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Tepoxalin on renal function and liver enzymes in cats exposed to hypotension with isoflurane

Tepoxalina sobre a função renal e as enzimas hepáticas em gatos submetidos à hipotensão com isofluorano

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ABSTRACT

This study aimed to evaluate the possible renal and hepatic toxicity of tepoxalin administered before or after isoflurane-induced hypotension, as well as for five consecutive days. Twelve healthy mixed-breed cats, adult males, weighing 4.0±0.8kg were allocated into two groups. They received 25mgkg^{-1} of tepoxalin orally, two hours before the anesthetic procedure (PRE) or after the procedure (POST) and daily for five days. Cats were anesthetized with isoflurane and the concentration was increased until mean arterial pressure reached 40-60mmHg and kept at this level for 60 minutes. During hypotension, the physiological variables were measured at time 0 and every 10 minutes until 60 minutes, and bleeding time was measured at time 0, 30 and 60 minutes. Blood samples were drawn for a hemogram and determination of concentrations of alanine aminotransferase, alkaline phosphatase, urea, creatinine and Na^+ at baseline, 24 hours, 48 hours and 7 days post-hypotension. Urine was collected at baseline, 24 hours, 48 hours and 7 days post-hypotension for determination of concentrations of creatinine, gamma-glutamyltransferase, urine specific gravity, protein, albumin and Na^+. During the anesthetic procedure there were no important variations in physiological variables and bleeding time. There were differences only in fractional excretion of Na^+, which was elevated at 7 days of evaluation in PRE and in the urine protein/creatinine ratio in PRE, which was higher than in POST at 24 and 48 hours post-hypotension. We conclude that tepoxalin does not cause alterations in hepatic enzymes but can cause discrete renal injury, resulting in proteinuria, in cats subjected to 60min of hypotension.

Key words: *non-steroidal anti-inflammatory drug, nephrotoxicity, hepatotoxicity.*

RESUMO

Este estudo teve como objetivo a avaliação da possível toxicidade renal e hepática da tepoxalina administrada antes ou após hipotensão induzida por isofluorano, assim como a sua administração nos cinco dias seguintes à hipotensão. 12 gatos adultos hígidos, machos, sem raça definida e com peso de 4,0±0,8kg foram alocados em dois grupos (n=6). Os animais receberam 25mgkg^{-1} de tepoxalina pela via oral, duas horas antes do procedimento anestésico (PRE) ou após o procedimento (POST) e diariamente por cinco dias consecutivos. Os gatos foram anestesiados com isofluorano, aumentando-se a sua concentração até que se atingisse uma pressão arterial média entre 40 e 60mmHg, sendo mantida durante 60 minutos. Durante o procedimento de hipotensão, os parâmetros fisiológicos foram mensurados no tempo 0 e a cada dez minutos até o fim do procedimento. O tempo de sangramento da mucosa oral foi avaliado no tempo 0 e aos 30 e 60 minutos de hipotensão. Amostras sanguíneas foram colhidas para a determinação de hemograma, alanina aminotransferase, fosfatase alcalina, ureia, creatinina e sódio no período basal e às 24 horas, 48 horas e sete dias pós-hipotensão. Amostras de urina foram colhidas por meio de cistocentese para a determinação de creatinina, gammaglutamiltransferase, densidade específica, proteínas, albumina e sódio. Durante o período anestésico, não ocorreram alterações referentes aos parâmetros fisiológicos e ao tempo de sangramento. Ocorreram alterações apenas na excreção fracionada de sódio, a qual demonstrou elevação no PRE aos sete dias, e na razão proteína/creatinina na urina, a qual demonstrou elevação do PRE em relação ao POST às 24 e às 48 horas de avaliação. Concluiu-se que a tepoxalina não causou alterações nas enzimas hepáticas, mas pode causar discreta injúria renal, com a presença de proteinúria, em gatos que foram submetidos à hipotensão.

Palavras-chave: *anti-inflamatório não esteroidal, nefrotoxicidade, hepatotoxicidade.*

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INTRODUCTION

The treatment of pain in cats has been historically neglected despite its known benefits (WRIGHT, 2002; JOUBERT, 2006; LASCELLES et al., 2007). This can be attributed to reduced ability of biotransformation via hepatic glucuronidationin this species, with consequent susceptibility to intoxication by drugs including non-steroidal anti-inflammatory drugs (NSAIDS) (WRIGHT, 2002). Another important point is the difficulty of recognizing and quantifying the intensity of pain in cats (BRONDANI et al., 2011), since these animals do not express evident signs of pain (WRIGHT, 2002).

There is evidence of the analgesic efficacy of NSAIDS in this species, for various surgical procedures (SLINGSBY & WATERMAN-PEARSON, 2000; AL-GIZAWIY & RUDE, 2004; BENITO-DE-LA-VIBORA et al., 2008; MURISON et al., 2010) or in musculoskeletal diseases (GIRAUDEL et al., 2010), resulting in minimal adverse effects.

Tepoxalin is an NSAID with a double inhibitory characteristic, with consequent anti-inflammatory action potentiated by inhibiting the COX and 5-LOX pathways (KNIGHT et al., 1996). Tepoxalin has been demonstrated to be a potent dual inhibitor in dogs (ARGENTIERI et al., 1994; KNIGHT et al., 1996; AGNELLO et al., 2005) and did not cause adverse effects during hypotension (LOPES et al., 2013). Tepoxalin is also known to inhibit COX and 5-LOX in cats (GOODMAN et al., 2010), but there are still no studies on its safety and efficacy in this species.

Preventive analgesia in surgical procedures has been shown to be beneficial, and tepoxalin is an advantageous option as part of multimodal analgesia protocols, because of its potent anti-inflammatory action and low incidence of side effects, as reported in dogs. Due to the real possibility of hypotension during anesthetic procedures, the aim of the present study was to evaluate the possible renal and hepatic toxicity of tepoxalin administered before or after isoflurane-induced hypotension, as well as for five consecutive days.

MATERIAL AND METHODS

Animals and experimental design

Twelve healthy cats were utilized: adult males, of mixed-breed, weighing 4.06±0.78kg. Cats were deemed healthy based on physical examination and laboratory tests: hemogram, serum levels of alanine aminotransferase (ALT), alkaline phosphatase (AP), urea (U) and creatinine (Cr), urinary concentrations of Cr, gamma-glutamyltransferase (GGT), total proteinand albumin, urine specific gravity, fractional excretion of sodium (FENa), and tests for feline immunodeficiency virus (FIV) and of feline leukemia virus (FeLV). The animals were housed in a cattery with solarium and individual cages, for a minimal period of 15 days for acclimation, and received commercial feed and water *ad libitum*.

Afterwards, the animals were allocated into two groups (n=6), which received tepoxalin[a] orally, two hours before the anesthetic procedure or after the procedure. Due to the commercial formulation of tepoxalin being available only in tablets and to avoid breaking them up, the dosage was adjusted so that each animal received a dose close to 25mgkg^{-1}. All cats received the same dose of tepoxalin every 24h, for five days after the procedure.

Hypotension procedure and physiological variables

Hypotension was induced by fasting the animals for 12 hours, and then anesthetizing them with isoflurane[b], in oxygen (Fi=0.6) and medical compressed air (Fi=0.4), administered via a Bain non-rebreathing system with a facemask and vaporization necessary for the procedure. Next, the animals were intubated with an endotracheal tube of adequate diameter and maintained undergeneral inhalation anesthesia. Mechanical ventilation was utilized at a pressure of 10cmH_2O (I/E 1:2), with the respiratory rate adjusted to maintain the end-tidal carbon dioxide partial pressure ($ETCO_2$) between 35 and 45mmHg. Physiological solution was administered at 3mLkg^{-1}h^{-1}, via a catheter placed in a cephalic vein, using an infusion pump[c].

Systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressure were measured by means of a sensor positioned in the dorsal pedal artery and connected to a transducer zeroed at the level of the sternum, heart rate (HR) and cardiac rhythm were measured by means of electrodes via derivation II, and hemoglobin oxygen saturation (SaO_2) were measured using a sensor positioned on the tongue[d]. The temperature of the animals was kept between 37 and 38°C, by use of a thermal mattress. Patient preparation and stabilization time was standardized to 30 minutes.

After the period of preparation and stabilization, HR, SAP, MAP, DAP, $ETCO_2$, end-tidal isoflurane concentration (ETIso), and SaO_2 (baseline) were measured. Afterwards, ETIso was elevated by 0.25% every 3 minutes until MAP reached 40 to

60mmHg. MAP was maintained within this range for 60min. In case MAP was below 40mmHg, ETIso was reduced. Afterwards, the variables were measured again (0 minute), and every 10minutes, for 60 minutes. Bleeding time was also determined before induction of hypotension and at 30 and 60 minutes, by puncture of the inner side of the ear using a lancet after antiseptic skin preparation.

Hepatic and renal evaluation

Blood samples were drawn by jugular venipuncture for determination of ALT, AP and U before the anesthetic procedure (baseline), and at 24 hours and 7 days post-hypotension. Cr and Na^+ were also determined at the described times plus at 48 hours post-hypotension. Total leukocytes, erythrocytes, hematocrit (Ht), hemoglobin (Hb), mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentrations were measured at baseline and 48 hours and 7 days post-hypotension.

A volume of 5mL of urine was collected by cystocentesis with a 24G needle, at baseline and at 24 hours, 48 hours and 7 days post-hypotension, for determination of Cr, GGT (DeSCHEPPER et al., 1989), urine specific gravity, protein, albumin and sodium concentrations.

Fractional excretion of Na^+ (FENa) was calculated using the equation $FENa = (U_{Na} \times P_{Cr}) / (P_{Na} \times U_{Cr}) \times 100$, where U_{Na} is the concentration of Na^+ in the urine, P_{Cr} is the plasma concentration of creatinine, P_{Na} is the plasma concentration of Na^+ and U_{Cr} is the urinary concentration of creatinine (WALDROP, 2008). Total protein and albumin in the urine were measured using commercial kits and spectrophotometry[e]. Urinary protein was determined by the pyrogallol red method[f] at 600nm and urinary albumin by the bromocresol green method[g] at 625nm. The results obtained were corrected using the volume of urine produced, considering the ratios between urine protein and creatinine, and between urine albumin and creatinine.

Finally, the animals were observed for possible clinical abnormalities such as anorexia, vomiting, diarrhea or constipation, emesis and gastrointestinal bleeding during the 7 days of evaluation.

Statistical analysis

The data were tested for normal distribution by the Kolmogorov-Smirnov[h] test and statistical analysis was carried out by repeated measures ANOVA followed by Dunnett's test for comparisons within each group, in relation to time 0min (anesthetic) or baseline (biochemical) for all variables, except clinical abnormalities, bleeding time, urine specific gravity, GGT, urine GGT-creatinine ratio, urine protein/Cr ratio and urine albumin-Cr ratio. Comparisons between the groups at each time were carried out using the unpaired t-test. Non-parametric data (bleeding time, urine specific gravity, GGT, urine GGT-creatinine ratio, urine protein-Cr ratio and urine albumin-Cr ratio) were evaluated by Friedman's test followed by Dunn's test for comparisons within each group, in relation to baseline, and by Mann-Whitney test for comparisons between the groups at each time. Parametric variables were expressed as mean ± standard deviation and non-parametric variables were expressed as median ± interquartile range. The differences were considered significant when $P<0.05$.

RESULTS

The doses of tepoxalin were similar between the groups: 25.1mgkg^{-1} for the PRE group (4.0±0.78kg) and 24.2mgkg^{-1} for the POST group (4.1±0.31kg).

The anesthetic procedure was effective in maintaining the target blood pressure. The variables evaluated remained stable and within the physiological range, with the exception of arterial pressures, obviously due to the induced hypotension with isoflurane (Table 1). No alterations were observed in bleeding time (Table 1).

There were no differences in ALT, AP, U, Cr, Ht and Hb in comparisons within or between groups at each time (Table 2). In urinary analysis (Table 2), there were no observed alterations in urine especific gravity, Cr, GGT and GGT-creatinine ratio. FENa was elevated only at 7 days of evaluation in PRE. The urine protein-creatinine ratio in PRE was higher than in POST at 24 and 48 hours post-hypotension, while no alterations were observed for the urine albumin-creatinine ratio (Table 2) or clinical abnormalities, during the study.

DISCUSSION

We studied the administration of tepoxalin in cats because of the scarcity of information on its clinical effects in this species and the easiness of administration since the commercially available tablets dissolve rapidly in contact with the moist oral cavity. The use before and after the anesthetic procedure allowed the comparison of administrations at different time points, because as noted, the use of NSAIDS is routine in analgesic treatment and since

Table 1 -Heart rate (HR), systolic (SAP), mean (MAP) and diastolic arterial preasure (DAP), hemoglobin oxygen saturation (SaO_2), end-tidal isoflurane concentration (ETIso) and bleeding time obtained from twelve cats subjected to hypotension with isoflurane and pretreated (PRE) or treated after hypotension (POST) with 25mgkg^{-1} of tepoxalin during 5 days. Values of HR, SAP, MAP, DAP, SaO_2 and ETIso expressed as mean ± SD. Bleeding time expressed as median ± interquartile range. P<0.05.

Group	Moments (min)							
	Baseline	0	10	20	30	40	50	60
HR (bpm)								
PRE	148±25	146±23	137±12	136±14	136±14	142±10	140±9	139±8
POST	148±27	145±22	144±26	134±18	132±18	128±16	126±16	132±7
SAP (mmHg)								
PRE	111±13	77±12	75±8	76±6	74±13	76±7	75±6	76±9
POST	99±18	76±8	79±9	75±5	77±8	78±3	76±11	88±15
MAP (mmHg)								
PRE	72±18	50±8	46±10	44±6	48±9	44±8	47±8	47±8
POST	71±13	45±5	50±7	46±5	49±3	47±2	48±8	57±12
DAP (mmHg)								
PRE	52±12	25±10	25±8	28±7	27±12	26±10	28±8	32±10
POST	44±17	26±3	29±8	25±3	31±7	29±2	30±13	36±10
SaO_2 (%)								
PRE	98±1	98±2	97±2	98±1	99±1	99±1	97±1	98±2
POST	98±1	98±1	98±1	98±1	99±1	98±1	98±2	97±2
ETIso (V%)								
PRE	2.0±0.4	2.5±0.6	2.4±0.6	2.3±0.5	2.3±0.6	2.4±0.5	2.4±0.6	2.2±0.8
POST	2.2±0.7	2.1±0.5	2.3±0.5	2.3±0.5	2.3±0.5	2.2±0.4	2.1±0.3	2.1±0.3
Bleeding time (seconds)								
PRE	90[45;150]	NA	NA	NA	75[60;180]	NA	NA	75[60;120]
PST	120[30;120]	NA	NA	NA	75[30;150]	NA	NA	75[30;120]

NA = not assessed.

hypotension is very common during anesthesia (PASCOE et al., 2006). Thus, it was possible to see if tepoxalin favored a possible worsening of renal ischemia, common in hypotension (POWER et al., 1992; PERKOWSKI & WETMORE, 2006).

Other studies have demonstrated that tepoxalin has an inhibitory action on COX-1 and 5-LOX in cats (GOODMAN et al., 2010), and contrary to findings in dogs (KNIGHT et al., 1996), its administration in cats does not cause inhibition of COX-2 (GOODMAN et al., 2010). One of the advantages associated with the use of tepoxalin in relation to NSAIDS, with action only on the COX pathway, is the reduced levels of leukotriene B_4, which is involved in the recruitment, activation and prolonged action of neutrophils and other inflammatory cells, resulting in injury to the gastrointestinal mucosa (RAINSFORD, 1993; BERTOLINI et al., 2001).

Gastrointestinal alterations are the main adverse effects related to the administration of NSAIDS in dogs (LUNA et al., 2007). In the present study, no clinical abnormalities indicative of gastrointestinal toxicity, such as anorexia, emesis and gastrointestinal bleeding, were found during the period of tepoxalin administration. However, laboratory tests and imaging would provide more accurate information in this respect.

In the present study, bleeding time evaluated the possible interference of tepoxalin with platelet function during the anesthetic period, since one of the posible adverse effects occuring after the administration of NSAIDS is reduced platelet function (PERKOWSKI & WETMORE, 2006), because these drugs can impair the production of thromboxane A_2, through the inhibition of COX (BOSTRÖM et al., 2006). However, there were no changes observed in the groups of cats treated with this drug during induced hypotension. This variable was also unchanged in dogs given preoperative tepoxalin (KAY-MUGFORD et al., 2004).

In vitro aggregation tests may be overly sensitive when used to predict drug interference with *in vivo* coagulation and hemostasis (LEMKE

Table 2 - Serum levels of alanine aminotransferase (ALT), alkaline phosphatase (AP), urea (U), creatinine (Cr), hematocrit (Ht) and hemoglobin (Hb) and Urine specific gravity, urinary concentrations of creatinine (UCr) and gamma-glutamyltransferase (GGT), urinary GGT-creatinine ratio, fractional excretion of sodium (FENa), urinary protein-creatinine ratio and urinary albumin-creatinine ratio obtained from twelve cats subjected to hypotension with isoflurane and pretreated (PRE) or treated after hypotension (POST) with 25mgkg^{-1} of tepoxalin during 5 days. Values of ALT, AP, U, Cr, Ht, Hb, UCr and FENa expressed as mean ± SD. Values of urine specific gravity, GGT, urinary GGT-Cr ratio, urinary protein-creatinine ratio and urinary albumine-creatinine ratio expressed as median ± interquartile range. P<0.05.

Group	Moments			
	Baseline	24 hours	48 hours	7 days
ALT (IUL^{-1})				
PRE	44±11	46±13	NA	45±11
POST	68±25	78±21	NA	54±16
AP (IUL^{-1})				
PRE	56±21	56±21	NA	53±29
POST	38±13	49±25	NA	35±8
U (mg dL^{-1})				
PRE	58±14	58±17	NA	60±10
POST	53±9	49±14	NA	59±5
Cr (mgdL^{-1})				
PRE	1.22±0.12	1.10±0.09	1.08±0.12	1.20±0.17
POST	1.32±0.18	1.20±0.13	1.13±0.18	1.17±0.10
Ht (%)				
PRE	42.3±4.5	NA	41.2±8.3	42.9±9.4
POST	43.9±2.9	NA	44.6±7.8	43.3±7.3
Hb (gdL^{-1})				
PRE	13.7±1.6	NA	12.9±2.4	13.6±2.9
POST	14.2±1.1	NA	14.3±2.65	13.7±2.4
Urinespecific gravity				
PRE	1.071±0.017	1.066±0.017	1.065±0.008	1.072±0.011
POST	1.060±0.013	1.075±0.006	1.066±0.008	1.059±0.010
UCr (IUL^{-1})				
PRE	276±56	233±32	241±26	264±67
POST	297±94	274±29	293±80	221±63
Urinary GGT (IUL^{-1})				
PRE	22±7.0	20±8.0	18±8.0	16±1.0
POST	25±6.0	15±3.0	28±15	16±14
Urinary GGT-Cr rate				
PRE	0.080±0.02	0.093±0.05	0.075±0.03	0.064±0.02
POST	0.098±0.05	0.055±0.01	0.094±0.43	0.097±0.02
FENa (%)				
PRE	0.55±0.13	0.66±0.06	0.85±0.20	0.94±0.45*
POST	0.60±0.15	0.65±0.15	0.52±0.39	0.79±0.24
Urinaryprotein-Cr ratio				
PRE	0.14[0;2.39]	1.79[0;2.02]^{A}	1.92[0;2.23]^{A}	1.61[0;1.91]
POST	0.24[0;0.59]	0.30[0;0.73]^{B}	1.15[0;3.07]^{B}	2.00[0;5.1]
Urinaryalbumin-Cr ratio				
PRE	0[0;0.03]	0[0;0]	0[0;0.1]	0[0;0]
POST	0[0;0]	0[0;0]	0.063[0;0.28]	0.061[0;3.58]

NA = not assessed.

* Differed from baseline.

Identical superscript letters indicate values that do not differ significantly.

et al., 2002). Bleeding time is the most common *in vivo* method used to investigate platelet function abnormalities (BRONDANI et al., 2009). Bleeding time was measured at the external surface of the ear, unlike previous studies in cats (CARROLL et al., 2005; BRONDANI et al., 2009) and the results were comparable to tests performed at the oral mucosa in cats (CARROLL et al., 2005). This test has been criticized when used as a screening test to predict surgical bleeding because of poor predictive performance (LIND, 1991). However, when serial tests are performed on the same patient, as in the present study, information can be gained about the effects of a treatment on *in vivo* platelet function (KAY-MUGFORD et al., 2004).

Serum creatinine and urea levels remained in the physiological range and showed no statistical differences between the groups. These are the routine tests used to investigate kidney function in cats treated with NSAIDs (SLINGSBY & WATERMAN-PEARSON, 2002; CARROLL et al., 2005; TOBIAS et al., 2006). However, it should be pointed out that these variables do not change until more than 66% of nephrons are non-functional (FINCO, 1995; DiBARTOLA, 2010). Thus, their interpretation is limited as a renal indicator. In this case, the evaluation of urinary enzymes is more reliable, which can be used to assess the degree of renal injury through the increase in their excretion, which is normally correlated with the severity of renal damage (CLEMO, 1998).

In the present study, we measured urinary GGT, a glycoprotein found in the microvilli of the proximal tubule, where increased levels give an early indication of injury to the renal tubules, since elevations of this enzyme are sometimes seen without changes in urea and creatinine concentrations (GRECCO et al., 1985; RIVERS et al., 1996). The reported reference values for urinary GGT activity in cats is $19.4\pm10.3 IUL^{-1}$ (MATSUOKA, 1995), and GGT levels of the cats studied stayed within this range, corroborating the findings in dogs subjected to hypotension, in which the administration of tepoxalin also did not cause alterations in urinary GGT excretion (LOPES et al., 2013).

Comparing the dose of tepoxalin indicated for dogs, which is $20 mgkg^{-1}$ on the first day and $10 mgkg^{-1}$on the following days (KAY-MUGFORD et al., 2004; AGNELLO et al., 2005), it should be noted that higher doses of tepoxalin were used in cats in the present study. Despite the apparent overdose, it should be pointed out that urinary GGT stayed within the physiological range, even after its administration on consecutive days, indicating the lack of injury to renal tubules in the cats in the present study.

Another indicator of early renal damage employed in this study was FeNa, in which again the values observed were within the normal range, that is, below 1% (DiBARTOLA, 2010; LEFEBVRE et al., 2008). The presence of electrolytes in the urine occurs as a result of processes of tubular reabsorption and secretion, and increase in FENa is an indicator of acute tubular dysfunction (LOBETTI & LAMBRECHTS, 2000; LEFEBVRE et al., 2008).

Damage to proximal tubules causes loss of microvillosities with consequent decrease in reabsorption and increase in protein excretion (RIVERS et al., 1996), which is of diagnostic or prognostic value in the initial detection and confirmation of renal disease, and can be of considerable importance in the evaluation of therapeutic efficacy and of renal disease progression (ROSSI et al., 2012). In healthy cats, urine protein-creatinine ratio is equal to or less than 0.2. A ratio between 0.2 and 0.4 is considered the limit; a ratio above 0.4 is indicative of chronic tubulointerstitial or glomerular renal disease; and a ratio above 2.0 is suggestive of glomerular disease (SYME et al., 2006; GRAUER, 2007).

The data refering to proteinuria and albuminuria in the present study suggest the occurrence of discrete renal injury, with urine protein-creatinine ratio above 0.4 in both groups, which could have been caused by hypotension as well as the administration of tepoxalin. Moreover, the increase in proteinuria occurred at the first moment in PRE (24h), suggesting that tepoxalin administered before the anesthetic procedure may have exacerbated the renal injury. In conscious healthy cats, short-term meloxicam administration did not alter proteinuria and glomerular filtration rate (GOODMAN et al., 2009). In cats with reduced renal mass, neither meloxicam nor acetylsalicylic acid caused significantly elevated proteinuria. This study assumes that glomerular filtration rate of euvolemic cats with normal or reduced renal function is not dependent on cyclooxygenase function (SURDYK et al., 2013). A long-term maintenance dose of meloxicam ($0.02 mgkg^{-1}$) can be safely administered in aged cats, even if they have chronic renal disease (GOWAN et al., 2011).

When proteinuria is detected, it is important to localize the source; unfortunately, sediment urinalysis was not done in this study. The cut off point for the urine protein-creatinine ratio does not detect patients with low-level albuminuria, and thus, the determination of the urine albumin-

creatinine ratio is important to avoid false-negative results of albuminuria (LYON et al., 2010).

In the present study, no hepatic alterations were observed, since there were no changes in the ALT and AP enzyme levels, even after the administration of tepoxalin for consecutive days. ALT and AP were within the physiological range for the species, and there was no difference between the groups. Hepatotoxicity due to the use of NSAIDS can occur due to the release of metabolites conjugated with glucuronic acid, which can cause a hepatic immunological response (BAILEY & DICKINSON, 2003). Furthermore, reduced hepatic glucuronidation of NSAIDS in cats can minimize this mechanism of metabolite formation (LASCELLES et al., 2007).

CONCLUSION

On the basis of our results, we conclude that tepoxalin administered prior to or after anesthesia-induced hypotension, as well as given daily for five days following anesthesia, did not cause alterations in hepatic enzymes, serum concentrations of urea and creatinine, fractional sodium excretion and urinary GGT in healthy cats. However, there were indications of discrete renal injury, resulting in proteinuria, in animals medicated with tepoxalin.

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COMMITTEE ON ETHICS AND BIOSAFETY

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SOURCES AND MANUFACTERS

a - Zubrin® - Intervet Schering-Plough Animal Health, Cruzeiro, SP, Brazil.
b - Forane® - Abbott Laboratórios do Brasil LTDA, São Paulo, SP, Brazil.
c - Digipump SR8X® - Digicare Biomedical Technology, Boynton Beach, FL, USA.
d - LifeWindow™ 6000V® - Digicare Biomedical Technology, Boynton Beach, FL, USA.
e - LabsystemsMultiskan MS® - Labsystems, Helsinki, Filand.
f - Sensiprot® - Labtest Diagnóstica SA, Lagoa Santa, MG, Brazil.
g - Albumina colorimétrico® - LaborlabProd. Lab. Ltda, Guarulhos, SP, Brazil.
h - GraphPad Prism 5.0 GraphPad Prism® - GraphPad Software Inc, San Diego, CA, USA.

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