Liposome Suppression of Proliferative Vitreoretinopathy

Rabbit Model Using Antimetabolite Encapsulated Liposomes

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The effects of the antimetabolites, cytarabine (Ara-C) and 5-fluorouridine 5’-monophosphate (FUMP), encapsulated in multivesicular liposome, on formation of vitreous fibroproliferative membranes in New Zealand white (NZW) rabbits were studied. In pharmacokinetic studies, the drug half-life in the vitreous cavity was 124 hr after intravitreal administration of 1.0 mg of FUMP in liposomes. By contrast, the drug half-life after a single injection in nonliposome-treated controls was only 4.5 hr. In a heterologous dermal fibroblast model of proliferative vitreoretinopathy (PVR), there was a 92% decrease in frequency of tractional retinal detachments in rabbits receiving a single intravitreal injection of liposome-encapsulated 0.1 mg of FUMP compared with controls receiving liposomes without drug. A dose of 1 mg of Ara-C in liposome-treated rabbits was associated with only a 46% reduction in tractional detachment compared with controls. Multivesicular liposome-encapsulated FUMP may be useful for inhibiting formation of fibroproliferative membranes in the vitreous after vitreoretinal surgery. Invest Ophthalmol Vis Sci 32:2891–2897, 1991

Proliferative vitreoretinopathy (PVR) is a major complication of vitreoretinal surgery. It also is associated with posterior segment trauma, giant retinal tears, and possibly, excessive retinal cryotherapy. It may be a consequence of the biologic process of wound healing.

Antimetabolites have been useful for suppressing wound healing after glaucoma filtering surgery and also may be effective in preventing PVR after repair of complicated retinal detachments.1–9 Because frequent periocular injections are inconvenient and associated with patient discomfort, a sustained drug delivery system to circumvent them is desirable. By eliminating initial peaks in drug concentration, sustained drug delivery also may reduce ocular toxicity.9–12

Multivesicular liposomes were used successfully for sustained delivery of antimetabolites in rabbits and owl monkeys after periocular administration.12–14 We evaluated the effects of intravitreal injection of the antimetabolites cytarabine (Ara-C) and 5-fluorouridine 5’-monophosphate (FUMP) encapsulated in liposomes in a rabbit dermal fibroblast model of PVR.

Materials and Methods

Multivesicular liposomes containing Ara-C and FUMP were synthesized as previously described.12–14 Briefly, 7.5 mg of dioleyl phosphatidylcholine and 1.5 mg of dimyristoyl phosphatidyl glycerol (Avanti Polar Lipids, Birmingham, AL), 1.7 mg of triolein, and 5.8 mg of cholesterol (Sigma, St. Louis, MO) were dissolved in 1 ml of chloroform. For preparation of Ara-C-encapsulated liposomes, 1 ml of 40 mM Ara-C solution at pH 1.5 was added dropwise to a vial containing the chloroform–lipid mixture. The new mixture then was vortexed for 4 sec. This mixture was transferred to a flask containing 250 mM lysine and passed under nitrogen (8 L/min) to evaporate any remaining chloroform. For preparation of FUMP-encapsulated liposomes, 1 ml of 40 mM Ara-C solution at pH 1.5 was added dropwise to a vial containing the chloroform–lipid mixture. The vial was vortexed for 10 min. Then 1 ml of this mixture was added rapidly to each of two vials containing 2.5 ml of 240 mM glucose. The new mixture then was vortexed for 4 sec. This mixture was transferred to a flask containing 250 mM lysine and passed under nitrogen (8 L/min) to evaporate any remaining chloroform. Phosphate-buffered saline (PBS) was added, and the mixture was centrifuged at 500 g for 10 min. The resultant liposomal pellet was isolated, resuspended in PBS, and recentrifuged three additional times to eliminate any uncaptured drug. The FUMP liposomes were synthesized as described with the following modifications. For pharmacokinetic studies, 14C-FUMP (Moravek, Brea, CA) and unlabeled FUMP (10 mg/ml) (Cal Biochem, La Jolla, CA) were dissolved at a...
concentration of 25 mM and specific activity of 10 mCi/ml of liposome suspension in 200 mM sucrose, pH 6.4. In preparing the FUMP liposomes for the PVR inhibition studies, we used unlabeled FUMP at a concentration of 2.5 mM in 225 mM sucrose solution. The percent capture of FUMP in the liposomes at synthesis was determined by high-performance liquid chromatography. The drug level in the supernatant and the centrifuge-isolated pellet each were determined. Capture efficiency, defined as the fraction of drug retained in the liposomes divided by the sum of drug in the liposomes and the supernatant, was 0.92.

Pharmacokinetics

New Zealand white rabbits weighing 2.5–3.0 kg were used for all animal experiments. The studies were conducted in accordance with the ARVO Resolution on the Use of Animals in Research. Only one eye per animal was studied. Intraocular injections for all experiments were done as follows. First, all animals were anesthetized by intramuscular injection with ketamine and xylazine (10.0 mg/kg each). Just before intravitreal injection, the pupil was dilated with 1% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride drops. Anterior chamber paracentesis was done with a 30-gauge needle to prevent an excessive increase in intraocular pressure. All intravitreal injections were monitored by indirect ophthalmoscopic observation. Using a 27-gauge needle on a tuberculin syringe, the vitreous cavity was entered transsclerally, 3.5 mm posterior to the limbus, and the injectables were administered to the midvitreous.

For the pharmacokinetic studies, each animal assigned to the experimental group (11 rabbits) received an intravitreal injection of 0.1 ml of liposome with encapsulated radiolabeled FUMP (1.0 mg) in one eye. Two animals were killed to determine the amount of labeled drug present immediately after injection. Three animals each were killed at 96, 168, and 336 hr. Aqueous-humor samples (50 μl) from both eyes of each animal were collected, and both eyes were enucleated. Blood samples were collected to obtain serum. The enucleated eyes were frozen rapidly by immersion in liquid nitrogen for 90 sec, and ocular tissue was removed, leaving only a mass of frozen vitreous. The vitreous was weighed, digested with tissue solubilizer, and counted in a scintillation counter. After solubilization, radioactivity of the serum (1 ml) and aqueous humor (50 μl) also were determined in a scintillation counter. In addition, we solubilized un.injected liposomes and measured the level of radioactivity to determine the amount of drug present in the liposomes. Quenching of the label was not detected in any group. Control animals (16 rabbits) received intravitreal FUMP (1.0 mg) without liposomes at a specific activity of 6 mCi/ml. One rabbit was killed immediately after drug administration, and three each were killed at 1, 4, 12, 24, and 96 hr. The contralateral eyes of these animals were not evaluated.

PVR Model

We established PVR in the rabbits according to a modification of the model of Tano et al.15 Heterologous rabbit dermal and scleral fibroblasts were grown from explants in Dulbecco’s minimal essential media with 15% fetal calf serum, gentamicin, and amphotericin B. Before injection, the cells were trypsinized and adjusted to a concentration of 2.5 million cells per milliliter in calcium- and magnesium-free saline.

To determine the efficacy in suppressing PVR, the rabbits were assigned randomly to one of three groups. The methods for intravitreal injections were as described. Approximately 250,000 fibroblasts (0.1 ml) were injected into the midvitreous of all animals, followed by injection of 0.1 ml of empty liposomes in control animals (13 rabbits), 0.1 ml of liposome-encapsulated 2.5 mM FUMP (0.1 mg) in the second group (14 rabbits), and 0.1 ml of liposome-encapsulated 40 mM Ara-C (1.0 mg) in the third group (8 rabbits). Only one eye per animal was injected.

The animals were anesthetized and observed weekly by indirect ophthalmoscopy for at least 4 weeks. The detachments were graded according to the following classification system: Stage 0, normal retina; Stage 1, localized pucker without detachment; Stage 2, tractional detachment of a medullary ray; Stage 3, total retinal detachment.

Statistical Analysis

The Wilcoxon two-sample test was used to assess whether the drug amount differed significantly between the liposome-encapsulated FUMP group and the free drug-treated group in the pharmacokinetic studies. A linear regression was fitted to the log of the drug amount in the liposome-treated eyes. The fit of the mean drug level at individual times from the control eyes to the regression was tested, using the predicted value from the regression and the standard error of prediction. A P value < 0.05 was considered significant. In the rabbit PVR studies, the Mann-Whitney U test was used to assess significance in the degree of PVR observed among the various groups. Again a P value < 0.05 was considered significant.

Results

Pharmacokinetics

The liposome-encapsulated FUMP (1 mg of drug) was cleared from the rabbit vitreous with a half-life of
124 hr (Fig. 1). The free unencapsulated FUMP alone was cleared with a half-life of 4.5 hr over the first 12 hr. After this time, drug levels fell below the inhibitory dose for 50% of fibroblasts (ID\textsubscript{50}, 50 \mu g/ml). Fourteen days after injection of liposome-encapsulated FUMP, almost 10% of the drug still remained in the vitreous cavity (56.0 ± 8.0 \mu g/ml, Table 1).

Aqueous drug concentrations in the liposome-encapsulated FUMP-treated eye peaked by 96 hr (0.2 ± 0.1 \mu g/ml). Concentrations in the vitreous of the fellow eye (data not presented) also were at a maximum (0.4 ± 0.0 \mu g/ml) by 96 hr and declined thereafter. Plasma concentrations of 0.3 \mu g/ml were measured at 96 hr and remained relatively constant throughout 336 hr. At 96 hr, the concentration of FUMP in the vitreous cavity of liposome-treated eyes was 1000-fold greater than in plasma. By contrast, at the same time, in the eyes receiving FUMP without liposomes, there was only a twofold greater drug concentration in the vitreous than in plasma. The difference in intravitreal drug levels between the liposome-treated and free drug-treated groups was significant (P < 0.001). Furthermore, the difference between mean drug level at individual times, comparing the free drug-treated controls and a linear regression fitted to the log drug amounts in the liposome-treated eyes, also was significant at each time (P < 0.001).

**PVR Model**

Twelve of 13 control rabbits (92%) that received empty liposomes were Stage 2 or higher 14 days after injection. At 30 days, six of the control eyes showed traction of one medullary ray (Stage 2), and six eyes had total retinal detachment (Stage 3). By day 14, four of the eight (50%) eyes treated with liposome-encapsulated Ara-C were already Stage 2 or higher. After 30 days, five of the eight (62%) were Stage 2 or higher. These differences between the nondrug, liposome-treated controls and liposome-encapsulated Ara-C-treated eyes were not significant at either the 14- or 30-day examinations (P > 0.10). By contrast, among the FUMP-treated group, only 1 of 14 (7%) eyes showed evidence of retinal detachment at 14 days (Stage 2). After 30 days, this eye was still Stage 2, and no other eye in this group had detachment. Overall, the FUMP-treated rabbits showed a 92% decrease in the retinal detachment rate compared with the control group at 30 days. The decreased frequency of detachment observed in liposome-encapsulated FUMP-treated eyes was significantly lower than in eyes treated with either Ara-C or with liposomes devoid of drug (P < 0.05 and P < 0.01, respectively) at both examination days. These data are summarized in Table 2 and Figure 2.

At the dose used to inhibit PVR (0.1 mg), no gross retinal toxicity was observed. This was confirmed by electroretinography and histopathologic examination, using light and electron microscopy, in a separate study. However, at significantly higher doses (1.0 mg/ml), small vitreous hemorrhages, attenuation of retinal vessels, and focal areas of retinal atrophy were observed within 14 days.

**Table 1.** Mean (± SD) 5-fluorouridine 5′-monophosphate (FUMP) concentration (\mu g/ml) following the intravitreal injection (n = 3)

<table>
<thead>
<tr>
<th>Time in hr</th>
<th>0</th>
<th>1</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>96</th>
<th>168</th>
<th>336</th>
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<tbody>
<tr>
<td>Liposome encapsulated FUMP</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous (FUMP + liposome)</td>
<td>700.0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aqueous (FUMP + liposome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
</tr>
<tr>
<td>Plasma (FUMP + liposome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3 ± 0.0</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.0</td>
</tr>
<tr>
<td>FUMP without liposomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous (FUMP)</td>
<td>700.0†</td>
<td>460.0 ± 65.0</td>
<td>240.0 ± 41.0</td>
<td>58.0 ± 14.0</td>
<td>13.0 ± 3.0</td>
<td>0.9 ± 0.3</td>
<td></td>
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<tr>
<td>Aqueous (FUMP)</td>
<td></td>
<td>6.1 ± 1.3</td>
<td>9.7 ± 2.0</td>
<td>8.2 ± 1.6</td>
<td>2.9 ± 0.6</td>
<td>0.3 ± 0.1</td>
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<tr>
<td>Plasma (FUMP)</td>
<td></td>
<td>0.1 ± 0.0</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.0</td>
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</table>

* n = 2.  † n = 1.
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Table 2. Degree of retinal detachment in each treatment group at 14 and 30 days

<table>
<thead>
<tr>
<th></th>
<th>Degree of detachment*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>FUMP† + liposome</td>
<td></td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(day 14, n = 14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUMP + liposome</td>
<td></td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>(day 30, n = 14)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ara-C† + liposome</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>(day 14, n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ara-C + liposome</td>
<td></td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>(day 30, n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (Liposomes without drug; day 14, n = 13)</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Control (Liposomes without drug; day 30, n = 13)</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

* Retina graded according to following classification system: normal retina (0); focal pucker without detachment (1); detachment of a single medullary ray (2); total retinal detachment (3).
† 5-fluorouridine 5'-monophosphate.
‡ Cytarabine.

Discussion

Our data show that the antimetabolite, FUMP, encapsulated in multivesicular liposomes and administered by intravitreal injection, may be a useful adjunctive therapy for inhibition of PVR. The half-life of FUMP in the vitreous of animals treated with liposome-encapsulated drug was nearly 30-fold greater than with the drug alone. Furthermore, in the rabbit model of PVR, a single 0.1-mg injection of this antimetabolite delivered in multivesicular liposomes, a nontoxic dose, reduced the incidence of tractional detachment by 92%. Under similar conditions, Ara-C was significantly less effective than FUMP, providing only a 46% reduction in tractional membranes. In a separate study, we found that a bolus injection of the same dose of 5-fluorouridine without liposomes resulted in only a 70% reduction in the incidence of detectable tractional detachment (submitted for publication, Hartzler et al).

These liposomes are useful vehicles for sustained drug delivery to the eye for several reasons as follows: (1) they are readily synthesized using sterile techniques; (2) they can incorporate precise drug amounts over a wide range of desired concentrations; (3) large drug amounts, per unit volume, can be incorporated; (4) prolonged drug transit time is achieved as a result of the traversal of numerous phospholipid membranes by the drug; (5) their large size (Fig. 3) helps to ensure that they remain localized at the injection site; and (6) their membranes are stable and may undergo severe deformation without disruption. Thus, a 27- or 30-gauge needle may be used for injection, even though the liposomal diameter may be greater than the lumen of the needle. Finally, liposomes themselves may block lymphatic and other drainage pathways, thereby retarding the rate of free-drug clearance. In this regard, while treating a rabbit model of Pseudomonas aeruginosa keratitis using subconjunctivally administered tobramycin liposomes, we found that, simply by mixing free drug with blank liposomes, there was a significant decrease in the bacterial population in preliminary studies. Although this reduction in colony count was not as great as that observed in animals treated with liposome-encapsulated drug, it was significantly greater than that in animals receiving free drug without any liposomes. It might, therefore, be interesting to evaluate the pharmacokinetics and efficacy of free drug when coadministered with blank liposomes in the vitreous.

We believe these properties make these liposomes well suited for sustained intravitreal drug delivery. In a study evaluating liposomal clearance from the vitreous, using liposomes 106 smaller by volume than ours, others reported rapid clearance of liposomes from lensectomized and vitrectomized eyes. They concluded that liposome-bound drugs might be cleared as rapidly from the postsurgical vitreous as unbound drug. In another study evaluating the effect of size and lipid composition on the pharmacokinetics of intravitreal liposomes, it was reported that the rate of clearance was related inversely to liposome size. This may, in part, explain the apparently rapid clearance of liposomes reported by others. Furthermore, the apparent rapid clearance in that study may have been the result of sampling from the central vitreous cavity. If reduction in liposomes in these samples reflects rapid clearance, we would expect significant systemic absorption; this was not observed. Fluid samples from the central vitreous cavity would yield low levels if the liposomes settled or were bound to the vitreous drainage pathways.

Fig. 2. Percent of rabbits in each group demonstrating tractional retinopathy was graded as follows: normal retina (O), localized retinal pucker without evidence of detachment (P), retinal detachment, either involving a single medullary ray (stage two), or the entire retina (stage three) (D).
proliferative membranes or ocular tissue. The authors reported that after repeated washings, a high percentage of the liposomes remained bound to ocular tissues; this is inconsistent with rapid clearance from the eye. Therefore, it would appear that even in vitrectomized and lensectomized eyes, liposomes might serve as sustained delivery vehicles.

These observations help explain the extended delivery rate of multivesicular, megaliposome-encapsulated FUMP compared with controls receiving free drug. At 96 hr, the intravitreal drug levels of rabbits treated with liposome-encapsulated FUMP is nearly 400-fold greater than in rabbits treated with this drug alone. Significant levels exceeding the ID$_{50}$ of FUMP are present at least 336 hr after intravitreal injection when encapsulated in multivesicular liposomes. By contrast, a single intravitreal injection of FUMP alone essentially is cleared from the vitreous in 24 hr. By maintaining significant drug levels for prolonged periods, liposomes eliminate the need for frequent drug administration.

This form of delivery also may improve treatment efficacy. Increasing the exposure time of fibroblasts to 5-fluorouridine in tissue culture, from 1 to 72 hr, resulted in a 20-fold increase in drug efficacy. Hence, the ID$_{50}$ of a drug, as determined in tissue culture, may be significantly higher than in a sustained delivery system, where drug exposure time is prolonged dramatically. With liposomal delivery systems, it is possible that the drug remains above a therapeutic concentration in the vitreous long after it has fallen below the in vitro-determined ID$_{50}$. Attempts at determining free drug levels in the vitreous for comparison to the ID$_{50}$ might, therefore, be superfluous.

Sustained delivery systems also may reduce toxicity associated with exposure to numerous drug peaks from frequent administration. It was shown that 5-fluorouracil-induced retinal toxicity was decreased when administered in split doses compared with a single bolus injection. Others recently reported a decrease in retinal toxicity of Ara-C in both vitrectomized and nonvitrectomized rabbit eyes when encapsulated in liposomes. The 1.0-mg FUMP dose used in the pharmacokinetics portion of this study was selected to facilitate detection of the drug over extended periods. This amount was shown later to be toxic to the retina. For the PVR experiment, we used a dose of 0.1 mg FUMP. In a separate study, we evaluated the retinal toxicity of FUMP, at 1, 10, and 30 days after intravitreal administration in NZW rabbits. Eyes receiving either free or liposome-encapsulated drug were compared with those receiving empty liposomes or 250 mM sucrose injection. Serial clinical examination, electroretinography, and histopathologic evaluation by light and electron microscopy did not show significant retinal toxicity by either the empty liposomes or 0.1 mg of FUMP (free drug or liposome encapsulated) compared with sucrose-injected controls at 30 days.

The use of highly potent drugs for sustained delivery systems is desirable because only limited amounts of the drug will be free for interaction at the target site. The drug Ara-C has been shown to be tenfold less potent by weight than FUMP for the inhibition of fibroblast proliferation in vitro. On this basis, we
chose to use an Ara-C dose (1.0 mg) tenfold greater than the FUMP dose (0.1 mg). The Ara-C exerts greater preferential toxicity (tenfold) on cell-cultured retinal pigment epithelial cells than on fibroblasts. This potentially deleterious characteristic was not observed in cell culture studies using FUMP.

Both Ara-C and the fluoropyrimidines (5-fluorouracil and its metabolites) were used to treat ocular conditions associated with wound healing, including glaucoma filtering surgery in eyes with a poor prognosis. The biologic basis of PVR also may be related to wound healing. It occurs in settings where tissue disruption has occurred, with resultant inflammation and wound healing. It may follow some cases of posterior segment trauma, giant retinal tears, vitreoretinal surgery, and possibly, excessive cryotherapy. Thus, any pharmacologic agent that inhibits cell-mediated contraction, proliferation, or chemotaxis should inhibit the fibroproliferative process and diminish the severity of PVR. Furthermore, adjunctive therapy aimed at inhibition of tractional detachment may be needed only for several weeks after the initial insult. In this regard, only 1 of 18 rabbits (in any group), which had not yet had a retinal detachment by 14 days, had one by 30 days in our study. Alternatively, this may demonstrate a defect of our model in the evaluation of PVR, because fibroblasts are introduced without concomitant vitreous detachment or tissue disruption. Vitreous detachment and tissue injury may be chronic stimuli for inducing fibromembranous proliferation, thus requiring prolonged drug therapy. Furthermore, the simultaneous addition of the antimetabolites and fibroblasts may result in acute fibroblast destruction. Hence, the enhanced efficacy provided by a sustained delivery system may be even greater than shown in our model. It would thus appear that an additional study evaluating the suppression of PVR in a more “chronic” model might be desirable. Our model of PVR was chosen because it was the most extensively used in evaluating antimetabolite inhibition of PVR.

Both FUMP and Ara-C were chosen for our study because they interfere with distinct phases of the cell cycle and are significantly more potent antiproliferative agents than 5-fluorouracil. The drug Ara-C is primarily an inhibitor of DNA synthesis. A metabolite of 5-fluorouracil, FUMP, is an extremely potent inhibitor of RNA synthesis and processing; thus it interferes with protein synthesis. In addition, FUMP has anticontractile effects for fibroblasts in vitro. Inhibitors of RNA and protein synthesis, but not of DNA synthesis, were found to decrease fibroblast and retinal pigment epithelial cell chemotaxis. Thus, FUMP may interfere with several phases of the cicatrical process, including chemotaxis, proliferation, and cell-mediated contraction; Ara-C only inhibits cellular proliferation. The drug, 5-fluorouracil, partially metabolized along the DNA pathway, is not as potent an inhibitor of fibrocellular proliferation as are its RNA-incorporated metabolites, 5-fluorouridine and FUMP. This difference in cell-cycle specificity between FUMP and Ara-C may explain partially the marked disparity in efficacy between these two drugs when tested in the rabbit PVR model. Only 7% of FUMP-treated rabbits had a retinal detachment at 30 days compared with a 62.5% retinal detachment rate for Ara-C-treated rabbits. It thus appears that a single intravitreal injection of multivesicular liposomes containing FUMP may be a useful adjunct to conventional vitrectomy surgical techniques.

Key words: antimetabolite, cytarabine, 5-fluorouridine, 5'-monophosphate, multivesicular liposomes, proliferative vitreoretinopathy

References


