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Formulation and in vivo evaluation of ocular insert containing phenylephrine and tropicamide

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Abstract

A Gelfoam® based ocular device containing 1.7 mg of phenylephrine and 0.6 mg of tropicamide was formulated and evaluated for pupillary dilation in rabbits. The manufacturing procedure is fairly simple and the required excipients are inexpensive. The in vivo results show that the mydriatic response produced by the proposed device is larger and longer lasting than that produced by eyedrops with an equivalent amount of phenylephrine and tropicamide. The results reported in this study, along with those of previous studies, imply that Gelfoam® is a versatile drug carrier for either local or systemic drug delivery via the ophthalmic route. © 1999 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

A fully dilated pupil is an important factor which allows for optimal ophthalmic examination of the fundus for disease as well as many ocular surgical procedures (Kergoat et al., 1989; Ho et al., 1992; Paggiarino et al., 1993; Zeise et al., 1996). Ocular instillation of pupil-dilating agent(s) is commonly used to produce mydriasis (Ho et al., 1992). An ideally dilated pupil should be large and stable to the intensive light stimulation encountered during ophthalmoscopic examination (Kergoat et al., 1989; Ho et al., 1992). The co-administration of phenylephrine hydrochloride and tropicamide solutions into the eye has been shown to be an effective combination in producing reliable mydriasis (Apt and Henrick, 1980; Levine,

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1982; Kergoat et al., 1989; Ho et al., 1992; Paggiarino et al., 1993; Zeise et al., 1996). Although the co-use of these drugs in eyedrops can produce mydriasis, it has a low local bioavailability due to rapid clearance from the ocular surface by the lachrymal system and requires a high frequency of drug instillation to produce satisfactory results (Durrani et al., 1996).

To produce an adequate pupil size, a patient will receive a total of 4–30 drops of tropicamide (1%) and phenylephrine (10%) solution (Brown and Hanna, 1978). This regimen is inconvenient for both physician and patient. Due to the limited volume that the conjunctival sac can hold, most of the eyedrop solution is either blinked out or drained into the nasal cavity allowing only a small portion of the drugs to reach their site of action. The drainage of both phenylephrine and tropicamide into the nasal mucosa could result in systemic absorption of these two agents and produce many unwanted systemic side effects including tachycardia, hypertension, and headache (Rengstorff and Doughty, 1982). In addition, it is well known that both phenylephrine and tropicamide solutions irritate the eye (Zeise et al., 1996).

Since the contact time is considered the most important factor in ophthalmic drug delivery, many attempts to improve efficacy have focused on prolonging the contact time of the drugs with the anterior surface of eye (Harris and Robinson, 1990; Maitani et al., 1997). Phenylephrine and tropicamide have each been formulated as a viscous solution (Saettone et al., 1984), a rod (Alani, 1978), a gel (Durrani et al., 1996), an oinment (Hendrickson and Hanna, 1977; Saettone et al., 1980) or a polyvinyl alcohol flag (O'Donnell and Gillibrand, 1995). Also, microdrop and dilute solution administration have been investigated for these drugs (Brown and Hanna, 1978; Forman, 1980; Gray et al., 1992; Elibol et al. 1997). The latter regimens are designed to slow the drainage by the lacrymal system and to reduce ocular irritation. Although the strategies described above are reasonable they are not routinely used. A need exists for a formulation of dilation agent(s) that can be administered easily in a single dose with reliable, rapid results and minimal risk of adverse effect to the patient.

Previously, a gelatin based ocular device was introduced by this laboratory for the systemic delivery of peptides such as melanotan II (Pinsuwan et al., 1997) and insulin (Simamora et al., 1996; Lee et al., 1997a,b), as well as for the local delivery of pilocarpine (Simamora et al., 1998). In vivo data from rabbits show that melanotan II has a 67% bioavailability if it is delivered by this device and a 25% bioavailability if it is delivered by eyedrop. The therapeutic efficacy of either insulin or pilocarpine was substantially improved with the device, and the duration of activity of these two drugs was also prolonged up to 10 and 8 h, respectively. Recently, the release rate of a wide variety of chemicals from Gelfoam® has been well documented by Hamalainen et al. (1998). In this study Gelfoam® is utilized as a local drug carrier, for both phenylephrine and tropicamide. Measurement of the change in pupil diameter and area were used to assess the efficacy of the proposed device.

2. Materials and methods

2.1. Materials

Gelfoam® (absorbable gelatin sponge, USP, size 100) was generously provided by Pharmacia and Upjohn (Kalamazoo, MI). Phenylephrine–HCl and tropicamide were purchased from Sigma (St. Louis, MO). Mydfrin® (phenylephrine·HCl, 2.5%) and Mydriacyl® (tropicamide, 1%) were purchased from Alcon (Humacao, PR). All other solvents and chemicals were of reagent or HPLC grade and were used as received from commercial suppliers.

2.2. Methods

2.2.1. Eye device fabrication

A Gelfoam disc of ≈ 4 mm diameter and 0.5 mm thickness was punched from a slab of Gelfoam sponge with a common hole punch and 1.7 mg of phenylephrine·HCl and 0.6 mg of tropicamide were dissolved in a 25 μl solution of 50% (v/v) ethanol in water. The solution was placed on and sorbed into the Gelfoam disc. The wet ma-

trices were dried under vacuum for at least 72 h. Placebo devices were also prepared by this method but without drug. Note that the doses of phenylephrine and tropicamide are equal to two drops each of Mydfrin® and Mydriacyl®.

2.2.2. In vivo mydriatic response measurement

2.2.2.1. Animal model. Six New Zealand white rabbits (Myrtle's Rabitry, Thompson Station, TN) with equivalent pupil–light response were used in the in vivo mydriatic tests. Each rabbit had a 6 day washout period and was acclimated to the light of the laboratory for 1 h prior to the instillation of drugs. Although they were kept in a restrainer, all animals were conscious and their heads were unencumbered so that all normal head and eye movements were maintained during the experiment.

2.2.2.2. Drug instillation and pupil size measurement. All of the formulations were instilled into the lower conjunctival sac of one eye and the fellow eye was used as a control. The dosing schedule of eyedrop formulations was a modification of the method by Eyeson-Annan et al. (1998). First, one drop of Mydfrin® was instilled into the eye followed 30 s later by one drop of Mydriacyl®. The same procedure was repeated 5 min later. The pupil diameters of both eyes were measured with the aid of a ruler. The efficacy of the formulation was calculated by the difference in pupil diameters between the control eye and the eye that received the formulation. The device was removed from the conjunctival sac at the end of the experiment, which was 4 h after the device instillation.

3. Results

Fig. 1 displays the pupil size of the control eye (×) and eyes treated with drug-loaded eyedrops (○), drug-loaded devices (●), and placebo devices (□) over 4 h. This time period is sufficient for a routine eye examination as well as for cataract

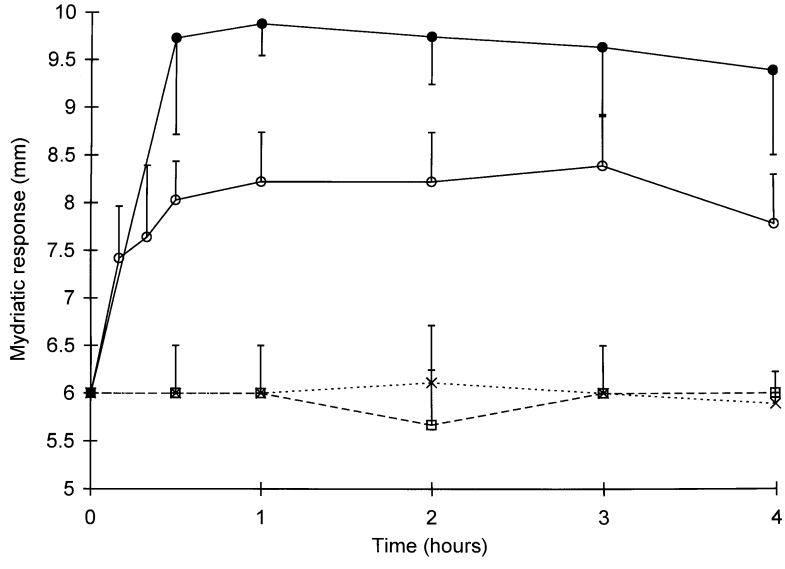

Fig. 1. Mean pupil diameter (mm) as a function of time of control eye (×) and the treated eye following instillation of placebo device (□), phenylephrine and tropicamide-loaded device (●), and two drops of 2.5% Mydfrin® plus two drops of 1% Mydrical® (○). Each data point represents $n = 6$ or more. The error bars represent the standard deviation of each data point. Note that both formulations contain 1.7 mg phenylephrine and 0.6 mg tropicamide.

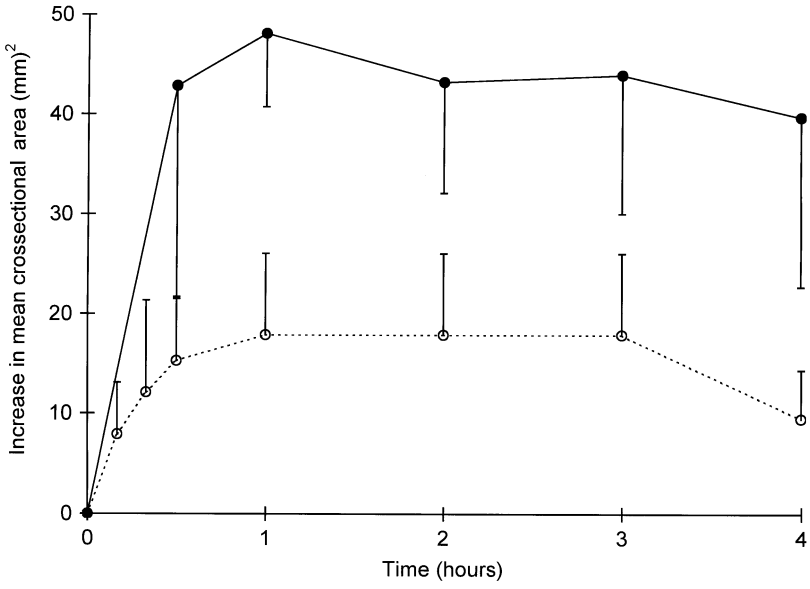

Fig. 2. Mean mydriatic response (increase in mm^2 of cross-section area) as a function of time following instillation of a phenylephrine and tropicamide-loaded device (●) and two drops each of 2.5% Mydfrin® and 1% Mydrical® (○). Note that this area was calculated from the diameters obtained in Fig. 1.

surgery. It can be seen from the figure that the instillation of placebo devices produces no pupil dilation. This agrees with previous studies (Simamora et al., 1996; Lee et al., 1997a,b; Simamora et al., 1998) which demonstrated that Gelfoam® serves only as a drug carrier and produces no effect on pupil size. The instillation of either drug-loaded eyedrop or drug-loaded device produces a significant mydriatic response. The response levels off at 30 min after instillation. The average increase of the pupil diameter produced by the eye device is 3.5 mm compared to 2.0 mm for the eyedrop. This corresponds to a 3-fold increase in the pupil viewing area.

Although the placebo devices produced no eye irritation (redness, lachrimation or ulceration), the phenylephrine and tropicamide-loaded eye devices produced local conjunctival hyperemia (or ulcer) at the site of the device placement. Similar studies in human produced no local ulceration (Negvesky et al., 1999). These healed in about 5 days. Both phenylephrine and tropicamide show no degradation in the device for more than 3 months. Stability studies are continuing.

4. Discussion

The mydriatic response produced by the eyedrops is consistent with a previous report (Levine, 1982) demonstrating that the time to reach the steady state pupil diameter is 30 min after instillation. The proposed eye device gives a similar time to steady state, suggesting that the dissolution of phenylephrine and tropicamide from the device is rapid.

Since the purpose of giving pupil-dilating agents is to allow the visualization of the ocular fundus, the total pupillary viewable area is an important parameter. Fig. 2 shows the total area (mm^2) generated by drug-loaded eyedrops and devices. (Note that all areas were calculated from the pupil diameters shown in Fig. 1.) As can be seen from Fig. 2, the use of Gelfoam® devices (●) increases the pupillary viewing area (mm^2) nearly 3-fold more than eyedrops (○). Thus, while both regimens contained the same amount of phenylephrine and tropicamide, the device substantially enhances the therapeutic efficacy of these two compounds relative to the eyedrop formulation.

The eye can effectively eliminate foreign materials (e.g. instillation of solution) by spillage and by dilution and drainage to the nasal cavity. Spillage causes only a small portion of drug to remain in the conjunctival sac, while dilution and drainage causes short contact time of dissolved drugs with the eye. Consequently, the efficacy of eyedrop delivery is low and of short duration. The advantage of using Gelfoam as a drug carrier is that once hydrated, it is pliable and soft, making it both comfortable in the eye and secure in its placement in the fornix during blinking. Consequently, the contact time of drugs with eye will be prolonged and therapeutic efficacy is enhanced.

It is known that the co-administration of phenylephrine and tropicamide produces eye irritation such as burning, tearing and stinging (Zeise et al., 1996). Since the placebo devices produced no irritation (Simamora et al., 1996; Lee et al., 1997a,b; Pinsuwan et al., 1997; Simamora et al., 1998), the ulcers caused by the drug-loaded device in rabbits are likely due to the high local concentration of these two drugs. Note that in human study, the proposed device produces no discomfort, irritation or ulceration in the eyes of human subjects (Negvesky et al., 1999).

In conclusion, a Gelfoam eye device containing both phenylephrine and tropicamide is introduced. The proposed device enables the delivery of these two compounds simultaneously and prolongs their therapeutic efficacy compared to that produced by eyedrop delivery. The results from this report and previous reports show that the Gelfoam gelatin sponge is a suitable drug carrier for ocular delivery. Stability studies at 4°C and ambient temperature indicate that both phenylephrine and tropicamide are stable in the device for at least three months. Continued stability and a clinical study of the proposed device are currently ongoing.

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