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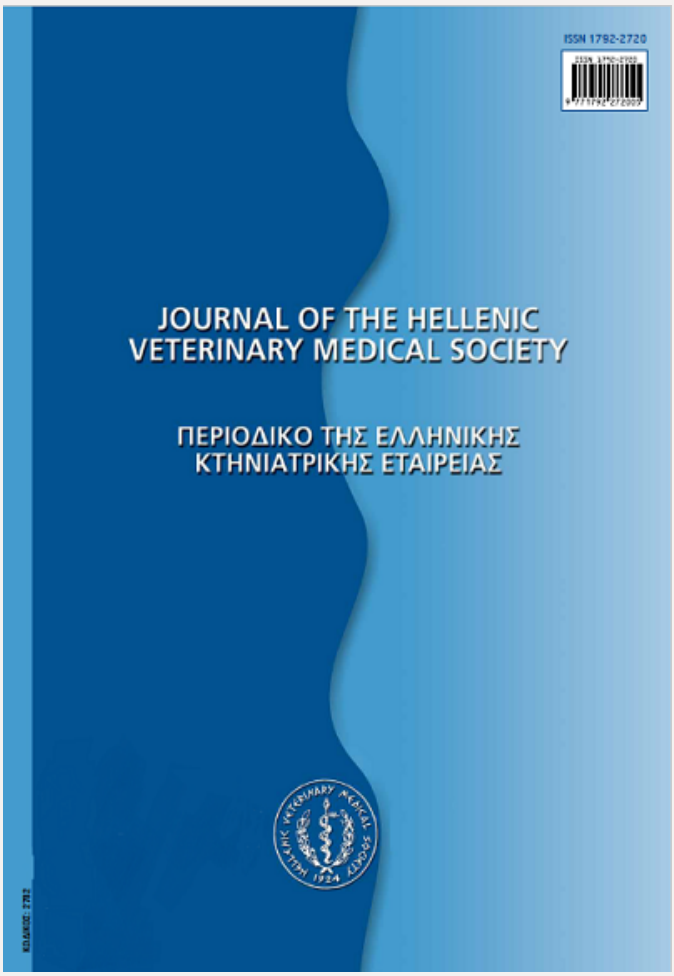

A review of the pharmacology of osmotic agents for the treatment of glaucoma in dogs

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Review article
Ανασκόπηση

A review of the pharmacology of osmotic agents for the treatment of glaucoma in dogs

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ABSTRACT. At present, the only proven way to treat glaucoma is to lower intraocular pressure (IOP). Osmotic agents constitute an important class of ocular hypotensive agents. These medications are used for the rapid reduction of IOP, typically in emergency situations, in which IOP is severely elevated and there is a high risk of permanent and irreversible damage of the optic nerve. This paper summarizes the current state of knowledge on the mechanism of action of osmotic agents and their effect on IOP in dogs. Moreover, it discusses the possible undesirable side effects of these medications and presents the current ideas about their role and status in the medical management of canine glaucoma.

Keywords: dogs, glaucoma, intraocular pressure, mannitol, osmotic agents.

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INTRODUCTION

Glaucoma is a heterogeneous group of disorders usually associated with elevated intraocular pressure (IOP) leading to optic nerve damage, retinal ganglion cell death, and permanent vision loss. It is one of the most common causes of irreversible blindness in dogs (Miller, 2013). The pathophysiological process of glaucomatous optic neuropathy is not fully understood, but it is likely to be a multifactorial result. An increase in IOP is the principal risk factor for glaucoma, and the primary goal of treatment is to reduce IOP to values that will halt the degeneration of retinal ganglion cells (Smith et al., 2010). There are two principal ways to reduce IOP medically: by lowering aqueous humour (AH) production and by increasing AH outflow, and these effects can be achieved *via* a number of different mechanisms of action. Although some ocular hypotensive drugs are likely to lower IOP by affecting both AH formation and outflow, based on the dominant way of action they are divided into following groups: (a) those that reduce AH production (i.e. carbonic anhydrase inhibitors [CAIs], β-adrenergic antagonists, and selective α2-adrenergic agonists), and (b) those that increase AH outflow (i.e. nonselective adrenergic agonists, parasympathomimetics, and prostaglandin F2α analogues). The third group of medications employed in the treatment of glaucoma are osmotic drugs; although these agents also enhance the outflow of AH and most probably reduce AH formation, they are traditionally distinguished as a separate class. The present paper constitutes the fifth and final paper in a series devoted to the pharmacological characterization of ocular hypotensive drugs in the context of their application for the therapy of glaucoma in small animals (Maślanka, 2014a, 2014b; Maślanka, 2015a, 2015b).

HISTORY & CLASSIFICATION

The earliest reports on use of this type of substances in therapy of glaucoma date back to 1904, when Cantonnet published results of a study on the effect of oral administration of lactose and sodium chloride on IOP of patients suffering from this disease. Ten years later, Hertel (1914) reported that intravenous administration of urea caused a decrease in IOP in rabbits. In 1958 Javid verified the IOP-lowering effect of urea, whereas in the 1960s it was discovered that the same effect is produced by mannitol (Weiss et al., 1962), glycerol (Virno et al., 1963) and isosorbide (Becker et al., 1967). Osmotic agents can be subdivided into two groups based on the route of administration:

- intravenously administered agents: mannitol and urea
- orally administered agents: glycerol and isosorbide

MECHANISM OF ACTION

With respect to the location of a target site, two types of mechanisms responsible for the IOP-lowering effect of osmotic agents are distinguished (Serle et al., 2003; Stamper et al., 2009; Toris, 2010):

Direct mechanism: Osmotic agents increase the osmolality of the intravascular fluid compared with the extravascular fluid. These agents penetrate very slowly into the avascular vitreous, since the blood-ocular barriers (i.e. blood-aqueous and blood-vitreous barriers) restrict their penetration into the eye, creating an osmotic gradient: extraocular fluids are hypertonic to intraocular fluids (i.e. AH and vitreous) (Serle et al., 2003). This osmotic gradient draws water from the intraocular space into the circulation *via* the blood vessels of the retina and uveal tract (Duncan et al., 1969, 1970; Stamper et al., 2009). The main effect is the dehydration of the vitreous body, causing a reduction of its volume (Robbins and Galin, 1969; Duncan et al., 1970). It has been demonstrated that the weight of the rabbit vitreous body was reduced by 2.7%, 3.7% and 3.9% after administration of glycerol, urea and mannitol, respectively (Robbins and Galin, 1969). It is held that reduction of the volume of the vitreous body is the primary mechanism responsible for the ocular hypotensive effect of osmotic agents (Duncan et al., 1969, 1970; Serle et al., 2003). It is assumed that shrinkage of the vitreous body displaces the iris-lens diaphragm posteriorly and subsequently opens the iridocorneal angle, which increases aqueous outflow facility (Craig, 1994; Willis, 2004; Regnier, 2007).

This claim is also supported by reports indicating that the use of mannitol leads to the enlargement of the anterior chamber depth (Weiss et al., 1963; O'Keeffe and Nabil, 1983). It is also proposed that the fluid movement described above, inhibits the ultrafiltration process that contributes to AH formation (Willis, 2004; Regnier, 2007). This suggests that the reduction in AH production could represent an additional mechanism involved in the IOP-lowering action of osmotic drugs.

Indirect mechanism: Osmotic agents reduce AH production *via* a central nervous system pathway involving osmoreceptors in the hypothalmus (Stamper et al., 2009). This theory is supported by several evidences obtained from studies performed in animal models and human patients. It was demonstrated that small doses of hyperosmotic agents that do not increase plasma osmolality, reduced IOP (Podos et al., 1971). Mauger et al. (2000) showed an ocular hypotensive effect of mannitol without reducing vitreous volume using a relatively low dose of mannitol. Krupin et al. (1973) found that administration of hypoosmotic agents into the third ventricle resulted in an elevation of IOP, while delivery of hyperosmotic agents lowered IOP. Moreover, the unilateral optic nerve transection in experimental animals reduced the IOP response to hypoosmotic and hyperosmotic agents, as it was shown in these studies along with some earlier investigations (Riise and Simonsen, 1969) This was the basis for formulating a hypothesis that a hypothalamic center with osmoreceptors participated in IOP regulations (most probably *via* its effect on AH formation) by efferent fibers in the optic nerve. However, subsequent studies did not reveal that the optic nerve transection affected the ocular response to the hypotensive action of osmotic agents (Serafano and Brubaker, 1978; Lam et al., 1980). Thus, these results do not support the hypothesis that the optic nerve carries fibers which are part of the control system for IOP (Serafano and Brubaker, 1978). Nevertheless, in light of the above results, it is probable that the hypothalamic center mediates part of IOP responses to osmotic agents; it is questionable whether this effect is mediated by efferent fibers in the optic nerve.

EFFECT ON IOP

The literature revealed only four studies on the effect of osmotic agents on IOP in dogs (Gilroy, 1986; Lorimer et al 1989; Volopich et al., 2006; Wasserman et al., 2013). Gilroy (1986) did not find any effect of a mannitol infusion (0.25 g/kg) on the IOP in dogs. The dose applied in this experiment was very low, although it is known that rates of mannitol in this order can lower IOP in human patients (Marshall et al., 1978). Gilroy (1986) assumed that the dosage of mannitol that was adequate to treat elevated IOP in humans did not affect IOP in normal dogs. Volopich et al. (2006) evaluated the effect of higher dose of mannitol (1 g/kg) and hypertonic hydroxyethyl starch (HES; 1.2 g/kg BaCl; 0.96 g/kg HES) on IOP in healthy normotensive dogs. A significant decrease in IOP from baseline value was found at 15, 30, 45, and 60 min after the start of mannitol administration (mean amplitude in IOP decrease 3.21 mmHg) and at 15 and 30 min in dogs treated with HES (mean amplitude in IOP decrease 2.43 mmHg). The authors of this study (Volopich et al., 2006) concluded that hypertonic HES is comparable to mannitol (at doses applied in the experiment) in lowering IOP in healthy normotensive dogs. But this effect lasted half an hour longer after mannitol. Moreover, they evaluated the potential IOP-lowering effect of hypertonic HES in six dogs with primary glaucoma. In 6/7 eyes with primary glaucoma, hypertonic HES decreased IOP (Volopich et al., 2006). In another study (Lorimer et al., 1989), the effect of mannitol (1.5 g/kg) or oral glycerol (1.4 and 2.0 g/kg) on IOP was investigated in normal dogs. Mean IOPs were significantly decreased from baseline values from 0.5 through 5.5 hr following mannitol administration with a mean maximum depression of 8.7 mmHg, which occurred 1.5 hr after administration. Administration of glycerin led to a significant IOP-lowering effect (with a mean maximal decrease of 5.4 mmHg), occuring within 1 hr and lasting 10 hr. Based on these results, it was concluded that both mannitol (1.5 g/kg) and glycerol (1.4 g/kg) are effective for decreasing IOP in normal dogs. This conclusion (regarding glycerol) does not agree with the recently published results of a study on the effect of oral isosorbide (1.5 g/kg) and glycerol (1.5 g/kg) on IOP in normal dogs (Wasserman et al.,

2013). The maximal reduction in IOP was 17% by 1 hr and 13.5% by 30 min after glycerol and isosorbide administration, respectively. However, the overall changes in IOP were not significant when compared to the controls. Therefore, the authors claim that neither glycerol nor isosorbide significantly affected IOP when compared to the control (Wasserman et al., 2013). Still they consider that it is possible that the trend of decreased IOP would have approached significance had this evaluation included glaucomatous subjects. This is supported by previous studies, which determined that both isosorbide (Wisznia et al., 1970; Kulshrestha and Mittal, 1972) and glycerol (Drance, 1964; Consul and Kulshrestha, 1965) are significantly more effective at lowering IOP in glaucomatous *versus* normotensive human patients (Wasserman et al., 2013).

CLINICAL USE

Osmotic drugs are used for the rapid reduction of intraocular pressure, typically in emergency situations in which IOP is severely elevated and there is a high risk of permanent and irreversible damage of the optic nerve (Toris, 2010). These medications are used only for short-term control of IOP, because their serious side effects and short duration of action, preclude their use for long-term glaucoma therapy. The most common osmotic medications used to treat glaucoma in dogs are mannitol and glycerol (Willis, 2004). Rapid reduction of IOP is usually achieved with mannitol rather than glycerol (Regnier, 2007). Oral glycerol (1 to 2 ml/kg) is an alternative to mannitol (Miller, 2013). The main advantage of glycerol is the low cost and the route of oral administration. Osmotic agents are used in emergency treatment of acute glaucoma an and before surgical procedures for glaucoma (Gelatt et al., 2007). These drugs are primarily used to lower IOP in acute primary closed-angle glaucoma (PCAG). Because the response of the eye to miotics does not occur when IOP is greater than approximately 50 mmHg [the pupillary sphincter muscle is ischemic and unresponsive to miotics when the IOP is above 40-50 mm Hg (Anderson and Davis, 1975)], reduction of IOP by these agents is essential (Gelatt et al., 2007). Mannitol may be employed both before and during surgical lens procedures (i.e. cataract surgery, removal of a luxated lens), because shrinkage of the vitreous body decreases the incidence and severity of vitreous prolapse (Regnier, 2007). With pupillary-block glaucoma in the dog, in which lens, vitreous, or both obstruct the pupil, administration of osmotic agents is essential (Gelatt et al., 2007). The integrity of the blood-aqueous barrier is important for these medications to be effective; IOP-lowering effect of osmotic agents may be reduced in patients with intraocular inflammation (Dugan et al., 1989).

According to treatment algorithms for various types of glaucoma recommended by Miller (2013):

- mannitol (1.0 to 1.5 g/kg) in combination with systemic CAIs and pilocarpine should be considered as a second-line or alternative option for emergency therapy of dogs with acute PCAG, when treatment with latanoprost is ineffective or its administration is impossible, respectively. The author (Miller, 2013) adds that because mannitol can be quite toxic, its application should be limited to eyes with the potential for vision.
- mannitol (1.0 to 1.5 g/kg) in combination with CAIs should be considered as a second line treatment for emergency therapy of lens luxation-associated glaucoma, when treatment with mydriatic agents and steroid anti-inflammatory drugs is ineffective.

If IOP remains elevated after a single injection of mannitol, the 1.0 g/kg dose may be repeated in 4 hr if necessary, but long-term use should be avoided (Miller, 2013).

SIDE EFFECTS

The major potential toxicity of i.v. administration of osmotic agents is related to their effect on the volume and distribution of body fluids (Regnier, 2007). These medications cause relative dehydration of the extracellular spaces and subsequently fluid shift into the intravascular space, which can lead to overload of the cardiovascular system, effect that is particularly evident in the case of mannitol (Borges et al., 1982; Dugan et al., 1989). These effects are responsible for many of the adverse effects of osmotic agents. Whereas healthy individuals can

tolerate these changes, the increased intravascular volume can induce acute cardiac failure and pulmonary edema in patients with chronic congestive heart failure (Borges et al., 1982; Dugan et al., 1989; Regnier, 2007). Atkins et al. (1973) investigated the cardiovascular response to 25% mannitol (in doses of 1.25 ml/kg and 5 ml/kg) in dogs. After the smaller dose, stroke volume and left ventricular maximal dp/dt rose significantly, while no change occurred in left ventricular end-diastolic pressure. At the larger dose, further increases in stroke volume and max dp/dt were accompanied by significant elevations in heart rate, mean aortic pressure, and left ventricular end-diastolic pressure (Atkins et al., 1973). Brock and Thurmon (1979) reported cases of deaths of dogs and cats due to pulmonary edema in anesthetized patients given mannitol during ophthalmic surgery. In a later study, Brock et al. (1985) demonstrated that the administration of mannitol in a dose of 2.2 g/kg to healthy anesthetized dogs was related to a risk of causing pulmonary edema. Nausea and vomiting are the most common adverse effects of osmotic agents, especially when given orally. Oral administration of glycerol (1.4 and 2.0 g/kg) in dogs was found to cause vomiting in some animals. The incidence of vomiting appeared to be dose related (Lorimer et al., 1989). Osmotic agents can increase diuresis. This results from the increased intravascular volume, as well as the urinary excretion of the agents themselves (Serle et al., 2003). It was demonstrated that in healthy anesthetized dogs, mannitol (2.2 g/kg) caused polyuria, serum hyperosmolarity, decreased urine specific gravity, and decreased urine osmolality (Brock et al., 1985). The use of mannitol to lower IOP is only recommended in patients with normal renal function (Willis, 2004). In high concentrations, mannitol decreases renal blood flow and glomerular filtration rate, which may negatively affect an already compromised kidney (Willis, 2004). When used in patients with compromised renal function, osmotic agents may lead to hyponatremia and hypokalemia. The resulting imbalance in electrolytes can lead to lethargy, seizures, and coma (Serle et al., 2003). Cerebral dehydration with resulting confusion and disorientation is more common with intravenously administered osmotic agents, due to the rapid onset of their effects (Serle et al., 2003). A life-threatening complication caused by these drugs in human patients, is subdural hematoma. This is due to the shrinkage of the cerebral cortex, that stretches and ruptures aqueous veins between the sagittal sinus and the brain surface (Stamper et al., 2009). Many of the serious side effects of osmotic agents are dose related, therefore in human medicine it is recommended that patients should receive the minimum dose necessary to reduce IOP to the desired level (Stamper et al., 2009).

CONCLUDING REMARKS

Two main mechanisms of action have been proposed for osmotic agents. Firstly, their IOP-lowering effect can be attributed to the dehydration of the vitreous body, which allows the lens and iris to move posteriorly, opening the iridocorneal angle and, secondly, to the reduction of AH production *via* a central nervous system pathway involving osmoreceptors in the hypothalmus. The most common osmotic medication used to treat glaucoma in dogs is mannitol. Osmotic drugs are used for the rapid reduction of intraocular pressure, typically in emergency situations in which IOP is severely elevated and there is a high risk of permanent and irreversible damage of the optic nerve. These drugs are primarily used to lower IOP in acute PCAG. Moreover, mannitol may be employed both before and during surgical procedures on the lens, because shrinkage of the vitreous body decreases the incidence and severity of vitreous prolapse. Because of their serious side effects and short duration of action, osmotic agents are not used for long-term therapy of glaucoma, but only for short-term control of IOP.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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