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Effects of fentanyl on intraocular pressure and pupil size in medetomidine-methadone premedicated dogs: a pilot study

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ABSTRACT

Background This is a pilot study to evaluate the effects of fentanyl on intraocular pressure (IOP) and pupil size (PS) in dogs premedicated with medetomidine and methadone.

Methods Sixteen dogs with a median (first quartile–third quartile) age of 3.5 (1.25–6) years and a mean (sd) weight of 18.6 (9.2) kg were included. Baseline readings of IOP and PS were recorded before all dogs were premedicated intramuscularly with medetomidine (10 µg/kg) and methadone (0.5 mg/kg). Both measurements were repeated 15 and 30 minutes later. Following this, the dogs were randomly assigned into two groups. The fentanyl group received intravenous fentanyl (10 µg/kg), while the control group received the same volume of saline solution intravenously. IOP and PS measurements were measured and recorded in both groups at one, five and ten minutes after intravenous injection. Data were analysed with one-way and two-way repeated-measures analysis of variance or their non-parametric equivalents.

Results PS was significantly decreased 15 and 30 minutes following intramuscular premedication and IOP was significantly increased in the fentanyl group at all time points following intravenous administration.

Conclusions Medetomidine, methadone and fentanyl combinations are not recommended for use in patients where an increase in IOP or decrease in PS is undesirable.

INTRODUCTION

Intraocular pressure (IOP) is determined by intraocular fluid (aqueous humour) volume, choroidal blood volume, vitreous humour volume, scleral rigidity and elasticity, extraocular muscle tone, and external pressure. IOP is maintained by a balance between the production and the outflow of aqueous humour.[1] At the same time, pupil size (PS) can affect IOP. Miosis reduces IOP by increasing aqueous humour drainage, while mydriasis can increase IOP by narrowing the iridocorneal angle.[2]

It is essential that the effects on ocular variables are taken into consideration when choosing an anaesthetic protocol for ophthalmic surgery or examination. Sudden increases in IOP during the whole perianaesthetic period can have disastrous effects on patients with certain ocular pathologies, such as deep corneal ulcers or glaucoma. An increase in IOP in a patient with a deep corneal ulcer could result in rupture of the globe or prolapse of extraocular structures.[3] Additionally, even slight increases in IOP can decrease axoplasmic flow in the optic nerve of animals with glaucoma, predisposing them to additional injuries.[4] Similarly, PS is important in some ophthalmic diagnostics and surgeries such as electroretinography and phacoemulsification, where mydriasis is mandatory.[5]

Medetomidine is an α_2 adrenergic agonist, and the predominant anaesthetic effects are sedation, anxiolysis, analgesia and dose-dependent relaxation of muscles.[6] In previous studies it has been reported that the administration of medetomidine intravenously decreases IOP and produces miosis.[7 8] Methadone and fentanyl are µ-opioids. These are very efficacious analgesic drugs available to control pain and contribute to sedation in small animals.[9] The effect of fentanyl on IOP has been described by other authors. A significant increase in IOP was found after administration of a bolus of fentanyl.[10] In contrast, a recent study found that the administration of a lower dose of fentanyl followed by an infusion resulted in no change in IOP.[11] The effects on IOP might be inconsistent when a combination of α_2 adrenergic agonists and opioids is used.[12 13]

The objective of this study was to evaluate the effects of fentanyl on IOP and PS in healthy dogs following administration of medetomidine-methadone. To the authors' knowledge, the effects of such a combination on IOP and PS have not been assessed. The authors hypothesised that medetomidine-methadone would decrease IOP and PS and

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fentanyl would result in persistence of decreased IOP and miosis.

MATERIALS AND METHODS

Animals

A total of 16 healthy dogs referred from a municipal animal shelter for castration and ovariohysterectomy were included in the study. Informed consent was obtained from the responsible individual of the municipal animal shelter.

The day before the study, all animals received an ophthalmic examination by a veterinarian blinded to the treatment group assignment. Ophthalmic examination included a Schirmer tear test I (Schering-Plough, Animal Health, New Jersey, USA), fluorescein staining (Bausch and Lomb Pharmaceuticals, Florida, USA), IOP (Tonopen XL, Mentor, Massachusetts, USA) and indirect ophthalmoscopy (Vantage Plus, Keeler, UK) after tropicamide (Colircusí Tropicamide, Alcon-Cusi Laboratories, Spain). All dogs also underwent preanaesthetic physical examination and blood analysis (haematology and biochemistry). Any dogs with abnormalities detected in either the preanaesthetic or ophthalmic examination and brachycephalic mixed breeds were excluded from this study; therefore, only American Society of Anesthesiologists (ASA) I animals with normal eyes were included.

Study protocol

Dogs had free access to water, but food was withheld for 12 hours before the experiment. In the first part of the study, and following initial readings (T0) of IOP and PS, all dogs (N=16) were administered intramuscular medetomidine (10 µg/kg) (Domtor, Dr Esteve SA Laboratories, Spain) and methadone (0.5 mg/kg) (Metasedin, Dr Esteve SA Laboratories). Both measurements were repeated 15 minutes (T15) and 30 minutes (T30) later. Twenty minutes after premedication with medetomidine-methadone, a 20G peripheral intravenous cannula (Becton Dickinson Infusion Therapy Systems, USA) was placed in a cephalic vein.

In the second part of the study, the dogs were randomly assigned to one of two groups of equal sample size using a computer-generated randomisation program (www.randomizer.org). The fentanyl group received an intravenous bolus of fentanyl (10 µg/kg) (Fentanest, Kern Pharma SL, Spain) 30 minutes after premedication, while the control group received the same volume of saline solution intravenously in order to differentiate from the possible influence of medetomidine-methadone over time on IOP and PS. Measurements (PS and IOP) were taken in both groups one minute (Tt1), five minutes (Tt5) and ten minutes (Tt10) after the administration of fentanyl or saline solution.

Measurements

Heart rate (HR) in beats per minute, respiratory rate (f_R) in breaths per minute, mean, systolic and diastolic non-invasive blood pressure (MAP, SAP, DAP) in mmHg with the cuff located on the metatarsal region, and rectal temperature (T) in °C were monitored with a multiparameter monitoring system (Datex-Ohmeda F-CM1-05, GE Healthcare, Helsinki, Finland).

IOP was measured in both eyes using an applanation tonometer (Tonopen XL, Mentor). Before each measurement the tonometer was calibrated, the probe was changed and topical local anaesthetic was applied to the cornea every 20 minutes (Tetracaine Hydrochloride 0.5%, Colircusi Anestésico Doble, Alcon-Cusi Laboratories). PS was measured using a Castroviejo calliper lightly touching the cornea with an accuracy of ±0.5 mm (Aesculap, Pennsylvania, USA).

All measurements were obtained and recorded by the same person who was blinded to the treatment group assignment. Measurements were taken in the morning and in the same room with artificial lights of 25 cd/m^2 measured at the level of the dog's eyes (Digital Lux YF-1065 tester, France).

The dogs were restrained in sternal recumbency and carefully handled to avoid pressure on the globe, jugular veins or eyelids.[14] The IOP reported was the mean for both eyes with three readings for each and only values with less than 5 per cent sd were considered, which were calculated directly by the tonometer. After all the required data were collected, gonioscopy (Goldmann lens, Lynnwood, Washington) was performed to complete the ophthalmic examination, and anaesthesia was induced with propofol and continued as appropriate in order to carry out the surgery.

Statistical analysis

All data were analysed using SigmaStat for Windows V.3.1 (Systat Software, Continous Quality, USA) and SPSS for Windows V.22 (SPSS, South, Illinois, USA). Normality of data was assessed using graphs and Shapiro-Wilk test. If the distribution was approximately normal, data were reported as mean (sd). However, if the distribution was not normal, data were reported as median (first quartile (Q1)–third quartile (Q3)). Age, weight, IOP, PS, SAP, MAP, DAP, HR, f_R and T at baseline (T0) were compared between groups with Student's *t* test for independent samples.

To assess differences in the variables between the times (T0, T15 and T30) after medetomidine-methadone administration, an analysis of variance (ANOVA) for repeated measures was carried out if the data were normally distributed. However, the Friedman test was used if the data were not normal. If significant differences were found between the times, an analysis was carried out to find the specific times where the differences existed. Consequently, three comparisons were carried out for each variable where differences were detected. Bonferroni multiple comparisons adjusted test or Wilcoxon test with corrections of significance for paired data were performed for normal and non-normal data distribution, respectively. For Bonferroni multiple comparisons, the adjusted Bonferroni P values were calculated and

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Table 1 IOP, PS and other variables measured before premedication intramuscularly (T0), then 15 (T15) and 30 (T30) minutes following premedication in 16 dogs

Variable time point (minutes)	T0	T15	T30
IOP (mmHg)	18.9 (4.3)	19.5 (3.2)	18.6 (4)
PS (mm)	8 (7–10)	3 (3–4.8) (P<0.0001)	2.5 (2–3.8) (P<0.0001)
SAP (mmHg)	148.7 (39.5)	147.9 (28.0)	138.0 (19.0)
MAP (mmHg)	108.4 (24.0)	111.6 (21.8)	106.5 (13.8)
DAP (mmHg)	94.1 (36.8)	89.4 (20.6)	85.4 (14.3)
HR (beats per minute)	116 (31)	58 (31) (P^b=0.001)	41 (10) (P^b<0.0001)
f_R (breaths per minute)	38 (11)	21 (7) (P^b<0.0001)	18 (7) (P^b<0.0001)
T (°C)	38.8 (0.6)	38.9 (0.6)	38.6 (0.5)

Data are given as mean (sd) if the distribution was normal or as median (first quartile–third quartile) if the distribution was not normal.
P values refer to significant differences with respect to those obtained at T0. For multiple comparisons in the case of PS, P<0.017 is considered significant. In the rest of the multiple comparisons, P^b denotes P value adjusted by Bonferroni correction, where P^b<0.05 is considered significant.
DAP, diastolic non-invasive blood pressure; f_R, respiratory rate; HR, heart rate; IOP, intraocular pressure; MAP, mean non-invasive blood pressure; PS, pupil size; SAP, systolic non-invasive blood pressure; T, temperature.

compared directly with P=0.05, considering P<0.05 as significant. However, in the case of the Wilcoxon test, P<0.017 was considered significant.

After the administration of fentanyl or saline in the groups, a two-way ANOVA test with repeated measures in one factor was used to compare the groups. If differences were detected between the groups, Bonferroni multiple comparisons test was carried out. PS was analysed in a single Mann-Whitney U test considering P<0.05 as significant. For Bonferroni multiple comparisons the adjusted Bonferroni P values were calculated and compared directly with P=0.05, considering P<0.05 to be significant.

RESULTS

A total of 16 dogs were assessed in this study, five males and 11 females of mixed breed, with a median age of 3.5 (1.25–6) years old and a mean bodyweight of 18.6 (9.2) kg. The fentanyl group consisted of eight dogs (six females and two males) aged 4.1 (2.7) years old with a weight of 16.9 (9) kg. The control group consisted of eight dogs (six females and two males) aged 3.8 (3) years old with a weight of 20.3 (9.7) kg. There were no significant differences in age, weight, IOP, PS, SAP, MAP, DAP, HR, f_R and T between groups at T0. Dysphoria was noted in some dogs following fentanyl administration. The variables measured at different time points are presented in tables 1 and 2 and the results are summarised in the following sections.

Intraocular pressure

No statistically significant differences were found in dogs following medetomidine-methadone administration (N=16) at T15 or at T30 compared with T0 values.

A statistically significant increase in IOP was observed in the fentanyl group at all times studied, Tt1, Tt5 and Tt10, in comparison with the control group.

Pupil size

After medetomidine-methadone administration, PS decreased significantly at T15 and at T30 compared with T0. Furthermore, a significant decrease was found between T15 and T30. Nevertheless, no significant differences in PS were found between the fentanyl group and the control group at any time point.

Cardiovascular variables, f_R and temperature

After medetomidine-methadone administration a significant decrease in HR was observed at T15 and at T30 compared with T0. Furthermore, a significant decrease was found in f_R at T15 and at T30 compared with T0, along with significant differences between T15 and T30.

Other variables measured remained unchanged (MAP, SAP, DAP and T) at all time points.

No significant differences were observed in any measured variables (MAP, SAP, DAP, HR, f_R and T) at any time point (Tt1, Tt5 and Tt10) between the groups.

DISCUSSION

This pilot study is the first to investigate the effects of medetomidine-methadone and later fentanyl administration on IOP and PS. Indeed, the study confirmed the authors' hypothesis about the effects of medetomidine-methadone, but the effect of fentanyl on IOP was unexpected. Medetomidine is an α_2 adrenergic agonist that reduces IOP in some species. Complex mechanisms have been proposed to explain the effects of α_2 adrenergic agonists in IOP modulation; the aqueous generation is attenuated by the suppression of noradrenaline release due to the stimulation of presynaptic α_2 receptors; likewise, ciliary vasoconstriction is produced when the postsynaptic α_2 receptors are activated, reducing the ciliary blood flow, and adenylate cyclase is inhibited by the stimulation of the postsynaptic epithelial α_2 receptors.[12 13] Pathology of the iridocorneal angle significantly affects IOP and PS. Therefore, this study only included animals with normal iridocorneal angle.[15]

Other authors have obtained similar results to this study regarding the use of medetomidine in healthy dogs. Several studies demonstrate that no changes in IOP were observed with medetomidine using doses of 45–100 µg/kg intravenously[7] or doses of up to 80 µg/kg intramuscularly.[8] Another study observed no change in IOP even at doses as low as 10 µg/kg of medetomidine intravenously.[10] Furthermore, other authors demonstrated that

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Table 2 IOP, PS and other variables measured at one (Tt1), five (Tt5) and ten (Tt10) minutes after intravenous administration of fentanyl (fentanyl group) or saline (control group)

		Time point (minutes)		
Variable	**Group**	**Tt1**	**Tt5**	**Tt10**
IOP (mmHg)	Control	19.0 (3.3)	18.1 (2.6)	17.5 (3.6)
	Fentanyl	21.7 (4.0) (P^b=0.048)	21.9 (3.2) (P^b=0.001)	22.9 (3.2) (P^b<0.0001)
PS (mm)	Control	2.5 (2–4)	3 (2–3.8)	3 (2–4.8)
	Fentanyl	2.5 (1.6–3)	3 (1.3–3)	2.5 (1.3–3)
SAP (mmHg)	Control	139.4 (19.5)	130.4 (27.3)	125.4 (17.1)
	Fentanyl	133.3 (17.2)	131.9 (20.3)	130 (18.3)
MAP (mmHg)	Control	106.8 (13.6)	94.6 (22.6)	94.0 (15.3)
	Fentanyl	101.6 (16.9)	101 (16.2)	97.3 (14.3)
DAP (mmHg)	Control	86.8 (12.8)	74.3 (20.4)	74.3 (14.8)
	Fentanyl	81.4 (17)	81.3 (13.7)	77.5 (13.3)
HR (beats per minute)	Control	64 (23)	60 (20)	54 (32)
	Fentanyl	50 (12)	41 (13)	50 (21)
f_R (breaths per minute)	Control	18 (9)	17 (6)	19 (6)
	Fentanyl	16 (7)	29 (41)	52 (59)
T (°C)	Control	38.7 (0.4)	38.3 (0.7)	38.2 (0.8)
	Fentanyl	38.5 (0.7)	38.2 (0.8)	38.3 (0.8)

Data are given as mean (sd) if the distribution was normal or as median (first quartile–third quartile) if the distribution was not normal. Comparisons were performed between groups at Tt1, Tt5 and Tt10. P^b denotes P value adjusted by Bonferroni correction, where P^b<0.05 is considered significant.
DAP, diastolic non-invasive blood pressure; f_R, respiratory rate; HR, heart rate; IOP, intraocular pressure; MAP, mean non-invasive blood pressure; PS, pupil size; SAP, systolic non-invasive blood pressure; T, temperature.

using 2 µg/kg of dexmedetomidine intramuscularly did not increase IOP.[16] One of the described premedication protocols combined dexmedetomidine with hydromorphone intramuscularly and the overall effect on IOP was minimal.[16] In the same way, it has been shown that a lower dose of dexmedetomidine (2 µg/kg) intravenously did not change IOP over time, which is similar to the results of the present study.[17] As the protocol in this study combined medetomidine and methadone, these drugs could not be evaluated separately nor could the findings be directly compared with previously published studies.

In this pilot study, the increase in IOP was observed at all time points following fentanyl administration. This finding matches the results in a previous study where the effect of fentanyl (10 µg/kg) on IOP was described as a unique agent.[10] In contrast, a different study found that the administration of a lower dose of fentanyl (5 µg/kg) intravenously followed by an infusion resulted in no change in IOP.[11] The increase in IOP observed could be due to a state of dysphoria as a result of adverse effects following fentanyl administration. This is a possibility because fentanyl has a high affinity for µ-receptors, but it also affects kappa and sigma receptors which can cause a state of dysphoria.[18] Dysphoria could prevent the extraocular muscles and external structures of the eye from relaxing adequately, resulting in an increase in IOP rather than a decrease. Despite differences in study design, another demonstrated that 23.9 per cent of dogs that received intraoperative fentanyl infusions developed a state of dysphoria.[19] Respiratory depression following fentanyl administration could also contribute to an increase in IOP. In fact, the production and outflow of aqueous humour can be affected by changes in pO_2[20] and pCO_2 in arterial blood.[21] It is well known that opioids in general, and especially fentanyl, result in some respiratory depression, causing pCO_2 levels to rise.[22] However, the data in this pilot study cannot confirm this statement because other variables such as pO_2 and pCO_2 were not recorded. Hypoventilation and hypercapnia could have played an important role in the IOP alterations.

In this study, the use of medetomidine-methadone resulted in a significant reduction in PS. The results match those of previous studies.[7 10 17] To date, there are no reports that fully explain the miosis mechanism caused by α_2 adrenergic agonists in dogs. Methadone and fentanyl are µ-opioid agonists which affect opioid receptors, stimulating the parasympathetic nervous system and causing miosis via the iris sphincter muscle.[23] The authors believe that medetomidine and methadone could have worked additively to cause miosis in this study.

This pilot study has some limitations which should be considered in future research. First is the small sample size per group (n=8); however, despite this, it has been enough to achieve statistically significant differences in

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IOP between groups. The authors believe that an increase in the sample size would lead to the same conclusions, but future studies with a larger sample size are needed to confirm this and provide more powerful evidence of this pilot study's results. Secondly, the sedation level was not evaluated using a proper sedative scale in this study, which is an important consideration for future studies to evaluate the effects of the drugs given in order to reduce individual variability. Thirdly, pO_2 and pCO_2 were not measured, which is an important limitation to this pilot study because respiratory depression could possibly explain the effect of fentanyl on IOP. These variables may be interesting to evaluate in future studies in order to find possible implications of arterial or venous gasometry in IOP. In cases where invasive measures are not possible, pulse oximetry could also provide information about the real grade of respiratory depression. Furthermore, the effect of fentanyl on IOP could be affected by the previous administration of medetomidine-methadone. To evaluate the real effect of fentanyl in future studies, previous administration of other drugs should be avoided. Additionally, it is worth mentioning that a different dose of fentanyl could produce different effects, so further investigation to compare different dosages is recommended. Finally, the calculations based in µg/kg in a patient population with an sd of 9.2 kg could have led to overdose or underdose in some individuals. To improve accuracy, dosage should have been based on body surface area in g/m^2, although to the authors' knowledge this is not clinically significant.

CONCLUSION

The intramuscular administration of medetomidine (10 µg/kg) and methadone (0.5 mg/kg) caused a significant decrease in PS of healthy dogs.

IOP values remained within the normal physiological range, but the administration of intravenous fentanyl (10 µg/kg) caused a statistically significant increase in this variable compared with the control group. These findings suggest that premedication with medetomidine and methadone followed by fentanyl administration is not recommended in patients where an increase in IOP or a decrease in PS is undesirable.

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