

DRUG ADMINISTRATION WITH OCULAR IONTOPHORESIS: REACHING MATURITY

LA IONTOFORESIS EN LA ADMINISTRACIÓN OCULAR DE FÁRMACOS: ALCANZANDO LA MADUREZ

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Most of the research in ocular drug delivery has been directed to the anterior tissues. Only recently, driven by the growth of pathologies that affect the posterior segment of the eye due to the aging of the population, the epidemic of diabetes and new issues in glaucoma, research focused at delivery to the tissues of the posterior segment.

In recent years, significant progress has been made in optimizing ocular drug delivery. The delivery of therapeutic doses of drugs to the tissues in the posterior segment of the eye, however, remains a significant challenge.

The conventional ophthalmic dosage forms can not achieve effective drug concentration to combat age-related macular degeneration, diabetic retinopathy, glaucoma, and retinitis pigmentosa. The treatment of these diseases is hindered by the poor penetration of topically or systematically administered drugs into the eye. Intravitreal injections, apart from inherent side-effect like retinal detachment, haemorrhages, endophthalmitis and traumatic-cataracts, require frequent injections, which are not always well tolerated by the patient.

Any drug delivery technology which purpose would be to lower administration pace or to replace these has gained a lot of interest in the community.

This recent interest in drug delivery to the back of the eye has stimulated new interest in ocular iontophoresis, broadly defined as the introduction of various ions into biological tissues by the means of electricity. A century ago, Leduc demonstrated the potential of the use of electrical current to introduce substances through the skin. At the same period, iontophoresis was experimented by Wirt in Germany, and many papers were published until the

50's by European investigators, where the technique was widespread and later by von Sallmann in the US (1). The lack of controlled studies and detailed toxicity studies shadowed the anecdotic successes reported and the techniques was not much studied until a kind of renaissance in the 80's when Maurice (2) studied some of the mechanistic aspects of the technique and what should be called «focal iontophoresis» with the use of high current densities to replace intravitreal injections, which brought some confusion in the mind of practitioners about the safety of this technique.

In ocular iontophoresis, a donor electrode containing the drug to be delivered into the eye is placed on the eye. To complete an electrical circuit through the body, a return electrode is placed on another body surface.

There are basically two types of iontophoresis, the transcorneal and the transscleral. Transcorneal iontophoresis results in high and sustained concentration of drugs in the cornea and in the aqueous humour, but because of the lens, virtually no drug reaches the vitreous body via this administration route.

Transscleral iontophoresis is the preferred mode to bypass the lens and may thus replace or supplement intravitreal injections. Its advantages are also the larger surface area compared to cornea, the higher tolerance to current and the fact any damage to the corneal surface will immediately affects the vision.

Eventhough iontophoretic delivery has been widely studied for transdermal administration of compounds, where several products are commercialized, and detailed analyses of the mechanistic aspects of iontophoresis phenomena derive from skin tissues studies, extrapolation of these findings to ocu-

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lar iontophoresis remains challenging, because scleral structure cannot be compared to skin, application time is limited by ocular tolerance and the science of ocular pharmacokinetics is still in its infancy.

Iontophoresis is at the crossroad of several sciences, involving multiple parameters related to the drug and its formulation, device design and eye's physiology, all of these in a shifting pattern due to the influence of electric current on each of these parameters.

First, the drug characteristic, such as its degree of ionization depending on the pH, its molecular size and shape, its concentration, will influence its transport.

A competition among all the ions present in the system to carry the applied charge will occur, some of these being introduced in the formulation to prevent pH shift induced by water electrolysis that results in potential chemical burns.

Iontophoresis may also have an effect on the organisation of the tissue itself.

Second, device design, such as application site, electrode distance from eye's surface to avoid pathway of least resistance for current inducing local high current densities, electrode structure to prevent the formation of competitive ions and application surface, being proportional to amount of drug transferred are also critical.

Transscleral devices benefit from higher tolerance of the sclera to current and also from the possibility to maximize application surface to lower the application time and the dose potential (time x current) (3).

Almost all types of therapeutic classes were experimented with iontophoresis, antibiotics, antiviral, antifungal, steroids and non-steroidal anti-inflammatory drugs, chemotherapeutic agents and more recently, several types of nucleic acids constructs.

On the other hand, a limited number of clinical studies were reported, even though promising. Few years ago, Iomed Inc (4), evaluated the ocular tolerance of a small surface applicator placed on the sclera and confirmed some of the limitations of iontophoresis, limited application time and current, highlighting the need for a specific device design to overcome these limitations. No further progress were reported but from another company, Aciont Inc, experimenting a similar design, and trying to overcome its limitation by adapting the formulation of a drug. This approach brings a large amount of regulatory work since the drug is highly modified.

No clinical study was reported from Aciont so far. Last, Eyegate Pharma Inc demonstrated the potential of iontophoresis for the treatment of severe uveitis in a pilot clinical trial on 89 patients with their first generation device. The result of the few minutes application time for the delivery of methylprednisolone on a subgroup of 17 patients suffering from graft rejection was published in 2004 (5) and looks very promising.

A better understanding of tissue interactions within the eye during electric current application, along with better design of ocular iontophoretic devices and probes adapted to the site of application, will definitely yield to efficient intraocular penetration of drugs and oligonucleotides using ocular iontophoresis at their respective therapeutic levels in the anterior and posterior segments of the eye.

The technology of ocular iontophoresis has reached maturity in the aspect of the device development. It is clearly seen that ocular iontophoresis has a clinical potential and importance as a local delivery system for many drugs, not only as an adjunct to local injection and implants, but also with the potential to replace these for initial or maintenance therapy.

It is a matter of time for iontophoretic administration mode to become a new tool that has its place in the limited spectra of administration modes of the practitioners, i.e. topical, injections or implants, and soon be routinely used in the ophthalmic field to provide a greater freedom in treating and/or preventing chronic eye diseases through optimal drug dosing and improved patient/physician compliance.

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