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ORIGINAL ARTICLE

Effects of preanesthetic administration of metamizole on renal function, blood parameters and bone marrow cells in healthy dogs

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Abstract This study evaluated the systemic effects of metamizole with or without general anesthesia in healthy dogs. Twelve mixed healthy dogs of either sex were divided randomly into two groups (control and anesthesia groups). Following a 12-h period of fasting (food and water), both groups received the first dose of metamizole (35 mg/kg) intravenously and then 4 doses intramuscularly every 12 h after receiving the first dose of metamizole. In the anesthesia group, the animals underwent halothane inhalation anesthesia for 2 h after receiving the first dose of metamizole. The vital signs were monitored but animals did not receive any fluid during anesthesia. Blood samples were taken before fasting, after 12 h of fasting and then 24 and 48 h after the first dose of metamizole for evaluation of CBC, blood urea nitrogen, and serum creatinine. Mucosal bleeding times (MBTs) and bone marrow samples were evaluated prior to the start of the study and after the last dose of metamizole in both groups. The total number of red blood cells, PCV, and BUN values showed a significant increase 12 h after fasting compared with baseline values in both groups. There were no significant differences in bleeding times or bone marrow function compared to baseline in either group. It was concluded that short-term use of metamizole, starting before surgery and anesthesia in normal dogs that have not received fluids, does not have adverse effects on renal, coagulation, blood, and bone marrow functions.

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Introduction

Analgesia should be considered in all surgical and post-traumatic patients and in those with chronic conditions. Non-steroidal anti-inflammatory drugs (NSAID) are commonly given to cats and dogs in the perioperative period to provide postoperative analgesia (Mathews et al. 2001; Carroll et al. 2005). The NSAIDs are believed to provide analgesia by inhibiting generation of prostaglandins via inhibition of cyclooxygenase enzymes. Prostanoids generated by COX enzymes are important players in inflammation as well as in homeostatic mechanisms that help to prevent gastric ulcers and renal damage attributable to hypovolemia (Papich and Messenger 2015).

Preoperative administration of analgesics (preemptive analgesia) can reduce the requirement of postoperative analgesic administration by decreasing peripheral and central sensitization to painful stimuli (Dahl and Kehlet 1993; Lemke et al. 2002b). NSAIDs mainly act at the site of tissue damage, and preoperative administration of NSAIDs may result in better penetration into tissues than when the drug is administered postoperatively (Lascelles et al. 1998; Carroll et al. 2005). NSAIDs have the advantage of being long acting, providing up to 24 h of analgesia, and they are not subject to the need for record keeping of controlled substances (Papich and Messenger 2015).

In healthy dogs and cats, the use of preoperative NSAIDs did not result in alterations of renal function, bleeding time, or any clinically relevant adverse effects (Al-Gizawiy and Rude 2004; Crandell et al. 2004; Forsyth et al. 2000; Slingsby and Waterman-Pearson 2002). Preoperative administration of NSAIDs has the beneficial effects of reducing inflammation

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at the surgical site, minimizing peripheral and central amplification of nociceptive input, and decreasing postoperative pain (Lemke et al. 2002a). However, in anesthetized dogs, hypovolemia (due to blood loss or dehydration) and hypotension may decrease renal perfusion and increase the risk of renal failure in dogs undergoing surgical procedures with concurrent administration of NSAID (Papich and Messenger 2015). Therefore, veterinarians are often reluctant to administer NSAIDs before surgery, because of concerns regarding possible adverse effects such as nephrotoxicity and increased bleeding at the operative site. Since the risk of nephrotoxicity may increase with pre-existing renal disease or hypotension secondary to anesthesia or blood loss, intraoperative fluid administration (crystalloid solutions, 5–10 mL/kg) has been recommended to provide volume replacement and cardiovascular support during anesthesia (Chohan and Davidow 2015).

Metamizole, also known as dipyrone, is an atypical nonsteroidal anti-inflammatory drug (NSAID) which is available in veterinary medicine as a mono-preparation containing 500 mg/mL metamizole sodium. The mechanism of action of metamizole has been postulated to be through the preferential inhibition of a COX-3 isoenzyme (Chandrasekharan et al. 2002). Metamizole has been used for post-operative analgesia in dogs undergoing ovariohysterectomy (Imagawa et al. 2011; Kalchofner Guerrero et al. 2015) or dogs with chronic cancer pain (Flôr et al. 2013). The analgesic and spasmolytic properties of metamizole make it a drug of choice in the therapy of visceral pains affecting the gastrointestinal, biliary, or urinary tracts (Hinz et al. 2007).

The purpose of this study was to mimic a typical 2 h of inhalation anesthesia with prior 12 h of preanesthetic food and water deprivation and investigate the effect of short-term administration of metamizole on kidney function, mucosal bleeding time (MBT), and hematologic and bone marrow parameters in anesthetized dogs that have not received any fluid during inhalation anesthesia.

Materials and methods

This study was approved by the Shiraz University Animal care and Use Committee. Twelve mixed breed dogs (6 males and 6 females) aged 8 months to 4.5 years (mean ± SD, 31 ± 8 months) and weighing 14.5–23 kg (19.3 ± 1.8 kg) were used in this study. All dogs were judged to be healthy based on physical examination, complete blood count (CBC), and serum biochemical analysis. The dogs were divided randomly into two groups: the anesthesia group (group undergoing inhalation anesthesia) and control group (without anesthesia). In both groups, food and water were withheld from dogs for 12 h under the same conditions.

In both groups (control and anesthesia), the first dose of metamizole sodium (35 mg/kg, Novasol, 500 mg/mL, Richter Pharma AG, Wels, Austria) was injected intramuscularly in quadriceps muscles 12 h after food and water deprivation, and then at 12-h intervals for 48 h (a total of 4 doses). Then, in anesthesia group, each dog received acepromazine (0.1 mg/kg, (Woerden-Holland) and morphine (0.5 mg/kg, Darou Pakhsh, Tehran, Iran) mixed in the same syringe and administered intramuscularly, approximately 20 min prior to induction of anesthesia. Anesthesia was induced with a combination of ketamine (5 mg/kg, IV, Alfasan, Woerden, Holland) and diazepam (0.25 mg/kg, IV, Gloucester, Phoenix, Pharma Ltd., England), administered via a pre-placed cephalic venous catheter. Following tracheal intubation, anesthesia was maintained for 2 h with halothane (1.5%, Rhodia Organique Fine LTD, Bristol, UK) in oxygen through a circle system using a small animal anesthetic machine. Dogs were positioned in left lateral recumbency and were allowed to breathe spontaneously throughout anesthesia. During anesthesia, the patient did not receive any fluids and heart (HR) and respiratory rates (RR), arterial oxygen saturation of hemoglobin (SpO_2 [%], by pulse oximetry), and end-tidal carbon dioxide (EtCO2-mmHg) (Oxicap 425, Soor Afarinesh Bartar Co., Tehran, Iran), and indirect arterial blood pressure (using oscillometric blood pressure measuring device, PM 9000; Mindray, P.R. China) and rectal temperature were monitored continuously throughout anesthesia. After the 2-h duration of anesthesia, halothane was discontinued, and dogs were allowed to recover. The dogs of this group, similar to control group, received the same dose of metamizole intramuscularly every 12 h for 48 h.

Sample collection for hematological and biochemical tests for evaluation of CBC, blood urea nitrogen (BUN), and serum creatinine (Cr), blood was collected from the cephalic vein of each dog before fasting (baseline), after 12 h fasting (before administering the first dose of metamizole), and then every 24 h for 2 days. Measurement of BUN and Cr concentrations were performed with urea and creatinine kits (Moarefsazan company, Tehran, Iran) using diacetylmonoxim and Jaffe methods, respectively. Concentrations were determined by the use of the colorimetric technique.

Bleeding time—Mucosal bleeding times (MBTs) were determined on upper lip prior to the start of the study and 5 h after the last dose of metamizole in both groups. A lancet was used to make a vertical incision of standard length and depth, and blood oozing from the incision was blotted using a filter paper. Timing was begun as soon as the mucosal incision was made and continued until the bleeding ceased from the incision, and the MBT was recorded in seconds. The same person performed all MBTs to reduce operator error, and the MBTs were recorded in seconds.

Bone marrow sampling—Bone marrow (BM) samples were collected from the ileum and was evaluated before the start of the study (baseline) and 3 days after the last dose of metamizole. The area was clipped and prepared aseptically. The skin, subcutis, muscle, and periosteum were injected with

2% lidocaine. Following a small stab incision through the skin, the bone marrow needle was inserted and advanced through cortical bone. Then the stylet was removed and bone marrow aspiration was performed using a 10 mL syringe. Slides of bone marrow smears were prepared, dried, and fixed by alcohol and stained by Giemsa stain. In each slide, 500 nucleated cells were counted, and the percentage of erythroid, myeloid, and other cell types (including lymphoid cells, mitotic cells, degenerated cells, etc.) were determined.

Statistical analysis—Data were assessed for normality using a Kolmogorov–Smirnov test. Hematological, biochemical, cardiovascular, respiratory (HR, RR, blood pressure, $EtCO_2$, O_2 saturation), and rectal temperature data during anesthesia were analyzed using repeated measure ANOVA, and if difference were found, Duncan test was performed for post hoc analysis. A paired *t* test was used to compare the paired data obtained from bone marrow analysis and bleeding time in each dog. The data were analyzed using SPSS (version 17; SPSS Inc., Chicago, USA) and a *p* value of ≤0.05 was considered statistically significant. Results are presented as mean ± SD.

Results

Age and bodyweight were not significant differences between groups. There was no significant difference for PCV, BUN, and Cr values between groups at baseline and after 12 h of food and water deprivation; therefore, data from all 12 animals were pooled. The total number of red blood cells, PCV, and BUN values showed a significant increase 12 h after fasting compared with baseline values ($p < 0.05$, Figs. 1 and 2). The increase in creatinine values was not significant ($p = 0.1$). The total number of lymphocytes showed a significant decrease after fasting compared to baseline values ($p < 0.05$). At day 1, BUN was significantly higher in anesthesia group compared to baseline but not with control group. The biochemical parameters assessed at the end of the study period were within normal limits for all dogs.

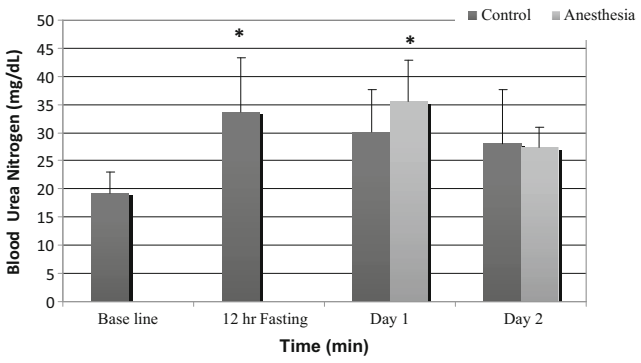

Fig. 1 Mean (± SD) values for blood urea nitrogen (BUN, mg/dL), before and after administration of metamizole in anesthetized ($n = 6$) and control ($n = 6$) groups. *Asterisk* denotes significant difference compared to baseline values ($p < 0.05$)

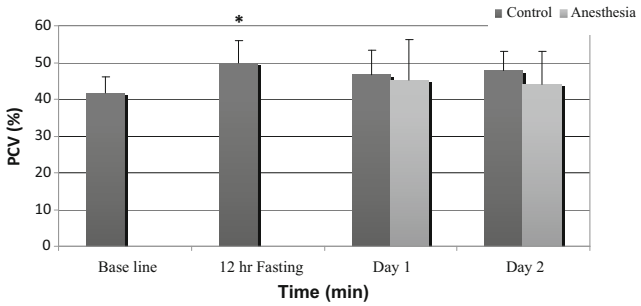

Fig. 2 Mean (± SD) values for packed cell volume (PCV, %), before and after administration of metamizole in anesthetized ($n = 6$) and control ($n = 6$) groups. *Asterisk* denotes significant difference compared to baseline values ($p < 0.05$)

The results of hematological (total number of white blood cells, neutrophils, monocytes, eosinophils, and band neutrophils) and bone marrow evaluation (myeloid, erythroid, and other bone marrow cell counts) did not show any significant change 72 h after the last metamizole injection compared to baseline in both groups ($p > 0.05$) (Data not shown).

Mucosal bleeding time did not change significantly in either group. Mean bleeding times at baseline for anesthesia and control dogs were 92 (± 10 s) and 93 s (± 13 s), respectively, and at 5 h after the last dose of metamizole, 90 (± 20 s) and 83 s (± 18 s), respectively.

No significant changes were observed in heart rate, respiratory rate, systolic arterial blood pressure, $EtCO_2$, and SpO_2 during anesthesia compared to baseline values ($p > 0.05$), but the mean arterial blood pressure (Fig. 3) and rectal temperature (Fig. 4) significantly decreased during anesthesia as compared to baseline values ($p < 0.05$).

Metamizole administration was well tolerated, and no relevant gastro-intestinal side effects, i.e., vomiting, diarrhea, and anorexia were observed in any dogs during this study.

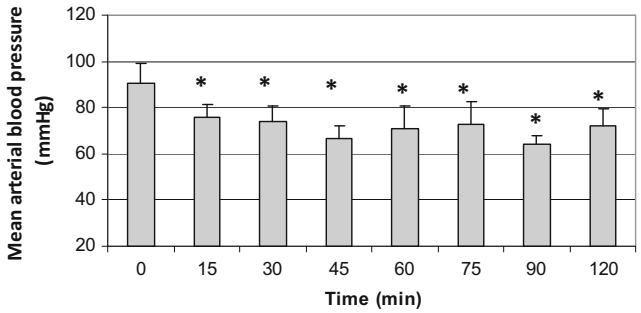

Fig. 3 Mean (± SD) values for arterial blood pressure (mmHg) in anesthetized dogs ($n = 6$. *Asterisk* denotes significant difference compared to baseline values ($p < 0.05$)

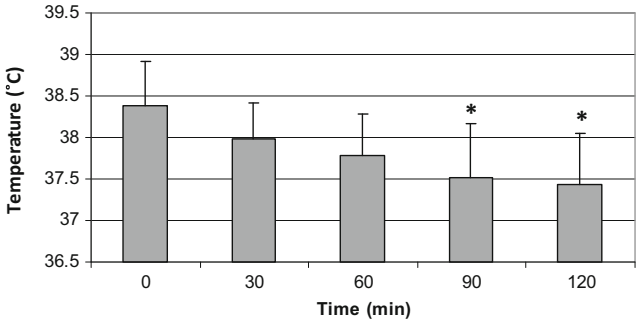

Fig. 4 Mean (± SD) values for rectal temperature (°C) in anesthetized dogs ($n = 6$). *Asterisk* denotes significant difference compared to baseline values ($p < 0.05$)

Discussion

This study shows that pre-anesthetic administration of metamizole in dogs undergoing 2 h of inhalation anesthesia, without receiving fluids, does not cause any significant changes in bleeding time, hematological, and biochemical values. Metamizole has powerful analgesic and antipyretic properties that seem to be related to the inhibition of COX-3 enzymes (Chandrasekharan et al. 2002).

Previous studies showed that metamizole provides appropriate post-operative analgesia with no laboratory parameters or clinical alterations in dogs (Imagawa et al. 2011; Kalchofner Guerrero et al. 2015). Metamizole may be prescribed for the treatment of acute and chronic pain in dogs. Metamizol is widely used in dogs by veterinarians in Brazil and New Zealand (Lorena et al. 2014; Williams et al. 2005). In some countries, metamizole is available in an injectable formulation in combination with an anticholinergic, butylscopolamine (hyoscine) and is used for treatment of equine colic.

Metamizole, in combination with tramadol and other NSAIDs (carprofen or meloxicam), has been used for pain management in dogs with chronic cancer pain (Flôr et al. 2013) and in dogs undergoing unilateral mastectomy with or without ovariohysterectomy (Teixeira et al. 2013; Zanuzzo et al. 2015). Pre-operative administration of metamizole (25 mg/kg, IV), with or without meloxicam, reduced the need for postoperative treatment with morphine following ovariohysterectomy in dogs (Zanuzzo et al. 2015). Although there appears to be a large margin of safety with metamizole-NSAID combination, it is worth noting that the concurrent administration of two different NSAIDs is not recommended due to significant exacerbation of adverse effects (Curry et al. 2005). Metamizole (25 mg/kg, IV) has been used as rescue analgesia in the post-operative period in dogs undergoing maxillectomy or mandibulectomy (Martins et al. 2010). The metamizole doses used in this study were based on previously published recommendations (Imagawa et al. 2011; Teixeira et al. 2013).

Metamizole, alone or in combination with opioids, is widely used in human medicine as an oral analgesic to provide perioperative pain relief, and the most severe adverse reaction to metamizole reported in human is a reversible but potentially fatal immune-mediated agranulocytosis. Agranulocytosis is a hematologic abnormality of acute onset in which the numbers of circulating neutrophils decrease, leading to a markedly increased susceptibility to bacterial infection. Interestingly, the risk of metamizole-associated agranulocytosis has been estimated to be at most only 1.1 cases/million human users (Schug and Manopas 2007). No agranulocytosis was observed in dogs receiving metamizole at a dose of 25 mg/kg, PO, every 8 h for 14 days (Flôr et al. 2013). To the authors' knowledge, there are no reports of metamizole-associated agranulocytosis in veterinary species (Baumgärtner et al. 2009).

Increased hematocrit, total number of red blood cells, and BUN could be attributed to mild dehydration following 12 h of water deprivation. Although, withholding water prior to anesthesia is not usually recommended in dogs, access to water was not allowed prior to anesthesia in the preset study to mimic the situations that inadvertent water deprivation may occur. Significant lymphopenia following 12 h of fasting may be due to stress of prolonged hunger and thirst and anxiety (Wolfle 2000). In the present study, no hematologic and biochemical abnormalities or significant prolongation of the bleeding time were observed following preanesthetic administration of metamizole in dogs undergoing 2 h of halothane anesthesia without intraoperative fluid administration.

Animals with decreased renal perfusion caused by dehydration and anesthesia are at greater risk for NSAID-induced renal ischemia (Curry et al. 2005; Papich and Messenger 2015). Preoperative administration of NSAIDs (ketoprofen, ketorolac, carprofen, and meloxicam) did not alter renal function in healthy dogs undergoing soft-tissue surgery (Ko et al. 2000; Lobetti and Joubert 2000; Mathews et al. 2001). Renal function tests failed to detect renal adverse effects after NSAIDs (carprofen and meloxicam) administration in dogs undergoing general anesthesia and submitted to hypovolemic and hypotensive stress (Bergmann et al. 2005; Frendin et al. 2006; Crandell et al. 2004; Bostrom et al. 2002; Bostrom et al. 2006).

In the present study, acepromazine was used for preanesthetic medication because it reduces blood pressure through blockade of alpha1-adrenoreceptors. A relatively high concentration of inspired halothane (1.5%) was chosen to maintain a deep level of anesthesia and further lowered blood pressure. Furthermore, no fluids were administered during anesthesia, so as not to offset anesthetic-induced hypotension.

Intraoperative administration of supportive fluids, which often is provided to alleviate hypotension, is frequently not used in clinical practice (Chohan and Davidow 2015). In this study, fluid administration was intentionally withheld in an

attempt to mimic a clinical situation in which the kidneys may be under maximal hypotensive stress and thus most affected by NSAID-induced nephrotoxicity.

In this study, we intentionally attempted to mimic a clinical setting in which NSAIDs may be used before anesthesia and routine surgical procedures of 2 h duration in healthy dogs. The lowest mean arterial blood pressure recorded in this study was 63 mmHg, which is significantly lower than mean baseline values (90 mmHg). This hypotension was likely attributable to the vasodilatory effects of acepromazine and the vasodilation and reduction in cardiac output associated with halothane. In order to ensure consistency in this study and despite the accompanying hypotension, deep plane of anesthesia was maintained using 1.5 MAC halothane, which is not generally necessary for surgical procedures.

The administration of NSAIDs can interfere with platelet function and increase bleeding time by inhibition of COX-1 production of thromboxane, the enzyme responsible for platelet aggregation (Papich and Messenger 2015). The extent and the duration of this inhibition, and its clinical relevancy, vary with the NSAID. With regard to NSAID-induced coagulopathy, several studies have failed to show a significant association between the use of NSAIDs and clinically significant bleeding disorders in healthy dogs (Bergmann et al. 2005; Blois et al. 2010; Brainard et al. 2007; Lemke et al. 2002a, Mathews et al. 2001; Mullins et al. 2012; Grisneaux et al. 1999; Hickford et al. 2001). In the present study, short-term administration of metamizole was not associated with prolongation of bleeding time in dogs. The effects of metamizole on coagulation have not been determined in dogs.

In spite of its extensive use in human, metamizole has not been associated with gastric or renal adverse effects known from non-steroidal anti-inflammatory drugs. Unlike other NSAIDs, metamizole is a non-acidic antipyretic, antispasmodic, and analgesic drug but devoid of anti-inflammatory effects. It is generally believed that metamizole is only a weak inhibitor of prostaglandin synthesis and a lack of other typical actions of NSAIDs, such as antiplatelet activity and gastrotoxicity (Schug and Manopas 2007). Physicochemical factors (lack of acidity) of metamizole may play a role in its good gastrointestinal safety profile as compared with acidic NSAIDs (Hinz et al. 2007).

Vomiting after oral and intravenous metamizole has been reported in 40–45% of dogs within 6 h after surgery (Imagawa et al. 2011; Kalchofner Guerrero et al. 2015). Since vomiting also occurred in the saline group, the authors concluded that it was possibly related to isoflurane anesthesia. In the present study, vomiting did not occur in any dogs. However, metamizole was administered intramuscularly, and no surgical procedures were performed on dogs.

Despite the fact that surgery was not performed on dogs, a mild but significant decrease in rectal temperature was observed during anesthesia, probably as a result of central and peripheral effects of acepromazine and halothane, a decreased rate of metabolism and muscular activity, impaired hypothalamic thermoregulatory mechanisms, and administration of cold inspired gases during anesthesia. While severe hypothermia may impair coagulation and platelet function, it does not usually occur until core temperature is below approximately 36 °C (Haskins 2015). The mean rectal temperature was never below 37.5 °C at any time point during anesthetic period.

In conclusion, the results of this study showed that preanesthetic metamizole (35 mg/kg) did not produce clinical signs of renal or GI disease or changes in bleeding time, complete blood counts, or blood chemistry profiles in healthy dogs under the conditions of this study. However, administration of NSAIDs should be reserved for normotensive, normovolemic dogs with no history of bleeding disorders or renal, hepatic, or gastrointestinal disease. Further investigation concerning prolonged use of metamizole in dogs undergoing both surgery and anesthesia is still needed.

Compliance with ethical standards

Ethical approval All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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Conflict of interest The authors declare that they have no conflict of interest.

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