Novel Drug Delivery Systems For Glaucoma

Dr Nikita Dash, 1st Yr P.G., S.C.B.M.C.H
Guide: Prof (Hod) Dr Sumita Mohapatra, Prof Dr P.K.Nanda, Prof Dr Indrani Rath

Glaucoma: drugs and targets

Glaucoma is the second leading cause of irreversible blindness, with an estimation of affecting over 67 million people worldwide. It is a disease where the axons of retinal ganglion cells(RGCs), which make up optic nerve, degenerate. Loss of RGCs, lead to loss of vision, thereby leading to blindness, if untreated. Current glaucoma therapy relies on drugs that lower intraocular pressure(IOP), and several glaucoma medications are effective in this matter when administered properly. However, poor adherence is a fundamental problem that increases with the patient's age, eventually leading to surgery in approximately 20% of the cases. An alternative treatment approach may lie in the use of neuroprotective agents, designed to promote RGC survival independent of IOP. However, as no such neuroprotective agents have been approved by the FDA as of now, hence there lies a necessity to develop newer and novel drug delivery systems,that target IOP, and do away with the challenges of patient adherence.

Considerations in the treatment of glaucoma: drugs and their deliveries

The two basic approaches considered for the treatment of glaucoma are as follows:

1) IOP Reduction

2) Neuroprotection

IOP Reduction :There is good evidence that lowering of IOP leads to reduction in the progress of the disease in approx. 90% of cases, including cases of normal tension glaucoma.The most common way of administration of IOP lowering drugs is topically as eye drops, one or two times daily. Proper administration of such drops requires the correct placement of the drop on the surface of the globe, the correct no. of administrations per day, and the correct time interval between multiple dosings or medications. It requires diligence and manual dexterity, which is difficult to practice, especially in older patients. Furthermore, <1% of topical drop is absorbed by aqueous humor and up to 80% is systemically absorbed leading to systemic side effects. As a result, topical application has become a challenge, especially for the ageing population, leading to lower adherence.

The various topical medications used effectively include prostaglandin analogues (eg:latanoprost), beta blockers (eg:timolol), alpha-adrenergics (eg:brimonidine), carbonic anhydrase inhibitors (eg:dorzolamide), and cholinergics (eg:pilocarpine). Each of these classes of drugs has its own specific characteristics that impact their delivery.

Pilocarpine is one of the oldest drugs to treat glaucoma. It reduces IOP by increasing the outflow of aqueous. As a drop, it requires four doses a day with side effects of brow ache, blurred vision, risk of retinal detachment as well as nausea, vomiting and diarrhea. However, it was one of the first drugs to be used in a sustained release implant (Ocusert). Timolol maleate is the US-FDA's "gold standard" drug for IOP reduction. A twice daily dosing is usually required for optimum function. It is extremely stable and highly water soluble, which makes it attractive for several methods of delivery, including novel drop formulations, implants, and injectables. Prostaglandin analogues are in turnhydrophobic drugs that are enzymatically cleaved to their active form in the eye, leading to less systemic effects. Their hydrophobic nature holds out a promise of drug delivery via many common hydrophobic polymers like poly-ethylene-co-vinyl acetate and polylactic acid.

Neuroprotection: A number of drugs have been studied in clinical trials for neuroprotection of nervous system. They include small molecules like statins, progesterone, memantine and cyclosporine A, as well as neurotrophic proteins including glial cell-derived neurotrophicfactor (GDNF), ciliaryneurotrophicfactor (CNTF), and erythropoietin. The delivery of proteins is particularly challenging because of their large size, conformation necessary for bioactivity, susceptibility to enzymatic degradation and relatively low affinity to typical materials used for drug delivery. Several alternative approaches have been developed to deliver neurotrophic factors to the ocular target tissue for sustained periods. Among them are, transfection of retinal cells with viral or non-viral particles carrying the gene of interest, and transplantation of stem cells to the retina, which are engineered to produce the neurotrophic factor of interest.

Clinically available delivery systems

Oral medications:

Oral carbonic anhydrase inhibitors have been available for decades and are stillvery effective in lowering IOP. However, their use is associated with systemic side effects like fatigue, diuresisand electrolyte imbalance. They are typically used as short term therapy when IOP is still very high on maximal topical medications.

Topical eye drops and gels:

Topical delivery is the current standard for glaucoma treatment. Delivery of drug to vitreous and retina is possible but transport of most medications to vitreous and retina is very low with limited bioavailability. The barriers to transport includethe increase in tear drainage with administration of eye drop, low corneal transport, and low conjunctival and scleral transport. Transport through ocular tissues is also dependent on the chemistry of the drug with hydrophobic drugs tending toaccumulate in the vitreous and hydrophilic ones in the aqueous. Several gel formulations have been devised to reduce the number of doses/day. Timolol can be delivered once daily with the use of gel formulations that are essentially timolol plus water soluble polymer, which increase the viscosity of the solution. Although, they reduce dosing and to some extent side effects, they lead to blurred vision.

Inserts and surgical implants:

One of the best known and widely studied ocular insert system is the Ocusert system, which consists of two membranes of polyethylene-co-vinyl acetate and a ring of the same material filled with pilocarpine. It is designed to be placed in the inferior fornix and deliver the medication for 7 days. Although effective, some patients complained that the device would fall out or cause discomfort. Inserts also require patient education to use the device successfully as well as manual dexterity to manipulate it properly, making it more popular in young glaucoma patients than in elderly.

Surgical implants have the potential to deliver drugs for very long period in eye. Implants like Ozurdex, Retisert, which are used to deliver ocular steroids intravitreally, are clinically available. In addition, Surmodics, another triamcinolone acetonide coated implant has undergone phase I clinical trial. They may provide an attractive option for the delivery of neuroprotective drugs, though they do have cost and invasiveness of initial surgery as disadvantages.

Novel delivery systems

Liposomes and nanospheres: improving topical formulations

Pilocarpine has been encapsulated in liposomes and delivered in solution as an eye drop. Monem et al studied the effect of charge on surface of liposomes on IOP reduction. Neutrally charged liposomes resulted in similar IOP reduction but lasted twice as long as conventional eye drop, suggesting liposomes increased the residence time of the drug, thus reducing the dosing from 4 times/ day to twice daily. DeCampos et al have studied the role of charge on colloidal solutions of nanocapsules administered as drops in the eye. They reported that neutral particles showed greater delivery of the drug than

negatively charged ones. The nanocapsules take an intracellular route through the corneal epithelium.

The strategy of providing the drug with a carrier that allows it to stay longer on the surface of the cornea is an effective approach to reduce the dosing frequency. However problems of adherence still remain.

Contact lenses as delivery vehicles

Soft contact lenses are hydrogels, water soluble polymers that are cross-linked to form networks. Hydrogels have a tremendous number of biomedical applications including drug delivery. However, the greatest challenge lies in the fact that water soluble drugs tend to elute very quickly from highly hydrated polymer networks. However soft lenses of polymers of N,N-diethylacrylamide and methacrylic acid , have shown to deliver timolol for longer periods. Hence, lenses may be an attractive option although constant need for hydration and difficulty in wearing constantly might be some constraints.

Sophisticated surgical implants

One novel approach is to implant a reservoir system in the subconjunctival space. The microelectrochemical system (MEMS) uses electrolysis to create bubbles that push the drug out of the reservoir of the device, which has a port that allows multiple loading of the drug. It has the potential of delivering both small and large neuroprotective molecules such as growth factors. MEMS-based system also allows for the regulation of drug release from device by controlling electrolysis. It also has potential for intravitreal administration as well as multiple drug administration.

Injectable systems

Unlike MEMS devices, they are passive delivery systems, capable of sustained, long-term delivery of medications. Injection of existing drugs into the subconjunctival space can lead to prolonged delivery. Use of a polymer based delivery vehicle is an attractive option. Bot non-degradable and degradable polymers have been studied for this. Though non-degradable polymers exhibit long term, constant rates of delivery they have a disadvantage of causing a foreign body reaction, something which makes degradable ones appealing. One formulation of polyester microspheres encapsulating timolol has been shown to deliver the drug for greater than 90 days in vitro. For neuroprotective molecules PLGA microspheres are being considered. The major factor that ought to be taken into consideration for the development of such injectable systems is the drug-polymer interaction that can affect the bioavailability, hence the dosing of the drug.

Summary

Many effective topical formulations of glaucoma drugs are currently available. But their clinically efficacy is limited by inefficient delivery systems, leading to poor bioavailability and patient adherence. Hence novel, more effective delivery systems are required to do away with patient adherence factor and associated side effects. Ultimately they will be a boon for glaucoma patients by the incorporation of both IOP lowering and neuroprotective agents in treatment modalities, thus ensuring variety of options and preservation of vision in glaucoma.

References:

1. Quigley HA. Number of people with glaucoma worldwide. Br J Ophthalmol 1996; 80(5): 389-393.
2. Leske MC, Nemesure B, He Q, Wu SY, Hejtmancik JF, Hennis A. Patterns of open-angle glaucoma in the Barbados Family Study. Ophthalmology 2001; 108(6):1015-1022.
3. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five year incidence of open-angle glaucoma: he visual impairment project. Ophthalmology 2002; 109(6): 1047-1051.
4. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998;126(4) : 498-505.
5. Danesh-Meyer HV, Levin LA. Neuroprotection:extrapolating from neurologic diseases to the eye. Am J Ophthalmol 2009; 148(2): 186-191e2.
6. Schultz CL, Poling TR, Mint JO.A medical device/drug delivery system for treatment of glaucoma. Clin Exp Optom 2009; 92(4): 343-348.
7. Shive M, Anderson J. Biodegradation and biocompatibilityof PLA and PLGA microspheres. Adv Drug Deliv Rev 1997;28(1):5-24
8. Cardillo JA, Paganelli F, Melo Jr LA, Silva Jr AA, PizzolittoAC, Oliveira AG. Subconjunctival delivery of antibiotics in acontrolled-release system: a novel anti-infective prophylaxisapproach for cataract surgery. Arch Ophthalmol 2010; 128(1):81-87.
9. Shield's Textbook Of Glaucoma, 6th Edition.