In a critical scene during the first act of the 1990s play Rent, the protagonists’ beepers go off, reminding them to take their zidovudine and revealing to the audience that many of the characters are HIV positive. In terms of compliance, the beepers are an active mnemonic that aids patients with the q4h dosing regimen required by oral zidovudine’s short duration of action. In the years since this musical was written, pharmacotherapies have been developed that include longer-acting reverse transcriptase inhibitors and other anti-HIV treatments that are easier for patients to use.

The theoretical work of Blackwell, the work of Kass et al using electronic monitors with q.i.d. pilocarpine and b.i.d. timolol, and more recent work using q.d. medications teach clinicians to be concerned that patients are less than ideally adherent to prescribed topical ocular therapy. One solution is to develop treatments that do not require as much effort by patients to achieve therapeutic efficacy. It could be argued that laser trabeculoplasty and filtering surgery meet this requirement, but these procedures are by definition more invasive than pharmacotherapy and present different risk/benefit profiles.

Published at the same time as the electronic monitoring work of Kass et al, a review by Shell presented the basic principles of keeping ocular levels just above the minimally effective concentration. Using proprietary technology, Alza Corporation (Mountain View, CA) applied these principles to pilocarpine to minimize the pulsatile delivery and acute untoward ocular effects of miosis and accommodative spasm (Ocusert) (Figure 1).

The cortisene, anecortave acetate—previously evaluated by posterior juxtascleral injection for the treatment of choroidal neovascularization—has more recently been studied by sub-Tenon’s injection for its ocular hypotensive efficacy. I was in the audience when this new work was presented at several scientific meetings and was intrigued by the magnitude of other attendees’ interest. Upon subsequent discussion with glaucoma specialists, I found that they were excited by the prospect of a single treatment that lasted 3 months, which could help alleviate problems with adherence. It appears that many glaucomatologists would like to see treatments that are more forgiving to patients who have trouble following frequent topical dosing regimens.

The local delivery of molecules to the eye may be achieved through many routes (Figure 2). In a recent review, I summarized the various ophthalmic drug delivery systems in research, development, and clinical use. These include aqueous formulations of eye drops with increased viscosity, prodrugs, contact lenses, collagen shields, lyophylates, iontophoresis, erodible implants for the lower cul-de-sac, intraocular implants (both erodible and not), and encapsulated cell technology. Many of these systems were initially explored for retinal disease, for which topical instillation is the least likely to provide therapeutic doses at the diseased tissue. I restricted this piece’s scope to full articles and published patents or applications as of spring 2009.

Advanced-stage delivery systems

Among the delivery systems for glaucoma therapy already marketed or in late-stage development are a...
thickened formulation of pilocarpine (Adsorbocarpine, no longer marketed), a gel-forming solution of timolol including gellan gum (Timoptic-XE; Aton Pharma, Inc., Lawrenceville, NJ), and a cationic exchange resin formulation of betaxolol (Betoptic-S; Alcon Laboratories, Inc., Fort Worth, TX). Prodrugs include dipivalyl epinephrine (prodrug for epinephrine); levobunolol, which itself is active, as is its ocular metabolite, dihydrolevobunolol; and at least four of the marketed prostaglandins (latanoprost, travoprost, unoprostone, and bimatoprost), although the last itself may be active.

NOVEL EXTRAOCULAR SYSTEMS

In order to deliver a drug as a solution in an eye drop, it must have aqueous solubility. Molecules of limited aqueous solubility (eg, corticosteroids) may be formulated as an aqueous suspension, which typically requires shaking by the patient before instillation. All eye drop formulations must be stable for the period from their manufacture until their use by the patient. In order to avoid some of these limiting pharmaceutics issues, Diestelhorst and colleagues have deposited a drug by lyophilization on Teflon strips (Figure 3). Although most studies have used fluorescein, there is clear potential utility for this technology in glaucoma for new molecules. In a related approach, investigators coated plastic rods with clonidine. Researchers have evaluated erodible implants for insertion in the lower cul-de-sac. In addition, several firms are using an electrical current to enhance the delivery of drugs through the cornea or sclera, an approach that may be useful for ocular hypotensive agents (DC current: ReAble Empi [St. Paul, MN; formerly Iomed Inc.], Aciont Inc. [Salt Lake City, UT], and Eyegate Pharma [Waltham, MA]; AC current: Macroesis [Buckeye Pharmaceuticals, Beachwood, OH]).

Investigators have evaluated a proprietary polycarbophil formulation (DuraSite; InSite Vision Incorporated, Alameda, CA) as a delivery system for pilocarpine, levobunolol, and fluorometholone as well as a recently approved formulation of azithromycin (AzaSite; Inspire Pharmaceuticals, Inc., Durham, NC). A cationic emulsion of cyclosporine is being developed for the treatment of dry eye and may have utility for ocular hypotensive agents.

NOVEL INTRAOCULAR SYSTEMS

The interest in treating chronic retinal diseases with ocular delivery systems has led to the availability of two intravitreal systems that are not erodible: a ganciclovir implant for the treatment of cytomegalovirus retinitis (Vitrasert; Bausch & Lomb, Rochester, NY) and a fluorocinolone acetonide implant for the treatment of recurrent posterior uveitis. In development by the inventors of the latter is a third-generation product with fluorocinolone acetonide for diabetic macular edema (Iluvien; Alimera Sciences Inc., Atlanta, GA). Other intraocular implants being developed that are not erodible are a helical, transconjunctival implant with triamcinolone acetonide, and a polycaprolactone-based subretinal implant. An erodible implant of dexamethasone is under development for intravitreal implantation to treat persistent macular edema (recently approved as Ozurdex [Allergan, Inc., Irvine, CA]). Neurotech USA, Inc. (Lincoln, RI), is assessing an encapsulated cell technology intravitreal implant containing cells that produce human ciliary neurotrophic factor as a treatment for retinitis pigmentosa and geographic atrophy. The company has stated that it is considering the system’s neuroprotective indications for glaucoma. Investigators have performed surgical microcannulation of the suprachoroidal space and the delivery of triamcinolone acetonide and dyes in animal models using a microcannula with fiber-optic illumination.
may be useful for the delivery of ocular hypotensive agents to the anterior segment or for the delivery of neuroprotective agents to the retina. The physical constraints of the eye place restrictions on the successful development of delivery systems for intraocular placement. Lower-potency drugs necessitate the construction of systems that become prohibitively large. Tiny devices with low-potency drugs may not produce therapeutic concentrations of the agent, or they will have a very short duration, which requires unacceptably frequent implantation procedures.12

REGULATORY AND DEVELOPMENTAL CONSIDERATIONS

In essence, the development of a drug delivery system involves two products, the active drug and the delivery system. If the system itself provides therapy (eg, a corrective contact lens that releases the drug), then it may be considered a combination product. The US FDA’s regulations for combination products may be found in 21 CFR 3.2(e) at http://www.fda.gov/oc/combo.13,41 If the active agent has been previously approved by the FDA, then the developer may employ the 505(b)(2) section, active agent has been previously approved by the FDA, which may result in some savings on the systemic toxicology and clinical safety required.43 Whatever the regulatory route, a substantial investment of time, money, and expertise will be required for any ocular drug delivery systems for glaucoma therapy to become available for general use in treating patients. 

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