overall pattern of wound healing is similar to scars found in humans,³¹ although more rapid. It has also been reported³² that a significant reduction in IOP may occur, even in the absence of a patent trabeculectomy, and bleb function is thus a more reliable index to assess the fistula's efficacy. Also, there are numerous anatomic differences between rabbit and human eyes. Notably, eyeball motion is more frequent in man, eyelid pressure is higher, and the iris is less prone to incarcerate the channel in rabbits than in man, so the potential for the mixture to ooze into the anterior chamber is higher in patients. However, we have seen that the concentrations obtained in the rabbit ante-

rior chamber after the administration of the POE 5-FU formulation were 10^3 times lower than reported toxic concentrations. As a consequence, it is improbable that 5-FU concentrations in the human anterior chamber would increase 3 orders of magnitude; however, this should be investigated.

This newly developed drug delivery system based on bioerodible POE has potential for clinical applications in glaucoma filtering surgery in patients who are at high risk of failed surgery. Scarring at the filtration site can be inhibited by a localized and sustained release of a very small yet efficient amount of the antifibroblastic agent 5-FU, therefore avoiding the need for frequent subconjunctival injections and decreasing toxic ocular side effects caused by intraoperative topical administration of higher amounts of drug. POE combines the advantage of a hydrophobic polymer, allowing a slow release of the hydrophilic drug 5-FU for 2 weeks, with a relatively fast biodegradability. Its proven biocompatibility makes it a biomaterial of choice to deliver drugs in a sustained, controllable way. A study over 6 months is currently under way to assess a long-term follow-up.

Acknowledgments

The authors thank Marie Marquise and Christian Mandon, animalists, as well as Frédéric Azan and Marianne Berdugo-Polak for surgical assistance.

References

- Tahery MM, Lee DA. Review: pharmacologic control of wound healing in glaucoma filtration surgery. *J Ocul Pharmacol.* 1989;5:155-179.
- Jampel HD, McGuigan IJB, Dunkelburger GR, L'Hernault NL, Quigley HA. Cellular proliferation after experimental glaucoma filtration surgery. *Arch Ophthalmol.* 1988;106:89-94.
- The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the fluorouracil filtering surgery study. *Am J Ophthalmol.* 1996;121:349-366.
- Chen CW, Huang HT, Bair JS, Lee CC. Trabeculectomy with simultaneous topical application of mitomycin-C in refractory glaucoma. *J Ocul Pharmacol.* 1990;6:175-182.
- Palmer SS. Mitomycin as adjunct chemotherapy with trabeculectomy. *Ophthalmology.* 1991;98:317-321.
- Kitazawa Y, Kawase K, Matsushita H, Minobe M. Trabeculectomy with mitomycin: a comparative study with fluorouracil. *Arch Ophthalmol.* 1991;109:1693-1698.
- Skuta GL, Beeson CC, Higginbotham EJ, et al. Intraoperative mitomycin versus postoperative 5-fluorouracil in high-risk glaucoma filtering surgery. *Ophthalmology.* 1992;99:438-444.
- Singh K, Egbert PR, Byrd S, et al. Trabeculectomy with intraoperative 5-fluorouracil vs mitomycin c. *Am J Ophthalmol.* 1997;123:48-53.
- Anderson JM. Mechanisms of inflammation and infection with implanted devices. *Cardiovasc Pathol.* 1993;2:33S-41S.
- Kay JS, Litin BS, Jones MA, et al. Delivery of antifibroblast agents as adjuncts to filtration surgery, II: delivery of 5-fluorouracil and bleomycin in a collagen implant: pilot study in the rabbit. *Ophthalmic Surg.* 1986;17:796-801.
- Hasty B, Heuer DK, Minckler DS. Primate trabeculectomies with 5-fluorouracil collagen implants. *Am J Ophthalmol.* 1990;109:721-725.
- Lee DA, Flores RA, Anderson PJ, et al. Glaucoma filtration surgery in rabbits using bioerodible polymers and 5-fluorouracil. *Ophthalmology.* 1987;94:1523-1530.
- Hostyn P, Villain F, Malek-Chehire N, et al. Implant biodégradable à libération contrôlée de 5-FU dans la chirurgie du glaucome: étude expérimentale. *J Fr Ophtalmol.* 1996;19:133-139.
- Charles JB, Ganthier R, Wilson MR, et al. Use of bioerodible polymers impregnated with mitomycin in glaucoma filtration surgery in rabbits. *Ophthalmology.* 1991;98:503-508.
- Trope GE, Cheng YL, Sheardown H, et al. Depot drug delivery system for 5-fluorouracil after filtration surgery in the rabbit. *Can J Ophthalmol.* 1994;29:263-267.
- Blandford DL, Smith TJ, Brown JD, Pearson PA, Ashton P. Subconjunctival sustained release 5-fluorouracil. *Invest Ophthalmol Vis Sci.* 1992;33:3430-3435.
- Skuta GL, Assil KK, Parrish RK, Folberg R, Weinreb RN. Filtering surgery in owl monkeys treated with the antimetabolite 5-fluorouridine 5'-monophosphate entrapped in multivesicular liposomes. *Am J Ophthalmol.* 1987;103:714-716.
- Kimura H, Ogura Y, Moritera T, et al. Injectable microspheres with controlled drug release for glaucoma filtering surgery. *Invest Ophthalmol Vis Sci.* 1992;33:3436-3441.
- Zignani M, Bernatchez SB, Le Minh T, et al. Subconjunctival biocompatibility of a viscous bioerodible poly(ortho ester). *J Biomed Mater Res.* 1998;39:277-285.
- Einmahl S, Behar-Cohen FF, Tabatabay C, et al. A viscous bioerodible poly(ortho ester) as a new biomaterial for intraocular application. *J Biomed Mater Res.* 2000;50:566-573.
- Merkli A, Heller J, Tabatabay C, Gurny R. The use of acidic and basic excipients in the release of 5-fluorouracil and mitomycin c from a semi-solid bioerodible poly (ortho ester). *J Control Release.* 1995;33:415-421.
- Einmahl S, Zignani M, Varesio E, et al. Concomitant and controlled release of dexamethasone and 5-fluorouracil from poly(ortho ester). *Int J Pharm.* 1999;185:189-198.
- Merkli A, Heller J, Tabatabay C, Gurny R. Synthesis and characterization of a new biodegradable semi-solid poly(ortho ester) for drug delivery systems. *J Biomater Sci Polym Ed.* 1993;4:505-516.
- Zignani M, Merkli A, Sintzel MB, et al. New generation of poly(ortho esters): synthesis, characterization, kinetics, sterilization and biocompatibility. *J Control Release.* 1997;48:115-129.
- Mannis MJ, Sweet EH, Lewis RA. The effect of fluorouracil on the corneal endothelium. *Arch Ophthalmol.* 1988;106:816-817.
- Khaw PT, Doyle JW, Sherwood MB, Smith MF, McGorray S. Effects of intraoperative 5-fluorouracil or mitomycin C on glaucoma filtering surgery in the rabbit. *Ophthalmology.* 1993;100:367-372.
- Doyle JW, Sherwood MB, Khaw PT, McGrory S, Smith MF. Intraoperative 5-fluorouracil for filtration surgery in the rabbit. *Invest Ophthalmol Vis Sci.* 1993;34:3313-3319.
- Weinreb RN. Adjusting the dose of 5-fluorouracil after filtration surgery to minimize side effects. *Ophthalmology.* 1987;94:564-570.
- Wang G, Tucker IG, Roberts MS, Hirst LW. In vitro and in vivo evaluation in rabbits of a controlled release 5-fluorouracil subconjunctival implant based on poly (D, L-lactide-co-glycolide). *Pharm Res.* 1996;13:1059-1064.
- Gould L, Trope G, Cheng YL, et al. Fifty:fifty poly (DL glycolic acid-lactic acid) copolymer as a drug delivery system for 5-fluorouracil: a histopathological evaluation. *Can J Ophthalmol.* 1994;29:168-171.
- Skuta GL, Parrish RK. Wound healing in glaucoma filtering surgery. *Surv Ophthalmol.* 1987;32:149-170.
- Miller MH, Grierson I, Unger WI, Hitchings RA. Wound healing in an animal model of glaucoma fistulizing surgery in the rabbit. *Ophthalmic Surg.* 1989;20:350-357.