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Influence of medetomidine, acepromazine, fentanyl and butorphanol on intraocular pressure and pupil size in healthy dogs

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ABSTRACT: The aim of this study was to assess the effects of four different drugs used for anaesthesia premedication on intraocular pressure and pupil size in dogs. A prospective, randomised, double-blind clinical study was carried out. The subjects were forty client-owned healthy dogs (20 males and 20 females), aged 8.0 ± 2.9 years, with body weights of 11.8 ± 8.5 kg (mean ± SD) and without ocular abnormalities that were scheduled for periodontal treatment. Animals were randomly allocated into four groups and received intravenously either medetomidine 0.01 mg/kg, acepromazine 0.02 mg/kg, fentanyl 0.01 mg/kg or butorphanol 0.2 mg/kg. Intraocular pressure, pupil size, heart rate, respiratory frequency and systolic and diastolic arterial pressures were measured prior to (baseline) and at five and 10 minutes after premedication (T5, T10). Data were analysed by Anderson-Darling, Bartlett's, ANOVA and Dunnett's tests ($P < 0.05$). Significant increases of intraocular pressure were observed at T5 and T10 in the fentanyl group. Significant decreases of pupil size at T5 and T10 were detected in the fentanyl, butorphanol and medetomidine groups. In the fentanyl group, heart rate dropped significantly at T10, while respiratory frequency was elevated at T5 and T10. In the medetomidine group, heart rate and respiratory frequency were decreased at T5 and T10. In the butorphanol group, systolic arterial pressure was decreased at T5 and diastolic arterial pressure was decreased at T5 and T10. In the acepromazine group, systolic arterial pressure was decreased at T10. Within ten minutes after intravenous administration in healthy dogs, fentanyl significantly increased intraocular pressure and fentanyl, butorphanol and medetomidine decreased pupil size.

Keywords: applanation tonometry; canine; sedation; opioids; ophthalmology

Intraocular pressure (IOP) is one of the key parameters that maintains ocular homeostasis and adequate function of the eye. IOP is determined as the pressure of intraocular fluids on the cornea and sclera of the eye and is influenced by numerous mechanisms, such as changes in the volumes of aqueous humour, choroidal blood and vitreous humour, rigidity of the sclera, the tone of extraocular muscles and external pressure on the globe, eyelid or extraocular muscles (Murphy 1985; Almeida et al. 2004). Normal canine IOP is approximately 10–25 mm Hg (Renwick 2002).

Fluctuations in IOP are caused by pathological processes in the eye, e.g. uveitis and ocular hypertension, but may occur in the healthy eye as well due to changes in ocular haemodynamics. The partial arterial pressure of carbon dioxide ($PaCO_2$) influences ocular blood flow affecting choroidal and retrobulbar blood volume (Hvidberg et al. 1981). Changes in systolic blood pressure can induce transient alterations of IOP (Cunningham and Barry 1986).

An increase in central venous pressure (CVP) changes intraocular vascular diameter, venous out-

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flow and drainage of aqueous humour and leads to increased IOP (Verbruggen et al. 2000).

Drugs affecting the sympathetic and parasympathetic nervous systems may influence IOP due to changes in aqueous humour production, intraocular blood pressure, vascular tone, muscular tone and impacts on the diencephalon (Almeida et al. 2004).

Medetomidine is an alpha-2 adrenoceptor agonist commonly used in small animal anaesthesia for sedation or general anaesthesia premedication. The haemodynamic effects of medetomidine are characterised by increased systemic vascular resistance, biphasic blood pressure response, decreased heart rate and increased central venous pressure. Minimum changes in pulmonary arterial pressure or pulmonary capillary wedge pressure have been reported (Murrell and Hellebrekers 2005). Intravenous administration of medetomidine decreases IOP (Verbruggen et al. 2000) and causes miosis (Kanda et al. 2015).

Acepromazine is a phenothiazine derivative antipsychotic drug used in veterinary medicine for sedation; it inhibits postsynaptic dopamine receptors resulting in decreased heart rate and respiratory frequency, blood pressure and body temperature. Its influence on IOP in combination with ketamine was compared to that of the ketamine-diazepam combination. Both combinations increased IOP after intramuscular application in rabbits; however, this effect was more pronounced in the ketamine-acepromazine group (Ghaffari and Moghaddassi 2010).

The effect of opioids on IOP was studied by Blaze et al. (2009). Increased IOP was recorded after hydromorphone, butorphanol, morphine and buprenorphine administration. Nevertheless, all measurements were within normal limits and were therefore considered insignificant (Blaze et al. 2009). On the other hand, fentanyl was reported to decrease intraocular pressure during general anaesthesia induced with a fentanyl-propofol-vecuronium combination in humans (Sator-Katzenschlager et al. 2004). A significant decrease in pupil size was observed after parenteral administration of morphine in dogs and rabbits. This effect is a result of parasympathetic nerve stimulation by morphine. In contrast, in cats, monkeys, rats and mice, mydriasis is promoted due to catecholamine release from adrenal glands (Murray et al. 1983).

The effects of different anaesthetic drugs administered for premedication or during general anaesthesia on canine IOP have been documented previously as mentioned above. However, no study to date has compared the short-term effects on IOP and pupil size of separately administrated sedatives or analgesics commonly used for sedation or analgesia in a clinical setting. Thus, the aim of the present study was to investigate changes in IOP and pupil size associated with clinically effective doses of medetomidine, butorphanol, fentanyl or acepromazine in healthy dogs. We expected to observe decreased IOP after MED or ACE administration and increased IOP after BUT or FEN administration.

MATERIAL AND METHODS

All procedures were carried out in accordance with current legislation of the Czech Republic and with the consent of the Ethics Committee of the University of Veterinary and Pharmaceutical Sciences Brno. The techniques described below did not go beyond commonly used clinical procedures. A prospective, randomised, double-blind clinical study was performed.

Animals. Forty healthy dogs (20 males and 20 females) aged (mean ± SD) 8.0 ± 2.9 years and weighing 11.8 ± 8.5 kg were enrolled in this study. Dogs without ocular abnormalities and scheduled for periodontal treatment were enrolled in this study. Dogs with ASA (American Society of Anesthesiologists) physical status I or II were included only. To assess health status, physical examination and preoperative blood panel were performed prior to scheduling patients for dental cleaning. An ophthalmic examination, including Schirmer's tear test, applanation tonometry, slit lamp biomicroscopy and indirect ophthalmoscopy was performed by an experienced individual blinded to the treatment groups. Dogs without ophthalmic abnormalities with IOP measured to be in the 10–25 mm Hg range prior to sedation were included only. Dogs with any health problems, eye pathology or with IOP values outside the described range were excluded.

Study protocol. Dogs were randomly allocated (www.randomizer.org) to one of four groups, MED, FEN, BUT or ACE, each containing ten animals. Following intravenous (*i.v.*) catheterisation of a cephalic vein, baseline measurements were performed. Group MED then received *i.v.* medetomidine 0.01 mg/kg (Domitor, Orion Pharma), group ACE *i.v.* acepromazine 0.02 mg/kg (Prequillan

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10 mg/ml, ATI Srl), group FEN *i.v.* fentanyl 0.01 mg/kg (Fentanyl Torrex, Torrex Chiesi) and group BUT *i.v.* butorphanol 0.2 mg/kg (Butomidor, Richter Pharma). A single investigator obtained all the measurements and was unaware of which drug had been administered.

All dogs were maintained in sitting position during measurement procedures without any manipulation or compression of the jugular vein or eye.

Measurements. In all dogs, intraocular pressure (IOP), pupil size (PS), heart rate (HR), respiratory frequency (f_R) and systolic and diastolic arterial blood pressures (SAP, DAP) were measured and recorded just before (baseline) and five (T5) and ten (T10) minutes after administration of the abovementioned drugs.

Intraocular pressure was measured using applanation tonometry (TonoPen XL, Medtronic). Prior to each new patient measurement, a new rubber cover was put in place and the tonometer was calibrated. In all dogs, IOP was measured on the left eye. Pupil size was measured using a pupil gauge. The respiratory frequency was measured by observation of chest movements. The heart rate was measured by auscultation of heart sounds. Non-invasive blood pressure was measured by a cuff applied to the front limb connected to a vital function monitor (Cardel 9401, Midmark). Cuff width was 40% of the circumference of the limb. Collected data included systolic and diastolic arterial pressures. Baseline and all measurements were performed in the morning after patient acclimatisation to lighting conditions in a quiet room for 10 minutes after intravenous catheterisation.

Statistical analysis. Statistical analysis was performed using KyPlot 2.0 beta 15 (Koichi Yoshioka) and MS Excel (Microsoft).

IOP, PS, HR, f_R, SAP and DAP parameters measured at the same time points in several groups were compared to each other. Intraocular pressure, PS, HR, f_R, SAP and DAP measured at T5 and T10 were compared with baseline.

Anderson-Darling and Bartlett's tests were used to confirm normal distribution of data and homogeneity of variance, respectively. All variables were compared between groups at each specific time point using one-way analysis of variance (ANOVA) techniques. For multiple comparisons between baseline and T5 and T10 within each group, Dunnett's test was used. $P < 0.05$ was considered statistically significant.

RESULTS

All results are displayed in Table 1. There were no significant differences between groups with regard to gender, body mass, age or selected parameters at baseline (IOP, PS, HR, f_R, SAP or DAP).

No statistically significant changes in IOP were observed within and between medetomidine, butorphanol and acepromazine groups at any time points. However, in the fentanyl group IOP increased significantly at T5 and T10 compared to baseline. These changes were not significant compared to other groups.

Pupil size decreased in all groups, significantly in fentanyl, butorphanol and medetomidine groups at T5 and T10 compared to baseline. No differences between groups were noted.

Heart rate decreased in all groups at both time points compared to baseline. Significant decreases in HR were detected in the medetomidine group at T5 and T10 and in the fentanyl group at T10 compared to baseline. In the acepromazine group, HR was significantly higher at T5 compared to fentanyl and medetomidine groups and at T10 compared to the medetomidine group. In the fentanyl and butorphanol groups, HR was significantly higher at T5 compared to medetomidine.

Significant increases in f_R were found in the fentanyl group at T5 and T10 compared to baseline. The increases of f_R in the fentanyl group were significant at T5 and T10 compared to other groups. In the medetomidine group, f_R was significantly decreased at T5 and T10 compared to baseline and significantly lower at T5 and T10 compared to butorphanol and acepromazine groups.

Systolic arterial pressure was significantly decreased in the butorphanol group at T5 and in the acepromazine group at T10 compared to baseline. In the butorphanol group, SAP was significantly lower at T5 compared to fentanyl, medetomidine or acepromazine groups and at T10 compared to the fentanyl group. In the acepromazine group, SAP was significantly lower at T10 compared to the fentanyl group.

Diastolic arterial pressure was significantly decreased in the butorphanol group at T5 and T10 compared to baseline and was significantly lower at T5 and T10 compared to fentanyl or medetomidine groups. At T10, DAP was significantly lower in the acepromazine group compared to fentanyl or medetomidine groups.

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Table 1. Changes in intraocular pressure (IOP), pupil size (PS), heart rate (HR), respiratory frequency (f_R) and systolic and diastolic arterial pressures (SAP, DAP) in dogs after treatment with either medetomidine (MED), acepromazine (ACE), fentanyl (FEN) or butorphanol (BUT). Data are expressed as mean ± standard deviation (ranges)

Group	Parameter	Time		
		baseline	T5	T10
MED	IOP (mm Hg)	19 ± 3 (14–25)	20 ± 3 (15–24)	19 ± 3 (15–27)
	PS (mm)	8 ± 1 (7–10)	8 ± 2 (4–9)†	5 ± 2 (3–9)†
	HR (beats/min)	110 ± 23 (80–139)	67 ± 31 (28–99)†	64 ± 21 (38–103)†
	f_R (breaths/min)	58 ± 59 (24–220)	22 ± 5 (16–30)†,4	20 ± 9 (12–40)†,4
	SAP (mm Hg)	175 ± 30 (133–232)	153 ± 34 (76–193)5	150 ± 29 (86–185)
	DAP (mm Hg)	129 ± 36 (89–204)	118 ± 36 (33–174)7	120 ± 34 (30–146)7,8
ACE	IOP (mm Hg)	20 ± 4 (14–24)	19 ± 4 (11–23)	19 ± 5 (11–26)
	PS (mm)	8 ± 1 (6–10)	7 ± 2 (5–10)	6 ± 1 (6–8)
	HR (beats/min)	140 ± 34 (100–193)	137 ± 28 (107–180)1,2	118 ± 22 (101–159)1
	f_R (breaths/min)	93 ± 70 (36–100)	43 ± 26 (24–100)3	41 ± 26 (24–100)3,4
	SAP (mm Hg)	173 ± 17 (138–191)	155 ± 17 (140–189)5	139 ± 22 (109–175)†,6
	DAP (mm Hg)	115 ± 27 (90–160)	93 ± 39 (46–170)	83 ± 13 (67–104)
FEN	IOP (mm Hg)	17 ± 4 (13–25)	19 ± 3 (15–26)*	21 ± 5 (14–28)*
	PS (mm)	7 ± 1 (5–9)	6 ± 1 (4–8)†	6 ± 1 (4–8)†
	HR (beats/min)	126 ± 24 (91–173)	96 ± 27 (60–151)1	91 ± 41 (45–187)†
	f_R (breaths/min)	66 ± 66 (18–240)	107 ± 98 (12–260)*	147 ± 89 (30–260)*
	SAP (mm Hg)	145 ± 35 (106–210)	160 ± 48 (103–258)5	175 ± 33 (134–223)5
	DAP (mm Hg)	107 ± 29 (82–189)	99 ± 36 (63–166)7	112 ± 30 (57–160)7,8
BUT	IOP (mm Hg)	18 ± 4 (11–25)	18 ± 6 (12–28)	20 ± 5 (12–27)
	PS (mm)	7 ± 1 (5–9)	6 ± 1 (4–8)†	6 ± 1 (5–8)†
	HR (beats/min)	110 ± 17 (74–132)	96 ± 22 (64–124)1	90 ± 27 (52–130)
	f_R (breaths/min)	37 ± 8 (24–48)	35 ± 12 (20–60)3,4	69 ± 71 (20–240)3,4
	SAP (mm Hg)	158 ± 35 (120–234)	131 ± 18 (91–165)†	133 ± 22 (78–155)
	DAP (mm Hg)	116 ± 41 (68–211)	71 ± 29 (46–140)†	81 ± 21 (41–102)†

*Significant increase of values compared to baseline

†Significant decrease of values compared to baseline

[1]Significantly higher HR compared to MED; [2]Significantly higher HR compared to FEN; [3]Significantly higher f_R compared to MED; [4]Significantly lower f_R compared to FEN; [5]Significantly higher SAP compared to BUT; [6]Significantly lower SAP values compared to FEN; [7]Significantly higher DAP compared to BUT; [8]Significantly higher DAP values compared to ACE

No other significant differences were detected.

DISCUSSION

In our study, within ten minutes after premedication with fentanyl we detected a significant increase in IOP. This finding contradicts a study on human patients, where no significant increase in IOP was observed (Domi 2010). In that earlier study, measurements were performed before and two minutes after fentanyl administration. In this study, measurements were taken five and 10 minutes after intravenous fentanyl administration. A decrease in IOP was observed by Sator-Katzenschlager et al. (2004) in patients anaesthetised with a fentanyl-propofol-vecuronium combination. Unfortunately, these findings cannot be compared with our observations because in the present study only fentanyl was administered at a dose which was 2–5 times lower (0.01 mg/kg) compared to Sator-Katzenschlager et al. (2004), where 0.02–0.05 mg/kg of fentanyl was administered.

Zacny et al. (1992) described the effect of fentanyl on pupil size in humans. After administration of 0.05 mg/70 kg of fentanyl, miosis was observed.

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In the present study, pupil size in dogs decreased significantly after intravenous administration of 0.01 mg/kg of fentanyl.

Alpha-2 agonists have been reported to reduce IOP via a reduction of aqueous humour production, ciliary body vasoconstriction and a decrease in ciliary blood flow (Artigas et al. 2012). We observed no changes in IOP after medetomidine administration, and our measurements are in agreement with those of our previous study (Rauser et al. 2016). In contrast, these findings are not in agreement with those of Verbruggen et al. (2000), where an increase in IOP in four dogs and a decrease in ten dogs five minutes after administration of medetomidine 0.15 mg/m^2 body surface area (corresponds to approximately 0.005 mg/kg) was reported. The dose of medetomidine in the present study was twofold higher when compared to the dose used by Verbruggen et al. (2000). The study by Kanda et al. (2015), where similar doses of medetomidine (0.01 and 0.02 mg/kg) were administered, did not report significant changes in IOP. Medetomidine has been reported to decrease pupil diameter (Verbruggen et al. 2000; Kanda et al. 2015). These data are in agreement with our previous (Rauser et al. 2016) and current findings.

The lack of changes in IOP after acepromazine administration is consistent with the results of a study comparing the effects of intramuscular application of acepromazine and hydromorphone on intraocular pressure (Stephan et al. 2003). Later, Kovalcuka and Birgele (2009) reported irregular changes in IOP within the initial 25 minutes followed by a decrease in IOP within 35 to 60 minutes after intramuscular administration of 0.01 mg/kg of acepromazine. A slower initial effect of the drug might explain why we did not observe significant changes in IOP. A recent study investigating the effects of intravenous administration of acepromazine and dexmedetomidine (Micieli et al. 2017) described no significant fluctuation in IOP after administration of 0.015 mg/kg of acepromazine. Although we did not observe any statistically significant change in pupil diameter, we observed a slight trend towards decreasing pupil size. In the report of Stephan et al. (2003), the adminstered dose of acepromazine was twice as high (0.04 mg/kg) as in our study (0.02 mg/kg) and pupil constriction was observed at 10 and 25 minutes after drug administration. Kovalcuka and Birgele (2009), on the other hand, observed a slow but consistent decrease in pupil diameter starting at five minutes and reaching significant constriction 25 minutes after acepromazine administration. Different doses, routes of administration and duration of experiments might explain the tendency towards decreased pupil diameter in our investigation. In contrast, Micieli et al. (2017) observed significant miosis at every time point of measurement starting five minutes after administration.

In a study describing the effects of butorphanol, Douet et al. (2018) reported a significant increase of IOP and decrease of pupil size. Butorphanol was administered intramuscularly at a dose of 0.2 mg/kg and the measurements were performed every 10 minutes. These findings do not match our observations. Intraocular pressure in dogs receiving butorphanol did not change in our study; however, we observed a significant decrease in pupil diameter. The lower dose of butorphanol and the shorter duration of the experiment in our case might explain the differing results. In contrast, Blaze et al. (2009) reported a transient but significant increase in IOP relative to baseline in dogs following *i.v.* administration of 0.1 mg/kg of butorphanol. The observed IOP values remained in the physiological range, therefore the changes were considered to be insignificant.

The haemodynamic effects of alpha-2 agonists have been described previously. The action of these drugs is biphasic. Peripheral vasoconstriction results in increased blood pressure, increased vagal tone and decreased heart rate; subsequently, vasoconstriction vanishes and a central hypotensive effect cause blood pressure to drop (Murrell and Hellebrekers 2005). These changes are dose-dependent. When a lower dose of medetomidine (0.01–0.02 mg/kg) is administered, the increase in blood pressure is less marked and a central hypotensive effect predominates (Pypendop and Verstegen 1998). This is in accordance with our findings of significantly lower heart rate and blood pressure in the group receiving medetomidine.

The beneficial effects of acepromazine are based on anxiolysis and sedation, especially when combined with opioids (Smith et al. 2001). The decreasing trend in heart rate and blood pressure values observed in the acepromazine group in our study was caused by this phenothiazine derivative blocking alpha-1 adrenoceptors in the blood vessel walls resulting in vasodilatation and decreased arterial blood pressure (Thurmon et al. 1996; Monteiro et al. 2007).

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Fentanyl induces changes in animal behaviour. A low dose of fentanyl (0.025 mg/kg) re-administered in 5-minute intervals induced mild restlessness with a small increase in heart and respiratory rates in response to the first two doses (Arndt at al. 1984). This might explain the increased respiratory rate and IOP in our patients. More commonly, and as seen in our study, bradycardia is observed after administration of an opium alkaloid regardless of the concentration due to stimulation of the vagal cardioinhibitory centre and acetylcholine release. Vasodilatation leading to a decrease in systemic blood pressure is caused by the impact of fentanyl on the vasomotor centre leading to inhibition of sympathetic basal discharge. This effect is observed only up to a certain drug concentration (Freye 1974).

Intraocular pressure fluctuates during daytime hours. Significantly lower values were observed in the afternoon (5.00–6.30 pm) and maximum IOP peaks were noted in the morning (8.30–10.30 am). Measurements were obtained every four hours (Giannetto et al. 2009) and every 1.5 hours (Martin-Suarez et al. 2014), respectively. In our study, we performed all manipulations, including acclimatisation, baseline measurements, drug application and T5 and T10 measurements, within 30 minutes. Thus, with respect to the duration of the experiment, diurnal variations in IOP are not significant in this investigation.

This study in not free of limitations. Our groups consisted of privately owned dogs scheduled for periodontal treatment as this was intended to be a clinical study. Therefore, we could not achieve the same uniformity in age, breed and sex that would have been possible if experimental animals were used. Neither gonioscopy of the pectinate ligaments nor high frequency ultrasonography for the ciliary cleft were performed. Gonioscopic findings do not directly correlate to levels of IOP or aqueous humour outflow (Gelatt et al. 2008). However, in some breeds, dysplasia of iridocorneal angle is associated with higher risks of IOP fluctuation or primary glaucoma (Ekesten and Narfstrom 1991; Bjerkas et al. 2002). In healthy dogs with normal IOP without any history of ocular problems, we assumed an iridocorneal angle without pathological abnormalities. Further investigation of the influence of the drugs evaluated in this study on IOP in dogs with iridocorneal angle abnormalities would be advisable. Another limitation of the present study was the short period of measurement. Such a short period was chosen to allow us to proceed with general anaesthesia and the planned procedure.

In conclusion, within 10 minutes after intravenous administration in healthy dogs, fentanyl significantly increased intraocular pressure and decreased pupil size; butorphanol and medetomidine administration resulted in decreased pupil size only. These findings should be considered when planning sedation of animals where elevation of IOP or miosis are undesirable.

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