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Comparison of the isoflurane concentration of using dexketoprofen or methadone at premedication during orthopedic surgery in dogs

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ABSTRACT

Thirty-two dogs were used in this prospective, randomized, clinical and double-blinded study. Dexmedetomidine was administered at 1 μg/kg IV, and randomly each dog received dexketoprofen 1 mg/kg IV (group DK) or methadone 0.2 mg/kg IV (group M). Dogs were induced with propofol and maintained with isoflurane in 100% oxygen. During surgery, the isoflurane concentration was changed depending on clinical signs of depth of anesthesia. Fentanyl and propofol could be used as required. Qualities of sedation and recovery were evaluated. A generalized linear mixed model or Mann–Whiney U test was used, and $P < 0.05$ was considered statistically significant. No significant differences were observed between groups in the qualities of sedation and recovery, isoflurane concentration and in the total amount of fentanyl and propofol used intraoperatively. This study shows that the administration of dexketoprofen at 1 mg/kg IV at premedication required a similar isoflurane concentration to maintain anesthesia as methadone at 0.2 mg/kg IV during orthopedic surgery in dogs. Further analgesia is recommended intraoperatively, because of the need of fentanyl and propofol in same animals in both groups.

1. Introduction

Pre-emptive analgesia has beneficial effects during the immediate perioperative period, including less inhalatory agent concentration during anesthetic maintenance and consequently less cardiopulmonary depression and an improvement in the anesthetic recovery period (Hellyer et al., 2007). Nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics or opioids are drugs used for this purpose in veterinary medicine. Methadone is a synthetic mu opioid agonist that has been demonstrated as effective for the control of pain in dogs (Leibetseder et al., 2006; Ingvast-Larsson et al., 2010). In addition to this analgesic effect, methadone may result in some adverse effects such as bradycardia and panting after intramuscular administration in a dose range of 0.3 to 1 mg/kg (Menegheti et al., 2014).

Another pharmacological group used to reduce postoperative pain includes the NSAIDs, which are synergistic in combination with opioids and have an opioid dose-sparing effect. The long duration of action and analgesic properties make the NSAIDs the ideal treatment for acute and chronic pain in veterinary patients (Lamont and Mathews, 2007). A NSAIDs of last generation is dexketoprofen [S(+)-ketoprofeno], the main enantiomer of the racemic mixture of ketoprofen, which is responsible for analgesic effects with less adverse effects than the racemic mixture (Mauleón et al., 1996; Neirinckx et al., 2011). Anyway, Forsyth et al. (1998) determined the safety of ketoprofen on gastrointestinal tract in dogs, who did not observe significant gastrointestinal lesions receiving oral ketoprofen during 28 days. Dexketoprofen exerts its mechanism of action by inhibition of the cyclooxygenases COX-1 and COX-2; in this way, there is an inhibition in the synthesis of prostaglandins in inflammatory processes and healthy tissues (Streppa et al., 2002). The pharmacokinetics of this drug has been previously evaluated after intravenous and oral administration in dogs (Serrano-Rodríguez et al., 2014), and only one study evaluated dexketoprofen as analgesic in the immediate postoperative period in dogs undergoing ovariohysterectomy (Morgaz et al., 2013), demonstrating it as an analgesic superior to buprenorphine.

Several studies have evaluated the effects of NSAIDs on the sparing effect of inhalatory anesthetic procedures in dogs (Tamura et al., 2014; Bufalari et al., 2012; Ko et al., 2000, 2009), rabbits (Turner et al., 2006) and rats (Santos et al., 2004). However, there are no studies that evaluate the isoflurane concentration required in dogs that received dexketoprofen in the premedication anesthesia. Therefore, the objective of the present study was to compare the isoflurane concentration obtained by premedication with dexketoprofen or methadone during orthopedic surgery in dogs. The hypothesis of the present study is that both drugs will require a similar isoflurane concentration to maintain anesthesia.

2. Materials and methods

In this study, dogs ASA I or II, with a good character and weighing more than 4 kg were included (physical status ≥3). Animals with

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gastrointestinal, hepatic, renal and cardiac diseases, with a convulsion history, pregnant or those that received NSAIDs or corticoids in the last two weeks before surgery, were excluded. With an alpha error of 0.05, a beta error of 0.80 and to detect a significant difference between means of 15%, considering an end tidal of isoflurane of 1.25 times the MAC of isoflurane in dogs (1.3% × 1.25 = 1.7% EtISO) and standard deviation of 0.20%, the size of dogs in each groups would be 14. We increase a 15% for potential losses of animals. We determined initially groups of 18 dogs. This study protocol was approved by the ethics committee of the University of Córdoba. In addition, informed consent was obtained from the dog owners.

First, one of the cephalic veins was catheterized with a 20- or 22-gauge catheter to drug and fluid administration with acetated Ringer's solution at 5 ml/kg/h. All animals received dexmedetomidine (Dexdomitor® 0.5 mg/ml, Esteve laboratories SA, Barcelona, Spain) at 1 μg/kg IV diluted with saline up to 5 ml. 5 min later and randomly, dexketoprofen (Enantyum® 50 mg/2 ml, Menarini laboratories S.A. Barcelona, Spain) at a dose of 1 mg/kg IV (group DK) or methadone (Metasedin® 1%, DR. Esteve laboratories S.A. Barcelona, Spain) at a dose of 0.2 mg/kg IV (group M) were administered. Both drugs were diluted with saline up to 3 ml for blind assessment by the researcher responsible for the evaluation. 20 min later, the quality of sedation was evaluated (Bell et al., 2011) (Table 1). Anesthesia was induced with propofol (Propofol Lipuro®1%, 10 mg/ml, B.Braun laboratories, Barcelona, Spain) at dose-effect, and the total dose used to allow endotracheal intubation was registered. After induction, animals received cefazoline (Cefazolina® Normon 1 g IV, Normon Laboratories SA, Madrid, Spain) at a dose of 22 mg/kg IV.

Anesthesia was maintained with isoflurane (IsoVet®, B.Braun VetCare laboratories SA, Barcelona, Spain) in 60% oxygen using a small animal anesthetic machine (Mc Kiley type 3, Everest. Veterinary Technology). Heart rate (HR, beats/min), invasive arterial blood pressures (MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure, mmHg), respiratory rate (RR, breaths/min), the hemoglobin saturation of oxygen (SpO_2, %), carbon dioxide partial pressure ($PECO_2$, mmHg), oxygen inspired fraction (FiO_2, %), end-tidal isoflurane (EtIso, %) and body temperature (T°, °C) were monitored continuously using a multiparameter monitor (Datex-Ohmeda® GE Healthcare®, Finland). Ventilation was controlled to maintain the $PECO_2$ between 35 and 45 mmHg (4.7–6 kPa), and body temperature was maintained within the normal range (37–39 °C) with a circulating warm-air blanket (Equator™ Smiths Medical ASD, Inc. Weymouth, USA). These parameters were measured three times before surgery and an average of the data was calculated (pre-incisional period, PIp). During the surgery procedure, these parameters were measured every 5 min until the end of the procedure (T5, T10, T15, etc.), and an average of these data was calculated (surgery period, Sp). The time from dexmedetomidine administration to the first incision was recorded (DEX-first incision).

Before the beginning of the surgery, the EtIso was set at 1.3% and held constant for at least 20 min. During the surgery procedure, the depth of anesthesia was evaluated using palpebral reflex, ocular position, mandibular tone and movements of the animals. The EtIso was reduced by 0.2% every 10 min if the anesthesia was considered adequate with minimum or absent palpebral reflex and without mandibular tone, movement and significant vascular changes. If the anesthetic level was considered inappropriate and the HR, RR or MAP were 25% greater than the pre-incisional score, the EtIso was increased by 0.5%. If there was a sudden change in the HR, RR or MAP of 25% greater than the pre-incisional value and the anesthetist observed signs of pain, a fentanyl bolus (Fentanest® 0.05 mg/ml, Kern Pharma laboratories SL, Tarrasa, Spain) at 2 μg/kg IV was administered without increasing the isoflurane concentration (Bosmans et al., 2012). If any movement of the head or limbs was observed without changes in physiological variables, propofol at 1.5 mg/kg IV was administered (Almeida et al., 2010). The number of animals that received fentanyl or propofol, and the total amount of each drug were registered. In our study, in order to minimize the subjectivity of evaluation, the same assessor was consistently responsible for evaluating the degree of anesthesia and was blinded to the treatment administered.

If the HR was less than 55 bpm during the surgery procedure, atropine (Atropina® 1 mg, B Braun laboratories, Barcelona, Spain) was administered at 10 mcg/kg IV. If the MAP was less than 60 mmHg and continued for more than 15 min, even after decreasing the isoflurane concentration, dopamine (Dopamin® 40 mg/ml, Grifols laboratories SA, Spain) was administered at 5 μg/kg/min until normal values were reestablished. If any of these drugs were used, the animal was removed from the study.

Once the surgery was completed, the surgery time was registered (from the first incision until the final surgery incision) and animals were transferred to X-ray rooms, marking the end of registering the above mentioned data. Once the radiographic study was finished, isoflurane was stopped and oxygen supplementation was continued at 100% until the endotracheal was removed. The quality of recovery was evaluated (Psatha et al., 2011) (Table 1). Animals continued receiving amoxicillin/clavulanic acid (Synulox® 40 ml, Zoetis Spain, S.L. Alcobendas, Spain) at 22 mg/kg q 24 h for 5 days.

Table 1
Description of sedation and recovery scores.

Sedation scores based on Bell et al. (2011)	
0: None	No visible signs of sedation.
1: Mild	Decreased alertness, response to acoustic stimuli.
2: Moderate	Sternal/lateral recumbency, minimal response to acoustic stimuli.
3: Profound	Sternal/lateral recumbency, no response to acoustic stimuli.
Recovery scores based on Psatha et al. (2011)	
1:Very smooth	No excitement. No paddling, vocalizing, trembling or vomiting. No convulsions.
2:Quiet smooth	A little excitement. Some head movement, possibly some shivering but paddling, vocalizing, trembling or vomiting. No convulsions.
3:Moderately smooth	Moderate excitement. Some paddling, vocalizing, trembling or vomiting. No convulsions.
4: Poor	Extreme excitement, aggression, vocalizing, violent movements or convulsions. Rescue sedation.

2.1. Statistical analysis

A commercial software program SPSS (SPSS Ltd., London, UK) for Windows was used for all analyses. Normality was evaluated using the Shapiro–Wilk test. A generalized linear mixed model was used to compare within and between treatments where the independent variable was the group and dependent variables were time and parameters (HR, EtIso, SAP, MAP, DAP, T°, RR, $PECO_2$, SpO_2). Data are represented as the mean ± SD. A Mann–Whitney U test between groups was used for age, weight, surgery time, DEX-first incision, qualities of sedation and recovery, total dose of propofol used at induction, and the total amount of each drug administered during the surgery period. Sex, breed, type of surgery and number of animals receiving fentanyl/propofol were analyzed by Chi-squared test. Data are represented as the median (minimum–maximum) or number of animals. A P value of <0.05 was considered statistically significant.

3. Results

A total of 36 dogs were included in this study (18 in DK and 18 in M). One dog in DK and two in M were treated with dopamine and were, therefore, excluded from the study. One dog in M received atropine, and it was removed from the analysis. In M, a dog had to be removed from the study at T60. During the first 60 min of anesthesia, it received three doses of fentanyl and at T60 continued with a CRI of fentanyl at