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Review

Autonomic drugs in the treatment of canine and feline glaucoma – Part I: Medications that lower intraocular pressure by increasing the outflow of aqueous humour

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Abstract

One characteristic of the most common types of glaucoma is increased intraocular pressure (IOP), which has a damaging effect on optic nerve axons, leading to progressive loss of retinal ganglion cells. Therefore, ocular hypotensive drugs are the mainstay of pharmacological therapy for glaucoma. This review article, which is the first part of a two-part series, is dedicated to autonomic drugs which lower IOP by increasing the outflow of aqueous humour. These agents are subdivided into two groups: (a) drugs that lower IOP by increasing the trabecular outflow and the uveoscleral outflow (i.e. nonselective adrenergic agonists), and (b) medications that lower IOP by opening of the drainage angle and by increasing the conventional outflow *via* the trabecular outflow (i.e. parasympathomimetics). This paper summarizes the current state of knowledge on the mechanism of action of these drugs and their effect on IOP in dogs and cats. Moreover, it discusses possible undesirable side effects of these medications and presents the current ideas about their role and position in the medical management of glaucoma in small animals.

Key words: glaucoma, IOP, adrenergic agonists, parasympathomimetics, dogs, cats

Introduction

„Glaucoma" is not a single entity. It refers to a group of ocular disorders; as these disorders have diverse features, perhaps „the glaucomas" as a plural would be better (Casson et al. 2012). In all species, this group of disorders is unified in their final common pathway of characteristic optic nerve and retinal pathology resulting in the loss of vision. Glaucoma is therefore widely considered a neurodegenerative disease (McLellan and Miller 2011). The pathophysiological process of glaucomatous optic neuropathy is not fully understood, but it is likely to be a multifactorial event. An increase in intraocular pressure (IOP) is the principal risk factor for glaucoma, and the primary goal of treatment is to reduce IOP to values that will halt the death of retinal ganglion cells (Smith et al. 2010). Pathologic elevation of

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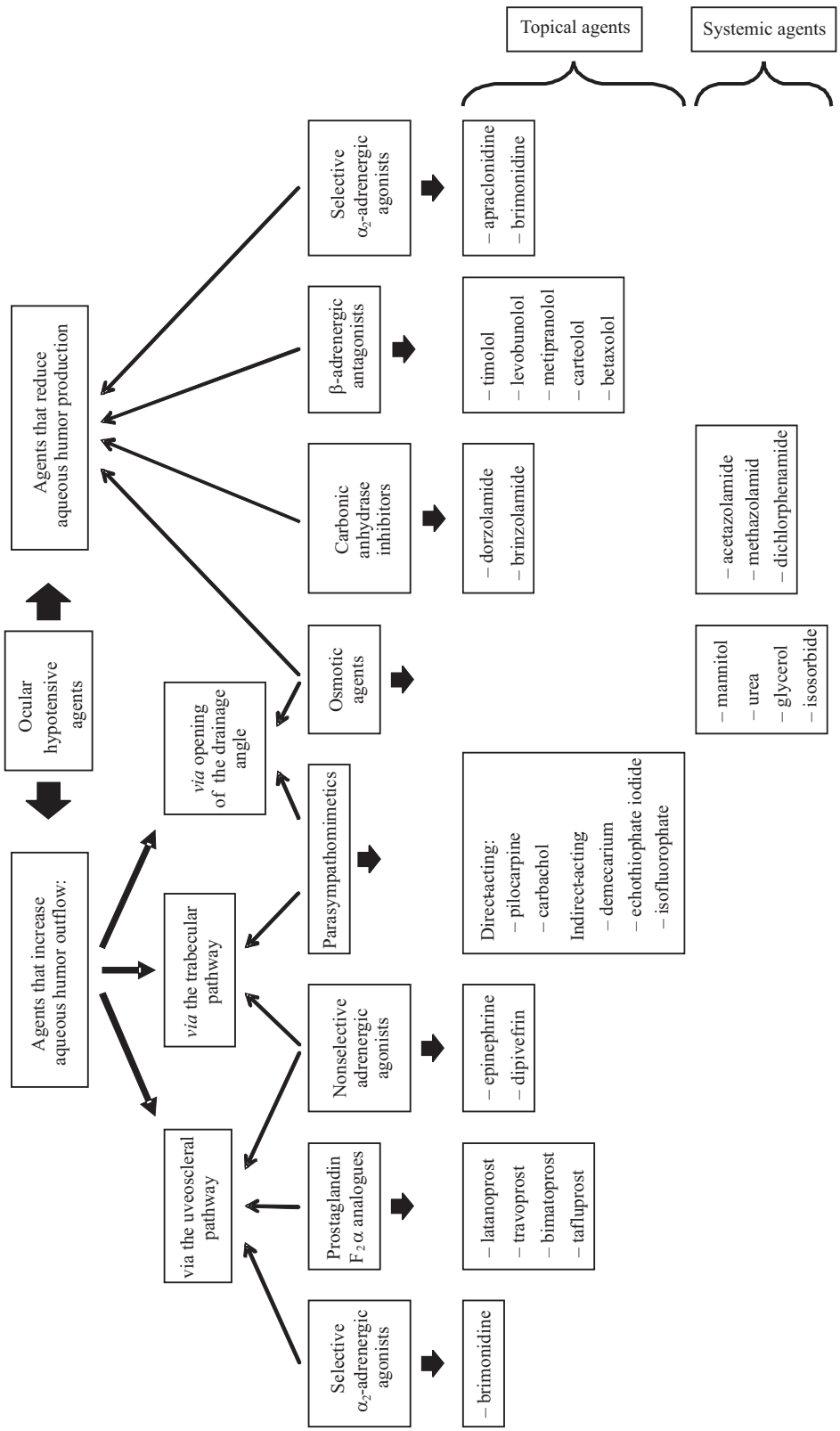

Fig. 1. Proposed classification of drugs used clinically to reduce IOP according to their way of action, target site and route of administration.

IOP is the consequence of obstruction or misdirection of the aqueous humour (AH) flow or outflow anywhere along its course from the posterior chamber through the pupil into the ciliary cleft, across the trabecular meshwork (TM), and into the scleral venous plexus (Grahn and Peiffer 2007). Elevated IOP

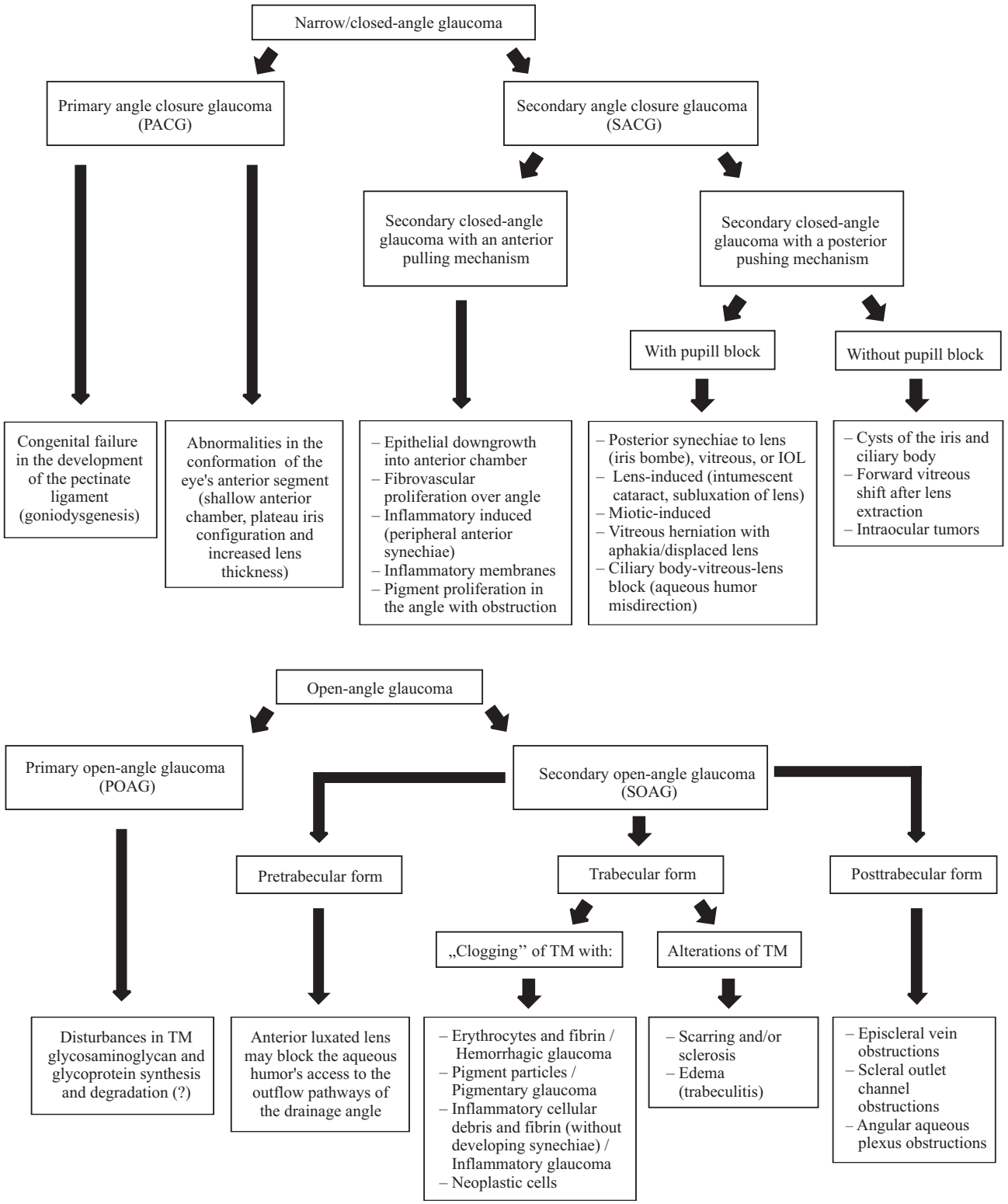

Fig. 2. Proposed classification of glaucoma in small animals.

almost invariably is the result of impaired AH outflow (Miller 2008). Separately or in addition to IOP, other factors [such as dysfunction of ocular blood-flow regulation with local ischemia-hypoxia (Flammer and Orgul 1998), excessive stimulation of the glutamatergic system (Brooks et al. 1997) and aberrations in immunity (Schwartz 2003)] can contribute to death of retinal ganglion cells (Greller et al. 2008).

The ultimate goal of glaucoma therapy is to delay or stop or sometimes reverse the glaucomatous

changes to the optic nerve and ganglion cell layer caused by raised IOP. Current pharmacological treatment of glaucoma focuses on indirect protection of the optic nerve, i.e. through IOP lowering. There are two ways to lower IOP: surgical and pharmacological treatment. Pharmacological treatment means topical and/or systemic application of ocular hypotensive drugs. There are two principal ways to reduce IOP pharmacologically: by lowering AH formation and by increasing AH outflow. Although some ocular hypotensive drugs are likely to depress IOP by affecting both AH formation and outflow, based on the dominant way of action they are divided into: (a) those that reduce AH production [i.e. carbonic anhydrase inhibitors (CAIs), β-adrenergic antagonists, and selective α_2-adrenergic agonists], (b) those that increase AH outflow [i.e. nonselective adrenergic agonists, parasympathomimetics, and prostaglandin $F_2\alpha$ analogues (PGAs)], and (c) those that dehydratate the intraocular space *via* osmotic gradient (although these agents also enhance the outflow of AH and most probably reduce AH formation, they are traditionally distinguished as a separate group). Further classification of ocular hypotensive drugs relies on their target site (e.g. selective α_2-adrenergic agonists), the way in which they increase the AH outflow and the route of administration (Fig. 1).

It is worth mentioning that literature data indicate large inter-species differences in the clinical efficacy of topical ocular hypotensive drugs in the therapy of human, canine and feline glaucomas. The major reasons are most probably species- and breed-related differences in (a) the ocular anatomy and AH dynamics, and in (b) the etiology, pathophysiology and epidemiology of glaucoma. Therefore, it would be unjustifiable to extrapolate from results of clinical efficacy of ocular hypotensive drugs used in the therapy of humans to their influence on animals. Unfortunately, there is currently a paucity of published, randomized, well-controlled, prospective clinical trials that have evaluated the efficacy and safety of these medications in the treatment of glaucoma in dogs and cats. However, results are available of many experimental studies in which the effect of different ocular hypotensive drugs on IOP in normal and glaucomatous canine and feline eyes has been evaluated. Based on these and other literature data, this review paper has been written, in which an attempt has been made to summarize the current state of knowledge about autonomic ocular hypotensive drugs acting through the autonomic nervous system in terms of their mechanism of action, efficacy, recommended use and unwanted effects in dogs and cats. For the sake of elucidating mechanisms of action and clinical applications of the discussed drugs, the paper also contains basic information about AH dynamics and the classification of veterinary glaucomas (Fig. 2).

Aqueous humor dynamics

AH is formed in the ciliary processes from arterial blood. Three mechanisms are involved in its formation: diffusion, ultrafiltration and active secretion. The first two processes are passive and do not entail active cellular participation. Active secretion is thought to be the major contributor to AH formation, responsible for approximately 80% to 90% of the total AH formation (Goel et al. 2010). After entering the anterior chamber *via* the pupil, the AH is drained by two different pathways, both located in the iridocorneal angle (also known as drainage or filtration angle):

– **The trabecular outflow (also known as conventional outflow)** is the drainage of AH sequentially through the ciliary cleft, the trabecular meshwork, Schlemm's canal, collector channels, episcleral veins, anterior ciliary veins and into the systemic circulation (Nilsson 1997). This pathway has been determined to be „pressure-dependent"; elevations in IOP cause a large difference in pressure between the anterior chamber and the episcleral vasculature, leading to a proportional increase in outflow through TM (Barrie et al. 1985). The trabecular pathway represents the main outflow route in the mammalian eye.

– **The uveoscleral outflow (also known as unconventional outflow)** refers to the AH leaving the anterior chamber *via* the ciliary cleft and subsequently through intercellular spaces among ciliary muscle bundles into the supraciliary and suprachoroidal spaces, from which it is drained through the sclera. Outside the eye, fluid is returned to the systemic circulation probably *via* the lymphatic vessels in the orbit. In contrast to trabecular outflow, uveoscleral outflow is effectively pressure-independent. The state of the ciliary muscle is important and contraction reduces while relaxation increases uveoscleral flow (Alm and Nilsson 2009). Uveoscleral outflow accounted for 15% and 3% of the total AH outflow in the normotensive dogs and in the advanced glaucomatous dogs, respectively. In the advanced glaucomatous Beagle, conventional and uveoscleral outflow pathways were reduced and contributed to the etiopathogenesis of glaucoma (Barrie et al. 1985). In cats the uveoscleral outflow seems to be of considerably less importance, constituting some 3% of the total drainage (Bill 1966, Nilsson 1997).

Drugs that lower IOP by increasing the trabecular outflow and the uveoscleral outflow, i.e. nonselective adrenergic agonists

This group consists of just one drug, which is epinephrine (adrenaline), a natural and non-specific adrenergic agonist, and its prodrug, dipivefrin (dipivalyl epinephrine), produced by adding two pivalic acid side chains to the parent compound. Dipivefrin is hydrolyzed by various corneal esterases, mainly cholinesterase to epinephrine (Nakamura et al. 1993) shortly after entry into the eye; the cornea is the major site of ocular hydrolysis (Anderson et al. 1980). The drug itself has little or no pharmacological activity until it is hydrolyzed into parent compound (Kaback et al. 1976). Dipivefrin is 600-fold more lipophilic than epinephrine (Wei et al. 1978) and therefore it penetrates the cornea approximately 17-fold greater than the parent drug (Mandell et al. 1978). This is an extremely valuable attribute of dipivefrin as it enables its application in much smaller doses (it is used in 0.1% concentration) than epinephrine (used in 0.25%, 0.5%, 1%, and 2% concentrations), yet producing a therapeutic effect in the eye comparable to that of the parent drug (Kaback et al. 1976); it was demonstrated that 0.1% dipivefrin gave an IOP reduction similar to that of 1% epinephrine (Krieglstein and Leydhecker 1978). Therefore, when dipivefrin is administered topically, systemic levels of epinephrine are much smaller than during the topical administration of ocular hypotensive preparations containing epinephrine. This is the reason why administration of dipivefrin is associated with a lower incidence of systemic side effects compared to epinephrine (Garzia 1982). Consequently, dipivefrin may be preferred over epinephrine because of reduced systemic reactions.

Mechanism of action

So far, despite efforts of numerous research teams, the mechanism of action through which epinephrine decreases IOP has not been unquestionably explained. The multitude and variety of concepts and achieved results (many of which contradict one another) concerning this problem are overwhelming. Basically, this is unsurprising because by being a non-selective agonist of all adrenergic receptors (including α-$_1$, α-$_2$, β-$_1$, β-$_2$ and β-$_3$) epinephrine can affect the activity of many ocular structures. Moreover, this receptor non-selectivity means evoking opposite effects on many processes, which automatically translates to mutual abolishment of various impacts. Another complication is the possible occurrence of epinephrine-induced desensitization of adrenergic receptors.

It seems that the hypothesis most firmly supported with scientific proofs is the one assuming that epinephrine decreases IOP by increasing the conventional outflow, and this effect is mediated by β_2-adrenergic receptors. Erickson-Lamy and Nathanson (1992) demonstrated that the IOP-lowering effect of epinephrine in the human eye was produced, at least in part, by an increase in the facility of outflow. This effect appeared to be mediated by β_2-adrenergic receptors and was correlated in time with increased cyclic AMP (cAMP) production in TM (cAMP is the second messenger for the β-adrenergic receptors). This hypothesis is supported by the research results showing that administration of an analogue of cAMP into the anterior chamber of the eye of the vervet monkey significantly increased outflow facility (Neufeld and Sears 1975). Moreover, Robinson and Kaufman (1990) demonstrated that epinephrine-induced improvement of AH outflow was prevented by pretreatment with timolol (a non-selective β-adrenergic receptor antagonist), but not with betaxolol (a selective β_1-adrenergic receptor antagonist). A question arises: which of the outflows is affected by epinephrine and how is it enhanced? The results obtained by Erickson-Lamy and Nathanson (1992) suggest that the drug affects the trabecular outflow, the claim which is supported by the study of Alvarado et al. (1998), where it was demonstrated that epinephrine increases flow through the paracellular pathway of Schlemm's canal endothelial (SCE) and TM cells through a β-receptor mediated response that widens the intercellular space and reduces cell area. These findings support the hypothesis that epinephrine decreases IOP by promoting fluid flow across the SCE and TM cells lining tissues of the major AH outflow pathway (Alvarado et al. 1998). There are also reports indicating that epinephrine reduces IOP by increasing the AH outflow through the uveoscleral outflow pathway (Bill 1969, Schenker et al. 1981, Coakes and Siah 1984). The mechanism by which it increases uveoscleral outflow is not clear. It seems likely that the effect is mediated by β_2-adrenergic receptors, because it has been evidenced that salbutamol (selective β_2-adrenergic receptor agonist) increased this type of outflow (Coakes and Siah 1984). As epinephrine is a β-receptor agonist, it may increase the uveoscleral outflow by relaxing the ciliary muscle (Alm and Nilsson 2009).

There are many indications suggesting that prostaglandin E_2 (PGE_2) in engaged in the induction of the ocular hypotensive effect by epinephrine (it is unknown if this is correlated with the effect of the medication on adrenergic-receptors, or else is an unrelated effect). It was demonstrated that approximately half of the increased outflow facility induced by epineph-

rine was inhibited by indomethacin, a PGE_2 synthesis inhibitor (Crawford et al. 1996). Moreover, it was found that epinephrine induced PGE_2 production by the iris-ciliary body of rabbits (Kaplan-Messas et al. 2003). Considering the fact that PGE_2, a nonspecific EP receptor agonist, has been shown to have a strong potential for IOP reduction (Gabelt et al. 2004), it is highly likely that this autacoid participates in the ocular hypotensive effect of epinephrine. It is suggested that the discussed effect can be achieved through the PGE_2-induced increase of the uveoscleral outflow, but at present there is no definite evidence that PGE_2 increases this type of outflow, even though there are some data (Nilsson et al. 2006) pointing to this possibility.

Some handbooks state that epinephrine lowers IOP by decreasing AH formation, which – in the light of the current state of knowledge in this area – seems very doubtful. There are a lot of arguments proving that physiologically endogenous epinephrine (and norepinephrine) increases AH formation (Brubaker 1998), which explains the ocular hypotensive effect of β-adrenergic receptor antagonists, such as timolol. Also short-term topical administration of epinephrine increases AH formation (Townsend and Brubaker 1980, Schenker et al. 1981, Anderson and Wilson 1990). This most clearly results from the stimulation of β_2-adrenergic receptors, because it has been demonstrated that salbutamol (Coakes and Siah 1984) and terbutaline (Gharagozloo et al. 1988), i.e. selective β_2-adrenergic receptor agonists, also exert this effect. The above data prove that administration of epinephrine should increase AH formation, although a reverse effect is theoretically possible. There are reports implying that the medication can induce desensitization of the adenylyl cyclase response to β-adrenoceptor stimulation (Bartels et al. 1983) and decrease the density of β-adrenergic receptors in the ciliary body (Neufeld et al. 1978). This would therefore lead to the reduction/elimination of the effect of endogenous epinephrine on the ciliary body epithelium, thus depressing the AH formation. However, this hypothesis has no sufficient proof at present to warrant acceptance. Besides, more recent investigations indicate that ocular hypotensive effects of adrenergic agonists cannot be explained simply by desensitization of adenylyl cyclase of ciliary processes (Cepelík et al. 1998). Epinephrine is also an agonist of α_1-adrenergic receptors, but nothing implies that this drug could decrease IOP *via* these receptors. It has been demonstrated that the stimulation of α_1-adrenergic receptors with phenylephrine, i.e. their selective agonist, did not affect IOP (Lee and Brubaker 1982); no effect of the selective blockade of α_1-adrenergic receptors using thymoxamine on the AH formation has been revealed either (Lee et al. 1981). Furthermore, topical administration of prazosin, i.e. another selective α_1-adrenergic receptor antagonist, caused reduction of IOP (Krupin et al. 1980). All the cited results demonstrate, either directly or indirectly, that epinephrine cannot reduce the AH formation by affecting β- and α_1-adrenergic receptors, because their activation either enhances (β-adrenergic receptors) or has no influence (α_1-adrenergic receptors) on this process. As the selective agonists of α_2-adrenergic receptors reduce AH formation, one could assume that epinephrine – by being an agonist to these receptors – might act the same way. If activation of postsynaptic α_2-receptors inhibits AH production, then, theoretically, epinephrine may enhance this process. But this is just speculation because the question whether these receptors participate in AH production is unresolved. The author's opinion is that it is rather unlikely for epinephrine to affect IOP *via* the activation of the presynaptic α_2-receptors. Presynaptic α_2-adrenergic receptors are inhibitory receptors, so that their activation leads to the inhibition of norepinephrine release from the presynaptic membrane of the axon terminal, that is to the decrease of the stimulation of postsynaptic adrenergic receptors (in the ciliary body epithelium). This cascade of events involves selective agonists of α_2-adrenergic receptors (e.g. apraclonidine). When non-selective adrenergic receptors agonists are applied, such as epinephrine, the simultaneous stimulation of α- and β-receptors precludes intrinsically the occurrence of effects related to the inhibition of norepinephrine release, because this substance „substitutes" endogenous catecholamines, i.e. it binds to and stimulates adrenergic receptors, including α_1-adrenergic receptors. Vasoconstriction is a response to activation of α_1-adrenoreceptors. Most probably, the stimulation of this receptor by epinephrine is responsible for the dipivefrin-induced reduction in the blood flow in the ciliary body in humans demonstrated by Michelson and Groh (1994). This action suggests a secondary effect such as reduced AH formation. This is the basis of an opinion that one of the mechanisms of action of epinephrine is the inhibition of AH production. However, epinephrine-induced vasoconstriction in the ciliary processes is reversed very rapidly to be subsequently supplanted by vasodilatation. Funk et al. (1992) demonstrated that after topical administration of epinephrine the vasoconstrictive phase lasted 15 min., after which a vasodilatory phase appeared, lasting for 40 to 60 min. The IOP was considerably reduced in the anemic phase and underwent further reduction in the in the hyperemic phase. Whether the initial IOP reduction was caused by depressed production of AH or by its increased outflow, the results of the cited experiments prove that the long lasting IOP reduction

after topical epinephrine cannot be due to vascular reactions in the ciliary processes.

Regarding the causes of the two-directional influence of epinephrine on vessels of the ciliary body, a hypothesis can be put forth stating that the initially occurring vasoconstrictive phase is induced by the agonistic action of the drug on α_1-adrenergic receptors, while the subsequently appearing vasodilatation resulted from the epinephrine-induced stimulation of β-adrenergic receptors. Until the quantitative distribution of particular subtypes of adrenergic receptors in the blood vessels of the ciliary body is known, answers to the above problem will remain mostly speculative.

Recapitulating, based on the current state of knowledge, it is justified to claim that the main way of action of the ocular hypotensive effect of epinephrine and dipivefrin consists of the enhanced AH outflow through the trabecular pathway and most probably an increased uveoscleral outflow. The claim that these drugs inhibit AH formation does not appear to have a sufficient body of supporting evidence at present.

Effect on IOP

Gwin et al. (1978) evaluated dipivefrin and epinephrine in various concentrations in normotensive and glaucomatous (open-angle glaucoma) Beagles. Their research revealed that 1% and 2% epinephrine and 0.5% dipivefrin significantly lowered IOP, although the decrease was very modest. It has been demonstrated that 2% epinephrine given to cats also caused a considerable reduction of IOP: treated eyes compared with contralateral control eyes showed a 27% reduction in IOP (Wang et al. 1999). The effect of dipivefrin on IOP in this species has not been assessed. No comparative data are available regarding the range of the hypotensive effect of dipivefrin or epinephrine relative to other IOP reducing drugs in small animals. Noteworthy is the fact that dipivefrin or epinephrine administered to humans should be considered as producing a moderate hypotensive effect. The long-term ocular hypotensive effect of epinephrine is similar or slightly worse than that achieved with timolol (Alexander et al. 1988). Dipivefrin is less potent than most β-blockers with exception of, perhaps, betaxolol 0.25% (Albracht et al. 1993).

Clinical use

The ocular hypotensive effect produced by epinephrine and dipivefrin alone is usually insufficient to treat effectively most types of canine glaucoma (Gelatt et al. 1983). Therefore they usually must be combined with other drugs to achieve the greatest decreases (Gelatt et al. 2007). Generally, an indication for prescribing these drugs could be open-angle glaucoma, although they are not the first line of choice but used as add-on therapy to other ocular hypotensive drugs (CAIs, β-blockers and parasympathomimetics). The distinct indications for the topical administration of epinephrine (1%) and dipivefrine (0.1%) are:

– Emergency therapy for uveitis-induced glaucoma and hyphema-associated glaucoma, as adjunctive medication if the expected IOP reduction has not been achieved despite topical (alone or in combination with timolol) or systemic administration of CAIs and appropriate anti-inflammatory treatment (Miller 2008).

– Emergency therapy for lens luxation-associated glaucoma, as adjunctive medication if the expected IOP reduction has not been achieved despite giving mannitol, CAIs (topically or systemically) and appropriate anti-inflammatory treatment (Miller 2008).

Thus, with respect to the above indications, epinephrine and dipivefrin are administered in order to enhance the IOP-lowering effect of other hypotensive drugs. In some cases, additional beneficial effect attributed to the use of these medications could be their mydriatic action. In cases of uveitis-induced glaucoma, induction of mydriasis reduces the risk of the formation of peripheral anterior synechiae. In turn, in cases of lens luxation-associated glaucoma, where the lens is caught in the pupil or anterior chamber, dilation of the pupil with these agents can help break the pupillary block. Opinions are heard that another benefit of using epinephrin and dipivefrin in patients with uveitic glaucoma and hyphema-associated glaucoma is their vasoconstrictive effect. In the former case, the drug-induced vasoconstriction should restrict the inflammation, while in the latter it should reduce the bleeding. However, we lack convincing evidence proving that such action does happen.

It is an accepted approach in ophthalmology that epinephrin and dipivefrin should not be used in patients with narrow-angle glaucoma or patients with a narrow angle, but no glaucoma (Ritch and Lowe 1996). Mydriasis means an increased thickness of the iris root and displacement of the iris toward the cornea, which equals a reduction in the width of the iridocorneal angle. Administration of these drugs to patients with a narrow-angle would evoke a serious increase of the resistance of AH outflow, promoting the occurrence of a closure or acute angle-closure glaucoma.

Side effects

There are no studies or reports from medical practice documenting the safety and possible side effects of the ocular instillation of epinephrine and dipivefrine in small animals. An exception is the paper by Gwin et al. (1978), who reported that mydriasis and local irritation consisting of mild conjunctivits and tearing occurred in the dog treated with 0.5% of dipivefrin. Without any doubt, the ocular instillation of these medications is associated with possible occurrence of local and systemic side effects in humans. It is reported that at least 50% glaucoma patients with use of topical epinephrine become intolerant to the therapy mainly due to its external side effects (Becker and Morton 1966). Conjunctival injection, tearing, blepharoconjunctivitis and irritation are the most common local adverse effects of epinephrine use (Kohn et al. 1979). Epinephrine can undergo oxidation to adrenochrome, a melanin pigment. Adrenochrome material is often found in the lower conjunctival sac (Cashwell et al. 1977), but it can also be deposited in the corneal epithelium (Kaiser et al. 1992) and nasolacrimal ducts (Spaeth 1967). Basically, these deposits do not cause any disorders although a case has been described of persistent superotemporal corneal erosion as a result of an adrenochrome deposit on the upper tarsus (Pardos et al. 1980). Topically administered epinephrine can produce systemic adverse effects including tachycardia, hypertension, and arrhythmias (Becker and Morton 1966). As already mentioned, the administration of dipivefrin is associated with a lower incidence of systemic side effects than that of epinephrine (Garzia 1982).

Drugs that lower IOP by opening the drainage angle and by increasing the conventional outflow *via* TM, i.e. parasympathomimetics (cholinomimetics)

Parasympathomimetics (also known as cholinomimetics, cholinergics or miotics) were introduced over 100 years ago and they were the first class of agents used for the treatment of glaucoma. These agents are classified according to their mechanism of action as:

– Direct acting agents i.e. muscarinic receptor agonists (pilocarpine, carbachol and aceclidine).

– Indirect acting agents, i.e. cholinesterase inhibitors, which, in turn, can be reversible (demecarium bromide, neostigmine and physostigmine) and irreversible (echothiophate iodide and isofluorophate).

Mechanism of action

Parasympathomimetics (directly or indirectly) stimulate muscarinic receptors (M_3) in the iris sphincter muscle and ciliary muscle, resulting in two effects:

– Widening of the drainage angle; contraction of the iris sphincter muscle decreases the total iris thickness and pulls away the iris from TM and cornea, which leads to widening of the drainage angle and miosis. This is the effect that shapes the efficacy of pilocarpine (as well as other parasympathomimetics) in therapy of patients with angle closure glaucoma, because in these cases the drug can widen or open the drainage angle, thus improving or enabling the access of AH to the trabecular and uveoscleral outflow pathways (Kobayashi et al. 1999).

– Enhancement of trabecular outflow facility/reduction in trabecular outflow resistance; although the precise mechanism of this effect has not been established, the most widely accepted explanation is that direct stimulation of the longitudinal muscle of the ciliary body causes stretching the TM, thereby widening the trabecular spaces, facilitating AH outflow through the conventional pathway (Erickson and Schroeder 2000). However, it has been demonstrated that agonists of muscarinic receptors also can increase outflow facility in humans independently on ciliary muscle, i.e. by directly stimulating the outflow tissues (Erickson and Schroeder 2000).

Effect on IOP

It has been demonstrated that pilocarpine in concentrations ranging from 0.5% to 8% caused miosis and largely decreased IOP in normotensive and glaucomatous Beagles (Gwin et al. 1977, Whitley et al. 1980, Carrier and Gum 1989, Sarchahi et al. 2012), and in a study by Gwin et al. (1977) it was shown that glaucomatous Beagles responded with a greater reduction of IOP than did the normotensive Beagles. The results obtained by Whitley et al. (1980) indicate that when pilocarpine is administered in the aforementioned concentrations, the ocular hypotensive effect of the drug is independent from the magnitude of a dose, but when the dose is higher, the intensity of side effects increases likewise. Administration of carbachol (0.75%, 1.5%, 2.25% and 3%) in normotensive and early glaucomatous Beagles also led to a considerable decrease of IOP (Gelatt et al. 1984). Another study demonstrated that N-demethyled carbachol (4% and 8%) markedly reduced IOP in glaucomatous dogs (Chiou et al. 1980). Analogously to pilocarpine, the carbachol-induced IOP reduction was not dose-dependent. There is just one report about

the effect of parasympathomimetics on IOP in cats. Topical administration of a single dose of pilocarpine (2%), reduced IOP by about 15% in the treated eye and caused miosis in both the treated and untreated eye of normal cats (Wilkie and Latimer 1991). This contralateral effect was observed following unilateral application, what indicates that systemic, adverse cholinergic effects might be anticipated during long-term treatment (McLellan and Miller 2011).

Clinical use

In the past, parasympathomimetics, and especially pilocarpine, were broadly used in therapy of canine glaucoma, but when more effective and safer ocular hypotensive drugs (PGAs and CAIs) were introduced, parasympathomimetics lost their importance. A similar tendency appears in human medicine, making most topical parasympathomimetics commercially unavailable, e.g. demecarium, echothiophate iodide and isofluorophate. Pilocarpine is the only commonly available parasympathomimetic drug and it still has some importance in the pharmacotherapy of canine glaucoma, lesser however than before the advent of topical PGAs and CAIs.

It might be presumed that with their dual mechanism of action parasympathomimetics should be highly effective in lowering IOP in animals with closure-angle glaucoma and with open-angle glaucoma, but these medications are usually not very effective in the glaucoma therapy in animals because of a typically high IOP when the condition is recognized and the physical obstruction present in the outflow pathway (Martin 2010). At present, pilocarpine and other parasympathomimetics seem to play an ancillary role in therapy of canine glaucoma, in the sense that these drugs are not usually given in monotherapy but combined with other IOP-decreasing medications in order to enhance the hypotensive effect, e.g.:

– Nowadays, combined administration of 2% pilocarpine with a systemic CAI (e.g. methazolamide) and mannitol is recommended as an alternative or second-line regimen for emergency therapy of dogs with acute primary angle closure glaucoma (PACG), if administration of latanoprost is impossible or its application was ineffective (Miller 2008). Monotherapy with pilocarpine or another parasympathomimetic in therapy of acute PACG in dogs does not seem to be a good choice because it is uncertain whether this therapy will lead to re-opening of the closed angle. The reason is that most of veterinary patients are presented with IOPs that are very high, i.e. > 50-60 mmHg (Martin 2010) and the pupillary sphincter muscle is ischemic and unresponsive to topical miotic agents when the IOP is above 40-50 mmHg (Anderson et al. 1975). Thus, the initial decrease of IOP *via* drugs decreasing AH formation (e.g. CAIs) and causing the dehydrating and shrinking of the vitreous body (osmotic agents) enables later manifestation of the miotic effect of parasympathomimetics.

– Parasympathomimetics combined with topical CAIs and β-blockers may be useful in the management of some primary glaucomas in non-inflamed eyes in dogs (Gelatt et al. 2007).

At present, the only recommendation for monotherapy with parasympathomimetics in dogs is limited to the administration of demecarium bromide (with a topical corticosteroid) in preventive management of the contralateral eye in canine patients after the diagnosis of an acute PACG in the other eye (Miller et al. 2000, Miller 2008). However, this drug is no longer commercially available.

Due to their ability to destabilize the blood-aqueous barrier (BAB) (Krohne 1994) and miotic effect, parasympathomimetics may exacerbate intraocular inflammation and predispose to posterior synechiae and pupillary block. Therefore these agents are generally contraindicated in glaucomas associated with uveitis and tendency to pupil block, especially in secondary glaucoma due to anterior lens luxation and in phacomorphic glaucoma. In the latter case, parasympathomimetics may aggravate the pupillary block not only by enlarging the lens-iris surface contact area (lens-iris apposition), but also by increasing the axial lens thickness and causing anterior lens movement, thus shallowing further the anterior chamber (Ritch and Liebmann 1996). It should be noted that parasympathomimetics increase the angle width in patients with narrow angles (Kobayashi et al. 1999) but they may paradoxically shallow the anterior chamber and increase the pupillary block (Hung et al. 1995). Because these drugs may increase the pupillary block by causing forward motion of the lens-iris diaphragm, they are contraindicated in conditions where the glaucoma is caused by anterior displacement of the iris-lens diaphragm. Bearing in mind the above mentioned contraindications to the use of parasympathomimetics and the etiopathogenesis of glaucoma in small animals, it becomes clear why these medications are not administered in many types of canine and feline secondary glaucoma. Practically speaking, parasympathomimetics are unimportant in the therapy of feline glaucoma, as up to 95-98% of cases of glaucoma in this animal species are secondary in nature and most often a consequence of anterior uveitis, intraocular neoplasia, lens trauma, or AH misdirection syndrome (Miller 2008, McLellan and Miller 2011), that is the conditions which are contraindications to the use of these drugs or the ones where no pharmacotherapy of glaucoma is conducted.

Side effects

Local side effects evoked by administration of pilocarpine with pH 4.5-5.5 may include blepharospasm, conjunctival hyperemia, chemosis, epiphora and prolapsed nictitans, although it should be underlined that the irritant action is not attributed to the active ingredient but stems from the low pH of pilocarpine solution. Instillation of pilocarpine in dogs should not cause any systemic effects associated with the activation of the parasympathetic system (Whitley et al. 1980). Topical application of pilocarpine and demecarium bromide transiently increases the permeability the BAB (Krohne 1994). Cholinesterase inhibitors show more severe side effects than direct parasympathomimetics, which is why these medications are withdrawn from therapy of glaucoma. They produce more severe ciliary and iridal spasma than does pilocarpine (Regnier 2007). Topical administration of these drugs, particularly in intensive treatment, may cause severe systemic toxicity with such manifestations as salivation, vomiting, and abdominal cramps (Regnier 2007).

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