Arq. Bras. Med. Vet. Zootec., **v.76, n.6, e13111, 2024**

http://dx.doi.org/10.1590/1678-4162-13111
Original Article - Veterinary Medicine

Effects of robenacoxib on the minimum alveolar concentration of isofluorane in domestic felines

[*Efeitos do robenacoxibe na concentração alveolar mínima do isofluorano em felinos domésticos*]

L. *Rosa*, A. *Rakoski*, L. *Rocha*, S. *Ronchi*, N. *Oleskovicz*

Universidade do Estado de Santa Catarina, UDES, Lages, SC, Brasil

ABSTRACT

Robenacoxib is a selective non-steroidal anti-inflammatory drug indicated for pain control in felines. The objective was to evaluate the effect of robenacoxib on the minimum alveolar concentration of isoflurane in cats. There were 30 cats that used one of the 3 treatments through therapy: GM – meloxicam (0.2 mg/kg), GR – robenacoxib (2 mg/kg) or GC – 0.9% saline solution (0.1 ml/kg) kg). We waited 30 minutes, and the animals were induced to general anesthesia with isoflurane in an induction box, intubated and anesthetized with 1.5 V% isoflurane. All animals were secured to a supramaximal nociceptive stimulus (tail pinch). Positive response was defined as proposed movement of the head and/or limbs. The method for determining MAC was up and down to Dixon, and calculation of the average of crossover values according to Monteiro (2016). The mean and standard deviation of ISO_{MAC} was 2.10±0.15%, 1.95±0.14%, and 1.7±0.15% in GC, GM, and GR, respectively. Robenacoxib reduced to 19.1% and 12.8% ISO_{MAC} when compared to a control group and a group that received meloxicam, respectively.

Keywords: cats, robenacoxib, CAM, NSAIDs

RESUMO

Robenacoxibe é um anti-inflamatório não esteroidal seletivo, indicado para controle de dor em felinos. Objetivou-se avaliar o efeito do robenacoxibe sobre a concentração alveolar mínima do isoflurano em gatas. Foram utilizadas 30 gatas, que receberam um dos três tratamentos pela via subcutânea: GM – meloxicam (0,2mg/kg), GR – robenacoxibe (2mg/kg) ou GC – solução fisiológica 0,9% (0,1mL/kg). Foram aguardados 30 minutos, e os animais foram induzidos à anestesia geral com isoflurano em uma caixa de indução, intubados e mantidos anestesiados com 1,5V% isoflurano. Todos os animais foram submetidos a estímulo nociceptivo supramáximo (pinçamento da cauda). Resposta positiva foi definida como movimento propositalda cabeça e/ou dos membros. O método para determinação da CAM foi "up-and-down", de Dixon, e o cálculo de média dos valores de crossovers conforme Monteiro et al. (2016). A média e o desvio-padrão da ISO_{CAM} foram de 2,10±0,15%, 1,95±0,14%, e 1,7±0,15% em GC, GM e GR, respectivamente. O robenacoxibe reduziu 19,1% e 12,8% a ISO_{CAM} quando comparado ao grupo controle e ao grupo meloxicam, respectivamente.

Palavras-chave: gatas, robenacoxibe, CAM, AINEs

INTRODUCTION

Domestic felines have gained space inside the houses in recent years, requiring specific care and, consequently, further studies on the particularities of the species. Studies on this species are still insufficient when compared to canines, and many treatments end up not being effective due to the lack of scientific evidence and indirect extrapolation of drugs and doses.

Robenacoxib is a non-steroidal anti-inflammatory drug (NSAID) classified as coxib, and its use is approved for the control of inflammation, pain and hyperthermia in cats

Corresponding author: luh-rosamona@hotmail.com
Submitted: July 26, 2023. Accepted: April 16, 2024.

(Giraudel *et al*., 2009 a, b). It has a high safety index in felines (King *et al.,* 2011) as it selectively distributes to inflamed tissues, remaining longer in these sites, inhibiting COX 2 and sparing COX 1 (Schmid *et al*., 2010; Pelligand *et al*., 2011). It was initially approved for use in felines in Europe in 2008, in the United States in 2011 and in Brazil in 2017.

The perioperative administration of NSAIDs can reduce the need for inhalational anesthetics, precisely because they produce great analgesic efficacy, with reductions similar to the use of opioids in humans (MOSS, *et al*. 1992). Knowing that, among the various indications for NSAIDs, one of them is in the perioperative period, their effect in reducing the need for inhalational anesthesia ends up optimizing their use even more. However, each NSAID has a specific mechanism for inhaled anesthetic's reduction and specific studies are required.

Gruet *et al*. (2011) found similar analgesic efficacy with the administration of robenacoxib or meloxicam in the preoperative period in dogs that underwent orthopedic surgery. Tamura *et al*. (2014) observed that robenacoxib 2 mg/kg subcutaneously 1 hour before anesthesia reduced the MAC for adrenergic response to sevoflurane in dogs by 17%, compared to the control group, when faced with a noxious electrical stimulus. Reed and Doherty (2018), in a review of drugs that reduce MAC in dogs, believe that the effect of reducing MAC with NSAIDs is still small and often considered within the margin of experimental error, as existing studies express low percentages of reduction. In felines, the evaluation of MAC reduction with NSAIDs is still little explored, there is a lack of studies that evaluate their real effects. Meloxicam was chosen for comparison in the present study because it is one of the most used NSAIDs in felines (Gruen, 2022).

Dose measurement for inhalational anesthetics is based on the Minimum Alveolar Concentration (MAC), and for your competence it is fundamental: the use of a supramaximal nociceptive stimulus; the programming of clear criteria to define the positive and negative motor responses triggered by nociceptive stimulation; and balance between anesthetic concentrations in alveolar air, arterial blood and central nervous system. There are several methods for engineering the CAM, the up-and-down method stands out, which can sequentially determine the doses, maintaining the same accuracy of conventional methods of coding effective digital doses. Moreover, it is necessary to provoke at least 4 crossover events (change of direction of isoflurane concentration at the end of expiration – EtIso - target sequentially, positive result, followed by negative result, or vice versa), for the result to be considered valid (Dixon, 1965).

Therefore, the present study aimed to evaluate the effect of robenacoxib on inhalational anesthesia in cats, expecting a consistent decrease in the final expired concentration of isoflurane compared to the control group and a greater sparing effect of inhalational anesthetic of robenacoxib when compared to meloxicam. Thus, its indication in the feline species can be treated with greater use in the perioperative.

MATERIAL AND METHODS

The study was approved by the Committee for Ethics in the Use of Animals under protocol number: 5782070619. The chosen samples recruited for the study were shot hair female domestic felines, clinically healthy, evaluated by physical and blood examination, considered to have a calm temperament, were used. Any animal that presented an abnormality in the physical or laboratory examination or was considered to have an aggressive temperament was not included in the study. Animals were referred from the clinical surgical routine of the Hospital de Clínica Veterinária (HCV) of the State University of Santa Catarina for elective ovariohysterectomy and were included through a consent form previously signed by the owners.

The animals were hospitalized the day before the study start in an isolated place from the hospital routine and kept in individual cages. Following acclimatation at the site, a solid fast of 12 h was performed with water "*ad libidum*". On the day of the study, animals were randomly separated into three groups: GM – received meloxicam at a dose of 0.2 mg/kg by the subcutaneous route (SC), GR – received robenacoxib 2mg/kg by the SC route and GC – received 0.9% saline solution 0.1mL/kg by the SC route. After applying the treatments, a 30-minute waiting period was followed, and then the animals were physically restrained, placed in a plastic induction box with

a capacity of 16.6 L and induced general anesthesia with 3 V% isoflurane and oxygen at a flow rate of 4 L/min (Figure 1). As soon as the animals remained in lateral decubitus, they were removed from the box and, afterwards, they were intubated with an appropriately sized Murphy-type endotracheal tube and connected to the total gas rebreathing system, maintained on pressure-cycled mechanical ventilation (microprocessor GE 9100c ventilator), starting with a pressure of 12 cm H2O, an inspiration:expiration ratio (I:E) of 1:2 and a respiratory rate (*f*) of 15 movements per minute, to maintain normocapnia (30 – 45 mmHg) under general inhalation anesthesia with 2V% isoflurane, using 100% oxygen as diluent gas with a flow of 50mL/kg/min. The reading of expired isoflurane concentration was performed using an anesthetic gas analyzer (D'Lite ® E-CAIOVX - GE B650). The vaporizer and the gas analyzer of the multiparametric monitor were calibrated using the DH-004 equipment (FI-21 Riken Keiki®) together with the DH-025 (Standard Gas Mixture, White Martins®).

Then, a cephalic vein was accessed with a 22G catheter, and Ringer lactate was administered at a rate of 3mL/kg/hour as maintenance fluid therapy. Anesthetic monitoring was performed using a multiparameter monitor (GE B650), assessing heart rate (HR) and peripheral oxyhemoglobin saturation (SpO_2) using a pulse oximeter with a sensor positioned on the tongue, respiratory rate (*f*) assessed through direct visualization of the multiparameter monitor, with a mainstream capnography sensor coupled between the endotracheal tube and the circular closed system, systolic blood pressure (SBP) using portable vascular Doppler, with the use of a cuff, with a width of 40 to 50% of the circumference of the animal's limb, positioned in the region just above the radiocarpal joint, concentration of carbon dioxide at the end of expiration ($EtCO_2$) through direct reading on the multiparametric monitor with spirometry module (D'Lite ® E-CAIOVX) coupled between the endotracheal probe and the pulmonary ventilator system (GE B650), and core temperature (T°C) by the esophageal thermometer positioned in the animal's esophagus, whose reading was provided by the multiparametric monitor.

After instrumentation, isofluorane vaporization was reduced to 1.5 V%, with a wait of 15 minutes to obtain equilibrium between pulmonary and cerebral anesthetic concentrations, and parameters were collected at M0. The initial vaporization of isoflurane, of the first animal of each group was 1.5 V% (Yackey *et al*., 2004), already determined in felines, for subsequent increase or decrease according to the animal's response.

The supramaximal nociceptive stimulus consisted of pinching the tail with a halstead hemostat (blade tips covered with plastic tubes, closed until the first ratchet) for 60 seconds or until a positive response, with the animal positioned in dorsal decubitus, whichever occurred first. The stimulus was always applied to the middle third of the tail of the animals, by an evaluator blind to the treatment groups, who evaluated the response of each animal. Positive response was defined as purposeful movement of the head and/or limbs occurring within the 60-second stimulation period; increased respiratory rate, coughing or swallowing were not considered positive responses. Negative response was defined as the absence of purposeful movement (Ferreira *et al*., 2011).

The motor response to the supramaximal nociceptive stimulus was evaluated by a single observer. The method for determining MAC was up and down. After the nociceptive stimulus, if the animal presented a positive response, the EtIso was increased by 10% for the next animal. Conversely, if the animal had a negative response to stimulation, the EtIso was reduced by 10% for the next animal. This procedure was repeated sequentially in all animals. Crossover events were recorded when there was a negative response followed by a positive one or contrariwise, requiring at least 4 events to determine the MAC. After the stimulus, the parameters were collected again, characterizing the M1. At this time, the animals ended their participation in the study, and were referred for elective ovariohysterectomy, being positioned in sternal decubitus, epidural anesthesia was performed in the lumbosacral space (L7-S1) with lidocaine 0.26 ml/kg and morphine 0.1 mg/kg, with previous trichotomy and antisepsis. After 10 minutes, the animals were positioned in dorsal decubitus and castrated following the techniques and protocols adopted in the hospital routine, receiving intravenous dipyrone at a dose of 25 mg/kg, immediately after the end of the surgical procedure. The animals in the CG group also

received meloxicam 0.2 mg/kg intravenously after the end of the surgical procedure. The animals were monitored throughout the surgical procedure until they fully recovered from anesthesia and were discharged on the same day, with postoperative medication and the usual recommendations.

Data were analyzed using the GraphPad Prism 8.4.3 software, being submitted to the Shapiro-Wilk normality test to verify the normal distribution. Parametric data were submitted to Student's t test for analysis between moments within the same group and for analysis between groups one-way analysis of variance (ANOVA) was used followed by Tukey's test. The difference was considered significant when $p \leq 0.05$. The minimum alveolar concentration was calculated using Dixon's up-and-down technique, and average calculation of crossover values according to Monteiro *et al*. (2016).

CASUISTRY

The casuistry was not pre-defined at the beginning of the experiment, because due to the experimental design, the animals were selected according to the demand for the appearance of crossovers. In this way, the number of animals (n) could increase or decrease according to experimental results.

RESULTS AND DISCUSSION

There was no significant difference between groups when age, weight and instrumentation time were compared ($p < 0.05$) and the number of animals needed for crossovers per group was very similar (Table 1).

Table 1. Mean and standard deviation of weight (kg) and age (months), as well as the required number of animals (n) per study group, in cats submitted to nociceptive stimulation, allocated in groups: control (GC), meloxicam (GM) or robenacoxib (GR)

Groups	N	Age (month)	Weight (kg)	Instrumentation time (minutes)
GC	11	22 ± 16	3.32 ± 0.78	5.7±1.3
GM	10	09 ± 05	2.74 ± 0.43	6.1±1.7
GR	9	17 ± 15	2.96 ± 0.53	5.7±1.4
MEAN	10 ± 1	16 ± 07	3 ± 0.29	5.8±0.23

ANOVA followed Tukey, p≤0,05. Source: Author himself.

The individual response to noxious stimuli for domestic cats is shown in Figure 2. The ISO_{MAC} mean and standard deviation were 2.10 ± 0.15 %, 1.95 ± 0.14 %, and 1.7 ± 0.15 % in GC, GM, and RG, respectively (Fig. 2 and 3). When compared with GC, the values for ISO_{MAC} in GM and GR were reduced by 7.15 % and 19.1 %, respectively. When compared to GM, values for ISO_{MAC} in GR were reduced by 12.8 %. ISO_{MAC} values in GR were significantly lower when compared to GC and GM (Fig. 3).

In the present study, four crossings were considered for MAC estimation, unlike the original MAC estimation technique described by Dixon (1965), where positive and negative responses generate a median effective dose. The method used in the present study was mathematical average, already described in more recent studies (Monteiro *et al*., 2016), with proof of producing values identical to the original method (Valverde *et al*., 2003).

The values of ISO_{MAC}, without the action of another drug (control group, CG) found in the present study were higher than that described by Yackey *et al*. (2004) who found values of ISO_{MAC} 1.51 ± 0.2 %. However, comparing the values found with the studies by Pypendop and Ilkiw (2005) and Brosnan *et al*. (2009), (ISO_{MAC} 2.21 ± 0.17 % and 1.94 ± 0.08 %, respectively), the present study reached very close values. In all these studies, the nociceptive stimulus applied to cats was the same as in the present study, the tail pinching.

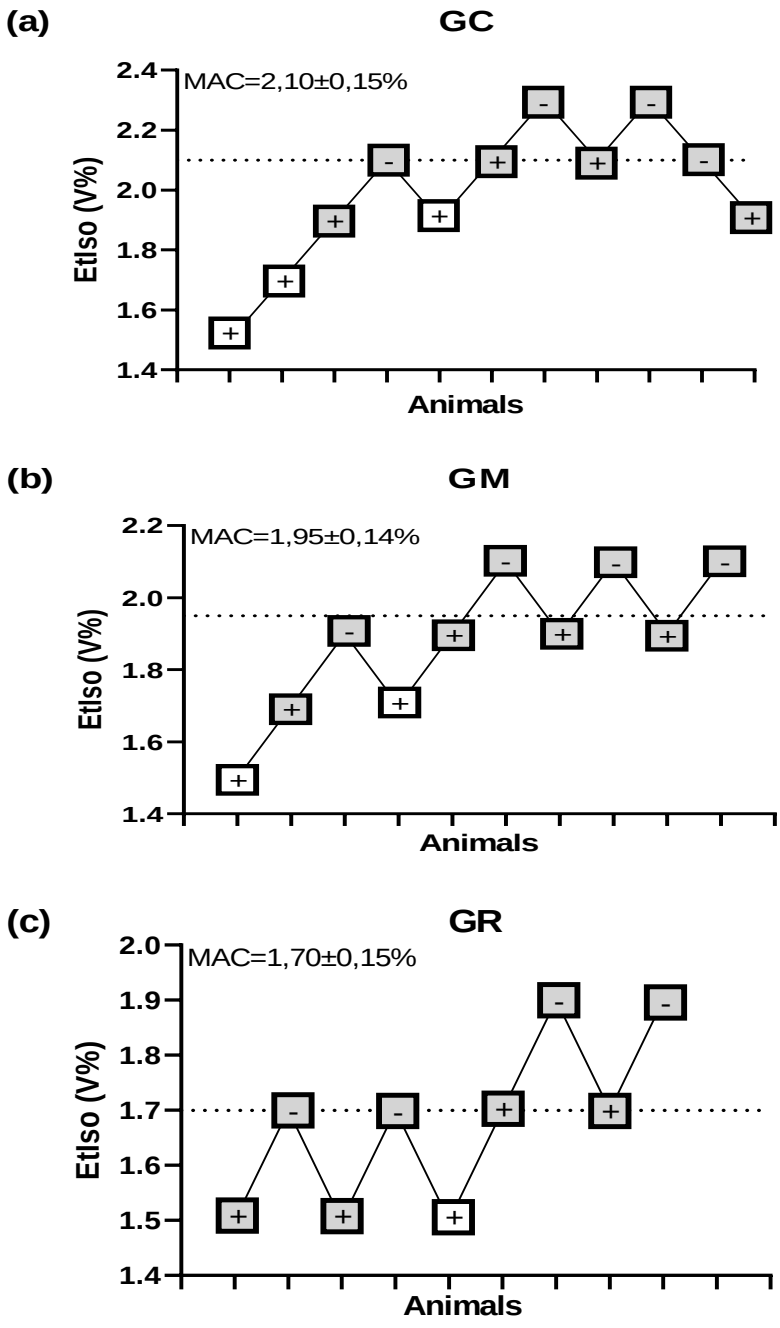
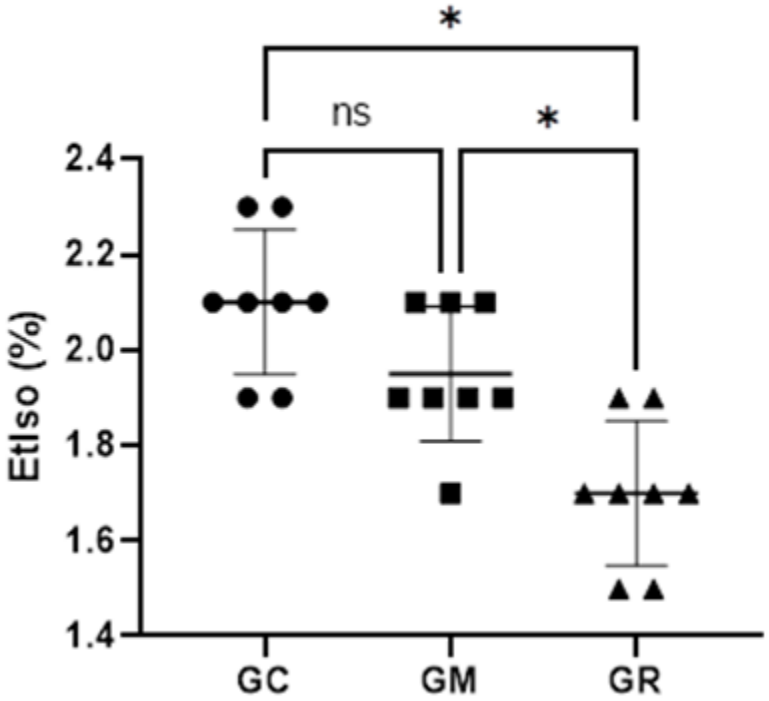


Figure 2. Response (positive or negative) for each of the 30 cats anesthetized with the respective expired concentrations of isoflurane (EtISO %). (a) control group (n = 11); (b) meloxicam group (n = 10); and (c) robenacoxib group (n = 9). (+) indicates a positive response (purposeful movement); (-) indicates a negative response (no purposeful movement); shaded squares indicate crossover events. The dotted horizontal lines indicate the average calculated with the ISO_{MAC} value.



One-way ANOVA followed by Tukey $p \leq 0.05$. ns – not significant * difference with GR. Source: Author himself.

Figure 3. Comparison of mean values (horizontal line) of ISO_{MAC} in the control group (GC), meloxicam group (GM) and robenacoxib group (GR) in cats submitted to nociceptive stimulation.

In most previous studies with robenacoxib, the focus was on analgesic evaluation, therefore, even the studies that evaluate its use before surgical stimulation do not provide data regarding the concentration of necessary inhalation anesthesia used. In the study by Kamata *et al*. (2012) testing robenacoxib in female cats undergoing soft tissue surgery, isoflurane was the maintenance agent, but there are no data on its perioperative requirement. Similarly, in the study by Staffieri *et al*. (2013) robenacoxib was administered 30 minutes before the ovariohysterectomy procedure in cats, and the maintenance agent of choice was isoflurane, but its concentrations were not presented in the study.

Mechanical stimulation (tail pinch) activates C-fiber and Aδ-fiber nociceptors ((Bessou and Perl, 1969). As NSAIDs inhibit COX-2 expression in injured tissues, they may prevent sensitization in peripheral C-fiber nociceptors, as well as decrease COX-2 expression in the central nervous system. Thus, NSAIDs can produce central analgesic effects, both by inhibiting COX and activating opioidergic mechanisms (Malmberg and Yaksh, 1992; Lauretti *et al*., 1998; Holmes and Horton, 1968). Because of these analgesic mechanisms, we can also observe a significant reduction in the MAC of isoflurane in the groups that received robenacoxib or meloxicam.

Compared to the study by Tamura *et al*. (2014) robenacoxib administered 1 hour before anesthesia reduced $SEVO_{MAC}$ by 17 % in dogs. In the present study demonstrated similar percentages, with a decrease of 19.1 %. However, in this study in dogs, the noxious stimulus was electrical, using an electrical stimulator (50 volts, 50 hertz for 10 seconds) and not mechanical as in the present study. Based on this, robenacoxib has a good potential for reducing the need for inhaled anesthetics during anesthesia and further studies are needed to validate and confirm its preventive application.

The greater reduction of ISO_{MAC} in GR compared to GM may imply a superior analgesic effect of robenacoxib. This effect may be related to its more selective preferential inhibition of COX-2, remaining in inflammatory and painful sites for longer and more effectively. In addition to this, coxibs end up not directly interfering in the inhibition of thromboxanes like oxicans and may have a greater clinical indication for administration preoperatively, as it provides a lower risk of hemorrhage (Schmid *et al*., 2010; Pelligand *et al*., 2011).

Regarding the parameters measured during anesthesia, there was a significant difference for HR and SBP before and after the surgical stimulus in all groups. There were no significant differences between treatment groups for the parameters measured. Although there is no statistical difference, an increase in f values after nociceptive stimulation can be observed, also explained by the sympathetic activation of nociception (Table 2).

Table 2. Mean values and standard deviation for heart rate (HR), respiratory rate (*f*), peripheral oxygen saturation (SpO_2), fraction of expired carbon dioxide ($EtCO_2$), systolic blood pressure (SBP) and body temperature (TºC) of cats submitted to nociceptive stimulus under isoflurane anesthesia, allocated in one of three groups: control (GC), meloxicam (GM) or robenacoxib (GR).

	Groups	Moments M0 (before the stimulus)	 M1 (after the stimulus)
FC (beatst/min)	GC	130±19	169±34 A
	GM	135±25	173±25 A
	GR	141±31	179±29 A
f (moves/min)	GC	12±4	13±8
	GM	14±8	18±11
	GR	14±8	15±7
SpO_2 (%)	GC	96±2	98±2
	GM	98±2	98±1
	GR	96±3	97±3
$EtCO_2$ (mmHg)	GC	32±2	32±4
	GM	34±6	34±5
	GR	36±3	36±3
SBP (mmHg)	GC	76±9	108±12 A
	GM	65±12	104±19 A
	GR	66±11	99±18 A
T (°C)	GC	36.9±0.8	36.9±0.8
	GM	37±0.7	36.9±0.7
	GR	37±0.5	36.9±0.6

Capital letters on the same line mean difference with the M0 (Student's t test). ($p \leq 0.05$). Source: Author himself.

SBP values before the noxious stimulus demonstrate hypotension, with values below the reference values. This effect is strictly related to isoflurane, which causes dose-dependent hypotension, mainly due to the decrease in systemic vascular resistance resulting from vasodilation, decrease in cardiac output and decrease in the tonus of the sympathetic autonomous nervous system (Mutoh *et al*., 1997). Hypotension has already been reported with similar concentrations of isoflurane in felines (Ilkiw, 1999).

Hypotension is an anesthetic complication considered common, which can culminate in cerebral and coronary hypoperfusion, which can affect the perfusion of all organs and increase the risk of death in critically ill patients (Redondo *et al*., 2007). In the present study, the hypotension observed was not treated due to the experimental design, since vasoactive agents end up interfering with the requirement for isoflurane. Furthermore, the animals selected for the study remained hypotensive for a short period and, considering that they were young and healthy

animals, there were no negative hemodynamic repercussions.

The increase in HR and SAP after stimulation is justified as a response to nociception. There is an activation of the autonomic system with adrenergic release in the circulatory current which, consequently, leads to an increase in hemodynamic parameters (Vaisanen *et al*., 2002; Ilkiw, 1999). The differences in HR and SBP after the nociceptive stimulus were expected in all groups, as tail pinching is considered a strong pain stimulus, non-steroidal anti-inflammatory drugs would not be able to abolish the sympathetic activation resulting from nociception.

CONCLUSIONS

Robenacoxib decreased by 19.1% and 12.8% the minimum alveolar concentration of isoflurane in cats submitted to supramaximal mechanical stimulus (tail pinching), when compared to the control group (saline solution) and meloxicam, respectively.

REFERENCES

BESSOU, P.; PERL, E. R. Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J. Neurophysiol.*, v.32, p. 1025-1043, 1969.

BROSNAN, R.J.; PYPENDOP, B.H.; SIAO, K.T.; STANLEY, S.D. Effects of remifentanil on measures of anesthetic immobility and analgesia in cats. *Am. J. Vet. Res.*, v.70, p.1065-1071, 2009.

DIXON, W.J. The up-and-down method for small samples. *J. Am. Statist. Assoc.*, v.60, p.967-978, 1965.

FERREIRA, T.H.; STEFFEY, E.P.; MAMA, K.R. *et al.* Determination of the sevoflurane sparing effect of methadone in cats. *Vet. Anaesth. Analg.*, v.38, p.310-319, 2011.

GIRAUDEL, J.M.; KING, J.N.; JEUNESSE, E.C. *et al.* Use of a pharmacokinetic/pharmacodynamic approach in the cat to determine a dosage regimen for the COX-2 selective drug robenacoxib. *J. Vet. Pharmacol. Ther.*, v.32, p.18-30, 2009.

GIRAUDEL, J.M.; TOUTAIN, P.L.; KING, J.N.; LEES, P. Differential inhibition of cyclooxygenase isoenzymes in the cat by the NSAID robenacoxib. *J. Vet. Pharmacol. Ther.*, v.32, p.31-40, 2009.

GRUEN, M.E.; LASCELLES, B.D.; COLLERAN, E. *et al*. AAHA Pain Management Guidelines for Dogs and Cats - veterinary practice guidelines. *J. Am. Anim. Hosp. Assoc.*, v.58, p.55-76, 2022.

GRUET, P.; SEEWALD, W.; KING, J.N. Evaluation of subcutaneous and oral administration of robenacoxib and meloxicam for the treatment of acute pain and inflammation associated with orthopedic surgery in dogs. *Am. J. Vet. Res*, v.72, p.184-193, 2011.

HOLMES, S.W.; HORTON, E.W. The identification of four prostaglandins in dog brain and their regional distribution in the central nervous system. *J. Physiol.*, v.95, p.731-741, 1968.

ILKIW J.E. Balanced anesthetic techniques in dogs and cats. *Clin. Tech. Small Anim. Pract.*, v.14, p.27-37, 1999.

KAMATA, M.; KING, J.N.; SEEWALD, W. *et al.* Comparison of injectable robenacoxib versus meloxicam for perioperative use in cats: results of a randomised clinical trial. *Vet. J.*, v.193, p.114-118, 2012.

KING, J.N.; HOTZ, R.; REAGAN, E.L. *et al.* Safety of oral robenacoxib in the cat. *J. Vet. Pharmacol. Ther.*, v.35, p.290-300, 2011.

LAURETTI, G.R.; REIS, M.P.; MATTOS, A.L. *et al.* Epidural nonsteroidal antiinflammatory drugs for cancer pain. *Anesth. Analg.*, v.86, p.117-118, 1998.

MALMBERG, A.B.; YAKSH, T.L. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *J. Pharmacol. Exp. Ther.*, v.263, p.136-146, 1992.

MONTEIRO, E.R.; COELHO, K.; BRESSAN, T.F. *et al.* Effects of acepromazine-morphine and acepromazine-methadone premedication on the minimum alveolar concentration of isoflurane in dogs. *Vet. Anaesth. Analg.*, v.43, p.27-34, 2016.

MOSS, J.T.; BAYSINGER, C.L.; BOSWELL, G.W. *et al.* Possible intraoperative anesthetic-sparing effect of parenteral ketorolac. *Ann. Pharmacother.*, v.26, p.922-924, 1992.

MUTOH, T.; NISHIMURA, R.; KIM, H.Y. *et al.* Cardiopulmonary effects of sevoflurane, compared with halothane, enflurane, and isoflurane, in dogs. *Am. J. Vet. Res.*, v.58, p.885-890, 1997.

PELLIGAND, L.; KING, J.N.; TOUTAIN, P.L. *et al.* Pharmacokinetic/pharmacodynamic modelling of robenacoxib in a feline tissue cage model of inflammation. *J. Vet. Pharmacol. Ther.*, v.35, p.19-32, 2011.

PYPENDOP, B.H.; ILKIW, J.E. The effects of intravenous lidocaine administration on the minimum alveolar concentration of isoflurane in cats. *Vet. Anaesth. Analg.*, v.100, p.97-101, 2005.

REDONDO, J.L.; RUBIO, M.; SOLER, G. *et al.* Normal values and incidence of cardiorespiratory complications in dogs during general anesthesia. A review of 1281 cases. *J. Vet. Med. Assoc. Physiol. Pathol. Clin. Med*., v.54, p.470-477, 2007.

REED, R.; DOHERTY, T. Minimum alveolar concentration: key concepts and a review of its pharmacological reduction in dogs. Part 2. *Res. Vet. Sci.*, v.118, p.27-33, 2018.

SCHMID, V.B.; SEEWALD, W.; LEES, P.; KING, J.N. In vitro and ex vivo inhibition of COX isoforms by robenacoxib in the cat: a comparative study. *J. Vet. Pharmacol. Ther.*, v.33, p.444-452, 2010.

STAFFIERI, F.; CENTONZE, P.; GIGANTE, G. *et al.* Comparison of the analgesic effects of robenacoxib, buprenorphine and their combination in cats after ovariohysterectomy. *Vet. J.*, v.197, p.363-367, 2013.

TAMURA, J.; ITAMI, T.; ISHIZUKA, T. *et al.* Sparing effect of robenacoxib on the minimum alveolar concentration for blunting adrenergic response (MAC-BAR) of sevoflurane in dogs. *J. Vet. Med. Sci.*, v.76, p.113-117, 2014.

VAISANEN, M.; RAEKALLIO, M.; KUUSELA, E. *et al.* Evaluation of the perioperative stress response in dogs administered medetomidine or acepromazine as part of the preanesthetic medication. *Am. J. Vet. Res.*, v.63, p.969-975, 2002.

VALVERDE A.; MOREY, T.E.; HERNÁNDEZ, J.; DAVIES, W. Validation of several types of noxious stimuli for use in determining the minimum alveolar concentration for inhalation anesthetics in dogs and rabbits. *Am. J. Vet. Res*., v.64, p.957-962, 2003.

YACKEY, M.; ILKIW, J.E.; PASCOE, P.J.; TRIPP, L.D. Effect of transdermally administered fentanyl on the minimum alveolar concentration of isoflurane in cats. *Vet. Anaesth. Analg.*, v.31, p.183-189, 2004.