CORTICOSTEROIDS

Corticosteroids consist of glucocorticoids and mineralocorticoids. Glucocorticoids (GC) influence metabolic and immune functions, while mineralocorticoids (MC) are responsible for electrolyte and water balance, primarily through influencing sodium retention/excretion in the kidney. Glucocorticoids are extremely effective anti-inflammatory agents, with multiple synthetic agents available based on the endogenous form, cortisol (hydrocortisone is the pharmacologic equivalent of cortisol). The physiologic effects of GC are widespread and non-specific, and include anti-inflammatory functions (i.e., decreased cellular and fibrinous exudation and tissue infiltration, decreased neovascularization, decreased capillary permeability) and effects on tissue regeneration and repair (i.e., decreased fibroblastic and collagen formation reactions, decreased epithelial and endothelial regeneration). These effects are produced via plasma protein-mediated transport of the GC to the cell, following by entry into and subsequent binding of the GC to the cytosolic GC receptor protein, the nature of which determines the sensitivity of an individual cell to GC. Glucocorticoids bind to this receptor and form a receptor-ligand dimer, which translocates to the nucleus to bind hormone responsive elements (HREs), or glucocorticoid response elements (GREs), located within the genomic DNA. Binding to the genomic DNA either increases (transactivation) or decreases (transrepression) gene expression, ultimately leading to the cellular effects of GC.

In general, anti-inflammatory genes (i.e., lipocortin) and genes modulating gluconeogenesis (i.e., glucose-6-phosphatase) are upregulated, while pro-inflammatory genes (i.e., interleukins, chemokines, cytokines) are downregulated in response to GC. Increased expression of lipocortin results in inhibition of phospholipase A₂, ultimately preventing biosynthesis of arachidonic acid, prostacyclin, thromboxane A₂, prostaglandins, and leukotrienes, all of which are mediators of inflammation. In addition to these genomic effects, GC reduce leukocyte migration to sites of inflammation, as well as stabilize lysosomal membranes, possibly via a cAMP-mediated effect. This stabilization effectively blocks white blood cell (neutrophil, mast cell, basophil) degranulation, decreasing the release of additional proinflammatory components such as proteases, histamine, and bradykinin. Vascular effects of GC include inhibition of angiogenesis and reduction of capillary permeability. Effects of GC on tissue regeneration and repair include decreased fibroblastic and keratocytic activity, increased collagenolytic activity, and inhibition of wound healing (including epithelial and endothelial regeneration).

The cellular effects of GC are exerted in response to virtually any type of inflammation, whether allergic, infectious, or traumatic, stimulating all aspects of their physiologic actions equally and resulting in situations in which the beneficial effects may be overcome by negative effects (i.e., reduced migration and activation of leukocytes in the presence of infection may limit the harmful effects of inflammation, however reduced host defenses in turn may potentiate infection in the absence of appropriate antimicrobial therapy).

The potency of a GC is determined by its base chemical structure, concentration, and dosage, all of which determine the strength of the binding to the transport protein, receptor, and DNA. The goal with therapy for inflammatory diseases is to utilize a corticosteroid with maximal anti-inflammatory (GC) effect and minimal MC effect, thus avoiding the electrolyte and water imbalances that occur with MC therapy. The MC effect is related to the relative sodium-retaining activity, compared to a value designation of 1 for cortisol/hydrocortisone (Table 1). Agents with lower sodium retention thus have less effect on water balance than do those with greater sodium retention.
Table 1. Relative Potencies of Commonly Encountered Corticosteroids (Adapted from Sendrowski DP et al., in Clinical Ocular Pharmacology1).

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Anti-inflammatory Potency</th>
<th>Sodium Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>20.0</td>
<td>125.0</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Ocular Bioavailability of Topical Steroid Preparations

The efficacy of a topically applied ophthalmic corticosteroid depends upon multiple drug- and patient-related factors, which influence transcorneal and intraocular penetration and anti-inflammatory activity. Of the drug-related factors, the base steroid and its relative potency, concentration, and formulation are critical, while patient-related factors include frequency and route of administration and presence of surface ocular disease.

As with all topical ophthalmic drugs, biphasic (lipid-soluble and water-soluble) preparations best penetrate the alternating hydrophobic-hydrophilic-hydrophobic corneal layers, and therefore are expected to achieve the greatest corneal tissue and intraocular levels. The solubility of individual steroids is manipulated by altering their chemical structures, with acetate derivatives the most lipophilic, alcohol derivatives of intermediate solubility, and salts (sodium phosphate or hydrochloride) the most hydrophilic.2-4 The derivative frequently dictates the ideal formulation, with hydrophilic derivatives more likely formulated as solutions and lipophilic derivatives more likely formulated as suspensions or ointments. While increasing the concentration of a topical ophthalmic medication frequently increases its clinical efficacy, prednisolone acetate 1.5% and 3.0% are no more efficacious at reducing inflammation than is prednisolone acetate 1.0%, even in the presence of greater intraocular penetration, in a rabbit model of corneal disease.5 If greater clinical efficacy is desired, the frequency of administration may be increased or the route of administration altered to achieve this goal.

A few interesting points regarding topical ophthalmic corticosteroids should be considered. The first is that, while dexamethasone and betamethasone are significantly more potent than prednisolone (Table 1), prednisolone acetate preparations have superior intraocular penetration and are thus better at controlling anterior uveitis (versus superficial inflammatory disease with dexamethasone or betamethasone).5 Additionally, while prednisolone acetate penetrates the intact corneal epithelium better than prednisolone phosphate, the phosphate derivative has superior penetration in the presence of corneal ulceration.3 This variation in penetration, while significant, should be considered in light of the relative anti-inflammatory efficacy, which indicates that prednisolone acetate is superior both in the presence and absence of the corneal epithelium, based on comparisons using a rabbit model of corneal inflammation (Table 2). This is highlighted by the greater bioavailability of dexamethasone phosphate preparations relative to alcohol or acetates, in contrast to the consistently superior anti-inflammatory activity of the acetate derivative (Table 2).
Table 2. Comparison of the Derivative of Ophthalmic Corticosteroids with Corneal Concentration (Adapted from Sendrowski DP et al., in Clinical Ocular Pharmacology)

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Epitheliun Intact</th>
<th>Epithelium Absent</th>
<th>Bioavailability (mcg/min/g corneal tissue)</th>
<th>Anti-Inflammatory Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone acetate 1%</td>
<td>X</td>
<td></td>
<td>2,395</td>
<td>51</td>
</tr>
<tr>
<td>Prednisolone acetate 1%</td>
<td></td>
<td>X</td>
<td>4,574</td>
<td>53</td>
</tr>
<tr>
<td>Prednisolone phosphate 1%</td>
<td>X</td>
<td></td>
<td>1,075</td>
<td>28</td>
</tr>
<tr>
<td>Prednisolone phosphate 1%</td>
<td></td>
<td>X</td>
<td>16,338</td>
<td>47</td>
</tr>
<tr>
<td>Dexamethasone acetate 0.1%</td>
<td></td>
<td>X</td>
<td>111</td>
<td>55</td>
</tr>
<tr>
<td>Dexamethasone acetate 0.1%</td>
<td></td>
<td>X</td>
<td>118</td>
<td>60</td>
</tr>
<tr>
<td>Dexamethasone alcohol 0.1%</td>
<td>X</td>
<td></td>
<td>543</td>
<td>40</td>
</tr>
<tr>
<td>Dexamethasone alcohol 0.1%</td>
<td></td>
<td>X</td>
<td>1,316</td>
<td>42</td>
</tr>
<tr>
<td>Dexamethasone phosphate 0.1%</td>
<td></td>
<td>X</td>
<td>1,068</td>
<td>19</td>
</tr>
<tr>
<td>Dexamethasone phosphate 0.1%</td>
<td></td>
<td>X</td>
<td>4,642</td>
<td>22</td>
</tr>
</tbody>
</table>

**Dexamethasone**

Dexamethasone is a long-acting synthetic corticosteroid, available as 0.1% alcohol or phosphate derivative suspensions or solutions, or as a 0.05% phosphate derivative ointment. The anti-inflammatory efficacy of the alcohol is superior to that of the phosphate derivative. Within 30 minutes of topical administration of either the alcohol or phosphate form, dexamethasone is detectable within the human aqueous humor, with peak drug levels occurring between 90 and 120 minutes. The persistence of detectable levels for up to 12 hours suggests that metabolism of dexamethasone in the human aqueous humor is minimal.

**Betamethasone**

Betamethasone is a long-acting synthetic corticosteroid, available as a 0.1% phosphate solution.

**Prednisolone**

Prednisolone is an intermediate-acting synthetic corticosteroid, available as 1% or 0.125% acetate suspension and 1% or 0.125% phosphate solution (Ak-Pred, Inflamase). The acetate derivative has superior anti-inflammatory activity to the phosphate derivative, and is considered the most effective drug for anterior uveitis.

**Evaluation in dogs**

Two pre-operative medication protocols in dogs undergoing cataract surgery were evaluated in a recent study, comparing administration of 1 drop of 1% prednisolone acetate q8h for seven days prior to surgery with administration of 1 drop three times the evening prior to surgery and four times the morning of surgery. Assessment of blood-aqueous barrier breakdown by anterior chamber fluorophotometry performed pre-operatively and 2 and 9 days post-operatively, along with subjective clinical assessments, found no significant difference in control of post-operative inflammation between the two treatment groups. A significantly greater incidence of postoperative ocular hypertension was found in dogs receiving prednisolone acetate for one week prior to surgery, when IOP was measured 4 and 8 hours post-operatively.

**Evaluation in cats**

Anterior chamber paracentesis was used to induce blood-aqueous barrier disruption in both eyes of normal cats, and was followed by unilateral application of a single dose of either 1% prednisolone acetate, 0.1% dexamethasone, 0.03% flurbiprofen, of 0.1% diclofenac immediately and at 6, 10 and 24 hours post-paracentesis (the contralateral eye served as an untreated control). Flare was measurement using a laser-flare meter at 4, 8, and 26 hours post-paracentesis, and the relative ability of each anti-inflammatory was assessed. A significant reduction in flare at all three time points was associated only with 1% prednisolone acetate; diclofenac 0.1% significantly reduced flare at the 8- and 26-hour timepoints; 0.1% dexamethasone significantly reduced flare at the 4-hour timepoint; and flurbiprofen 0.03% did not significantly reduce flare at any timepoint.
**Triamcinolone**

Triamcinolone acetonide is an intermediate-acting synthetic corticosteroid, with the primary uses in ophthalmology being subconjunctival injection for anterior segment inflammatory diseases or intravitreal injection for posterior segment inflammatory disease. As a very hydrophobic molecule, it has a long residence time following injection, thereby conferring a long duration of action (up to 5-6 months in humans following intravitreal injection).8

**Evaluation in dogs**

Intravitreal injection of triamcinolone acetonide (8 mg once) in the normal eyes of research dogs under sedation documented an increase in IOP in all eyes immediately following injection (also occurred in eyes receiving intravitreal saline control), as well as visible drug crystals within the vitreous.9 In the 3 months following injection, no increase in IOP was documented, and the crystals remained in 5/11 eyes. Conjunctival hyperemia was the most significant side effect of injection.

**Evaluation in horses**

Intravitreal injection of 10 mg, 20 mg, or 40 mg of triamcinolone acetonide in normal horses resulted in sustained drug ocular concentrations for a minimum of 3 weeks following injection.10 All eyes had transient corneal edema, and 33% (4 eyes, 1 treated and 3 control) developed bacterial endophthalmitis. Additionally, no significant differences in IOPs or ERG parameters of treated or control (BSS) eyes were documented.10

**Fluorometholone**

Fluorometholone is a structural analogue of progesterone (rather than cortisol), available as a 0.1% alcohol ointment or suspension, a 0.25% alcohol suspension, or a 0.1% acetate suspension (FML Forte Liquifilm®, FML Liquifilm®, FML S.O.P®). The anti-inflammatory efficacy of fluorometholone alcohol is slightly lower than that of prednisolone acetate or dexamethasone alcohol, while that of the acetate derivative is comparable to prednisolone acetate.1 Its tendency to raise IOP is lower at 0.1% concentration, but increases with the 0.25% concentration.

**Medrysone**

Medrysone is also a synthetic derivative of progesterone available as a 1.0% suspension (HMS®), and has lower corneal penetration and clinical efficacy, demonstrating minimal effect on intraocular (versus surface ocular) inflammation.

**Loteprednol etabonate**

Loteprednol etabonate is a soft drug, meant to decrease drug-related side effects, available as a 0.5% suspension (Lotemax®) and 0.2% suspension (Alrex®). A soft drug is one that is synthesized from an inactive, nontoxic metabolite of an active drug. Modification of the inactive metabolite creates a metabolically unstable active compound that is transformed in vivo to the inactive metabolite, after its pharmacologic effects have been expressed at the desired site of action. In placebo-controlled clinical trials, loteprednol etabonate demonstrated good clinical effect in patients with conjunctivitis, while its effect in the treatment of acute anterior uveitis, while evident, was less than that of prednisolone acetate.1 A benefit of loteprednol etabonate is its reduced risk of inducing an IOP elevation.11-13

**Rimexolone**

Rimexolone is available as a 1% suspension (Vexol®) that has comparable efficacy to prednisolone acetate for the treatment of uveitis only when administered in aggressive pulsed doses to patients with mild to moderate inflammation.1

**Side Effects**
Ocular side effects of ophthalmic corticosteroids can be numerous, including the development of cataracts, increased IOP, infection, decreased wound healing, mydriasis, and calcific keratopathy. While these side effects may be frequent in humans, some are less common in animals. With the exceptions of mydriasis and calcific keratopathy, these side effects may occur in association with systemically administered corticosteroids as well.

Systemic side effects of topical ophthalmic corticosteroids include glucocorticoid-induced hepatopathy, suppression of endogenous glucocorticoid production, or local alopecia. It is important to note that such side effects occur more readily with systemic administration of corticosteroids, but occur in a dose- and duration-dependent manner following topical ophthalmic administration. Following administration of topical 0.1% dexamethasone ointment to normal horses every 5 to 9 hours for 8 days, dexamethasone was detectable in the serum and urine for up to 1 day following cessation of therapy. In calves, dexamethasone administered parenterally in an experimental situation resulted in bilateral exophthalmos due to aberrant orbital adipose deposition, in the absence of such deposition elsewhere in the body.

Cataracts
Posterior subcapsular cataracts may develop in humans following all routes of administration (topical, systemic, cutaneous, inhalation), with generally minimal effect on vision. Correlations with dosage and duration exists, with patients receiving oral prednisone at < 10 mg/day demonstrating an 11% incidence of cataract development, a 30% incidence with 10 – 15 mg/day doses, and 80% incidence with > 15 mg/day over 1 to 4 years. Additionally, children receiving corticosteroids will develop cataracts on lower doses for shorter durations. It is apparent that other factors (i.e., genetics, environment, age) also play a role. Discontinuation of therapy frequently stops progression of the cataract, and in children has been reported to result in resolution or partial resolution of the cataract. Development of such cataracts in small animals has not been reported.

The pathophysiology of cataract development is not fully known. Postulated mechanisms include metabolic disturbances involving glucose or its metabolism, lenticular enzyme systems, or lenticular protein synthesis; altered osmotic and/or ionic balances due to steroid-induced Na+/K+-ATPase modulation; loss of protection from oxidative injury leading to conformational changes in proteins and formation of disulfide bonds and creating protein aggregates; direct addition of steroids to lens proteins to form protein adducts; or aberrant lens epithelial cell behavior due to altered growth factor production induced by corticosteroids.

Ocular Hypertension or Glaucoma
Significant but frequently reversible increases in IOP occur in humans following systemic or topical corticosteroid therapy. The elevations generally occur within 2 to 8 weeks following initiation of therapy, and resolve within 1 to 3 weeks following discontinuation. Elevations are generally more severe in glaucomatous (open-angle) eyes versus normal eyes, ranging from a few mmHg to greater than 15 mmHg increase. Factors involved that increase the susceptibility of an individual to steroid-induced IOP elevations include a genetic predisposition (greater increase in IOP in eyes of relatives of patient with open-angle glaucoma), age, the presence of myopia of 5D or greater, and duration of therapy (long-term systemic therapy induces greater increase). Certain steroids (dexamethasone, betamethasone, and prednisolone, versus fluorometholone alcohol or medrysone) are associated with a greater chance of IOP elevation as well, possibly due to varied intraocular bioavailability, receptor specificity, pharmacokinetic half-life, or metabolism.

The pathophysiology of glaucomatous reactions to corticosteroids is thought to involve activation of glucocorticoid receptors in the trabecular meshwork. The resulting alterations in gene expression affect the extracellular matrix, cytoskeletal elements, and cell adhesion molecules, altering the morphology of the trabecular meshwork to increase the resistance to AH outflow.

Ocular hypertension has been reported in Beagles with primary open-angle glaucoma following topical administration of 0.1% dexamethasone, however a similar increase did not result in healthy dogs following oral administration of hydrocortisone for 5 weeks. It has also been induced experimentally in cats and cattle following administration of topical dexamethasone or prednisolone acetate.

Infection
Due to their mechanism of action on the immune system, steroids increase susceptibility to infection. In humans with bacterial infections of the cornea, topical corticosteroids may be administered with the goal of
minimizing subsequent corneal scarring, however it is imperative that an appropriate, specific, therapeutic antibiotic be administered at the same time. Use of corticosteroids in the presence of fungal infections is generally not advised, regardless of the degree of anticipated scarring. Use of corticosteroids in the presence of viral infections prolongs the course of disease, and is generally reserved only for those cases with a significant stromal inflammatory component, which is likely indicative of an immune-response to viral infection, as opposed to active viral replication. In veterinary ophthalmology, use of corticosteroids in the presence of bacterial or fungal corneal infections is contraindicated. Although decreased corneal scarring would be ideal, the risks of such therapy are far too great in our patients to justify such a therapeutic protocol.

Aside from potentiating existing infections, an additional concern with prophylactic topical antibiotic and corticosteroid therapy is the potential to alter the normal ocular surface microflora to potentially more deleterious pathogens. A study utilizing normal horses evaluated this potential by treating eyes three times daily for 2 weeks with either neomycin/polymyxin B/bacitracin, prednisolone gentamicin, neomycin/polymyxin B/dexamethasone, or artificial tears, and taking serial ocular surface bacterial and fungal cultures. In that study, although number of positive cultures and population of organisms did change slightly at various time points, no overall significant detrimental effects of treatment on normal ocular flora were found.

**Decreased Wound Healing**

Separate from potentiating ocular surface infections and thereby inhibiting wound healing, the increased collagenolytic activity induced by the topical corticosteroids likely directly decreases wound healing as well. While more pronounced with topical administration, systemic administration has also be reported to adversely affect epithelial regeneration. Fibroblast activity and collagen deposition necessary to heal deeper corneal wounds is also inhibited by corticosteroid administration, manifesting as reduced tensile strength. This may have significant implications post-operatively, as intraocular surgical procedures requiring corneal incisions are often treated with topical corticosteroids post-operatively. Not surprisingly, different base steroids and derivatives have variable effect on wound healing, with dexamethasone phosphate appearing to be least deleterious of the commonly used topical corticosteroids. A study comparing the in vitro effects of dexamethasone, prednisolone, and hydrocortisone on cultured canine corneal epithelial found dexamethasone to have fewer effects on cell morphology and migration than the other corticosteroids, however negative effects have been reported on human keratocytes, emphasizing the consideration that topical administration of corticosteroids with a corneal wound, even when necessary, should be initiated with awareness.

**Mydriasis**

Mydriasis has been induced in healthy human volunteers within 1 week following initiation of topical dexamethasone application, as well as in monkey eyes. It may occur in conjunction with ptosis, and the supposition is that a component of the drug vehicle induces the effects.

**Calcific Band Keratopathy**

Calcium deposition in the cornea in conjunction with topical application of corticosteroids has been reported in people. Patients with persistent epithelial defects, as occur post-operatively, in association with herpesvirus infection, or dry eye, are potentially predisposed.

**Contraindications**

Contraindications to the use of topical ophthalmic corticosteroids in veterinary medicine include corneal ulceration, known or suspected corneal infection, or a known hypersensitivity to any particular formation. Corticosteroids (topical or systemic) should be administered with caution and regular in patients with diabetes mellitus or other endocrine diseases, infectious diseases, chronic renal failure, congestive heart failure, systemic hypertension, or gastric ulceration. When necessary to administer (i.e., post-phacoemulsification in a diabetic dog), the minimal dose required should be administered for the shortest period of time required.
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Inflammation is mediated by prostaglandins (PGs), specifically the pro-inflammatory series 2 PGs (PGE₂, PGD₂, PGF₂α, PGI₂: series 1 and series 3 PGs are anti-inflammatory), and leukotrienes. Series 2 PGs and thromboxane A₂, which is critical for platelet production and aggregation, are produced from arachidonic acid (derived from cell membrane phospholipids under the influence of phospholipase A₂) by the cyclooxygenase (COX) enzyme system. COX exists in two prominent isoforms, COX-1 (constitutive) and COX-2 (inducible). COX-1 is present in most tissues under normal circumstances and produces PGs responsible for homeostatic functions, while COX-2 is present primarily in response to cellular insult or injury. Leukotrienes, which produce lesser inflammatory responses than PGs, are produced from eicosapentanoic acid (also a precursor to anti-inflammatory series 3 PGs) by the enzyme lipoxygenase. Ocular effects of PGs (particularly PGE₂) include miosis, increased IOP, reduced blood-aqueous barrier stability, conjunctival and iridal vasodilation and vascular permeability, and corneal vascularization.³³ It is important to note however, that COX enzyme localization and expression, subsequent PG expression, and PG receptor sensitivities vary significantly among species, thus modulating effects of tissue injury and response to pharmacologic intervention.³³

Nonsteroidal anti-inflammatory drugs (NSAIDs) target the COX pathway, with individual NSAIDs exhibiting variable selectivity for either the COX-1 or COX-2 isoform. The molecular action of the drug is based upon competitively blocking the enzyme active site in a reversible or irreversible manner. Selective inhibition of the inducible COX-2 isoform is believed to lead to fewer deleterious side effects, as protective functions mediated primarily by COX-1 are spared. It is also believed however, that COX-2 is expressed by vascular endothelial cells and, when downregulated by COX-2 selective NSAIDs, the relative increase in thromboxane levels associated with normal COX-1 activity may in turn negatively impact the cardiovascular system. Additional anti-inflammatory effects of NSAIDs, independent of COX inhibition, include decreased neutrophil chemotaxis and migration, decreased expression of inflammatory cytokines, decreased mast cell degranulation, and free-radical scavenging.³⁴ Due to the fact that they are organic acids, NSAIDs accumulate at sites of inflammation, increasing their overall anti-inflammatory effect.

Ophthalmic NSAID Usage

NSAIDs, administered topically or systemically, are used in ophthalmology to control inflammation and provide analgesia. Preoperative administration of NSAIDs prior to cataract removal is utilized to attain maximal mydriasis and minimize breakdown of the blood-aqueous barrier associated with surgical manipulation and subsequent release of PGs. Postoperative administration is helpful to decrease inflammation and minimize negative effects on corneal wound healing, however corticosteroids remain the gold standard topical ocular anti-inflammatory medication. Administration of topical NSAIDs in humans following surgical refractive procedures is highly effective as pain control, and also as treatment for postoperative cystoid macular edema.¹ Many topical ophthalmic NSAIDs are also approved for use in allergic conjunctivitis.³⁴

NSAIDs safe for topical ophthalmic use include indole acetic acid, aryl acetic acid, and aryl propionic acid derivatives, which are readily formulated as solutions due to their water-soluble nature (Table 3). Salicylates, fenamates, and pyrazolones are too toxic for topical ocular use. As most NSAIDs are weakly acidic, they exist in their ionized form in the tear film pH and thus only weakly penetrate the cornea. Reducing the pH of topical formulations increases the unionized fractions and intraocular penetration, however it also increases the local irritant effects following administration. Additionally, the anionic nature of NSAIDs favors formation of insoluble complexes with cationic quaternary ammonium preservatives such as benzalkonium chloride.³⁵,³⁶

<table>
<thead>
<tr>
<th>Derivative Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Indole acetic acid</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Aryl acetic acid</td>
<td>Diclofenac, Ketorolac, Nepafenac, Bromfenac</td>
</tr>
<tr>
<td>Aryl propionic acid</td>
<td>Ibuprofen, Flurbiprofen, Ketoprofen, Suprofen, Naproxen</td>
</tr>
</tbody>
</table>
Local side effects occurring with topical administration of NSAIDs are most commonly related to direct ocular surface irritation (hyperemia, contact dermatitis). Superficial punctate keratitis has also been reported with chronic NSAID use, possibly in relation to decreased corneal sensitivity (diclofenac has been implicated as having the greatest impact. Significant keratomalacia has also been reported with topical NSAIDs, particularly diclofenac (brand name and generic) and ketorolac, primarily when administered following cataract removal or photorefractive surgeries.  

Investigation of NSAID-induced corneal toxicity has elucidated multiple possible mechanisms. In terms of the direct pathways of inflammation, NSAID administration may exacerbate disease processes. Corneal epithelial arachidonic acid metabolism involves COX, lipoxygenase, and cytochrome P450 enzymes, each of which result in production of various inflammatory mediators (PGs, leukotrienes, and eicosatetraenoic acid derivatives, respectively). In cases of trauma, infection, or autoimmunity, each pathway is stimulated, while in cases of hypoxia, stimulation of the COX enzyme system is decreased and activation of the leukotriene and cytochrome P450 systems, thus increasing (rather than decreasing) the inflammatory response. Additionally, PGE2 may play a role in decreasing production of matrix metalloproteinases (MMP), which are in part responsible for keratomalacia. Inhibition of PGE2 therefore may serve to promote MMP production. Finally, NSAIDs may induce direct cellular damage that inhibits wound healing. An in vitro study utilizing cultured canine epithelial cells noted dose-dependent adverse alterations in cell morphology and wound healing following treatment with suprofen. The same study also evaluated thimerosal, a preservative commonly used in ophthalmic preparations (including NSAIDs), and found a significant deleterious effect on epithelial cell morphology and wound closure.

As with any topical ophthalmic medication, systemic side effects may occur. Nonselective COX inhibitors are classically associated with an increased risk of gastrointestinal side effects (primarily gastric ulceration) related to inhibition of COX-1 and subsequent decreased production of protective PGs. Altered platelet function also occurs due to decreased production of thromboxane A2, which stimulates production and aggregation of platelets (this effect is most pronounced with aspirin, as its inhibition of COX is irreversible). Renal side effects may also be noted due to reduced production of vasodilatory PGs, which increase renal blood flow. In humans, bronchial asthmatic attacks have been reported, likely in association with shunting of arachidonate to the lipoxygenase pathway due to decrease COX activity. This results in increased production of leukotrienes, which are potent nonvascular smooth muscle spasmogens. In veterinary medicine, gastrointestinal disease is the most notable complication, while cats also experience bone marrow suppression.

**Systemic Agents**

Multiple agents are available for systemic administration in veterinary medicine, including aspirin, flunixin meglumine, phenylbutazone, etogesic, carprofen, meloxicam, deracoxib, firocoxib, and tolmetin acid. Evaluation of flunixin meglumine, carprofen, and tolmetin acid in experimentally-induced blood-aqueous barrier breakdown in dogs indicated that all three are effective at limiting ensuing intraocular inflammation. In dogs with blood-aqueous barrier breakdown associated with topical administration of pilocarpine, flare production was inhibited by 68% in dogs receiving pre-treatment with oral carprofen relative to untreated controls. Dogs undergoing repeat AH paracentesis demonstrated statistically significantly lower elevations in intraocular PGE2 levels following pretreatment with oral carprofen, compared with placebo-treated controls. Also in dogs with experimentally-induced blood-aqueous barrier breakdown associated with repeated AH paracentesis, pre-treatment with oral tebufloxacin significantly inhibited the intraocular production of PGE2, relative to dogs pre-treated with oral meloxicam or carprofen, or untreated controls. Clinical evaluation of the efficacy of carprofen as an analgesic in dogs undergoing enucleation was evident in comparison with tramadol, with fewer dogs receiving pre-operative carprofen requiring post-operative rescue analgesia (1/22) than those receiving pre-operative tramadol (6/21) (Delgado JAVMA 2014). Evaluation of the intraocular penetration of firocoxib versus flunixin in horses demonstrated significantly greater intraocular firocoxib levels, however no significant difference in intraocular PGE2 levels were present between horses receiving firocoxib orally or flunixin orally (Hilton JVIM 2011).
Topical Agents

Topical agents include preparations of ketorolac, diclofenac, indomethacin, flurbiprofen, suprofen, bromfenac, and nepafenac, available as solutions or suspensions, with most containing preservatives.

Ketorolac

Ketorolac, available as 0.4%, 0.45%, and 0.5% solutions, is approved for use in reducing ocular pain and inflammation after corneal refractive surgery and cataract surgery, and is also effective as treatment for post-operative cystoid macular edema (due to PGE2) and ocular surface inflammatory conditions. The 0.45% solution of ketorolac was developed in part to reduce potential deleterious effects of topical NSAIDs on the corneal epithelium, as it is formulated without the preservative present in the 0.4% and 0.5% concentrations, as well as present in other topical NSAIDs, and it is formulated with carboxymethylcellulose as a carbomer that may increase epithelial wound healing.50,51 In support of this possibility, a comparison of the effect of different formulations of ketorolac, bromfenac 0.09%, and nepafenac 0.1% on epithelial wound healing in an ex vivo porcine wound model identified increased rate of healing with the 0.45% ketorolac formulation relative to the other topically applied NSAIDs.50

Multiple studies comparing the relative efficacy of ketorolac with that of other topical NSAIDs in humans undergoing cataract surgery or vitrectomy exist, which generally indicate superior penetration and superior PGE2 inhibition by ketorolac.52,53 Compared to bromfenac and nepafenac, ketorolac 0.45% reached significantly greater AH levels following one day of pre-operative dosing to human patients undergoing cataract surgery.54 Additionally, inhibition of AH PGE2 activity in patients receiving drug for one day prior to phacoemulsification was significantly greater in patients receiving ketorolac 0.45% versus nepafenac 0.1%, with a trend toward greater inhibition with ketorolac versus bromfenac 0.09%.55 Treatment with ketorolac 0.4%, bromfenac 0.09%, or nepafenac 0.1% (versus untreated controls) prior to vitrectomy identified greater intravitreal concentrations of ketorolac than bromfenac, nepafenac, and amfenac (the active metabolite of nepafenac), as well as significantly reduced intravitreal PGE2 levels in patients treated with ketorolac versus nepafenac or control (untreated) patients.56

While ketorolac demonstrates stronger pharmacodynamics and potential clinical effect in patients undergoing phacoemulsification or vitrectomy, nepafenac has been demonstrated to have a few advantages over both bromfenac and ketorolac in patients undergoing photorefractive keratectomy (PRK). Comparison of the effects of ketorolac 0.4% (with preservative) versus nepafenac 0.1% on corneal epithelial wound healing and pain control following PRK revealed no difference in reepithelialization rates nor in overall pain assessment between the two treatment groups, however ketorolac was associated with significantly greater discomfort upon instillation.57 A similar study compared the effects of three different drug combinations on corneal epithelial wound healing and pain control following PRK: ketorolac 0.4% with gatifloxacin 0.3%; bromfenac 0.09% with gatifloxacin 0.3%; and nepafenac 0.1% with moxifloxacin 0.5%.58 Time to reepithelialization was significantly shorter in the nepafenac group (mean 5.5 days versus 7.2 days for bromfenac group), while the ketorolac group demonstrated intermediate healing time. Postoperative pain scores were significantly reduced in patients receiving nepafenac on postoperative days 1 and 3, while statistically significant pain score reductions were not present until day 3 in patients receiving bromfenac and nepafenac.

Diclofenac

Diclofenac (0.1% solution) is approved for use in achieving mydriasis for cataract surgery, and is also used to reduce ocular pain following corneal refractive surgery. Following topical administration, it reaches high corneal tissue levels in normal and inflamed corneas, however it poorly penetrates into the aqueous humor in the presence of corneal inflammation.59 Its ability to control blood aqueous barrier breakdown in dogs following anterior chamber paracentesis was greater than that of flurbiprofen and suprofen in one study,60 while in a study utilizing pilocarpine to induce blood-aqueous barrier breakdown, diclofenac was inferior to flurbiprofen.51

Evaluation in cats

Anterior chamber paracentesis was used to induce blood-aqueous barrier disruption in both eyes of normal cats, and was followed by unilateral application of a single dose of either 1% prednisolone acetate, 0.1% dexamethasone, 0.03% flurbiprofen, of 0.1% diclofenac immediately and at 6, 10 and 24 hours post-
paracentesis (the contralateral eye served as an untreated control). Flare was measured using a laser-flare meter at 4, 8, and 26 hours post-paracentesis, and the relative ability of each anti-inflammatory was assessed. A significant reduction in flare at all three time points was associated only with 1% prednisolone acetate; diclofenac 0.1% significantly reduced flare at the 8- and 26-hour timepoints; 0.1% dexamethasone significantly reduced flare at the 4-hour timepoint; and flurbiprofen 0.03% did not significantly reduce flare at any timepoint. Evaluation of systemic absorption of diclofenac following four-times daily bilateral administration for 7 days revealed measurable plasma diclofenac concentrations, with a reduction in glomerular filtration rate presumed to be associated with study-induced volume contraction (Hsu AJVR 2015).

**Indomethacin**

Indomethacin (0.5% solution) is available in some countries as either a solution or a suspension, with the solution demonstrating equivalent efficacy to the suspension in preventing miosis and blood-aqueous barrier breakdown in dogs in association with aqueous paracentesis. It has good intraocular penetration.

**Flurbiprofen**

Flurbiprofen, available as a 0.03% solution, is approved for maintaining mydriasis in association with cataract surgery, and also is used in the treatment of cystoid macular edema. Following topical administration, intraocular levels are comparable to those achieved with diclofenac, however diclofenac has a longer intraocular residence time than does flurbiprofen (~7 hours versus ~4 hours, respectively). It is effective at reducing intraocular inflammation following laser anterior capsulotomy, however its efficacy relative to that of diclofenac is variable.

**Bromfenac**

Bromfenac is available as a 0.09% solution. Its chemical structure is identical to that of amfenac (see below), however it has a bromine atom that imparts favorable pharmacological properties. The first benefit of the bromine addition is enhanced lipophilicity, which increases transcorneal penetration and potential efficacy. The second benefit is increased duration of analgesic and anti-inflammatory activity, and the third benefit is increased COX-2 inhibition. Although difficult to truly mimic in vitro, the COX-2 inhibitory activity of bromfenac measured as an IC<sub>50</sub> (inhibitory concentration 50%, or concentration of drug required to inhibit COX activity by 50%) is greater than that of diclofenac, amfenac, and ketorolac, based on in vitro studies. Bromfenac also has excellent intraocular penetration following topical administration, achieving measurable corneal, aqueous humor, and intraocular tissue levels following application of a single dose in normal rabbits. Administration of a single drop in human patients prior to cataract removal demonstrated clinically effective aqueous humor bromfenac concentrations up to 12 hours post-administration. Comparison of PGE<sub>2</sub> inhibitory activity demonstrated greater inhibition with ketorolac, while bromfenac more effectively inhibited COX-2 than did ketorolac. Bromfenac also demonstrated superior clinical anti-inflammatory effect to that of diclofenac following cataract removal, with a lower incidence of corneal epitheliopathy. A comparison of post-surgical clinical efficacy of bromfenac and 0.1% betamethasone, alone or in combination, demonstrated no significant difference in visual acuity, IOP, flare, or corneal swelling among the individual drugs or combination. Comparison of bromfenac with celecoxib-impregnated IOL and prednisolone acetate therapy in dogs undergoing phacoemulsification identified increased aqueous flare in bromfenac-treated eyes at 24 hours post-operatively, as well as increased IOP in bromfenac-treated eyes at 4 and 12 weeks post-operative, decreased PCO in bromfenac-treated eyes at 54 weeks post-operatively (Brookshire VO 2015). Evaluation of prevalence of post-operative ocular hypertension (POH) in dogs following phacoemulsification and receiving either flurbiprofen or bromfenac pre- and post-operatively identified an increased tendency toward elevated IOP at 2-hours post-operatively, as well as a slower decrease in IOP in the 6 weeks following surgery, in dogs treated with bromfenac (Lu VO 2016).

**Nepafenac**

Nepafenac is available as a 0.1% suspension, and is the only NSAID prodrug formulation currently available. As an amide prodrug, nepafenac is not a free acid, and being less polar with less ionic influence, the
corneal epithelium less effectively limits its intraocular penetration. While nepafenac itself is only weakly inhibitory of COX enzymes relative to other NSAIDs, it has excellent intraocular penetration, allowing it to reach the presumable sites of hydrolytic conversion (iris, ciliary body, retina, choroid – not the cornea) to the active form amfenac. Patients receiving either nepafenac, bromfenac, or ketorolac prior to cataract removal had significantly greater aqueous humor nepafenac concentrations (205.3 ng/ml) than either bromfenac or ketorolac (25.9 ng/ml and 57.5 ng/ml, respectively), and those levels were reached within 30 minutes (bromfenac and ketorolac maximum concentrations were reached at 240 and 60 minutes, respectively). Comparison of the in vitro COX-1 and COX-2 inhibitory activity of nepafenac, bromfenac, ketorolac, and amfenac found ketorolac had the greatest COX-1 inhibitory activity while amfenac and bromfenac then ketorolac had the greatest COX-2 inhibitory activity (nepafenac had least COX-1 and COX-2 activity), supporting the ability of nepafenac to penetrate the cornea and the likely clinical efficacy of its active metabolite amfenac to control intraocular inflammation. Clinical evaluation of the ability of nepafenac to control pain and inflammation associated with cataract surgery is supportive of nepafenac’s overall efficacy, however comparison relative to ketorolac largely indicates comparable effects. Following corneal refractive surgery however, one study showed marked corneal haze and delayed epithelialization associated with nepafenac, while other studies have not documented the same deleterious effects in the short-term.

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