RESEARCH PAPER

Effect of tepoxalin on renal function and hepatic enzymes in dogs exposed to hypotension with isoflurane

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Abstract

Objective   To evaluate the possible renal and hepatic toxicity of tepoxalin in dogs exposed to hypotension during isoflurane anesthesia.

Study design   Prospective, randomized experimental study.

Animals   Twenty adult mixed-breed dogs, weighing 18.8 ± 2.8 kg.

Methods   The animals received 10 mg kg^{-1} tepoxalin orally 2 hours before the anesthetic procedure (PRE; $n = 6$), or 30 minutes after anesthesia (POST; $n = 6$), along with a control group (CON; $n = 8$), which were only anesthetized. The PRE and POST groups also received the same dose of tepoxalin for 5 days post-procedure. All dogs were anesthetized with propofol and maintained with isoflurane and the end-tidal isoflurane (Fᴇ′Iso) was increased until mean arterial pressure decreased to 50–60 mmHg. These pressures were maintained for 60 minutes. Heart rate, arterial pressures and Fᴇ′Iso were recorded at 0, 10 and every 10 minutes up to 60 minutes of hypotension. Blood gases, pH, electrolytes and bleeding time were analyzed before and at 30 and 60 minutes of hypotension. Renal and hepatic changes were quantified by serum and urinary biochemistry and creatinine clearance.

Results   Serum concentrations of alanine amino transferase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT), blood urea nitrogen (BUN) and creatinine (Cr), and urinary output, urinary Cr, Cr clearance, and GGT:Cr ratio remained stable throughout the evaluations. During the anesthetic procedure there were no important variations in the physiological parameters. No side effects were observed in any of the groups.

Conclusions and clinical relevance   Tepoxalin did not cause significant effects on renal function or cause hepatic injury in healthy dogs exposed to hypotension with isoflurane, when administered pre- or postanesthetic and continued for five consecutive days.

Keywords hepatotoxicity, inhalation anesthesia, nephrotoxicity, nonsteroidal anti-inflammatory drugs.

Introduction

Whenever surgery is performed, pain is an expected effect and analgesics should be administered as a preventive treatment, in order to improve peri- and postoperative analgesia (Hellyer & Gaynor 1998). Nonsteroidal anti-inflammatory drugs (NSAIDs) used preoperatively are effective in the treatment of acute perioperative pain (Lascelles et al. 2005). However, some of these drugs can cause adverse

effects on digestive, renal, hepatic or platelet function (Kay-Mugford et al. 2004).

Geriatric, dehydrated or hypotensive animals have a greater risk of renal side effects with the use of NSAIDs (Lascelles et al. 2005), and that is why these patients are rarely included in clinical studies with these drugs (Breyer & Harris 2001). A decrease in peripheral perfusion associated with the inhibition of local production of prostaglandins caused by NSAIDs might lead to renal ischemia (Perkowski & Wetmore 2006).

Some NSAIDs such as flunixin meglumine, phenylbutazone and ketoprofen are classified as nonspecific cyclooxygenase (COX) inhibitors (Lees et al. 2004a; Fox 2006). Others, such as carprofen, meloxicam and nimesulide, inhibit COX-2 in a preferential way; the coxibs, such as valdecoxib, rofecoxib, lumaricoxib, etoricoxib and firocoxib, act selectively (Lees et al. 2004a; Less et al. 2004b; Clark 2006). Finally, there are those that interfere with the COX and lipoxygenase (LOX) pathways, as in the case of tepoxalin (Clark 2006; Fox 2006).

The use of tepoxalin has been cited as a way of reducing the risks of renal side effects associated with the use of NSAIDs (Gambaro & Perazzella 2003). Oral administration after a single preoperative dose in healthy dogs did not cause significant effects on hemostasis or renal and hepatic functions (Kay-Mugford et al. 2004). Similarly, there were no significant differences found between the administration of tepoxalin and placebo in dogs, either in the pre-anesthetic period or 24 hours afterwards, with respect to complete blood count, biochemical variables or urinalysis (Matthews et al. 2007).

Reports in the literature have demonstrated the safe use of this drug in young, healthy dogs (Kay-Mugford et al. 2004; Matthews et al. 2007). However, there are no studies assessing the deleterious effects caused by the preventive administration of tepoxalin in hypotensive dogs, as well as the effects of a 5-day course of tepoxalin administration in these animals. Thus, the aim of the present study was to evaluate renal and hepatic alterations caused by the pre- and postanesthetic administration of tepoxalin in dogs exposed to hypotension, and also to determine the effects caused after daily administration in these animals, following the anesthetic procedure. We hypothesized that tepoxalin would not cause measureable renal or hepatic changes in dogs following hypotension under anesthesia and a 5 day course of the drug.

Material and methods

This study was approved by the Institutional Animal Care Committee. Twenty adult mixed dogs were included in the study, males and females, weighing 18.8 ± 2.8 kg. The health of each animal was established by a physical examination and laboratory tests, with a complete blood cell count and biochemical profile. The animals were acclimatized for at least 2 weeks prior to the experiment, housed in individual cages of $1 \ m^3$, and with free access to commercial food and water. Seven days before the anesthetic procedure, in order to assess the renal health of the animals, complete blood count, biochemical tests (renal and hepatic), glomerular filtration rate (GFR), by means of urinary output (UO), and creatinine clearance, were performed. The values obtained were utilized as baseline values for later comparisons.

For the measurement of creatinine clearance, the animals were anesthetized with 5 mg kg^{-1} propofol (Diprivan 1%; Cristália Prod. Quím. Farm. Ltd, Brazil), intravenously (IV), to carry out bladder catheterization. The dogs were fasted for a 12 hour period prior to anaesthesia to place the urinary catheter and they were maintained catheterized for a period of 24 hours in order to obtain total volume of urine and urinary creatinine concentration. This was repeated on days 2 and 7. Blood samples were collected 12 hours after placement of the urinary catheter, to quantify serum creatinine. Creatinine clearance was determined utilizing the following formula (Kay-Mugford et al. 2004):

$$\text{Creatinine clearance} = \frac{[\text{urine creatinine}] \times \text{urine volume}}{[\text{serum creatinine}] \times kg \times \text{minutes}}$$

Experimental design

The animals were divided into three groups and targeted to receive 10 mg kg^{-1} of tepoxalin (Zubrin; Intervet Schering-Plough Animal Health, São Paulo, Brazil) orally 2 hours before the anesthetic procedure (PRE; $n = 6$, actual dose $= 10.2 \pm 0.6$ mg kg^{-1}), or the same dose of drug 30 minutes after anesthesia (POST; $n = 6$, actual dose $= 10.8 \pm 0.8$ mg kg^{-1}), along with a control group (CON; $n = 8$), which were only anesthetized. Moreover, the PRE and POST animals also received the same dose of tepoxalin, placed on the tongue of animals every 24 hours for 5 days post-procedure.

The animals were fasted for a 12-hour period prior to general anesthesia. A 22-gauge 2.5 cm length

cephalic venous catheter (Nipro Medical Ltd, São Paulo, Brazil) was placed percutaneously. Propofol (5 mg kg^{-1} slowly administered) was used IV for the induction of anaesthesia and saline (NaCl 0.9%; JP Ind Farm SA, São Paulo, Brazil) was administered at 5 mL kg^{-1} hour^{-1}. The dogs were orotracheally intubated with an endotracheal tube and connected to a semiclosed circle system, and kept at 1.3% end-tidal isoflurane (Fe′Iso) (Forane; Abbott, Brazil), diluted in 100% oxygen. Mechanical ventilation was initiated at 15 cmH$_2$O peak inspiratory pressure and inspiration/expiration ratio of 1:2.

Immediately after connecting the endotracheal tube to the anesthetic system, a dorsal pedal artery was catheterized with a 22-gauge 2.5 cm length catheter, connected to a pressure transducer filled with heparin solution and zeroed at the level of the manubrium and connected to a multiparametric monitor (PM 9000 Express–Mindray Medical International Ltda, Shenzhen, China), to measure systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures and to collect blood for determination of pH, blood gases and electrolytes. Bladder catheterization was performed for later evaluation of creatinine and UO. Respiratory rate was adjusted so that the end-tidal carbon dioxide tension (Pe′CO$_2$) remained between 35 and 45 mmHg (4.7–6 kPa), measured by a gas analyzer (Poet IQ2-Criticare System, model 8500Q, Inc, WI, USA). Heart rate (HR) and cardiac rhythm were monitored by means of a lead II electrocardiogram. The body temperature of the animals was measured using a digital thermometer and kept between 36 and 37.5 °C, using a thermal mattress (Ortovet Ltd, Brazil). Time to stabilize and prepare the patient was standardized to 30 minutes.

After the above period, HR, SAP, MAP, DAP and Fe′Iso were determined, and these data were considered baseline, where Fe′Iso remained at 1.3%. Fe′Iso was increased by 0.25% every 3 minutes, until MAP reached values of 50–60 mmHg (0 minutes). The parameters were recorded at 0 minutes and every 10 minutes for 60 minutes of hypotension. One mL of arterial blood was collected in heparinized syringes, at 0, 30 and 60 minutes, for immediate analysis (Roche OMNI C, Brazil) of pH, partial pressures of oxygen (PaO$_2$) and carbon dioxide (PaCO$_2$), bicarbonate (HCO$_3^-$), sodium (Na$^+$) and potassium (K$^+$) concentrations, and percent oxygen saturation of hemoglobin (SaO$_2$–based on human hemoglobin). Bleeding time was also evaluated at 0, 30 and 60 minutes, with the help of a lancet. First, the

inside of the ear was aseptically cleaned and then punctured, where bleeding time was determined with the use of a filter paper and expressed in seconds. Hematological parameters, as complete blood count (CBC), hemoglobin (Hb), packed cell volume (PCV), total protein (TP) and leukocytes were evaluated at 24 hours and 7 days post-hypotension.

Renal and hepatic evaluation

Venous blood samples were collected 7 days before the procedure to determine health, and at 12 hours, 24 hours and 7 days post-hypotension. Serum concentrations of blood urea nitrogen (BUN), creatinine (Cr), alanine amino transferase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT). Urine samples (5 mL) were also obtained 7 days before the procedure to determine health, and at 12 hours, 24 hours and 7 days post-hypotension to measure the urinary concentrations of GGT, Cr and calculate the urinary GGT:Cr ratio. During the 7-day interval, the urinary catheter was removed (on 2nd and 7th days) and the dogs were maintained with free access to water and food. Creatinine clearance was measured over 24 hours on the day following the anesthetic procedure and on the 7th day postanesthesia, in order to examine for possible changes in GFR, indicating renal injury. Finally, the animals were observed for possible side effects such as anorexia, emesis or gastrointestinal bleeding, in any phase of evaluation. At the end of the study, all animals were neutered and adopted.

Statistical analysis

Data were tested for normal distribution by the Kolmogorov–Smirnov test and statistical analysis (GraphPad Prism, GraphPad Software Inc., San Diego, CA, USA) was carried out by analysis of variance (ANOVA) for repeated samples followed by Dunnett's test for comparisons within each group in relation to time 0 minutes (perianesthetic) or preanesthetic (biochemistry) for all parameters, except side effects, bleeding time, leukocytes, Urinary Cr, and GGT:Cr ratio. For those parameters, in the comparisons among groups at each time, a Tukey test was used. Non-parametric data were evaluated by Friedman's test followed by Dunn's test for comparisons within each group, in relation to baseline, and by Kruskal-Wallis test for comparisons among groups at each time. Parametric values were

Table 1 Values of $F_E'Iso$ (%), HR (beat minute^{-1}), SAP, MAP and DAP (mmHg) and bleeding time (seconds) from dogs exposed to hypotension with isoflurane (CON) and pretreated with 10 mg kg^{-1} tepoxalin orally (PRE) or after hypotension (POST). Values of $F_E'Iso$, HR, SAP, MAP and DAP are expressed as mean ± SD. Bleeding time is expressed as median and interquartile ranges

	Group	Minutes Baseline	0	10	20	30	40	50	60
$F_E'Iso$ (%)	CON	1.4 ± 0.4	1.9 ± 0.5	2.4 ± 0.5	2.5 ± 0.5	2.5 ± 0.5	2.6 ± 0.8	2.5 ± 0.6	2.7 ± 0.5
	PRE	1.3 ± 0.3	2.4 ± 0.7	2.3 ± 0.6	2.4 ± 0.4	2.5 ± 0.6	2.6 ± 0.6	2.7 ± 0.6	2.7 ± 0.6
	POST	1.1 ± 0.2	2.0 ± 0.8	2.1 ± 0.7	2.0 ± 0.4	2.5 ± 0.8	2.5 ± 0.8	2.7 ± 0.8	2.8 ± 0.9
HR (beat minute^{-1})	CON	109 ± 21	114 ± 17	112 ± 18	110 ± 19	112 ± 18	112 ± 18	112 ± 16	113 ± 14
	PRE	97 ± 16	98 ± 8	101 ± 14	99 ± 12	101 ± 10	104 ± 9	102 ± 7	106 ± 10
	POST	105 ± 10	112 ± 13	102 ± 11	102 ± 11	102 ± 10	100 ± 10	106 ± 10	107 ± 10
SAP (mmHg)	CON	100 ± 13	76 ± 4	73 ± 5	73 ± 7	73 ± 6	74 ± 10	68 ± 5	72 ± 11
	PRE	105 ± 9	81 ± 2	76 ± 5	74 ± 7	74 ± 7	74 ± 4	75 ± 7	73 ± 5
	POST	107 ± 14	73 ± 6	72 ± 7	78 ± 3	75 ± 7	71 ± 8	75 ± 8	73 ± 10
MAP (mmHg)	CON	70 ± 6	55 ± 3	54 ± 3	54 ± 5	55 ± 3	55 ± 4	53 ± 3	55 ± 4
	PRE	74 ± 3	57 ± 2	55 ± 4	56 ± 3	55 ± 6	55 ± 4	55 ± 5	54 ± 3
	POST	77 ± 10	54 ± 1	53 ± 2	56 ± 3	55 ± 2	54 ± 2	55 ± 4	54 ± 3
DAP (mmHg)	CON	56 ± 6	44 ± 3	45 ± 4	44 ± 5	47 ± 4	46 ± 3	44 ± 3	46 ± 4
	PRE	59 ± 4	44 ± 2	45 ± 3	47 ± 3	46 ± 5	45 ± 4	46 ± 4	44 ± 3
	POST	61 ± 10	44 ± 2	43 ± 3	46 ± 5	48 ± 6	45 ± 2	46 ± 5	45 ± 3
Bleeding time (seconds)	CON	105[60;180]	NA	NA	NA	105[30;150]a	NA	NA	150[60;210]ab
	PRE	135[120;420]	NA	NA	NA	180[120;210] b	NA	NA	210[120;300] b
	POST	135[90;150]	NA	NA	NA	120[60;180] ab	NA	NA	105[90;120] a

Values with the same letter do not differ within a column ($p < 0.05$). NA, not assessed.

expressed as mean ± standard deviation and non-parametric values were expressed as median ± interquartile range. The differences were considered significant when $p < 0.05$.

Results

The Fᴇ′Iso necessary for the maintenance of MAP in the established range was 2.5% (Table 1). During the anesthetic procedure, after the establishment of hypotension, HR, SAP, MAP and DAP did not show significant changes, in comparison with 0 minutes, as well as between the groups at each time (Table 1). Bleeding time did not change during the anesthetic procedure when compared within each group. However, this parameter was significantly greater in PRE compared with CON at 30 minutes and from POST at 60 minutes (Table 1).

Blood gases and electrolytes remained stable and within the reference intervals for the species (DiBartola 2011). However, at 60 minutes, Na^+ concentrations were lower than baseline in PRE and POST, and in comparison between groups, both concentrations in PRE and POST were higher than in CON at 0 minutes. Higher concentrations of K^+ were observed only in POST at 60 minutes, when compared to baseline (Table 2).

The variables corresponding to creatinine clearance (Fig. 1a), urinary Cr, GGT:Cr ratio and UO, remained stable during the evaluations (Table 3). However, the urinary concentrations of GGT were lower in POST in relation to CON at 24 hours and 2 days after hypotension (Fig. 1b). It should be noted that despite the differences between the groups, urinary GGT concentrations remained near the reference interval for the species (13–92 IU L^{-1}) (De Schepper et al. 1989). The serum concentrations of ALT, ALP, BUN and Cr remained within the reference interval for dogs (ALT: 21–102 IU L^{-1}; ALP: 20–156 IU L^{-1}; BUN: 21.4–59.92 mg dL^{-1}; Cr: 0.5–1.5 mg dL^{-1}; GGT: 1.2–6.4 IU L^{-1}) (Table 3).

On the seventh day after hypotension, there was a reduction in leukocyte count in the PRE animals ($p = 0.041$), compared to CON and POST animals, but still within reference range for the species (6000–17000 μL^{-1}). The other hematological parameters remained stable and within reference values (Table 4). No side effects were observed in any of the groups.

Table 2 Values of pH, $PaCO_2$ (mmHg), SaO_2 (%), HCO_3^- (mmol L^{-1}), Na^+ (mmol L^{-1}) and K^+ (mmol L^{-1}) obtained from dogs exposed to hypotension with isoflurane (CON) and pretreated with 10 mg kg^{-1} tepoxalin orally (PRE) or after the hypotension (POST). Values are expressed as mean ± SD.

Parameters	Group	Times (minutes)		
		0	30	60
pH	CON	7.28 ± 0.03	7.28 ± 0.05	7.25 ± 0.06
	PRE	7.29 ± 0.08	7.28 ± 0.04	7.27 ± 0.05
	POST	7.30 ± 0.06	7.32 ± 0.05	7.29 ± 0.07
PaO_2 (mmHg)	CON	377 ± 49.9	373 ± 30.2	371 ± 19.2
	PRE	365 ± 59.3	376 ± 66.1	367 ± 72.5
	POST	396 ± 48.6	373 ± 51.9	374 ± 40.9
$PaCO_2$ (mmHg)	CON	50 ± 6.1	48 ± 4.6	51 ± 5.6
	PRE	49 ± 9.6	48 ± 4.9	50 ± 4.9
	POST	52 ± 3.3	48 ± 3.6	52 ± 9.6
SaO_2 (%)	CON	99.9 ± 0.06	99.9 ± 0.04	99.9 ± 0.06
	PRE	99.9 ± 0.09	99.9 ± 0.09	99.9 ± 0.08
	POST	99.9 ± 0.05	99.9 ± 0.05	99.9 ± 0.08
HCO_3^- (mmol L^{-1})	CON	22.7 ± 2.1	22.2 ± 1.5	21.9 ± 1.2
	PRE	22.9 ± 1.3	22.2 ± 1.6	22.3 ± 1.7
	POST	24.4 ± 1.6	23.7 ± 1.9	24.0 ± 2.1
Na^+ (mmol L^{-1})	CON	145.6 ± 1.7 a	145.2 ± 2.6	145.2 ± 1.9
	PRE	148.5 ± 1.4 b	147.7 ± 1.4	147.1 ± 1.4*
	POST	148.7 ± 1.1 b	147.7 ± 2.3	146.9 ± 1.7*
K^+ (mmol L^{-1})	CON	4.4 ± 0.5	4.7 ± 1.0	4.8 ± 1.2
	PRE	4.4 ± 0.4	4.5 ± 0.6	4.9 ± 0.9
	POST	4.3 ± 0.1	4.5 ± 0.4	4.9 ± 0.4*

a,b, different letters at each time point are significantly different ($p < 0.05$). *Significantly different from 0 minutes ($p < 0.05$).
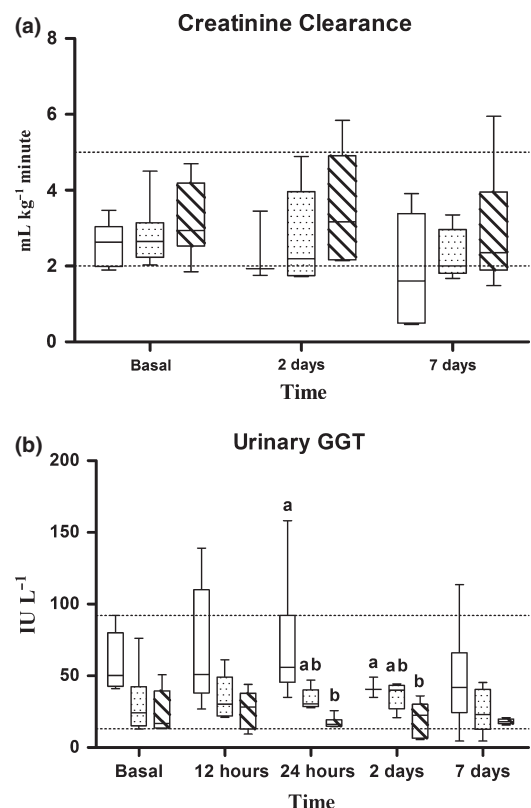
(a)

Creatinine Clearance

(b)

Urinary GGT

Figure 1 Creatinine clearance (mL kg^{-1} minute^{-1}) (a) and urinary GGT (IU L^{-1}) (b) from dogs exposed to hypotension with isoflurane (CON–blank boxes) and pre-treated with 10 mg kg^{-1} tepoxalin orally (PRE–dashed boxes) or after the hypotension (POST–diagonal line boxes). Values expressed as median (trace) and 2.5–97.5 interquartile range. Dashed lines represent the reference range for dogs. Reference intervals: creatinine clearance: 2–5 mL kg^{-1} minute^{-1}; urinary GGT: 13–92 IU L^{-1}

Discussion

Tepoxalin did not cause significant effects on renal and hepatic enzymes, when administered in the preoperative period of young, healthy dogs (Kay-Mugford et al. 2004), but this NSAID had not been tested in hypotensive dogs. Arterial hypotension is one of the most common complications observed during anesthesia in small animals and, according to the findings at the Ontario Veterinary College (1998–2001), 36% of all ASA II dogs submitted to anesthesia had some hypotension (mean arterial pressure <60 mmHg) at some point in the anesthetic period (Chen et al. 2007). This situation hinders the use of NSAIDs in the preoperative period due to the risk of causing renal ischemia, through inhibition of prostaglandin synthesis (Perkowski & Wetmore 2006).

In the present study, we chose to maintain hypotension, with MAP values between 50 and 60 mmHg, using isoflurane concentration (Bernard et al. 1990). Some similar studies did not administer fluids during the anesthetic procedure (Boström et al. 2006; Junot et al. 2008), but we decided to provide fluids at 5 mL kg^{-1} hour^{-1}, according to the recommended basal administration rate of fluids (DiBartola & Bateman 2011), to avoid interference with MAP values.

As some NSAIDs can contribute to an increase in bleeding time, many clinicians prefer to administer these drugs in the postoperative period (Bonnie 2002). However, the bleeding time was not significantly different in dogs treated with tepoxalin or placebo, in the preoperative period (Kay-Mugford et al. 2004).

We chose to determine creatinine clearance and urinary levels of GGT, besides using routine parameters, i.e., the determination of serum urea and creatinine. Since creatinine is produced by the metabolism of phosphocreatine and excreted by glomerular filtration, the clearance of creatinine can be used to estimate GFR, which is considered a more sensitive indicator of renal function compared to serum biochemical parameters (Heiene & Moe 1998). In the present study, creatinine clearance was stable, where there were no differences between the measurements at all times evaluated in both groups. These findings differ from that previously reported for other NSAIDs, such as carprofen and cetoprofen (Forsyth et al. 2000), proving that tepoxalin did not alter GFR in dogs submitted to hypotension, and therefore, demonstrating it to be a safe NSAID with respect to a renal function.

γ-glutamyl transferase is a glycoprotein that comes from the microvilli of the proximal tubule and of the hepatic and biliary epithelium and high concentrations in urine indicate damage to tubular cells, reflecting greater release as well as incapacity of reabsorption of the glycoprotein. Therefore, an increase in the urinary concentrations of GGT indicates early damage of the renal parenchyma, since elevated concentrations of GGT are often present without changes in concentrations of urea and creatinine (Uechi et al. 1994; Palácio et al. 1997). Thus, the determination of urinary GGT can be useful in the identification of acute nephrotoxicity (Clemo 1998). Although urinary GGT can show a temporary increase after anesthesia in dogs (Knight et al. 1996), in this study, the concentrations

Table 3 Urinary Cr (mg dL⁻¹), GGT:Cr ratio, urinary output (mL kg⁻¹ hour⁻¹), serum ALT (IU L⁻¹), ALP (IU L⁻¹), BUN (mg dL⁻¹), Cr (mg dL⁻¹) and GGT (IU L⁻¹) obtained from dogs exposed to hypotension with isoflurane (CON) and pretreated with 10 mg kg⁻¹ tepoxalin orally (PRE) or after the hypotension (POST). Values are expressed as mean ± SD. Urinary Cr and GGT:Cr are expressed as median and interquartile ranges.

Parameter	Group	Times				
		Baseline	12 hours	24 hours	2 days	7 days
Urinary Cr (mg dL⁻¹)	CON	144 [114;167]	176 [156;178]	210 [115;208]	120 [115;208]	178 [153;188]
	PRE	180 [103;225]	148 [66;207]	151 [111;173]	172 [157;231]	193 [142;218]
	POST	158 [124;182]	171 [131;199]	151 [136;176]	136 [111;156]	148 [118;162]
GGT: Cr	CON	0.31 [0.16;0.50]	0.33 [0.21;0.57]	0.25 [0.17;0.64]	0.23 [0.19;0.33]	0.16 [0.11;0.48]
	PRE	0.12 [0.11;0.14]	0.24 [0.14;0.75]	0.23 [0.19;0.30]	0.17 [0.14;0.22]	0.13 [0.08;0.19]
	POST	0.16 [0.09;0.23]	0.22 [0.15;0.27]	0.11 [0.09;0.13]	0.10 [0.06;0.23]	0.11 [0.11;0.19]
Urinary output (mL kg⁻¹ hour⁻¹)	CON	0.9 ± 0.5	NA	NA	0.6 ± 0.2	0.7 ± 0.3
	PRE	1.2 ± 1.1	NA	NA	0.6 ± 0.2	0.7 ± 0.4
	POST	0.9 ± 0.3	NA	NA	1.0 ± 0.3	0.9 ± 0.1
ALT (IU L⁻¹)	CON	32 ± 12	36 ± 18	32 ± 18	NA	37 ± 21
	PRE	38 ± 12	32 ± 6	28 ± 9	NA	30 ± 12
	POST	24 ± 7	36 ± 27	38 ± 29	NA	28 ± 8
ALP (IU L⁻¹)	CON	59 ± 15	63 ± 25	59 ± 24	NA	68 ± 34
	PRE	51 ± 55	43 ± 22	44 ± 17	NA	37 ± 10
	POST	76 ± 23	80 ± 19	84 ± 31	NA	85 ± 22
BUN (mg dL⁻¹)	CON	35 ± 9	36 ± 12	31 ± 7	NA	33 ± 13
	PRE	39 ± 23	41 ± 18	36 ± 15	NA	33 ± 14
	POST	27 ± 8	44 ± 8	41 ± 11	NA	35 ± 16
Cr (mg dL⁻¹)	CON	0.9 ± 0.1	0.8 ± 0.1	0.9 ± 0.1	NA	0.9 ± 0.2
	PRE	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.1	NA	1.0 ± 0.2
	POST	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	NA	1.0 ± 0.4
GGT (IU L⁻¹)	CON	3.4 ± 1.8	5.4 ± 2.6	5.7 ± 2.1	NA	5.2 ± 1.8
	PRE	4.9 ± 2.4	4.4 ± 3.0	6.5 ± 3.0	NA	3.4 ± 1.6
	POST	5.6 ± 2.1	6.4 ± 2.9	7.6 ± 3.7	NA	5.4 ± 3.2

NA, not assessed. Reference interval for the laboratory: ALT: 21–102 IU L⁻¹; ALP: 20–156 IU L⁻¹; BUN: 21–60 mg dL⁻¹; Cr: 0.5–1.5 mg dL⁻¹; GGT: 1.2–6.4 IU L⁻¹.

Table 4 Erythrocytes ($\times 10^6$ μL^{-1}), Hb (g dL^{-1}), PCV (%), TP (g dL^{-1}) and leukocyte (μL^{-1}) obtained from dogs exposed to hypotension with isoflurane (CON) and pretreated with 10 mg kg^{-1} tepoxalin orally (PRE) or after the hypotension (POST). Values are expressed as mean $\pm$ SD.

Parameter	Group	Times		
		Baseline	24 hours	7 days
Erythrocytes	CON	5.5 $\pm$ 0.5	5.7 $\pm$ 0.4	5.5 $\pm$ 0.6
($\times 10^6$ μL)	PRE	6.0 $\pm$ 0.8	6.4 $\pm$ 0.6	5.9 $\pm$ 0.6
	POST	5.4 $\pm$ 0.7	5.7 $\pm$ 0.9	5.8 $\pm$ 0.6
Hb (g dL^{-1})	CON	12.6 $\pm$ 1.6	13.1 $\pm$ 1.8	12.7 $\pm$ 1.8
	PRE	14.4 $\pm$ 2.4	15.0 $\pm$ 1.8	13.8 $\pm$ 0.9
	POST	11.1 $\pm$ 1.4	11.6 $\pm$ 1.6	11.7 $\pm$ 1.3
PCV (%)	CON	39 $\pm$ 4.3	40 $\pm$ 3.5	38 $\pm$ 4.1
	PRE	44 $\pm$ 6.5	45 $\pm$ 4.3	42 $\pm$ 2.8
	POST	34 $\pm$ 3.3	36 $\pm$ 5.7	36 $\pm$ 3.7
TP (g dL^{-1})	CON	8.0 $\pm$ 0.5	7.7 $\pm$ 0.7	7.7 $\pm$ 0.5
	PRE	7.8 $\pm$ 0.4	7.8 $\pm$ 0.4	7.6 $\pm$ 0.4
	POST	8.2 $\pm$ 0.7	8.2 $\pm$ 0.3	8.0 $\pm$ 0.3
Leukocyte (μL^{-1})	CON	11033 $\pm$ 2936	15317 $\pm$ 3850	13017 $\pm$ 2308[a]
	PRE	10100 $\pm$ 2178	12640 $\pm$ 2113	9220 $\pm$ 1374[b]
	POST	8517 $\pm$ 2342	15983 $\pm$ 2087	10150 $\pm$ 2812[a]

Different letters at each time point are significantly different ($p < 0.05$). Reference interval to laboratory: Erythrocytes: 5.5–8.5 $\times$ 10^6 μL^{-1}; Hb: 12–18 g dL^{-1}; PCV: 37–55%; TP: 6–8 g dL^{-1}; leukocyte: 6000–17000 μL^{-1}.

remained within the reference intervals, including animals that received tepoxalin 2 hours before hypotension induction.

Renal autoregulation is a feedback mechanism that maintains GFR with variations in blood pressure (Forsyth et al. 2000). However, this process can be ineffective with respect to the maintenance of GFR at MAP below 80 mmHg (Kirchheim et al. 1987). All the dogs in this study showed MAP values below the lower limit supposedly necessary for renal autoregulation to occur and, therefore, all the animals should have been at risk of renal damage. The UO was measured by collecting urine through the urinary catheter. It should be emphasized that the UO values remained close to the lower limit of the reference range (1–2 mL kg^{-1} $hour^{-1}$) for dogs (DiBartola & Bateman 2011) in the majority of evaluations; but this finding was probably influenced by the presence of the urethral catheter, which can causes some discomfort in the animals (Anderson & Day 2008).

Although NSAIDs are primarily biotransformed by the liver, cases of hepatotoxicity are not usually associated with its use in dogs (Knight et al. 1996). In this study, ALT, ALP and GGT stayed within the reference intervals in both groups, demonstrating that tepoxalin does not significantly alter hepatic function in dogs exposed to hypotension.

Conclusions

Prior administration of tepoxalin, or given after the hypotensive procedure, did not cause significant effects on renal function or create hepatic injury in healthy dogs exposed to hypotension for 60 minutes. Similarly, daily administration for 5 days, following the anesthetic procedure, did not alter these organ functions.

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