NEW TRENDS IN CONTROLLED DRUG DELIVERY TO POSTERIOR SEGMENT

CESIÓN CONTROLADA DE FÁRMACOS EN EL SEGMENTO POSTERIOR. NUEVAS TENDENCIAS

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The pathologies involving the posterior segment of the eye are characterized by being devastating and compromising eyesight in a large amount of subjects. Due to the severity of these diseases, it is crucial to establish treatment rapidly and maintain efficient concentrations in the area of action for the longest possible time. However, the therapeutic efficacy of pharmacological treatments in this area are limited mainly by the difficulty of the active substance to access the target tissues.

At present, 4 types of administration are utilized in order to achieve efficient concentrations in the posterior area of the eye. Accordingly, drugs are administered via the topical, systemic, intraocular and periocular routes. When administering a drug topically, at the time of application different mechanisms take place to eliminate it from the corneal area (it is estimated that under 5% of the dosage is able to reach the inside of the eye), with the result that efficient concentrations cannot be achieved in the vitreous, retina and choroids. If the drug is administered systemically, the dosage needed to achieve therapeutic levels in the area of action are very high, leading in many cases to undesired side effects. In turn, directly placing the drug in the globe through intravitreous injections is, considering the severity of the disease, a good option because from the start the active principle achieves efficient concentrations in the vitreous. However, intravitreous injections entail side effects such as retina detachment, hemorrhage, endophthalmitis and cataracts. In addition, treatment usually require the administration of repeated injections which are not always well tolerated by the patient. To avoid frequent reinjections, controlled delivery systems are utilized for specific active principles adapted to the administration. The non-biodegradable intravitreous devices comprise two implants known as Vitrasert and Retisert. The former includes ganciclovir and has been utilized for treating posterior segment uveitis. However, implants require surgery and must be replaced regularly with the risk of producing effects similar to those associated to intravitreous injections, based on rejection responses.

In any case, none of said systems is fully satisfactory. The dosage of medications to the posterior segment of the eye calls for new, less aggressive administration pathways as well as the development of new formulation having more advanced properties.

In what concerns the first requirement, the periocular administration of drugs has aroused a great deal of interest. Depositing the active substance in areas adjacent to the zone of action, as is the case of administration in periocular tissues, requires the drug to pass through the sclera (due to simple diffusion) to access the inside of the eye. Although there may be a loss of active substance, periocular injections are less aggressive and are being regarded as advantageous alternatives to intravitreous injections.

The administration of the drug in solution entails a shorter duration of its effect, because it depends on the semi-life of the active substance. For this reason researchers for years have been designing and researching new formulations to prolong the effect of active substances in order to reduce the number of interventions. Within the systems in the evaluation stage we find nanoparticles (1-1000 nm) and microparticles (1-1000 µm). By controlling the

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delivery of the active substance, these systems can produce more or less prolonged deliveries of the drug. The main advantage of these formulations is that they can be administered as a conventional injection, as intraocular or periocular injections. If a controlled delivery device is utilized, the selection of materials which make up the systems of these formulation is vital because they must not only regulate the delivery of the drug, they must also be highly biocompatible and free of any toxicity. The same applies for the degradation products. These stringent requirements considerably reduce the number of materials which can be utilized.

For over 30 years, lactic and glycolic acid polymers have been the most widely used biomaterials in biomedicine, mainly the copolymer derived from lactic and glycolic acid. The success of these biodegradable polymers is based on their excellent biocompatibility coupled with the absence of toxicity of their degradation products. Polymer chains are hydrolyzed to form natural metabolites which are eliminated from the body by Kreb's cycle. Depending on their composition and molecular weight, these polymers can have degradation rates ranging from months to years. In addition, their application can be selected on the basis of their characteristics. For example, high molecular weight polyactic acid is utilized as suture material when high mechanical forces are required. In contrast, low molecular weight amorphous polymers are useful in the development for controlled delivery systems in which the material must disappear from the zone of action after producing the desired effect.

The quest for new materials has increased pace in recent years: active substances having activity rates which multiply many times those of usual drugs have been designed, we now have highly active molecules obtained through biotechnology and approved by the FDA, such as the case of Lucentis® (ranibizumab), an inhibitor of the vascular endothelial growth factor (VEGF) for treating exudative Age-related macular degeneration (ARMD). Aware of the importance of these findings, labs have taken their research a step further to focus not only on the protection of the new substances but also on the search of new materials having characteristics vastly superior to those in use and which, in turn, can be utilized for preparing controlled delivery ophthalmic systems. In the research pipeline we find hydrogel-forming polymers and others which are sensitive to different factors such as temperature, specific ions or the pH of the environment. But regardless of the nature of these materials, they are required to possess optimum biocompatibility characteristics and properties allowing them to work as modulating agents in the release of active substances.

Clearly, there is a lot to be said and done in this field. Which direction are we taking? In this year's meeting of ARVO (Association for Research in Vision and Ophthalmology) the current and innovative techniques for delivering active substances in the posterior segment will be assessed in a conference organized by the Pfizer Ophthalmic Research Institute. The techniques to be assessed will be related to the treatment of ARMD, macular edema in diabetic patient, pigmentary retinitis, neuroprotection of ganglionar cells in glaucoma patients and treatment of ocular tumors. The presentations and discussions of said conference will be published in the Investigative Ophthalmology & Visual Science journal. Let us await the opinion of the experts.

REFERENCES