OPHTHALMIC DRUGS: WHICH ONES, WHEN, WHY AND WHY NOT?
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Introduction

The ocular surface provides an interface that facilitates local treatment of ophthalmic disease, enabling us to minimize systemic side effects and maximize concentration of medications in ocular tissues. The access of topically applied medications does, however, diminish as we move deeper into the eye, and systemic administration of medication is preferable in some cases. In general, ocular surface disease is amenable to topical treatment, eyelid and posterior segment disease (chorioretinitis) is best treated systemically, and anterior uveitis and glaucoma can be addressed via both routes; however, posterior penetration of antiglaucoma and other medications have been demonstrated. Both corneal and conjunctival absorption allow drug molecules to access the anterior chamber and anterior uvea. Via the nasolacrimal system, conjunctiva, aqueous humor, and anterior uvea, medication will eventually access the vascular system and be systemically distributed as well.

This lecture will focus on topical ophthalmic medications primarily. Important considerations in design and selection of topical medication include facilitating absorption of medication at the target tissue, minimizing potential irritants (such as preservatives, where possible), and limiting systemic effects. Factors in absorption include pH, hydrophobic or hydrophilic nature of the drug molecule, ocular barriers (corneal layers, conjunctiva, sclera, choroid/uvea), molecule size, etc.

On a daily basis, we are unlikely to consider these factors in detail, but we are regularly faced with deciding whether to prescribe a solution, suspension, gel, or ointment, and these formulations can significantly impact efficacy. Solutions and suspensions should mimic the tear film as much as possible with regard to osmolality and pH (range 4.5-9, however low pH drops like pilocarpine are often not well tolerated). Lipophilic/hydrophobic drugs (such as cyclosporine) generally must be suspended in an oil or ointment, whereas hydrophilic molecules are amenable to aqueous solutions or ointment preparations. With solutions or suspensions, the liquid drop mixes with the tear film upon administration, and will then be absorbed via the cornea and/or via the conjunctiva; medication is also evacuated from the ocular surface via nasolacrimal drainage, after which it may enter the nasopharynx and be swallowed in some patients. Importantly, the volume of fluid that can be retained on the surface of the eye is limited, and is generally less than the volume of a single drop from a dropper bottle. Thus, the majority of medication may be immediately lost. Next, tear turnover will account for removal of the remainder of the unabsorbed medication in the tear film within the next 10 minutes. So, two drops are not better than one, as more medication will simply be lost and/or absorbed systemically via the nasolacrimal system.

In contrast, ointment preparations have been shown to remain on the ocular surface for up to 4 hours. Petrolatum ointments also show better retention on the ocular surface than
gels such as methylcellulose. Because ointments affect the administration and absorption of liquid preparations, ointments should be given last. It is imperative that ointments are avoided in deep corneal ulcers at risk of rupture or with full thickness corneal lacerations to avoid potential contamination of the anterior chamber with petrolatum or mineral oil and subsequent severe inflammatory response.

In general, ophthalmic drops are frequently easier to administer and more precise, but may require more frequent administration for certain purposes; ophthalmic ointments may be more difficult to administer precisely but provide longer contact time and thus improved absorption and expand treatment interval. Specific considerations for formulation choice and treatment frequency in various clinical settings will be presented below.

Briefly, ocular toxicity is also important to remember. Commercially available ophthalmic medications must all contain a bacteriostatic preservative, of which benzalkonium chloride is thought to be the most irritating. Inflammatory corneal conditions can occur with chronic use of topical medications with preservatives in rare cases (mainly documented in humans). More commonly encountered examples of negative drug reactions in veterinary species are local hypersensitivity reactions to neomycin and dorzolamide. Neomycin is avoided in cats by most ophthalmologists due to anecdotal reports of anaphylaxis and death upon administration.

Select Ocular Therapeutics by Category and Condition

Section 1: Topical Ophthalmic Antiinflammatory Medications
Section 2: Antiglaucoma Medications in Veterinary Medicine: Focus on The Dog
Section 3: Ophthalmic Medications for Treatment of Ulcerative Keratitis and Uveitis
Section 4: Comprehensive Treatment of Dry Eye
Section 5: Focus on Felines: Herpetic Keratoconjunctivitis and Eosinophilic Keratitis

1: Topical Ophthalmic Antiinflammatory Medications

I. Review:
   a. Select effects of prostaglandins on the eye: miosis, reduced intraocular pressure, disruption of blood aqueous barrier (flare), vasodilation (i.e., conjunctival hyperemia).
   b. Goal of anti-inflammatory medications is to counteract these effects, as well as those of other pro-inflammatory mediators.

II. Corticosteroids:
   a. Mechanisms of action in suppressing inflammation:
      i. Inhibit production of proinflammatory mediators
         1. Prostaglandins, leukotrienes, histamine, cytokines, complement...
         ii. Suppress PG synthesis directly at level of COX pathway
         iii. Decrease vascular permeability
         iv. Inhibit clonal expansion of T and B cells
v. Inhibit fibroblast activity/scar tissue formation; may slow wound healing
vi. Stabilize membranes to prevent degranulation of mast cells, neutrophils
vii. Etc.
b. Indications:
i. Topical administration of corticosteroids is used for anterior segment inflammatory or suspected immune-mediated disease to achieve desired effects while limiting systemic absorption.
ii. Examples: immune-mediated blepharitis, suspected allergic conjunctivitis, follicular conjunctivitis, dacyrocystitis (one component of therapy), nodular granulomatous episcleritis, diffuse episcleritis, chronic superficial keratitis, presumed immune-mediated keratitis (poorly defined in dogs and cats), anterior uveitis (infectious, post-operative, lens-induced, traumatic, neoplastic, etc.), and others.
c. Precautions:
i. Effects on epithelial physiology and collagen metabolism can slow healing and potentiate stromal melting when used in the presence of corneal ulcerations.
ii. Local immunosuppression may increase risk of septic ulcerative keratitis (and fungal keratitis in equids).
iii. Topical and oral steroid administration are known to induce ocular FHV-1 reactivation in cats; I recommend avoiding topical steroids in cats unless absolutely necessary.
iv. May induce and/or exacerbate lipid +/- mineral degeneration of the cornea (steroid keratopathy) with chronic use.
v. Combination formulations with antibiotics should especially be avoided for chronic use to reduce risk of development of bacterial resistance.
vi. Should NOT be used for a red eye of unknown etiology unless keratoconjunctivitis sicca, corneal ulceration, uveitis, and glaucoma have first been properly ruled out. Too many dry eyes, glaucomatous eyes, or ulcerated eyes are treated empirically for “being red” with a topical steroid as a first line approach and develop significant complications or blindness as a result.
vii. Suppression of hypothalamic-hypophyseal-adrenal axis demonstrated with QID topical treatment with prednisolone acetate 1% and dexamethasone 0.1% in dogs. Clinical signs rarely appreciated aside from anecdotally reported increase in insulin requirements in very small diabetic patients receiving frequent topical steroids.
viii. Increase in intraocular pressure documented in humans, dogs, cats, cows with chronic use (>2 weeks).
ix. Potential for cataract induction with chronic use (documented in cats, small rodents).
d. Choice and application
Topical Application: corneal epithelium is hydrophobic, affecting absorption.

1. Therefore, while most ophthalmic formulations are effective for ocular surface disease (conjunctivitis, keratitis), efficacy for anterior uveitis varies significantly depending on the corneal penetration of each formulation:

2. “Acetates” and “alcohols” → lipophilic → good penetration
   A. Suspensions and ointments
   B. Prednisolone Acetate 1% Suspension; Dexamethasone Alcohol 0.1% (not currently available)

3. “Sodium phosphate” salts → water soluble → poor penetration
   A. Solutions
   B. 0.1% dexamethasone sodium phosphate

4. Relative corneal penetration (i.e. appropriateness of use for intraocular inflammation): hydrocortisone < dexamethasone s.p. < prednisolone acetate

Systemic Administration:
1. Adjunct treatment for uveitis, if not suspicious of infectious etiology or lymphoma (otherwise, may consider systemic NSAID depending in case/patient)
2. Indicated route (rather than topical) for most adnexal inflammatory disease (i.e. severe/suspected immune mediated blepharitis), suspected immune-mediated disease of the posterior segment/optic nerve

Summary: Topical corticosteroids are powerful tools in treatment of specific ocular inflammatory conditions, but significant potential complications and side effects occur and should be taken into consideration when selecting medications. Systemic steroids play a key role in control of select adnexal and intraocular diseases.

III. Non-steroidal anti-inflammatories:
   a. Review:
      i. Mechanism of action:
         1. General: inhibition of prostaglandin synthesis
         2. Effects within the eye: reduce blood-aqueous barrier breakdown (i.e. treat and prevent uveitis); aid in maintaining mydriasis during cataract surgery; also shown to modulate ocular surface inflammatory disease in humans, less commonly employed for this purpose in veterinary medicine (i.e. corneal neovascularization).

         ii. Rabbit iris and ciliary body demonstrated to contain both cox-1 and cox-2 receptors.

         iii. Human globes demonstrated cox-1 and cox-2 in the nonpigmented ciliary body epithelium but not elsewhere.
iv. Relatively little work in canine, feline, equine; one study demonstrated similar cox-2 expression and distribution in canine globes with and without neoplasms.

b. Indications:
   i. Topical administration of nonsteroidal anti-inflammatories is indicated largely for control of intraocular inflammation (uveitis), for example after cataract surgery. While systemic therapy may be more effective, chronic use of systemic NSAIDs is undesirable, and topical application allows us to minimize systemic effects.
   ii. There is currently no evidence that we should be using these medications for pain relief in veterinary patients. While in human medicine, several papers have demonstrated a short term (<30 minutes) anesthetic effect, a recent paper (Dorbandt et al, Veterinary Ophthalmology - E-pub April 2016) found no short or long term effects of flurbiprofen or diclofenac on corneal sensitivity in the eyes of non-brachycephalic dogs.
   iii. Examples of use in veterinary medicine: Chronic anti-inflammatory treatment for cataractous eyes not undergoing surgery, pre-and-postoperative use in eyes undergoing cataract surgery (preferable to chronic topical steroid use in diabetic patients, may be combined to reduce required frequency of topical steroid). Some clinicians use topical NSAIDs for conjunctivitis/dacryocystitis, although there is no evidence for efficacy in these conditions in veterinary species.

c. Precautions:
   i. *Corneal melting or sterile stromal keratitis* reported in humans receiving topical NSAIDs; considered to be most likely in “at risk” corneas and therefore to be used only with extreme caution and careful monitoring in cases of dry eye, reduced corneal sensitivity, corneal ulceration, patients with immune-mediated disease, diabetic patients, etc. Superficial punctate keratitis, corneal infiltrates also reported in humans.
   ii. Topical NSAIDs *delay epithelial wound healing*. For example, experimental superficial corneal ulcers in rabbits exhibited delayed epithelial healing when treated with diclofenac, flurbiprofen, or prednisolone sodium phosphate in comparison with the controls (Hersh et al 1990).
   iii. Topical NSAIDs *may exacerbate infectious keratitis*. One study showed similar negative effects of flurbiprofen and dexamethasone on experimental herpetic keratitis in rabbits, while a later paper by the same author (Trousdale, MD) refuted this finding.
   iv. Topical NSAIDS *increase IOP*. Use with caution in glaucomatous or eyes at risk of glaucoma: IOP elevation demonstrated in dogs and cats treated with topical NSAIDs; topical NSAIDs may reduce efficacy of topical PG analog antiglaucoma medications.
   v. *Systemic absorption* demonstrated in cats receiving topical NSAIDs OU 4 times daily (flurbiprofen reached higher concentrations
than diclofenac, may indicate that diclofenac is a safer choice in cats); one study demonstrated decreased GFR after 7 days QID administration 0.1% diclofenac OU to 4 cats, but this finding may have been related to hypovolemia secondary to frequent blood draws – caution was recommended in volume-contracted or systemically ill cats.

d. Choice and application

i. Topical Application:

1. Commercially available formulations:
   A. Bromfenac 0.09%
   B. Nepafenac 0.1%
   C. Ketorolac 0.4%, 0.5%
   D. **Diclofenac 0.1%**
   E. **Flurbiprofen 0.03%**
   F. Indomethacin – not available in the USA.

2. Diclofenac and flurbiprofen best evaluated in veterinary species, most widely used, most cost-effective.

3. Relative efficacy varies by study; diclofenac may be more effective than flurbiprofen, and may also persist for longer periods of time in the anterior chamber; flurbiprofen appears to have a higher degree of systemic absorption in rabbits and cats. Diclofenac may, therefore, be the preferred choice.

4. Bromfenac was demonstrated to be as effective as prednisolone acetate at controlling intraocular inflammation after cataract surgery in dogs, but is currently significantly more expensive than diclofenac or flurbiprofen. Bromfenac may result in increased risk of post-operative elevations in intraocular pressure after cataract surgery in comparison with flurbiprofen.

ii. Systemic Administration:

1. Anti-inflammatory of choice for analgesic purposes.

2. May be the most effective method of addressing intraocular inflammation with uveitis, but potential systemic side effects must be taken into consideration.

3. Should be selected over topical anti-inflammatory treatment for adnexal inflammation (eyelids, orbital, etc.).

e. Summary:

i. Topical NSAIDs are important tools in veterinary ophthalmology, but they are not indicated and, in fact, are likely **contraindicated in cases of ulcerative keratitis**.

IV. **Non-steroid Immunosuppressive/Immunomodulatory Agents**

a. Review:

i. Cyclosporine, tacrolimus, pimecrolimus, rapamycin are agents isolated from fungi that inhibit T-cell proliferation. There are suspected but poorly defined lacrimogenic effects, independent of immunosuppressive mechanisms, as well.
ii. Cyclosporine and tacrolimus are the best studied and most commonly employed at this time. Optimmune (0.2% cyclosporine ophthalmic ointment) is the only FDA approved product in this class for veterinary ophthalmic use.

iii. Topical cyclosporine has been shown to: increase tear production in dogs with keratoconjunctivitis sicca, decrease corneal blood vessel formation, reduce corneal pigmentation in dogs, increase goblet cell production of mucin (can improve dry eye symptoms even if STT value does not improve).

iv. Topical tacrolimus appears to be at least as effective as cyclosporine for management of canine dry eye, and cases refractory to treatment with cyclosporine may respond to tacrolimus.

v. Suprachoroidal cyclosporine implants can be placed surgically to reduce frequency and severity of equine recurrent uveitis flare ups in equids. Episcleral cyclosporine implants have been used experimentally and in select clinical cases for dogs with keratoconjunctivitis sicca where patients could not be treated topically or had refractory disease. Further evaluation of efficacy of episcleral implants is indicated and use is considered experimental; based on one paper, it is thought that efficacy should persist for at least 1 year.

b. Indications:
   i. Topical administration of cyclosporine or tacrolimus in veterinary medicine:
      1. Keratoconjunctivitis sicca, chronic superficial keratitis (German shepherd pannus), pigmentary keratitis, presumed immune-mediated keratitis, eosinophilic keratitis (cats and horses), nodular granulomatous episcleritis, granulomatous episclerokeratitis, superficial punctate keratitis, etc.
   ii. Oral administration:
      1. Oral cyclosporine has been used for ophthalmic immune-mediated conditions including episcleritis, extraocular myositis, immune-mediated retinopathy, uveodermatologic syndrome, etc.

c. Precautions:
   i. **Hypersensitivity reactions/ocular discomfort:** Most common with corn or olive oil preparations in my experience; per an experienced compounding pharmacist, coconut oil is tolerated best; having switched, I have had very few patients report intolerance of drops when compounding is necessary.
   ii. **Corneal squamous cell carcinoma:** While rare, this condition has been documented more frequently in dogs receiving tacrolimus or cyclosporine than in dogs not receiving either medication. However, chronic corneal inflammation was present in concurrence with medication administration, preventing a direct conclusion about a link between the administration of a topical calcineurin-inhibitor and the
development of the neoplasm. Brachycelphalic breeds also at risk of KCS were overrepresented in one case series.

iii. **Local protozoal infections:** One report indicates the rare development of localized ocular surface protozoal infections (keratitis, conjunctivitis) with chronic topical use of cyclosporine or tacrolimus in dogs (5 cases – Beckwith-Cohen et al).

iv. **Systemic absorption:** Topical calcineurin inhibitors are routinely successfully and safely used in canine and human patients. Two studies by Gilger et al in 1995, 1996 indicated that peripheral T-cell activation was affected by topical administration of cyclosporine for dry eye in dogs; Williams et al repeated the study in 2010 and found no measurable absorption or alteration in lymphocyte proliferation. Consideration of reduced dosing frequency and/or concentration of formulations may be indicated in small patients or those with known immunosuppressive or neoplastic diseases such as lymphoma.

d. Choice and application

i. **Topical Application:**

1. Cyclosporine 0.2% ophthalmic ointment (commercially available product); approved for management of chronic keratoconjunctivitis sicca and chronic superficial keratitis in dogs

   A. Compounded formulations range from 1-2%

   i. Should use OIL not AQUEOUS, as cyclosporine very poorly soluble in water.

   ii. Higher concentration for solutions vs. ointment, as contact time/absorption will be reduced.

   iii. Coconut oil anecdotally seems to cause fewer hypersensitivity reactions vs. corn, olive, etc.

   iv. IMPORTANT: consider “off label” laws if prescribing a compounded alternative to Optimmune.

   v. Also consider: compounding pharmacies are generally required to dispense patient-specific medications only. If a non-patient specific supply is to be provided, special permitting is required in CT; in NY, non-patient-specific medication compounding is illegal outside of that performed by FDA registered medication manufacturers. This means that we cannot keep stocks of compounded medications on our shelves to be dispensed to clients.

   B. KCS: 80% of cases of canine dry eye will respond to twice daily topical cyclosporine; if initial tear values are severely reduced, response rate may be lower; response may take 2-3 weeks or up to several months. Therapy must be continued indefinitely twice daily in
most cases; if excessive tearing occurs, frequency can be reduced to SID or EOD but STT values should be monitored.

2. Tacrolimus 0.02% or 0.03% in oil, in aqueous
   A. Ointment formulations can be requested, keeping in mind that this will likely increase absorption relative to solutions due to increased contact time.

   A. Appears to be currently available via Wedgewood.

e. Summary: Optimmune should be the primary prescription for canine KCS and CSK, as it is the only FDA approved formulation of an ophthalmic calcineurin inhibitor for these conditions. If off label use is elected, topical formulations of cyclosporine should be made in oil, while tacrolimus can be compounded an oil or aqueous solution. While we have years of clinical experience and several papers indicating efficacy of calcineurin inhibitors for KCS, we do not fully understand the lacrimogenic mechanism of this class of medications. Similarly, we have clinical experience with these medications for control of corneal pigmentation, but we have yet to develop an understanding of the mechanisms of pigment formation or suppression. Chronic topical use may lead to a degree of local immunosuppression permissive of local parasite proliferation and epithelial transformation to produce squamous cell carcinoma.

2: Antiglaucoma Medications in Veterinary Medicine: Focus on The Dog

I. Review:
   a. Elevated intraocular pressure in the dog primarily occurs secondary to angle closure glaucoma (primary glaucoma) or secondary glaucoma (in association with uveitis, lens luxations, intraocular neoplasms, post-intraocular surgery, hyphema, etc.).
   b. Primary glaucoma is a progressive, blinding, and painful disease in dogs, despite treatment. Unilateral pressure elevation is most common at time of first presentation for primary glaucoma in dogs, with the second eye becoming involved within the subsequent year in most cases (median 8 months). Prophylactic treatment of the “at risk” or second eye has been shown to delay the onset of elevated pressure, increasing the interval from 8 months to ~30 months in one study (Miller et al, 2000).
   c. Given that pressure increases arise secondary to reduced outflow of fluid from the eye, therapeutic targets include reduction of fluid production and improvement of fluid outflow. This is most often addressed medically, with the addition of surgical procedures depending on patient and owner factors.

II. Commonly employed antiglaucoma medications:
   a. Beta-Adrenergic Antagonists (“Beta Blockers”) (BBs)
i. Timolol 0.5% is the most commonly employed in veterinary medicine. It is nonspecific, meaning it blocks both B1 and B2 receptors. Lowers IOP by reducing aqueous humor production, although the exact mechanism has yet to be elucidated. Timolol has been shown to lower IOP in dogs, cats, and horses. However, potency is minimal when used as a sole agent in comparison with CAIs and PG analogs in veterinary species.

ii. Side effects/Contraindications:
   1. Systemic absorption is known to occur, with studies demonstrating reduced IOP and pupil diameter in the contralateral/untreated eye, as well as a reduction in heart rate in treated animals. Lower concentration formulations (0.25% timolol) may therefore be indicated in small patients (cats and dogs <20 lbs).
   2. Contraindicated in humans with severe heart failure, bronchial asthma due to cardiopulmonary effects of beta blockade. There are no documented guidelines for treatment in veterinary species with concurrent asthma, but caution is recommended in such cases.
   3. Causes reduction in pupil diameter in dogs, cats, horses (caution with pupillary block glaucoma).
   4. Generally well tolerated topically, although ocular surface irritation upon instillation and inflammation with chronic use are reported.

b. Carbonic Anhydrase Inhibitors (CAIs)
   i. The enzyme carbonic anhydrase (CA) plays a key role in production of aqueous humor at the nonpigmented ciliary body epithelium. CAIs compete with carbonic acid to inactivate the enzyme. At least 98% of the isoform CA II must be inhibited to achieve maximal IOP reduction. Topical therapy is preferred over oral, due to the significant potential side effects of systemic CAI administration. Because the mechanism of action is reduction of aqueous humor production, CAIs are safe for any type of glaucoma (primary, secondary, congenital).
   1. Topical formulations: Dorzolamide hydrochloride 2%, Brinzolamide 1%.
      a. Dorzolamide appears to be effective in dogs, cats > horses.
      b. Brinzolamide appears to be effective in dogs, horses > cats.
      c. Effectiveness is <12 hours, so TID dosing is required when used as a sole agent.
      d. Brinzolamide more costly, may be less irritating in cases where sensitivity reaction to Dorzolamide is suspected.
e. Dorzolamide 2% - Timolol 0.5% fixed combination drops are synergistic (greater degree of efficacy) and provide longer duration of effect, allowing BID dosing. Clinically, some ophthalmologists resort to TID dosing of this product when IOP begins to rise.

2. Systemic CAIs: Methazolamide 50 mg tablets; Acetazolamide – do not use due to side effects; dichlorphenamide – no longer available, significant side effects.
   a. 5 mg/kg methazolamide as effective as BID or TID dorzolamide in glaucomatous beagles in one study; 2-3 mg/kg TID more commonly recommended.

ii. Side effects:
   1. Topical 2% dorzolamide has a more acidic pH than brinzolamide, and dorzolamide is more likely to cause irritation upon topical instillation; blepharitis may be a rare side effect of dorzolamide as well, and there is some discussion of a possible relationship with reduced tear production as these are sulfonamides.
   3. Rare potential for hypokalemia, metabolic acidosis in cats receiving chronic topical CAIs.

c. Prostaglandin Analogs:
   i. Modifications of PGF2α; increase uveoscleral outflow of aqueous humor; may also increase corneoscleral (conventional) outflow; mechanism of action thought to be modulation of matrix metalloproteinase activity.
   ii. Due to cost and experience, latanoprost 0.005% (Xalatan) currently more commonly employed in veterinary medicine vs. bimatoprost or travaprost.
   iii. Efficacy:
       1. Dogs: BID more effective than SID dosing in healthy and glaucomatous dogs. This class of drug achieves the most dramatic, rapid reduction in IOP in cases of acute glaucoma in dogs.
       2. Cats: Not effective in lowering IOP in healthy cats, possibly effective in some glaucomatous patients, but effect reduced over time; causes an increase IOP in some cases; will cause marked miosis. Avoid with secondary glaucoma. Do not use as first line therapy in cats.
       3. Horses: poor or no efficacy and may exacerbate uveitis. Not recommended.
   iv. Side effects/Precautions:
       1. Miosis (dogs, cats; mixed evidence in horses; not in humans).
2. Conjunctival hyperemia in some cases.
3. Increased iris pigmentation, eyelash growth in humans.
4. BID dosing less effective than SID dosing in humans; while BID dosing considered more effective than SID in dogs, we do not have evidence to show that TID is more effective than BID and it is possible that the reverse could be true. I do not recommend latanoprost administration above BID for this reason.

v. Contraindications:
   1. Absolute contraindications: Anterior lens luxation, feline aqueous humor misdirection syndrome, other causes of pupillary block glaucoma – miosis will exacerbate IOP elevation in such cases.
   2. Case-dependent contraindications: Anterior uveitis – PG analogs have the potential to exacerbate uveitis and miosis is also not desirable in the face of uveitis due to risk of axial posterior synechia formation. However, when IOP elevation is significant and nonresponsive to CAIs, PG analogs may be required.

d. Other miotics:
   i. Parasympathomimetic topical ophthalmic preparations cause miosis and reduction in IOP via increase in aqueous humor outflow. Generally require more frequent dosing, have more side effects, and are less easily obtained than PG analogs, CAIs, and BBs.
   ii. Direct acting: Pilocarpine 1% or 2%: low pH associated with irritation upon topical administration; associated with significant “brow ache” in humans; may require QID dosing (duration of effect <8 hours).
   iii. Indirect-Acting (anticholinesterases): Demecarium bromide can be compounded at 0.125% and 0.25%; long lasting miosis and moderate IOP reduction; requires BID dosing to avoid IOP spikes.

iv. Side effects:
   1. Marked miosis.

v. Contraindications:
   1. As for PG analogs – pupillary block, uveitis
   2. Topical sensitivity

e. Hyperosmotics: Dehydrate the vitreous to decrease IOP; transient effect only; contraindicated in patients with cardiovascular disease or renal insufficiency. Because effect is transient, the clinical utility of this approach is solely to achieve an abrupt reduction in IOP to alleviate ongoing damage to the optic nerve whilst allowing time for topically applied antiglaucoma medications to take effect. In some cases, a severely elevated IOP may be refractory to topical medications alone, but topical medications can later
maintain a reduced IOP once achieved by administration of hyperosmotics (or aqueous centesis).

i. Mannitol – 1-2 g/kg; given slowly IV over 20-30 min; withhold water for 4 hours for best results; effect may last 6-10 hours.

ii. Glycerin – 1-2 g/kg PO/d, water restriction for best results; nausea common; contraindicated in diabetic patients. Generally poor documentation of efficacy in the literature.

III. General protocols

a. Canine primary glaucoma is most frequently treated with a combination of the following:
   i. TID Dorzolamide +/- BID Timolol
      OR
   ii. BID-TID Dorzolamide-Timolol Fixed Combination
      AND
   iii. BID Latanoprost when necessary (i.e. markedly elevated IOP upon initial presentation or development of elevated IOP in an eye receiving a CAI +/- BB)

b. The safest medication is a topical CAI such as dorzolamide, appropriate for use in any patient with any type of glaucoma.

c. The most effective medication for immediate reduction of elevated IOP in acute glaucoma is a PG analog such a latanoprost, but this must be avoided if there is a possibility that the glaucoma is secondary to anterior lens luxation or other causes of pupillary block.

d. In order of potency for canine glaucoma:
   i. timolol < dorzolamide < dorzolamide-timolol combination < latanoprost

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3: Ophthalmic Medications for Treatment of Ulcerative Keratitis and Uveitis

I. Ulcerative keratitis and reflex uveitis in small animals:

   a. Frequency and choice of topical therapy is dependent on the nature of the corneal ulceration and degree of secondary/reflex uveitis:
      i. Superficial ulcers: after ruling out ongoing underlying causes, topical treatment aims to prevent infection, alleviate discomfort.
      ii. Deep/stromal ulcers: topical treatment aims to treat infection, halt the process of keratomalacia (corneal melting)/stromal loss, alleviate discomfort. Point of care cytology is important for initial selection of topical microbial therapy, and corneal culture and sensitivity testing is highly recommended.
      iii. Therefore, superficial ulcers frequently only require prophylactic TID topical antibiotic therapy +/- QD-BID atropine +/- systemic analgesic therapy, whereas presumably infected stromal ulcers require therapeutic administration of topical antimicrobials and matrixmetalloproteinase inhibitors every 1-6 hours, atropine every 12-24 hours, systemic NSAIDs if tolerated, +/- systemic opioids. Frequency of
treatment with stromal ulcers is dictated by subjective assessment of severity of active stromal loss and reflex uveitis.

b. Commonly Employed Antibiotics for Topical Ophthalmic Use:
   i. Review:
      1. The most common organisms resulting in septic ulcerative keratitis are Staph spp (S. intermedius), Strep spp (often beta-hemolytic), and Pseudomonas aeruginosa.
      3. Bactericidal: Aminoglycosides, Bacitracin, Cephalosporins, Fluoroquinolones, Polymyxin B.
   ii. Cefazolin (first generation cephalosporin) – 50 mg/mL in artificial tear solution; keep refrigerated. Not commercially available, can be compounded.
      1. First generation cephalosporin
      2. Spectrum:
         a. Primarily gram positive infections, such as Streptococcus spp., Staph. intermedius.
         b. No efficacy against P. aeruginosa.
      3. Side effects: potential to delay wound healing due to epithelial toxicity. Potential for hypersensitivity reaction if administered systemically; I am not aware of documented systemic hypersensitivity reaction upon topical administration in any species, although such reactions to intravitreal injection of cephalosporins have been documented in humans.
   iii. Bacitracin:
      1. Spectrum: Gram positive – such as S. intermedius, beta-hemolytic Strep. spp.
      2. Indications: superficial ulcers only, as this medication has poor corneal penetration. Combination with neomycin and polymyxin B in ophthalmic ointment provides a broad spectrum therapeutic for superficial ulcers.
      3. Side effects: potential local hypersensitivity reaction.
   iv. Polymyxin B:
      1. Spectrum: Gram negative – such as P. aeruginosa.
      2. Indications: superficial ulcers only, as this medication has poor corneal penetration. Combination with neomycin and Bacitracin in ophthalmic ointment provides a broad spectrum therapeutic for superficial ulcers.
      3. Side effects: potential for local hypersensitivity reaction.
   v. Gramicidin:
      1. Spectrum: Gram positive.
      2. Stable in solution, thus replaces Bacitracin in triple antibiotic solutions (neopolyGRAM is a solution, neopolyBAC is an ointment).
      3. Side effects: Potential for delayed wound healing due to epithelial toxicity.
vi. Aminoglycosides: Neomycin, Gentamicin, Tobramycin
   1. Spectrum: strong efficacy for gram negative organisms such as P. aeruginosa; also effective against Staph spp (not MRSA), but otherwise poor gram positive efficacy.
   2. Should not be combined in the same vial with beta-lactam antibiotic (such as cefazolin), as the beta-lactam can inactivate the aminoglycoside.
   3. Neomycin:
      a. Poor corneal penetration – use prophylactically for superficial ulcers/surface ocular infections.
      b. Contact hypersensitivity not uncommon – avoid if history of hypersensitivity reaction.
      c. Anecdotal/poorly documented reports of anaphylaxis in cats, therefore avoided in cats by many ophthalmologists.
   4. Gentamicin 0.03%
      a. Poor choice potentially as a sole agent in prophylaxis due to lack of gram positive efficacy.
      b. Significant potential for epithelial toxicity/delayed wound healing – avoid high frequency application.
   5. Tobramycin:
      a. Similar to gentamicin – evidence suggests good efficacy for Pseudomonas, S. intermedius, poor for Strep.
      b. Mixed evidence regarding potential for delayed wound healing.

vii. Oxytetracycline
   1. Spectrum: Good for Chlamydophila, less reliable for Staph and Strep spp due to potential for resistance, poor for Pseudomonas.
   2. Formulated as Terramycin, containing oxytetracycline and polymyxin B.
   3. Indication in ulcerative keratitis: refractory/indolent/Boxer type ulcers have been shown to heal more quickly after debridement when treated with oxytetracycline/polymyxin B TID vs oral doxycycline, oral cephalaxin, or topical neopolybac. This may be related to the MMP-inhibiting effects of tetracyclines, as well as the fact that tetracyclines are known to have anti-inflammatory and free radical reducing properties.

viii. Erythromycin:
   1. Spectrum: Gram positive.
   2. Limited literature documenting efficacy against corneal pathogens; primarily used for feline mycoplasma and Chlamydophila conjunctivitis.

ix. Chloramphenicol:
   1. Spectrum: Broad – gram positive, gram negative, Chlamydophila, Mycoplasma; POOR for Pseudomonas aeruginosa.
   2. Little epithelial cytotoxicity.
3. Contraindications: Human exposure should be avoided due to the potential for bone marrow suppression or aplastic anemia, although risk is considered to be low even with topical administration in humans.

x. Ciprofloxacin, ofloxacin: Second generation fluoroquinolones
   1. Reserve for use in stromal/infected corneal ulcers to reduce prevalence of resistance.
   2. Spectrum: Broad - good for pseudomonas and some gram positive organisms, although development of resistance has been well documented.
   3. Good corneal penetration and relatively broad spectrum make ciprofloxacin or ofloxacin excellent choices for monotherapy in stromal (presumed infected) corneal ulcers.
   4. Some clinicians combine with cefazolin to improve gram positive coverage, depending on cytology findings and clinical progression.
   5. Side effects: potential for delayed wound healing.

xi. Gatifloxacin, moxifloxacin: Fourth generation fluoroquinolones
   1. Reserve for use in severe stromal/infected corneal ulcers to reduce prevalence of resistance.
   2. Spectrum: Improved gram positive spectrum vs Ciprofloxacin and Ofloxacin, with reduced efficacy against Pseudomonas.
   3. Development of resistance to fourth generation fluoroquinolones is less likely, as two mutations are required.
   4. Significantly more costly than second generation fluoroquinolones at this time.

xii. Examples of empiric treatment for stromal corneal ulcers:
   1. Cipro- or ofloxacin +/- cefazolin – I routinely use ciprofloxacin as primary agent for these cases, adding cefazolin if I am not happy with response to therapy or in some cases if numerous cocci are present on cytology.
   2. Moxifloxacin or gatifloxacin (reserve for very severe cases).
   3. If fluoroquinolones not available:
      a. Tobramycin or gentamicin + cefazolin

c. Antiproteolytics for stromal ulcerative keratitis:
   i. Proteinases released from migrating leukocytes and bacteria can result in further loss of corneal stroma, and interruption of this process is an important therapeutic target. In general, the more severe the ulcer, the more frequently I apply both topical antiproteolytics and antibiotics, prioritizing both. Initial therapy for a severely malacic ulcer might involve q1 hour treatment with topical antimicrobials and antibiotics for 6 hours, followed by q2-4 hours for 48 hours/until the disease process appears to be stable or improving, after which therapy is reduced to q6 hours.
   ii. **Autologous serum:** Frequently also collected from a healthy donor (i.e. allogeneic, not autologous). Recently, I have transitioned to using pre-made 5 ml frozen aliquots of frozen plasma, as equivalent efficacy has
been demonstrated. Care with sterility in preparation of serum or plasma and client education on constant refrigeration and monitoring for development of signs of contamination is important. We recommend discarding a vial after 2 weeks.

iii. **N-acetylcysteine**: compounded as a 5-10% solution in saline or artificial tears.

iv. **EDTA**: Compounded as a 0.2% solution.

v. **Tetracyclines** (topical oxytetracycline; oral doxycycline): As I recommend avoiding the use of ointment in any stromal corneal ulcer, I do not use terramycin for this purpose. I do administer oral doxycycline in some cases in addition to use of autologous serum or frozen plasma.

d. **Cycloplegics/Mydriatics**:

i. To relieve ciliary muscle spasm and associated discomfort, photosensitivity that occurs with reflex uveitis secondary to keratitis, and reduce risk of posterior synechia formation.

ii. **Atropine Sulfate 1% Ophthalmic Solution**: Cholinergic antagonist.

1. Maximal dilation occurs at ~1 hour in dogs, effect may last up to 5 days. Effect depends on degree of uveitis, with increased number of doses and slower onset of mydriasis in more severely inflamed eyes.

2. Indications in ulcerative keratitis: suspected reflex uveitis (miosis, flare, hypopyon, keratic precipitates, etc) to alleviate discomfort; additionally, to reduce the risk of posterior synechia formation.

3. Contraindications/side effects:
   a. Keratoconjunctivitis sicca
   b. Glaucoma
   c. Copious salivation may occur in cats (and reportedly dogs) — therefore, ointment formulation (to minimize run off into NL system/pharynx) is preferred for cats with the exception of those with very deep or perforating corneal lesions, where the risk of ointment entering the anterior chamber outweighs the risk of salivation and a solution should be employed.
   d. Contact hypersensitivity reactions, rare.
   e. Topical atropine rarely reported to be associated with delirium in humans, older dogs (circling that resolves with discontinuation of treatment).

iii. **Tropicamide**: While useful for examination purposes, duration of action is short and thus tropicamide is not useful in relief of ciliary muscle spasm for cases of reflex uveitis.

e. Systemic anti-inflammatory, analgesic medications indicated depending on perceived degree of reflex uveitis and patient discomfort.

II. **Uveitis in Small Animals**

a. Systemic evaluation and treatment must aim to determine and address underlying cause.

b. Symptomatic treatment can be initiated concurrently:
i. Combine topical and systemic anti-inflammatory agents.
   1. Topical: NSAIDs, steroids; BID-QID depending on severity.
   2. Systemic: NSAIDs, steroids; choice may depend on suspicions regarding underlying cause – i.e. infectious vs. neoplastic (lymphoma).

ii. Topical mydriatic therapy, as described above for reflex uveitis.

4: Comprehensive Treatment of Dry Eye

I. Therapeutic goals in treatment of keratoconjunctivitis sicca (focus on the dog):
   a. Increase aqueous tear production.
   b. Alleviate discomfort and ongoing trauma/exposure associated with inadequate tear film coverage of the ocular surface.
   c. Control/prevent bacterial overgrowth arising secondary to impaired ocular surface immunity and reduced removal of organisms due to tear film deficiency.
   d. Reduce/eliminate ocular discharge.
   e. Control ocular surface inflammation/keratitis.

II. Treatment options to increase production of aqueous tears:
   a. Topical calcineurin inhibitors – see section on topical immunomodulatory medications, above, for more detail.
   b. BID 0.2% cyclosporine ointment (Optimmune, the approved product), 2% cyclosporine in oil (coconut preferred), 0.02-0.03% tacrolimus in oil or aqueous.
   c. Note that clinical improvement may occur in severe cases despite lack of improvement in STT value, possibly due to increase in conjunctival goblet cells.
   d. Client education critical, as 4-6 weeks of treatment may be required before a significant effect is detected. Additionally, many clients discontinue medications once improvement is noted, not understanding that this is a life-long, autoimmune disease.

III. Supplementation of tears:
   a. Improve lubrication, comfort, vision; reduce risk of further corneal disease/ulcerative keratitis.
   b. Preservative free (single use vials) preferred when frequent use needed, as preservatives can be epitheliotoxic; practically, preservative-containing artificial tear products are more easily accessible and less costly, and their benefits seem to outweigh potential harm.
   c. Numerous options available commercially. Increased viscosity associated with longer duration of effect (solutions < gels < ointments).
      i. Genteal gel for severe dry eye is available over the counter, easy to administer.
      ii. If severe KCS, I generally use an ointment (paralube, Rugby artificial tear ointment, genteal ointment for overnight use, etc.).
iii. Aqueous tear supplementation is abundant in the human market, as humans can apply medications as frequently as needed and the aqueous solutions cause less visual disturbance vs. ointments or gels. In my experience, there is not often a good indication for these products in veterinary medicine.

iv. Products containing sodium hyaluronate may have additional beneficial effects, including improved wound healing.

d. Autologous serum: Not frequently employed in veterinary medicine, but shown to be effective for improving ocular surface health and discomfort in humans.

IV. Treatment options to control/prevent bacterial overgrowth:

a. Topical antimicrobials are not required in all cases, and certainly not recommended indefinitely. However, including an antimicrobial in initial therapy for a KCS patient with severe mucopurulent ocular discharge will result in more rapid and dramatic improvement.

i. Neopolybac or neopolygram, gentamicin, tobramycin, etc. Do not reach for fluoroquinolones, as we like to reserve these for stromal ulcers. TID dosing recommended.

b. Flushing the eyes with unmedicated over the counter eye wash is tolerated surprisingly well by some patients.

c. Artificial tear supplementation.

V. Ameliorating mucoid ocular discharge:

a. Frequent cleaning and flushing of the ocular surface.

b. N-Acetylcysteine – 5-10% solution BID-QID can result in remarkable and swift improvement in clinical signs in my experience, which tends to improve owner compliance as they see rewarding results.

VI. Antiinflammatory therapy:

a. Addition of topical corticosteroids is helpful in some cases, but caution should be used, as eyes with KCS are also prone to development of corneal ulcerations.

b. Most importantly, eyes with KCS may show initial improvement in response to topical steroids alone, but these should never be used chronically as sole therapy; without concurrent initiation of lacrimostimulants (cyclosporine, tacrolimus) to improve the patient's own tear production, this therapy is simply masking the disease and leaving the patient at risk of complications.

VII. Pilocarpine:

a. For neurogenic KCS only – confirmed with concurrent diagnosis of ipsilateral xeromycteria (dry nose), but may also affect lacrimal innervation alone depending on the site of the neurologic lesion.

b. Potential for SLUD (salivation, vomiting, diarrhea, cardiac arrhythmias, etc.) toxicity with oral administration, therefore recommendations are to start with very low doses (1 drop 2% PO on food BID per 10 kg body weight, then increase 1 drop at a time - 2 drops SID/1 drop BID, 2 drops BID, then TID, etc.), gradually increasing dosage until tear production improves or SLUD is noted.
c. Alternately (and the way I practice), dilute pilocarpine can be compounded for topical use. Compounded 0.125% or 0.25% pilocarpine applied topically q8 is generally well tolerated (as opposed to full strength pilocarpine, which is quite irritating) and without observable systemic side effects. Important to stress to owners that medication must be administered the morning of recheck, as tear production is being stimulated by each dose, not sustained over time.

d. Reported side effects of topical pilocarpine include miosis and ocular surface irritation, but I have not seen this clinically at the concentrations indicated above.

5: Focus on Felines: Herpetic Keratoconjunctivitis and Eosinophilic Keratitis

I. Therapeutics for Herpesvirus keratoconjunctivitis:

a. Review: FHV-1 infects epithelial cells, including those of the respiratory tract, conjunctiva, and cornea. Cell lysis occurs after viral replication, damaging the tissue and leading to inflammation (largely neutrophilic). Primary infection is most common in young kittens, who then become latent carriers at risk of viral recrudescence later in life. Studies have shown seropositivity in 80-90+% of surveyed cats. FHV-1 keratoconjunctivitis or conjunctivitis varies in severity and may be unilateral or bilateral. Topical and oral steroid administration has been shown to trigger viral reactivation in carriers, and stressful events may be associated with flare-ups in some patients. For this reason, topical steroid administration should be avoided in cats unless absolutely necessary. Cytology can be helpful in some cases to rule out Chlamyphilia felis conjunctivitis. Corneal ulcers caused by FHV-1 are superficial; while punctate and dendritic ulcers are classic findings of FHV-1, this stage is frequently missed clinically, and patients present with geographic regions of ulceration. Other conditions may arise secondarily, including stromal keratitis and corneal sequestration.

b. The most easily obtained and frequently employed topical antivirals for treatment of feline viral keratoconjunctivitis are currently idoxuridine and cidofovir.

i. Idoxuridine: 0.1% compounded solution – generally well tolerated but not well studied in cats. Requires frequent application (6+ times daily for first 48 hours).

ii. Cidofovir: 0.5% compounded solution – metabolites remain within cells for significant period of time, creating a depot effect, with efficacy demonstrated at BID dosing.

iii. Trifluridine is the only commercially available topical antiviral, and is effective against FHV-1 in vitro; it is reportedly poorly tolerated topically in cats.

c. Famciclovir (oral): Significant reduction in clinical signs and viral shedding have been demonstrated experimentally, and excellent clinical responses are reported anecdotally with this treatment. The current
pharmacodynamics/pharmacokinetics studies indicate a dose of 40 mg/kg TID should be adequate to achieve therapeutic tear film levels. Clinically, due to expense and initial lack of data, many ophthalmologists and veterinarians have employed much lower doses (frequently administering ¼ of a 125 mg tablet BID-TID PO per cat) with good success. Tiny tabs (62.5 mg) from Wedgewood are based on administration of ½ of a 125 mg tab and one study showed clinical improvement at this dose. Famciclovir is generally quite safe in cats, whereas other human antiviral medications are not, and should not be substituted for famciclovir therapy. Famciclovir has become a mainstay of therapy for FHV-1 ocular surface disease. The safety of chronic use has not been evaluated.

d. If anti-inflammatory therapy is needed, topical cyclosporine may be beneficial, but this is controversial amongst veterinary ophthalmologists. Optimmune has been shown to ameliorate clinical signs, but others are not comfortable with immunosuppression in the face of viral reactivation.
e. Topical steroids are absolutely contraindicated.
f. Interferon: May protect uninfected cells, some evidence of shortened disease course and reduced severity in humans and of reduced viral activity in vitro with feline corneal epithelial cells. This therapy is favored by some ophthalmologists and discredited by others.
g. L-Lysine: Mixed results from different studies, some indicating amelioration of disease course or severity, some indicating no effect or even exacerbation of clinical signs. I generally do not dissuade clients from use of L-Lysine, but I also do not actively encourage it.

II. Therapeutics for feline eosinophilic keratitis:
a. Review: This disease presents with unilateral or bilateral keratoconjunctivitis including distinct, granular, raised white plaques on the corneal or conjunctival surface that contain few or many eosinophils and mast cells (amongst lymphocytes, plasma cells, and neutrophils) on cytology. Degree of discomfort is variable. Client education is important, as this is a disease that is controlled, not cured, and lifelong therapy at some minimal frequency will be required once initial control of disease is achieved.
b. Once confirmed cytologically, this is a rare exception to the rule of avoiding topical steroids in cats, as steroids are indicated. Combination of topical steroids and cyclosporine may allow more rapid tapering of topical steroids once the disease is controlled, and long term remission can often be maintained with once daily or every other day cyclosporine. Initial therapy consists of BID-TID topical steroid and cyclosporine, depending on severity of disease, with a recheck at 3-4 weeks, and tapering of topical steroid prior to cyclosporine. If active ulceration is present, initial therapy may consist of cyclosporine alone, or cyclosporine and a topical non-steroidal anti-inflammatory, and a slower response to therapy should be expected.
c. Historically (and currently), some veterinarians and ophthalmologists have employed systemic megestrol acetate for control of eosinophilic keratitis (5 mg/d for 5d, then 5 mg EOD for 7 days, then once weekly for maintenance).
However, the risk of inducing diabetes mellitus and neoplasia, as well as responsiveness of most cases to topical medications, call this therapy into question. More recently, clinicians have begun to employ and report success with topical megestrol acetate, with one pilot study showing an 88% response rate to treatment with 0.5% topical megestrol acetate q8-12 hours and long term control of disease with once daily to once weekly application (Stiles et al 2016).

Selected References


