Lacrimostimulants and lacrimomimetics

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A thorough understanding of tear film physiology and the clinical manifestations of tear film abnormalities enables the veterinarian to diagnose and treat quantitative (decreased aqueous layer) and qualitative (decreased mucin or lipid layers) tear film abnormalities accurately and to monitor the responses to lacrimostimulatory and lacrimomimetic therapy. This article reviews the embryology, anatomy, and physiology of the lacrimal glands; glands of the nictitating membrane; goblet cells; and tarsal glands as well as the pathophysiology of tear film deficiencies. We also review lacrimostimulants, including cyclosporine, tacrolimus, sirolimus, pilocarpine, and lacrimomimetics (tear film replacements).

Embryology, anatomy, and physiology of tear-producing glands and tears

The tear film is a complex fluid layer composed of mucous (produced by conjunctival goblet cells), aqueous tears (produced by the lacrimal gland and the gland of the third eyelid), and lipid (produced by the tarsal glands) (Fig. 1). The tear film is essential in maintenance of corneal clarity, and it serves as the anterior refracting surface and provides nutrition to the corneal surface [1]. Tear evaporation increases tonicity, and this creates an osmotic gradient that partially determines the movement of fluid through the cornea. In dry eye states, the increased tonicity dehydrates the ocular surface [2–4]. The tonicity of tear film can be manipulated with hypertonic solutions to assist in removal of corneal edema or with hypotonic solutions to retain ocular surface hydration [1]. In addition to the nutrient component of tears, this complex film serves as the primary source of oxygen to the corneal surface to support aerobic metabolism [5]. Tears also provide at least three

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antimicrobial substances, including betalysin, lysozyme, and lactoferrin, and this film distributes leukocytes to the corneal surface [1]. Tears lubricate the ocular surface and eyelids and flush debris from the ocular surface.

The tear film is approximately 7 to 10 μm in thickness and has three distinct layers: a thin adherent mucous layer (0.1 μm), a thick aqueous layer (7 μm), and a thin lipid covering (0.01–0.05 μm) (see Fig. 1) [5].

The mucous layer is produced by goblet cells distributed predominantly within the fornix and palpebral conjunctiva of dogs and cats (see Fig. 1). The goblet cells are derived from surface ectoderm during the middle stages of embryogenesis [6]. This mucous is synthesized by the endoplasmic reticulum and the Golgi apparatus and is stored within granules within the apical goblet cells [1]. The induction stimuli for mucous secretion by conjunctival goblet cells are unknown. However, several agents, including parasympathetic agonists, histamines, and prostaglandins, stimulate goblet cells to produce mucin [1]. This tenacious substance attaches to small villi on the surface of the epithelial cells. A secondary nongoblet cell, mucous secretion by specialized cells within the conjunctiva has been reported [7]. It has been determined that the mucous layer is bilayered [8]. The corneal epithelial cells secrete the inner glycocalyx, and the goblet cells secrete the thicker outer portion of the mucin layer. This portion consists mainly of glycoproteins [8].

This bilayer adheres the tear film to the ocular surface. Reduction of mucous secretion by the goblet cells is manifested with an accelerated tear film breakup in dogs and cats. Tear film breakup times are estimated by timed
observation of the tear film, and normal tear film breakup times are approximately 20 seconds [9]. Mucin deficiencies manifest with tear film breakup times of less than 5 seconds in dogs [10] and cats [11]. Conjunctival biopsies and light microscopic examination of periodic acid–Schiff–stained sections allow the examiner to assess goblet cell morphology and numbers. Decreased numbers of goblet cells in conjunction with rapid tear film breakup times support the diagnosis of tear mucous insufficiency in the dog and cat [10,11]. Goblet cells numbers vary based on the location sampled within the conjunctiva, however, and the mucin can be easily expressed by tissue compression. Therefore, it is important to examine control counts and to compare them with basal epithelial counts (goblet/epithelial cell ratios) from similar locations in the dog and cat [9–11]. The ventral nasal fornix is considered an optimal location for goblet cell assessment in the dog and cat [9–11]. The conjunctiva must be handled carefully with small atraumatic forceps to avoid expression and collapse of the goblet cells during the biopsy and processing for histologic examination. In addition, the goblet cell–to–epithelial cell ratio varies; it approximates 0.30 in normal dogs and 0.68 in cats [11,12]. Mucin deficiency keratopathies are characterized by goblet cell–to–epithelial cell ratios as low as 0.05 in dogs [12] and 0.08 in cats [11].

The lacrimal glands and the gland of the third eyelids are derived from surface ectoderm in midembryogenesis (lacrimal glands develop in the fourth month in human beings) [13]. The lacrimal glands and the gland of the nictitans are tubuloacinar. The histologic morphology and their seromucinous secretions are similar. The lacrimal glands produce approximately 60% of the total aqueous portion of the tears, whereas the gland of the third eyelid produces approximately 40% [14,15]. The lacrimal glands are attached to the dorsal temporal episclera, and multiple ducts exit near the conjunctival fornix [16]. The gland of the third eyelids is attached to the base of the cartilage in the nictitans, and multiple ducts exit on the bulbar surface of the third eyelid amid follicles of lymphocytes and plasma cells. The lacrimal glands and the glands of the nictitans receive their blood supply and venous drainage via the lacrimal and nictitans arteries and veins, respectively [16]. The lacrimal glands and glands of the nictitans are innervated by parasympathetic and sympathetic nerves [16]. The primary control of aqueous tear secretion is via the parasympathetic nervous system. It has been reported that a significant basal secretion of tears is present continuously and that increases in tear flow are stimulus driven [17]. Nevertheless, there is some controversy on basal secretion, and some investigators report that most of the aqueous tears are produced by active stimuli and that basal tear production is low during sleep and general anesthesia [18]. The aqueous tear production is estimated by Schirmer tear tests (STTs) [19]. Two types of STTs have been reported in dogs (abbreviated as STT 1 and STT 2) [20]. In veterinary medicine, the STT 1 measures reflex aqueous tear production and the STT 2 measures the basal tear production after topical anesthetic is applied [20]. In association with
typical clinical manifestations, STT 1 values less than 10 in the dog and less
than 5 in the cat confirm the diagnosis of keratoconjunctivitis sicca (KCS)
[19]. The phenol-red-thread tear test is also used to estimate tear production
[21]. A small phenol-red thread is placed in the ventral conjunctival fornix
for 15 seconds, and the normal reference range of wetting is 30 to 38 mm in
dogs [21].

The tarsal glands are also derived from surface ectoderm during
midembryogenesis [13]. Approximately 40 of these modified sebaceous
 glands lie within the tarsal plate (see Fig. 1). They line the inner surface of
both eyelids and can be observed through the palpebral conjunctiva. The
ducts of these glands empty onto the surface of the eyelids through orifices
along the edges of the eyelids. Contraction of the orbicularis oculi muscle is
partially responsible for expression of the lipid secretions onto the tear film.
Their lipid secretion contains waxy esters, sterols, triglycerides, cholesterol,
and some polar lipids. This lipid mixture coats the surface of the tear film
and retards tear evaporation [9]. The lipid layer of tears can be assessed by
biomicroscopic examination [22] and tear film breakup times [9].

Pathophysiology and etiologies of tear film abnormalities

Quantitative and qualitative tear film abnormalities often have similar
clinical signs, including blepharospasm, ocular discharge, ulcerative keratitis,
corneal vascularization, pigmentation, and cellular infiltrates (Fig. 2).

Conjunctivitis, indolent corneal ulceration, keratitis with pigmentation,
vascularization, and cellular infiltrates are common clinical manifestations
of goblet cell insufficiency in dogs and cats [9–11]. The etiologies of goblet
cell suppression and mucin deficiency are poorly understood. Most goblet
cell deficiencies are assumed to be acquired and related to other chronic
primary inflammatory ocular diseases in the dog and cat [9–11]. Congenital
and developmental goblet cell anomalies have not been reported.

Fig. 2. An illustration of the common clinical manifestations of qualitative or quantitative tear
film abnormalities in the dog and cat.
Aqueous tear film deficiency manifests acutely with ocular discomfort, mucopurulent ocular discharge, and conjunctivitis, and the cornea may be ulcerated [9,23]. Chronic aqueous tear film deficiencies often manifest with indolent corneal ulcers, vascularization, pigmentation, and degeneration of the cornea and ocular discharge [9,23]. There are many reported etiologies for diminished aqueous tear production, including immune-mediated lacrimal gland disease [24], congenital absence of glands and ducts [9,25], neurogenic KCS (absence of parasympathetic innervation to the lacrimal glands) [9], drug suppression of or toxic damage to lacrimal acini, and traumatic or viral destruction of the lacrimal glands or ducts [9,26–28]. Because the etiology of canine KCS cannot be determined in most cases, an immune-mediated etiology is assumed. This assumption is based on histologic studies that revealed mononuclear cell infiltrates and associated lacrimal gland atrophy and the response of these cases to T-lymphocyte suppression with topical cyclosporine therapy [24,29,30].

Lipid tear film deficiency may be observed in older dogs. The clinical manifestations include abnormal tarsal gland secretion, multiple chalazion, degenerative corneal disorders, and rapid tear film breakup times [9]. Meticulous examination of the eyelid margins with a biomicroscope confirms abnormalities of the tarsal glands and ducts. Tarsal gland insufficiency is usually an acquired disorder. Expression of normal tarsal glands produces a clear viscous oil, whereas abnormal gland secretions are opaque and creamy, consistent with tarsal acinar pathology [9]. Dogs and cats with abnormal tarsal glands and rapid tear film breakup times benefit from petroleum tear replacements to stabilize the tear film. Antibiotic therapy may be indicated when bacterial tarsal gland adenitis is confirmed with biopsy as well as with bacterial culture and sensitivity testing. Surgical curettage of impacted glands and chalazion may be indicated to eliminate frictional irritation to the cornea and to help to restore some tarsal gland secretion. Rarely, a congenital absence of the tarsal glands associated with an eyelid coloboma is accompanied by accelerated tear film breakup times [9]. These dogs and cats benefit from lipid tear film replacements and surgical correction of the eyelid abnormalities to decrease exposure keratitis.

**Lacrimalstimulants**

Lacrimalstimulants are medications that stimulate tear production and include immunomodulators (cyclosporine, tacrolimus, and sirolimus) and cholinergics (pilocarpine).

**Immunomodulators**

**Cyclosporine**

Cyclosporine (CsA) is a noncytotoxic immunosuppressant that stimulates tear production in the dog. This drug is recommended as a topical therapy
in most if not all dogs with KCS [29–36]. Most of the benefits of CsA are the result of its selective T-helper lymphocyte suppression by inhibition of calcium-dependent phosphatase calcineurin [37]. This allows for a predominance of T-suppressor cells that suppress immune-mediated disorders [38]. CsA also inhibits fibroblast proliferation and has direct lacrimostimulatory properties [29]. When CsA is administered systemically to human beings, their tear flow increases; however, the mechanism by which this occurs is not completely understood [39]. Similar lacrimostimulatory properties are observed in dogs, and all these properties make it an ideal topical medication to treat KCS in animals [9,29]. CsA is lipophilic, and it absorbs into the cornea in high concentrations [29]. There is a limited amount of CsA detectable within the eye or systemically after topical application. Altered lymphocyte proliferation has been reported in dogs receiving topical ophthalmic CsA [40,41]. Despite these findings, systemic side effects or toxicities have not been reported in dogs after long-term topical ocular application. Ocular complications are also uncommon in dogs and cats treated with CsA. There are few if any contraindications for topical CsA in dogs and cats, except demonstrated conjunctival hypersensitivities. Occasionally, a dog develops marked conjunctival hyperemia and irritation after topical application of CsA. If these clinical signs abate after the CsA is discontinued and return when the CsA is reapplied, other topical formulations or lacrimostimulants should be considered. CsA is available commercially in a 0.2% concentration as an ointment and may be formulated in a 1% or 2% concentration in corn or olive oil. Twice-daily therapy with topical cyclosporine ointment or solution is the recommended initial therapy for all forms of KCS in dogs and cats. More than 75% of the reported dogs diagnosed with KCS and treated with twice-daily CsA responded with decreased ocular discharge, improved corneal clarity, and increased STT values [9,29,30]. In addition, significant numbers of dogs that do not increase their tear production experience significant reduction in conjunctival and corneal inflammation [29,30]. Reduction to once-daily therapy with CsA has been reported when the STT results are above 20 mm/min, provided that the STT results do not decrease after reduction to once-daily therapy [9]. Significant goblet cell stimulation and increased mucous secretion are also reported with topical CsA therapy [42]. This effect also makes topical CsA a useful therapy for the qualitative tear film disorders that develop secondary to mucin deficiency. Topical CsA also has significant therapeutic benefits in the treatment of immune-mediated corneal disorders, including pannus [43], and it is useful in corneal transplantation because it reduces graft rejection [44].

Tacrolimus

Tacrolimus (FK506) is a cytokine suppressor that is a calcineurin inhibitor similar to CsA [45–48]. There is considerable anecdotal clinical information that topical tacrolimus stimulates tear production as well as or
better than CsA in dogs. Given that this immunomodulator is similar in structure and action to CsA, it is quite likely that application of this medication topically on the eyes of dogs with KCS improves their ocular condition. At this time, however, there are only two abstracts of clinical trials of this medication in dogs, and the results of applying 0.02% or 0.03% are quite different, with an adequate tear stimulation noted with 0.02% solution and nonsignificant tear stimulation noted with 0.03% solution [49,50]. The long-term effects of this medication on the lacrimal glands, nictatans glands, goblet cells, and tarsal glands as well as on the eye are unknown, and, most importantly, possible toxicities and side effects from topical application are also unknown at this time. Until clinical trials conclusively prove efficacy and safety, prescribing this medication is discouraged.

**Sirolimus**

Sirolimus is another immunomodulating calcineurin inhibitor [51,52] that may have lacrimostimulatory effects. Similar to tacrolimus, sirolimus has also received some anecdotal reports of usefulness in treating KCS in animals. The mechanism of action of sirolimus is somewhat similar to that of CsA and tacrolimus, and it may increase tear production. Clinical trials of this medication have not been completed, however, and its topical use should be limited until such research has confirmed its efficacy and safety.

**Cholinergics**

**Pilocarpine**

Pilocarpine is a parasympathomimetic that is a nonspecific stimulant of the parasympathetic nervous system. This stimulation includes the parasympathetic receptors of the lacrimal glands and the glands of the third eyelids when it is given orally or topically on the eye [53,54]. Pilocarpine has received a small resurgence in popularity in topical therapy of the neurogenic forms of KCS. This is related directly to increased identification of neurogenic forms of KCS in some of the dogs that do not respond to CsA. Neurogenic KCS cases are often unilateral, and they usually respond poorly to topical cyclosporine alone. Pilocarpine may be administered orally at one drop per 10 kg of body weight of a 1% or 2% solution, and the dose can be increased gradually until signs of systemic toxicity (eg, salivation, vomiting, diarrhea, bradycardia) develop or until the STT score increases [9]. Dilute pilocarpine administered topically to the eye has also been recommended [9]. The STT should be monitored frequently over several months of therapy to assess whether significant stimulation of aqueous tears develops as the oral or topical doses increase. Smith et al [54] reported no significant stimulation of tears in the eyes treated with pilocarpine. Nevertheless, veterinary ophthalmologists have shared anecdotal experiences whereby increases in tear production in dogs with unilateral or,
occasionally, bilateral neurogenic KCS were observed after being non-responsive to months of topical CsA therapy. We recommend several months of trial topical or oral therapy with pilocarpine in dogs with suspected neurogenic KCS. Significant increases in STT scores in these dogs support the diagnosis of neurogenic KCS and warrant continued cholinergic therapy. Pilocarpine that is administered topically on the eye induces a significant uveitis with miosis and conjunctival hyperemia. Simultaneous topical nonsteroidal and anesthetic medications reduce the inflammation associated with topical pilocarpine [55]. Diluting topical pilocarpine (eg, to 0.25% in artificial tears) may also alleviate or minimize problematic inflammatory reactions.

**Lacrimomimetics**

Lacrimomimetics include tear film substitutes that attempt to supplement all or parts of the three tear film layers. An appropriate lacrimomimetic should be selected based on nature of the tear film abnormality and owner compliance. Lacrimomimetics are recommended as adjunctive therapy to lacrimostimulatory therapy of qualitative and quantitative tear film abnormalities. When the mucous, aqueous, and lipid tear layers are restored, the lacrimomimetic therapy may be discontinued.

Many commercial tear film supplements are available, including solutions, gels, and ointments (Table 1). Factors like cost, packaging, and availability may affect the clinician’s choice of a lacrimomimetic agent. However, the primary objectives of lacrimomimetic therapy remain, minimizing ocular surface desiccation and epithelial cell death and improving the animal’s comfort.

To achieve these therapeutic objectives, the veterinarian should consider the electrolyte concentration, the presence or absence of a preservative, and the type of viscosity agent before recommending a lacrimomimetic solution or ointment.

Most lacrimomimetics are hypotonic or isotonic electrolyte solutions. The tear film with qualitative or quantitative tear abnormalities is often hypertonic [56]. The hypertonicity develops secondary to increased tear film evaporation because of lipid and mucin abnormalities. Hypertonic tears are toxic to the corneal epithelium [57]. Hypotonic and isotonic electrolytes restore dry eye surfaces, increase conjunctival goblet cell density, and decrease tear osmolarity [58]. Bicarbonate is also added to some tear solutions. Bicarbonate may be useful in maintaining mucin on the ocular surface [59].

Preservatives are included in tear replacements to maintain stable solutions in multiple-dose bottles and to prolong shelf life. Preservatives used in lacrimomimetics include benzalkonium chloride, chlorobutanol, methylparaben, polyquarternium, propylparaben, sodium perborate, sorbic acid, and thimerosal (see Table 1). Edetate disodium (EDTA) is a common additive to many lacrimomimetics, and it augments the efficacy of preservatives.
Table 1
Common lacrimomimetic solutions and ointments

<table>
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<th>Preservative</th>
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However, EDTA by itself is not a preservative [58]. Preservatives are safe for use in ophthalmic solutions provided that the frequency of application is less than six times per day [58]. When an ophthalmic solution with a preservative is applied more frequently, epithelial toxicity may be noted [58,59]. As a result, preservative-free tear solutions have been developed to avoid epithelial toxicity when frequent application is required. The disadvantages of preservative-free lacrimomimetics include added expense and inconvenience related to manufacturing and the necessity of the owner carrying multiple single-dose vials, respectively.

Viscosity agents in lacrimometrics include polyvinyl alcohol, cellulose, polymers, viscoelastics, glycerin, and petroleum. The presence of preservatives and the electrolyte concentration vary within each commercial lacrimomimetic (see Table 1).

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Polyvinyl alcohol is a hydrophilic resin that adheres to the cornea, and this is a common ingredient in many tear film supplements [60]. It is less viscous than some cellulose products; however, it has excellent adhesive properties and is a common constituent of many lacrimomimetic solutions. Polyvinyl alcohol is well tolerated by animals, and solutions containing it are frequently used to treat mucin and aqueous tear film disorders.

Cellulose products (eg, methylcellulose, hydroxycellulose) are also commonly used in tear film supplements. They are nonirritating and assist with lubrication and retention of tears. They do not interfere significantly with corneal or conjunctival epithelial healing, and they are inert water-soluble.
products [61,62]. Lacrimomimetics containing cellulose products are most commonly used in aqueous tear film disorders.

Linear polymers (eg, dextran, polyvinylpyrrolidone) have mucinomimetic properties, and they are often combined with cellulose products to provide mucin and aqueous supplementation. These polymers help to retain the tears on the cornea longer, and they are common in many lacrimomimetic solutions [60–62].

Viscoelastic substances (eg, sodium hyaluronate, chondroitin sulfate) have excellent mucinometric properties, and they stabilize and improve tear retention [63]. Sodium hyaluronate has been reported as efficacious in treating KCS in dogs. The responses of the corneas and conjunctivae in these dogs were related to the viscoelastic and lubricating properties, because the tear production was unaffected [64]. A hyaluronan-derived viscoelastic tear replacement (Hylashield) is available. This product has excellent mucinomicetic properties and is a superior ocular protectant [9,64].

Petroleum and mineral oil products supplement the tear lipid, retard tear evaporation, and are the base of most tear replacement ointments [9]. These tear ointments restore a lipid layer on the ocular surface, mimic tarsal gland secretion, and retard tear evaporation. These ointments blur vision and are most commonly applied at bedtime to animals with tear film deficiencies.

In conclusion, to be effective as a sole topical therapy for aqueous tear film abnormalities, lacrimomimetic solutions need frequent application, often greater than six times per day. This frequency, although attainable in human ophthalmology, is often unattainable by pet owners. Lacrimomimetic ointments maybe considered because they are retained on the surface longer and they retard tear evaporation. Ointments are generally more difficult for most owners to apply, and they blur vision and often accumulate on the eyelids as a discharge. In addition, even when ointments are applied four times per day the response to therapy of aqueous tear film deficiency in animals is usually not optimal. These shortcomings often preclude the effectiveness of lacrimomimetics as a sole therapy for all but the mildest aqueous tear film abnormalities in animals. Nevertheless, lacrimomimetics are useful for treating qualitative tear film abnormalities and as a supplement to lacrimostimulants for quantitative tear film abnormalities. They improve ocular surface lubrication and stabilize and maintain an isotonic tear film and patient comfort while lacrimostimulation therapy is initiated.

References

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