

EFFECTS OF TOPICAL AND SYSTEMIC ATROPINE SULFATE ON INTRAOCULAR PRESSURE AND PUPIL DIAMETER IN DOG'S EYE

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Abstract

The objective of this study was to determine the effects of topical 1% atropine sulfate and systemic atropine sulfate on intraocular pressure (IOP) and horizontal pupil diameter (HPD) in dog's eyes.

Ten adult dogs for each treatment were used in this study. Dogs of different age, breed and sex were examined clinically and ophthalmologically. All animals were clinically and ophthalmologically healthy.

One drop of topical 1% atropine sulfate was used in ten dogs unilaterally, with the contralateral eye acting as a control. IOP and HPD were measured every 5 minutes. In ten dogs systemic atropine sulfate were used intramuscularly (IM) with IOP and HPD measured every 5 minutes. In both study phases IOP and HPD were measured over a total duration of 60 minutes.

After unilateral application of topical atropine, IOP increased significantly in the treated eye. A maximum average IOP of 20.3 mmHg in the treated eye was observed 20 minutes after treatment. Maximal pupil dilatation in the treated eye was observed 35 min after treatment. Measurements made after systemic atropine showed an IOP increase in both eyes, showing maximum average IOP increase 25 minutes post-treatment. Maximum average values of HPD were obtained 25 minutes after treatment. The HPD started to decrease 30 minutes after treatment but it was still significantly higher than before treatment ($P < 0.05$).

Because of atropine sulfate's ability to cause significant increase in IOP, it should not be used for diagnosis and treatment of glaucomatous eyes.

Key words: atropine sulfate, dog, intraocular pressure, horizontal pupil diameter.

Introduction

It is known that atropine sulfate is a parasympatholytic agent which interacts with muscarinic receptors on effector cells and prevents acetylcholine from binding to the receptor area (Jones et al., 1977). Atropine blocks the cholinergic fibers of the short ciliary nerve and relaxes the sphincter muscle of the iris, dilating the pupils (Thurmon et al., 1996). It is a commonly used topical agent for a treatment of acute iritis, iridocyclitis and keratouveitis by relieving ciliary spasm and helping to prevent synechia formation (Smith and Reynard, 1992; Ward, 1998). Topical atropine or another parasympatholytic agent such as tropicamide is essential for the examination of the posterior segment of the eye (including retina, retinal vessels, optic nerve, and peripheral areas of the lens) (Ward, 1998).

It is proven that in humans increase of intraocular pressure (IOP) has been observed after use of topical

mydriatics like atropine (Gartner and Billet, 1957), tropicamide and phenylephrine (Harris, 1968; Harris and Galin, 1969) together with sympathomimetics (Rengstorff and Doughty, 1982). Mydriatic drugs can cause a significant rise in intraocular pressure in patients with narrow angle (Harris and Galin, 1969) and primary open angle glaucoma (Shaw and Lewis, 1986; Marchini et al., 2003).

In a study with 10 adult cats the effects of local atropine and phenylephrine demonstrate a significant intraocular pressure (IOP) increase after atropine, but no effect after the phenylephrine. The highest IOP was measured in treated eye between 5 and 28 h after treatment and these differences were statistically significant at 1, 3, 6, 12 and 16 h post-treatment (Stadtbaumer et al., 2006). In a study with horses, topical 1% atropine did not show significant changes of IOP in the first and second day (Herring et al., 2000), or there was a small but significant

lowering effect (Mughannam et al., 1999).

Regarding on parameters of pupil diameter in the literature such research has been done on horses and cats. The maximum of pupil dilation was obtained 30-60 min after topical atropine in dogs, cats and cattle (Gelatt et al., 1973; Gelatt et al., 1995 a, b; Gelatt and MacKey, 1998). In cats, 24 hours after topical atropine, horizontal pupil diameter (HPD) started to reduce and after 96 hours the pupil returned to the initial size (Stadtbaumer et al., 2006). In the study with horses, a significant increase in vertical pupil diameter (VPD) was observed 30 min after treatment, but maximum values appeared between two and four hours. No significant differences were obtained in maximum VPD based on age, breed or sex (Mughannam et al., 1999; Davis et al., 2003). In another study with horses where VPD was measured every 24 hours for 14 days, significant increase of VPD was measured in all time points; and it was ascertained that duration of mydriasis after topical 1% atropine sulfate application was greater than 14 days (Davis et al., 2003).

Topical ocular use of atropine sulfate can cause salivation in dogs and cats. Apparently, the mydriatic exits through the nasolacrimal system and, when in contact with the glosal mucosa, elicits copious salivation (Gelatt, 1978). This could cause systemic effects of topical atropine used unilaterally.

For a long time ophthalmologic atropine has been known for its mydriatic and cycloplegic effect. Contradictory findings regarding the effects of atropine on the dynamics of aqueous humor outflow have been reported (Bill, 1967; Bill, 1969; Green and Elijah, 1981; Miichi and Nagataki, 1982). In a study with monkeys, atropine was shown to increase uveoscleral outflow through the relaxing of the ciliary muscle (Bill, 1967; Bill, 1969). There are authors who have mentioned that atropine could change aqueous outflow (Harris, 1968; Valle, 1974), but others have found that mechanical obstruction of iridocorneal angle could be the possible cause of IOP increase (Stadtbaumer et al., 2006). Author has observed that maximum dilatation of the pupil lasts longer than statistically significant increase on IOP, arguing against mechanical obstruction of iridocorneal angle (Stadtbaumer et al., 2006).

Systemic atropine is frequently used to control smooth muscle spasms and is routinely used as adjunct to general anesthesia, particularly with inhalant anesthesia, to decrease salivary and airway secretion.

It is mentioned that systemically administrated atropine has wide systemic effects acting on the cardiovascular, gastrointestinal, bronchial, urinary, central nervous system, sweet gland and ocular systems (Jones et al., 1977; Ward, 1998; Birģele et al., 2005).

In the literature there are no clear data about influence of systemical atropine on IOP and HPD in the dog. Therefore the aim of our study was to determine the effects of topical and systemical atropine sulfate on functional state of the eye.

The purpose of this study was:

- 1) to determine the effects of topical 1% atropine sulfate on IOP and HPD in dog's eye;
- 2) to determine specific intraocular effects after systemic atropine sulfate application in dog.

Materials and Methods

All animals were outpatients examined at Preclinical Institute of the Faculty of Veterinary Medicine of the Latvia University of Agriculture in 2007. This study was accepted by the Animal Protection and Ethical Commission of 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 this study were examined clinically and ophthalmologically. Examination included slit lamp-biomechanics, direct ophthalmoscopy and monocular indirect ophthalmoscopy with *Pan Optic*[®]. Information about animal breed, age and sex were noted. Prior to the study, all patients were determined to be free of ocular lesions which could alter IOP from normal.

This study was organized in two phases. In the first phase we used 10 healthy dogs of different sex and breed: mixed breed (n=5), Golden Retriever (n=2), Boxer (n=1), Staffordshire Bull Terrier (n=1), and Dachshund (n=1). In these dogs the effect of local 1% atropine sulfate on IOP and HPD was ascertained. All animals received one 30 μ drop of 1% atropine sulfate (Martindale Pharmaceuticals Ltd. UK) in the right eye; the left eye served as a control. The first measurement was taken before treatment, avoiding any tension on the animal's neck. After treatment, IOP and HPD were measured every five minutes (T_0 ; T_5 ... T_{55} ; T_{60}) for a complete period of 60 minutes.

In the second phase 10 dogs (mixed breed (n=9) and Golden Retriever (n=1)) were used to ascertain

the effect of systemical atropine sulfate on IOP and HPD. Atropine sulfate at the dose of 0.06 mg kg^{-1} (Jones et al., 1977) was administered systemically by intramuscular injection. IOP and HPD were measured every 5 minutes for a total period of 60 minutes.

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

Horizontal pupil diameter was measured with *Jameson* callipers under fixed light conditions at the same time of day.

To determine the effect of topical and systemical atropine sulfate, arithmetic mean values (X) and standard deviation (SD) of the IOP and HPD were calculated for each eye. Changes in IOP and HPD between eyes and in a time period were evaluated using a paired two-sample T-test. P values less than 0.05 were considered to be statistically significant.

Results and Discussion

During this study no signs of irritation or pain were detected.

At first we estimated initial position of the

animals' eye – IOP before application of atropine sulfate, and established that normal IOP varies between $14.2 \pm 3.58 \text{ mmHg}$ till $17.7 \pm 3.13 \text{ mmHg}$. Data from the literature shows that normal IOP in dogs varies between $16.7 \pm 4 \text{ mmHg}$ (Miller et al., 1993) and $18.7 \pm 5.5 \text{ mmHg}$ (Gellat and MacKey, 1998). Therefore, our results about normal IOP in dogs are similar to those in the literature.

It should be mentioned that before treatment there were no significant differences in IOP between the left and right eye ($P > 0.05$). The average IOP before application of 1% atropine sulfate in the right eye was $17.7 \pm 3.12 \text{ mmHg}$ and $17.3 \pm 2.75 \text{ mmHg}$ in the left eye.

The dynamics of IOP increase after topical application of 1% atropine sulfate is shown in Fig. 1. The radical increase of IOP began five minutes after treatment and continued till 20 minutes after treatment. IOP started to decrease 20 minutes after treatment and 25 minutes after treatment it reduced to 19.5 ± 2.55 ; the lowest level of IOP (18.5 ± 2.32) was measured 30 minutes after treatment. There was a small increase of IOP 35 minutes after treatment reaching 19.1 ± 2.42 , but this was not statistically significantly different from the value at 30 minutes. Slight decreases of IOP were measured till 60 minutes after treatment but values did not decrease lower than pre-treatment values ($P < 0.05$).

The average IOP in the treated eye compared to the untreated eye was significantly higher ($P < 0.05$) from 10 till 25 minutes after treatment (Fig. 1).

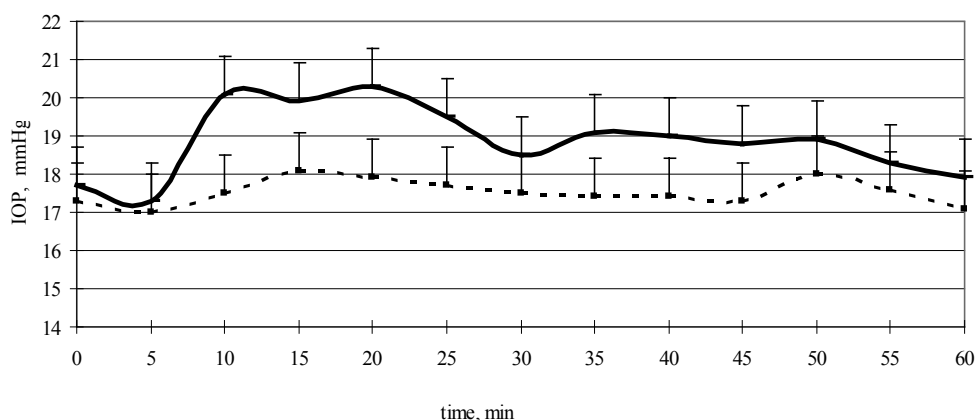


Figure 1. IOP changes after unilateral application of 1% atropine sulfate (--- right eye,left eye).

In the control eye, where topical atropine sulfate was not administrated, IOP varied from 17 ± 3.23 to 18.1 ± 3.90 . There was no significant increase in IOP compared to pre-treatment values ($P > 0.05$). It can be concluded that during monocular topical administration of topical atropine sulfate there do not appear to be any systemic effects on the contralateral eye, which also indicated in a similar study with horses (Herring *et al.*, 2000).

Our results about influence of topical 1% atropine on horizontal pupil diameter (HPD) show that average HPD before topical atropine in the right eye

was 7.8 ± 3.58 mm and 7.7 ± 3.59 mm in the left eye (Fig. 2). There were no significant differences in HPD between eyes before treatment. We established that after application of 1% atropine, pupil diameter in treated eye started to dilate ten minutes after treatment, gaining 8.1 ± 3.46 mm and continued to increase in size till 55 minutes after treatment gaining maximum of average values - 12.13 ± 1.55 mm. The pupil remained at maximal dilatation level till 60 minutes after treatment (Fig. 2). Differences in HPD between the treated and untreated eye were statistically significant ($P < 0.003$).

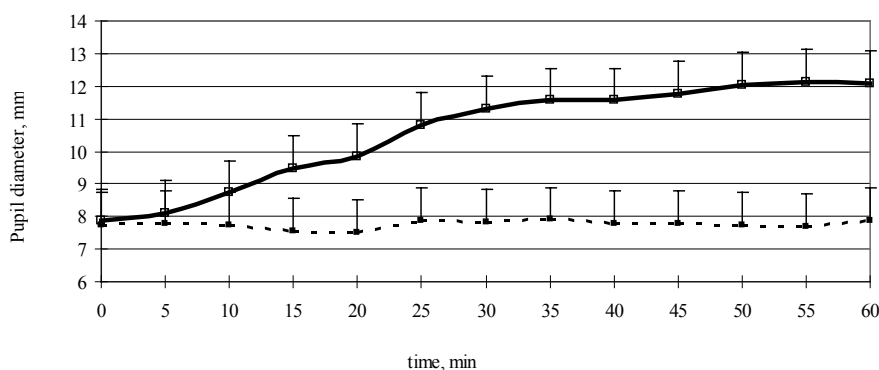


Figure 2. Changes in horizontal pupil diameter after unilateral application of 1% atropine sulfate (--- right eye,left eye).

In the second phase we investigated the changes in intraocular pressure (IOP) in dogs after injection of atropine sulfate at the dose of 0.06 mg kg^{-1} . The average IOP before systemic atropine application was 14.2 ± 3.58 mmHg in the right eye and 14.4 ± 3.50 mmHg in the left eye (Fig. 3). The differences between the right and left eye in average IOP values were not significant ($P > 0.05$). Five minutes after IM application of atropine sulfate, IOP increased reaching 16.3 ± 4.47 in the right eye and 16.2 ± 4.56 in the left eye. Increase of IOP compared to pre-treatment values was statistically significant in both

eyes ($P < 0.02$). IOP continued to increase and 25 minutes after application reached the greatest IOP gaining 17.1 ± 5.23 mmHg in the right eye and 17.3 ± 4.57 mmHg in the left eye ($P < 0.05$). IOP slightly decreased 30 minutes after treatment gaining 16.4 ± 4.88 in the right eye and 16.4 ± 5.05 in the left eye, but these values are still significantly higher than pre-treatment values (Fig. 3). There were no significant differences in IOP between eyes ($P > 0.05$). In conclusion the significant bilateral increase of IOP confirms a systemic influence of topical atropine.

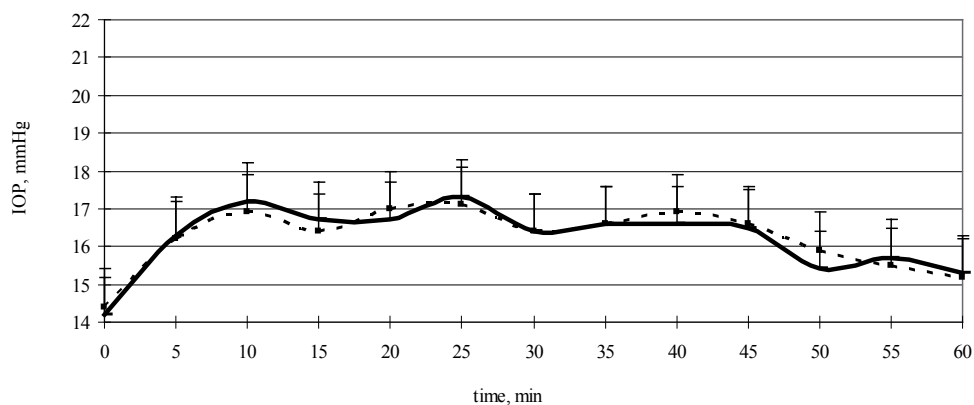


Figure 3. IOP changes after systemic administration of atropine sulfate (--- right eye,left eye).

In relation to HPD we observed that average HPD before systemical administration of atropine sulfate was 6.75 ± 2.13 mm in both eyes. There were no differences in HPD between eyes before treatment. HPD increased significantly ten minutes after systemic atropine sulfate administration in both eyes (Fig. 4) and linearly continued to increase until 25 minutes after treatment ($P < 0.05$). There were no significant differences between eyes ($P > 0.05$). Maximum of average values (9.75 ± 3.61 mm

and 9.93 ± 2.56 mm) in right and left eyes were obtained by 25 minutes after administration. The value of HPD started to decrease 30 minutes after administration but was still significantly higher than before treatment throughout the study period ($P < 0.05$). Sixty minutes after treatment, HPD was 8.8 ± 2.85 in the right eye and 9.3 ± 2.96 in the left eye; these values were significantly higher than pre-treatment values.

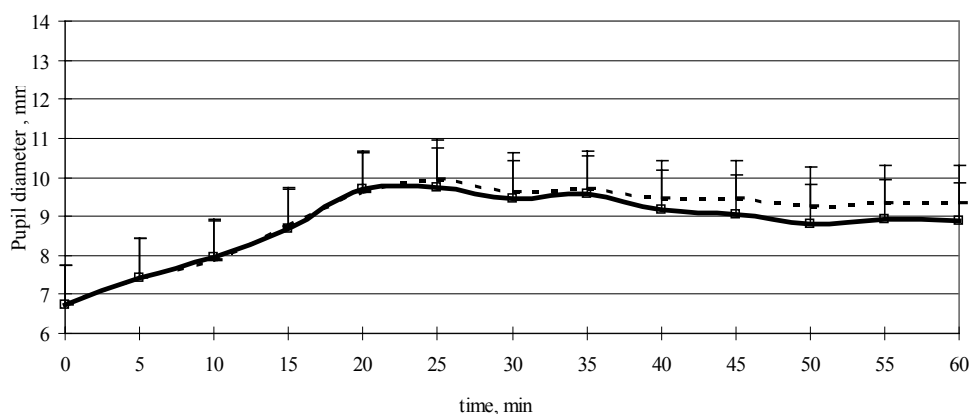


Figure 4. Changes in horizontal pupil diameter after systemic application of atropine sulfate (— right eye, ---- left eye).

Our research demonstrates that systemic administration of atropine sulfate does have a significant influence on IOP and HPD in dog's eyes.

These results are novel, since there has been no similar or analogical research done on influence of systemical atropine sulfate on IOP and HPD in animals, nor research on the effects of topical atropine on intraocular pressure in the canine eye as shown here. The research in this field is still in process.

Conclusion

Results based on this study show that topical atropine does have a significant influence on IOP and HPD in the treated eye but not in the contralateral untreated control eye. Systemic use of atropine influences IOP and HPD in both eyes. It is thus important not to give atropine topically or systemically to dogs predisposed to, or actually affected by glaucoma. Further research is required to more completely define the mechanism of influence of atropine on aqueous humor production and outflow in the dog.

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