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Restasis® for the treatment of ‘dry eye’ in *Aotus nancymae*

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Abstract

Background—This case report describes the treatment of three male owl monkeys (*Aotus nancymae*) diagnosed with chronic dry eye with a topical cyclosporine product, Restasis®, approved for use in humans. These owl monkeys had ocular disease resulting from procedures performed at a bio-technology company. They were moved to the Center for Neotropical Primate Research and Resources at University of South Alabama to be incorporated into the breeding colony.

Materials and methods—Schirmer tear testing was performed initially and during the course of treatment to monitor efficacy of twice daily administered Restasis®. The goals of treatment were to reduce pain and/or distress and if possible to quantitatively increase tear production.

Results and discussion—All animals had improvements in conjunctival inflammation and had an increase in tear production.

Keywords

cyclosporine; ocular disease; owl monkey

Introduction

Aotus spp. are small arboreal, New World primates that live in monogamous social groups. The adult male is the care-giver of offspring and can frequently be seen interacting and even playing with infants and juveniles [1, 6, 9]. Owl monkeys have been used as the non-human primate model of choice for ocular research [2–6]. As nocturnal animals, they have large protuberant eyes and have been used in ocular studies ranging from color vision [4] and retinal physiology [3, 5] to studies on corneal irritation [2].

Whenever possible, as an alternative to euthanasia, owl monkeys have been retired from ocular experimental protocols to breeding colonies. These animals can be valuable and productive members of breeding social groups but can also have long-standing ocular disease as a sequella of prior experimentation that needs to be managed. Dry eye is one of the more common ocular maladies following ocular biomedical research. Dry eye results

from defects in the tear film layer. This defect can originate from a lack of production of a sufficient quantity of tears or can be attributed to a change in mucin composition of the tear film layer [7]. Chronic dry eye can result in inflammation and excoriation of the conjunctiva and cornea. If chronic dry eye is unilateral and is severe, enucleation may become necessary in primate patients. Enucleation can be performed as a relatively quick surgical procedure and post-operative recovery is usually rapid and without complication. Alternative treatments have concentrated on replacing the tear film with artificial tears and other saline products. Replacement of tears requires that the animal be removed from the family unit multiple times a day, preferably every 3 hours. Additionally, the tear film is unstable and degrades rapidly. More viscous products can be used in an effort to increase the interval between administrations. However, these products do not treat the underlying defect in quantity of tears produced or quality of the tear film and do not have any anti-inflammatory properties.

Restasis® is a product marketed for human use for the treatment of moderate to severe dry eye. Restasis® is a cyclosporine-containing emulsion with both lacrimostimulant and anti-inflammatory properties. This case report describes our findings when we used Restasis® to treat dry eye in three adult male owl monkeys diagnosed with severe dry eye.

Case report

Animals

A group of *Aotus nancymae* were acquired from a biotechnology firm and were introduced into the owl monkey breeding colony housed during this study at the University of South Alabama, but now housed at the Michale E. Keeling Center for Comparative Medicine and Research of the University of Texas M. D. Anderson Cancer Center. All animals in the breeding colony were fed a commercial diet (Old World Monkey Chow 5049, Purina, Richmond, IN, USA) and seasonal produce. All breeding and experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of South Alabama and were in accordance with the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*.

Several of these animals arrived at our breeding facility with ocular disease resulting from prior experimentation. No further ocular experimentation was performed on these animals while at the University of South Alabama. The goal was to treat underlying conditions, ameliorate any pain or distress, integrate these animals into small social groups or breeding pairs, and improve quality of life.

Schirmer tear test

Tear production was quantified by the Schirmer tear test (STT). To perform a STT, the animal was hand caught and lightly anesthetized with an intramuscular injection of 10 mg ketamine hydrochloride and 1 mg xylazine. The STT was not a painful procedure, however, anesthesia was required to ensure that the animal stayed immobile during the test. A small paper strip, Schirmer test strip (Schering-Plough Animal Health, Kenilworth, NJ, USA), was

positioned with the notched end in the lower conjunctival sac [8, 10]. Tearing was measured in millimeters after 5 minutes.

Treatment for dry eye

Three adult male owl monkeys diagnosed with chronic dry eye were selected for treatment with Restasis® (Allergan, Inc, Irvine, CA, USA). All three had little or no measurable tear production (quantified by STT), corneal scarring, and conjunctival erythema/inflammation. Animal health technicians reported that the animals could be observed rubbing their eyes multiple times a day. To test the effectiveness of Restasis® on the treatment of chronic dry eye in these animals, STTs were performed initially and subsequently at monthly intervals for the duration of treatment to monitor efficacy of treatment. One animal, 85484, had a unilateral enucleation of his right eye after the onset of treatment. While tear production increased in his right eye from 0 to 5 mm during the course of treatment with Restasis®, the conjunctiva remained inflamed and the cornea irritated. Therefore, for humane reasons, we removed the right eye. In addition, the condition of his remaining eye was severe enough to warrant adjunctive therapy with Genteal®, a viscous artificial tear product, three times a day in addition to twice daily treatment with Restasis®. The other two animals, 85475 and 85466, were treated with Restasis® in both eyes twice a day. All three animals received a food treat with each treatment. Treatment is ongoing in all three animals and to date has not been discontinued.

Findings

Results of the STT were variable among animals and even between eyes of the same animal (Table 1). However, over the first year of treatment, tear production increased in all animals. The highest STT results were reached by one animal within 6 months on treatment and by the remaining two within a year. To date, STT results are variable from month to month among animals but are consistently improved over the initial measurements. Also, all three animals experienced a decrease in inflammation of the conjunctiva as evidenced by a reduction in conjunctival hyperemia. Hyperemia was evaluated subjectively. Behavior also was affected in all cases: the three animals became more active and playful, and animal care technicians reported that they rarely saw the animals rubbing at their eyes. This suggests that these monkeys may have been experiencing discomfort before the initiation of treatment that was alleviated by the Restasis® regimen. In addition, all three animals appeared to enjoy being treated; at a minimum, they associated the treatment with positive reinforcement. As treatment progressed, all three could be easily caught and treated without the use of protective leather gloves. Based on their behavior and acceptance of treatment, it appeared that quality of life was improved for all three animals.

Discussion

This report documents the use of Restasis®, a product approved for the treatment of dry eye in humans, in owl monkeys with severe dry eye. Cyclosporine has been used with success in the treatment of keratoconjunctivitis sicca (KCS, a form of naturally occurring dry eye) in dogs [7]. Cyclosporine has lacrimimetic effects and when administered to a canine model for KCS, tearing significantly increases. The mechanism for this effect is unknown. The

effects of cyclosporine on KCS are likely to be twofold, the composition of the mucin layer of the tear film is changed and amount of tears is increased [7]. Restasis® is a sterile, preservative-free 0.05% cyclosporine ophthalmic emulsion. Allergan, Inc, the producer of Restasis®, attributed the increase in tear production to the anti-inflammatory actions of the product. Restasis® increased the quantity of tears and affected the mucin content of the tear film resulting in relief from the symptoms of moderate to severe dry eye.

The STT was used to quantify tear production. In one animal, 85466, tear production was substantially increased in both eyes. 85475 had an increase in tear production in one eye. All animals had some increase in tear production with treatment. Even though these animals, after treatment, still had inadequate tear production, treatment was considered successful for several reasons: hyperemia of the conjunctiva was reduced; the animals exhibited more normal species-specific behavior; and, while anecdotal, they were observed to rub their eyes less frequently. We accomplished the goal of ameliorating pain and distress associated with chronic dry eye and enabled these animals to be retired into the breeding colony in a low-stress environment.

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Table 1

Effect of treatment with Restasis[®] on the Schirmer Tear Test¹ in three adult owl monkeys during the first year of treatment

Owl monkey ID	85484	85475	85475	85466	85466
Eye tested:	OS	OD	OS	OD	OS
Initial STT (mm)	0	0	0	0	0
Mean STT during treatment ² (mm)	2.17 ± 1.5	5.5 ± 3.5	1 ± 1.0	6.78 ± 2.42	6.56 ± 1.26
Highest STT (mm)	5	9	2	12	9

OS = left eye, OD = right eye.

¹The Schirmer Tear Test (STT) is a measure of tear production and is determined in mm.

²Mean ± SEM.