Novel therapeutic approaches for uveitis and retinitis

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A virtual increase in the number of patients undergoing immunosuppressant therapy and those suffering from AIDS has created a unique class of population suffering from virulent uveitis and retinopathies. A very common pathogen implicated in retinopathy in such patients is the cytomegalovirus (CMV).

Delivery of antiviral drugs to the vitreous cavity has been attempted by various routes, which suffer from some weakness or the other. Recent developments in this field have been in the form of some novel devices like intravitreal and scleral implants and iontophoretic delivery. In this paper we have described these devices and highlighted on the advantages and disadvantages associated with them.

Most ocular diseases are treated with topical application of solutions administered as eye drops. These conventional dosage forms account for nearly 90% of the currently accessible marketed formulations. Eye drops used for soluble drug require frequent administration of highly concentrated solutions. The practical reasons for selecting solutions are the generally favorable cost advantage, the greater simplicity of formulation development and production and acceptance by patients despite a little blurring[1].

One of the major problems encountered with the topical delivery of ophthalmic drugs is the rapid pre-corneal loss caused by drainage and tear turn over. After instillation of an eye drop, typically less than 5% of the applied drug penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is often absorbed systemically via the conjunctiva and naso-lacrimal duct[2].

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PHYSIOLOGICAL CONSIDERATIONS

The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. The cornea is a trilaminate tissue, consisting of the epithelium, stroma and the endothelium, that are the main absorptive barriers. The epithelium facing the tears with lipophilic cellular layers acts as a barrier to ion transport. The tight junction of corneal epithelium serves as a selective barrier for small molecules and prevents the diffusion of macromolecules via the para-cellular route. The stroma beneath the epithelium is a highly hydrophilic layer making up 90% of the cornea. The corneal endothelium is responsible for maintaining normal corneal hydration. Obviously then, the more lipophilic the drugs are, the more resistance they will find crossing the stroma. The more hydrophilic a drug, the more resistant the epithelium, whereas the stroma and the endothelium are limited in their resistance.

The conjunctiva is a thin, vascularized mucus membrane that lines the inner surface of the eyelid and covers the anterior part of the sclera up to the cornea. Owing to the relatively high porosity, rich blood flow and large surface area, conjuctival uptake of a topically applied drug from tear fluid is typically an order of magnitude greater than corneal uptake[3].

Topically applied drugs reach the blood stream mainly via absorption across the mucosa in the nasal cavity, which is continuous with the conjuctival sac[4]. Consequently, delivery systems that prolong the residence time of the applied dose in the conjuctival sac would be expected to reduce systemic drug absorption.

Physico-chemical drug properties such as lipophilicity[5], solubility, molecular size and shape[6-8], charge[9,10] and degree of ionization[11-13] affect the route and rate of permeation in cornea.

TREATMENT APPROACHES IN OPHTHALMOLOGY

The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of more successful ocular delivery system. Potent immuno suppressant therapy in transplant patients and the developing epidemic of Acquired Immuno Deficiency Syndrome (AIDS) have generated an entirely new population of patients suffering from virulent uveitis and retinopathies.

Uveitis is an inflammation of middle vascular tunic of the eye (uveal tract). It is a specific organ disease frequently considered being autoimmune. Uveitis can occur as an ocular manifestation of a variety of autoimmune diseases such as juvenile rheumatoid arthritis, Reiter's syndrome, and inflammatory bowel diseases[14] and sarcoidosis[15]. When associated with Behcet's disease uveitis frequently leads to blindness[16].

Uveitis can be treated with topical or systemic steroids but frequently recurs after discontinuation of therapy[17]. Complications of topical steroids use include cataract formation, poor wound healing, toxicity to corneal epithelium and increased intra-ocular pressure[18]. Complications arising from systemic administration of steroids are varied and often extremely unpleasant[19]. To overcome the disadvantages of steroid administration (both topical and systemic) in the treatment of uveitis, non-steroidal anti-inflammatory drugs such as indomethacin have been investigated. In recent years, cyclosporin and cyclosporin A has been used to treat some forms of uveitis.

Cyclosporin is an effective secondary agent in the treatment of uveitis. Usually reserved for patients with advanced bilateral disease despite high doses of prednisolone, its main effect is on the recruitment and activation of T cells. It is believed to act by interfering with interleukin 2 (I-2) in the activation of T cell genes.[20, 21] Although CD4 lymphocytes are the main target, CD8 cells are also suppressed. Systemic administration is usually through the oral route as a suspension. Some of the most common side effects at a dose of 10 mg/kg include paraesthesias and hyperaesthesia (40%), hypertension (24%), epigastric burning (20%), hypertrichorism and gingivitis (20%).[22] Many patients require long term management, thereby increasing the risk of complications and making careful monitoring of their renal function, blood pressure and surveillance for malignancy, being an important part of their management.

The extent of penetration after topical application has been the subject of some controversy with some groups reporting no significant permeation in to the aqueous[23] and others finding therapeutic levels in this compartment[24]. No one has reported therapeutic levels in the vitreous or posterior uvea after topical application and unfortunately intermediate and posterior uveitic syndromes are those most likely to result in severe and irreversible vision loss[25]. The National Eye Institute (USA) recommends that sustained local delivery would treat the diseases effectively.

Historically, the bulk of the research has been aimed at drug delivery to the anterior tissues of the eye. Only recently has research been directed at delivery to the tissues of the posterior globe (the uveal tract, vitreous, choroid and retina).

The conventional ophthalmic dosage forms are no longer sufficient to combat these diseases. The treatment of many ocular diseases is hindered by the poor penetration of topically or systemically administered drugs in to the eye. Barriers presented by the cornea, lens and rapid aqueous turnover make it very difficult to achieve therapeutic drug concentration in the vitreous after topical administration. After systemic administration the tight junctions between epithelial cells reduce drug availability to the aqueous and vitreous availability is reduced by tight junctions of retinal pigmented epithelial cells and between the endothelial cells of retinal capillaries[26]. Plasma binding of many drugs further decreases their penetration from the systemic circulation to the eye[27]. Poor ocular permeability can sometimes be overcome by increased systemic dosing although this may cause systemic toxicity.

Cytomegalovirus (CMV) is the most common cause of viral retinitis in patients with AIDS, affecting approximately 25% of the patients[28-34]. If left untreated blindness inevitably results[35]. Intravenous Ganciclovir and Foscarnet are effective in the treatment of CMV retinitis, but require frequent intravenous dosing. Serious dose-limiting side effects are associated with both drugs necessitating a two-week period of induction therapy

followed by indefinite lower dose maintenance therapy. Retinitis normally reactivates while patients are on maintenance therapy with either drug, with a mean reactivation time of 56 days for Ganciclovir and 59 days for Foscarnet[36]. Other problems associated with systemic administration include sepsis related to permanent indwelling catheters of long infusion times.

Intravitreal Ganciclovir injections provide a higher intraocular drug concentration than systemic therapy and reduce systemic exposure to the drug. The intravitreal half-life of Ganciclovir in the human eye necessitates frequent injection (at least once each week) to maintain therapeutic levels in the eye[37]. Repeated intravitreal injections have an attendant risk of cataract formation, retinal detachment, cystoid macular edema, progressive retinal toxicity and endophthalmitis[38].

The main approaches investigated in treatment of uveitis and CMV retinitis using sustained release ophthalmic formulation to internal structures of the eye are;

INTRAVITREAL ADMINISTRATION THROUGH NOVEL DELIVERY VEHICLES

Approaches for uveitis

Intravitreal injections of cyclosporine have been used in the rat model to treat EAU (experimental autoimmune uveitis) without significant blood levels[39]. However, the intra ocular half-life of cyclosporine would require multiple weekly injections, making such a delivery impractical[40]. Other studies in rabbits have demonstrated that intravitreal administration of 100 μg of cyclosporine is non-toxic to retinal structures[41].

Approaches for CMV retinitis

Although the intravenous administration of ganciclovir is used for the treatment of bilateral CMV retinitis and control of CMV infection of other sites[42], the high toxicity levels of this route has necessitated the search for direct placement of a device in the vitreous.

Akula et al[43] have studied treatment of CMV retinitis with intravitreal injections of liposome-encapsulated ganciclovir (GCV) in a patient with AIDS. To overcome the risk to and poor tolerance by end stage patients, GCV was encapsulated in liposomes, to increase the intravitreal retention of the drug, thereby decreasing the frequency of injections. The right eye of the patient was injected with liposome encapsulated GVC and the left eye served as the control, receiving intravitreal free GVC. The right eye showed no retinal hemorrhages or detachment; but vision declined initially, stabilizing later. Weekly examination showed neither progression of CMV retinitis nor new lesions in the right eye, but the left eye showed reactivation of CMV retinitis.

A single application of 20% aqueous solution of GCV by trans-scleral Iontophoresis (1.0mA for 15 minutes) in rabbit eyes[44] gave a vitreal/retinal level of GVC at 74±17 μg/ml at 2 hours as determined by HPLC. At 24 hours after iontophoresis, the vitreal/retinal level was above the therapeutic level at 4.2±0.6 μg/ml. At 72 hours, there were still detectable levels in the vitreous/retina. Thus trans-scleral iontophoresis is able to deliver effective dose of GCV into the vitreous and multiple applications of iontophoresis should be examined as a possible means of CMV treatment.

The intra ocular safety and the anti viral treatment efficacy of the sustained lipid pro-drug of GVC, 1-o-hexa decyl propanediol-3-phospho-GVC (HDP-P-GCV) as an intra vitreal injectable drug system for CMV retinitis were evaluated by Cheng et al[45]. HDP-P-GCV was formulated into liposomes. The antiviral activity was assessed by DNA reduction *in vitro* and intraocular safety was assessed by ophthalmoscopy, electrophysiology, and histology after intravitreal injections, with resultant intravitreal concentration of 0.2, 0.632, 1.12 and 2 mM. The treatment efficacy was evaluated by simultaneous intravitreal injection of HDP-P-GCV and Herpes simplex type I (HSV-I) or by intravitreal injection of HDP-P-GCV at various times before HSV-I intravitreal inoculation. The IC_{50} (*in vitro*) of HDP-P-GCV against HSV-I and human cytomegalovirus (H CMV) infected cell was 0.02 and 0.6 μM, respectively. In rabbits, HDP-P-GCV dispersed evenly and maintained a good vitreous clarity at all doses except 2 mM final intravitreal concentration.

INTRAVITREAL AND SCLERAL IMPLANTS

In the area of ocular drug administration, important efforts concern the conception and design of new biodegradable implantable systems to interior parts of the eye to prolong the residence time. The use of implants,

which are solid devices to be placed trans-sclerally by minor surgery represent possibilities to achieve increased residence time. The use of biodegradable polymeric devices offers certain advantages over more conventional formulations. If drug release kinetics can be controlled, target tissue concentration of the drug can be maintained in the therapeutically appropriate range and harmful side effects associated with intravitreal and intravenous administration can be reduced. Continuous long-term administration can eliminate the discomfort associated with multiple dosing and improve patient compliance.

These potential advantages must be viewed in light of the disadvantages that if it does not biodegrade, the device may require surgical removal. The implanted polymer must be biocompatible, causing no tissue irritation, and if it is biodegradable its breakdown products must be non-toxic. The device must be adequately designed to eliminate possible dumping of the dose. There are also problems associated with the removal or the shutting off of release from the implant.

Implantable intravitreal devices slowly release medication into the vitreous cavity. The device is a small reservoir of drug with a polymer coating that control the release rate. They have the potential to ameliorate a variety of chronic infections or inflammatory ocular diseases.

An implant has been designed for the long term intravitreal release of cyclosporine A. It bypasses the systemic circulation avoiding the side effects associated with cyclosporine A, while administering therapeutic doses of the medication to the eye over an extended period of time. The implant consists of a drug pellet coated with silicone attached to a poly vinyl alcohol (PVA) anchor strut. This design has been used to create implants that can release the drug at several rates, depending on the material used to coat the drug pellet. Experimental studies have shown that devices releasing cyclosporine at a rate of 1.3μg / day can achieve intravitreal levels over a 6 month period of 500 ng/ml, or 5 times the therapeutic level needed to suppress T-cell activation.[40, 46] Systemic doses of at least 5 mg/kg are usually necessary to achieve intravitreal levels of 100 ng/ml.[47]

Scleral implants of indomethacin with sodium alginate as carrier were evaluated in uveitis induced rabbit eye-model. The pharmacodynamic studies showed a marked improvement in the various clinical parameters; congestion, keratitis, flare, clot, aqueous cells and synechias, in the implanted eye when compared to the control eye in the rabbits[48].

Devices giving zero order release of GCV was implanted intravitrealy first in rabbits and then in eight patients with AIDS associated CMV retinitis as part of phase I clinical trial[49]. Steady state intravitreal GCV levels were obtained and elimination rate constants were calculated assuming first order pharmacoknetics. Normalizing for retinal surface area, distribution volume and anatomic volume, the retinal elimination rate constants were found to be 0.017 cm^{-2} hr^{-1} in rabbits and 0.015 cm^{-2} hr^{-1} in humans. The study indicated that rabbit eye could serve as a good model for studying IV pharmacokinetic and suggested a common elimination mechanism, which may be trans vitreal.

Smith et al[50] developed devices that release GCV at rates of 2μg/ h and 5μg/ h in-vitro. When implanted into the vitreous of rabbit eyes, mean intravitreal GCV levels of 9mg/L and 16mg/L were maintained for more than 80 and 42 days, respectively. The devices were found to be well tolerated and may prove useful in the clinical management of CMV retinitis in patients with AIDS.

A surgically implantable device for sustained intravitreal release of GCV was reported[51]. The device delivered GCV intraocularly over approximately 4 to 5 months. Eight patients with AIDS and associated CMV retinitis were recruited as part of phase 1 study. Thirteen eyes with active CMV retinitis underwent surgical implantation of the GCV device. All eyes showed resolution of the CMV retinitis; none showed progression. Surgical complications included mild vitreous hemorrhage, astigmatism and suprachorodial placement of the device.

A randomized controlled clinical trial to assess the safety and efficacy of a 1μg/h GVC implant for the treatment of CMV retinitis in AIDS patients was conducted.[52] Patients with previously untreated peripheral CMV retinitis were randomly assigned either to imme-

diate treatment with GCV implant or to deferred treatment. Standardized fundus photographs were taken at 2-week intervals and analyzed in a masked fashion. The GCV implant was found to be effective for the treatment of CMV retinitis.

Morley et al[53] reported their surgical experience in replacing empty GVC implants in patients with AIDS related CMV retinitis. Nine eyes in eight patients received two or more implants and the average time before a second implant was needed was 6 months. CMV retinitis was controlled in all patients except one. Three patients required intermittent intravenous exogenous anti-CMV therapy, one for persistent CMV retinitis and two for systemic CMV infection. Visual acuity of 20/40 or better was maintained in five of eight patients, despite a long standing history of CMV retinitis.

SUMMARY

Routes and problems of drug administration in uveitis, retinopathies:

Intravenous and intravitreal injections

- Frequent Administration
- Poor drug penetration into ocular tissues
- Dose related bone marrow depression
- Cataract formation
- Retinal detachment
- Endopthalmitis
- Reactivation

Intravitreal non-erodible implants, Liposomes

- Extended duration of drug release, but surgical implantation under general anesthesia.
- Device removal necessary
- Visual disturbances
- Low drug loading and poor physico-chemical stability of Liposome

Iontophoresis (very limited investigation)

- One iontophoretic application is effective for only 48-72 hours.
- Only institutionalized patients eligible
- Possible iontophoretic burns on long term usage

Scleral implants

- Displacement of device due to breaking of device.
- Drug release, if not well modulated, may result in multiple burst releases with short periods of slow release.

CONCLUSIONS

A surgically implantable device for sustained intra-vitreal release of drug can be achieved. The device delivers drug intra-ocularly over approximately 4-5 months and reaches effective intravitreal therapeutic concentration. They have the potential to ameliorate a variety of chronic infection or inflammatory ocular diseases. Most importantly biodegradable implants do not require removal after drug delivery. Additionally, adverse tissue reactions from the implanted polymers are ameliorated as the polymers biodegrade.

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