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Influence of fentanyl, ketamine or lidocaine infusion on the intraocular pressure and pupil size in conscious dogs

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Abstract: Fifty-five healthy conscious dogs were included in a prospective randomised double-blinded clinical study. The dogs allocated to one of four groups received intravenous bolus followed by infusion of fentanyl (FEN-group), or ketamine (KET-group), or lidocaine (LID-group), or saline (SAL-group). The intraocular pressure (IOP), pupil size (PS), heart rate (HR) and mean arterial pressure (MAP) were measured prior to and at 2, 5, 10, 20 and 30 min after initiation of the drug administration. The data were analysed using an analysis of variance and the Steel-Dwass test. No significant difference in the IOP within or between the groups was detected. In the FEN-group, the PS decreased significantly at all the measured times. In the KET-group, the PS increased significantly at 2, 5 and 10 minutes. The PS was significantly smaller in the FEN-group compared to the KET-group at 2, 5, 10 and 20 min, compared to the SAL-group at 5, 10, 20 and 30 minutes. In the FEN-group the HR significantly decreased compared to the baseline and was significantly lower compared to the KET-group and LID-group. Fentanyl, ketamine or lidocaine administered at the doses studied as a bolus followed by a 30-min infusion seem to cause no effect on the IOP in healthy conscious non-painful dogs without ocular abnormalities. Fentanyl decreased and ketamine transiently increased the PS.

Keywords: analgesics; canine; eye; pain; tonometry

An important factor for ocular homeostasis is the intraocular pressure (IOP). Changes in the IOP can have major consequences on the stability of the eye structure. The physiological values of canine IOP are 15–25 mmHg (Plummer et al. 2013). The IOP is influenced by several factors, including the blood pressure, pressure on the globe, arterial carbon dioxide and oxygen tensions or drugs administered. The IOP is also affected by the pupil size (PS) – miosis is known to reduce the IOP by increasing the aqueous humour outflow (Plummer et al. 2013).

The effects of anaesthetics on the IOP have been widely studied, where a recent systematic review

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has been published (Pierce-Tomlin et al. 2020). However, information on the effects of separately administered analgesics on the IOP is sporadic.

Pain management is an essential component of painful conditions. Frequently used analgesics in dogs include fentanyl, ketamine, and lidocaine. One of the adverse reactions of analgesics in dogs can be the influence on the IOP.

Fentanyl is a potent μ-opioid agonist, ketamine is an *N*-methyl-D-aspartate (NMDA) antagonist and lidocaine is a local anaesthetic. All of these drugs are administered continuously intravenously to achieve sufficient analgesia. Fentanyl administered as a bolus in doses of 0.01 mg/kg has been shown to increase the IOP and decrease the pupil size (PS) within 10 minutes (Mrazova et al. 2018). Ketamine administered as a bolus in doses of 5 mg/kg (Hofmeister et al. 2006a) or 20 mg/kg (Kovalcuka et al. 2013) has been shown to increase the IOP and PS. Systemic intravenous administration of lidocaine at 2 mg/kg also increased the IOP (Hofmeister et al. 2006b).

Although the effect of fentanyl, ketamine and lidocaine on the IOP and PS has been described, the doses studied differ from those used in clinical practice (Mathews et al. 2018).

In addition, in previously published studies, the drugs were administered without a subsequent continuous infusion.

The aim of this study was to investigate the 30-min effects of fentanyl, ketamine, or lidocaine administered at commonly used analgesic doses by a single bolus injection followed by infusion on the IOP and PS in healthy dogs, which have not been published yet. It was hypothesised that fentanyl or ketamine would each induce an increase in the IOP, all the drugs would be associated with changes in the PS.

MATERIAL AND METHODS

This prospective randomised "double-blinded" study was performed in accordance with the consent of the Ethics Committee of the University of Veterinary Sciences Brno, Czech Republic. The animal owners provided informed consent to have their animals participate in the study. The study protocol was adopted from our previous study (Rauser et al. 2019), to which it directly follows, complements and extends.

Study animals

A total of 55 healthy dogs aged 2–8 years and weighing 5–20 kg undergoing periodontal treatment were included. All the dogs had an American Society of Anesthesiologists physical status I or II. They were classified healthy based on the medical history, physical examination, and complete blood analysis. The dogs were fasted for 12 h, with free access to water.

All the dogs were prepared for the periodontal treatment. All the measurements were performed in the awake animals before the administration of sedatives. An ophthalmic examination, including a Schirmer tear test I (STT-I), applanation tonometry, slit lamp biomicroscopy, gonioscopy and indirect ophthalmoscopy was performed by an experienced ophthalmologist. Only dogs without eye abnormalities, with an IOP measured at 15–25 mmHg prior to the sedation and an STT-I higher than 12 mm/min were included. Brachycephalic breeds were excluded.

Procedure

Randomising software (www.randomizer.org) was used to allocate the animals into four groups – fentanyl (FEN-group, n = 15), ketamine (KET-group, n = 15), lidocaine (LID-group, n = 15) and control – saline (SAL-group, n = 10) groups. An intravenous cannula was placed into the cephalic vein in all the dogs. After 10 min, the intraocular pressure (IOP), pupil size (PS), heart rate (HR) and mean arterial pressure (MAP) were measured and recorded (baseline).

A fentanyl (Fentanyl Torrex; Chiesi Pharmaceuticals, Vienna, Austria) bolus injection of 0.005 mg/kg was administered in the FEN-group over 20 s followed by a constant rate infusion of fentanyl of 0.005 mg/kg/h.

A ketamine (Narketan 100 mg/ml; Vetoquinol, Lure, France) bolus injection of 0.6 mg/kg was administered in the KET-group over 20 s followed by a constant rate infusion of ketamine of 0.6 mg/kg/h.

A lidocaine (Lidocaine 2%; Egis Pharmaceuticals Budapest, Hungary) bolus injection of 1 mg/kg was administered in the LID-group over 20 s followed by a constant rate infusion of lidocaine of 1 mg/kg/h.

A saline bolus injection of 0.3 ml/kg was administered in the SAL-group over 20 s followed

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by a constant rate infusion of saline of 2 ml/kg/h. All the drugs were diluted with saline to produce a total volume of 0.3 ml/kg for the bolus injection and 2 ml/kg/h for the subsequent infusion administered by an identical calibrated syringe infusion pump (Perfusor Compact; B. Braun, Melsungen, Germany).

All the data were collected in the morning after a 20-min acclimatisation period, in the same quiet room with no windows and constant light conditions.

All the dogs were maintained in that same room for the whole study period in a standing or sitting position without jugular vein or eye compression. The measurements were performed by the same person unaware of which drug had been administered and assistant.

In all the dogs, the IOP, PS, HR and MAP, always in that same order, were measured and recorded 5 min before (baseline) and 2, 5, 10, 20 and 30 min after the administration of the initial bolus followed by a constant rate infusion of all the above-mentioned drugs.

The IOP was measured using applanation tonometry (TonoPen XL; Medtronic, Minneapolis, USA). Prior to the measurement, a new rubber cover was placed and the tonometer was calibrated. In all the dogs, the IOP was measured only on the left eye. Three measurements with a 5% error were averaged and the result recorded. In all the dogs, the PS was measured only in the right eye using a pupilometer (Haab's pupilometer; Merck Sharp & Dohme, Kenilworrth, NJ, USA). The HR was measured by auscultation of the heart sounds over 30 s and multiplied by two. The MAP was measured noninvasively with vital function monitor (Cardel 9401; Midmark, Versailles, USA) by a cuff applied to the front limb, the cuff width was as 40% of the circumference of the limb.

After the measurements, the administration of the analgesics continued, the dogs were induced with general anaesthesia, given another analgetic and the periodontal treatment was started. After introduction to general anesthesia, no data were recorded.

Statistical analysis

To determine the minimum sample size, the IOP parameter was used. For comparison of two means MedCalc (MedCalc, Ostend, Belgium) using $\alpha = 0.05$, $\beta = 0.2$, difference of means = 5 mmHg, standard deviation = 4 mmHg and a ratio of sample sizes = 1.5/1 was applied. The test of the power indicated a minimal number of 14 dogs in each study group and 10 dogs in the control group.

All the data were analysed using InStat v3.06 (GraphPad, San Diego, USA), KyPlot v2.0 Beta 15 (KyensLab, Japan) and Excel 365 (Microsoft, Syracuse, USA). Anderson-Darling and Bartlett's tests were used to confirm the normal distribution of the data and homogeneity of variance, respectively. The data measured at 2, 5, 10, 20 and 30 min were compared to the baseline using an analysis of variance (ANOVA) for repeated measures with a Bonferroni correction. All the variables were compared between the groups at each specific time point using the Steel-Dwass test for multiple comparisons ($P < 0.05$).

RESULTS

A total of 55 dogs, 28 males and 27 females, aged 5.3 ± 3.6 years, and weight 11.4 ± 6.3 kg, were included. No significant differences were noted between the groups with respect to the sex, body weight, age, or measured variables at baseline.

No significant differences were observed in the IOP within or between the groups at any time points.

Relative to the baseline, the PS decreased significantly in the FEN-group at 2 min ($P = 0.039$), 5 min ($P = 0.006$), 10 min ($P = 0.006$), 20 min ($P = 0.001$) and 30 min ($P = 0.003$), respectively (Table 1). In the KET-group, the PS increased significantly at 2 min ($P = 0.025$), 5 min ($P = 0.009$) and 10 min ($P = 0.009$) compared to the baseline. The pupil size was significantly smaller in the FEN-group compared to the KET-group at 2 min ($P = 0.007$), 5 min ($P = 0.001$), 10 min ($P = 0.001$) and 20 min ($P = 0.005$), respectively. Likewise, the PS was significantly smaller in the FEN-group compared to the SAL-group at 5 min ($P = 0.044$), 10 min ($P = 0.032$), 20 min ($P = 0.038$) and 30 min ($P = 0.021$), respectively.

Relative to the baseline, the HR was significantly decreased in the FEN-group at 20 and 30 minutes. The HR in the FEN-group was significantly lower at 30 min compared to the KET-group, and at 2, 10, 20 and 30 min compared to the LID-group. No other significant differences in the measured parameters were observed.

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Table 1. Changes in the intraocular pressure (IOP), pupil size (PS), heart rate (HR) and mean arterial pressures (MAP) in 55 healthy conscious dogs after a fentanyl (FEN-group), ketamine (KET-group), lidocaine (LID-group) or saline (SAL-group) bolus injection followed by a 30-min infusion

Study group	Variable	Time (minutes)					
		Baseline	2	5	10	20	30
FEN-group	IOP (mmHg)	22 ± 4	21 ± 3	22 ± 4	23 ± 4	22 ± 4	22 ± 4
	PS (mm)	5 ± 1	5 ± 1[*‡]	4 ± 1[*‡§]	4 ± 1[*‡§]	4 ± 1[*‡§]	4 ± 1[*§]
	HR (beats/minute)	111 ± 25	91 ± 24[¶]	96 ± 39	91 ± 20[¶]	88 ± 25[*¶]	79 ± 18[*‡¶]
	MAP (mmHg)	120 ± 32	119 ± 32	128 ± 25	135 ± 27	116 ± 24	117 ± 28
KET-group	IOP (mmHg)	21 ± 4	25 ± 4	25 ± 5	25 ± 4	25 ± 4	25 ± 5
	PS (mm)	5 ± 1	6 ± 1[†]	6 ± 1[†]	6 ± 1[†]	5 ± 1	5 ± 1
	HR (beats/minute)	110 ± 23	116 ± 32	120 ± 30	111 ± 30	114 ± 36	117 ± 27
	MAP (mmHg)	121 ± 41	121 ± 32	136 ± 31	130 ± 31	124 ± 26	128 ± 31
LID-group	IOP (mmHg)	22 ± 3	23 ± 4	23 ± 5	24 ± 5	23 ± 5	23 ± 5
	PS (mm)	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1
	HR (beats/minute)	106 ± 18	125 ± 35	121 ± 32	121 ± 22	130 ± 31	116 ± 21
	MAP (mmHg)	127 ± 37	152 ± 41	152 ± 40	143 ± 38	137 ± 34	129 ± 31
SAL-group	IOP (mmHg)	22 ± 4	21 ± 4	22 ± 4	24 ± 5	23 ± 4	21 ± 2
	PS (mm)	5 ± 1	5 ± 1	6 ± 1	6 ± 1	6 ± 1	6 ± 1
	HR (beats/minute)	125 ± 26	119 ± 35	113 ± 34	106 ± 16	110 ± 13	101 ± 23
	MAP (mmHg)	114 ± 15	124 ± 30	133 ± 30	142 ± 43	135 ± 40	132 ± 37

[*]Significant decrease compared to the baseline; [†]Significant increase compared to the baseline; [‡]Significantly lower values compared to the KET-group; [§]Significantly lower values compared to the SAL-group; [¶]Significantly lower values compared to the LID-group; Data are expressed as the mean ± standard deviation

DISCUSSION

The continuous administration of drugs maintains a stable plasma concentration avoiding reactions caused by the re-administration of boluses. In the present study, we did not notice an increase in the IOP with any of the administered drugs.

Mrazova et al. (2018) described significant increases in the IOP at 5 and 10 min after a bolus injection of fentanyl in dogs. However, they used a double dose compared to that used in the present study.

In dogs medicated with fentanyl, we detected a significant decrease in the PS at all the measured times. Pupil constriction has been described after administration of other μ-opioids in dogs (Blaze et al. 2009), which is also consistent with the results of our study. Fentanyl decreases the PS by using either 0.01 mg/kg administered by a single injection, which was recorded by Mrazova et al. (2018) or 0.005 mg/kg followed by 0.005 mg/kg/h within 30 min, which was detected in our study. Surprisingly, we did not find a decrease in the IOP despite a decrease in the PS caused by fentanyl.

The panting, often observed in our dogs, limits the interpretation of the respiratory frequency, therefore, we do not mention it. The changes in the HR observed in both our study and the study of Mrazova et al. (2018) did not affect the IOP. We also did not notice any significant changes in the blood pressure that could affect the IOP.

The increase in the IOP after the ketamine administration has been attributed to an increase in the extraocular muscle tone caused by ketamine (Pierce-Tomlin et al. 2020). In our study, we did not find an increase in the IOP using lower doses than in the previously mentioned studies (Hofmeister et al. 2006a; Kovalcuka et al. 2013). When ketamine at 10 mg/kg was combined with diazepam, there was a transient increase in the IOP (Hofmeister et al. 2006a), when 15 mg/kg was combined with midazolam (Ghaffari et al. 2010), there was no increase in the IOP. We did not detect a significant increase in the IOP after an injection of ketamine

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of 0.6 mg/kg followed by 0.6 mg/kg/h. This fact is probably because we used a very low dose sufficient for a multimodal analgesia, but insufficient to increase the muscle tone.

Similar to the findings of Kovalcuka et al. (2013), we observed an increase in the PS 2, 5 and 10 min after initiation of the ketamine administration. Kovalcuka et al. (2013) also detected an increase in the PS associated with an increase in the IOP. In our study, we only observed a transient increase in the PS without a significant influence on the IOP. However, this fact shows that a transient increase in the PS also occurs at very low ketamine doses.

Compared to Hofmeister et al. (2006b), who describe an increase in the IOP after the administration of lidocaine at a dose of 2 mg/kg, we did not observe any changes in the IOP using a half-dose of lidocaine. Smith et al. (2004) described the systemic intravenous administration of lidocaine at a 1 mg/kg bolus followed by infusion of 1.5 mg/kg/h for pain management during and after cataract surgery. A change in the IOP was not detected. However, the IOP was measured at 3, 6 and 24 h after surgery. Information on IOP fluctuations in the initial 30 min of the lidocaine administration is missing. Moreover, the presented data were influenced by the general anaesthesia. However, a higher dose of lidocaine for the infusion was used, compared to our study, but the results on the minimal impact on the IOP agree with our observations.

The present study is limited to a 30-min data collection period during infusion of only one analgesic in healthy dogs without any eye pathology. A suggestion for further research is the observation of the IOP and PS during a longer infusion duration, use of different co-administered analgesics or administration in dogs with an eye pathology or co-morbidity.

Fentanyl, ketamine or lidocaine administered at the doses studied as a bolus followed by a 30-min infusion seems to cause no effect on the IOP in healthy conscious non-painful dogs without ocular abnormalities. Fentanyl decreased and ketamine transiently increased the PS.

Conflict of interest

The authors declare no conflict of interest.

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