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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 ($F_E'$Iso) was increased until mean arterial pressure decreased to 50–60 mmHg. These pressures were maintained for 60 minutes. Heart rate, arterial pressures and $F_E'$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 & Perazella 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 ± 0.6 mg $kg^{-1}$), or the same dose of drug 30 minutes after anesthesia (POST; $n = 6$, actual dose = 10.8 ± 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