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Iontophoresis in ophthalmology: a review of the literature

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ABSTRACT

Drug delivery to the inner part of the eye is still a problem in treatment of ocular disease. Iontophoresis has been used in the field of medicine for many years. This technique consists of applying a weak electrical current to drive charged drug molecules across tissue barriers. Transcorneal iontophoresis delivers a high concentration of drug to the anterior segment of the eye (cornea, aqueous humor, ciliary body, iris, and lens), for the treatment of anterior segment diseases. There are different types of iontophoresis such as ophthalmic, transdermal, transungual, oral, buccal, and transnasal. The benefit of iontophoretic drug delivery in ophthalmology lays in its capacity to provide high drug tissue concentration safely, while minimizing the systemic drug exposure. This review summarizes basics of ocular iontophoresis and iontophoretic device, trans corneal and transscleral iontophoresis, and the applications of iontophoresis in ophthalmology.

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Introduction

Delivery of the drug to the inner part of the eye is still a problem in the treatment of ocular disease. Topical administration of drugs by means of solutions, ointments, and suspensions are relatively inefficient methods for delivery of the drug; often only 1% of the drug is absorbed (1).

Blood-aqueous and blood-retinal barriers restrict the access of systemic drugs to the eye. Injection of the drug in the eye has its own disadvantages in addition to the patient incompliance. Although retrobulbar and subconjuctively injection of the drug do not provide enough drug concentration,

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direct intracameral or intravitreal injection of the drug may lead to some intraocular complications (2).

Iontophoresis, is one of the proposed alternative noninvasive techniques for delivery of therapeutic drug doses to the inner eye. Iontophoresis consists of applying a weak electrical current to drive charged drug molecules across the barriers of the tissue. There is one electrode with similar charge to the drug, and one ground electrode with opposite charge, which can be placed anywhere on the body in order to complete the circuit. The drug conducts the current through the tissue. This technique expands range of the compounds that can be applied topically (1).

Iontophoresis employs low voltages (<10 V), and low currents (~ few mA) over long periods (minutes to tens of minutes or more) to provide a sustained and regulated driving force. Enhanced iontophoretic permeability is based on the classical laws of electrochemical diffusion, repulsion, and migration of charged and polar species (3).

The major factors influencing the iontophoretic compound penetration can be divided into the physiochemical properties of the compound itself (molecular size, concentration, and charge), the solution (buffer type , presence of other compounds, and pH), the technical and electrical factor (different types of current, electrodes, treatment length, and current density), biological or physiological variations (site, humidity, and regional blood flow) (2).

As already mentioned, iontophoresis is a procedure of ion movement enforced through the application of an electrical field. Thus, the optimum pH for iontophoretic delivery is where the compound exists mainly in its ionized form. This was demonstrated for different solutes (2).

There are two types of iontophoresis: transcorneal and transscleral.

Transcorneal iontophoresis

Transcorneal iontophoresis delivers a high concentration of drug to the anterior segment of the eye (cornea, aqueous humor, ciliary body, iris, and lens) used for the treatment of anterior segment diseases, such as: glaucoma, dry eyes, keratitis, corneal ulcers, and ocular inflammations (1). Transcorneal iontophoresis does not have the potential to penetrate a drug into posterior segment of the eye (4).

Transscleral iontophoresis

For topically applied drugs, lens-iris diaphragm is the main barrier to posterior tissues of the eye such as vitreous and retina. Transscleral iontophoresis passes this barrier and delivers drugs to the vitreous and retina through the choroid. The iontophoretic device is placed on the conjunctiva, over the pars-plana area to avoid current damage to the retina. Transscleral iontophoresis proves to be an effective alternative for multiple intravitreal injections or systemic therapy used for posterior ocular disorders, such as retinitis, optic nerve atrophy, uveitis, endophthalmitis, pediatric retinoblastoma and agerelated macular degeneration (AMD) (1).

Review of literature

Iontophoresis has been used in the field of medicine for many years. Establishment of the iontophoresis for drug delivery in medicine was marked by Leduc During in the early twentieth century (5). Numerous studies of iontophoresis application were performed in several fields of medicine in subsequent decades.

Iontophoresis was studied in otolaryngology. In 1959, Gibson and Cooke demonstrated that sweating could be induced by iontophoretic application of pilocarpine (6).

In 1973, Corneau and Brummett used iontophoresis for administration of local anesthesia of the ear (7). Gangarosa and

Hill applied iontophoresis of vidarabine monophosphate for the treatment of herpes orolabialis in 1986 (8). Rigano and his colleagues in 1992 demonstrated usefulness of iontophoresis of gentamicin for the management of burned ears (9). Gangarosa and his co-workers studied the use of iontophoresis in dentistry (10). Further studies were published in dermatology during the eighteen centuries. Delivery of the drug by iontophoresis is widely studied for transdermal administration, but extrapolation of these findings to ocular tissues remains uncertain. Wirtz employed iontophoresis in ophthalmology as early as 1908. He passed electric current through electrolyte–saturated cotton sponges placed over the eye globe for the treatment of conditions such as corneal ulcers, keratitis, and episcleritis (11).

By the turn of the last century, iontophoresis was extensively studied by a number of european investigators such as Birkhauser, Fietta, and Morisot for a series of ophthalmologic conditions like corneal leukemia, recalcitrant posterior synechiae, scleritis, glaucoma, cataract, or optic atrophy (12-15). In 1942, Witzel and colleagues applied iontophoresis for delivery of a variety of antibiotics such as tetracyclines, chloramphenicol, penicillin, streptomycin, neomycin, and bacitracin in a rabbit model (16).

In 1984, Hughes and Maurice demonstrated an increased penetration of gentamicin and fluorescein by the application of iontophoresis to rabbit eyes (17). Iontophoresis was limited by the technological development of the devices and ocular electrodes. Thus, this technique lost its popularity and it was never adopted as a standard procedure in ophthalmology (18).

After 1980, the iontophoresis attracted attentions again and many investigators showed enthusiasm for studying this technique. A study in 1984 by fishman and colleagues evaluated the intraocular penetration of gentamicin (50 mg/ml) into aphakic rabbit eyes following anodal iontophoresis (0.75 mA for 10 min). Gentamicin levels were determined at 0.5, 4, 8, 16, and 24 hrs after iontophoresis. Peak levels were obtained at 30 min after iontophoresis. The peak vitreous level was found at 16 hr after iontophoresis. Therapeutic levels were still present in the vitreous humor 24 hr after iontophoresis. Iontophoresis appears to be an effective noninvasive method for delivering therapeutic levels of gentamicin into ocular tissues and fluids of the aphakic rabbit eye (4).

In 2003, Monti and colleagues studied the effect of iontophoresis on the permeation of the two β-blocking agents, timolol maleate (TM) and betaxolol hydrochloride (BX) across rabbit corneas in vitro. They assessed the level of corneal damage by measuring the corneal hydration level following applying continuous or pulsed current of variable intensity and duration. They demonstrated that iontophoresis was more effective in increasing the permeation of the more hydrophilic TM than lipophilic BX. They found that transcorneal permeability was only associated with current density and overall time of treatment irrespective of the type of treatment (single or repeated) and electric current (constant or pulsed). For both drugs increased permeation was accompanied by a significant increased corneal hydration (19).

Domb A and colleagues in 2005 provided an overview about the iontophoresis which is a non-invasive technique for drug delivery through the orbit. They discussed the development of iontophoresis devices and reported toxicity of this technique. They focused on the experimental results of transcorneal and transscleral iontophoresis of different drugs, and emphasized on the electric current density that was applied and duration of the treatment used by the investigators (20).

In 2006, Hayden B and colleagues studied the pharmacokinetics and toxicity of systemic versus focal subconjunctival and transscleral Coulomb controlled iontophoresis (CCI) of carboplatin administration in the rabbit eye (21).

Saraaf D and colleagues performed a review study in 1994 to educate the reader about the essential features of iontophoresis and discussed the past and future role of iontophoresis in delivery of the drug through the orbit (22).

Cohen AE and colleagues performed a study in 2012 to determine the safety, effectiveness, and iontophoretic dose (s) of EGP-437 (dexamethasone phosphate formulated for iontophoresis) in patients with noninfectious anterior uveitis. Forty of 42 randomized patients received an iontophoresis treatment in 1 qualifying eye and completed the study. Patients were randomized into 1 of 4 iontophoresis dose groups (1.6, 4.8, 10.0, or 14.0 mA-min), treated with EGP-437 via the EyeGate II Delivery System (EGDS), and followed until day 28. Approximately two thirds of the patients reached an ACC score of zero within 28 days, after only receiving 1 iontophoresis treatment. The lower doses seemed to be the most effective dose, and treatments were well-tolerated (23).

In 2013, Patane MA and colleagues studied the toxicokinetics and tolerability of transscleral dexamethason iontophoresis in the rabbit eye. Female rabbits received dexamethasone phosphate transsclerally to the right eye. The study included 2 control groups (1) a noniontophoresis control and (2) an iontophoresis control. The results of their investigation show that repeated transscleral iontophoresis with dexamethasone phosphate can be safe in the treatment of inflammatory disorders of the orbit which require prolonged and/or repeated corticosteroid treatment (24).

The iontophoretic device

Basically, iontophoretic devices consist of continuous DC source and two electrodes. The ionized drug is placed in the vicinity of electrode compartment that has the same charge, while the ground electrode location is elsewhere on the body surface.

There are two approaches for drug retention in the iontophoretic device. The most commonly used method is filling the eye cup with drug solution and submerging a metal electrode which is extended from the current supply into the solution. The 5-10 mm eye cup is placed over the eye. During the iontophoresis the drug is infused to the cup continuously. There are two ports on the eye cup: one for delivery of the drug solution and the other for holding the metal electrode and aspirating air bubbles. The ground electrode is placed usually in the animal's ear close to the first electrode, which have minimum resistance (1). Eye cup has different shapes including an annular shape silicone probe, which is used for transscleral iontophoresis (called Eyegate, Optis, France). Its opening is 13 mm which avoids contact with cornea (25-27).

The second approach is delivery probe containing drug-saturated gel. Jones and Maurice (28), firstly used this method to deliver fluorescein into the anterior chamber of the orbit (1).

Advantage and disadvantages

Iontophoresis is a local non-invasive technique of administration of drugs associated with minimal discomfort for the patient. The advantage of iontophoresis is that it provides high intraocular drug tissue concentration safely, while minimizing the systemic drug exposure. The possibility of repeatedly applying the drug by this technique makes this treatment modality very useful for chronic and long-term intraocular diseases. This delivery system minimizes the

risk of trauma, infection, inflammation, and hemorrhage. Its advantage in treating the local conditions lies in the reduced incidence of systemic side effects due to minimal systemic uptake of administered drugs and in high local drug concentrations (2).

Like every drug administration method, iontophoresis may have some side effects, which can be due to its application itself or to the administered drug, or the combination of both factors.Reported side effects include localized electrical burns, corneal epithelial or conjunctival edema, mucous discharge, decreased corneal endothelial cell counts which may be due to applying high current densities to small ocular surface. Histopathological changes such as hemorrhagic necrosis, edema, and infiltration of polymorphonuclear cells could be observed (22,29-32).

Conclusion

It is proved that ocular iontophoresis is a beneficial local delivery system for many drugs. Still more studies are necessary to clarify the interactions in the eye tissue during electric current application and better design of devices and probes. The iontophoretic treatment is already a promising tool for delivering anti-inflammatory and antibiotic drugs to the eye. Experiments are needed to determine the ability of these techniques to deliver a variety of other chemotherapeutic agents, treat other bacterial infections, determine safety over an extended period of time, and to determine the efficacy in humans.

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Conflict of Interest

The authors declare no conflict of interest.

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