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Short Communication

Firocoxib on hematological and biochemical parameters and anesthesia propofol dose in dogs

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This study evaluated the hematological and biochemical changes, the safety, as well as the change in propofol dose required for anesthesia induction in dogs, pretreated or not, in response to a single dose or continuous use of the nonsteroidal anti-inflammatory drug (NSAID) firocoxib. Thirty animals mean weighing 8.1 kg and mean aged 3.38 years were included. The animals were then divided into groups: Group I (GI) did not receive firocoxib, Group II (GII) received a single dose (5 mg/kg) 90 minutes before anesthesia induction, and Group III (GIII) received the same dose (5 mg/kg) for 40 consecutive days before induction of anesthesia with propofol. Hematological and biochemical evaluations were conducted. The times of collection were defined by the mean time of maximum concentration and constant concentration in the blood of the NSAID. All variables remained within the reference range, but averages differed statistically between GII and GIII, according to the Tukey test ($p < 0.05$). The average doses of propofol were 6.6 mg/kg, 6.1 mg/kg, and 7.8 mg/kg for GI, GII, and GIII, respectively. Hematological and biochemical changes and increased propofol dose for induction of anesthesia in GIII, despite this can be safely used in association with propofol at the time of anesthesic induction; which must be taken into account because it may also change doses of the drug in other anesthetic methods.

INTRODUCTION

Firocoxib is a non-steroidal anti-inflammatory drug (NSAID) that acts through the selective inhibition of cyclooxygenase-2 (COX-2) (CLARK, 2006). After oral administration in doses of 5 mg/kg, approximately 96% of firocoxib connect to plasma proteins, and may lead to decreased serum albumin levels and possible adverse effects on the gastrointestinal system (CLARK, 2006). As a drug used continuously and safely, this NSAID is present in different therapeutic protocols, and it is known that during treatment there may be the possibility of these animals needing and being submitted to anesthetic-surgical procedures, as well as clinical information of the drug interaction (CLARK, 2006).

Albumin is the most abundant protein in total plasma protein. It is non-glycosylated multifunctional protein with property of binding, transport, antioxidant roles, and enzymatic activity (SLEEP, 2015). Binding to albumin is a determining factor in the distribution and pharmacokinetics of several drugs, including anesthetics, consequently, the binding with albumin is a key element in pharmacological activity for increasing drug sensitivity (SIMARD et al., 2005). It is known that propofol binds to plasma proteins, albumin, and cases of

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hyper or hypoalbuminemia result in alterations in the required dose of this anesthetic in human´s patient (SCHYWALSKY et al., 2005).

In veterinary medicine, therapeutic protocols that standardize the use of COX-2 inhibitors are lacking. The study aimed to investigate the changes in hematologic and biochemical parameters and propofol doses to be used at the time of anesthesia induction in response to single or continuous use of firocoxib, as well as their safe use in animals that will be anesthetized. The hypothesis of a change in dose of propofol required for anesthesia induction in dogs is based on the property of firocoxib and propofol to bind to plasma proteins. In addition, the safety of administration the anesthesic drug was evaluated.

MATERIAL AND METHODS

Animals

This study was approved by the Ethics Committee for Animal Use of the Federal University of Mato Grosso under protocol number 23108.097695/2015-26 and written informed consent was obtained from the owners of the dogs used in the study. Thirty dogs (12 females and 17 males) of different breeds, with a mean aged of 3.38 years (range from 1 year to 12 years) and mean body mass of 8.1 kg (range from 4 to 31.8 kg), were selected from the routine of elective sterilization surgeries of the Veterinary Hospital of the Federal University of Mato Grosso. The dogs were clinically healthy based on the results of clinical exams, blood count [erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration (MCHC), leukocytes, neutrophils, eosinophils, lymphocytes, monocytes, platelets, and total plasma protein] and serum biochemical tests [urea, creatinine, total protein, albumin, globulin, cholesterol, aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), glucose, and alkaline phosphatase (ALP)]. All animals were previously dewormed and recevied food based on commercial feed.

Experimental design

The dogs were divided into three groups: Group I (GI, *n* = 10), did not receive firocoxib (Previcox, MERIAL, Saúde Animal Ltda., SP, Brazil); Group II (GII, *n* = 10), received a single dose of 5 mg/kg of firocoxib orally in different moments: at 1 hour and 30 minutes before induction of anesthesia with propofol; and Group III (GIII, *n* = 10), received firocoxib (5 mg/kg), once a day, orally for 40 consecutive days (RYAN; MOLDAVE; CARITHERS, 2008) before induction of anesthesia. Blood was collected at during the animals' clinical evaluation and on different moments in each groups: GI - on the day of the anesthetic procedure; GII - 1 hour and 30 minutes after administration of firocoxib; GIII - 40 days after administration of firocoxib. The times of collection were defined by the mean time of maximum concentration and constant concentration in the blood of the NSAID.

Laboratory analysis

Blood samples were collected from the jugular vein (10 mL) in tubes without anticoagulant and in tubes containing the anticoagulant ethylenediaminetetraacetic acid. An automatic device (poch 100iV Diff - Sysmex Corporation, Kobe, Japan) was used for the blood test [erythrocytes, hemoglobin, hematocrit, MCV, MCHC, leukocytes, neutrophils, eosinophils, lymphocytes, monocytes, platelets, and TPP], followed by microscopic examination for differentiation cells count. Regarding the biochemical analysis, urea, AST, and ALT levels were determined using the UV kinetic method; creatinine, GGT, and ALP levels were determined using the kinetic colorimetric method; total protein was determined using the colorimetric-biuret method; albumin level was determined using the colorimetric bromocresol green method; and cholesterol and glucose concentrations were determined using the enzymatic colorimetric method (Trinder) and quantified using a semi-automatic analyzer (Celm SB-190, CELM - Cia. Equipadora de Laboratórios Modernos, SP, Brazil).

Anesthetic Procedure

After fasting for 12 hours and water intake for 3 hours, the animals were classified according to American Society of Anesthesiologists (ASA) grading as ASA I. Vein catheterization was performed through the cephalic vein with an intravenous catheter (Solidor, Bio-Med Healthcare Products Pvt. Ltd., HR, India), and a NaCl solution (0.9%) was administered (10 mL/kg/h).

We opted for the non-use of premedication to avoid effects of other drugs on anesthesia induction. Anesthesia was induced with propofol (10 mg/mL, Cristália – Produtos Químicos e Farmacêuticos – Ltda., SP, Brazil), administered in increments of 0.5 mg/kg for 15 seconds, with a dosing interval of approximately 15 seconds until loss of mandibular tone and absence of gag reflexes and tensile strength of the tongue (RASZPLEWICZ; MACFARLANE; WEST, 2013). Induction quality was assessed and expressed according to clinical criteria as good (good muscle relaxation, easy intubation, and lack of mandibular tonus), intermediate (poor muscle relaxation, difficulty in intubation), or bad (excitability and impossible intubation) (INTELISANO, 2008). The final volume in milliliters was recorded for analysis and comparison between groups. After, morphine sulfate (0.4 mg/kg) (Dimorf® 10 mg/mL, Cristália – Produtos Químicos e Farmacêuticos Ltda., SP, Brazil) was administered as anesthesic pre medication for pain control protocol. The protocols employed in each animal by the clinical pathologist and

anesthesiologist were unknown and always performed by the same person.

Statistical analysis

The Kolmogorov–Smirnov test ($p > 0.05$) was conducted to verify that the data followed a normal distribution. Later, an analysis of variance was conducted, followed by a Tukey test with a significance level of 5%. SAS Software was used for all analyses (University Edition, SAS Institute Inc., NC, USA).

RESULTS

Regarding hematological and biochemical variables, statistical differences with lower values were observed for erythrocytes ($p = 0.0044$), hemoglobin ($p = 0.0040$), hematocrit ($p = 0.0161$), MCHC ($p = 0.0369$) and in ALP ($p = 0.0102$) in GII compared to GIII and GI; and in albumin ($p = 0.0076$) in GIII compared to GI and GII (Table 1). Other variables not presenting statistical differences, and total leukocyte and neutrophil counts were lower in GIII. There was a change serum concentration of, total protein, globulin, GGT, and glucose were higher, and those of cholesterol, AST, and ALT lower in GIII compared to the other two groups. All variables remained within the reference range during the study.

The propofol doses (mg/kg; mean ± standard deviation) required for anesthesia induction were 6.6 ± 0.5, 6.1 ± 0.5, and 7.8 ± 0.7 for GI, GII and GIII, respectively, with no significant differences between them.

Table 1. Mean values and standard desviation of the variables measured, hematological parameters [erythrocytes, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), leukocytes, neutrophils, eosinophils, lymphocytes, monocytes, platelets, and total plasma proteins (TPP)] and biochemical parameters [urea, creatinine, total protein, albumin, globulin, cholesterol, aspartate, aminotransferase (AST), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), glucose, and alkaline phosphatase (ALP)], before induction of anesthesia with propofol in dogs with no treatment (Group I, *n* = 10), 1 hour and 30 minutes after a single oral administration of firocoxib (5 mg/kg) (Group II, *n* = 10) and after 40 days of oral administration of firocoxib (5 mg/kg), once a day (Group III, *n* = 10).

	GROUP I	GROUP II	GROUP III
Hematological Parameters			
Erythrocytes (10^6/mm^3)	7.3 ± 0.2[a]	6.4 ± 0.3[b]	7.3 ± 0.3[a]
Hemoglobin (g/dL)	16.6 ± 0.6[a]	14.0 ± 0.6[b]	16.5 ± 0.8[a]
Hematocrit (%)	47.2 ± 1.5[a]	42.2 ± 1.5[b]	47.7 ± 2.0[a]
MCV (μ^3)	64.8 ± 0.6	64.9 ± 0.4	64.9 ± 0.5
MCHC (g/dL)	35.0 ± 0.3[a]	33.6 ± 0.3[b]	34.5 ± 0.4[a]
Leukocytes (10^3/mm^3)	12.3 ± 1.0	10.7 ± 0.8	9.3 ± 0.7
Neutrophils (10^3/mm^3)	7.1 ± 0.6	6.8 ± 0.7	5.2 ± 0.5
Eosinophils (10^3/mm^3)	1.3 ± 0.3	1.6 ± 0.5	1.6 ± 0.5
Lymphocytes (10^3/mm^3)	2.5 ± 0.4	1.7 ± 0.2	2.2 ± 0.3
Monocytes (10^3/mm^3)	0.8 ± 0.1	0.7 ± 0.1	0.5 ± 0.1
Platelets (10^3/mm^3)	271.4 ± 17.9	283.9 ± 25.2	285.2 ± 17.1
TPP (g/dL)	6.8 ± 0.3	6.7 ± 0.2	6.9 ± 0.5
Biochemical Parameters			
Urea (mg/dL)	36.5 ± 5.5	38.6 ± 2.6	42.4 ± 3.9
Creatinine (mg/dL)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.05
Total protein (g/dL)	7.0 ± 0.2	7.4 ± 0.6	7.4 ± 0.4
Albumin (g/dL)	3.7 ± 0.1[a]	3.6 ± 0.1[a]	3.5 ± 0.1[b]
Globulin (g/dL)	3.5 ± 0.3	3.7 ± 0.7	3.9 ± 0.4
Cholesterol (mg/dL)	175.6 ± 13.6	175.0 ± 20.1	151.1 ± 11.1
AST (UI/L)	35.7 ± 4.9	29.1 ± 3.4	29.3 ± 2.7
GGT (UI/L)	4.8 ± 0.6	6.4 ± 0.7	5.3 ± 0.7
ALT (UI/L)	49.0 ± 8.2	39.9 ± 3.3	43.3 ± 5.9
Glucose (mg/dL)	115.3 ± 9.4	127.0 ± 5.7	117.4 ± 6.0
ALP (UI/L)	67.8 ± 10.3[a]	55.5 ± 14.2[b]	69.3 ± 15.0[a]

Different low case letters within the same row are significantly different ($p < 0.05$).

DISCUSSION

Andrès; Maloisel (2008) correlated anemia, neutropenia, and acute agranulocytosis with the single administration and chronic use of NSAIDs, in humans. Which suggests that therapeutic doses of firocoxib do not cause adverse effects related to hematological variables, and can be used reliably.

It is suggested that the changes in hepatic profile observed at the end of the 40 days of use of firocoxib were related to is pharmacokinetics, metabolization by dealkylation and glucuronidation in the liver, and elimination through bile, but the fact that these values remained within the reference range, combined with the absence of clinical signs related to liver dysfunction, demonstrates the safety of the drug, a result corroborated by Ryan; Moldave; Carithers (2008) and Steagall et al. (2007).

During the study, the animals underwent clinical evaluations and received adequate diet and no disease or clinical manifestation that justified the change in albumin values was detected. This change was associated with the use of firocoxib and its potential for binding to plasma proteins, disagreeing the results of Clark (2006), who linked firocoxib use to hypoalbuminemia.

Despite serum urea and creatinine are not highly sensitive markes, remained within the reference range because of the use of the recommended dose, and there were no pre-existing clinical manifestations associated with renal dysfunction. Our results differed from those of Borges et al. (2012), who found decreased and impaired renal function in dogs upon prolonged therapy with celecoxib, by laboratory tests.

The propofol dose required for anesthesia induction in GIII was higher, in line with the findings of Camargo et al. (2011), who observed that, for dogs receiving firocoxib (5 mg/kg), the dose of propofol required for induction of anesthesia was higher even when using neuroleptanalgesia. We attribute this to the hematological effects of using this NSAID, in agreement with the findings of an *in vitro* study by Schywalsky et al. (2005), which revealed a variation in concentration of albumin bound to propofol in cases of hyper- or hypoalbuminemia, resulting in a change in the required dose of the anesthetic agent.

The limitation of this study may be related to the size of the study population, variations depending on the different modes of administration of firocoxib or even dosing in patients with comorbidities, could add new concepts.

Our results indicated mild hematological and biochemical changes, as well as variation in the propofol dose required for anesthesia induction, in response to a single dose as well as continuous administration of firocoxib. Despite this, firocoxib can be safely used in association with propofol at the time of anesthesic induction. The dose of anesthetic should be taken into account in animal populations treated with this NSAID because it may also have an effect when other anesthetic methods, such as total intravenous anesthesia, are used.

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