

# Topical Ocular Therapeutics in Small Animals



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## KEYWORDS

- Topical ocular therapeutics • Antimicrobials • Anti-inflammatories
- Antiglaucoma medications • Lacrostimulants

## KEY POINTS

- Topical ocular medications penetrate the eye via corneal and noncorneal routes.
- Bioavailability is affected by composition of the preparation as well as interactions with the tear film.
- Systemic absorption of topical medications does occur, with potential adverse effects.

## BACKGROUND

Topical ophthalmic medications are widely used to treat a variety of ocular diseases. The topical route of administration is often chosen over systemic, due to its relative ease of administration and potential for reduced systemic side effects. Considerations of topical administration should include the desired target ocular structure within the anterior segment of the eye, potential barriers to absorption, the ability to achieve therapeutic concentrations at the target site, potential adverse effects, and patient compliance. This article aims to discuss the administration of topical ophthalmic medications as well as the indications, pharmacology, and adverse effects of commercially available topical ocular therapeutic agents used in the therapy for anterior segment diseases.

## CONSIDERATIONS OF TOPICAL OCULAR THERAPEUTICS

### *Relevant Anatomy and Physiology*

#### *Cornea*

Topical medications can penetrate the corneal epithelium by both the transcellular and paracellular routes.<sup>1,2</sup> The ability of medications to penetrate the cornea via the transcellular route is related to each medication's oil/water coefficient due to the lipophilic epithelium.<sup>3</sup> The paracellular route is complicated by the tight intercellular junctions (Zonula occludens), which fuse the plasma membranes of adjoining cells in numerous

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places and result in an intercellular space of 0.6 nm to less than 3 nm. Lipophilic medication molecules can cross through the transcellular route, whereas the tight intercellular junctions ensure that the paracellular route is only accessible to the smallest hydrophilic molecules.<sup>4</sup> The corneal stroma is easily penetrated by hydrophilic medications and acts as a barrier to lipophilic substances. The endothelium is easily permeable, and it has been demonstrated that there is limited resistance to the passage of lipophilic or hydrophilic medications.<sup>5</sup>

### ***Conjunctiva and sclera***

The conjunctiva is up to 25 times easier to penetrate than the cornea, and the most of the absorption occurs through the paracellular route.<sup>5-7</sup> Following penetration of the conjunctiva, the medication can then diffuse into the anterior chamber via the sclera and cornea, or pass through scleral vessels into the anterior uvea.<sup>8</sup> Ophthalmic preparations formulated with a mucoadhesive polymer, which promotes prolonged contact time with the bulbar conjunctiva, will favor this noncorneal route of topical medication absorption.<sup>9</sup>

Medications penetrate the sclera 10 times more easily than the cornea.<sup>5,7,10</sup> The ability for a medication to penetrate the sclera is largely based on its molecular radius, and hydrophilic medications can cross more easily than lipophilic.<sup>5,7,10</sup> The amount of absorption, which occurs through the scleral route versus the corneal route has been demonstrated to be significant for certain medications.<sup>8</sup>

### ***Administration of Topical Medications***

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#### ***Interactions with tear film and volume***

Once applied, topical medications mix with the tear film on the ocular surface and within the conjunctival sac. The median basal tear volume has been reported to be 65  $\mu\text{L}$  in dogs and 32  $\mu\text{L}$  in cats,<sup>11</sup> and the average volume of a drop of an ophthalmic preparation is 40  $\mu\text{L}$  (range of 25–70  $\mu\text{L}$ ).<sup>12</sup> Consequently, the tear film significantly dilutes all topical medications.<sup>11</sup> In dogs and cats, the rate of continuous tear film turnover is 11% to 12% per minute.<sup>11</sup> As a result, the volume of topical medication that reaches the ocular surface, and does not immediately overflow the eyelid margin or into the nasolacrimal puncta, is estimated to be completely removed within 10 minutes following administration.<sup>11</sup>

Factors influencing the nasolacrimal drainage of topical ocular medications include the volume of the drop administered, the viscosity of the ophthalmic preparation, and the rate of blinking. A loss of between 80% and 90% of the medication occurs either via the nasolacrimal system or by directly overflowing the eyelids following administration.<sup>13,14</sup> Studies have demonstrated that providing a larger volume of a drop only increases the rate of nasolacrimal drainage.<sup>13,14</sup> Administering more drops of topical medication increases nasolacrimal drainage and eyelid spillage in a manner that is proportional to the time between installation of these additional drops.<sup>8</sup> This is why a period of at least 5 to 10 minutes between applications of one drop of serial topical ocular medications is recommended.<sup>13-15</sup>

#### ***Composition of ophthalmic preparations***

Topical ocular medications consist of solutions, suspensions, ointments, and gels. Solutions are composed of molecules completely dissolved in a solvent, which is usually suspended in aqueous but occasionally lipid based. In addition to the aqueous base, most solutions will have organic or inorganic carriers, buffers, emulsifiers, or wetting agents to enhance the stability and sterility of the medication.<sup>16</sup> Advantages of solutions are ease of administration and minimal associated discomfort after application, therefore often superior owner compliance. Disadvantages are a shorter shelf life in

comparison to other formulations, such as ointments. When the therapeutic agent is not water soluble, a suspension in acetate or alcohol may be required.<sup>17</sup>

A suspension is composed of solid particles of the medication (active ingredient) within liquid dispersing and suspending agents. Suspensions are harder to stabilize, and this can lead to accumulation of the suspended particles and a nonuniform dispersion. As with solutions, an advantage of suspensions is ease of administration to small animals. Another advantage is prolonged contact time in comparison to solutions, which can enhance bioavailability.<sup>17</sup> Disadvantages include the need for the medication to be well shaken before administration to ensure appropriate dosing, and the potential for a crystal or particle within the suspension that may cause mild ocular discomfort to the animal.<sup>16,17</sup>

Ointments are traditionally used when a prolonged contact time is desired. Most ointments have a white petrolatum and liquid petrolatum (mineral oil) base, with or without a water-miscible agent, that is, lanolin.<sup>16,17</sup> The mineral oil component ensures that the ointment melts at room temperature for ease of application, and the lanolin is used to retain water-soluble medications within the ointment. Once administered, the ointment is contained in the conjunctival sac until it melts, allowing the water-soluble medication particles to be dissolved into the tear film.<sup>17</sup> This prolongs the interval between administration and when peak drug concentration within the target tissue is reached, in comparison to solutions or suspensions.<sup>17,18</sup> Ointments are retained far longer than solutions or suspensions due to their larger molecule size, viscosity, reduced nasolacrimal drainage and interactions between ointment base and tear film.<sup>18,19</sup> Studies have reported that ointments can be found on the ocular surface up to 4 hours following administration.<sup>20</sup> Advantages of ointments include less frequent dosing due to the prolonged retention on the ocular surface and increased shelf life. A disadvantage is when multiple medications are required, the retention of the ointment on the ocular surface complicates dosing intervals and one should wait at least 20 to 30 minutes between topical ocular ointments. Ointments do not have a manufactured “dropper,” therefore their dosing is less precise. When ointments are applied with solutions or suspensions, they need to be applied last.<sup>21</sup>

Ophthalmic gels use natural gum, hyaluronic acid, cellulosic components, or polyacrylic acids to increase the viscosity of an ophthalmic preparation.<sup>22</sup> These medications are ideal for hydrophilic therapeutic agents because it increases the contact time with the ocular surface through the viscosity and higher molecular weight.<sup>23</sup> Ophthalmic gels can be a preformed gel, or they may undergo gelation once in contact with the ocular surface under the influence of pH, temperature, and electrolyte concentrations.<sup>22</sup> Advantages of ophthalmic gels are increased contact time, and currently no significant adverse effects associated with the gel composition have been reported.

Regardless of the preparation, the medication should mimic the eye's natural tonicity and pH as closely as possible to minimize local irritation and discomfort.<sup>24,25</sup> Most ophthalmic preparations have a tonicity of approximately 300 mOsm/kg, which is based on the osmolality of human tears and close to that reported in cats and dogs.<sup>26,27</sup> The pH must be within the range of 4.5 to 9.0, and most ophthalmic topical medications have a pH between 7.0 and 7.7 to maximize comfort.<sup>25</sup> This pH range of 7.0 to 7.7 has been shown to be consistent with the pH of tears in small animals.<sup>24</sup> If the ophthalmic preparation is formulated in a way that causes irritation and increased lacrimation, the volume of medication lost through nasolacrimal drainage and eyelid spillage increases and this impairs absorption.<sup>15</sup> In dogs and cats, reflex tearing will increase the rate of tear film turnover and, therefore, excretion of topically applied medications by up to 5 times.<sup>11</sup>

### **Systemic Effects of Topical Medications**

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It is important to acknowledge that systemic absorption will occur with all topically applied ophthalmic medications. The conjunctiva is a major site of systemic absorption, due to the large surface area and permeability of the blood vessels of the bulbar conjunctiva and episclera.<sup>6,28</sup> The nasolacrimal duct epithelium has been demonstrated to absorb lipophilic medications in rabbits,<sup>29</sup> and the nasal and oral mucosa is thought to be a significant contributor to systemic absorption of topical medications across various species.<sup>28,29</sup> As topical medications exceed the volume that the conjunctival fornixes can retain, the excess medication is drained through the nasolacrimal system, where it reaches the nasopharynx,<sup>14</sup> and eyelid seepage occurs. Because the nasopharyngeal mucosa has similar permeability to that of conjunctiva, systemic absorption readily ensues. Because these methods of systemic absorption bypass the first-pass hepatic metabolism, their potential systemic effects have been compared with those of a slow intravenous injection,<sup>28</sup> and this should be considered carefully in small animals. Adverse systemic effects have been associated with topical phenylephrine; timolol; glucocorticoids and atropine in dogs, cats, and other small animals<sup>30–35</sup>; and for the topical nonsteroidal anti-inflammatory (NSAID) diclofenac in cats.<sup>36</sup> Further evidence of systemic absorption of topical medications is seen when the contralateral eye displays the effects of the medications administered such as timolol.<sup>37,38</sup>

## **COMMERCIALY AVAILABLE TOPICAL OCULAR MEDICATIONS**

### **Antibiotics**

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#### ***Bacitracin, neomycin, Polymyxin-B***

Bacitracin is a polypeptide bacteriostatic antibiotic, which has a mostly gram-positive spectrum of activity. It demonstrates good activity against *Staphylococcus intermedius* and beta hemolytic *Streptococcus* in dogs with bacterial keratitis.<sup>39</sup> Bacitracin is commercially available as a combination ointment with neomycin and polymyxin-B (BNP), which increases its spectrum of antibacterial activity.

Neomycin is a bactericidal aminoglycoside with a predominantly gram-negative spectrum and is another component of the triple-antibiotic commercial preparation with bacitracin and polymyxin B. *S intermedius* is highly susceptible<sup>39</sup> and methicillin-resistant staphylococcus aureus (MRSA) and *Pseudomonas* are mostly susceptible<sup>39,40</sup>; however, beta hemolytic *Streptococcus* spp are highly resistant.<sup>39</sup>

Polymyxin-B is a bactericidal polypeptide antibiotic with a gram-negative only spectrum of activity, and good activity against *Pseudomonas* isolates.<sup>39</sup> Local hypersensitivity following topical application of bacitracin has been reported.<sup>41</sup> Additionally, there is a report of anaphylaxis occurring in 61 cats following topical application of polymyxin-B,<sup>42</sup> and this warrants caution when considering administration to cats. Because both the individual antimicrobials and the combination solutions or ointments have very limited ability to penetrate an intact cornea, BNP ointment is indicated as prophylaxis in cases of superficial ulcerative keratitis and the treatment of general superficial ocular surface infections.<sup>43</sup>

#### ***Aminoglycosides: gentamicin and tobramycin***

Gentamicin is a bactericidal aminoglycoside, which is often used for the treatment of bacterial keratitis in veterinary ophthalmology. Studies have demonstrated some resistance from beta hemolytic *Streptococcus* strains in dogs, however good efficacy against *Pseudomonas* and *S intermedius* spp.<sup>39</sup> A recent study has also demonstrated high susceptibility of MRSA isolates.<sup>40</sup> Due to its narrow gram-negative spectrum, and the predominantly gram-positive ocular microflora of small animals,<sup>44–47</sup> gentamicin is

not generally used as a first-line agent in cases of corneal ulceration. Gentamicin has minimal ability to penetrate an intact cornea, although this is improved slightly when there is concurrent keratitis.<sup>48,49</sup> This antibiotic has been demonstrated to have damaging effects on corneal epithelial cell wound healing in vitro.<sup>50–52</sup>

Tobramycin has bactericidal activity against *Staphylococcus* and *Pseudomonas* isolates.<sup>39</sup> There are conflicting reports on its epithelial toxicity, with some studies demonstrating minimal effects on the healing of epithelial cells,<sup>50,51</sup> whereas another study showed significant prolongation of healing time in comparison to other agents.<sup>52</sup> Tobramycin is indicated as a first-line topical antibiotic in cases of ulcerative keratitis.

### **Macrolides: erythromycin and azithromycin**

Macrolides are a group of antibiotics that exert their action via binding the 30s ribosomal subunit and inhibiting the peptide chain lengthening required for bacterial mRNA translation.<sup>41</sup> They have a mostly gram-positive spectrum of activity and are primarily bacteriostatic with bactericidal activity at high concentrations. Erythromycin, a macrolide with demonstrated efficacy against *Mycoplasma* and *Chlamydomphila*, is commercially available as a 0.5% ointment. It has minimal efficacy demonstrated in dogs with aerobic ocular bacterial infections and, therefore, is not indicated as prophylaxis in cases of corneal ulceration.<sup>53</sup> Erythromycin's primary clinical indication is in cats with *Chlamydomphila* and *Mycoplasma*-associated conjunctivitis.

Azithromycin is a newer medication with increased gram-negative coverage<sup>41</sup> and is available commercially in a 1% ointment and solution. Topical administration of azithromycin at varying concentrations has resulted in therapeutic levels in the conjunctiva<sup>54</sup> and cornea<sup>55</sup>; however, these levels were not reached in the AH.<sup>54</sup> Compared with other commercially available medications, azithromycin has been shown to be less effective against *Rickettsia rickettsii*<sup>56</sup> and *Bartonella*,<sup>57</sup> and there has been a report of resistance developing rapidly.<sup>58</sup>

### **Fusidic acid**

Fusidic acid is a bacteriostatic antibiotic that has a good spectrum of activity against gram-positive organisms, especially *Staphylococcus* spp, and limited activity against gram-negative organisms.<sup>59</sup> It is commercially available as a 1% carbolic gel, and labeled for minor ocular surface infection, such as secondary bacterial conjunctivitis in cases of keratoconjunctivitis sicca (KCS).

### **Sulfonamides**

Sulfonamides are bacteriostatic antibiotics that inhibit bacterial folate metabolism. Sulfonamides are commercially available as 10% ophthalmic solution. The transcorneal penetration of topical sulfonamides is highly variable, and between 96% and 100% of aerobic organisms in small animals are susceptible.<sup>53</sup>

### **Fluoroquinolones: ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, sparfloxacin, gemifloxacin, levofloxacin, gatifloxacin, moxifloxacin, and besifloxacin**

Fluoroquinolones are bactericidal antibiotics that inhibit bacterial DNA gyrase. Ciprofloxacin 0.3%, ofloxacin 0.3%, norfloxacin 0.3%, and lomefloxacin 0.3% are available as commercial preparations as second-generation fluoroquinolones. These medications are broad spectrum with strong efficacy against gram-positives and *Pseudomonas* spp. The spectrum of gram-positive activity increases with each generation of fluoroquinolones.<sup>60</sup> In canine bacterial keratitis, 100% of *Staphylococcus* spp and *Streptococcus* spp and 35% of MRSA were susceptible to ciprofloxacin 0.3%.<sup>39,40</sup> Good efficacy against *Pseudomonas* (93%–100% susceptibility) has also been demonstrated in dogs.<sup>39,61</sup> Topical ofloxacin has been shown to reach higher,

and more therapeutic, aqueous humor concentrations than topical ciprofloxacin in dogs.<sup>62</sup> Several third-generation fluoroquinolones, sparfloxacin 0.3%, gemifloxacin 0.3%, and levofloxacin 0.5% or 1.5%, are available as topical ophthalmic therapeutic agents. In dogs, 100% of *Pseudomonas* isolates were susceptible to levofloxacin.<sup>61</sup> Fourth-generation fluoroquinolones, gatifloxacin 0.3% or 0.5%, moxifloxacin 0.5%, and besifloxacin 0.6%, are also available as commercial preparations. *Pseudomonas* isolates in a canine study of bacterial keratitis demonstrated resistance to both gatifloxacin and moxifloxacin.<sup>61</sup> Moxifloxacin has an increased ability to penetrate the cornea and achieve intraocular therapeutic concentrations, in comparison to several other fluoroquinolones.<sup>63</sup> Besifloxacin was developed specifically for topical ophthalmic use, and contains a mucoadhesive polymer, which is designed to increase its contact time and enhance its ability to maintain therapeutic concentrations within the cornea and aqueous humor.<sup>64</sup> It is recommended that fourth-generation fluoroquinolones be reserved for complex ophthalmologic infections in dogs and cats to minimize antimicrobial resistance.<sup>41,63</sup> Reported adverse effects include the development of a white crystalline corneal plaque following topical levofloxacin administration.<sup>65</sup> Additionally, cytotoxic damage and reduced stromal keratocyte proliferation with the use of ciprofloxacin, ofloxacin, and norfloxacin has been demonstrated in vitro.<sup>66</sup>

### **Tetracyclines**

Tetracyclines are another group of medications that exert their antibacterial activity by interacting with the 30S ribosomal subunit to inhibit bacterial mRNA translation.<sup>41</sup> These medications can be short acting (tetracycline, oxytetracycline), intermediate acting (demeclocycline), or long acting (doxycycline, minocycline). Overall, tetracyclines have broad-spectrum activity, however many bacteria have developed resistant strains.<sup>41</sup> Rickettsial organisms are consistently susceptible, compared with *Staphylococcus* and *Streptococcus* spp, which have resistance reported to be developing.<sup>41,56,67</sup> In addition to antibacterial activity, tetracyclines are reported to be reactive oxygen species scavengers, and therefore exert some anti-inflammatory effects.<sup>68,69</sup> This was thought to contribute to the significantly shorter healing times noted in dogs receiving topical oxytetracycline in a study of canine refractory ulcers.<sup>69</sup>

### **Antivirals**

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#### **Thymidine analogs**

Idoxuridine and trifluridine are both thymidine analogs that impede viral replication.<sup>70</sup> Idoxuridine has strongly specific activity against feline herpes virus (FHV-1); however, it does not penetrate the eye well.<sup>71,72</sup> It is commercially available as a 0.1% solution and is reportedly well tolerated,<sup>73,74</sup> although it may not be very efficacious in cats with herpetic keratitis. Trifluridine also has good in vitro specificity for FHV-1,<sup>72</sup> and is commercially available as a 1% solution but is poorly tolerated in cats.<sup>73,74</sup> Both idoxuridine and trifluridine are virostatic, and therefore require frequent dosing, with topical administration required at intervals of 4 to 6 hours.<sup>74</sup> Dogs with CHV-1 infections have demonstrated a good response to the treatment with 1% trifluridine and no signs of discomfort were associated with topical administration.<sup>75</sup>

### **Antifungals**

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#### **Natamycin**

Natamycin is currently the only topical ophthalmic antifungal approved for use and commercially available as a 5% suspension.<sup>76</sup> Its ability to penetrate an intact cornea is poor. An in vitro study demonstrates severe cytotoxic effects on equine

keratocytes.<sup>77</sup> Unfortunately, there are no veterinary studies evaluating the use of natamycin topically in cats or dogs.

## **Anti-inflammatory**

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### **Corticosteroids**

There are several commercial preparations of corticosteroids available for use in small animals. These are available in varying concentrations with either a water-soluble salt solution or lipophilic acetate or alcohol solutions. For conjunctivitis or nonulcerative keratitis, a water-soluble salt preparation may be the most suitable. For cases of intra-ocular inflammation, due to the lipophilic corneal epithelium, prednisolone acetate 1% or dexamethasone alcohol 0.1% achieves superior absorption and corneal penetration.<sup>78,79</sup> Frequency of dosing is based on the severity of clinical signs and ranges from hourly administration to once per day or every other day use. Previous studies have demonstrated a rebound effect of inflammation if medications are discontinued abruptly, and therefore, tapering of corticosteroid administration is recommended.<sup>80</sup> Use of topical steroid medications has been associated with exacerbation of ocular infection through inhibition of leukocyte migration and suppression of macrophage activity.<sup>81</sup> Corticosteroids applied topically also impede corneal wound healing (epithelial and stromal),<sup>82</sup> inhibit fibroblast formation and limbal blood vessel formation,<sup>83</sup> and potentiate corneal collagenase leading to keratomalacia.<sup>84</sup> As a result, topical corticosteroids are contraindicated in almost all cases of ulcerative keratitis except the uncommon to rare Moorens ulcers and erosive corneal dystrophies in dogs. Cataract formation has been experimentally induced in cats.<sup>85</sup> An elevation in intraocular pressure (IOP) has been documented in cats and dogs with glaucoma.<sup>85–87</sup> Lipid keratopathy has been associated with chronic use of topical steroids and systemic absorption can lead to adrenal suppression, suppression of the hypothalamic-hypophyseal-adrenal axis and hepatic pathologic condition.<sup>30,88</sup> Interestingly, diabetic dogs treated with a topical corticosteroid compared with a topical NSAID demonstrated no clinical differences in the control of their diabetes.<sup>89</sup>

### **Nonsteroidal anti-inflammatory**

Many topical ocular preparations of NSAIDs are commercially available including bromfenac (0.07%, 0.075%, 0.09%), diclofenac (0.1%), flurbiprofen (0.03%), ketorolac (0.4%, 0.45%, 0.5%), and nepafenac (0.1%, 0.3%). Flurbiprofen has been shown to be more effective than topical prednisolone in reducing the disruption of the blood aqueous barrier (BAB) and maintaining mydriasis in the face of inflammation.<sup>90</sup> Diclofenac 1% was demonstrated to be superior to other topical NSAIDs (flurbiprofen, suprofen, tolmetin) in preventing BAB disruption in dogs,<sup>91</sup> and 0.1% diclofenac significantly decreased intraocular inflammation in cats in comparison to the less effective flurbiprofen.<sup>92</sup> Ocular inflammation has been shown to decrease the amount of diclofenac that reaches the anterior chamber, and this results in high corneal levels but low aqueous humor concentrations.<sup>93</sup> The most common adverse effect reported with the use of topical NSAIDs is a transient local irritation. They should also be used with caution in ocular infections and keratitis in rabbits.<sup>94</sup> Topical NSAIDs may also increase the amount of leukotrienes synthesized from arachidonic acid and lower leukocyte infiltration.<sup>95</sup> Furthermore, topical NSAIDs have been demonstrated to reduce epithelial healing<sup>96,97</sup> and have been associated with keratomalacia in human studies.<sup>98–100</sup> This has not been reported in the canine or feline species. Slight increases in IOP have been reported in dogs<sup>101,102</sup> and cats,<sup>92</sup> and this warrants consideration when ocular hypertension or glaucoma is present.<sup>103</sup> Topical flurbiprofen is reported to reduce the antiglaucoma efficacy of latanoprost.<sup>104</sup> Systemic absorption of topical NSAIDs also occurs, with detectable plasma levels present within 7 to

14 days of administration to healthy cats.<sup>36,105</sup> Despite detectable feline plasma levels, cats did not demonstrate any appreciable effects or increase in biochemical markers.<sup>105</sup> Caution is advised when administering topical NSAIDs when a reduction in glomerular filtration rate in volume contracted cats is present.<sup>36</sup>

### **Antiglaucoma Medications**

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#### **Carbonic anhydrase inhibitors: dorzolamide and brinzolamide**

In healthy dogs, 2% topical dorzolamide achieved a mean reduction in IOP of 3.1 mm Hg (18%), during 30 minutes to 6 hours following administration.<sup>106</sup> Dogs with normal IOP had a maximum decrease in IOP of 6 mm Hg after 5 days of treatment every 8 hours.<sup>107</sup> In glaucomatous eyes, dorzolamide was demonstrated to decrease IOP by mean of approximately 30%.<sup>34</sup> Topical 1% brinzolamide administered twice daily reduced IOP to a similar extent to dorzolamide, with the maximal effect demonstrated between 5 and 6 hours following treatment in dogs with normal IOP.<sup>108</sup> In this study, the mean IOP returned to its premedication value 10 to 11 hours after treatment, thus administration every 8 hours is recommended.<sup>108</sup> The clinical efficacy of dorzolamide has also been demonstrated in feline eyes.<sup>109,110</sup> Dosing twice per day in cats has been shown to be as effective as 3 times daily dosing in dogs.<sup>106,109</sup> In cats with congenital glaucoma, dorzolamide decreases IOP by nearly 46% with TID administration.<sup>111</sup> Brinzolamide administered every 12 hours did not influence IOP in feline eyes<sup>112</sup>; however, it did reduce IOP if given every 8 hours.<sup>113</sup> In normotensive cat eyes, brinzolamide reduced IOP less than dorzolamide.<sup>113</sup> Side effects included renal tubular acidosis in a cat,<sup>114</sup> and blepharitis and keratitis<sup>115</sup> in dogs following application of 2% dorzolamide solution.<sup>116</sup>

#### **Beta-adrenergic antagonists: timolol**

Timolol is commercially available as a 0.25% or 0.5% solution in a maleate salt. In healthy dogs, a mean reduction in IOP of 16% (2.5 mm Hg) was noted within 2 to 4 hours following topical administration of 0.5% timolol.<sup>38</sup> Dose-related decreases in IOP were found inconsistently in normotensive dogs and consistently in glaucomatous dogs when timolol administered at concentrations of 4% to 6%.<sup>117</sup> Glaucomatous beagle eyes had a decrease in IOP of 4 to 5 mm Hg.<sup>118</sup> Conflicting studies have been reported with 0.25% and 0.5% that revealed limited to no reduction in IOP in dogs with normal IOPs.<sup>35,118</sup> In healthy cats, a single dose of 0.5% timolol reduced IOP by 22% (4.1 mm Hg) with peak effect within 6 to 12 hours following installation.<sup>37</sup> Combined with dorzolamide, a significant reduction of IOP was seen in eyes of glaucomatous beagles.<sup>34</sup> Combination of timolol and prostaglandin analogs (PG) has been reported to further reduce IOP than either drug individually.<sup>35</sup> A significant reduction in pupil size is seen in canine and feline patients administered with topical timolol maleate.<sup>37,38</sup> This miosis is more pronounced in cats than dogs, can persist up to 1 week following discontinuing treatment.<sup>38</sup> Systemic absorption of topical timolol is demonstrated by a reduction in IOP and pupil diameter in the contralateral eye.<sup>38</sup> Additionally, a significant decrease in heart rate has been demonstrated in beagles that have normal IOP and those with glaucoma when they received topical timolol (0.5%–8%).<sup>34,117,118</sup> To minimize potential systemic effects, it is recommended to use 0.25% timolol instead of 0.5% in cats and small dogs (<10 kg).<sup>119</sup> Additionally, timolol is contraindicated in cats with asthma because it may cause bronchoconstriction.<sup>120</sup>

#### **Prostaglandin analogs (PGs): latanoprost, travoprost, and bimatoprost**

Prostaglandin analogs are indicated for primary glaucoma in canine patients.<sup>119</sup> PGs, such as latanoprost, travoprost, and bimatoprost, are commonly used topical ocular antiglaucoma medications. At a concentration of 0.005%, latanoprost significantly

reduces IOP in dogs with normal eyes and those with glaucoma.<sup>121</sup> With once daily or twice daily dosing, topical latanoprost resulted in a 25% decrease in IOP of dogs with normal eyes and a 50% reduction in IOP of glaucomatous eyes.<sup>121,122</sup> A similar reduction in IOP was demonstrated in glaucomatous canine eyes with administration of 0.03% bimatoprost<sup>121,122</sup> and 0.004% travoprost.<sup>123,124</sup> Twice daily administration demonstrated less daily fluctuations in the IOP of dogs<sup>122,123,125</sup> and 3 times per day dosing further decreased IOP.<sup>126,127</sup> Concurrent use of anti-inflammatories may reduce the efficacy of PGs in glaucomatous eyes, based on some conflicting reports.<sup>104,128</sup> Conjunctival hyperemia, epiphora, and blepharospasm have been reported in dogs after topical administration.<sup>121</sup>

Prostaglandin analogues are reported to be much less effective in cats, with studies of once daily 0.005% latanoprost<sup>121</sup> or 0.03% bimatoprost<sup>129</sup> or twice daily bimatoprost,<sup>130</sup> all reporting no significant IOP reductions. The commercial PGs are all prostaglandin-F (FP) receptor agonists, and in the feline, the FP receptor is not significantly involved in alterations in IOP in response to administration of PGs.<sup>131</sup> Latanoprost 0.005% did transiently lower IOP in cats with one dose but after 3 weeks of twice daily dosing, this hypotensive effect was reduced.<sup>132</sup>

### **Lacrostimulants**

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KCS is prevalent in veterinary ophthalmology and often has an immune-mediated cause. Lacrostimulants used in the management of KCS exert their anti-inflammatory and lacrostimulatory effects by impeding the formation and activation of T-cell lymphocytes.<sup>133,134</sup> Commonly used topical medications include cyclosporine (CsA) and tacrolimus.

#### **Cyclosporine**

CsA is commercially available as a 0.2% ointment (Optimmune) and topical twice per day therapy is recommended.<sup>135</sup> An increase in STT of greater than 5 mm 3 to 4 weeks following the initiation of treatment is considered a positive response.<sup>135</sup> For dogs with an excellent response to treatment (STTs > 20 mm/min), once per day application with continued careful monitoring can be considered.<sup>135</sup> Studies report that 80% of KCS cases respond well to CsA,<sup>135,136</sup> with the STT increasing with 3 to 4 weeks after continual therapy.<sup>136</sup> Some dogs will require 2 to 3 months of therapy with CsA before a significant increase in STT will occur,<sup>135</sup> and in cases of severe or absolute KCS, the success of CsA therapy is often significantly reduced.<sup>135</sup> Tear production can reduce dramatically in 12 to 24 hours following discontinuation of cyclosporine, so reducing CsA therapy to once a day should warrant caution.<sup>136</sup>

#### **Tacrolimus**

Tacrolimus has been a recent addition in the treatment of canine KCS with promising results. There are no commercial preparations available; however, it is typically compounded in a 0.02% or 0.03% solution or ointment.<sup>137</sup> There have been various studies comparing the efficacy of topical tacrolimus compared with CsA. A 2003 study demonstrated that dogs treated for KCS with 0.03% tacrolimus yielded similar results to those treated with 2% CsA.<sup>138</sup> This finding has been supported by other studies using the same<sup>139</sup> and increased concentrations of tacrolimus.<sup>140</sup> There is also evidence that tacrolimus may be more effective in cases of KCS which did not respond to previous CsA treatment,<sup>139</sup> or in more severe cases of KCS.<sup>141,142</sup> Additionally, tacrolimus has been reported to be superior in the reduction of corneal pigmentation.<sup>140</sup>

It is important to note that while there are anecdotal reports of the use of CsA or tacrolimus in feline patients for KCS, there is currently no peer-reviewed evidence

that these medications improve the STT values in feline patients. This subject warrants further investigation but currently the treatment of KCS in feline patients involves supplementation of tears and treatment of any underlying conditions such as feline herpes virus. There has been demonstrated efficacy of CsA in the treatment of feline eosinophilic keratitis.<sup>143</sup>

### **Mydriatics and Cycloplegics**

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Pharmacologic dilation of the pupil in veterinary ophthalmology allows examination of the lens and posterior segment, facilitates surgical procedures, and has therapeutic intervention in cases of iridocyclitis. Depending on the clinical situation, different pharmacologic agents will be used; however, for the purposes of this review, cholinergic antagonists will be the focus.

#### **Cholinergic antagonists: tropicamide, atropine, scopolamine, cyclopentolate**

Cholinergic antagonists reversibly block cholinergic receptors in smooth muscle resulting in pupillary dilation. Following topical application of cholinergic antagonists, salivation, and occasional vomiting can occur, attributed to the bitter taste.<sup>144–146</sup> A significant reduction in tear production has also been reported.<sup>147,148</sup> Systemic absorption also occurs, with a significant elevation in heart rate reported in dogs.<sup>31</sup> A preliminary ocular examination including measurement of IOP and assessment of lens position is recommended before administration of mydriatic agents because dilation of the pupil can result in a significant elevation of IOP in cats<sup>149,150</sup> and variable elevation in dogs.<sup>151–153</sup> Additionally, an unstable lens can luxate anteriorly when the pupil is dilated, potentially resulting in secondary glaucoma.<sup>154</sup> Commercially available topical cholinergic antagonists include tropicamide (0.5% and 1% solution), atropine sulfate (0.5%–2% solution, 1% ointment), homatropine (1%–5%), scopolamine (0.25% solution), and cyclopentolate (1% and 2% solutions).

Tropicamide has a rapid onset of action with mydriasis evident from 15 minutes after application and maximal dilation evident at 30 minutes in dogs<sup>146</sup> and 1 to 2 hours in cats.<sup>144,149</sup> The pupillary dilation is not prolonged and declines after 2 hours in dogs<sup>146</sup> and 4 hours in cats.<sup>144,149</sup> The rapid onset and return to normal pupillary diameter makes tropicamide an appropriate medication for diagnostic mydriasis, as well as pre-surgical pupillary dilation. However, its cycloplegic properties are not as pronounced; therefore, it is not indicated in the treatment of uveitis.<sup>155–158</sup> Following application, STT values were unaffected in dogs but transiently decreased in cats.<sup>148</sup> Cats with normal IOP and those with glaucoma demonstrated a significant elevation in IOP following administration of tropicamide.<sup>150,159</sup>

Atropine has strong cycloplegic properties in addition to mydriasis and, therefore, is the recommended therapeutic agent for treating the discomfort associated with iridocyclitis and reducing the chance of posterior synechiae formation. Following administration of the 1% solution, peak mydriasis is evident at 60 and 30 to 45 minutes, and lasts 96 to 120 and 60 hours in dogs<sup>146</sup> and cats,<sup>144</sup> respectively. Eyes with darkly pigmented irises may exhibit a longer duration of action due to melanin binding of atropine.<sup>160,161</sup> In small animals, side effects of topical atropine administration are most commonly salivation or vomiting associated with the bitter taste, and this can be reduced by using an ointment rather than solution.<sup>144,146</sup> Less common adverse effects include periocular dermatitis<sup>41,154</sup> and neurologic signs.<sup>162</sup>

Homatropine is rarely used in dogs and cats because it has a longer time until onset of action and does not achieve maximal pupillary dilation.<sup>144,146</sup> Conversely, the administration of scopolamine in canine patients results in a rapid and prolonged mydriasis.<sup>146</sup> Cyclopentolate is more comparable to atropine, with both mydriatic

and cycloplegic properties and a similar duration of action in dogs and cats.<sup>144,146</sup> Maximal mydriasis is not reached until 12 hours following administration in dogs.<sup>163</sup> Side effects include conjunctival edema in dogs<sup>146</sup>; however, IOP and tear production are unaffected.<sup>163</sup>

## SUMMARY

Topical ocular therapeutics are essential for the treatment of veterinary ophthalmic diseases. To maximize patient outcomes, a thorough understanding of ocular anatomy and physiology and factors affecting the bioavailability of topical medications is required. It is important to recognize that systemic absorption of topical medications occurs and adverse effects can arise; as such, individual patients should be carefully considered for any potential contraindications.

## CLINICAL CARE POINTS

- Administration of multiple consecutive drops of an ophthalmic preparation will not enhance bioavailability but rather increase the rate of nasolacrimal drainage and decrease contact time. A single drop per dose is recommended.<sup>14</sup>
- Wait 5 to 10 minutes between solutions or suspensions<sup>11</sup> and always apply ointments last.
- Consider comorbidities when prescribing topical medications, especially NSAIDs, corticosteroids and beta-blockers.<sup>34,88,89,105,114,117</sup>
- Topical corticosteroids are contraindicated in the presence of corneal ulceration.<sup>96–100</sup>
- Topical NSAIDs should be used with caution in small animals with glaucoma and the IOPs monitored.<sup>92,101–103</sup>

## DISCLOSURE

The authors have nothing to disclose.

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