OPTIMIZED OPHTHALMICS:
ADVANCES IN THE MEDICAL TREATMENT OF OCULAR DISEASE

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As with other medical disciplines, ophthalmology and vision science is a rapidly expanding branch of clinical medicine. The efforts of physicians, veterinarians, research investigators, and other medical professionals have contributed invaluably to the current body of knowledge regarding eye disease, ocular health, and the vision sciences. In turn, medical treatment options for various conditions and pathologies continue to evolve, presenting practitioners with better tools with which to treat their patients. Though not exhaustive, this discussion aims to present some of the pharmacologic advances that show great potential to help our veterinary patients.

OCULAR PHARMACOLOGY: AN OVERVIEW

The eye's response to a medication (topical or oral) is reliant on many factors, all of which contribute to the drugs effective activity and concentration at the intended site of action. These factors include (but are not limited to):

- Mode of administration (suspension, ointment, oral, parenteral)
- Route of absorption
- Molecular state of the drug
- Ocular surface dynamics
- Integrity of ocular barriers/disease status of the treated eye

Given the potential physiologic barriers associated with absorption of oral and/or parenterally-administered medications, topical ophthalmic medications are often the preferred mode of quick and efficient delivery of medication to the eye. The specific features of an eye drop's pharmacologic design, help to ensure its acceptability to the patient, its bioavailability, and its respective efficacy at the intended site of action. In theory, the "perfect" eye drop would need to bear the following characteristics.

- pH 4.5-9.0
- Osmolality of 200-600 mOsm/kg
- Uniform particle size (< 10 micron diameter)
- Non-protein-bound
- Hydrophilic and hydrophobic drug states
- Balance of ionized and unionized states (balanced PKa)

Each of these characteristics will influence how effectively a topically-applied drug will penetrate through the ocular surface and into the eye. In turn, those drugs that do not readily penetrate the ocular surface tissue (cornea, conjunctiva, sclera) are poorly suited to treat intraocular disease. (See Appendix, Table 1)

As practitioners, we have no direct control over an eye drop's pharmacologic characteristics. We can, however, maximize drug delivery by controlling dose volume. Once instilled, an eye drop will mix with the tear film, allowing dispersal of the drug across the ocular surface. The average volume of a commercial eye drop, however, is 40-50 microliters, exceeding the maximum average volumes of the tear film and palpebral fissure. Therefore, the vast majority of a single eye drop is lost within the first 15-30 seconds after instillation, either by lid overflow or via the

nasolacrimal duct system. In addition, instillation of an eye drop may also lead to reflex tearing (especially if the formulation is irritating), increasing dilution of the drug at the ocular surface. Most drugs are cleared from tear film turnover at a rate of 15% per minute. It has been proven, therefore, that administration of a smaller drop volume will minimize drainage rate and enhance drug absorption.

Strategies that could be employed to reduce drainage rate of an eye drop include control of blinking frequency, control of tear flow dynamics, or control of the size of the drop. In our veterinary patients, we have no control over the former two, and unfortunately, production of bottles with control over drop volume has proven very expensive to drug companies and is therefore not commonly employed. Our best strategy, therefore, is to (1) avoid administration of multiple drops when dosing and (2) to separate administration of consecutive drops by at least 5 minutes.

ANTIBIOTICS

Microbiology is an ever-expanding field whose growth is characterized by constant changes in microbial nomenclature and classification, and most clinically relevant, an increase in the incidence of bacterial resistance to available antibiotics. The approach to choosing an antibiotic, however, has not changed and emphasis should be placed upon not WHAT antibiotics we use as practitioners, but HOW we use them. Antibiotic choice should be based upon several factors including:

- Suspected contaminant or contaminant risk
- Culture and sensitivity (if available)
- Penetration into the tissue of interest
- Species, age, or breed-specific considerations

One of the most common indications for administration of topical antibiotics in veterinary ophthalmology is corneal ulceration, and early and appropriate antibiotic choice can certainly affect the long-term outcome for the patient. Certain clinical characteristics of an ulceration may increase suspicion for a more severe infection. For example, green-yellow discoloration of corneal stroma is highly suggestive of corneal sepsis. Some corneal changes may be reflective of infection with *specific types of bacteria*. For example, malacia or "melting" of a corneal ulceration is highly suggestive of infection with *Pseudomonas aeruginosa*. In those ulcerations suspected to be infected, culture samples can be readily obtained from the ocular surface using a swab, Kimura spatula, or the blunt end of a scalpel blade. Whether due to the lack of clinically obvious infection, client-related limitations, or limited accessibility, however, corneal ulcerations are often treated empirically based on clinical suspicion or simply to prevent bacterial infection of an active ulceration. For example, a broad-spectrum triple antibiotic (neomycin-polymyxin-bacitracin/gramicidin) may be used prophylactically in treatment of an uncomplicated or non-infected corneal ulceration, while any malacic or "melting" corneal ulceration should be treated presumptively for *Pseudomonas spp.* Infection with a more aggressive antibiotic such as a topical fluoroquinolone.

The ability of an antibiotic to penetrate ocular tissue and concentrate within the corneal stromal will also influence its efficacy. When ulceration is present, the defect within the hydrophobic epithelium permits penetration of the majority of antibiotics into the corneal stroma. Most of these antibiotics, however, have only a limited capacity to penetrate intact corneal epithelium. Fluoroquinolones carry excellent capacity not only to penetrate an intact corneal epithelium, but also to accumulate within the corneal stromal tissue, in excess of the MIC for many bacterial

contaminants. Chloramphenicol also readily penetrates an intact corneal epithelium, but bacterial resistance to this antibiotic (particularly Pseudomonas spp.) and human health concerns (aplastic anemia) may limit is usefulness. Topical ophthalmic antibiotics of use in the dog may include:

- Triple antibiotic preparations: neomycin-polymyxin-gramicidin/bacitracin
- Aminoglycosides: tobramycin, gentamicin
- Chloramphenicol
- Tetracyclines: oxytetracycline
- Fluoroquinolones: ofloxacin, ciprofloxacin, moxifloxacin

In cats, however, this presenter prefers to avoid the use of topical neomycin-polymyxin-gramicidin/bacitracin due to species-specific differences in the ocular surface microflora. In cats, ocular surface pathogens like Chlamydia felis and Mycoplasma felis are not susceptible to triple antibiotic preparations. These organisms are, however, frequently susceptible to the following:

- Tetracyclines: oxytetracycline
- Macrolides: erythromycin
- Fluoroquinolones: ofloxacin, ciprofloxacin, moxifloxacin

For a long period of time in veterinary medicine, there have been anecdotal reports of anaphylactic reactions (some fatal) in cats to triple antibiotic preparations, with neomycin putatively identified as the causative agent. For this reason, many practitioners have withheld administration of these antibiotics to feline patients in all clinical situations. A recent study was performed, surveying a large group of practitioners through the Veterinary Information Network (VIN®) while also gathering data from cases of feline anaphylaxis to topical ophthalmic medication reported to the Federal Drug Administration. There were a total of 998 survey respondents. Only 61 cats fit the inclusion criteria established by the authors. As anticipated, results were difficult to interpret due to a wide age-range and great variation in clinical setting, patient health status, the reported clinical manifestations of anaphylaxis, and in the topical antibiotic applied. Ultimately, this study demonstrated that the anaphylaxis following administration of a topical antibiotic was exceptionally rare. 56% of cats reported to have experienced an anaphylactic event, did so within 10 minutes of topical administration. Overall, survival rate was high (82%). The most successful approach to treating affected cats included intravenous fluids, flushing of the ocular surface(s), systemic corticosteroids, and systemic diphenhydramine. A wide range of topical antibiotics (and some products not containing antibiotics) were reported to have resulted in anaphylaxis. Perhaps the most interesting result of this study was the finding that the only antibiotic common to all reported cases was polymyxin-B, which is in triple antibiotic preparations and also Terramycin (with oxytetracycline). Though this study is limited by its design, the information can be useful to the practitioner. The "take-home message" is that, though rare, any topical agent can cause anaphylaxis in any patient and recognition of the signs is critical.

Delivery of oral or parenteral antibiotics to the eye, particularly the ocular surface, is complicated by several factors including:

- Integrity of the blood-aqueous barrier
- Normal corneal avascularity
- Poor lacrimal availability

One notable exception, however, is the tetracycline class of antibiotics. Antibiotics like tetracycline or doxycycline are actively secreted by the lacrimal gland and may reach therapeutic levels within the tear film after oral or parenteral administration. This provides an alternative in animals that are refractory to topical treatment. Since tetracyclines are also effective anti-

collagenase agents, this can also be of use in treating patients with malacic or "melting" corneal ulcerations.

ANTI-INFLAMMATORY MEDICATIONS

Anti-inflammatory therapy is a cornerstone of treatment for many diseases affecting veterinary patients. As such, there are numerous medications available and it seems that the veterinary pharmaceutical market develops and produces new generations of these medications each year. Anti-inflammatory therapy can be a critical component of treatment of many ocular diseases including (but not limited to):

- Blepharitis
- Conjunctivitis
- Keratitis (ulcerative or non-ulcerative)
- Uveitis (anterior, posterior or both)
- Prophylaxis for lens-induced uveitis
- Retinal detachment
- Orbital disease (inflammatory, infectious, neoplastic)

As with other disciplines, the two classes of anti-inflammatory most commonly employed in veterinary ophthalmology are corticosteroids and NSAIDs. Commonly prescribed medications include (but are not limited to) those listed in Appendix, Table 2.

With numerous options for topical anti-inflammatory therapy, it can be difficult for practitioners to know WHICH medication to choose, and WHEN. Dissimilar to other fields, there are few concrete rules guiding use of ophthalmic anti-inflammatories in veterinary patients. The following list of four "rules", however, may provide some guidance for making this decision at the point-of-care for a patient.

Rule 1: When A Corneal Ulceration is present, AVOID TOPICAL CORTICOSTEROIDS!

Early in our veterinary education, we are taught that topical corticosteroids are contraindicated in the face of a corneal ulceration. This clinical rule is still of great importance today. Corticosteroids can impair corneal wound healing via a number of mechanisms including inhibition of epithelial proliferation and migration, suppression of local immune factors, and promotion of collagenase enzyme production. The latter of the three is what predisposes to sometimes catastrophic malacia or "melting" of corneal stromal tissue. This can occur even in the absence of infection with organisms like *P. aeruginosa* as corneal stromal cells (keratocytes) and epithelial cells carry the capacity to produce their own damaging metalloproteinase enzymes. In an ideal world, topical NSAIDs would provide a safe alternative to corticosteroids in the face of corneal ulceration. Unfortunately, exacerbation of corneal ulceration, specifically progression to malacic corneal ulceration, has been reported in human medicine (and anecdotally in veterinary medicine) after topical NSAID application. Though the mechanism is poorly understood, it is reasonable to say that topical NSAIDs should be used cautiously in patients with active corneal ulcerations

Rule 2: Avoid topical NSAIDs in patients with glaucoma or predisposition to glaucoma.

Topical NSAID administration in dogs has been shown to increase intraocular pressure by decreasing the facility of aqueous outflow through the iridocorneal angle. This mechanism is not well understood but has been clearly demonstrated in experimental study. Therefore, administration of this medication in dogs with controlled glaucoma or predisposition for primary glaucoma carries a risk (though the percentage is undetermined) for exacerbating or eliciting

glaucoma. It should therefore be used judiciously in acutely inflamed eyes at risk for increased intraocular pressure. For example, many ophthalmologists will avoid using topical NSAIDs in the immediate postoperative period following cataract surgery. It is noteworthy, that a similar risk has NOT been demonstrated with use of systemic NSAIDs.

Rule 3: Hydrocortisone is a very weak topical anti-inflammatory agent.

Topical ophthalmic formulations containing hydrocortisone are commonly found on veterinary hospital shelves. While hydrocortisone can be an effective treatment for some mild forms of allergic canine conjunctivitis, this medication penetrates the surface ocular tissues only very poorly, acting mainly at the level of the corneal and conjunctival epithelia. It does not penetrate the deeper layers of the cornea or conjunctiva well and does not achieve penetration into the anterior chamber. When treating deeper corneal/conjunctival disease or uveitis, prednisolone acetate, dexamethasone, or topical NSAIDs are better therapeutic choices.

Rule 4: When treating POSTERIOR disease, use systemic anti-inflammatories.

As discussed in the first section, the characteristics of a particular medication will influence how well it penetrates the ocular surface and accumulates within different ocular tissues. None of the commonly-prescribed topical corticosteroids or NSAIDs will achieve therapeutic concentrations beyond the lens and ciliary body. In other words, they will not successfully treat inflammatory disease of the vitreous, retina, posterior sclera, optic nerve, or choroid. In addition, they will not successfully treat orbital inflammation behind the globe.

Similar to the blood-brain barrier, the blood-aqueous and blood-retinal barriers are physiologic "walls" that restrict permeability between the general circulation and ocular structures/humors. In health, this also restricts delivery of drugs from the bloodstream to the intraocular environment. In the face of ocular inflammation, however, these barriers are compromised, enhancing drug passage and accumulation.

When unsure of whether to choose a topical or oral anti-inflammatory medication, this presenter's guidelines can be found in Appendix, Table 3.

** While concurrent administration or oral/parenteral NSAIDs and corticosteroids carries significant risks to a patient, concurrent use of oral NSAID and topical corticosteroid (and vice versa) carries low risk in otherwise healthy animals. One exception to this are patients of small body weight (< 5 kg) in which systemic absorption of topical medications is more significant.

GLAUCOMA MEDICATIONS

Despite ongoing investigation into surgical or ablative procedures for the treatment of glaucoma in veterinary medicine, medical treatment remains a critical part of successful management of the disease and preservation of vision. In health, aqueous humor is produced at a constant rate by the ciliary body, immediately posterior to the base of the iris and peripheral to the lens. Aqueous humor flows through the pupil and into the anterior chamber, providing nutrition to the anterior intraocular structures. The bulk of aqueous humor leaves the anterior chamber through the iridocorneal angle between the posterior cornea/sclera and the anterior iris base. This is known as the conventional aqueous outflow pathway. Aqueous humor outflow can also occur via the unconventional pathway in which fluid is reabsorbed through spaces within the ciliary and iris stroma. This pathway represents a comparatively small percentage of outflow in our domestic animal species.

Aqueous outflow through the iridocorneal angle can become impaired or obstructed due to either primary (inherited) structural changes of the iridocorneal angle or secondary causes (i.e. as a result of chronic intraocular hemorrhage or uveitis, intraocular neoplasia, or lens luxation). It is

noteworthy that the vast majority of cases of feline glaucoma are secondary, being related to pre-existing uveitis or intraocular neoplasia. Regardless of the underlying cause, the end result of this impairment is backup of aqueous humor, leading to elevated intraocular pressure (IOP), exceeding the normal physiologic range of approximately 15-25 mmHg. Elevated IOP places great physiologic stress on the optic nerve and retina, with permanent degenerative consequences that can lead to blindness, sometimes within hours if the pressure increase is severe enough.

The goals of glaucoma treatment are threefold. First and foremost, elevated IOP must be swiftly reduced and controlled. If present, predisposing causes for secondary glaucoma (such as uveitis or anterior lens luxation) should be identified and treated. More recently, the concept of specific neuroprotection has been investigated in both human and veterinary medicine, though its benefits are still unclear.

Most ophthalmologists approach reduction of elevated IOP with multi-drug therapy, as different medications may complement each other by reducing pressure via different mechanisms. Classically, treatment recommendations for acute glaucoma include administration of an osmotic agent like intravenous mannitol, to dehydrate the vitreous body and enhance aqueous outflow. While mannitol acts quickly to reduce intraocular pressure, disadvantages include the need for intravenous catheter placement and hospitalization, and systemic risks to patients with clinical dehydration, cardiac disease, or renal insufficiency. Carbonic anhydrase inhibitors (CAIs) such as topical dorzolamide and brinzolamide or oral methazolamide reduce aqueous humor production by inhibiting carbonic anhydrase activity within the ciliary body. CAIs have been shown to significantly reduce IOP in both normal and glaucomatous canine and feline eyes. Their effects, however, are not as rapid as with osmotic agents and, therefore, CAIs are not used as sole therapeutic agents in cases of acute glaucoma. Oral CAIs (methazolamide, acetazolamide) can be as effective as topical agents but can be associated with systemic side effects (vomiting, diarrhea, hypokalemia, metabolic acidosis), particularly in cats. For this reason, the author only uses **topical** CAIs in cats with glaucoma. Topical beta-blockers (timolol, betaxolol) may act synergistically with CAIs or other glaucoma medications, but as sole agents, these medications are relatively weak in their pressure-reducing effects. In addition, even topical administration can be associated with cardiopulmonary side effects (bradycardia, airway constriction), particularly in cats or smaller dogs, so it should be prescribed judiciously in patients with pre-existing cardiopulmonary disease.

Perhaps the most significant advance in the medical treatment of glaucoma has been the development of topical prostaglandin analogs (PGA). Latanoprost (Xalatan®), travoprost (Travatan®), and bimatoprost (Lumigan®) are widely-prescribed in both human and veterinary medicine. Latanoprost is often employed in veterinary medicine as it is available in generic formulation and is more affordable for many pet owners. Latanoprost is a PGF2α analog that increases aqueous outflow through the unconventional pathway. Though the exact mechanisms by which this occurs is unknown, there is a high concentration of receptors for PGF2α within the iris sphincter and longitudinal fibers of the ciliary muscle in humans. Stimulation of these receptors with an analog like latanoprost leads to a complex second messenger pathway, resulting in remodeling of the extracellular matrix within the iridal tissue and ciliary muscle, and subsequent increase in aqueous outflow.

PGAs are highly effective agents for reduction of intraocular pressure in dogs. Numerous studies have demonstrated their efficacy in both non-glaucomatous and glaucomatous eyes. Despite their efficacy in dogs, however, the same pressure-reducing effect has not been appreciated in cats with glaucoma. This is related to the absence of feline ocular PGF2α receptors within the ciliary

muscle. PGAs like latanoprost can dramatically reduce elevated intraocular pressure, sometimes within 20-60 minutes after administration of a single topical dose. For this reason, many ophthalmologists prefer to use latanoprost instead of mannitol as acute therapy for IOP reduction. It is noteworthy, however, that mannitol may still be necessary in those patients that do not have a favorable or rapid response to a PGA. PGAs are most commonly prescribed on a q12-24 hour basis, particularly when used as long-term maintenance therapy.

Topical PGA has not been associated with systemic side effects. Local ocular side effects may include blepharospasm, conjunctival "flushing" or hyperemia, transient aqueous flare, and even iridal hypermelanosis after chronic administration. Many of these effects are reflective of transient blood-aqueous barrier compromise due to stimulation of uveal prostaglandin receptors. For this reason, PGAs should be used with great caution in dogs with glaucoma secondary to uveitis as these drugs may exacerbate pre-existing uveal inflammation. Miosis, sometimes dramatic, is invariably seen in dogs after topical administration of PGAs. This is non-painful and only rarely vision impairing. PGA-induced miosis can, however, be problematic in patients with anterior lens luxation. When a displaced lens luxates into the anterior chamber, it greatly obstructs flow of aqueous humor through the pupil, leading to increased intraocular pressure. Further reduction of the pupillary diameter will worsen this obstruction even further, and could greatly exacerbate the often already severe secondary glaucoma associated with anterior luxation. All efforts should be taken to ensure that a lens luxation is not the cause for glaucoma prior to administration of a PGA.

Neuroprotection has become a popular topic in human medicine amongst glaucoma specialists as mitigation of glaucomatous/ischemic damage to the optic nerve and retina would theoretically enhance preservation of long-term vision. Various mechanisms of neuroprotection have been suggested in humans and animals including vasodilation of optic nerve and retinal vasculature, antagonism of glutamate-induced excitotoxicity to retinal ganglion cells, and provision of anti-oxidant/free-radical scavengers. While investigation of the vasodilatory effects of calcium channel blockers and the effects of NMDA antagonists have been widely studied, the knowledge of their efficacy in both human and veterinary patients remains limited at this time.

**Two algorithms for treatment of canine and feline glaucoma are included within the Appendix. These treatment regimens are reflective of the author's preference for treatment of acute glaucoma.

LACRIMOSTIMULANT MEDICATIONS

The ultimate clinical abnormality in keratoconjunctivitis sicca (KCS) is a deficiency in aqueous tear production. Decreased aqueous tear production invariably leads to desiccation of the corneal surface, corneal vascularization and/or pigmentation (melanosis), and clinical signs of discomfort such as blepharospasm and ocular "itchiness". It is also commonly associated with corneal ulceration.

The vast majority of cases of canine KCS are **idiopathic**. Studies have demonstrated lymphoplasmacytic glandular ""inflammation (adenitis), associating these idiopathic cases with a presumed immune-mediate or autoimmune cause. There are other causes of KCS, however, that must be considered. These include:

- Removal of the third eyelid gland (iatrogenic)
- Drug administration (sulfa antibiotics, etodolac, inhalant anesthetics)
- Loss of nerve supply to the lacrimal gland (neurogenic KCS)
- Metabolic disease (diabetes mellitus, hypothyroidism)

- Traumatic (most commonly following proptosis or severe orbital disease/inflammation)
- Congenital lacrimal gland hypoplasia/aplasia
- Distemper virus infection (rare)

The most commonly employed means of diagnosing KCS is the **Schirmer tear test**. The technique involves placing the Schirmer tear strip within the lower conjunctival fornix and measuring the strip "wetting" after one minute. Tear values exceeding 15 mm within one minute are considered normal in dogs. Those dogs with STT values between 10 and 15 mm within one minute can be considered suspicious for having KCS, particularly if clinical signs (see above) are present. STT values less than 10 mm within one minute are unequivocally consistent with KCS in dogs.

Cyclosporine A

The cornerstone of KCS therapy in veterinary ophthalmology has been topical administration of topical **lacrimostimulants** (medications that stimulate tear production from the lacrimal glands). The most widely-used lacrimostimulant agent to date is **cyclosporine A (CsA),** due to both its anti-inflammatory and lacrimostimulant effects. CsA is a calcineurin inhibitor and exerts its anti-inflammatory effect by inhibiting T-lymphocytes. CsA binds an intracellular protein, cyclophilin, interrupting a protein cascade and inhibiting the cell's activity. The stimulant effects on tear production, however, are not as well-understood. CsA has also been shown to enhance mucin production from conjunctival goblet cells. Therefore, its effects are also beneficial in enhancing tear film stability and use is indicated in cases of *qualitative* tear deficiency as well.

Currently, CsA is available in both commercial and compounded ophthalmic preparations. Optimmune® is a commercial ointment, containing 0.2% CsA. Compounded forms are more commonly formulated in 1 or 2% ophthalmic ointments, oil immersions, or aqueous preparations. In general, most preparations are well-tolerated by the majority of dogs. It is noteworthy that ophthalmic CsA (Restasis®) is also on the market for treatment of human KCS. The concentration of CsA in Restasis® (0.05%), however, is much lower than the levels necessary to control the same disease in canine patients. Other than sporadic cases of topical irritation with CsA, there are no reports of adverse effects, though 2% preparation has been shown to suppress systemic lymphocyte activity in one study after 1-3 months of use. Whether the degree of lymphocyte inhibition is clinically significant, however, remains unknown.

A favorable clinical response to CsA is measured by both an increase in Schirmer tear test (STT) values as well as abatement of clinical signs of conjunctivitis and keratitis. It has been shown that a higher proportion of dogs will respond to CsA if the STT is greater than 2 mm/min at the time of diagnosis. Those with STT of 0 at the time of diagnosis have a diminished prognosis for response. In some cases, however, improvement of clinical signs may precede or even exceed objective improvement (STT values), warranting continued use of the drug. It is also important to inform clients that a maximal response to the medication may not be seen for up to 8 weeks after beginning therapy.

Tacrolimus

Tacrolimus (TAC) is also a calcineurin inhibitor and also exhibits anti-inflammatory, lacrimogenic, and mucinogenic properties. Formerly known as FK506, TAC is anecdotally 10 to 100-fold more potent than CsA in its therapeutic effects. In one study, all dogs controlled with CsA could be controlled with TAC and in approximately 25% of those dogs, tear production rose an additional 5 mm/min or more with administration of TAC. In addition, approximately 50% of those dogs that did not experience increased tear production with CsA did so with TAC.

As no commercial product is available, ophthalmic TAC is commonly compounded into both ointment and suspension preparations, most commonly in a 0.02% concentration. There are no known short or long-term risks or side effects, but no formal studies on this have been published in veterinary ophthalmology. It has been commercially used as a human dermatologic anti-inflammatory, Protopic®, primary as a treatment for conditions such as eczema. Recently, particularly in pediatric patients, there have been some concerns about risks for lymphoma, squamous cell carcinoma and other tumors in patients using Protopic® long-term. Whether or not there is a similar risk with use in veterinary ophthalmology is unknown, but its use should very likely be reserved for severe cases or those that are refractory to treatment with CsA.

ANTIVIRAL MEDICATIONS

Feline herpesvirus-1 (FHV-1, feline rhinotracheitis virus) is a ubiquitous alpha herpesvirus, affecting the domestic cat population as well as other felids. FHV-1 bears a short reproductive cycle and rapidly propagates, resulting in swift disease progression via destruction of infected cells. Infection of the upper respiratory tract commonly causes rhinitis and/or sinusitis. When infecting the ocular surface, lysis of epithelial cells leads to conjunctivitis, keratitis (corneal inflammation), and conjunctival or corneal ulceration. FHV-1 is also notorious for establishing latency within a feline host, leading to life-long risk for recurrent ocular and/or respiratory disease.

Definitive diagnosis of herpesviral disease can be challenging, and most commonly, a presumptive diagnosis is made based upon history and clinical signs. Techniques such as virus isolation and immunofluorescence assay but may be heavily influenced by delayed sample handling, varying refrigeration temperatures, or repeated thawing. Polymerase chain reaction (PCR) has demonstrated the most promise in providing a reliable means for diagnosis, estimated in one study to be 80% more sensitive than VI. With increasing sensitivity, however, comes a capacity for diminished specificity as latent or low amounts of FHV-1 DNA NOT contributing to disease are detected.

Given these diagnostic challenges, the majority of cases of feline conjunctivitis or keratitis are presumed to be herpesviral in nature, and treated accordingly. A primary component of treatment of presumed or confirmed FHV-1 conjunctivitis and/or keratitis should be aimed at decreasing viral load. In cases where a herpesviral etiology is suspected, antiviral medication should be considered the cornerstone of medical therapy to suppress viral replication within ocular tissues. A wide variety of antiviral agents have been developed for treatment of human herpesviral syndromes, but not all can be directly applied to treatment of FHV-1-related diseases and currently, no antiviral drugs are approved specifically for veterinary use in the US.

Most antiviral drugs are nucleoside analogs and exert their antiviral effects by interfering with viral DNA replication. To inhibit viral DNA synthesis, these drugs must act at the cytoplasmic level. Therefore, topical or systemic administration may have variable toxic effects on either the corneal/conjunctival cells or other rapidly dividing cells within the body. Use should thus be limited to those proven to be safe and effective for use in cats (see below). Aggressive and compliant treatment of cats with FHV-1 is more likely to halt disease progression and to minimize any frequency and/or severity of future recurrences. It is noteworthy that many topical antiviral agents are “virostatic”, requiring relatively frequent application. This can pose a significant challenge to some cat owners.

Acyclovir

Acyclovir (ACV) is a commonly employed antiviral in human medicine, namely for treatment of those diseases associated with herpes simplex virus (HSV). To be successfully activated after administration, it must undergo three consecutive phosphorylations, the first by a viral kinase (thymidine kinase). Since activation of ACV depends upon a viral enzyme, it exhibits relatively low toxicity for cells not infected by herpes virus.
The IC50 (half maximal inhibitory concentration) reported for ACV against FHV-1 is 80 micromolar. Subsequent study, however, has shown that ACV only reaches peak serum concentration of 33 micromolar in cats after systemic administration. In addition, some cats exhibited toxic effects including leukopenia and/or anemia at the dose administered in this study. This suggests that ACV is metabolized differently in felines and its use may be limited in treatment of feline herpetic disease.

Valacyclovir

Valacyclovir, an ester pro-form of ACV, is metabolized to active ACV via intestinal and/or hepatic metabolism. In people, this form has approximately 3-fold greater bioavailability than ACV in humans and similarly, 2.3-fold greater bioavailability in cats. Administration in cats, however, is associated with **severe bone marrow suppression**, **hepatic necrosis**, and **renal tubular epithelial necrosis**. In addition, it has not been shown to exert significant antiviral effects. Therefore, its use in cats is strictly contraindicated.

Idoxuridine

Idoxuridine (IDX), has demonstrated potency against FHV-1 in vitro and is a commonly employed topical antiviral drug for FHV-1 infection. It does not require a viral kinase enzyme for activation. As a result, it carries less specificity than ACV for infected cells and may be more commonly associated with toxicity to normal non-infected cells. The degree of toxicity, however, does not preclude its use in cases of suspected feline herpetic ocular disease and it is generally well-tolerated by most cats. It is not available in a commercial formulation, but is commonly compounded into 0.1% ophthalmic preparations. Dosing recommendations vary, but administration at least 5 times daily is required to control viral replication.

Trifluridine

Trifluridine (Viroptic®), like IDX, is activated independent of viral kinase activity. In an in vitro study, it was shown to have the highest potency against FHV-1. In addition, it has been shown to achieve higher intraocular levels after topical administration in human patients. It does, however, carry the greatest cytotoxicity of all antiviral agents in one in vitro study. It is also poorly tolerated in many cats due to ocular discomfort associated with administration, sometimes limiting its use in patients requiring topical therapy.

Cidofovir

Like other topical antiviral agents, cidofovir does not require activation by viral kinases and it carries in vitro efficacy comparable to IDX. A recent clinical, in vivo study showed that **twice daily** topical administration of 0.5% cidofovir was safe and significantly reduced viral shedding and clinical signs of ocular herpetic disease. A clear advantage of this drug is the need for less frequent application, which may be preferred by clients who find frequent dosing challenging. Cidofovir is not currently available in commercial formulations, but can be prepared into ophthalmic formulations by numerous compounding pharmacies.

Penciclovir

Famciclovir (Famvir®) is a prodrug that is metabolized to the active antiviral agent penciclovir. Penciclovir is similar in structure to ACV and like that agent, must be phosphorylated by viral kinases to become active. Penciclovir has demonstrated activity against FHV-1 in vitro and

numerous recent and forthcoming studies have evaluated its effects in vivo. The metabolism of penciclovir after oral administration in cats appears to follow complex, non-linear pharmacokinetics. In one study, administration of an oral dose similar to that used in humans (15 mg/kg), failed to achieve plasma penciclovir concentrations with activity against FHV-1. This finding has brought into question the relatively low doses recommended in common veterinary formularies. Further investigation has determined that oral doses of 90 mg/kg TID achieve therapeutic plasma concentrations and reduce circulating FHV-1 antibodies, while significantly diminishing clinical signs of experimental herpetic conjunctivitis and rhinitis. This dose was also tolerated by all cats, with no adverse side effects either on serial physical examinations or serial CBC/chemistry evaluation.

High dose therapy is often cost-prohibitive to pet owners as these antiviral agents are expensive, even in generic formulations, so further investigation has sought to determine if more intermediate doses are clinically effective. A recent in vivo study confirmed that oral doses of 40 mg/kg achieve similar plasma concentrations and presumably similar antiviral efficacy to that produced by higher dosing. Another recent in vivo study using these more intermediate doses confirmed that the tear film concentration of penciclovir approximated that of plasma, confirming lacrimal secretion of the drug onto the ocular surface. In a significant number of these patients, the tear film concentration was in excess of the MIC for FHV-1. The presenter's current recommendation to clients is therefore a dose of 40-50 mg/kg BID. A safe dose of famciclovir has not yet been determined for young kittens.

Table 1

Minimal Penetration	Enhanced Penetration
• Neomycin-polymyxin-bacitracin/gramicidin • Aminoglycoside antibiotics • Tetracycline antibiotics • Antiviral medications • Hydrocortisone • Cyclosporine/tacrolimus	• Fluoroquinolone antibiotics • Chloramphenicol • Prednisolone acetate/dexamethasone • Flurbiprofen/diclofenac • Glaucoma medications (latanoprost, dorzolamide, timolol)

Table 2

Topical	Oral/Systemic
• Corticosteroids – Prednisolone acetate – Dexamethasone – Hydrocortisone • NSAIDs – Flurbiprofen – Diclofenac sodium (Voltaren®)	• Corticosteroids – Prednisone/prednisolone – Dexamethasone • NSAIDs – Carprofen (Rimadyl®) – Meloxicam (Metacam®) – Deracoxib (Deramaxx®) – Piroxicam (Feldene®) – Robenacoxib (Onsior®) – *Tepoxalin (Zubrin®)*

Table 3

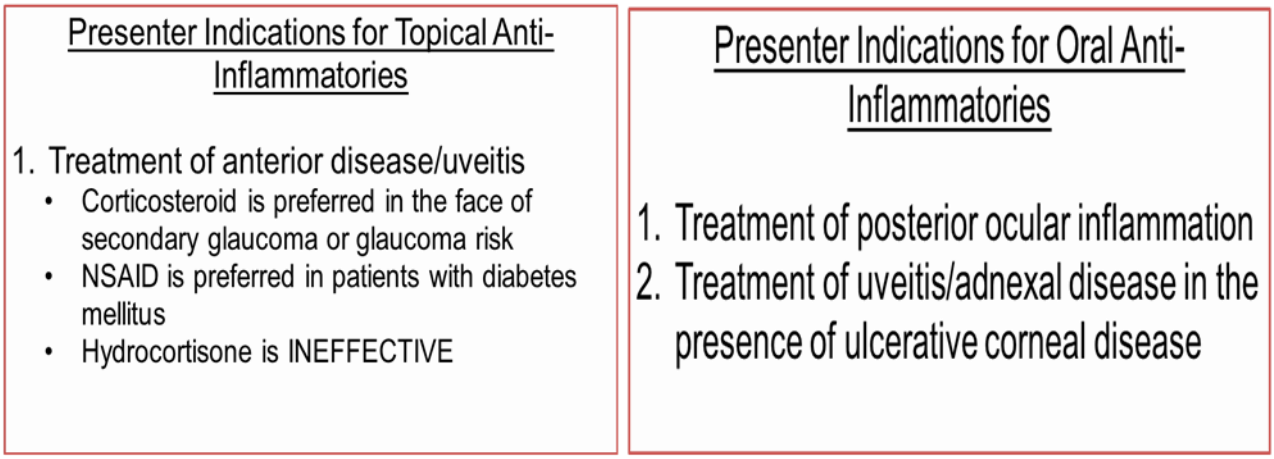
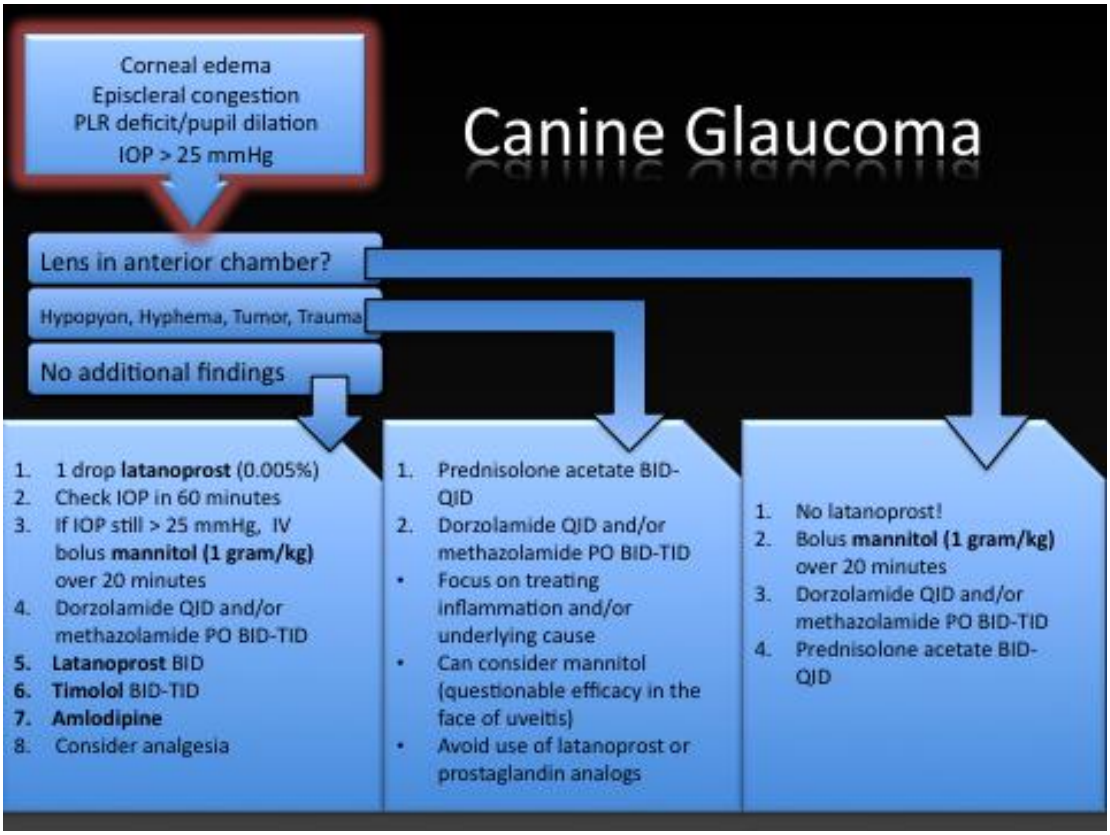


Table 4

DRUG	PREPARATION	RECOMMENDED DOSE
Idoxuridine (Compounded)	0.1% solution, 0.5% ointment	Apply 4-6 times daily
Cidofovir (Compounded)	0.5% solution	Apply twice daily
Trifluridine (Viroptic®)	1% solution	Apply 4-6 times daily
Vidarabine (Compounded)	3% ointment	Apply 4-6 times daily
Famciclovir (Famvir®)	125 mg and 250 mg tablets	40-50 mg/kg BID
Acyclovir (Zovirax®)	Tablets, capsules, oral suspension	Fails to reach effective plasma concentrations in cats; may have systemic side effects
Valacyclovir (Valtrex®)	Tablets	**Causes severe and possibly fatal side effects in cats; Do not administer**

Algorithm 1



Algorithm 2