The Effects of Some Premedication and General Anesthesia Drugs on Intraocular Pressure and Pupil Diameter in Dog's Eyes
Acs iekšējā spiediena un acs zīlītes diametra izmaiņas suņiem dažu premedikācijas un vispārējās anestēzijas līdzekļu ietekmē

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Abstract. The objective of the study was to determine the effects of the premedication and general anesthesia combination on intraocular pressure (IOP) and horizontal pupil diameter (HPD) in dog's eyes. Ten dogs of different age and sex were used, and all animals were approved for a planned surgery – castration or ovariohisteroectomy. For premedication, the combination of 0.1% atropine sulphate and 1% acepromazine maleate solution was used intramusculary, but for general anesthesia – 10% ketamine hydrochloride together with 0.5% diazepam solution was used intravenously. Ten clinically healthy dogs with a similar weight and age were used as a control. Instead of premedication and general anesthesia, 0.9% NaCl solution was injected. It was established that the combination of atropine sulphate and acepromazine maleate causes irregular changes in the intraocular pressure. A significant and rapid IOP increase was obtained in both eyes immediately after intravenous injection of general anesthesia – combination of ketamine hydrochloride and diazepam. Premedication induces small and fluctuating changes in the horizontal pupil diameter in both eyes, but ketamine hydrochloride together with diazepam significantly increased it. The premedication and general anesthetic drugs cause a significant increase in the intraocular pressure, therefore their administration in dogs should be considered in various eye pathologies.
Key words: premedication, general anesthesia, dog, intraocular pressure, horizontal pupil diameter.

Introduction

Atropine sulphate and acepromazine maleate as a premedication, and general anesthetics – ketamine hydrohloride together with diazepam – are commonly used in veterinary medicine.

To develop a model of general anesthesia for ophthalmic surgery, a constant cardio-pulmonary function and intraocular pressure (IOP) should be considered as important (Brunson, 1980; Collins, Gress et al., 1995).

Some drugs, including general anesthetics, may affect the intraocular pressure. In human medicine, general anesthetics and some premedication drugs decrease intraocular pressure and reduce the pupil diameter, causing miosis, with the exception of ketamine hydrochloride, which, on the contrary, increases the IOP and causes dilation of the pupil – mydriasis (Hahnenberger, 1976; Frischmeyer, Miller et al., 1993; Verbruggen, Akkerdaas, Hellebrekers, 2000; Vanags, Sondore, 2008).

Atropine sulphate is normally used in premedication in the combination with acepromazine maleate to minimize or prevent vagal effects that may induce bradycardia. Also these drugs reduce potential smooth muscle spasms, gastrointestinal motility and secretion, salivation and animal respiratory secretion, as well as decrease the tear production during anesthesia and in awake (Thurmon, Tranqcuilli, Benson, 1996; Vanags, Sondore, 2008). Overall, the administration of atropine sulphate decreases intraocular pressure (Hahnenberger, 1976; Frischmeyer, Miller et al., 1993; Verbruggen, Akkerdaas, Hellebrekers, 2000), or it does not cause significant changes in intraocular pressure (Vanags, Sondore, 2008).

Atropine sulphate together with acepromazine maleate is widely used to calm the animal, to gain a faster sleap and muscle relaxation, and also to prevent vomiting and spontaneous movement of the animals during surgery (Thurmon, Tranqcuilli, Benson, 1996). Acepromazine maleate blocks α-adrenoreceptors in

vascular walls, dilates blood vessels, and decreases arterial pressure (Muir, Werner, Hanalin, 1975; Thurmon, Tranqcuilli, Benson, 1996).

Regarding the effects of acepromazine maleate on the intraocular pressure, studies in dogs have shown that acepromazine given intramuscularly in combination with morphine hydrochloride does not cause significant changes in IOP 10 or even 25 minutes after injection (Stephan, Vestre et al., 2003). However, the effects of the atropine sulphate and acepromazine maleate combination on the intraocular pressure in animals have not been studied.

In veterinary medicine, ketamine hydrochloride is usually used in combination with other anesthetic drugs and in mononarcosis as a strong analgetic agent (Wright, 1982; Haskins, Farver, Platz, 1985; Hartsfield, 1992; Thurmon, Tranqcuilli, Benson, 1996). In Latvia, a combination of ketamine hydrochloride and diazepam is used for general anesthesia.

Ketamine hydrochloride in dogs induces increase in cerebral blood flow and intracranial and cerebrospinal fluid pressure as a result of cerebral vasodilatation, and elevated arterial blood pressure (Booth, 1982; Thurmon, Tranqcuilli, Benson, 1996). Therefore increased IOP is mentioned as a possible side effect. In humans, a slight but significant increase in IOP occurs independently of the changes in blood pressure (Corssen, Hoy, 1967; Yoshikawa, Murai, 1971; Thurmon, Tranqcuilli, Benson, 1996).

Concerning effects of ketamine hydrochloride on intraocular pressure, a significant IOP increase has been obtained in rabbits and cats (Hahnenberger, 1976; Antal, Musci, Faludi, 1978). In a similar study with dogs, a dose of 10 mg kg^{-1} of ketamine hydrochloride in combination with acepromazine or xylazine has been administred, but increase in IOP was not obtained (Gelatt, Gwin et al., 1977). Some authors suggest that ketamine and xylazine injection causes increase in intraocular pressure in dogs, but in horses, conversely, results in decrease (Trim, Colbern, Martin, 1985; Thurmon, Tranqcuilli, Benson, 1996).

Also diazepam is often used in general anesthesia for its sedative, tranquilizing, and muscle relaxant and anticonvulsant effects (Purviņš, 1994). Studies show that diazepam decreases systemic arterial pressure, cerebral blood flow and cerebral pressure that presumably decreases IOP (Vanags, Sondore, 2008). Another study with human subjects has shown that diazepam decreases IOP and is recommended to use in general anesthesia, especially in ophthalmological cases such as perforated cornea, corneal ulcers, trauma or glaucoma (Cunningham, Albert et al., 1981).

As to the effects of diazepam, it has been found that diazepam used alone does not cause a decrease in IOP in dogs. At the same time, authors report that diazepam in combination with ketamine hydrochloride increases IOP in the first 5 minutes after intravenous injection (Hofmeister, Mosunic et al., 2006).

Despite the fact that some of premedication and general anesthesia drug pharmacokinetics and pharmacodynamics are rather well investigated, data on their effects on functional parameters of the eye, such as intraocular pressure and pupil diameter in animals and especially dogs, are few, incomplete and quite controversial.

Therfore our **aim** was to investigate the summary effect of premedication drugs atropine sulphate and acepromazine maleate and general anesthetic drugs ketamine hydrochloride and diazepam on dog's intraocular pressure and horizontal pupil diameter (HPD).

Materials and Methods

All animals were outpatients of the Preclinical and Clinical Institute of the Faculty of Veterinary Medicine of the Latvia University of Agriculture in 2008– 2009. This study was approved by the Committee for Animal Protection and Ethics of the Latvian State Food and Veterinary Service. In all cases, an informed consent was obtained from the pet owners for the study.

All animals included in the study were examined clinically and ophthalmologically. Ocular examination included slit lamp-biomicroscopy, direct ophthalmoscopy, and monocular indirect ophthalmoscopy with the Pan Optic® (Welch Allyn, USA). Prior to the study, all patients were determined to be free of ocular lesions which could alter IOP from normal.

A total of 20 mixed breed adult dogs of both sexes were used. To ascertain the effects of premedication and general anesthesia on the intraocular pressure and horizontal pupil diameter, ten dogs were used. All animals were approved for a planned surgery – castration or ovariohisteroectomy. As a premedication, a combination of atropine sulphate (0.04 mg kg^{-1}) and acepromazine maleate (0.1 mg kg^{-1}) was used intramuscularly, but for general anesthesia – a combination of ketamine hydrochloride (5.5 mg kg^{-1}) and diazepam (0.25 mg kg^{-1}) was used intravenously. The dose of premedication and general anesthesia has been

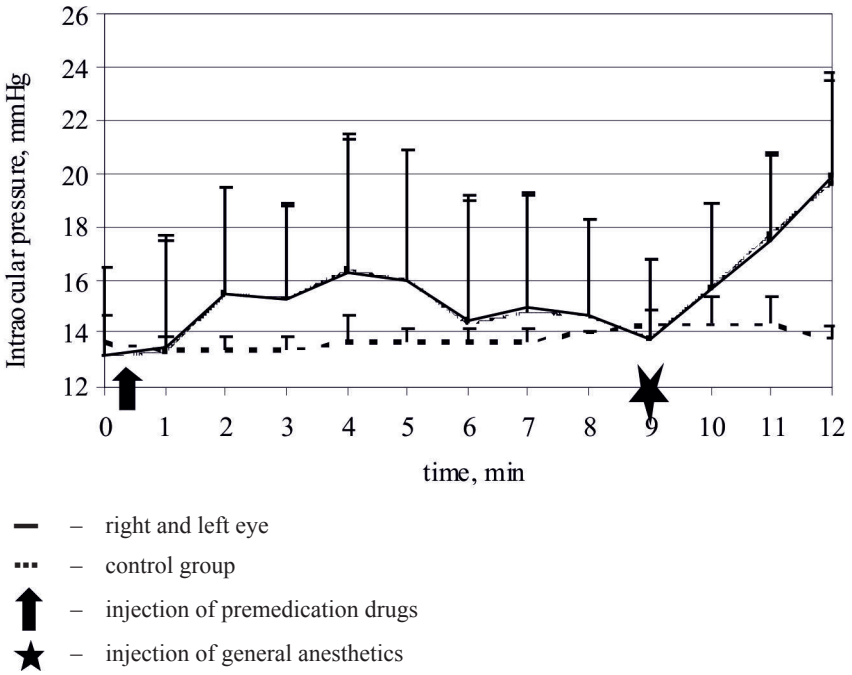

Fig. 1. The effects of premedication and general anesthesia on the intraocular pressure (IOP) in the dog's eyes (mean values±SD).

recommended by researchers as suitable for dogs (Thurmon, Tranqcuilli, Benson, 1996).

Ten clinically healthy dogs with a similar weight were used as a control. Instead of premedication and general anesthesia, a NaCl solution was injected (0.1 ml kg^{-1}).

All tonometric measurements were performed by the same person with the rapid and minimal stress inducing method of rebound tonometry with a tonometer (TonoVet®, Tiolat Ltd, Finland) using values that achieve less than 5% standard deviation. For this tonometer it is not necessary to use topical anesthesia. Some authors have noticed that the corneal endothelial and systemic toxicity could occur with a frequent use of topical anesthesia (Judge, Najafi et al., 1997; McGee, Fraunfelder, 2007).

Horizontal pupil diameter was measured with Jameson calipers (USA) under fixed daylight conditions at the same time of the day.

In all dogs, IOP and HPD measurements were taken before premedication, every minute after premedication till general anesthesia was injected, and three minutes after, avoiding any tension on the animal's neck (Pauli, Bentley et al., 2006).

To determine the effect of premedication drugs atropine sulphate and acepromazine maleate and of general anesthetics ketamine hydrochloride and diazepam, arithmetic mean values (X) and standard deviation (SD) of the IOP and HPD were calculated for each eye. Changes in IOP and HPD between the right and left eye and between the pretreatment and treatment period in a time period were evaluated using a paired two-sample t-test, and *p*-values less than 0.05 were considered to be statistically significant (Arhipova, Bāliņa, 2006).

Results

Prior to premedication, the initial position of the animal's eye – intraocular pressure – was estimated. It was established that there was no difference in the IOP measurements between the right and left eye – 13.1±3.4 mmHg. The influence of premedication and general anesthesia is shown in Figure 1.

A significant IOP increase was obtained immediately after injection of premedication drugs. The IOP increased in both eyes for an average of 2.4±2.4 mmHg, reaching 15.5±4.4 mmHg *(p*<0.01). In the next two to four minutes after treatment, IOP was varying: at first the values decreased, but in the third treatment minute –repeatedly increased.

Five minutes after the treatment, intraocular pressure decreased from an average of 16.0±4.5 mmHg to 14.5±4.7 mmHg, but in the next three minutes – varied between 13.8±3.0 mmHg and 14.9±4.4 mmHg (Fig. 1).

Nine minutes after injection of premedication drugs, general anesthesia – a combination of ketamine hydrochloride and diazepam – was added. A significant IOP increase was obtained immediately

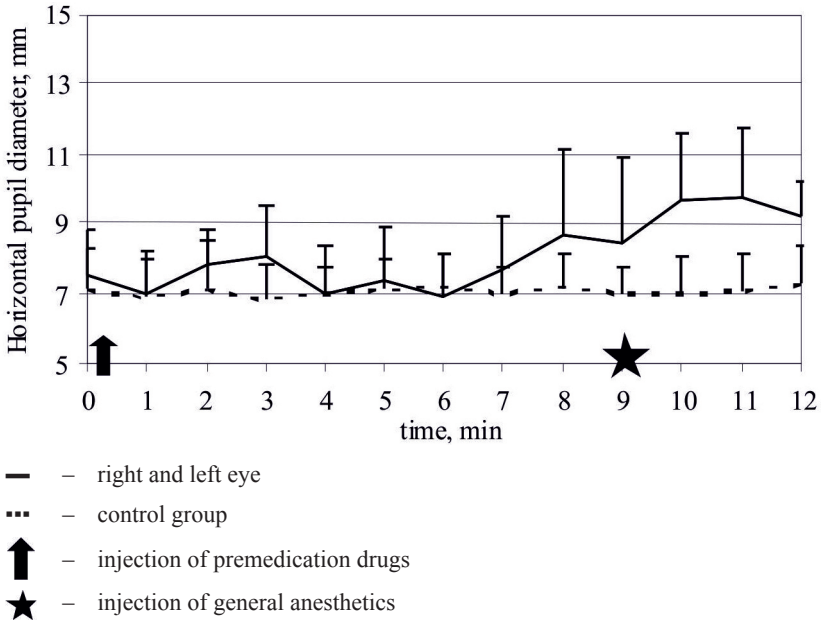

Fig. 2. The effects of premedication and general anesthesia on the horizontal pupil diameter (HPD) in the dog's eyes (mean values±SD).

after administration of general anesthesia ($p<0.05$), and in the 10th minute of treatment IOP gained an average of 15.7±3.1 mmHg in both eyes (Fig. 1). Comparing the measurements done before and 12 minutes after the treatment it was seen that IOP had increased for an average of 6.8±4.4 mmHg, reaching 19.9±3.9 mmHg ($p<0.01$). No significant differences in intraocular pressure between the right and the left eye were found during the research (Fig. 1).

In the control group, no changes in IOP were determined after injection of saline instead of premedication and general anesthesia. IOP values during all the treatment period were varying in both eyes between 13.3±0.5 mmHg and 14.3±1.0 mmHg (Fig. 1).

The effects of the premedication and general anesthesia drugs on the other functional parameter – horizontal pupil diameter – are shown in Figure 2.

Before the injection of premedication drugs, HPD was practically equal in both eyes – 7.5±1.3 mm. In the first treatment minute, HPD in both eyes decreased to an average of 7.0±1.2 mm, but afterwards increased, and three minutes after treatment gained an average of 8.0±1.5 mm. In the next treatment minutes (three to six minutes after premedication), the pupil diameter was varying between 7.4±1.5 mm and 6.8±1.3 mm, but starting from the sixth minute – increased and reached 8.6±2.5 mm on average (Fig. 2).

In the first minute after injection of the ketamine hydrochloride and diazepam combination, HPD increased significantly in both eyes for an average of 1.2±1.1 mm, reaching 9.6±2.0 mm ($p<0.01$). It continued to increase one more minute till reaching 9.7±2.0 mm. In the 11th treatment minute HPD started to decrease, and in the 12th minute reached an average of 9.2±1.0 mm (Fig. 2). Comparing the measurements done before and at the end of the treatment it was found that HPD had increased for an average of 1.6±1.7 mmHg ($p<0.01$). During the research, no significant differences in HPD between the right and the left eye were detected (Fig. 1).

In the control group, HPD values were similar in both eyes – they had not changed significantly during the research and varied between 6.8±1.0 mm and 7.2±1.0 mm ($p>0.05$).

Discussion

The results of this study show that in dogs a significant increase in IOP was obtained immediately after the injection of premedication drugs atropine sulphate and acepromazine maleate. During pemedication, the higest IOP increase was obtained two to five minutes after the treatment.

In the literature it is mentioned that atropine sulphate blocks the mediator acetylcholine in the M-cholinergic postganglionar synapses in the short ciliary muscles (Jones, 1977; Thurmon, Tranqcuilli, Benson, 1996; Block, Beales, 2004; Vanags,

Sondore, 2008), which leads to relaxiaton of the ciliary muscles, thereby inhibiting the outflow of the aqueous humor through the uveoscleral pathway (Bill, 1967, 1969; Harris, 1968; Valle, 1974). Also in our study IOP increase can be related to mechanical obstruction of the iridocorneal angle due to pupilary dilatation (Stadbaumer, Frommlet, Nell, 2006).

In our study, a rapid and significant IOP increse was obtained immediately after injection of ketamine hydrocloride and diazepam, which continued till the 12th treatment minute. These results, to some extent, are similar to the data of other authors, who have recorded a significant IOP increase in dogs five minutes after injection of the ketamine and diazepam combination (Hofmeister, Mosunic et al., 2006).

There are some factors which, in our opinion, explain the effects of ketamine hydrochloride and diazepam on intraocular pressure. First of all, complete sedation did not occur in animals immediately after injection of the general anesthetics, and small muscle contractions were observed, which, to some extent, could increase the intraocular pressure. It is confirmed by the authors that ketamine hydrochloride can cause strong muscle contractions and convulsions (Thurmon, Tranqcuilli, Benson, 1996), so it is an evidence that mechanical pressure on the animal's neck or squeezing of the neck muscles significantly increases the IOP (Pauli, Bentley et al., 2006). Secondly, it is noted that ketamine hydrochloride in dogs increases arterial pressure, thus increasing the blood supply to the brain and also intracranial and intracerebral pressure (Thurmon, Tranqcuilli, Benson, 1996), possibly at the same time increasing the intraocular pressure.

As to the effects of premedication agents like atropine sulphate and acepromazine maleate on pupil diameter, our study showed variable effects – increase and decrease in HPD. However, before injecting general anesthetics ketamine hydrochloride and diazepam, HPD was already increased in both eyes and later, after the injection, continued to increase for two more minutes.

To explain the effects of an individual drug on intraocular pressure and pupil diameter accurately, further research is required.

Conclusion

1. It was established that injection of premedication drugs atropine sulphate and acepromazine maleate caused irregular changes in the intraocular pressure in dogs.
2. A significant and rapid increase in IOP was obtained in both eyes immediately after intravenous injection of general anesthetic drugs ketamine hydrochloride and diazepam.
3. Administration of the combination of premedication drugs atropine sulphate and acepromazine maleate caused fluctuating changes in the horizontal pupil diameter in both eyes in dogs. Injection of the ketamine hydrochloride and diazepam combination continued to increase the horizontal pupil diameter.
4. The total effect of the general anesthetic drugs on the IOP and HPD should be taken into account in various ocular pathologies diagnosed in animals.

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Anotācija

Pētījuma mērķis bija noskaidrot premedikācijas līdzekļu atropīna sulfāta un acepromazīna maleāta un narkozes līdzekļu ketamīna hidrohlorīda un diazepāma summāro ietekmi uz acs iekšējo spiedienu un

acs zīlītes diametru suņiem. Pētījumā iekļāva desmit klīniski veselus dažāda vecuma un dzimuma suņus, kuriem tika nozīmēta plānveida operācija – kastrācija vai ovariohisteroektomija. Dzīvniekiem premedikācijā tika lietots atropīna sulfāta (0.04 mg kg^{-1}) un acepromazīna maleāta (0.1 mg kg^{-1}) šķīdums, kuru ievadīja intramuskulāri, bet vispārējā anestēzijā – ketamīna hidrohlorīda (5.5 mg kg^{-1}) un diazepāma (0.25 mg kg^{-1}) šķīdumu kombinācija, kuru ievadīja intravenozi. Kontroles grupā atkārtoti iekļāva desmit klīniski veselus līdzīga svara un vecuma suņus, kuriem premedikācijas un vispārējās anestēzijas līdzekļu vietā attiecīgi ievadīja NaCl šķīdumu. Tika konstatēts, ka premedikācijas līdzekļu atropīna sulfāta un acepromazīna maleāta intramuskulāra injekcija suņiem izraisa viļņveidīgu un nevienmērīgu acs iekšējā spiediena palielināšanos un pēc narkozes līdzekļu ketamīna hidrohlorīda un diazepāma intravenozas ievadīšanas būtiski un strauji ($p<0.01$) palielinās intraokulārais spiediens abās acīs. Premedikācijas līdzekļi suņiem izraisīja svārstīgas izmaiņas acs zīlītes diametrā abās acīs. Intravenozi ievadītais ketamīna hidrohlorīds kopā ar diazepāmu izraisīja būtisku acs zīlītes horizontālā diametra palielināšanos ($p<0.01$). Vispārējās anestēzijas līdzekļu ietekme uz acs funkcionālajiem parametriem jāņem vērā, suņiem konstatējot dažādas acs patoloģijas.