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Use of an ophthalmic formulation of megestrol acetate for the treatment of eosinophilic keratitis in cats

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Abstract

Objective To evaluate a compounded ophthalmic formulation of 0.5% megestrol acetate to treat eosinophilic keratitis in cats.

Study design Prospective study.

Animals studied Seventeen client owned cats with eosinophilic keratitis in one or both eyes.

Methods Eosinophilic keratitis was confirmed by cytology. At each visit, fluorescein staining and photography were performed. Cats were initially treated q 8–12 h with 0.5% megestrol acetate in an aqueous base. Serum glucose was measured at the first or second reexamination.

Results Fifteen of 17 (88%) cats had a positive response to treatment, with 6 of 17 (35%) having complete resolution at the first reexamination (2–4 weeks). Two of 17 (12%) cats did not respond to treatment. Most cats required a treatment frequency of once daily to once weekly to maintain remission of disease. No ocular irritation or systemic side effects were noted in any cat.

Conclusions and clinical relevance The use of an ophthalmic formulation of 0.5% megestrol acetate is a viable option for treating feline eosinophilic keratitis.

Key Words: cat, eosinophilic keratitis, feline, megestrol acetate, proliferative keratitis

INTRODUCTION

Eosinophilic, or proliferative, keratitis in the cat is characterized by a cellular infiltrate into the corneal stroma and epithelium that consists of eosinophils, mast cells, neutrophils, lymphocytes, plasma cells and occasionally histiocytes.[1,2] The presenting clinical signs of eosinophilic keratitis include a visible cellular corneal infiltrate, often initially observed at the dorso-lateral limbus, conjunctival hyperemia, tearing and blepharospasm. The size of the lesion varies with chronicity and cats often become more uncomfortable as the lesion progresses. The cause of the condition remains obscure in many cats. Feline herpesvirus 1 (FHV-1) has been associated with eosinophilic keratitis based on polymerase chain reaction (PCR) assay in one study.[3] While some cats have clinical disease suggestive of FHV-1 that includes an eosinophilic keratitis component, many cats with eosinophilic keratitis do not have a history or clinical signs that point toward FHV-1 as a cause.

The most common form of treatment for cats with eosinophilic keratitis has been anti-inflammatory drugs. Topical corticosteroids such as prednisolone and dexamethasone are often effective,[4,5] but run the risk of exacerbating FHV-1 if present. Topical 1.5% cyclosporine led to improvement in 31 of 35 (89%) cats in one study.[6] Combination therapy with a topical NSAID and 0.2% cyclosporine ointment is effective in some cats.[4] In many cats, eosinophilic keratitis requires ongoing therapy to control the disease.

Megestrol acetate is a potent progestogen with glucocorticoid-like activity.[7,8] This oral drug has been used to treat eosinophilic keratitis in cats with great success. While highly effective, oral megestrol acetate carries the risk of potentially serious side effects in cats, including development of diabetes mellitus, adrenal suppression, behavior changes, weight gain and mammary hyperplasia or neoplasia.[7]

The purpose of this prospective study was to evaluate a topical formulation of megestrol acetate for the treatment of eosinophilic keratitis in cats. The hypotheses were that corneal lesions would regress with the use of topical megestrol acetate and that no systemic side effects would be noted.

MATERIALS AND METHODS

Cats were eligible for the study if they had a diagnosis of eosinophilic keratitis but did not have clinical signs suggestive of active herpetic disease (corneal ulcer that preceded eosinophilic keratitis, chronic or recurring conjunctivitis, sneezing). Cats could not have received topical or systemic anti-inflammatory or antiviral drugs within the preceding 2 weeks, nor any oral megestrol acetate within the preceding 2 months. The use of a topical or oral antibiotic did not exclude cats from the study. The study protocol was approved by the institutional animal care and use committees of Purdue University and Angell Animal Medical Center. Each client gave written informed consent.

In the first phase of the study, seven cats without ocular disease were used to assess any potential ocular irritation from the compounded product. One drop of a 0.5% aqueous based ophthalmic suspension of megestrol acetate compounded by a licensed pharmacist was used q 12 h in each eye for 48 h, and the cats observed for blepharospasm or tearing. Conjunctival hyperemia and corneal health were evaluated by slit-lamp biomicroscopy by one author (JS) at the 48-h point. Scores of none, mild, moderate or severe were used for conjunctival hyperemia. Corneal health was evaluated using fluorescein staining as well as observation for any opacity or vascularization.

The second phase of the study involved enrollment of clinical patients at the authors' institutions. Each cat was examined by one of the two authors by use of slit-lamp biomicroscopy and indirect ophthalmoscopy. The diagnosis of eosinophilic keratitis was confirmed by cytology (Fig. 1). Fluorescein staining (BioGlo Sterile Strips; HUB Pharmaceuticals, Rancho Cucamonga, CA, USA) of the cornea was performed, and photographs were taken at each visit. The prescribed treatment frequency of topical megestrol acetate was one drop q 8–12 h, depending on severity of the lesions. The first reexamination was recommended at 2–4 weeks after starting treatment. Clients were instructed in what to look for regarding any possible ocular irritation (blepharospasm, tearing, conjunctival hyperemia) or systemic side effects (polydipsia, polyphagia, weight gain, depression). Serum glucose measurement was performed at the first or second reexamination appointment. Adrenal function testing was not included in the study. Tapering of the medication frequency was based on disease response and clinician discretion.

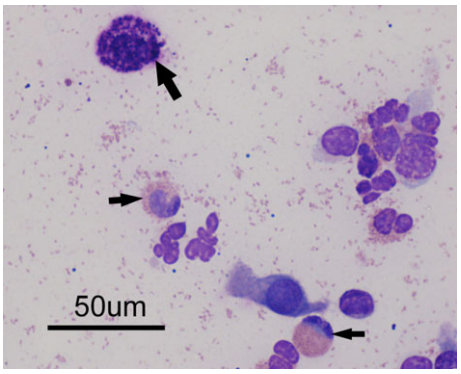

Figure 1. Cytologic preparation from an eosinophilic keratitis lesion. Eosinophils (small arrows), a mast cell (large arrow), neutrophils and an epithelial cell are present. Note granules from eosinophils and mast cells scattered in the background. Wright's stain.

RESULTS

Seventeen cats with adequate follow-up were enrolled in the second phase of the study. Sixteen cats were domestic short or long hair and 1 was a Persian. The age of cats ranged from 3 to 17 years, with a mean of 7.3 years. Eleven were neutered males, and six were spayed females. Thirteen cats had unilateral disease, and four had bilateral disease. Of those with unilateral disease, eight were affected on the right and five on the left. The duration of disease prior to the initial evaluation ranged from 2 weeks to 2 years, with a mean of 4 months. Follow-up during the study ranged from 4.5 to 26 months with a mean of 10 months.

Fifteen of 17 (88%) cats had a positive response to treatment, as evidenced by reduction in size or disappearance of eosinophilic plaques, regression of corneal vascularization, and resolution of previously noted fluorescein positive areas. Of the 15 cats, 6 (35%) had complete resolution of lesions by the first reexamination (Figs 2,3), whereas eight had improved but not completely resolved (Fig. 4). These eight cats went on to complete resolution in a mean of 6 weeks. One of the 15 cats made slow but gradual improvement, finally resolving at the 3-month point. Two of 17 (12%) cats did not have improvement and were dropped from the study at different time points. One of these cats was reexamined at 3 weeks and had no improvement. Therapy was changed at the client's insistence. The second cat was treated for 3 months with no improvement, and then, therapy was changed.

Ten of 17 cats had serum glucose evaluated at one or more time points. All were within the reference range except one cat with preexisting diabetes. This cat had no worsening of its diabetes control while on topical megestrol acetate therapy.

Six of 17 cats had positive fluorescein staining of superficial corneal ulcers, over or immediately adjacent to the eosinophilic plaques, at the beginning of therapy. No dendritic ulcers were observed. All ulcers went on to heal while on treatment with topical megestrol acetate and an antibiotic. No cat in either phase of the study experienced ocular irritation, nor were any systemic signs noted by clients or clinicians.

As with other therapies for eosinophilic keratitis in cats, ongoing treatment was required to control the disease. Treatment frequency was gradually decreased based on

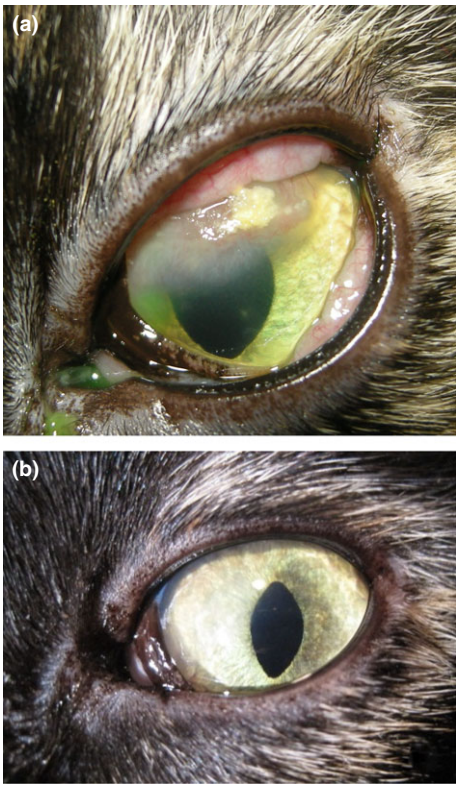

Figure 2. (a) Eosinophilic keratitis with corneal edema is present in the dorsal cornea. Conjunctivitis is also present. (b) Four weeks after treating with topical 0.5% megestrol acetate q 8 h, the lesion has resolved.

response and severity of initial disease. Tapering was typically done by dropping the frequency of daily treatment by one drop every 2 weeks after complete resolution of lesions. The frequency of treatment required to maintain remission varied among cats (Table 1). Five of 15 cats had recurrence of disease when the frequency was tapered too low or when the client discontinued treatment. All cats responded when therapy was reinstituted or the frequency was increased. No correlation between initial severity of disease and frequency of treatment required to maintain remission was observed. No cat developed clinical signs consistent with FHV-1-related disease even with prolonged treatment.

DISCUSSION

This study demonstrates that the use of a compounded topical 0.5% megestrol acetate suspension is a viable treatment option for cats with eosinophilic keratitis. A large majority of cats responded well to treatment and were able to be maintained in a controlled disease state with no ocular irritation or obvious systemic side effects. Because oral megestrol acetate has the potential to cause serious side effects, the use of a low concentration topical formulation may pose less risk to the cat but have the same benefit of controlling eosinophilic keratitis.

Megestrol acetate is a progestogen with prolonged glucocorticoid activity.[7] It was first reported as a treatment for eosinophilic keratitis in two individual cats in 1979[9,10] and in a series of cats in 1987.[2] The glucocorticoid activity is the presumed mechanism by which the drug controls eosinophilic keratitis as well as various dermatologic conditions for which it has been used in cats,[11] although the hormonal effects may not be completely understood. In a study using human mononuclear leukocytes *in vitro*, megestrol acetate demonstrated a binding affinity to glucocorticoid receptors at 46% that of dexamethasone and twice that of cortisol.[12] Recommended induction doses when used orally in cats range from 2.5 to 5 mg daily to every third day.[7] Once remission of clinical disease has occurred,

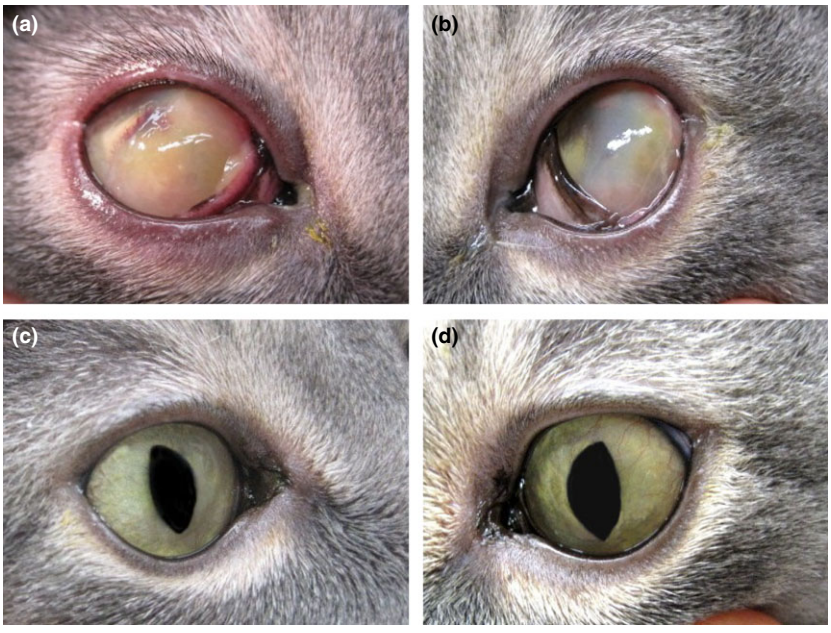

Figure 3. (a) Eosinophilic keratitis is present throughout the right cornea. (b) The left cornea is similarly affected although to a lesser degree. (c, d) Three weeks after treating with topical 0.5% megestrol acetate q 8 h in both eyes, the lesions have resolved. Mild residual corneal vascularization is visible in the left eye (d).

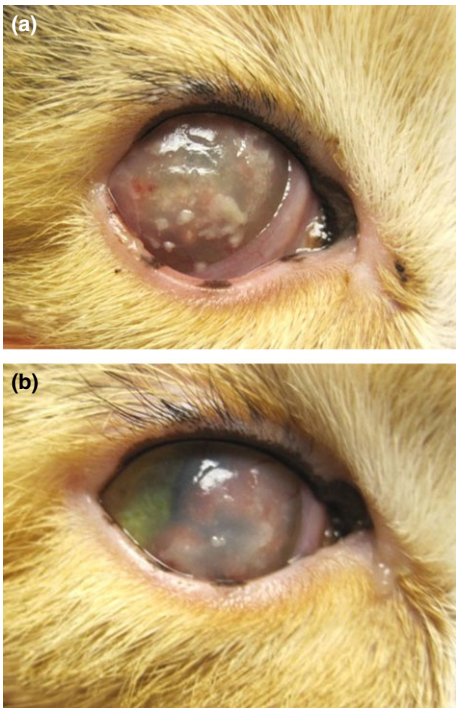

Figure 4. (a) Eosinophilic keratitis is present throughout the cornea. (b) Four weeks after treating with topical 0.5% megestrol acetate q 8 h, the lesion has decreased in area and density. The lesion completely regressed after an additional 3 weeks of treatment.

Table 1. Frequency of topical 0.5% megestrol acetate required to maintain remission of eosinophilic keratitis in 15 cats as of the last examination

Frequency	2X/ day	1X/ day	1X EOD	2X/ week	1X/ week	No treatment
Number of cats	2	3	4	2	3	1

EOD, every other day.

maintenance therapy of 2.5–5 mg every 7–14 days or longer can be used. In the study reported here, a cat dosed at one drop q 8 h would have received a maximum daily dose of 0.75 mg, although with ocular overflow it is unlikely any cat absorbed this amount. In cats given 5 mg of megestrol acetate once daily for 14 days, fasting hyperglycemia occurred as well as suppression of basal and corticotropin-stimulated cortisol levels.[13] Suppression of cortisol levels have also been demonstrated in humans receiving megestrol acetate.[14] Another study in which cats received 5 mg megestrol acetate once daily for 16 days demonstrated glucose intolerance and suppressed cortisol levels that took three or more months to return to normal following cessation of the drug.[15] In a study of the long-term effects of oral megestrol acetate, cats received 5 mg daily for 2 weeks, followed by 5 mg three times per week for 1 year.[16] Cats developed fasting hyperglycemia, decreased mean plasma glucose clearance rates, decreased resting plasma cortisol levels as well as decreased cortisol levels in response to ACTH stimulation. After cessation of treatment, glucose and cortisol levels had returned to baseline by 3 months. In a study on the prevalence of diabetes mellitus in cats, 25% of male cats treated with megestrol acetate developed diabetes compared to 1.6% of female cats.[17] However, dosages and reasons for treatment were not reported; it was hypothesized that the male cats were treated for longer for behavior modification, compared to females who were more likely treated short term for estrus suppression.

These studies indicate that a cat receiving oral megestrol acetate should be gradually tapered down or off the medication as for any potent glucocorticoid. Although no evaluation of adrenal function was undertaken in the study reported here, it would be prudent to follow the same gradual tapering guidelines for the topical use of megestrol acetate.

The use of potent corticosteroids such as prednisolone and dexamethasone topically also tends to control eosinophilic keratitis well in cats. The use of these drugs may allow for FHV-1 to recrudesce, whether its presence in the cornea is in that of a dormant state or whether the virus is related to eosinophilic keratitis in a more active way. Some studies have demonstrated that close to 50% of clinically normal appearing cat corneas harbor FHV-1 DNA, making its demonstration by PCR difficult to relate to specific disease conditions.[18–20] One study documented virulent FHV-1 in clinically normal feline corneas.[20] This finding supports the theory that repeated application of a topical corticosteroid might activate viable FHV-1 already present in the tissue. In the study reported here, no cat developed herpetic disease while being treated with topical megestrol acetate. This should not be interpreted, however, as an inability for this drug to activate FHV-1. Since it is a drug with prolonged glucocorticoid activity, it has the potential to exacerbate FHV-1 and clinicians and clients should be aware of this possibility.

In this study, 6 of 17 cats had positive fluorescein uptake at the initial examination. Despite this finding, megestrol acetate was begun and all lesions went on to heal. Epithelial loss over an eosinophilic plaque and in the cornea surrounding it is common. One study of 45 cats with eosinophilic keratitis found those who had corneal ulceration or a history of ulceration had a higher percentage of positive FHV-1 PCR samples (67%) than cats with no corneal ulcer at any time (22%).[5] This finding is interesting, but cannot be interpreted specifically as FHV-1 leading to the ulceration. In humans with atopic keratoconjunctivitis, the presence of extracellularly located toxic eosinophil protein deposits has been documented.[21] These protein deposits can interfere with corneal epithelial cell viability and migration, leading to ulceration. Although not described in the cat, it is probable the same process occurs, leading to epithelial loss over and around the

cellular infiltrates. This can lead to confusion for the clinician about whether it is safe to use a topical drug with glucocorticoid activity. A corneal ulcer caused by FHV-1 should not be treated thusly, whereas a corneal ulcer caused by toxic eosinophil protein would improve with a topical glucocorticoid.

In conclusion, the use of a topical formulation of 0.5% megestrol acetate led to regression of eosinophilic keratitis lesions in 88% of cats evaluated. This novel drug formulation provides another option to clinicians for the treatment of feline eosinophilic keratitis and may have less of an effect systemically than does the use of oral megestrol acetate.

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