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Ocular hypotensive drugs

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Glaucoma remains a leading cause of blindness in human and veterinary ophthalmology. The recent literature favors the term *the glaucomas*, referring to a set of diseases with a common end point of progressive retinal ganglion cell (RGC) and optic nerve degeneration associated with elevations in intraocular pressure (IOP), although the details as to how these events are linked and the chronology of their interrelation remain somewhat enigmatic. Pathologic elevation of IOP results from an obstruction to aqueous flow or outflow anywhere along its course from the posterior chamber through the pupil into the ciliary cleft, across the trabecular meshwork, and into the scleral venous plexus [1]. Although advances in cycloablative surgery and aqueous outflow enhancement procedures have improved our ability to manage glaucoma in animals, medical therapy continues to be an important component of glaucoma treatment.

Most medications used in the management of glaucoma are targeted at decreasing IOP. These drugs may be categorized by their basic mechanism of action into drugs that reduce the production of aqueous humor, those that increase aqueous humor outflow without reducing production, and those that induce alteration of both physiologic pathways on ocular fluid dynamics [2]. Although veterinarians can benefit from the variety of pharmacologic choices available for the treatment of glaucoma in human beings, it is important to recognize that many species-related differences in ocular anatomy and physiology can limit the usefulness of certain drugs in each of our animal species. Additionally, the individual mechanisms associated with the different forms of glaucoma seen in animals versus people may have an impact on the appropriateness of a given drug in a particular species or even in an individual animal. Extrapolation of topical drug efficacy data from human beings to other species is therefore not recommended. Fortunately, many commercially available products have been evaluated for their hypotensive effect and safety in companion animal species.

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Most ophthalmologists adopt a multifaceted approach to the treatment of glaucoma using a combination of drugs that stimulate the reduction of aqueous humor production, increase aqueous humor outflow, and provide neuroprotection to the retina and optic nerve. This article reviews well-established topical and systemic medications used in the management of glaucoma as well as the more recently available products that have shown promising ocular hypotensive effects in companion animals. In addition, the concepts of prophylactic topical therapy and neuroprotection are discussed.

Systemic therapy for glaucoma

Although the trend in modern glaucoma management is toward topical therapy, the usefulness of systemically administered drugs cannot be discounted for acute and chronic forms of the disease.

Osmotic agents

Osmotic agents reduce aqueous flow by decreasing the rate of plasma ultrafiltration in the ciliary blood vessels [3]. After oral or intravenous administration, osmotic agents are distributed in the extracellular fluids, resulting in an increase in plasma osmolality. The resultant osmotic gradient promotes diffusion of water from the intraocular fluids back into the plasma. This fluid shift affects IOP in two ways. First, the ultrafiltration process that contributes to the formation of aqueous humor is impaired, and, second, the volume of the vitreous body is reduced. As the vitreous body shrinks, the plane of the iris-lens diaphragm is shifted caudally, which subsequently opens the iridocorneal angle to improve aqueous drainage [3].

The efficacy of osmotic agents relies on an established blood-aqueous and blood-vitreous barrier, and their effect is reduced in the face of intraocular inflammation. The molecular weight of the drug as well as its bioavailability and dosage affects the establishment of an adequate osmotic gradient. It is also important to note that withholding water from the patient for up to 4 hours is required to enhance blood osmolality and produce the desired ocular hypotensive effect [4]. The most common osmotic agents used to treat glaucoma in veterinary ophthalmology are mannitol and glycerin.

Mannitol

Mannitol is an osmotic diuretic indicated in the emergency management of primary glaucoma and in glaucoma occurring secondary to anterior lens luxation. The ocular hypotensive effect of mannitol may be reduced in patients with intraocular inflammation; however, because of its high molecular weight, mannitol diffuses less than other osmotics into inflamed eyes [4]. Mannitol is not metabolized to a significant degree and thus may be

used in diabetics without creating metabolic problems related to hyperglycemia (Fig. 1). Because mannitol can quickly expand extracellular fluid volume and overload the cardiovascular system, its use may precipitate pulmonary edema in patients with cardiac compromise or in patients under general anesthesia [5]. The use of mannitol to reduce IOP is only recommended in patients with normal renal function. In high concentrations, mannitol decreases renal blood flow and glomerular filtration rate, which may negatively affect an already compromised kidney. Urine output should be monitored and is expected to increase after mannitol administration.

The 20% solution of mannitol is the form most commonly used in veterinary patients. The dose range is 1 to 2 g/kg given slowly intravenously over a period of 20 to 30 minutes. The result is typically a reduction in IOP within 30 minutes to 1 hour, with the effect lasting for approximately 6 to 10 hours [6]. Care should be taken to ensure that mannitol is not delivered extravascularly, because tissue sloughing can result. In patients with cardiovascular stability and a normal preexisting hydration status, mannitol may be repeated in 24 hours, but the systemic status must be monitored closely, because mannitol induces systemic dehydration.

Glycerin

Glycerin is an osmotic diuretic administered orally, and it should not be given intravenously. Because it is administered orally, it can be given in the examination room with minimal patient preparation. It is most often used in the acute stage of glaucoma, but because of uncertain absorption, the hypotensive response to glycerin can be variable.

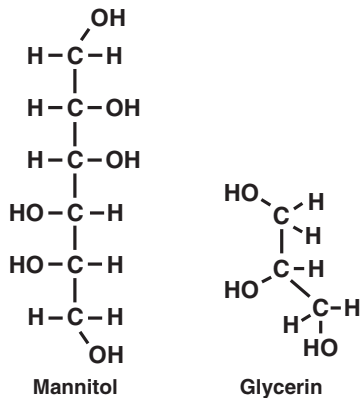

Fig. 1. A schematic description of the mannitol and glycerin molecules. Mannitol is not metabolized and thus may be used in diabetics without creating metabolic problems related to hyperglycemia. Because of its metabolism into glucose, glycerin can induce hyperglycemia and glucosuria and is thus not the ideal choice for the glaucomatous diabetic patient.

Common side effects of glycerin administration include nausea, vomiting, and weight gain if used over an extended period. Because of its metabolism into glucose, glycerin can induce hyperglycemia and glucosuria and is thus not the ideal choice for the glaucomatous diabetic patient (see Fig. 1). Glycerol aqueous levels are appreciably higher in the inflamed eye than in the normal eye, suggesting that a decreased osmotic effect occurs with uveitis [3].

Glycerin is available in 50% and 75% solutions and is rapidly absorbed from the gastrointestinal tract. The typical dose is 1 to 1.5 g/kg mixed in a palatable liquid or food (eg, baby food, canned pet food slurry). Glycerin produces a significant decrease in IOP in dogs within 1 hour, with the hypotensive effect lasting approximately 10 hours [7].

Carbonic anhydrase inhibitors

Carbonic anhydrase (CA) catalyzes the following reaction:

$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$$

In the ciliary body, the formation of bicarbonate moves sodium and, secondarily, water into the eye, forming aqueous humor. CA inhibition decreases bicarbonate production and subsequently reduces the synthesis of aqueous humor. Metabolic acidosis is a common side effect of systemic carbonic anhydrase inhibitor (CAI) therapy and has been proposed as a possible mechanism of action for reducing IOP; however, the hypotensive effect of the CAIs has been shown to be unrelated to blood or aqueous pH [8].

Because CAIs work by reducing the production of aqueous humor, they may have a therapeutic role in primary and secondary forms of glaucoma. The CAIs are the only systemic agents used in the long-term treatment of glaucoma in human patients and are also frequently used in veterinary patients. CA is present in many body tissues, including the kidney, red blood cells, pancreas, lung, and central nervous system [8]. Inhibition of the CA enzymes in these tissues is related to the systemic side effect observed. Common clinical and biochemical side effects seen in companion animals include gastrointestinal disturbances (eg, anorexia, vomiting, diarrhea), increased diuresis, malaise, and panting secondary to metabolic acidosis [9]. Hypokalemia is also a concern with short- and long-term use of the systemic CAIs, and although normal food intake usually prevents serious potassium depletion, patients with preexisting hypokalemia or anorexic patients should be monitored closely during treatment. Cats may be more susceptible to the side effects of systemic CAIs [9].

Although dichlorphenamide has limited commercial availability, acetazolamide and methazolamide are available in an oral form; however, acetazolamide is not recommended in cats and dogs because of its higher

prevalence of systemic effects. Methazolamide has less plasma protein binding than the other CAIs and can reportedly reduce IOP to a greater extent than acetazolamide in the absence of metabolic acidosis [10]. Methazolamide is available in 25- and 50-mg tablets. The dose range is 5 to 10 mg/kg every 8 to 12 hours, with the lowest effective dose recommended.

In recent years, topical forms have largely replaced the systemic CAIs because oral CAIs are commonly associated with adverse effects in human and animal patients (also see section on topical CAIs).

Topical hypotensive therapy

Significant advances have recently been achieved in the development of topical glaucoma medications. The primary advantage of a topical preparation is the reduced incidence of adverse systemic effects attributable to a given drug compared with its systemically administered counterpart. Because the strong protective barrier of the eye forces topical ophthalmic preparations to be highly concentrated, they still may have the potential to produce unwanted systemic effects in some cases, particularly in small animals.

Many of the topical preparations that effectively reduce IOP in human beings have been evaluated in companion animal species. Anatomic and physiologic characteristics, such as corneal and conjunctival surface area, rate of blinking, and tear turnover, vary among animal species and can affect drug absorption and thus target tissue response [11].

Cholinergic agents

Cholinergic stimulation results in the contraction of the ciliary body musculature, leading to miosis and decreased resistance of aqueous humor passage through the outflow pathways [12]. Several cholinergic drugs have been used as adjunctive agents to treat glaucoma in companion animal species. Cholinergic drugs can be separated into direct- and indirect-acting parasympathomimetic agents. Direct-acting cholinergic agents stimulate cholinergic receptors directly to create their effect, whereas the indirect-acting cholinergic agents inhibit acetylcholinesterase (AChE), resulting in an accumulation of acetylcholine at receptor sites.

Pilocarpine

Topical pilocarpine is a direct-acting parasympathomimetic agent. Pilocarpine may be useful in the management of some primary glaucomas in the dog and cat [13], although it may have limited benefit in glaucoma associated with goniodysgenesis [14]. Side effects include transient blepharospasm, epiphora, conjunctival hyperemia, and elevation of the nictitating membrane [15]. These effects may be related to the relatively low pH of the solution (range: 4.5–5.5). The miosis produced by pilocarpine may lead to

reduced vision in conditions of low illumination or in patients with axial cataract. A transient increase in aqueous protein content may occur in eyes treated with pilocarpine, which is the result of an increase in the permeability of the blood-aqueous barrier [12]. Pilocarpine caused an increase of flare compared with nontreated control Beagle eyes [16]. By 31 hours, flare had decreased with three daily topical treatments. By 55 hours, the flare measurement was in the pretreatment range. IOP decreased in the treated eyes compared with the nontreated eyes, and a maximal decrease in IOP was observed at the same time as maximal flare. Although this response is transient, pilocarpine may not be the best first-line choice for eyes with glaucoma secondary to uveitis.

Pilocarpine is available in concentrations ranging from 0.5% to 8%. No significant difference was noted in the ocular hypotensive effect of the varying concentrations in glaucomatous Beagles, with all concentrations creating miosis and reduction in IOP for at least 6 hours [15]. The advised frequency of administration is therefore every 6 to 8 hours. A 4% pilocarpine gel given once daily reduced IOP in glaucomatous dogs [17]. The 2% solution administered once or twice daily did not significantly change IOP in normotensive equine eyes, although pupil size was reduced [18]. The author concluded that the frequency and concentration of pilocarpine might have to increase to create a significant hypotensive effect in the equine eye.

Carbachol

Carbachol contains portions of the acetylcholine and physostigmine molecules, giving it direct and indirect actions. In veterinary ophthalmology, the most common indication for carbachol is to reduce the risk of IOP spikes after cataract surgery. Results of one study suggested that intracameral administration of 0.01% carbachol at the end of surgery was a safe and efficacious method of preventing the 3- to 6-hour postoperative increase in IOP frequently associated with phacoemulsification in dogs [19]. Four carbachol concentrations significantly lowered IOP and reduced pupil size after a single dose in normotensive and early glaucomatous Beagles [20]. In addition to the side effects observed with the administration of pilocarpine, carbachol causes more severe headache and accommodative spasms of the eye in human beings than does pilocarpine, but these symptoms tend to decrease after several days of treatment [12].

Intracameral administration of 0.01% sterile carbachol, 0.5 mL, immediately after surgery may prevent postoperative ocular hypertension after phacoemulsification [19]. Topical carbachol in a 1.5% solution produces a more intense and considerably more pronounced miosis than does a 2% solution of pilocarpine in human beings and has a more prolonged action [12]. It is therefore usually prescribed for use only two to three times daily. The safety and efficacy of carbachol use for chronic glaucoma in animal species have not been determined, however.

Demecarium bromide

Demecarium bromide (DB) is an extremely potent long-acting AChE inhibitor and is the most toxic of the clinically available AChE-inhibitor drugs [12]. DB may be used in the management of primary glaucoma in dogs. Topically applied DB (0.125% and 0.25%) induced long-term miosis and a decrease in IOP in normotensive and glaucomatous Beagles. DB (0.125% and 0.5%) decreased IOP for 49 and 55 hours, respectively. The miosis associated with both concentrations of DB generally paralleled the decreases in IOP.

Common side effects include ciliary spasm and superficial and deep vascular congestion [12]. The effect of topically applied 0.25% DB on aqueous humor flare was evaluated while treating normal eyes of Beagles three times daily for 8 days [16]. DB induced aqueous flare and a decrease in IOP, with peak effect seen at 31 hours. After 8 days of treatment three times daily, flare values had returned to normal. The transient increase in aqueous humor protein concentration did not result in ocular or visual damage, and long-term changes were not seen. Systemic toxicity may develop with any cholinesterase inhibitor and may include salivation, vomiting, diarrhea, and abdominal cramping [2]. Topical ocular application of 0.25% DB was recently shown to cause transient suppression of systemic AChE levels in dogs [21]. In some individuals, AChE levels were suppressed to levels approaching clinical toxicity; however, by day 3, AChE levels had risen to levels above baseline in most dogs. Dogs receiving such therapy should be monitored for signs of AChE toxicity, and concomitant use of other AChE inhibitors should be avoided. DB is typically used once daily; nevertheless, twice-daily administration is recommended to regulate IOP and to avoid the occasional peaks that may be destructive in the glaucomatous eye [22]. Echothiophate (phospholine iodide), another AChE inhibitor historically administered as a topical hypotensive agent, is no longer commercially available.

Adrenergic agents

Agonists

Epinephrine and dipivalyl epinephrine

Epinephrine and an epinephrine prodrug, dipivalyl epinephrine (dipivefrin), are sympathomimetic agents that have been evaluated for use in the management of primary canine glaucoma [23]. Although the specifics regarding their mechanism of action are not completely understood, it is generally believed that sympathomimetic agents reduce formation of aqueous humor and increase aqueous outflow. Epinephrine possibly has a vasoconstrictive effect on the vasculature of the ciliary body, subsequently diminishing blood flow to the ciliary processes and reducing aqueous humor formation. Increased facility of aqueous outflow is mediated by α_2-adrenergic receptors and is correlated with increased cyclic adenosine monophosphate

(cAMP) production by the trabecular meshwork. Dipivefrin and L-epinephrine were evaluated in various concentrations in normotensive and glaucomatous Beagles [23]. One percent and 2% epinephrine and 0.5% dipivefrin produced significant lowering of IOP. Mydriasis and some local irritation consisting of mild conjunctivitis and tearing occurred. Because anticholinesterases can inhibit the corneal esterases that convert dipivefrin to epinephrine, the combined use of indirect-acting miotics (eg, DB) and dipivefrin is not advised [24].

Apraclonidine

Apraclonidine hydrochloride is a potent and relatively selective α_2-agonist used in the management of glaucoma in human beings. By stimulating α_2-receptors on the nonpigmented ciliary epithelium, apraclonidine is hypothesized to inhibit adenylate cyclase activity, thereby impairing the conversion of adenosine triphosphate (ATP) to cAMP and the production of aqueous humor [25]. Another mechanism of apraclonidine activity is speculated to be vasoconstriction of the afferent arterioles of the ciliary body, subsequently reducing ciliary body blood flow and inhibiting aqueous humor production [26]. Apraclonidine may also influence secondary avenues of aqueous outflow, such as uveoscleral outflow, and may affect conjunctival and episcleral vascular flow [27,28].

Apraclonidine has been approved for use in the prevention of elevated IOP after laser trabeculoplasty and iridotomy and has potential uses in preventing an IOP rise after laser posterior capsulotomy and cataract surgery in patients already on other glaucoma medications [27]. Apraclonidine is also effective in blunting IOP spikes occurring with cycloplegia in patients with open-angle glaucoma [29]. In normotensive clinically normal canine eyes, apraclonidine reduced mean IOP by 3.0 mm Hg (16%) 8 hours after treatment [30]. Apraclonidine also reduced IOP in clinically normal feline eyes, with a mean reduction in IOP of 4.8 mm Hg (24%) occurring 6 hours after treatment [31].

Because apraclonidine may reduce pulse and blood pressure, caution in using drugs like β-blockers (ophthalmic and systemic), antihypertensive agents, and cardiac glycosides is advised. The most prominent ocular side effect of 0.5% apraclonidine in dogs was mild blanching of the conjunctiva [30]. In addition to reducing IOP, administration of apraclonidine reduced resting heart rate in individual dogs in one study, but overall mean heart rate in the study population was not significantly reduced. Apraclonidine also caused pupillary mydriasis in this group of dogs. Although apraclonidine is predominantly an α_2-agonist, it has some α_1-activity. The mechanism by which apraclonidine induced mydriasis in dogs was speculated to be via stimulation of α_1- and α_2-adrenergic receptors. Mydriasis may result from the drug's interaction with inhibitory prejunctional α_2-receptors on nonadrenergic nerves to the iris sphincter muscle or by stimulation of α_1-receptors on the iris dilator muscle [30].

Adverse ocular effects of apraclonidine in cats included occasional blepharospasm and mild blanching of the conjunctival vessels [31]. Apraclonidine also induced miosis in these clinically normal feline eyes. This effect was in contrast to the mydriasis observed in dogs and the lack of change or negligible mydriasis seen in people. Resting heart rate was also reduced in cats in this study. Most of these cats also vomited after administration of apraclonidine, and some continued to vomit for up to several hours after treatment. Apraclonidine may induce vomiting by stimulating α_2-receptors in the chemoreceptor trigger zone, a mechanism that has been demonstrated for other α_2-agonists, such as clonidine, medetomidine, and xylazine [32,33]. These effects in cats could be a function of the distribution of an absolute dose of topical apraclonidine with a smaller body weight or a greater sensitivity of cats to α_2-adrenergic agents [31]. Cardiovascular and contralateral ocular effects were observed in monkeys given unilateral apraclonidine, and these effects were attributed to the monkeys' small body weight [34]. Apraclonidine is therefore not recommended for use in cats.

Brimonidine

Brimonidine tartrate is a selective α_2-adrenergic agonist that is 28 times more selective than apraclonidine [35]. Brimonidine reduces IOP by decreasing the rate of aqueous humor formation and increasing aqueous humor outflow [28]. The most common side effects in people were blurred vision and oral dryness [36]. A recent evaluation of the effects of 0.2% brimonidine in the glaucomatous Beagle model demonstrated a decrease in IOP, a statistically significant miosis, and a reduced heart rate [37]. Because of the limited drug-induced ocular hypotension, however, it was concluded that brimonidine should be combined with other drugs when used for the glaucomas in the dog.

Antagonists

β-blockers

β-blockers decrease IOP by decreasing the inflow rate of aqueous humor [38]. As a result of β-adrenoreceptor blockade in the ciliary body, decreased aqueous secretion, ultrafiltration, or both may occur. Two of the most commonly used topical β-blockers in veterinary ophthalmology are betaxolol and timolol maleate.

Betaxolol. Betaxolol was the first β_1-selective ophthalmic β-blocker to be marketed. Although the cardiovascular effect of betaxolol has been evaluated in research models using dogs, limited studies are available evaluating the efficacy of betaxolol in reducing IOP in veterinary patients. A recent study evaluated the ability of 0.5% betaxolol (one drop topically every 12 hours) to prevent glaucoma in the fellow eye of dogs with unilateral primary closed-angle glaucoma in a multicenter open-label clinical trial. Untreated control dogs developed glaucoma significantly sooner (median = 8 months) than dogs treated with betaxolol (median = 30.7 months) [39].

Timolol maleate. Timolol maleate is a nonselective β-blocker. Topical administration of timolol maleate resulted in a reduction of IOP in treated and contralateral eyes of normotensive dogs and cats. In addition, the treated eye became miotic. This effect may indicate β-adrenergic inhibition or α-adrenergic activation of the iris sphincter muscle. β-adrenergic blockade may result in miosis [40,41]. Peak effect was seen between 2 and 4 hours after treatment in dogs [41] and between 6 and 12 hours in the cat [40]. Another investigation of the effect of timolol in the Beagles found that 0.25% and 0.5% timolol solutions were ineffective in normotensive eyes but lowered IOP in glaucomatous eyes [42]. A dose-related decrease in IOP was seen in normotensive dogs after administration of 2%, 4%, 6%, and 8% timolol in one study [42]. The IOP lowering effect of 4% and 6% timolol was more marked and consistent in glaucomatous Beagles than in normotensive Beagles in another study [43]. A significant decrease in pulse rate was observed in these dogs [42,43]. Although there are no specific guidelines for the use of 0.25% timolol in companion animals, it may be appropriate to consider using 0.25% timolol in cats or in dogs with smaller body weight (eg, less than 20 lb) and the 0.5% concentration in dogs weighing greater than 25 lb. Provided an anticipated ocular hypotensive effect is achieved, using this lower concentration of timolol may reduce the risk of potential side effects of the β-blocker on patients with lower body weight.

Timolol is available commercially in 0.25% and 0.5% solutions. Dosing of 0.5% timolol is typically every 8 to 12 hours in dogs and every 12 hours in cats. The most commonly reported side effects of timolol administration in people include local irritation and conjunctival hyperemia. Potential systemic risks associated with topical timolol use are related to systemic β-adrenoreceptor blockade. Cardiac arrhythmias, heart block, and bradycardia can occur with β_1-blockade, whereas pulmonary effects, such as bronchospasm and airway obstruction, can result from β_2-blockade [44]. β-blocking agents are not recommended for first-line glaucoma therapy in patients with cardiovascular compromise or a history of pulmonary disease.

Carbonic anhydrase inhibitors

Two recently developed topical CAIs, dorzolamide and brinzolamide, have shown promise in reducing IOP in animals. By the systemic route, a CAI is effective when the free drug concentration in plasma is 2.5 μM [45]. With dorzolamide, the plasma concentration is approximately 100 times lower, but the concentration in the ciliary processes is 2 to 10 μM, comparable to that after systemic drug delivery. The concentration in plasma (reflecting free drug) of dorzolamide, a topical CAI, is about 1/200 of that needed to induce the systemic effects seen after systemic CAI administration [45].

Dorzolamide

Two percent dorzolamide was shown to significantly reduce IOP and aqueous humor flow in dogs when administered to both eyes every 8 hours [46]. In another study, dorzolamide reduced IOP by a mean of 3.1 mm Hg in normotensive canine eyes [47]. The maximum IOP decrease was observed 5 to 6.5 hours after -treatment, returning to pretreatment values at 10.5 hours after treatment. This observation supports a dosing regimen of every 8 hours for dorzolamide in dogs. Over the short term, dorzolamide instilled every 12 or 8 hours produced significant decreases in IOP in glaucomatous Beagles [48]. Application of 2% dorzolamide twice daily resulted in a significant decrease in IOP of normotensive cats over the treatment phase in a recent study, suggesting that it may be useful in the management of glaucoma in this species [49].

Two percent dorzolamide may be administered every 12 hours in cats and every 8 hours in dogs. Dorzolamide has also been evaluated in normotensive equine eyes [16]. Mean IOP was decreased significantly over the short term with treatment every 12 hours. This reduction was not dramatic, however, equating to a mean reduction in IOP of less than 2 mm Hg compared with baseline. In the large equine eye, surface absorption and tissue-binding characteristics as well as time of residence for 2% dorzolamide at active sites in the ciliary epithelium are currently unknown; higher concentrations or increased frequency of administration may be required for this and other topical preparations to be effective in the horse. If dorzolamide is used for glaucoma therapy in a horse, dosing every 8 hours is recommended. Side effects associated with topical dorzolamide use in human beings are ocular stinging, burning, or discomfort on instillation. Dorzolamide can cause irreversible corneal edema in glaucoma patients with corneal endothelial cell compromise [50]. The author has observed blepharitis in several dogs treated with dorzolamide, which resolved after discontinuation of the drug.

Brinzolamide

Administration of 1% brinzolamide was associated with a mean reduction in IOP of 3.5 mm Hg in normotensive canine eyes [47]. Short-term administration of brinzolamide every 12 hours did not significantly reduce IOP in a small sample of normotensive cats [51]. No adverse effects were seen in treated dogs or cats. Infrequent side effects of administration in people include blurred vision, ocular discomfort, and abnormal taste [52]. The pH of 1% brinzolamide is 7.5, which is more physiologic than the 5.6 pH of 2% dorzolamide [53]. This may result in a better tolerance to brinzolamide.

Although the most significant benefit of topical CAI therapy is to replace systemic CAI use and thus reduce the adverse effects of oral CAIs, practitioners still commonly use combined oral and topical CAI therapy. In human patients, treatment with dorzolamide reduced aqueous humor flow significantly compared with placebo but less than a maximum dose of

acetazolamide. Small doses of acetazolamide added to dorzolamide treatment did not further enhance this decrease in aqueous flow [54]. In a group of glaucomatous Beagles, dorzolamide combined with oral methazolamide, 5 mg/kg, administered every 12 hours produced similar but not additional declines in IOP compared with dorzolamide administered alone [48]. These results suggest that the concomitant use of a topical and systemic CAI is not warranted in glaucoma therapy.

Dorzolamide-timolol

A commercial combination of 2% dorzolamide and 0.5% timolol maleate is available. In human beings, the IOP lowering effect of this dorzolamide-timolol combination given twice daily is comparable to that of dorzolamide given three times daily plus timolol administered twice daily and was maintained for up to 1 year [55].

An improved IOP lowering effect was observed in normotensive horses given the dorzolamide-timolol combination versus dorzolamide alone [56]. This combination product may be more useful in the patient with increasing IOP than either dorzolamide or timolol alone. Recommended frequency of administration of the dorzolamide-timolol combination is every 12 hours; this reduces the daily treatment frequency from five doses to two doses, which may significantly improve owner and patient compliance. In human beings, however, the adverse ocular and local adverse effects were greater for dorzolamide and the dorzolamide-timolol combination than for timolol alone, with ocular burning or stinging being most frequently reported [57].

Prostaglandin analogues

Prostaglandin (PG) analogues are highly effective ocular hypotensive agents. Preliminary investigations of the efficacy of the topical PGs latanoprost and unoprostone have been performed in some companion animal species, and these analogues show promise in their ability to reduce IOP.

Latanoprost

Latanoprost at a 0.005% concentration is a prostanoid selective FP-receptor (receptors specific for prostaglandin-F [PGF]) agonist. Latanoprost reduces IOP by increasing aqueous humor outflow via remodeling of the ciliary muscle extracellular matrix, subsequently increasing uveoscleral outflow [58,59]. Topical administration of the rapidly metabolized and locally acting synthetic PG latanoprost has limited systemic absorption, thus avoiding systemic side effects [60]. In normotensive canine eyes, latanoprost was shown to reduce IOP significantly [61]. In normotensive feline eyes in the same study, however, latanoprost did not significantly lower IOP. Another study confirmed a dose-dependent IOP reducing effect of

latanoprost in dogs and the lack of such an effect in cats [62]. Latanoprost also reduced IOP in normotensive equine eyes [63].

Reported side effects related to latanoprost use in people (ie, iris and eyelid hyperpigmentation, hypertrichosis, conjunctival hyperemia) [64,65] are limited in veterinary patients. Although not reported in people receiving latanoprost therapy, a moderate to intense miosis is consistently observed in the latanoprost-treated eyes of cats, dogs, and horses [60, 63]. In some horses, this response is accompanied by characteristics of ocular pain [63]. The degree of miosis associated with latanoprost administration can occasionally be visually debilitating, particularly in those animals with axial cataracts.

Latanoprost is indicated for treatment of primary glaucoma in dogs and may replace mannitol as a first-line drug in the emergency management of acute primary glaucoma. The author has observed a dramatic reduction of IOP in the eyes patients with acute and chronic glaucoma within 20 minutes of administering latanoprost. Latanoprost should not be used in patients with anterior lens luxation, because the induction of a potentially intense miosis behind an anteriorly luxated lens may result in pupillary block as a result of vitreous entrapment. Conversely, latanoprost may be helpful as a miotic agent in cases of ocular hypertension secondary to lens subluxation or posterior luxation, where lensectomy is not elected or is deemed otherwise inappropriate for an individual patient. Latanoprost is labeled for administration every 24 hours in human patients. It is the author's opinion that latanoprost is most effective in glaucomatous dogs when applied every 12 hours.

Latanoprost should be used with caution in dogs with glaucoma secondary to intraocular inflammation or in pseudophakic and aphakic patients, especially those with retinal vascular fragility or other factors that may predispose to the breakdown of the blood-retinal barrier [66]. Because recurrent uveitis seems to be a risk factor for glaucoma in horses, topical latanoprost may potentiate PG-mediated inflammatory disease in affected horses [63].

Unoprostone

Unoprostone isopropyl at a concentration of 0.12% is the first docosanoid compound approved for treatment of glaucoma in human beings. This compound may lower IOP by affecting aqueous outflow, most probably via conventional outflow pathways, through inhibition of endothelin-dependent mechanisms. Although primarily Ca^{2+}-sensitive signal transduction pathways seem to be involved, effects of unoprostone on Ca^{2+}-independent pathways and uveoscleral outflow cannot be excluded [67]. Unoprostone caused a significant and long-lasting decrease in IOP in normotensive canine eyes, suggesting that unoprostone is potentially efficacious in treatment of canine glaucoma [68].

A summary of conventional topical and systemic ocular hypotensive agents is provided in Table 1.

Table 1
Summary of selected commercially available ocular hypotensive drugs

Drug	Classification	Concentration available	Packaging information	Indications	Cautions
Mannitol	Osmotic diuretic	5–20% IV solution	Store at room temperature; if crystallizes, warm solution to dissolve	Short-term use in acute 1° or 2° glaucoma	For slow IV use only, do not use in dehydrated patient or in patient with cardiac compromise
Glycerin	Osmotic diuretic	50% oral solution	220 mL Store at room temperature	Short-term use in acute 1° or 2° glaucoma	Oral use only, do not use in dehydrated patient or in patient with cardiac compromise, avoid in diabetic patients
Methazolamide	Oral CAI	25-, and 50-mg tablets	Store at room temperature	Acute and chronic 1° and 2° glaucoma	Can cause anorexia, vomiting, diarrhea, increased diuresis, malaise, and panting secondary to metabolic acidosis or hypokalemia
Pilocarpine	Direct-acting cholinergic, parasympathomimetic miotic	1%, 2%, 4%, 6%, or 8%for topical use	15–30 mL Store at 46°F–80°F (8°C–27°C)	Acute and chronic 1° glaucoma	Avoid in patients with anterior lens luxation, uveitis, or pupillary block
Carbachol	Direct-and indirect-acting cholinergic, parasympathomimetic miotic	0.75%, 1.5%, 2.25%, or 3% for topical use	15–30 mL Store at 46°F–80°F (8°C–27°C)	Acute and chronic 1° glaucoma	Can produce systemic toxicity; avoid in patients with cardiorespiratory disease, hyperthyroidism, or hypertension; can induce headache from ciliary spasm
		0.01% for intracameral use	1.5-mL sterile glass vial Store at 59°F–86°F (15°C–30°C)	Achieving miosis during intraocular surgery (after ICLE or phacoemulsification) to reduce risk of postoperative IOP spike	For single-dose use only; can produce systemic toxicity; avoid in patients with cardiorespiratory disease, hyperthyroidism, or hypertension; can induce headache from ciliary spasm

Demecarium bromide	long-acting cholinesterase (AChE) inhibitor, miotic	0.125% or 0.25% for topical use	5 mL Protect from excessive heat or cold	Chronic glaucomas amenable to miotic therapy	Use only when shorter acting miotics have proven inadequate
Epinephrine	Adrenergic agonist sympathomimetic	0.5%, 1%, and 2% for topical use	15 mL Store at room temperature and protect from light	Acute and chronic 1° open-angle glaucoma	Avoid in patients with narrow-angle glaucoma, hypertensive cardiac disease, and asthma
Dipivalyl epinephrine	Adrenergic agonist sympathomimetic	0.1% for topical use	5, 10, and 15 mL Store at room temperature and protect from light	Acute and chronic 1° open-angle glaucoma	Avoid in patients with narrow-angle glaucoma, hypertensive cardiac disease, and asthma
Apraclonidine	Selective α_2-agonist	0.5% for topical use	5 and 10 mL Store at 36°F–80°F (2°C–27°C)	For use in the prevention of elevated IOP after laser procedures and cataract surgery; also effective in blunting IOP spikes occurring with cycloplegia in patients with open-angle glaucoma	Avoid in cats and in patients with cardiovascular, hepatic, and renal disease, or in patients receiving MAO inhibitors
Brimonidine	Selective α_2-agonist	0.2% for topical use	5, 10, and 15 mL Store at or below 77°F (25°C)	Acute and chronic 1° open-angle glaucoma	Avoid in cats and in patients with cardiovascular, hepatic, and renal disease, or in patients receiving MAO inhibitors

(*continued on next page*)

Table 1 (*continued*)

Drug	Classification	Concentration available	Packaging information	Indications	Cautions
Betaxolol	Selective β_1-antagonist	0.25% or 0.5% for topical use	2.5–15 mL Store at room temperature, shake well	Acute and chronic 1° and 2° glaucoma	Caution in patients with diabetes, hyperthyroidism, or cardiac disease or severe respiratory disease
Timolol maleate	Non-selective β-antagonist	0.25% or 0.5% solution and gel-forming solution for topical use	2.5 and 5 mL Store at 59°F–77°F (15°C–25°C) and protect from light	Acute and chronic 1° and 2° glaucoma	Avoid in patients with asthma, severe obstructive pulmonary disease, or cardiac disease; caution in patients with diabetes or hyperthyroidism
Dorzolamide	CAI	2% for topical use	5 and 10 mL Store at 59°F–86°F (15°C–30°C) and protect from light	Acute and chronic 1° and 2° glaucoma	Avoid in patients with severe renal compromise or patients sensitive to sulfonamides
Brinzolamide	CAI	1% for topical use	2.5–15 mL Store at 39°F–86°F (4°C–30°C)	Acute and chronic 1° and 2° glaucoma	Avoid in patients with severe renal compromise or patients sensitive to sulfonamides
Dorzolamide-timolol	CAI/nonselective β-antagonist combination	2% dorzolamide–0.5% timolol for topical use	5 and 10 mL Store at 59°F–77°F (15°C–25°C) and protect from light	Acute and chronic 1° and 2° glaucoma	Refer to cautions for dorzolamide and timolol
Latanoprost	Prostaglandin analogue	0.005% for topical use	2.5 mL Refrigerate unopened bottle at 36°F–46°F (2°C–8°C); store opened bottle at room temperature for up to 6 weeks	Acute and chronic 1° glaucoma	Avoid in patients with uveitis or those with severe renal or hepatic disease; induces miosis in dog, cat, and horse; avoid in patients with pupillary block glaucoma or anterior lens luxation

Abbreviations: AChE, acetylcholinesterase; CAI, carbonic anhydrase inhibitor; ICLE, intracapsular lens extraction; IOP, intraocular pressure; IV, intravenous; MAO, monoamine oxidase; 1°, primary; 2°, secondary.

Prophylaxis in primary glaucoma

It is common practice in veterinary ophthalmology to treat the contralateral unaffected eye prophylactically in cases of confirmed or presumed primary glaucoma. Until recently, this practice was of questionable efficacy. The ability of either 0.5% betaxolol (one drop topically every 12 hours) or a combination of 0.25% DB and a topical corticosteroid (gentamicin/betamethasone [GB], one drop of each (DB/GB) topically every 24 hours) to prevent glaucoma in the fellow eye of dogs with unilateral primary closed-angle glaucoma was investigated in a multicenter open-label clinical trial. Untreated control dogs developed glaucoma sooner (median = 8 months) than dogs treated either with DB/GB (median = 31 months) or betaxolol (median = 30.7 months). Although DB/GB and betaxolol equally delayed or prevented the onset of glaucoma in the second eye, the authors proposed that the less frequent dosing schedule for DB/GB suggested that the DB in combination with a topical corticosteroid might be preferable to betaxolol in preventing primary open-angle glaucoma in dogs [39]. The potential for other topical agents or combinations of agents to prevent or delay the onset of clinical disease in an eye predisposed to glaucoma warrants further investigation in veterinary patients.

Neuroprotection in glaucoma

The concept of neuroprotection in the management of glaucoma has gained popularity in human and veterinary ophthalmology. Medications addressing neuroprotection may not be restricted to therapies that specifically reduce IOP; however, the future of glaucoma therapy may include such agents.

Pressure-mediated damage of the optic nerve has been explained variously by a direct mechanical effect, compromise of the retinal and optic nerve microcirculatory vasculature (an ischemia effect), and an indirect physical effect that results in compression of the ganglion cell axons as they course posteriorly through the lamina cribrosa [1]. Retinal ischemia may establish the cellular conditions that create a fatal biochemical cascade; specifically hypoxia, followed by high excitotoxic levels of glutamate, causes pathologically elevated levels of intracellular calcium, resulting in neuronal cell death via apoptosis or necrosis. Impaired ocular perfusion, primarily as a result of abnormal autoregulation or vasoconstriction caused by endothelin-1 (ET-1), may contribute to the ischemic milieu [69]. The aqueous humor of dogs with hypertensive glaucoma contains significantly higher levels of ET-1 than that of healthy dogs [70]. Glutamate concentrations potentially toxic to RTCs are associated with the pathogenesis of primary glaucoma in dogs [71].

Neuroprotection, the preservation of neurons that were either not damaged or only slightly damaged during a primary insult, has become

important for the clinician when considering glaucoma treatment options. Although many aspects of the glaucomas in animals differ from the disease complex in human beings, the concepts of neurotoxicity and neuroprotection are areas of current research in dogs. The calcium channel antagonist nifedipine can prevent ET-1–induced vasospasm and ameliorate the effects of elevated glutamate in people [72]. Systemically administered amlodipine did not alter IOP but increased blood flow velocities and decreased vascular resistance index in the ophthalmic artery, short posterior ciliary arteries, and long posterior ciliary arteries in normal dogs [73]. Calcium channel blockers may have a role in early glaucoma or in prophylaxis therapy for the unaffected contralateral eye in primary glaucoma, but additional research is needed to determine safety and efficacy in animals.

Some topical glaucoma medications have demonstrated neuroprotective effects. Laser Doppler flowmetry has shown that dorzolamide and brinzolamide improve blood flow to the optic nerve head in pigmented rabbits after topical administration without producing an increase of blood P_{co_2}, indicating a potential for a local vasodilatory effect involving the optic nerve head circulation [74]. In an ischemia animal model, unoprostone protected RGCs in a dose-dependent manner. Unoprostone inhibits glutamate stimulation and opens maxi-K channels, which are potassium channels that reach an activation threshold only during depolarization or at high intracellular calcium concentrations. The resultant large efflux of potassium hyperpolarizes the cell, thereby closing voltage-gated calcium channels and limiting neuronal damage by decreasing influx of intracellular calcium. Additionally, unoprostone has vasorelaxant properties as evidenced by increased choroidal blood flow and inhibition of vasoconstrictors, such as ET-1. [69] In addition to their known effect of lowering IOP, α_2-adrenoreceptor agonists seem to exert a neuroprotective effect. Topical apraclonidine therapy prevented IOP elevation and protected optic nerve fibers in a rat model of glaucoma [75]. In addition to its effect on IOP, brimonidine exhibited neuroprotective effects in a rat optic nerve crush model [76].

Summary

The glaucomas are vision-threatening diseases that commonly result in blindness. In addition to knowledge of the at-risk breeds and predisposing factors for glaucoma as well as the clinical signs of the disease, regular IOP screening with tonometry is required to confirm glaucoma and to monitor the status of the eye. Early intervention with a combination of medications that are capable, in a given species, of reducing aqueous production and increasing aqueous outflow as well as potentially reducing progressive neurosensory degeneration is key to the medical management of this disease.

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