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ADVANCES IN OCULAR PHARMACOLOGY

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Over the past few years, our understanding of the absorption, distribution, and biotransformation of ophthalmic pharmacologic agents has increased markedly. Such advances, coupled with a greater appreciation of the ocular autonomic nervous system and of the dynamic and physical properties of biological and synthetic membranes, have resulted in the development of new drugs and drug delivery systems.

In this chapter, we examine recent advances in glaucoma therapy, including membrane drug-delivery systems; timolol, a β-adrenergic blocking agent; and a pharmacologic approach to reducing aqueous outflow resistance by medical trabeculocanalotomy. In addition, we briefly review the current state of ocular antiviral therapy and the development of artificial tear inserts for the treatment of dry eyes.

ADVANCES IN GLAUCOMA THERAPY

Synthetic Membrane Delivery Systems

The control of a chronic problem like glaucoma requires the patient's strict adherence to a disciplined regimen of topical medications. Given the symptomless nature of the disease and the demands of daily life, poor compliance in many patients is unfortunate but understandable. Even with strict compliance, the regular interval dose of the medication is based on a first-order delivery system. In such a system there is an initial high dose on absorption followed by a decline to a relatively low level before the next dose. Obviously, a more desirable situation would be a zero-order delivery system, in

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which the delivery of drug is constant and where overdose/underdose situations are avoided. The development of synthetic membrane delivery systems is an attempt to achieve such zero-order delivery.

Synthetic membranes are polymers of long-chain molecules which have either hydrophilic or lipophilic qualities, depending on their basic structure. Such membranes must be sufficiently free of impurities, additives, residues, and structural abnormalities to be safe and must be compatible with the drugs they contain. The material most widely used for this purpose is silicone (1).

The most important functional property of these membranes is permeability, which can be achieved by both porous and nonporous membranes. Solubility of the drug in the membrane and the size and charge of the molecule are also important factors in the design of membrane systems.

RESERVOIR MODULE The reservoir module membrane delivery system (Ocusert®) is based on a nonporous membrane. A central reservoir of drug is surrounded by a polymeric membrane which allows a constant movement of drug into the tissue. A controlled rate of delivery is provided by the interaction between the membrane molecules and the molecules of drug.

A major factor in the rate of drug release is the driving force of the concentration gradient, which is maintained by the saturated concentration of the drug in reservoir. As long as this gradient exists, there is zero-order drug delivery through the membrane.

Another factor in the rate of release is the concentration of drug "outside" of the membrane. Released drug must be removed or the driving force will be reduced. The eye provides an excellent environment for such a system because tear secretion prevents the buildup of a stagnant layer of drug around the module. This type of drug delivery system is less effective in other tissues because of the absence of this washing effect.

The reservoir module is in current use for the delivery of pilocarpine to reduce intraocular pressure. The drug is released at a rate of 20 μg per hour. Pilocarpine in the central reservoir is in equilibrium between the ionized, water-soluble form and the un-ionized, lipid-soluble form. In the aqueous tear layer, the lipid form of the drug is released.

Upon insertion of the Ocusert, there is an initial higher pulse release of pilocarpine from the drug dissolved in the membrane. For eight hours, the drug is delivered at the rate of 64 μg per hour. Thereafter, constant delivery at 20 μg per hour is maintained until the drug level in the central core is no longer saturated. The delivery module is then removed and replaced with a fresh insert. The amount of pilocarpine released in seven days is approximately 3500 μg, much less than would be delivered by seven days of topical pilocarpine administration. The reservoir membrane delivery system is capable of only a very low release rate; however, with a zero-order delivery

system, the therapeutic effect can be achieved with much smaller amounts of drug, altering the therapeutic index (maximum effective dose versus minimum toxic dose). Consequently, many drugs that have been rejected for clinical use due to toxicity might be usable if delivered by the membrane system.

ERODIBLE MODULE In the erodible module, drug molecules are incorporated into the matrix of a synthetic polymeric membrane. When such a module is exposed to aqueous media, hydrolyzable bonds are ruptured leading to the release of surface polymer and the concurrent release of drug. This system has the advantage of requiring only periodic replacement with no spent module to retrieve. However, the membrane must be manufactured with hydrolyzable bonds within the polymer molecule and not just between the polymers to prevent the possible problem of long-chain residues accumulating in the eye.

OSMOTIC PUMPING MODULE In the osmotic pumping module, there is an impermeable compartment with a tiny opening separated from a salt-filled semipermeable compartment by a thin elastic membrane. When placed in an aqueous environment, the salt-filled compartment takes up fluid and slowly expands the elastic membrane into the drug-filled compartment, squeezing drug out of the aperture at a constant rate. This system avoids complex drug/membrane interaction but must be retrieved when exhausted, which places some physical limitations on its use.

In summary, membrane drug delivery systems offer several advantages in the delivery of medication and the control of intraocular pressure. First, they minimize the problem of patient compliance with directed drug use. Second, their zero-order delivery avoids the high dose/low dose characteristics of first-order delivery systems. Third, lower doses of drugs given in this manner produce the desired therapeutic effects (at least with pilocarpine), decreasing the incidence of undesirable side effects. However, these inserts have proved somewhat difficult to use, which has limited their general clinical therapeutic utility.

New Drugs for the Reduction of Intraocular Pressure

TIMOLOL MALEATE Timolol maleate (Timoptic®) is a β-adrenergic blocking agent applied topically to reduce intraocular pressure. Some of the advantages noted above for membrane delivery systems also apply to this drug. First, the twice-a-day dose schedule is expected to enhance patient compliance. Second, there have been minimal side effects reported. Third, it is often effective at low doses. In addition, the topical dosage regimen is familiar to patients and physicians, providing, in convenient flexible form, a powerful, apparently safe drug for the control of glaucoma.

Mechanism of action The precise mechanism of action of timolol is not clear. Among the possibilities are its β-adrenergic blocking effects on the formation of aqueous humor, on facility of outflow, or on some combination of these two. Non-β-blocker effects include possible changes in the corneal scleral envelope, central nervous system effects, or effects from surface anesthetic or quinidine-like properties (2).

Nevertheless, most experimental evidence points to timolol's action on the β-adrenergic receptors in the eye as the mechanism of its effect on intraocular pressure. It has been shown that D-isomers of propranolol do not block β-adrenergic receptors and do not lower intraocular pressure (3). Therefore, the β-adrenergic blocking effects on inflow and/or outflow appear to best explain this drug's mechanism of action. Several groups have shown, in single-drop studies, that there is no significant change in outflow as measured by tonography when timolol decreases intraocular pressure (4, 5). Other long-term studies have indicated a slight increase in outflow with continued use. On the other hand, fluorophotometric studies (6, 7) have shown a definite decrease in the rate of aqueous formation. Further, electro-oculogram studies and studies on healthy volunteers (8) have contributed evidence that this decrease in intraocular pressure is primarily due to decreased aqueous formation.

However, the timolol-induced decrease in aqueous formation probably cannot be explained solely by the blocking of the β-adrenergic receptors. Neufeld (9) points out that the control of intraocular pressure is unlike other physiologic phenomena in which α-and β-adrenergic stimulation have opposite effects which are elicited or blocked by appropriate pharmacological agents. In fact, therapeutic decreases in intraocular pressure can be achieved by applying either an α- or β-adrenergic agonist or antagonist to the eye.

This somewhat perplexing response may be explained by the multiple factors (vascular, epithelial, and endothelial) affecting the control of intraocular pressure. In each of these areas the effects attributable to adrenergic receptor activity undoubtedly represent a sum of the responses to stimulation or blockade of these receptors which are of variable sensitivities in different cellular locations. Zimmerman & Chiou (10) have theorized that the α- and β-receptor effects are competitively balanced and the tone of either influences the effect of the other.

The β-adrenergic blocking effect of timolol must be seen as only a single, but important, factor in the complex interrelationship of adrenergic receptors and intraocular pressure. The effect of timolol is to tip the balance of adrenergic tone in favor of decreased aqueous formation.

Efficacy Timolol has been shown to have an ocular hypotensive effect in normal volunteers, ocular hypertensives, and patients with chronic open

angle glaucoma. Katz (11) showed that timolol, in concentrations of 0.5%, 1.0%, and 1.5%, significantly decreased intraocular pressure in 30 normal volunteers.

In another series of 518 patients, timolol was shown to be more effective than either pilocarpine or epinephrine (12, 13). Optimal dosage appeared to be 0.25% or 0.5% once or twice daily. Duration of action was 24 hr for 0.25% and 0.5% timolol and 8 hr for 0.1% timolol. Maximal decrease in intraocular pressure occurred 12 hr after topical application.

An interesting effect was noted in some patients who initially showed an excellent response to timolol. After several weeks of continued use, intraocular pressure increased slightly, stabilizing at an approximate 20% to 25% decrease from pretreatment levels (14). This effect is presently being investigated.

The efficacy of timolol has been shown when used alone, either initially or as a substitute for other topical medications. In a study of 20 patients, it was found that timolol also had an additive effect when added to a regimen of maximal medical therapy (15). As noted above, timolol appears to decrease the rate of aqueous formation. This effect is additive with other agents (epinephrine and the carbonic anhydrase inhibitors) which also decrease the rate of aqueous formation (16).

If an effect on intraocular tension is noted when timolol is added to an existing medical regimen, the other medications may be gradually withdrawn to see whether timolol alone will provide sufficient control. Lack of response to added timolol is usually noted in the first four to six weeks. Full explanations of possible mechanisms of interaction with concurrent therapy need further study and observation.

Safety Timolol exerts its ocular hypotensive effect with an apparently high therapeutic index, that is, with maximal efficacy coupled with minimal toxicity. The drug has been shown to cause a minimal decrease in tear production. It produces less conjunctival hyperemia than epinephrine and shows no adverse effects in contact lens wearers. There is a minimal effect on pupil size and no accommodative spasm. Few patients complain of burning, tearing, discharge, foreign body sensation, itching, soreness, browache, or headache (12).

Studies with aphakic patients have shown a significant intraocular pressure reduction with timolol (13). In addition, no aphakic patient treated with timolol developed cystoid macular edema. Since timolol blocks both β_1- and β_2-adrenergic receptors, its possible systemic effects must be closely monitored. To date, few clinically significant effects have been noted on the systolic or diastolic blood pressure. In one study, resting pulse rate did decrease slightly (as much as 6 beats per minute). However, this was seen only during the first six months of therapy, after which the effect disap-

peared (12, 13). While the exact cellular mechanism for the action of timolol is unclear, its potent ocular hypotensive effects are well documented. Possible long-range side effects, both ocular and systemic, are presently being closely watched. If the adverse effects continue to be minimal, this may be the drug of choice for glaucoma.

DIPIVALYL EPINEPHRINE, A PRO-DRUG Pro-drugs are pharmacological agents that must undergo biotransformation before exhibiting their effects. Such drugs have been explored as a means of providing better absorption, sustained effect, increased solubility, less toxicity, and site-specific drug delivery. To illustrate this concept, dipivalyl ephinephrine (DPE) is discussed below (17, 18).

DPE is an analogue of epinephrine which differs from epinephrine by the addition of two pivalyl side chains which causes a marked increase in the drug's lipophilicity. Experiments in rabbits have shown that eight to ten times more DPE is absorbed into the eye as compared to epinephrine. In the eye, DPE is rapidly hydrolyzed to epinephrine; its effect on intraocular pressure is the same as that of the parent drug.

Clinical studies have shown DPE to be an effective ocular hypotensive agent. Trials using the drug in 0.025%, 0.1%, and 0.25% concentrations showed lowered intraocular pressure produced by all three formulations. There was no significant difference in results using either 0.1% or 0.25% concentrations. In a single-drop study there was no difference in results using 0.5%, 0.1%, and 0.25% DPE. In concentrations greater than 0.1% there were more epinephrine-like side effects: stinging, hyperemia, mydriasis with blurring vision, and intolerance. Since DPE is effective at the 0.025% concentration and is converted to epinephrine *inside the eye,* fewer systemic effects are to be expected.

N-DEMETHYLATED CARBACHOL (DMC) Carbachol is another drug that has been manipulated biochemically. A methyl group has been removed making the drug molecule isoelectric and increasing penetration without greatly decreasing potency. This compound is currently undergoing its first clinical trials in humans.

MARIJUANA Marijuana or cannabis is being widely "legalized" by some state legislatures for various medical uses including the treatment of glaucoma. It must be remembered that marijuana is still a Schedule One drug that has "no currently accepted medical use in treatment" (19). Furthermore, its mechanism of action in lowering intraocular pressure is not at all clear.

Marijuana is a mixture of 20 closely related cannabinoids. The primary active ingredient is Δ9 tetra-hydrocannabinol (Δ9 THC).

Conjunctival hyperemia seen in known users suggested that marijuana might have other ocular effects. However, it was not until 1971 that a fall in intraocular pressure was quantitated after the drug's use (20, 21). The maximum intraocular pressure fall was noted to coincide with the hyperemia. Also, all other ocular functions except for slight decrease in tear flow were unchanged. Further studies with intravenous cannabinoids showed a general correlation between the efficacy in reducing intraocular pressure and the level of euphoria. However, Δ10 THC causes decreased intraocular pressure with less euphoria than Δ9 THC.

The mechanism for the ocular response is complex as Δ9 THC appears to act in the eye on aqueous inflow and outflow and to have central nervous system activity which affects intraocular pressure. Again, the exact mechanism is not clear.

Much more research must be done before marijuana can be used in the treatment of glaucoma. The drug's "high" would be an undesirable and unacceptable effect in the average patient. Whether the psychoactive effects can be separated from the ocular hypotensive effects is not known. Much experimentation is needed to put the drug in an acceptable, possibly topical, dosage form and to assess its interaction with other glaucoma medications.

CYTOCHALASIN B (MEDICAL TRABECULOTOMY) The major site of resistance to aqueous humor outflow is found in the trabecular meshwork and the inner wall of the canal of Schlemm. Most resistance is found in the juxtacanalicular meshwork. The endothelial cells of the inner canal wall and the corneo-scleral and uveal portions of the meshwork contain cytoplasmic actin microfilaments which may be capable of contraction. The contraction of these filaments may play a role in aqueous outflow (22–24). In an excellent review, Kaufman & Svedbergh have discussed pharmacologic approaches to disrupting these filaments and altering outflow (25).

Cytochalasin B is a fungal metabolite which disrupts cytoplasmic microfilaments, altering the shape and motility of many cell types. Injection of this substance into the anterior chamber causes a profound but reversible reduction in outflow resistance (26). This reduction is essentially due to decreased resistance to flow through the tissues between the anterior chamber and Schlemm's canal. Increased numbers of transcellular aqueous pathways and ruptures in the inner wall of Schlemm's canal with endothelial cell separation and "washout" of debris have been demonstrated (27).

It has also been noted that similar effects have been created by the irrigation of the anterior chamber with a calcium-free "mock" aqueous or EDTA, which is a potent chelator of the calcium ion. Again, with these two techniques an enormous decrease in resistance to outflow was reported. The cellular alterations in the angle were similar to those mentioned with cytochalasin B (28, 29).

The presence of cytochalasin B or the absence of calcium in the anterior chamber appears to cause decreased outflow resistance, increasing the rate of outflow of aqueous and reducing intraocular pressure. The common mechanism is the disruption of the cytoskeleton and the contractile elements of the endothelial cells. Also, the washout of debris may further enhance outflow. Obviously, much further study is needed before the exciting prospect of a medical trabeculocanalotomy is a possibility.

ADVANCES IN OCULAR ANTIVIRAL THERAPY

Antiviral Drugs for Treatment of Herpesvirus

At present, in the United States there are two commercially available drugs for the therapy of ocular herpes infections, idoxuridine (IDU) and vidarabine (Ara-A). Both drugs show similar efficacy and toxicity when used topically in the eye; however, vidarabine is effective systemically for the treatment of herpetic iritis and uveitis. Trifluorothymidine (TFT) is commercially available for topical use in Europe.

IDOXURIDINE The first drug used to treat virus infections was idoxuridine (30). Many double-blind clinical trials (31–35) confirmed the original animal studies showing it to be effective against epithelial herpetic keratitis. IDU, however, has a low solubility which makes its therapeutic activity less than ideal. It also produces allergies and toxicities, especially with chronic use, and truly resistant virus can develop.

VIDARABINE Vidarabine was the next clinically useful drug developed to treat virus infection (36). When administered topically as a 3% ointment, vidarabine is similar in effect to IDU (37–39) but does not show cross-resistance to IDU.

Vidarabine, however, is a systemically active drug which does not inhibit the bone marrow or the patient's own cell-mediated immunity (40–42). Although vidarabine is also relatively insoluble and must be administered with large volumes of fluid, intravenous use is effective. Vidarabine was proven effective in a double-blind controlled intravenous trial on patients with herpetic keratouveitis (43) and a beneficial effect was seen. Although disease was not eradicated, some patients responded; however, others did not. The positive responses were sufficiently dramatic to make it worth trying in patients who do not respond to other forms of therapy.

TRIFLUOROTHYMIDINE In experimental trials trifluorothymidine (TFT) is extremely effective against epithelial herpes (44, 45). Recent double-blind clinical trials have established that TFT is also effective in humans

and is the drug of choice (46–48). TFT is rapidly hydrolyzed in the blood stream but is less toxic than vidarabine to the healing epithelium (49, 50). TFT is a solution that does not blur vision and therefore may have improved patient acceptability.

Trifluorothymidine is also very effective when used in combination with corticosteroids. It can be used with the same frequency as the corticosteroids for the treatment of stromal disease or keratouveitis, and it effectively prevents the undesired epithelial infection that usually follows steroid treatment in the face of virus multiplication.

NEWER DRUGS The drugs described thus far are not selective in their action but inhibit normal cellular activity as well as viral activity. Newer drugs are being developed and tested that are phosphorylated only by virus-infected cells, and are therefore more selective for disease-causing agents.

Acyclovir and AIU Currently under study are several newer drugs such as acyclovir (51–53), 5-iodo-5-amino-2',5-dideoxyuridine (AIU) (54), and thymidine arabinoside (Ara-T) (55); these are phosphorylated only by virus-infected cells.

In animal studies, acyclovir is more potent than AIU and Ara-T (56, 57). It is effective against experimental herpetic iritis when given systemically and appears to be effective against stromal disease (unpublished data, Varnell, E. D., Kaufman, H. E.). Many studies have investigated whether acyclovir can prevent colonization of the trigeminal ganglion with herpesvirus and, once colonization is present, whether acyclovir can eradicate virus (58–60). Most of these studies are still preliminary and leave unanswered questions, but they offer hope that something may be done to remove the site of virus which probably is responsible for recurrences of ocular herpes.

Human leukocyte interferon Human leukocyte interferon is only moderately effective as a therapeutic agent for treating ocular herpes infections, but it is extremely effective in preventing herpetic keratitis in monkeys (61). There is no true experimental recurrence model available in primates, but preventing infection in rodents parallels preventing recurrences of ocular herpes (62). The early trials (63) of human leukocyte interferon utilized material which had a low titer and therefore was not effective in preventing recurrences. It has not been possible to obtain sufficient quantity of high titer interferon to do the proper controlled trials, but recently reported trials against herpes labialis (64) support our hypothesis that interferon should also have an effect in preventing ocular recurrences.

ADVANCES IN DRY EYES THERAPY

Slow-Release Artificial Tears for the Treatment of Keratitis Sicca

Dry eyes is a severe problem that remains a difficult and often frustrating eye disorder to treat. Although many patients suffering with this problem are adequately treated with topical artificial tear substitutes, a significant number of patients do poorly both subjectively and objectively with this treatment regime.

In the search for a successful artificial tear, we have tried to reproduce the composition and physiology of normal tears. It has proven ineffective, however, to mimic the composition of normal tears without producing the constant flow which continually bathes the cornea and lids, lubricates the eye, and keeps it moist. We have found no compound which can be instilled as infrequently as every one to two hours and yet will maintain moisture and comfort in patients with dry eyes. The effect of periodic administration of artificial tears is so different from that of normal physiology that the search for an artificial tear similar to natural tears may not be the best way to approach the problem of dry eyes.

One solution to this problem may be an improved delivery system, such as the slow-release artificial tear (SR-AT) (65). A pellet of a cellulose polymer, without preservative, is inserted below the tarsus of the lower lid and dissolves slowly during the day, continually providing a source of tear film stability and lubrication to the eye.

In its dehydrated state, the SR-AT is a solid rod of a cellulose polymer measuring approximately 1 mm in diameter by 10 mm in length, containing 5 mg of unmedicated synthetic polymer. It is supplied to the patient in hermetically sealed blister packs and is easily inserted into the lower conjunctival cul-de-sac beneath the tarsal plate by means of an applicator. Its hypertonicity probably permits it to imbibe fluid from the capillaries of the conjunctiva even in the absence of tear production.

Sixty keratoconjunctivitis sicca (KCS) patients have been treated to date. All had moderate to extreme symptoms of burning, photophobia, foreign body sensation, dryness, or itching, combined with a Schirmer 1 test of 10 mm or less of wetting and a tear-film breakup time (BUT) of 10 seconds or less.

Of the 60 patients entered in the long-term SR-AT study, only 12 patients have dropped out. One patient who discontinued use of the SR-AT was unable to insert it because of severe rheumatoid arthritis, and a second patient had difficulty with insertion due to bilateral aphakia. By far the most common side effect experienced in this group of patients was blurring of vision after four to six hours. Most of the patients have been able to

minimize or eliminate the blurred vision by removing the insert after three to four hours and inserting a second SR-AT several hours later.

The slow-release artificial tear seems useful in the treatment of patients with keratitis sicca whose symptoms are difficult to control with artificial tears alone. This continuous delivery of a tear-like substance seems to be more similar to the natural, physiologic condition than the intermittent instillation of artificial tears and, particularly in patients with long-standing, severe dry eye problems, appears to alleviate both corneal findings and subjective symptoms.

CONCLUSIONS

Current advances in ocular therapy comprise new drugs developed for the treatment of glaucoma, herpesvirus, and dry eyes and new delivery systems for limiting ocular therapy to the eye, with the concomitant prevention of systemic side effects.

Among the new drug therapies for glaucoma are timolol, a β-adrenergic blocking agent which reduces intraocular pressure with minimal side effects; DPE, a chemically altered form of epinephrine with greater penetrability across the cornea allowing the use of smaller doses; DMC, another altered molecule with increased penetrability; marijuana derivatives, which are still in the early testing stages; and cytochalasin B, a fungal metabolite which may prove to lower intraocular pressure by mechanically reducing outflow resistance, thus providing a sort of medical trabeculotomy. New drug delivery systems are being developed to smooth out the rate of delivery of these drugs and to improve ease of administration, with the long-range goals of reducing systemic and ocular side effects and improving patient compliance.

Antiviral therapies for ocular herpes include IDU and vidarabine, both proven clinically useful in controlled trials; and trifluorothymidine, which is still being tested for efficacy and safety in clinical trials. Newer drugs currently in the testing stages are acyclovir and AIU, which appear to be more selective for virus-infected cells than earlier drugs. Systemic administration with these drugs should permit the more effective treatment of deeper infections. Human leukocyte interferon shows promise for the prevention of recurrences of ocular herpes, if and when the problems associated with obtaining the material in high titer can be solved.

Treatment of dry eyes (keratitis sicca) requires both a satisfactory artificial tear and a method of delivery that eliminates the need for frequent application. The SR-AT attempts to supply both these needs by steady release of a tear substitute that maintains sufficient wetting of the corneal surface to prevent the pain and damage of dry eyes.

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