Available online at www.sciencedirect.com

SCIENCE DIRECT®

Journal of Controlled Release 106 (2005) 386–390

journal of controlled release

www.elsevier.com/locate/jconrel

Transcorneal and transscleral iontophoresis of dexamethasone phosphate using drug loaded hydrogel☆

Esther Eljarrat-Binstock [a], Frederik Raiskup [b], Joseph Frucht-Pery [b], Abraham J. Domb [a,*]

[a] *Department of Medicinal Chemistry and Natural Products, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem 91120, Israel*

[b] *Department of Ophthalmology, Hadassah University Hospital, Jerusalem 91120, Israel*

Received 1 March 2005; accepted 19 May 2005
Available online 18 July 2005

Abstract

Purpose: To evaluate dexamethasone penetration to the eye after a short transcorneal and transscleral iontophoresis using a drug loaded hydrogel assembled on a portable iontophoretic device.

Methods: Iontophoresis of dexamethasone phosphate was studied in healthy rabbits using drug loaded disposable HEMA hydrogel sponges and portable iontophoretic device. Corneal iontophoretic administration was performed with a current intensity of 1 mA for 1 and 4 min. Transconjunctival and transscleral iontophoresis were performed twice for 2 min at two near places in the pars-plana area, on the conjunctival membrane or directly on the sclera. Dexamethasone concentrations were assayed using HPLC.

Results: Dexamethasone levels in the rabbit cornea after a single transcorneal iontophoresis for 1 min were up to 30 fold higher compared to those obtained after frequent eye drop instillation. Also, high drug concentrations were obtained in the retina and sclera 4 h after transscleral iontophoresis.

Conclusions: A short low current non-invasive iontophoretic treatment using dexamethasone-loaded hydrogels has potential clinical value in increasing drug penetration to the anterior and posterior segments of the eye.

Keywords: Iontophoresis; Dexamethasone; Eye; Hydrogel

1. Introduction

Ocular inflammations are commonly treated with steroids applied topically in cases such of corneal graft rejection, filtering bleb scarring, and immune or traumatic iritis and uveitis. Subconjunctival and retrobulbar injections of steroids are used to treat

☆ This work is part of the PhD thesis of E. Eljarrat-Binstock.

* Corresponding author. Tel.: +972 2 6757574; fax: +972 2 6757076.
E-mail address: adomb@md.huji.ac.il (A.J. Domb).

0168-3659/$ - see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.jconrel.2005.05.020

severe ocular inflammations whereas, systemic steroid therapy is rarely used [1].

Due to the serious systemic side effects of steroids, topical application using eye drops is the preferred way of treatment in ocular inflammatory cases [2]. However, this mode of administration is inconvenient to the patient and medical staff, due to the required frequent instillation, and the insufficient drug penetration to the anterior and posterior segments of the eye [3].

In order to enhance the permeability of drugs into the intra-ocular sites of action, iontophoresis technique can be very useful. Iontophoresis uses a low electric current to carry ionized drug across tissues in a noninvasive technique. Transcorneal iontophoresis delivers high concentrations of a drug to the anterior segment of the eye, whereas transscleral iontophoresis bypasses the lens–iris diaphragm and produces adequate vitreous levels [4].

Very little work was published on dexamethasone iontophoresis to the eye and even less on transcorneal iontophoresis. Lam et al. demonstrated high levels of dexamethasone phosphate in the vitreous (140 μg/ml) after transscleral iontophoresis compared to 0.2 and 0.3 μg/ml after subconjunctival and retrobulbar injections, respectively [5]. The effectiveness of dexamethasone iontophoresis was also investigated, by Behar-Cohen et al., on ocular inflammation induced by endotoxin [6]. However, the iontophoretic duration and current density applied are high, and the iontophoretic apparatus used is clumsy using a drug solution cup which can cause damage to the eye surface.

The purpose of this study was to evaluate the penetration of dexamethasone, a negative charged drug, to the anterior and posterior segments of the eye after a short iontophoretic treatment using a drug loaded hydrogel and a portable novel iontophoretic device.

2. Material and methods

2.1. The iontophoretic device

The iontophoretic device that was applied in this study is a battery operated portable device (designed in our laboratory) [7,8], that applies a variable electrical current for pre-set periods of time. The cylindrical drug-loaded hydrogel (5 × 5 mm) is mounted on the end of the electrode of the device.

2.2. Preparation of hydroxyethyl methacrylate (HEMA) hydrogel sponges

The preparation of the hydrogel sponges have been described elsewhere [7,8]. In brief, a mixture of hydroxyethyl methacrylate (HEMA), ethylenglycol dimethacrylate (EDGMA), and dionized water (2.0, 0.04, and 6.5 ml, respectively) was polymerized with 2% sodium persulfate $Na_2S_2O_8$ (0.05 ml), 2% sodium metabisulfite $Na_2S_2O_5$ (0.05 ml), and 2% ammonium ferrous sulfate $Fe(NH_4)_2(SO_4)_2$ (0.025 ml). Cylinders of 5 mm height and 5 mm diameter were obtained. The hydrogels were dehydrated by lyophilization overnight to form spongy cylinders, which were immersed in 10% (w/v in water) dexamethasone phosphate solution 2 h before use.

2.3. Animal studies

Healthy New Zealand white male rabbits ($n=32$) weighing 2.0–3.0 kg were used in the study.

The animals were anesthetized by injection of ketamine and xylazine solution (IM, 25 and 2.5 mg/kg, respectively) and topically anesthetized with 0.4% benoxinate eye drops. Two groups ($n=8$, group 1–2) underwent corneal iontophoresis and two groups ($n=4$, group 4–5) underwent transconjunctival and transscleral iontophoresis, respectively. The dexamethasone-loaded hydrogel sponge was inserted into the cylindrical well of the iontophoretic device and placed gently onto the cornea (groups 1–2), onto the conjunctiva (group 4), or directly onto the sclera after removing a piece of the conjunctival membrane (group 5). The complementary electrode was attached to the ear of the rabbit by means of an alligator clip.

Cathodal iontophoretic administration was performed on one eye per rabbit with a current intensity of 1 mA (5.1 mA/cm^2) for 1 or 4 min (group 1–2, respectively). The reference group (group 3) was treated with topical drops of 0.1% dexamethasone phosphate (Sterodex®) every 5 min for 1 h. Iontophoretic treatment on the transconjunctival and transscleral experimental groups (groups 4–5) were performed twice for 2 min at two near places of the upper-back sclera (pars-plana area), with a current intensity of 1 mA (5.1 mA/cm^2).