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The Effects of Premedication with Methadone on Intraocular Pressure in Dogs and Cats

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Abstract

Background: The effects of premedication agents on the ocular physiology should be thoroughly understood by the ophthalmic surgeon so that Intraocular Pressure (IOP) values are kept stable. The purpose of this study was to determine the effects of methadone as a solo-agent of anesthetic premedication on IOP in healthy dogs and cats.

The study group included 60 clinically healthy patients, 40 dogs and 20 cats. Ophthalmological examination, including baseline IOP (T0) of the subjects, was performed before methadone administration at a dosage of 0.2 mg kg^{-1}. IOP variations were registered fifteen (T15) and thirty (T30) minutes later. IOP values were compared at each specific time point (T0, T15 and T30) using a repeated-measures Analysis of Variance (ANOVA) and differences were considered significant when $P<0.05$.

Results: The mean ± SD baseline (T0) and post-treatment (T15, T30) IOP values were, respectively, 16.8 ± 3.84 mmHg, 17.6 ± 3.01 mmHg and 16.1 ± 3.28 mmHg for dogs and 17.1 ± 3.31 mmHg, 16.6 ± 3.40 mmHg and 16.61 ± 2.81 for cats. There were no statistically significant differences between baseline and post-treatment values in dogs ($p=0.107$) or cats ($p=0.077$). The sedative effect of methadone did not affect the ocular globe or nictitating membrane position nor the menace response, dazzle reflex, corneal blink reflex or palpebral reflexes in any case. None of the animals studied presented with the secondary effects associated with opioids such as salivation, nausea, vomit, defecation, dysphoria or a clear modification of the respiratory pattern.

Conclusion: The administration of methadone as a solo-agent of anesthetic premedication at a dosage of 0.2 mg kg-1 did not cause significant changes on IOP values in dogs or cats. Methadone presented as a safe alternative for sedation, anesthetic premedication or analgesia in ophthalmological patients since it did not interfere with IOP regulation.

Keywords: Methadone; Premedication; Intraocular pressure; Ophthalmology

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Background

Animals with a suspected or confirmed uveitis or glaucoma diagnosis that are presented for ophthalmic surgery may represent a challenge due to the premedication and anesthetic drugs effects on IOP. Other severe ocular conditions in which a complete rupture of the globe integrity is at stake, such as descemetoceles, deep corneal ulcers or trauma, should also benefit from a careful selection of sedative/anesthetic agents regarding IOP changes. Anesthetic management should be aimed at minimizing changes in IOP over the entire anesthesia period in both ophthalmic and non-ophthalmic surgeries [1].

Presently, one of the most commonly used pre-anesthetic agents' categories are opioids. The most important advantages of the use of opioids are the potent analgesia and sedation they provide without direct myocardial depression, although they do depress the medullary respiratory control centers which can lead to a decreased responsiveness to high carbon dioxide levels and, in return, to hypoventilation [2]. One frequently used drug nowadays for premedication and analgesia in small animal clinics is methadone [2].

Methadone has a slightly higher affinity for the μ-opioid receptors than morphine and is also antagonist at the N-methyl-D-aspartate receptors as well as norepinephrine and a serotonin uptake inhibitor [3]. The appropriate routes for its administration in cats and dogs are intravenous,

intramuscular and subcutaneous and, unlike morphine, methadone rarely induces emesis, which can be of value in patients with increased intraocular or intracranial pressure [3].

Adverse effects reported with morphine such as nausea, vomiting, defecation, and dysphoria have not been reported with methadone [4]. Apart from the prominent sedation, a dose-dependent respiratory depression can occur but it is typically clinically insignificant within the appropriate dosages of 0.1 mg/kg to 0.5 mg/kg in dogs [5].

The recommended methadone dosage for intravenous administration in cats is not consensual, ranging from 0.2 mg/kg to 0.4 mg/kg [5] and 0.1 mg/kg to 0.3 mg/kg [6], this drug appearing to cause less excitation or vomiting comparing to other μ agonists [6].

The main answer sought in this work is to discover if methadone may represent an adequate alternative as an anesthetic premedication when it comes to intraocular surgery or in the need of sedation or analgesia of ophthalmological patients, if no interference in IOP can be proven, since a good anesthetic management should avoid any major changes fluctuations in IOP values in order to minimize any potential ocular side effects. To the authors' knowledge, the effects of methadone on IOP in dogs and cats have not been assessed yet.

Methods

Subject population

A prospective cohort study comprising 40 client-owned dogs and 20 cats, admitted at the teaching hospital of the faculty of veterinary medicine of Lisbon University, was conducted. All the animals were admitted for elective surgery and underwent a complete physical and ophthalmological examination before the drug administration.

This study was approved by the Ethics Committee of the Faculty of Veterinary Medicine, University of Lisbon and owners gave informed consent for the use of clinical data related to their animals. All methods were carried out in accordance with institutional relevant guidelines and regulations.

Inclusion criteria

All the patients included in the study had a normal physical examination, normal CBC profile and biochemistry analysis (kidney and liver parameters) and also a completely normal ophthalmic examination, including Schirmer tear test, IOP levels biomicroscopy, fluorescein staining, direct and indirect ophthalmoscopy. IOP pressures were considered normal when the values were between 10 mmHg to 20 mmHg for both dogs and cats [7]. Water and food were withdrawn 8 h before admission.

Drug administration and IOP measurements

The basal IOP for all patients was registered at admission and before any type of manipulation or restraint or drop topical administration (T0). IOP values were measured using a rebound tonometer (Icare TonoVet®, Helsinki, Finland) with each animal being positioned in a sitting position or in sternal recumbency, without e-collars and with the head maintained relaxed at thorax level (Figure 1).

After that, dogs were catheterized either in the cephalic vein on the forelimb or in the lateral saphenous veins on the hindlimb, using a fixation wings intravenous catheter (Braun Introcan Safety® W) and intravenous administration of methadone (Semfortan® 10 mg/ml, Dechra Veterinary Products, Barcelona, Spain) at the 0.2 mg/kg dosage was performed. The same dosage was administered by intramuscular route in cats, according to the adopted protocol at our Hospital.

IOP values were then measured fifteen (T15) and thirty (T30) minutes after the drug administration, separately from each eye. The final result for each individual time point considered in the statistical analysis was the mean of three consecutive values obtained for each eye. All the measurements were obtained during the morning period, between 9 and 10 a.m.

Statistical data analysis

The data was collected and registered using Microsoft Office Excel (Microsoft Office® 2011 for Mac) and, for all variables, mean and standard deviations were calculated. IOP values were compared between eyes with a paired *t*-test and also at each specific time point (T0, T15 and T30) using a repeated-measures Analysis of Variance (ANOVA). The differences were considered significant when $p<0.05$.

Results

The group of 60 animals (120 eyes) studied included 40 dogs (21 males and 19 females) and 20 cats (9 males and 11 females). The mean age corresponded to 8.2 ± 3.65 years in dogs and 8.1 ± 4.38 years in cats.

The dogs' breeds corresponded to 20, including mongrel (8/40), Maltese Dog (4/40), Yorkshire Terrier (4/40), German Shepherd Dog (3/40), French Bulldog (3/40), Poodle (2/40), Portuguese Podengo (2/40), Pit Bull (2/40), Rottweiler (1/40), Jack Russel Terrier (1/40), Cocker Spaniel (1/40), Boxer (1/40), Great Dane (1/40), German Spitz (1/40), West Highland White Terrier (1/40), Basset Hound (1/40), Staffordshire Terrier (1/40), Pointer (1/40), Fox Terrier (1/40) and Weimaraner (1/40).

The cats' breeds included European Shorthair (14/20), Persian (4/20), British Shorthair (1/20) and Siamese (1/20).

IOP measurement results

In the canine group, the mean IOP values at baseline (T0) and post-treatment periods (T15, T30) were, respectively, 16.8 ± 3.84 mmHg, 17.6 ± 3.01 mmHg and 16.1 ± 3.28 mmHg while in the feline group they were, respectively, 17.1 ± 3.31 mmHg, 16.6 ± 3.40 mmHg and 16.6 ± 2.81 mmHg. There were no statistically significant differences between baseline values and post-treatment values neither in T15 nor in T30, either in dogs ($p=0.107$) or in cats ($p=0.070$). Also, there were no statistically ($p=0.267$) nor clinically significant differences between the left and right eye of each animal. The mean IOP values obtained from the 40 dogs and from the 20 cats (120 eyes)

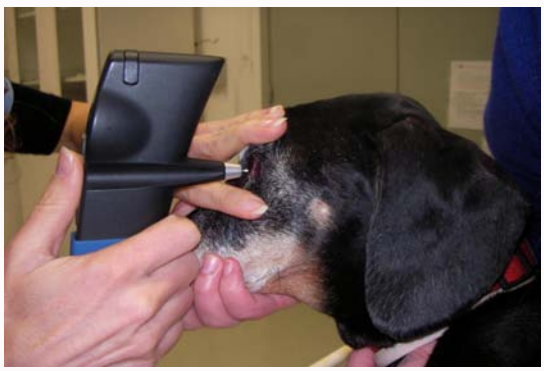

Figure 1: Measurement of IOP levels with the Icare® tonometer in a dog. The animal is positioned in sternal recumbency, with the head maintained relaxed at torax level, no pressure being applied over the eyelids.

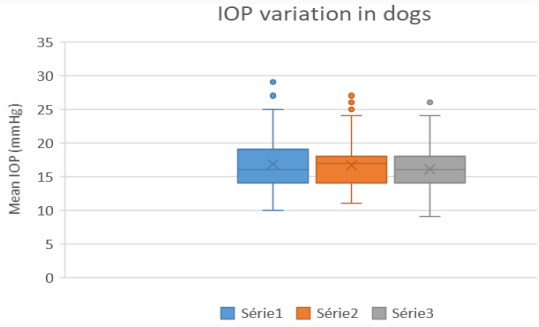

Figure 2: Variations of mean IOP and standard deviation in 40 dogs sedated with methadone. IOP means are represented by the boxes and respective standard deviations given by the lines extended vertically from the mean boxes. Series 1 corresponds to T0, series 2 to T15 and series 3 to T30.

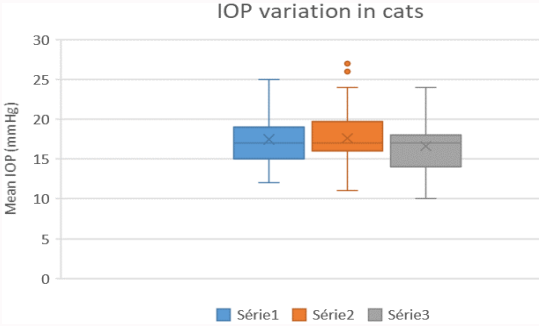

Figure 3: Variations of mean IOP and standard deviation in 20 cats sedated with methadone. IOP means are represented by the boxes and respective standard deviations given by the lines extended vertically from the mean boxes. Series 1 corresponds to T0, series 2 to T15 and series 3 to T30.

examined during the study at the three moments of examination are displayed graphically (Figure 2, 3).

The sedative effect of methadone did not affect the ocular globe or nictitating membrane position nor the menace response, dazzle reflex, corneal blink reflex or palpebral reflexes in any case. None of the animals studied presented with the secondary effects associated with opioids such as salivation, nausea, vomit, defecation, dysphoria or a clear modification of the respiratory pattern.

Discussion

IOP is determined by aqueous humor volume, choroidal blood volume, vitreous humor volume, scleral rigidity and elasticity, extraocular muscle tone, and external pressure. IOP is maintained by a balance between production and outflow of aqueous humor [8]. It is essential that the effects on ocular pressure are taken into consideration when choosing an anesthetic protocol for ophthalmic surgery or examination. Sudden changes in IOP during the whole perianesthetic period can have disastrous effects on patients with certain ocular diseases, such as deep corneal ulcers or glaucoma [9].

Sedation may be of extreme value as an adjunct to manual restraint to ease the handling of veterinary patients, and also to reduce anxiety associated with ophthalmic examination. Ocular pain, when severe enough to prevent a thorough ophthalmic examination or when present due to ocular disease, should also be minimized with analgesics. For these reasons, the need for understanding the effects on intraocular pressure of opioids on behalf of animals suffering from ophthalmic diseases or animals undergoing intraocular surgery is of paramount importance.

Preanesthetic agents can be useful to reduce stress and anxiety, to facilitate restraint; decrease the dose requirement of potentially more dangerous drugs used in general anesthesia, to smooth the induction phase, to enhance perioperative analgesia, and to reduce arrhythmogenic autonomic reflex activity [10]. Presently, one of the most common sedative/preanesthetic/analgesic agents' categories is opioids. This class of drugs has very few negative effects on haemodynamics. The stimulation of the vagus nerve may cause a decrease in heart rate which can be managed by co-administration of an anticholinergic agent, if necessary [10]. Most opioids have minimal effects on cardiac output in dogs, except for methadone, which may produce more consistent decreases. The choice and dosage of the appropriate opioid depends upon the anticipated level of pain caused by the lesion and/or procedure and its duration [10].

The purpose of this study was to determine the effects of methadone on IOP values in dogs and cats, as a solo agent of sedation, analgesia or anesthetic premedication. The selection of this particular opioid was due to the fact that presently it is the most commonly used drug for sedation and pre-medication protocols at our Hospital and for being an effective analgesic agent both in dogs and cats, even superior to butorphanol in the latter species [11]. Methadone, when used alone, produces minimal sedation [10], but for ophthalmic diagnostic procedures such as electroretinographies, the authors still find the level of sedation appropriate. Its combination with acepromazine can provide a powerful sedation, similar to morphine in dogs [10]. Apart from methadone, no other drugs were administered before all IOP measurements were collected. However, in some dogs, acepromazine was administered after T30 due to the need of a more profound sedation [12].

According to our results, no significant changes in IOP values were detected after premedication with methadone in clinically normal dogs or cats. This could be due to the low administered dosage. The presence of opiate receptors has previously been documented in the iris of rabbits and man, and the intraocular injection of morphine was reported to induce a significant decrease in the pupillary size of conscious rabbits as well as a pupillary constriction after a morphine conjunctival instillation in man [13]. Drugs with sympathetic or parasympathetic actions may alter IOP due to their effects on aqueous humor formation, intraocular blood volume and vascular resistance and/or extraocular muscle tone the different drugs used to tranquilize, sedate and/or anaesthetize patients may affect IOP directly by influencing the dynamics of the aqueous humor, or indirectly if hypercapnia or hypoxemia occurs or if changes in extraocular muscle tone are caused. Sedatives, tranquilizers, and anesthetic drugs tend to cause lowered IOP readings, probably because of reduced extraocular and adnexal muscle tone, while ketamine may cause a slightly elevated IOP reading [7]. The mechanisms by which most opioids lower intraocular pressure or may increase aqueous outflow drainage are still unknown, but hypothesis such as changes in the permeability of iris vessels or the inhibition of aqueous humor production at the ciliary body are the ones considered.

IOP can be measured through paracentesis of the anterior chamber which, due to its invasiveness, is highly impractical in clinical practice [14]. All of the currently available tonometers do not actually measure IOP directly but evaluate physical properties of the cornea and use them to estimate true IOP [14]. Rebound tonometry was used in this study. The tonometer Tonovet® creates a magnetic

field ejecting a small probe at a fixed distance from the cornea and, after it reaches the cornea surface, it returns to the instrument. The instrument assesses the probe deceleration (rebound), which allows for the conclusion that eyes with a higher IOP cause a more rapid deceleration of the probe and shorter return time of the instrument than those with a lower IOP [14].

An altered ocular surface tension as seen with the application of topical medications (including topical anesthesia) can affect the results obtained with rebound tonometry. For this reason, this technique should be performed before the application of such medications [7]. With the method described, it is extremely important to perform a careful restraint of the patient to prevent an IOP overestimation, avoiding an excessive compression both of the neck, where the jugular veins are located, and around the periocular area when retracting the eyelids [7]. It is also advisable to obtain more than one IOP measurement and, if possible, at different periods of the day. We obtained three different measurements for each eye and for each time point to decrease errors. We elected the morning period in order to obtain the values after patient admission for surgery and to decrease variability in IOP due to the circadian rhythm [15,16].

Comparison of IOP between both eyes of the same animal is always critical for achieving a correct diagnosis, and the variation should not exceed 20% [8]. A low or high IOP should not be the only diagnostic criteria for uveitis or glaucoma, respectively, the patient requiring assessment for other signs compatible with those diagnoses [7].

One study limitation is the fact that the sedative effects of opioids, in this case methadone may differ significantly depending on the animal's breed, character and level of excitement or aggressiveness, and our study could have been implemented with a sedation assessment. Another study limitation is the lack of higher dose studies and additional measurements latter in time, but the patients' diagnostic or surgical procedures had to be performed while the patients were under the drug's effect.

Conclusion

The present study has shown that administration of 0.2 mg/kg of methadone did not appear to significantly affect IOP levels neither in dogs nor in cats. The awareness of the effects of methadone in IOP regulation is important when considering its possible use not only before intraocular surgeries but also as an analgesic drug during the post-operative period or as a unique sedative agent before examinations in animals with ophthalmic conditions.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Authors' Contribution

MN and ED designed the study and collected the patient data. AS performed the statistical analysis. ED and MN interpreted the results and were major contributors in writing the manuscript. ED, AS and MN read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Faculty of Veterinary Medicine, University of Lisbon, and owners gave informed consent for the use of clinical data related to their animals.

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