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The use of corticosteroids to treat ocular inflammation

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Use of corticosteroids to treat ocular inflammation began more than 50 years ago when systemic administration of the hypophyseal-derived adrenocorticotrophic hormone caused significant improvement in human patients with uveitis [1,2]. Around the same time, topical therapy with cortisone was begun for patients with uveitis, sclerokeratitis, pemphigus, corneal alkali burns, and vernal keratoconjunctivitis [2]. Since then, corticosteroid therapy has been used extensively to control and prevent sequelae of ocular inflammation. This article reviews the common drugs, routes, indications, and side effects guiding corticosteroid therapy in small animal patients with ocular and periocular disease.

Mechanisms of action

Ocular inflammatory responses are mediated by several factors including cytokines, neuropeptides, and lipid-derived substances. Of these, metabolites of arachidonic acid have received the most attention. Arachidonic acid (AA) is found within the phospholipid bilayer of cell membranes and is released by the enzymatic action of phospholipase A_2 (PLA_2) in response to mechanical or chemical stimuli. Once present in the cytosol, AA is metabolized through two main pathways: the cyclooxygenase and the lipoxygenase (Fig. 1). Both pathways have been demonstrated within cells of conjunctiva, cornea, and uvea [3]. Major products of these pathways include

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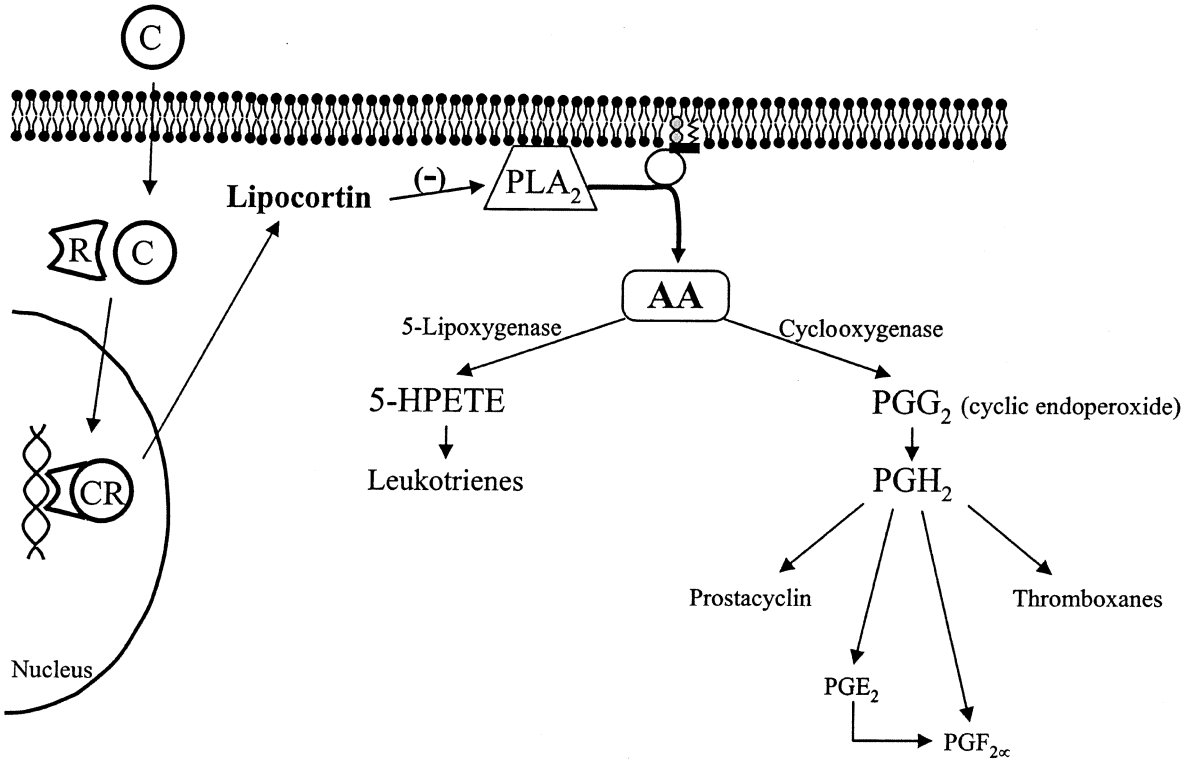

Fig. 1. Arachidonic acid (AA) is released from the phospholipid bilayer by phospholipase A_2 (PLA_2) to yield pro-inflammatory agents via the cyclooxygenase and lipoxygenase pathways. Corticosteroids (C) bind to intracytoplasmic receptors (R) to form a steroid receptor complex (CR). This complex binds to DNA and upregulates the transcription of lipocortin. Lipocortin inhibits the function of PLA_2 preventing the inflammatory cascade. PG, prostaglandin; HPETE, hydroxyeicosatetraenoic acid.

prostaglandins (PGs) and thromboxanes (produced by the cyclooxygenase pathway), and hydroxy–eicosatetraenoic acids and leukotrienes (produced by the lipoxygenase pathway). Collectively, these metabolites have been named eicosanoids [4]. Both hydroxy–eicosatetraenoic acids and leukotrienes act as chemoattractant molecules for inflammatory cells, whereas leukotrienes have an additional direct effect on vascular permeability [3,4].

PGs, specifically PGE and PGF-2α, are the predominant metabolites present in ocular tissues during inflammatory events [5]. PGs disrupt the integrity of vascular endothelium, resulting in breakdown of the blood–ocular barrier, which is normally maintained by the tight junctions of the ciliary body nonpigmented epithelium, iris and retinal vascular endothelium, and retinal pigmented epithelium [6]. If left untreated, elevated intraocular PG concentrations can lead to a self-perpetuating cycle of inflammation with vision-threatening consequences. PGs are removed from the eye by active transport by the ciliary body and degradation by PG15-dehydrogenase. Unlike other organs, the eye contains little PG15 dehydrogenase [7]. Active transport by the uvea is a saturable and sodium-dependent system that is impaired with inflammation.

Clinical signs of acute intraocular inflammation include uveal vasodilation, miosis, ocular hypotension, and exudation of protein (aqueous flare) and cells into the aqueous humor. More chronic sequelae of ocular inflammation include corneal or uveal scarring, synechia formation, cataract formation, vitreous liquefaction, glaucoma, retinal detachment, retinal degeneration, optic nerve degeneration, and phthisis bulbi. Anti-inflammatory therapy is therefore essential. Potential mechanisms of action include interference with synthesis or release of inflammatory mediators or antagonism of mediator-specific receptors. To date, receptor antagonists have not been identified. Therefore, all current anti-inflammatory medications act by reducing production of metabolites of the AA cascade.

Corticosteroids are lipophilic 21-carbon proteins derived from cholesterol. Both endogenous and administered corticosteroids bind to intracytoplasmic glucocorticoid receptors (see Fig. 1). These receptors are almost ubiquitously expressed and regulate cells' response to inflammation [8]. Once bound, corticosteroids change the receptor's tertiary conformation so as to release a chaperone protein and reveal a DNA-binding region [9]. The corticosteroid–receptor complex then is translocated to the nucleus, where it binds to specific DNA sequences called glucocorticoid response elements. Interaction with these motifs alters cell gene expression and, ultimately, protein synthesis. Some genes are inhibited, although most, including lipocortin, are upregulated [10]. Lipocortin inhibits proinflammatory substances, such as platelet-activating factor (PAF) and PLA_2, the enzyme responsible for initiating the AA cascade [8]. Additional evidence suggests glucocorticoids have a direct negative influence on PGE isomerase, resulting in reduced PGE synthesis [11] and increased vascular stability.

At a cellular level, such inhibition of proinflammatory pathways is manifested in the eye as decreased exudation of cells and fibrin, inhibition of fibroblastic and collagen-forming activity, retardation of epithelial and endothelial regeneration, stabilization of lysosomal membranes, reduced neovascularization, and stabilization of the blood–ocular barrier [12].

General therapeutic considerations

Ocular therapy with corticosteroids should not be indiscriminate. Before initiation of ocular therapy, a number of factors should be considered. These include but are not limited to cause, severity, and site of inflammation, likely duration and dose of treatment, type of corticosteroid, and route of administration. Five routes of ocular administration are used commonly: topical, subconjunctival, systemic, retrobulbar, and intravitreous. Retrobulbar and intravitreous applications are not recommended because they are technically difficult to perform and may result in blinding complications; additionally, systemically administered corticosteroids reach a near equal therapeutic concentration.

Topical administration of corticosteroids

The topical route of corticosteroid administration is perhaps the most common used in veterinary practice because of ease of application, high local drug concentration, relatively poor penetration of the blood–ocular barrier by some systemically administered agents, and minimal systemic side effects. Dose frequency varies greatly and should be tailored to the degree of inflammation. Severe inflammation should be treated aggressively (at least every 4–6 hours) until clinical evidence of improvement is seen. The frequency of application should then be gradually tapered to decrease the possibility of recurrence and to diminish side effects.

Ophthalmic corticosteroids vary in their preparation, potency, and degree of corneal penetration. Ophthalmic solutions provide the most rapid uptake and highest peak tissue levels. Dexamethasone can be detected in the aqueous humor within 15 to 30 minutes after topical application of a single drop of an ophthalmic solution [13]. Higher drug concentrations permit greater intraocular concentrations [14]. Duration of action of topically applied solutions is limited by rapid clearance from the ocular surface. After application, the drug settles in the conjunctival sac and then is actively pumped through the nasolacrimal apparatus, limiting contact time.

Contact time, and thereby corneal and aqueous humor concentrations and therapeutic effect, can be increased by using suspensions or ointments [15]. Dexamethasone sodium phosphate ointment is one exception, because lipid-based ointment vehicles retain the drug and decrease its bioavailability [16].

Ointments tend to accumulate along the adnexa, and some owners find them more difficult to administer than ophthalmic solutions. Although ointments decrease visual acuity, this is usually of less significance in veterinary patients than in human patients. Suspensions consist of poorly water-soluble crystalline drug particles in a saturated aqueous solution and are an ideal preparation for lipophilic corticosteroids. They deliver higher drug concentrations than solutions, but care must be taken to mix the preparation adequately by vigorous shaking before application. Inadequate mixing results in variable drug concentration. Few side effects are reported with suspensions, but they do cause mechanical irritation in some patients [17].

To exert a therapeutic effect intraocularly, ophthalmic preparations must penetrate the cornea. The cornea consists of hydrophobic epithelium, which is highly impenetrable to aqueous compounds, and hydrophilic stroma. Lipophilic acetate and alcohol preparations penetrate the cornea up to 20-fold greater than water–soluble phosphate preparations [18] and thus should be chosen for treatment of intraocular inflammation.

Currently available ophthalmic corticosteroids suitable for topical application include prednisolone acetate, dexamethasone alcohol, dexamethasone sodium phosphate, betamethasone, and hydrocortisone (Table 1). Dexamethasone and betamethasone are approximately 5- to 10-fold more potent than prednisolone and 25-fold more potent than hydrocortisone [15,19]. The difference in potency between dexamethasone and prednisolone is somewhat obviated in the clinical setting by the fact that prednisolone is commonly available at a 10-fold higher concentration than is dexamethasone. Additionally, when prepared as an acetate suspension, prednisolone has superior penetration into the anterior chamber through intact corneal epithelium, making it the drug of choice for anterior uveitis [20]. In sharp contrast, hydrocortisone, which is a typical constituent of the common triple antibiotic/corticosteroid medications, does not penetrate the cornea. Therefore, hydrocortisone is ineffective for the treatment of intraocular inflammation and should not be used.

Topically administered corticosteroid therapy is indicated for some forms of conjunctivitis, dacryocystitis, episcleritis, keratitis, and anterior uveitis. Because topically applied corticosteroids do not achieve therapeutic concentrations in the eyelids, posterior segment, or orbit, other routes of administration should be used for inflammation at these sites. Topical corticosteroid therapy for conjunctivitis is aimed at decreasing clinical signs and discomfort. Because conjunctivitis is a surface disease, it can be treated with hydrocortisone. A potent corticosteroid often is required, however, particularly in the treatment of immune-mediated conjunctivitis, such as pannus. In these cases, prednisolone acetate or a phosphate preparation of dexamethasone should be selected. Caution should be exercised when treating feline conjunctivitis, because this disease is invariably infectious in nature. Typical causes, such as feline herpesvirus, *Chlamydophila felis*, and *Mycoplasma* spp, often are exacerbated by corticosteroid therapy [21,22].

Table 1
Commonly used and commercially available corticosteroid agents for ophthalmic use

Route	Commercially available drugs	Suggested dose[a]
Topical		
	Ointments	
	Dexamethasone sodium phosphate (0.1%) (usually with neomycin-polymyxin)	1/4′′ strip q2–48 hours
	Hydrocortisone (1%) (with neomycin-polymyxin-bacitracin)	1/4′′ strip q2–48 hours
	Solutions/suspensions	
	Dexamethasone sodium phosphate (0.1%) (usually with neomycin-polymyxin)	1 drop q2–48 hours
	Prednisolone acetate (1% or 0.125%)	1 drop q2–48 hours
Subconjunctival		
	Solutions	
	Dexamethasone (2, 4, or 10 mg/mL)	0.5–1.0 mg
	Triamcinolone acetonide (6 or 40 mg/mL)	3–15 mg
	Betamethasone acetate (6 mg/mL)	1–3 mg
Systemic		
	Injectable	
	Dexamethasone sodium phosphate (2, 4, or 10 mg/mL)	0.2 mg/kg IM or IV
	Prednisolone acetate/sodium succinate (25, 50, 100 mg/mL)	2–4 mg/kg IM or IV
	Oral (tablets or suspension)	
	Dexamethasone (0.25–4.0 mg, tablets)	0.1–1.0 mg/kg/d
	Prednisone (1–50 mg, tablets; 1–5 mg/mL, suspension)	0.5–2.0 mg/kg/d
	Prednisolone (5–20 mg, tablets; 3 mg/mL, suspension)	0.5–2.0 mg/kg/d

Abbreviations: IM, intramuscular; IV intravenous; q, every.
[a] Doses are recommended starting doses and should be tapered as inflammation decreases.

Treatment of dacryocystitis involves first establishing patency of the nasolacrimal system by cannulation and flushing. A combined antibiotic and corticosteroid solution is then used to preserve patency. Ointments should be avoided because they penetrate the nasolacrimal apparatus poorly as a result of their high viscosity. Adjunctive therapy with systemically administered antibiotics or corticosteroids may be warranted.

Primary episcleritis is an immune-mediated disease manifesting as either simple episcleritis or nodular granulomatous episcleritis (NGE). Simple episcleritis is not associated with systemic disease, responds well to corticosteroid therapy, and may be self-limiting [23]. Nodular granulomatous episcleritis presents as a raised, fleshy, pink-red mass that originates near the limbus but may infiltrate the adjacent cornea. Treatment involves long-term topical corticosteroid therapy combined with systemically administered immunosuppressive agents, such as azathioprine. Therapy should be gradually tapered over a period of months to prevent recurrences,

although they are still common [23]. Left untreated, secondary keratitis or lipid keratopathy may develop.

There are numerous causes of keratitis in small animals that may require immunomodulation as part of the therapeutic approach. This is perhaps most important for those forms of keratitis, such as chronic superficial keratitis (pannus) and feline eosinophilic keratitis, and NGE that have an underlying immune-mediated basis. In many forms of keratitis, maintenance of optical clarity through retardation or prevention of corneal neovascularization, scarring, or melanosis is an important goal. For this reason, topical corticosteroid therapy may be required even when the keratitis does not have an immunologic basis. Topically applied immunomodulating drugs, such as cyclosporine, are often used in conjunction with topically applied corticosteroids for synergistic anti-inflammatory effects. Feline eosinophilic keratitis undoubtedly represents an exuberant immunologic response. Feline herpesvirus DNA can be detected in the cornea of approximately 75% of patients with this disease and many cases are also ulcerative [24]. Therefore, topical corticosteroid therapy may not be advisable in all cases. In many cases, simultaneous antiviral therapy is recommended when using topically applied corticosteroids in cats with eosinophilic keratitis.

There is a plethora of endogenous and exogenous causes for uveitis, including intraocular or corneal trauma (including ocular surgery), corneal wounds, infection (bacterial, viral, fungal, protozoal, or parasitic), neoplasia, toxins, and immune-mediated disease. The exact etiopathogenesis may be difficult or even impossible to identify in every clinical case, but an effort to discern the cause should be made before initiating therapy to prevent exacerbation of the disease process. With anterior uveitis, the blood–aqueous barrier is breached and intraocular PG concentration may increase 200-fold [5]. Blocking the synthesis and production of these PGs requires intraocular penetration of anti-inflammatory agents. Topically administered 1% prednisolone acetate or 0.1% dexamethasone achieves therapeutic concentrations in the aqueous humor and inhibits 40% to 50% of protein exudation from the iris and ciliary body [25]. These corticosteroid agents may provide more potent stabilization of the iridal vascular endothelial membranes than those of the ciliary body epithelium [26] but do not inhibit protein exudation completely, because other nonarachidonic acid cascade inflammatory factors are also involved [25]. Frequency of topical application of a corticosteroid for anterior uveitis depends on the severity of clinical signs but typically ranges from once every 2 to 48 hours. Dosage interval initially should be short and then can be increased once a response to therapy is achieved. Systemically administered steroidal or nonsteroidal anti-inflammatory, antimicrobial, or antineoplastic agents may be necessary in conjunction with topically administered corticosteroids to decrease or resolve uveitis.

Regardless of the ocular condition being treated, topical administration of corticosteroids is not without risk. Therapy should not be initiated

without an understanding of the disease process being treated and the potential complications and side effects of these potent anti-inflammatory agents. After topical application the drug acts locally, but is also absorbed systemically through the conjunctiva and nasal or oral mucosa after traveling through the nasolacrimal apparatus [27]. Approximately 1% to 35% of the total topical dose is systemically absorbed and can be recovered in the serum, plasma, urine, kidneys, bile, gallbladder, liver, and adrenal glands [18,27,28]. Although the total systemic dose achieved with topical therapy is rarely greater than 0.1 mg/kg/d, this concentration can alter the hypothalamic-hypophyseal-adrenal axis. Adrenal suppression was induced in dogs within as little as 2 weeks of beginning four times daily treatment with 1% prednisolone acetate or 0.1% dexamethasone, irrespective of the patient's weight [29–31]. Clinical signs of hyperadrenocorticism became evident in these patients, and liver biopsy results were consistent with corticosteroid hepatopathy. Adrenal suppression and clinical signs were reversible but were dependent on duration and cumulative dosage of exogenous corticosteroid treatment as well as on the degree of adrenal atrophy [30]. Dogs receiving chronic topical corticosteroid therapy should routinely be examined for signs of iatrogenic hyperadrenocorticism and corticosteroid hepatopathy.

When topically administered corticosteroids are used appropriately, ocular side effects are encountered infrequently but may include glaucoma, progressive cataract formation, and corticosteroid keratopathy. Topical administration of dexamethasone sodium phosphate or prednisolone acetate to normal cats and glaucomatous dogs induced a mild gradual increase in intraocular pressure (IOP) over a 1- to 3-week period [32,33] that was most likely secondary to decreased aqueous humor outflow facility [34]. IOP normalized within 7 days of cessation of corticosteroid treatment [32,33], suggesting only transitory induction of ocular hypertension. Although the changes in IOP were of statistical significance, their clinical significance is less clear. Adding to the complexity of this issue, there are numerous factors affecting the susceptibility of some human beings to elevated IOP after topical application of corticosteroids, with up to two thirds of the normal human population not experiencing elevated IOP after corticosteroid administration. The IOP-raising effect of corticosteroids in some people has led to the development of corticosteroid preparations, such as rimexolone, fluorometholone, loteprednol, and others, which are less likely to raise IOP. The authors are aware of few trials of their IOP-altering effects in small animal patients [35].

In small animal patients, cataracts are seen rarely if ever as a side effect of ocular corticosteroid use. In one experimental report, however, 28% to 50% of cats receiving topically administered 1% prednisolone acetate or 0.5% to 1% dexamethasone sodium phosphate developed cataracts [33]. This surprisingly high incidence is not borne out in clinical practice. Similar to that described in human beings [36], we have observed diffuse, punctate,

subepithelial, sparkly white corneal opacities in several patients receiving either 1% prednisolone acetate or 0.1% dexamethasone sodium phosphate for surface or intraocular inflammation. These opacities develop over several months in a small percentage of patients and often lessen after cessation of topical corticosteroid treatment.

Many actions of corticosteroid therapy can be undesirable in some patients. Phagocytosis of microorganisms and intracellular killing of bacteria are decreased and collagenase activity is increased with corticosteroid therapy [37,38], thereby leading to worsening corneal ulceration and delaying healing. Corneal wound strength may be further decreased because of reduced keratocyte proliferation and migration and impaired collagen production in patients receiving corticosteroid therapy [39,40]. Bacterial, fungal, and viral disease also may be activated or exacerbated with topical corticosteroid therapy [37]. For all these reasons, corticosteroids should not be used topically in patients with infectious or ulcerative keratitis. Before starting topical corticosteroid therapy, the corneal surface should be examined carefully for ulcerative defects using fluorescein stain. In particular, cats experiencing primary herpetic keratoconjunctivitis frequently develop severe stromal keratitis and shed the virus for longer periods if corticosteroids are used [24].

Subconjunctival administration of corticosteroids

The major advantage attributed to the subconjunctival route of administration is reduced reliance on frequent topical application. This route may also establish a greater intraocular concentration of drug than is possible using frequent topical applications. Subconjunctivally injected corticosteroids suppress surface (corneal) inflammation less effectively than topically instilled corticosteroids [41]; therefore, the subconjunctival route should generally be reserved for those patients in which sufficiently frequent topical application of medication is not possible, or it should be used as an adjunct to topical therapy. After subconjunctival injection, most of the drug is believed to reach the ocular surface by leakage back out the needle tract and into the tear film [42]. This leads to a rapid reduction of the drug depot. Some drug is also absorbed by conjunctival and episcleral blood vessels and dissipated within the systemic circulation as occurs after injection of drugs at any vascular site. A small percentage of the drug may also be absorbed directly across the sclera. The local depot effect and diffusion of subconjunctivally injected corticosteroids make them potentially beneficial in cases of keratitis, episcleritis, and anterior uveitis.

The technique for subconjunctival injection is relatively simple, but great care must be taken to avoid globe perforation or damage to intraocular structures. Injections should always be made under the bulbar conjunctiva, approximately 3 to 4 mm behind the corneoscleral limbus. The dorsal or

dorsolateral region of the globe is usually preferred for ease of access. Solutions should not be injected under the palpebral conjunctiva, because absorption from this site is largely systemic, decreasing ocular bioavailability. In compliant patients, subconjunctival injections can be performed using only topical anesthesia. One drop of an ophthalmic anesthetic solution, such as proparacaine, is applied to the ocular surface, followed by more sustained application using a cotton-tipped applicator soaked in the same anesthetic agent and held against the conjunctiva at the intended injection site. In small animal patients, the drug volume injected should be limited to 0.25 to 0.5 mL injected through a 25-or 27-gauge needle. An obvious bleb results but reduces in size relatively quickly. Human beings experience mild pain that may persist for up to 12 hours after subconjunctival injection [12]. Potential complications of this technique include globe perforation and retinal detachment [43], granuloma formation at the injection site [44,45], extraocular muscle paralysis [46], and periocular atrophy or fibrosis [47]. Depending on the duration of effect of the product injected, one potential complication is a change in the patient's condition that necessitates cessation of corticosteroid therapy. In some such cases, the need to discontinue corticosteroid therapy may be urgent or serious enough that surgical removal of the corticosteroid depot and associated conjunctival and subconjunctival tissues is necessary.

Solutions injected subconjunctivally must be well tolerated in the subconjunctival space and on the ocular surface itself. As a general rule, corticosteroid solutions intended for parenteral injection may be administered subconjunctivally. To the authors' knowledge, however, no preparations are currently licensed for subconjunctival use. A list of preparations commonly administered by this route is provided in Table 1. Dexamethasone is believed to have a duration of effect of approximately 1 to 2 days, whereas betamethasone and triamcinolone act as repositol preparations with effects up to 3 weeks. Methylprednisolone acetate should not be used because it has been associated with notable and sometimes uncomfortable subconjunctival plaques that require surgical removal. Ophthalmic preparations intended for topical application should not be injected subconjunctivally, because the preservatives contained in these compounds can be irritating to the subconjunctiva.

Systemic administration of corticosteroids

Because the topical and subconjunctival routes of corticosteroid administration do not achieve therapeutic concentrations in the adnexa, posterior segment, or orbit, systemic treatment with corticosteroids is frequently necessary in veterinary ophthalmology. This route of administration is indicated for the management of inflammatory disorders of the adnexa, choroid, retina, optic nerve, and orbital contents once an infectious cause has

been ruled out. Patients with anterior uveitis may also be treated with systemically administered corticosteroids either to augment topically administered corticosteroid agents or because the presence of a corneal ulcer prohibits topical use of such agents. The same anti-inflammatory (or occasionally immunosuppressive) dosages that are used for other systemic conditions are appropriate for ocular and periocular diseases. Oral or parenteral administration of prednisone, prednisolone, or dexamethasone is appropriate. Concerns regarding short-term side effects of corticosteroid therapy and the induction of endocrinopathies after longer term therapy apply equally whether treating ocular or systemic disease.

Summary

Corticosteroids are invaluable therapeutic agents for treatment of ocular inflammation in small animal patients. The use of potent anti-inflammatory agents carries with it the risk of some side effects, however. Although some of these may be lessened by topical or subconjunctival administration, these routes are associated with specific ocular side effects about which the practitioner must be aware. With judicious use, corticosteroids remain a mainstay for the prevention and treatment of many painful and potentially blinding ocular diseases.

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