

Nonsteroidal anti-inflammatory drugs in veterinary ophthalmology

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Central to the management of all ophthalmic disease processes is preservation of vision and maintenance or restoration of ocular comfort. The etiology of ophthalmic disease varies and may involve adnexal, surface, or intraocular pathologic findings of primary or secondary causes. Regardless of the inciting problem or ocular region affected, inflammation is a common sequela of disease and may result in keratitis sicca, corneal pigmentation or vascularization, fibrosis, cataract, glaucoma, synechia, optic nerve atrophy, retinal degeneration, retinal detachment, phthisis bulbi, or blindness [1]. Prompt appropriate treatment of ocular inflammation is essential if additional ocular discomfort and loss of vision are to be prevented.

Several excellent reviews discuss the management of ocular inflammation, and the reader is referred to those sources for a general overview of this topic [1–3]. This article discusses the current uses of nonsteroidal anti-inflammatory drugs (NSAIDs) in veterinary ophthalmology. Specifically, review of the recent veterinary ophthalmic literature regarding the indications and efficacy of systemic and topical NSAIDs is discussed.

Mechanism of action of nonsteroidal anti-inflammatory drugs

Ocular inflammation occurs in response to mechanical, chemical, or thermal injury or endogenous influences of cellular or humoral origin secondary to infectious or immune-mediated causes. In-depth reviews of the pharmacologic action of NSAIDs have recently been published [4–6]. After cell membrane damage, membrane phospholipid is released and hydrolyzed by phospholipase A₂, resulting in the formation of arachidonic acid (Fig. 1). Metabolism of arachidonic acid occurs by the cyclooxygenase (COX) and

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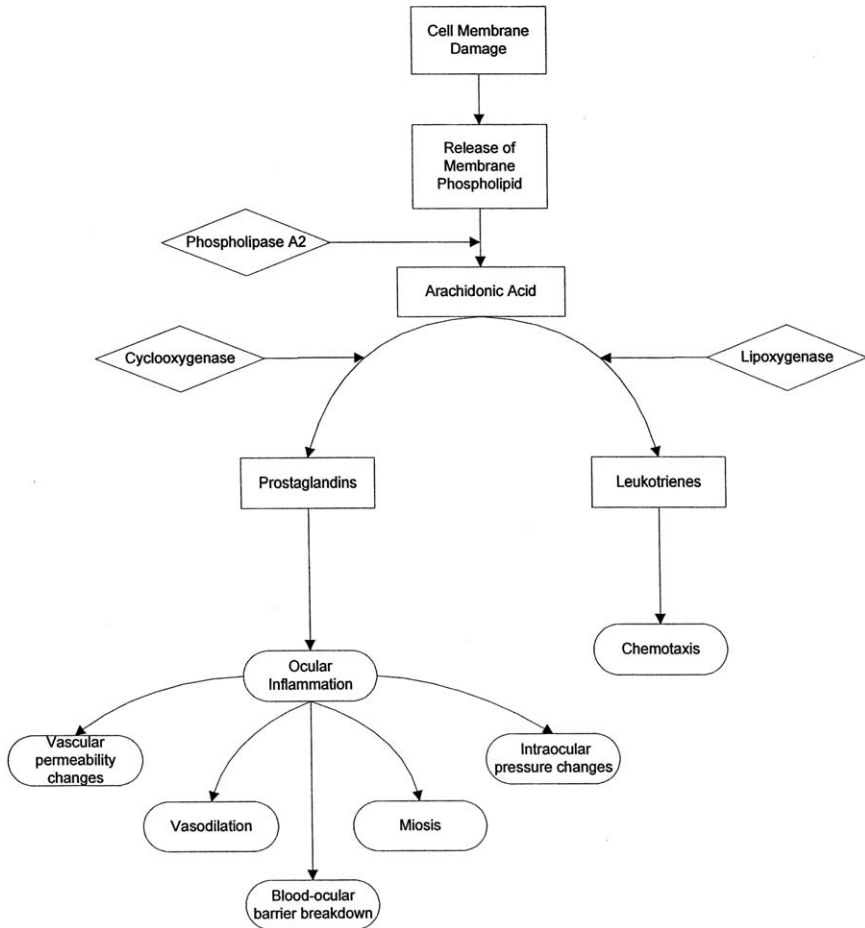


Fig. 1. The arachadonic acid cascade and effects on ocular structures.

lipoxygenase pathways. COX activity results in thromboxane A₂, prostaglandin E₂, (PGE₂), PGF_{2 α} , and PGI₂ (prostacyclin) production, whereas lipoxygenase activity results in the formation of leukotrienes (LTs). PGs, the main substances that result in the clinical manifestations of inflammation, potentiate the effects of other inflammatory mediators, cause breakdown of the blood–aqueous barrier (BAB), exacerbate photophobia, and lower the ocular pain threshold [7].

NSAIDs drugs inhibit the constitutive form of COX (COX-1) as well as the inducible form (COX-2). Constitutive COX-1 enzymes are expressed on the endoplasmic reticulum of all cells, including platelets; gastrointestinal (GI) mucosa; vascular endothelium; renal medullary collecting ducts; interstitium; and pulmonary, hepatic, and splenic sites [8]. COX-1 is important for normal physiologic function, and PGs, prostacyclin, and

thromboxane synthesized by this enzyme are needed for maintaining a healthy GI tract and renal system, functional platelets, and blood flow to specific tissues. By contrast, COX-2, synthesized by macrophages and inflammatory cells that have been stimulated by cytokines and other inflammatory mediators, is considered to be associated with inflammation and pain [9]. It follows that selective inhibition of COX-2 and sparing of COX-1 provides the ideal anti-inflammatory and analgesic NSAID without the common side effects associated with COX-1 inhibition, including GI and renal toxicity and inhibition of thrombocyte function. Although currently used NSAIDs in veterinary ophthalmology vary in their COX-1 and COX-2 selectivity, most inhibit both isoenzymes [9,10].

Evidence suggests that NSAIDs may exert additional anti-inflammatory actions other than COX inhibition [8]. Suppression of polymorphonuclear leukocyte (PMN) cell locomotion and chemotaxis may occur through a direct effect on the PMN [11]. In experimental models of ocular allergy, NSAIDs have been shown to decrease expression of inflammatory cytokines as well as mast cell degranulation [12]. NSAIDs may also exert an anti-inflammatory effect as free radical scavengers [13]. Finally, as organic acids, NSAIDs accumulate at sites of inflammation, enhancing their local anti-inflammatory effects [8,13].

Systemic nonsteroidal anti-inflammatory drugs in veterinary ophthalmology

Acetylsalicylic acid (aspirin) was first synthesized more than 100 years ago, but the anti-inflammatory, analgesic, and antipyretic properties of salicylates have been known for more than 3000 years. Currently, many different systemic NSAIDs are available, including acetylsalicylic acid, ibuprofen, phenylbutazone, flunixin meglumine, ketoprofen, ketorolac, piroxicam, acetaminophen, carprofen, etodolac, meloxicam, tolfenamic acid (TA), naproxen, and deracoxib. Certain NSAIDs have COX-1 and COX-2 inhibitory effects (eg, aspirin, ketoprofen), whereas others preferentially inhibit COX-2 or are COX-1 sparing to varying degrees (eg, meloxicam, carprofen, etodolac, deracoxib) [14–17]. In-depth discussion of the pharmacologic considerations and indications for the numerous currently available systemic NSAIDs is beyond the scope of this article, and the reader is referred to several excellent recent veterinary reviews of this subject [5,6,10,14,18]. Dose recommendations of commercially available systemic NSAIDs used by veterinary ophthalmologists can be found in Table 1.

Veterinary ophthalmologists most commonly use systemic NSAIDs in treating uveitic conditions for which corticosteroids are contraindicated, such as infectious diseases and diabetes mellitus, and before cataract surgery for their effects on maintaining mydriasis [2]. Acetylsalicylic acid, phenylbutazone, and flunixin meglumine have traditionally been the most

Table 1

Nonsteroidal anti-inflammatory drugs useful for systemic therapy of ocular inflammation in dogs, cats, and horses

Drug	Species	Indication	Dose, route, frequency
Carprofen	Dog	Surgical	≤ 4.0 mg/kg IV, SC, IM once at induction
		Anti-inflammatory	≤ 2.2 mg/kg PO q12–24 hours PRN
	Cat	Surgical	≤ 4.0 mg/kg SC lean weight once at induction
	Horse	Anti-inflammatory	0.7 mg/kg IV, PO q12–24 hours PRN
Flunixin meglumine	Dog	Surgical	0.25–1.0 mg/kg IV, SC, IM q12–24 hours for 1–2 treatments
	Cat	Surgical	0.25 mg/kg SC q12–24 hours for 1–2 treatments
Meloxicam	Horse	Anti-inflammatory	1.1 mg/kg IV, IM, PO q12–24 hours
	Dog	Surgical	≤ 0.2 mg/kg IV, SC once ≤ 0.1 mg/kg IV, SC, PO q12–24 hours thereafter
		Anti-inflammatory	≤ 0.2 mg/kg PO once ≤ 0.1 mg/kg PO q24 hours thereafter
	Cat	Surgical	≤ 0.2 mg/kg SC, PO once ≤ 0.1 mg/kg SC, PO lean body weight q2–3 days
		Anti-inflammatory	≤ 0.2 mg/kg SC, PO once ≤ 0.1 mg/kg SC, PO lean body weight q2–3 days
	Horse	Anti-inflammatory	0.6 mg/kg IV q12–24 hours
Ketoprofen	Dog	Surgical	≤ 2.0 mg/kg IV, IM, SC, PO once ≤ 1.0 mg/kg q24 hours thereafter
		Anti-inflammatory	≤ 2.0 mg/kg PO once ≤ 1.0 mg/kg q24 hours thereafter
	Cat	Surgical	≤ 2.0 mg/kg SC once ≤ 1.0 mg/kg PO q24 hours thereafter
		Anti-inflammatory	≤ 2.0 mg/kg PO once ≤ 1.0 mg/kg PO q24 hours thereafter
Phenylbutazone	Horse	Anti-inflammatory	2.2 mg/kg IV, IM q12–24 hours
	Dog	Anti-inflammatory	10–14 mg/kg PO q8–12 hours
Aspirin	Horse	Anti-inflammatory	2.2–4.4 mg/kg IV, PO q12–24 hours
	Dog	Anti-inflammatory, antithrombotic	10 mg/kg q12 hours PO
	Cat	Anti-inflammatory, antithrombotic	10–20 mg/kg q48–72 hours PO
	Horse	Anti-inflammatory, antithrombotic	17 mg/kg q48 hours PO
Ketorolac	Dog	Surgical	0.3–0.5 mg/kg IV, IM
	Cat	Surgical	0.25 mg/kg IM q12 hours for 1–2 treatments
Etodolac	Dog	Anti-inflammatory	≤ 15 mg/kg PO q24 hours
Deracoxib	Dog	Anti-inflammatory	≤ 4 mg/kg PO q24 hours

Abbreviations: IM, intramuscular; IV intravenous; PO, per os; PRN, as needed; SQ, subcutaneous.

Data from Refs. [5,6,14,15,33,72].

commonly prescribed NSAIDs in dogs, cats, and horses by veterinary ophthalmologists [2]. With the advent of US Food and Drug Administration (FDA) approval for newer systemic NSAIDs with fewer reported side effects, however, drugs like carprofen and etodolac are being used with increasing frequency.

Various models of uveitis via disruption of the BAB have been used in the veterinary ophthalmic research setting, including modified paracentesis [19,20], disruption of the anterior lens capsule using a neodymium:yttrium aluminum garnet laser (Nd:YAG) [21–23], topical drug application [24–26], and corneal surgery [27]. Ward et al [19] used anterior chamber fluorophotometry to compare the BAB stabilizing effect of several topical and systemic anti-inflammatory agents in a modified paracentesis model of BAB disruption in the dog. Evaluation of systemic NSAIDs used in this study revealed that flunixin meglumine offered good BAB protection, with aspirin being moderately protective compared with placebo; however, both drugs were noted to cause some GI bleeding. A second study conducted by Millichamp et al [22] found that intravenously administered flunixin meglumine had a significant effect in limiting miosis and reducing production of PGE₂ in the aqueous humor after acute inflammation induction by laser disruption of the anterior lens capsule in normal adult dogs. Krohne et al [26] used topical pilocarpine to induce breakdown of the BAB, resulting in aqueous flare. Using a Kowa FC-1000 (Kowa, Tokyo, Japan) laser flare cell meter to perform laser flare photometry, the authors found that carprofen pretreatment resulted in a 68% inhibition of flare, thus providing evidence that carprofen was an effective systemic ocular anti-inflammatory drug using this pilocarpine irritative model in dogs. TA, approved for use in cats and dogs in Europe and Canada, was investigated by Roze et al [27] for its value in controlling ocular inflammation in the dog when administered subcutaneously 2 hours before surgery. Intraocular inflammation was induced in this study with a 5-mm incision on the cornea, which was subsequently closed with nonabsorbable suture in a simple interrupted pattern. Researchers found that TA-treated dogs demonstrated a statistically significant reduction of miosis compared with untreated dogs and a trend toward reduced ocular discharge and corneal edema. Additionally, TA-treated dogs had significantly lower PGE₂ levels in their aqueous humor than control dogs after surgery.

Side effects of systemic nonsteroidal anti-inflammatory drugs

Although the usefulness of systemic NSAIDs in veterinary ophthalmology is well known, clinicians should be aware of adverse effects that can occur with use. Systemic treatment with NSAIDs has been associated with a number of systemic side effects, of which GI adverse effects are considered the most significant in people and animals [28,29]. These side effects may necessitate cotreatment with other medications (ie, PG analogues, histamine-2 receptor antagonists, proton pump inhibitors) or result in premature

discontinuation of systemic therapy because of anorexia, hematemesis, severe anemia, or, rarely, perforation of gastroduodenal ulcers [30,31]. The exact mechanisms by which NSAIDs induce GI disease are not fully understood. Some NSAIDs, including aspirin, are weak acids and easily transported into GI epithelial cells because of their nonionized and lipophilic state in intraluminal gastric pH. Once incorporated into epithelial cells, they become ionized, mitochondrial injury ensues, and direct toxicity results [32]. In addition to this direct topical effect, NSAIDs impair PG-dependent mucosal-protective mechanisms through nonselective COX inhibition, resulting in reduced bicarbonate secretion, reduced mucus formation, and vascular effects [30].

The incidence of GI adverse effects in dogs treated with oral NSAIDs is currently unknown, because no large study of dogs receiving NSAIDs has been performed. Nevertheless, individual reports of NSAID-associated GI side effects in dogs have been reported secondary to naproxen, aspirin, piroxicam, indomethacin, flunixin meglumine, ibuprofen, carprofen, and etodolac administration and have been reviewed elsewhere [31]. Clinical signs have included melena, vomiting, diarrhea, hematemesis, and GI ulceration. Clinicians should be aware of these potential adverse effects when prescribing any oral NSAID for the treatment of ocular inflammation.

Of all veterinary ophthalmic patients commonly treated with systemic NSAIDs, the horse seems to be at greatest risk from NSAID-associated side effects. The risks of gastric ulceration and more fatal conditions, such as colitis, cannot be overemphasized. Recall that even highly selective COX-2 inhibitors continue to inhibit COX-1 to some extent; thus, GI side effects that occur with traditional NSAIDs, although greatly minimized, are not eliminated completely. At this time, selective COX-2 inhibitors are still under patent; thus, no generic forms are currently available. Use of the human products in horses is generally prohibitively expensive. Etodolac, a veterinary drug, may be an alternative systemic NSAID for use in horses particularly in need of a drug with fewer GI side effects (eg, the chronic uveitis patient that has already had some side effects on traditional NSAIDs) [33,34]. The cost difference is significant when compared with more traditionally prescribed NSAIDs, although not necessarily prohibitive, and this drug merits consideration in selected equine cases. A prudent approach until COX-2 inhibitors become widely available and affordable for equine use is to ensure that when systemic NSAIDs are indicated, they are prescribed in safest possible manner. The maximum dose of flunixin is 1.1 mg/kg twice daily and the maximum dose of phenylbutazone is 4.4 mg/kg twice daily [6,35]. Clinicians should avoid using systemic NSAIDs at a higher frequency than intended (ie, more than twice daily), not use maximum doses for prolonged periods, and reduce drug dose as soon as clinical signs indicate. Special caution should be exercised in horses that have other systemic medical problems, such as dehydration, to avoid further exacerbating known NSAID side effects.

Additional reported side effects associated with systemic NSAID use other than the aforementioned GI disturbances include blood dyscrasias; hypoproteinemia; bronchoconstriction; hepatopathy; nephrotoxicity; fetal abnormalities when administered to a pregnant animal; and cellulitis, thrombophlebitis, and tissue necrosis associated with intramuscular or perivascular injections [14,30,33,35–37]. Hepatotoxicity has been reported dogs receiving carprofen at clinical doses; although analysis of the data supported an idiosyncratic cytotoxic hepatocellular drug reaction, the authors advocate evaluation of renal and hepatic function before the administration of carprofen [38].

Systemic NSAID use in cats has been associated with bone marrow suppression, GI ulceration, hemorrhage, vomiting, and diarrhea [39]. Cats are highly susceptible to the toxic effects of salicylates because of slow clearance, lack of glucuronide metabolism, and dose-dependent elimination [40,41]. Clinical signs associated with salicylate toxicity in cats include hyperthermia, metabolic acidosis with compensatory respiratory alkalosis, methemoglobinemia, hemorrhagic gastritis, and renal and hepatic injury [10]. Accidental feline poisonings as a result of oral acetaminophen ingestion have also been well documented; therefore, this drug should be avoided in cats [10]. Duodenal perforation in a cat after oral carprofen treatment has been reported [42]. Other reports have found that carprofen may be safely administered to cats after surgery with equally efficacious results compared with other NSAIDs [43,44]. Aspirin, phenylbutazone, and ketoprofen can be administered systemically provided that careful dosing and conscientious screening for possible side effects are monitored [39].

In summary, when systemic NSAIDs are prescribed, patients should be monitored for hematochezia or melena, vomiting, increased water consumption, and nonspecific changes in demeanor. If adverse clinical signs develop, owners should be instructed to discontinue the medication and consult their veterinarian promptly. If NSAID therapy is prescribed for chronic use, intermittent monitoring of creatinine and alanine aminotransferase is advisable [14].

Topical nonsteroidal anti-inflammatory drugs in veterinary ophthalmology: overview and literature review

Topical NSAIDs have been widely investigated for the past several years, and their use in veterinary ophthalmology is expanding. A list of the current topical agents available in the United States includes ketorolac, diclofenac, flurbiprofen, and suprofen (Table 2). Topical ophthalmic preparations containing indomethacin are commercially available only in Canada and Europe at this time. Topical NSAIDs have been approved by the FDA to reduce postoperative inflammation and photophobia after cataract surgery, control symptoms of allergic conjunctivitis, and alleviate pain after refractive surgery [7,8]. In human beings, topical NSAIDs have also proven

Table 2

Commercially available topical nonsteroidal anti-inflammatory agents available in the United States

Generic name	Brand name	Manufacturer	Buffer	Preservative	FDA-approved use
Ketorolac tromethamine 0.5%	Acular	Allergan	None	Benzalkonium chloride 0.01%	Postcataract surgical inflammation Discomfort from seasonal allergic conjunctivitis
Ketorolac 0.5%	Acular PF 0.5	Allergan	None	None	See above
Diclofenac 0.1%	Voltaren	Novartis Ophthalmics	Boric acid	Sorbic acid	Postcataract surgical inflammation Pain after refractive surgery inflammation
Flurbiprofen 0.03%	Ocufen	Allergan	Sodium citrate	Thimersol 0.005%	Prophylaxis of surgical miosis
Suprofen 1%	Profenal	Alcon	None	Thimersol 0.005%	Prophylaxis of surgical miosis

Abbreviation: FDA, US Food and Drug Administration.

Data from Refs. [8,45,73].

useful in decreasing the incidence of cystoid macular edema (CME) and in treating CME once it occurs [7]. In addition to the FDA-approved uses of topical NSAIDs, these agents have been beneficial before surgery in preventing PG-induced ocular inflammation and undesired intraoperative miosis [45].

Although topical corticosteroids and NSAIDs are widely used by veterinary ophthalmologists, corticosteroids possess additional actions that can be detrimental to the management of ocular disease. These steroid-mediated effects include impaired host defenses by reducing the migration of neutrophils and macrophages, thereby increasing the risk of infection (particularly keratomycosis); decreased vascular permeability; suppressed action of various lymphokines; delayed corneal wound healing by decreasing keratocyte proliferation and collagen deposition; potentiation of corneal collagenase activity; and decreased epithelial healing rates [1,8,46]. Other risks of topical steroids well recognized by physician ophthalmologists include cataracts and glaucoma [47]. Topical NSAIDs represent a more selective modality with which to treat ocular inflammation and a more prudent therapeutic choice when treating infectious ocular diseases, such as ulcerative keratouveitis or stromal abscesses. Mechanism of action has already been described (see Fig. 1). They are often used concurrently with topical corticosteroids to improve control of ocular inflammation and may

permit less frequent application of topical steroids, thereby reducing the side effects associated with corticosteroid treatment alone. Typically, topical NSAIDs are applied two to four times per day, pending the severity of anterior segment ocular inflammation [8,39,45].

Preliminary research by veterinary ophthalmologists was aimed at determining those inflammatory mediators that caused uveitis in select companion animals and at establishing methods by which to accurately assess the degree of inflammation present in animal eyes. Dziezyc et al [48] injected various concentrations of $\text{PGF}_{2\alpha}$, LTD_4 , and phosphate-buffered saline solution (control) into the anterior chamber of dogs. At the time of anterior chamber injection, a 10% solution of sodium fluorescein was injected intravenously (at a rate of 14 mg/kg of body weight). Effects on pupil size, intraocular pressure (IOP), and anterior chamber fluorescence were evaluated. This study revealed that $\text{PGF}_{2\alpha}$ was a potent miotic and significantly increased the breakdown of the BAB compared with LTD_4 . No statistically significant increase in IOP was found when compared with control animals. Ward et al [49] investigated a specific 5-lipoxygenase inhibitor, PF5901, on disruption of the BAB in the dog using anterior chamber fluorophotometry in a unilateral paracentesis canine model. Results of this study demonstrated that LTs are not important mediators of BAB disruption in this model and that LT inhibitors may actually exacerbate disruption because of shunting of arachidonate metabolism toward the COX or epoxygenase pathways.

Evaluation of topical anti-inflammatory drug efficacy with regard to intraocular inflammation can be studied with different techniques, including slit lamp biomicroscopy, anterior segment fluorophotometry, and laser flare and cell measurement (LFCM). Both fluorophotometry and LFCM provide quantitative data to assess the permeability of the BAB [45]. Fluorophotometry determines a parameter called the “fluorescein diffusion coefficient” of the BAB, which reflects the BAB permeability toward molecules with the properties of fluorescein [50]. LFCM allows observer-independent detection of the permeability status of the BAB toward proteins [51]. Ward et al [52] established a protocol for performing slit-lamp fluorophotometry of the anterior chamber in dogs. The technique was then used to develop a model of BAB disruption that could be used for comparative testing of ophthalmic anti-inflammatory drugs. This group determined that barrier disruption induced by a slow controlled paracentesis of a small volume of aqueous humor provided the most reliable model for drug testing. Fluorophotometry was shown to be a sensitive and accurate means of detecting breakdown of the BAB. Krohne et al [53] established a noninvasive, accurate, and sensitive quantitation of aqueous humor protein concentration in dogs using laser flaremety.

With research models of uveitis developed in veterinary ophthalmology [19–22,24–27] and established techniques by which to quantify BAB breakdown [52,53], veterinary ophthalmologists have begun to investigate

the effects of topical NSAIDs in their patient population. A fundamental understanding of the mechanisms by which different research models induce BAB breakdown is important to the interpretation of studies that examine the efficacy of anti-inflammatory drugs as inhibitors of uveitis. Mediators known to play a role in BAB breakdown across different species include PGs, LTs, platelet-activating factor, neuropeptides like calcitonin gene-related peptide and substance P, interleukins, and bradykinin [24,54]. Trigeminal nerve stimulation of the cornea and secondary axonal stimulation of inflammatory mediators is a well known cause of uveitis secondary to ulcerative keratitis [54,55]. In a study by Ward et al [49], the effects of proparacaine, a topical anesthetic, and flurbiprofen were evaluated on BAB disruption and pupil size after anterior chamber paracentesis. Flurbiprofen decreased BAB breakdown and miosis, but proparacaine suppressed neither. Results from this study suggest that PGs, which are inhibited by flurbiprofen, are more important mediators of the ocular irritative response in the dog than are sensory neuropeptides, which are blocked by proparacaine.

In a later study performed by Krohne et al [24], the mechanism by which topical pilocarpine causes increased aqueous humor flare, hypotony, and miosis in dogs was investigated. Using the pilocarpine uveitic model [25], six dogs with normal eyes were treated bilaterally with topical 2% pilocarpine, and one eye of each dog was additionally treated with commercially available ophthalmic solutions. Results of this study demonstrated that flare from BAB breakdown, quantitated using laser flaremety, was inhibited (most to least) by flurbiprofen more than by diclofenac, proparacaine, or suprofen, which were more than 0.125% or 1.0% prednisolone. Inhibition of BAB breakdown seemed to be dose dependent and caused consensual inhibition in the contralateral eye. Intraocular pressure was decreased only in proparacaine-treated eyes and increased in eyes treated with topical NSAIDs. Additionally, flurbiprofen and proparacaine were the most effective at blocking miosis. Because miosis and increased aqueous humor flare were inhibited equally by proparacaine or NSAIDs, the authors suggest that these signs were caused by neuropeptide release into the aqueous humor from antidromic stimulation, which subsequently triggers PG production.

Further evidence that NSAID inhibition of corneal pain is mediated by a reduction of corneal nerve activity is provided by Chen et al [54]. In this study, the responsiveness of feline corneal polymodal nociceptors to chemical stimuli was diminished, in decreasing order of potency, by 0.1% indomethacin, 0.1% sodium diclofenac, and 0.03% sodium flurbiprofen. The mechanisms by which the diminished responsiveness occurred seem to be twofold: first, by a direct effect of the NSAIDs on the excitability of polymodal nerve endings and, second, by an inhibition of the formation of COX products, such as PGs. The latter effect reduces the enhanced responsiveness of nociceptors caused by local release of arachidonic acid metabolites from injured cells.

Several additional veterinary studies have compared the relative efficacies of topical NSAIDs in the treatment of uveitis. In studies in which inflammation was induced with an anterior capsulotomy using an Nd:YAG laser, Millichamp and Dziezyc [21] found topical flurbiprofen to be as effective as flunixin meglumine administered intravenously at maintaining mydriasis compared with untreated controls.

Dziezyc et al [56] examined the effects of pretreatment with 0.03% flurbiprofen and 1.0% prednisolone acetate suspension in normal dogs before laser capsulotomy on pupil size, IOP, and fluorescence in the anterior chamber. Results indicated that flurbiprofen was effective at maintaining mydriasis and effectively decreased fluorescein leakage in the anterior chamber compared with the control group. Dogs pretreated with topical corticosteroid became miotic and demonstrated fluorescein leakage similar to control animals. There was no significant difference in IOP between the groups.

In an anterior chamber paracentesis model, the relative efficacies of 1% suspensions of diclofenac, flurbiprofen, suprofen, or tolmetin were compared in normal dogs [57]. As measured by fluorophotometry, the order of statistically significant BAB stabilizing efficacy among groups was: diclofenac > flurbiprofen > suprofen > tolmetin, the latter of which was equal to control solution. Finally, two formulations of indomethacin eye drops (0.1% solution and 1% suspension) were compared using an anterior chamber paracentesis model in 24 Beagles. Pupillary constriction and increase in aqueous humor protein concentrations after BAB breakdown were significantly reduced in the indomethacin-pretreated eyes compared with controls; however, no significant difference between the inhibitory effects of the two formulations of indomethacin was found [58].

Side effects of topical nonsteroidal anti-inflammatory drugs

Adverse effects associated with the use of topical ophthalmic NSAIDs are somewhat species specific and may result from systemic absorption of the agent through the nasal mucosa, local irritating effects to the conjunctiva, direct corneal cytopathy, and decrease on facility of aqueous outflow [45,59]. Absorption of topical ophthalmic NSAIDs through the nasal mucosa results in systemic exposure. Occurrence of adverse systemic events secondary to topical administration, although rare, has been reported in human beings as an exacerbation of bronchial asthma [60,61]. NSAID-induced asthma attacks in people is believed to be the result of arachidonate shunting from the COX pathway to the lipoxygenase pathway within the respiratory tract and subsequent production of various LTs, including LTD₄ and LTE₄, with resultant spasm of nonvascular smooth muscle [8].

Topical ophthalmic NSAIDs can cause local ocular irritation, including conjunctival hyperemia, burning, stinging, and corneal anesthesia [8].

Corneal complications associated with topical NSAIDs include corneal infiltrates, epithelial defects, and superficial punctuate keratitis [62,63]. Recently, Hendrix et al [64] examined the effects of commonly used ophthalmic corticosteroids, suprofen, polysulfated glycosaminoglycan, and preservatives on morphologic characteristics and migration of canine corneal epithelium grown in cell culture. Results indicated that suprofen caused no apparent changes in morphologic characteristics at the lowest concentrations tested, but at higher concentrations, there was a concentration-dependent degree of epithelial cell rounding and shrinkage. Thimerosal, a preservative used in some topical NSAIDs (see Table 2) caused severe changes, inhibited migration of canine corneal epithelial cells at all concentrations, and may thus contribute to poor epithelialization of ulcers treated with preservative-containing drugs. Results of this *in vitro* study may support the possible pharmacodynamic explanations of NSAID-induced corneal injury in clinical practice. Proposed mechanisms include direct toxicity caused by cytotoxic agents, such as surfactants, solubilizers, and preservatives found in topical NSAID ophthalmic preparations, and adverse effects on corneal epithelial healing and collagen remodeling through promotion of matrix metalloproteinase activity via inhibition of PGE production. The toxicity noted with the use of topical ophthalmic NSAIDs in people may be attributed to the vehicle, solubilizer, or preservative found in the solution rather than to the active drug [8].

The most serious complication related to topical ophthalmic NSAID use reported to date in human beings has been the association of these drugs with full-thickness corneal melting. Careful analysis of reported complications revealed that the agent primarily responsible was the generic diclofenac product, diclofenac sodium ophthalmic solution, manufactured by Falcon Laboratories [8]. The significant increase in reports of severe corneal complications associated with use of this generic product resulted in its removal from distribution and use in September 1999. It should be noted that although much less common, keratitis and keratomalacia have also been associated with other ophthalmic NSAID products subsequent to various invasive corneal procedures [65,66].

In a study performed by Millichamp and Dziezyc [21], dogs were treated with the COX inhibitor flunixin meglumine administered intravenously or flurbiprofen administered topically, and acute inflammation was induced in the eyes by disruption of the anterior lens capsule using an Nd:YAG laser. Although both drugs maintained mydriasis, they also demonstrated an increase in IOP in the inflamed eyes compared with untreated controls. In this study, the IOP of the flurbiprofen-treated eyes was higher than that of flunixin-treated eyes; however, the difference was not statistically significant. In another study, Millichamp et al [59] investigated the effect of topically applied flurbiprofen on aqueous outflow from cannulated canine eyes using a constant-pressure perfusion technique. Inflammation was again induced using an Nd:YAG laser anterior capsulotomy. Topical flurbiprofen caused

a decrease in aqueous outflow that was more pronounced in inflamed versus control (nonlasered) canine eyes. This study indicates that NSAIDs should be used with caution in acutely inflamed canine eyes because of their potential to increase IOP. The authors advocate determining if an anatomic predisposition to glaucoma exists, via gonioscopy to assess conventional outflow, before using this drug in dogs with uveitis. Other reports in the veterinary literature have found similar IOP elevations associated with topical NSAID use [24]. One possible explanation for increased IOP associated with COX-inhibiting drugs is a reduction of aqueous outflow. It is possible that NSAIDs acting in the experimentally induced inflamed eyes could reduce the uveoscleral outflow (which has been shown to be mediated by PG in primates and other species) and thus increase IOP [67–71].

Summary

Uveitis is a common sequela to many ocular diseases. Primary treatment goals for uveitis should be to halt inflammation, prevent or control complications caused by inflammation, relieve pain, and preserve vision. Systemic and topical NSAIDs are essential components of the pharmaceutical armamentarium currently employed in the management of ocular inflammation by general practitioners and veterinary ophthalmologists worldwide. NSAIDs effectively prevent intraoperative miosis; control postoperative pain and inflammation after intraocular procedures, thus optimizing surgical outcome; control symptoms of allergic conjunctivitis; alleviate pain from various causes of uveitis; and circumvent some of the unwanted side effects that occur with corticosteroid treatment. Systemic NSAID therapy is necessary to treat posterior uveitis, because therapeutic concentrations cannot be attained in the retina and choroid with topical administration alone, and is warranted when diseases, such as diabetes mellitus or systemic infection, preclude the use of systemic corticosteroids.

Risk factors have been identified with systemic and topical administration of NSAIDs. In general, ophthalmic NSAIDs may be used safely with other ophthalmic pharmaceuticals; however, concurrent use of drugs known to affect the corneal epithelium adversely, such as gentamicin, may lead to increased corneal penetration of the NSAID. The concurrent use of NSAIDs with topical corticosteroids in the face of significant preexisting corneal inflammation has been identified as a risk factor in precipitating corneal erosions and melts in people and should be undertaken with caution [8]. Clinicians should remain vigilant in their screening of ophthalmic and systemic complications secondary to drug therapy and educate owners accordingly. If a sudden increase in patient ocular pain (as manifested by an increase in blepharospasm, photophobia, ocular discharge, or rubbing) is noted, owners should be instructed to contact their veterinarian promptly.

Acknowledgment

The author thanks Marie E. Kerl, Diplomate, American College of Veterinary Internal Medicine (SAIM) and American College of Veterinary Emergency and Critical Care, for her help in the preparation and careful review of this manuscript.

References

- [1] Wilkie DA. Control of ocular inflammation. *Vet Clin North Am Small Anim Pract* 1990; 20(3):693–713.
- [2] Miller TR. Anti-inflammatory therapy of the eye. In: Bonagura J, editor. *Kirk's current veterinary therapy XII, small animal practice*. Philadelphia: WB Saunders; 1995. p. 1218–22.
- [3] van der Woerd A. Management of intraocular inflammatory disease. *Clin Tech Small Anim Pract* 2001;16(1):58–61.
- [4] Brooks PM, Day RO. Nonsteroidal anti-inflammatory drugs: differences and similarities. *N Engl J Med* 1991;324(24):1716–25.
- [5] Hulse D. Treatment methods for pain in the osteoarthritic patient. *Vet Clin North Am Small Anim Pract* 1998;28(2):361–76.
- [6] Moses VS, Bertone AL. Nonsteroidal anti-inflammatory drugs. *Vet Clin North Am Equine Pract* 2002;18(1):21–37.
- [7] Nichols J, Snyder RW. Topical nonsteroidal anti-inflammatory agents in ophthalmology. *Curr Opin Ophthalmol* 1998;9(4):40–4.
- [8] Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. *Drug Saf* 2002;25(4):233–50.
- [9] Johnston SA, Budsberg SC. Nonsteroidal anti-inflammatory drugs and corticosteroids for the management of canine osteoarthritis. *Vet Clin North Am Small Anim Pract* 1997;27(4): 841–62.
- [10] Papich MG. Principles of analgesic drug therapy. *Semin Vet Med Surg (Small Anim)* 1997; 12(2):80–93.
- [11] Perianin A, Roch-Arveiller M, Giround JP, Hakim J. In vivo effects of indomethacin and flurbiprofen on the locomotion of neutrophils elicited by immune and non-immune inflammation in the rat. *Eur J Pharmacol* 1985;106(2):327–33.
- [12] Leonardi A, Busato F, Fregona I, Plebani M, Secchi A. Anti-inflammatory and antiallergic effects of ketorolac tromethamine in the conjunctival provocation model. *Br J Ophthalmol* 2000;84(11):1228–32.
- [13] Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol* 1992;36(4): 259–84.
- [14] Mathews KA. Non-steroidal anti-inflammatory analgesics: a review of current practice. *J Vet Emerg Crit Care* 2002;12(2):89–97.
- [15] Smith SA. Deracoxib. *Compend Contin Educ Pract Vet* 2003;25(6):419–21.
- [16] Armstrong S. Effects of R and S enantiomers and a racemic mixture of carprofen on the production and release of proteoglycan and prostaglandin E₂ from equine chondrocytes and cartilage explants. *Am J Vet Res* 1999;60(1):98–104.
- [17] Kay-Mugford P, Benn SJ, LaMarre J, Conlon P. In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. *Am J Vet Res* 2000;61(7):802–10.
- [18] Papich MG. Pharmacologic considerations for opiate analgesic and non-steroidal anti-inflammatory drugs. *Vet Clin North Am Small Anim Pract* 2000;30(4):815–37.
- [19] Ward DA, Ferguson DC, Ward SL, Green K, Kaswan RL. Comparison of the blood-aqueous barrier stabilizing effects of steroidal and nonsteroidal anti-inflammatory agents in the dog. *Prog Vet Comp Ophthalmol* 1992;2(3):117–24.

- [20] Regnier A, Whitley RD, Benard P, Bonnefoi M. Effect of flunixin meglumine on the breakdown of the blood-aqueous barrier following paracentesis in the canine eye. *J Ocul Pharmacol* 1986;2(2):165–70.
- [21] Millichamp NJ, Dziezyc J. Comparison of flunixin meglumine and flurbiprofen for control of ocular irritative response in dogs. *Am J Vet Res* 1991;52(9):1452–5.
- [22] Millichamp NJ, Dziezyc J, Rohde BH, Chiou GC, Smith WB. Acute effects of anti-inflammatory drugs on neodymium:yttrium aluminum garnet laser-induced uveitis in dogs. *Am J Vet Res* 1991;52(8):1279–84.
- [23] Dziezyc J, Millichamp NJ, Rohde BH, Smith WB. Comparison of prednisolone and RMI-1068 in the ocular irritative response in dogs. *Invest Ophthalmol Vis Sci* 1992;33(2):460–5.
- [24] Krohne SG, Gionfriddo J, Morrison EA. Inhibition of pilocarpine-induced aqueous humor flare, hypotony, and miosis by topical administration of anti-inflammatory and anesthetic drugs to dogs. *Am J Vet Res* 1998;59(4):482–8.
- [25] Krohne SG. Effect of topically applied 2% pilocarpine and 0.25% demecarium bromide on blood-aqueous barrier permeability in dogs. *Am J Vet Res* 1994;55(12):1729–33.
- [26] Krohne SG, Blair MJ, Bingaman D, Gionfriddo JR. Carprofen inhibition of flare in the dog measured by laser flare photometry. *Vet Ophthalmol* 1998;1(2–3):81–4.
- [27] Roze M, Thomas E, Davot JL. Tolfenamic acid in the control of ocular inflammation in the dog: pharmacokinetics and clinical results obtained in an experimental model. *J Small Anim Pract* 1996;37(8):371–5.
- [28] Bjorkman DJ. Nonsteroidal anti-inflammatory drug-induced gastrointestinal injury. *Am J Med* 1996;101(Suppl 1A):25S–32S.
- [29] Reimer ME, Johnston SA, Leib MS, Duncan RB, Reimer DC, Marini M, et al. The gastroduodenal effects of buffered aspirin, carprofen, and etodolac in healthy dogs. *J Vet Intern Med* 1999;13(5):472–7.
- [30] Editorial Neiger R. NSAID-induced gastrointestinal adverse effects in dogs—can we avoid them? *J Vet Intern Med* 2003;17(3):259–61.
- [31] Ward DM, Leib MS, Johnston SA, Marini M. The effect of dosing interval on the efficacy of misoprostol in the prevention of aspirin-induced gastric injury. *J Vet Intern Med* 2003;17(3):282–90.
- [32] Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999;340(24):1888–99.
- [33] Davidson G. Etodolac. *Compend Contin Educ Pract Vet* 1999;21(5):494–5.
- [34] Budsberg SC, Johnston SA, Schwarz PD, DeCamp CE, Claxton R. Efficacy of etodolac for the treatment of osteoarthritis of the hip joints in dogs. *JAMA* 1999;281(2):206–10.
- [35] Jones SL, Blikslager AT. The future of anti-inflammatory therapy. *Vet Clin North Am Equine Pract* 2001;17(2):245–62.
- [36] Johnson AG, Quinn DI, Day RO. Non-steroidal anti-inflammatory drugs. *Med J Aust* 1995;163(3):155–8.
- [37] Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1984;310(9):563–72.
- [38] MacPhail CM, Lappin MR, Meyer DJ, Smith SG, Webster CRL, Armstrong PJ. Hepatocellular toxicosis associated with administration of carprofen in 21 dogs. *J Am Vet Med Assoc* 1998;212(12):1895–901.
- [39] Powell CC, Lappin MR. Diagnosis and treatment of feline uveitis. *Compend Contin Educ Pract Vet* 2001;23(3):258–66.
- [40] Davis LE. Clinical pharmacology of salicylates. *J Am Vet Med Assoc* 1980;176(1):65–6.
- [41] Wright BD. Clinical pain management techniques for cats. *Clin Tech Small Anim Pract* 2002;17(4):151–7.
- [42] Runk A, Kyles AE, Downs MO. Duodenal perforation in a cat following the administration of nonsteroidal anti-inflammatory medication. *J Am Anim Hosp Assoc* 1999;35(1):52–5.

- [43] Taylor PM, Delatour P, Landoni FM, Deal C, Pickett C, Shojaee Aliabadi F, et al. Pharmacodynamics and enantioselective pharmacokinetics of carprofen in the cat. *Res Vet Sci* 1996;60(2):144–51.
- [44] Slingsby LS, Waterman-Earson AE. Comparison between meloxicam and carprofen for postoperative analgesia after feline ovariohysterectomy. *J Small Anim Pract* 2002;43(7):286–9.
- [45] Schalnus R. Topical nonsteroidal anti-inflammatory therapy in ophthalmology. *Ophthalmologica* 2003;217(2):89–98.
- [46] Abrams KL. Ocular drug reactions and toxicities. In: Bonagura J, editor. *Kirk's current veterinary therapy XII, small animal practice*. Philadelphia: WB Saunders; 1995. p. 1223–6.
- [47] Raizman M. Corticosteroid therapy of eye disease. Fifty years later [comment]. *Arch Ophthalmol* 1996;114(8):1000–1.
- [48] Dziezyc J, Millichamp NJ, Keller CB, Smith WB. Effects of prostaglandin F2 alpha and leukotriene D4 on pupil size, intraocular pressure, and blood-aqueous barrier in dogs. *Am J Vet Res* 1992;53(8):1302–4.
- [49] Ward DA, Ferguson DC, Kaswan RL, Green K. Leukotrienes and sensory innervation in blood-aqueous barrier disruption in the dog. *J Ocul Pharmacol* 1992;8(1):69–76.
- [50] van Best JA, Kappelhof JP, Laterveer L, Oosterhuis JA. Blood aqueous barrier permeability versus age by fluorophotometry. *Curr Eye Res* 1987;6(7):855–63.
- [51] Schalnus R, Ohrloff C. Quantification of blood-aqueous barrier function using laser flare measurement and fluorophotometry—a comparative study. *Lens Eye Toxic Res* 1992;9(3–4):309–20.
- [52] Ward DA, Ferguson DC, Kaswan RL, Green K, Bellhorn RW. Fluorophotometric evaluation of experimental blood-aqueous barrier disruption in dogs. *Am J Vet Res* 1991;52(9):1433–7.
- [53] Krohne SG, Krohne DT, Lindley DM, Will MT. Use of laser flaremetry to measure aqueous humor protein concentration in dogs. *J Am Vet Med Assoc* 1995;206(8):1167–72.
- [54] Chen X, Gallar J, Belmonte C. Reduction by antiinflammatory drugs of the response of corneal sensory nerve fibers to chemical irritation. *Invest Ophthalmol Vis Sci* 1997;38(10):1944–53.
- [55] Bill A, Stjernschantz J, Mandahl A, Brodin E, Nilsson G. Substance P: release on trigeminal nerve stimulation, effects in the eye. *Acta Physiol Scand* 1979;106(3):371–3.
- [56] Dziezyc J, Millichamp NJ, Smith WB. Effect of flurbiprofen and corticosteroids on the ocular irritative response in dogs. *Vet Comp Ophthalmol* 1995;5(1):42–5.
- [57] Ward DA. Comparative efficacy of topically applied flurbiprofen, diclofenac, tolmetin, and carprofen for the treatment of experimentally induced blood-aqueous barrier disruption in dogs. *Am J Vet Res* 1996;57(6):875–8.
- [58] Regnier AM, Dossin O, Cutzach EE, Gelatt KN. Comparative effects of two formulations of indomethacin eyedrops on the paracentesis-induced inflammatory response of the canine eye. *Vet Comp Ophthalmol* 1995;5(4):242–6.
- [59] Millichamp NJ, Dziezyc J, Olsen JW. Effect of flurbiprofen on facility of aqueous outflow in the eyes of dogs. *Am J Vet Res* 1991;52(9):1448–51.
- [60] Sheehan GJ, Kutzner MR, Chin WD. Acute asthma attack due to ophthalmic indomethacin. *Ann Intern Med* 1989;111(4):337–8.
- [61] Sharir M. Exacerbation of asthma by topical diclofenac. *Arch Ophthalmol* 1997;115(2):294–5.
- [62] Sher NA, Krueger RR, Teal P, Jans RG, Edmison D. Role of topical corticosteroids and nonsteroidal antiinflammatory drugs in the etiology of stromal infiltrates after excimer photorefractive keratectomy. *J Refract Corneal Surg* 1994;10(5):587–8.
- [63] Shimazaki J, Saito H, Yang HY, Toda I, Fujishima H, Tsubota K. Persistent epithelial defect following penetrating keratoplasty: an adverse effect of diclofenac eyedrops. *Cornea* 1995;14(6):623–7.

- [64] Hendrix DVH, Ward DA, Barnhill MA. Effects of anti-inflammatory drugs and preservatives on morphologic characteristics and migration of canine corneal epithelial cells in tissue culture. *Vet Ophthalmol* 2002;5(2):127–35.
- [65] Lin JC, Rapuano CJ, Laibson PR, Eagle RC Jr, Cohen EJ. Corneal melting associated with use of topical nonsteroidal anti-inflammatory drugs after ocular surgery. *Arch Ophthalmol* 2000;118(8):1129–32.
- [66] Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc* 2001;99:205–12.
- [67] Toris CB, Yablonski ME, Wang YL, Hayashi M. Prostaglandin A2 increases uveoscleral outflow and trabecular outflow facility in the cat. *Exp Eye Res* 1995;61(6):649–57.
- [68] Weinreb RN, Toris CB, Gabelt BT, Lindsey JD, Kaufman PL. Effects of prostaglandins on the aqueous humor outflow pathways. *Surv Ophthalmol* 2002;47(Suppl 1):S53–64.
- [69] Linden C. Therapeutic potential of prostaglandin analogues in glaucoma. *Expert Opin Invest Drugs* 2001;10(4):679–94.
- [70] Schachtschabel U, Lindsey JD, Weinreb RN. The mechanism of action of prostaglandins on uveoscleral outflow. *Curr Opin Ophthalmol* 2000;11(2):112–5.
- [71] Yousufzai SY, Ye Z, Abdel-Latif AA. Prostaglandin F2 alpha and its analogs induce release of endogenous prostaglandins in iris and ciliary muscles isolated from cat and other mammalian species. *Exp Eye Res* 1996;63(3):305–10.
- [72] Fox SM, Johnston SA. Use of carprofen for the treatment of pain and inflammation in dogs. *J Am Vet Med Assoc* 1997;210(10):1493–8.
- [73] Bartlett JD. Anti-inflammatory agents. In: Bartlett JD, editor. *Ophthalmic drug facts*. St. Louis: Wolters Kluwer; 2003. p. 85–98.