



Comparison of the analgesic effects of robenacoxib, buprenorphine and their combination in cats after ovariohysterectomy



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ABSTRACT

The aim of this study was to compare the postoperative analgesic effects of robenacoxib and buprenorphine alone or in combination, in cats after ovariohysterectomy. Thirty healthy cats were randomly assigned to receive buprenorphine (0.02 mg/kg, $n = 10$; GB), robenacoxib (2 mg/kg, $n = 10$; GR) or their combination at the same dosages ($n = 10$; GBR) SC. After 30 min cats were sedated with an IM administration of medetomidine (0.02 mg/kg) and ketamine (5 mg/kg). General anaesthesia was induced with propofol and after intubation was maintained with isoflurane. Before premedication and at 1, 2, 3, 4, 6, 8, 12 and 24 h after extubation, pain and sedation were assessed using a simple descriptive pain scale, ranging from 0 (no pain/no sedation) to 4 (intense pain/ deep sedation). If the pain score was ≥ 3 , rescue analgesia was provided using buprenorphine (0.02 mg/kg) administered IM.

Pain score was higher in GB at 2, 3, 4, 6 and 8 h compared to baseline and compared to GBR at the same study times. Moreover, the pain score was also higher in GB compared to GR at 2, 3, 4 and 6 h. Pain score was similar at all study times between GR and GBR. Sedation at 1 and 2 h was higher than baseline values in all groups. Cats in GB received rescue analgesia more often than cats assigned to GR or GBR. Robenacoxib was an effective analgesic drug in cats up to 24 h after ovariohysterectomy. The addition of buprenorphine did not provide any additional analgesic effects compared to robenacoxib alone.

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Introduction

Ovariohysterectomy is the most commonly performed surgical procedure in cats (Fox et al., 2000). The noxious stimulation related to ovariohysterectomy can persist in the postoperative period up to 24 h and can modify the behaviour of affected cats (Fox and Johnston, 1997). Analgesia in cats has traditionally suffered from a lack of species-specific knowledge of pain-related behaviour and drug metabolism (Dohoo and Dohoo, 1996a,b; Robertson and Taylor, 2004; Taylor and Robertson, 2004). A multimodal approach might produce better results than a single agent, because each drug works at a different level of the pain pathway and combining drugs could permit lower doses of each to be used (Robertson, 2008). Opioids and non-steroidal anti-inflammatory drugs (NSAIDs) have been proven to be effective for the alleviation of pain in cats both in clinical and experimental conditions (Polson et al., 2012; Shih et al., 2008; Steagall et al., 2007; Taylor et al., 2007).

The most widely used analgesics in veterinary and human medicine are NSAIDs, which target peripheral and central nervous system (CNS) mediators of nociception (Hinze and Brune, 2004;

McCormack, 1994). They are effective in alleviating acute and chronic pain in most species and a variety of NSAIDs have been shown to be effective ameliorators of perioperative pain in cats (Balmer et al., 1998; Lascelles et al., 1995; Slingsby et al., 1998; Slingsby and Waterman-Pearson, 1998, 2000, 2002). Robenacoxib is a new COX-2 selective NSAID approved for use in cats, which possesses analgesic, anti-inflammatory and anti-pyretic effects (Giraudel et al., 2009a,b). Robenacoxib has a good safety index in cats since it distributes selectively to inflamed tissues and inhibits COX-2, while sparing COX-1 at clinically recommended dosages (Kamata et al., 2012; King et al., 2012; Pelligand et al., 2012; Schmid et al., 2010). Recently, robenacoxib was found to be superior compared with meloxicam using a number of outcome variables in cats (Kamata et al., 2012).

Buprenorphine is a potent semi-synthetic, high lipophilic opioid, with partial agonistic activity at mu (MOP) opioid receptors, and is authorized for use in cats in several countries (Robertson and Taylor, 2004). It is characterized by a delayed onset of action and long-acting analgesic properties with few adverse effects (Giordano et al., 2010). Buprenorphine is one of the most effective analgesic drugs in cats for its antinociceptive properties and its lack of important side effects (Robertson et al., 2005). Stanway et al. (2002) deemed buprenorphine preferable over morphine

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for postoperative pain control in cats undergoing soft tissue and orthopaedic procedures. Several studies have demonstrated the analgesic efficacy of buprenorphine after neutering in cats alone or in combination with NSAIDs and/or α_2 agonists (Giordano et al., 2010; Polson et al., 2012; Steagall et al., 2009; Taylor et al., 2010).

The aim of this study was to test the hypothesis that robenacoxib, alone or in combination with buprenorphine, could be an effective treatment for postoperative pain in cats undergoing ovariohysterectomy.

Materials and methods

The study was conducted in compliance with the Italian Welfare Act and statutes of the University of Bari relating to the use client-owned animals in clinical investigation.

Animals

Thirty healthy adult client-owned female mixed-breed cats scheduled for elective ovariohysterectomy were enrolled in the study. Written informed owner consent was obtained. Pre-operative screening included a complete physical examination and blood analysis. Cats that were pregnant or lactating, or animals that were aggressive on handling were excluded. Only cats ranked as American Society of Anesthesia (ASA) physical status 1 were included in the study. Cats were assigned randomly to one of three treatment groups and each group ($n = 10$) received a different analgesic regimen.

Anaesthesia and surgery

Cats were admitted to the veterinary hospital at least 12 h before surgery in order to acclimatize to the new environment and to the investigators. The cats were housed individually in cages in a quiet environment and were fasted overnight with free access to water until premedication was administered. Thirty minutes prior to the procedure, cats received analgesic drugs based on random allocation to one of three treatment groups: (1) 2 mg/kg robenacoxib SC (Onsior, Novartis; Group R, GR); (2) 0.020 mg/kg buprenorphine SC (Temgesic, Schering Plough; Group B, GB); or (3) the combination of 0.020 mg/kg buprenorphine SC and 2 mg/kg robenacoxib SC (Group RB, GRB). Cats were premedicated with a combination of 5 mg/kg ketamine IM (Ketavet 100, Intervet) and 0.02 mg/kg IM medetomidine (Domitor, Pfizer).

Once an adequate level of sedation had been achieved, a cephalic vein was catheterized using an aseptic technique and an infusion of Ringer's solution (5 mL/kg/h) was administered with an infusion pump (Perfusor, Braun). An IV bolus of 1–2 mg/kg propofol (Propofol, Esteve) was given in case the depth of anaesthesia was not adequate for intubation with a cuffed endotracheal tube (3–3.5 mm ID). Cats were connected to a non-rebreathing (Bain-type) system and anaesthesia maintained with isoflurane (Isoba, Schering-Plough) in 100% oxygen (200 mL/kg/h).

Respiratory rate (RR, breaths/min), heart rate (HR, beats/min), end-tidal concentrations of carbon dioxide (EtCO₂, mmHg) haemoglobin oxygen saturation (SpO₂, %), ECG, and body temperature (T , °C) were continuously monitored (SC 6002XL, Siemens) and recorded every 5 min. Systolic arterial blood pressure (SAP, mmHg) was measured on the palmar common digital artery using a Doppler technique (Ultrasonic Doppler flow detector, Model 811-BL, Parks Medical Electronics).

Surgery began approximately 15 min after induction of anaesthesia, and was always performed by the same surgeon, using a standard midline abdominal approach. At the end of surgery, isoflurane was discontinued and the cats were extubated when the swallowing reflex had returned. Fluid therapy and heating support were discontinued when cats were fully awake and rectal temperature was above 37.5 °C, respectively. The duration of surgery (from the first incision until the placement of the last suture), anaesthesia (from the induction to the discontinuation of isoflurane) and the time required for the cat to recover sternal recumbency (from the discontinuation of isoflurane to the sternal recumbency) were recorded for each cat.

Assessment of postoperative pain and sedation

In order to evaluate the postoperative analgesic effects of the drugs, the degree of pain and sedation were assessed before the cats were premedicated (PRE) and at 1, 2, 3, 4, 6, 8, 12 and 24 h after extubation, using the same procedures systematically performed at each study time. Each cat was first observed without being removed from its cage or disturbed. Then, while observing its reaction and behaviour, the cat was approached, spoken to, and the cage door was opened. Each animal was gently handled and petted and encouraged to walk. Finally, the incision site and surrounding skin was gently palpated. Pain was scored based on a simple descriptive scale (SDS) ranging between 0 (no pain) and 4 (excessive pain; Table 1). Sedation was also scored according to a SDS scale ranging between 0 (no sedation)

and 4 (deep sedation; Giordano et al., 2010; Steagall et al., 2009). All evaluations were performed by the same investigator (LD) who was unaware of the analgesic treatment assignment.

Postoperative rescue analgesia

Buprenorphine (0.020 mg/kg) was administered IM if the pain score was ≥ 3 at any study time. In cases where rescue analgesia was required, pain was reassessed at 30 and 60 min after buprenorphine administration in order to confirm the efficacy of the treatment. The total additional doses of buprenorphine administered over the observation time (24 h) were recorded for each cat. The number of cats requiring rescue analgesia, the number requiring more than one administration, the average consumption of buprenorphine over 24 h and the time of the first rescue administration were recorded for each group.

Statistical analysis

Data were tested (MedCalc version 9.2.1.0) for normal distribution with the Kolmogorov–Smirnov test and mean \pm SD (parametric data) or the median and range (non-parametric data) were calculated. Non-parametric data (pain and sedation scores) were tested with the Friedman's test followed by the Dunnett test for within group comparisons and with the Kruskal–Wallis Chi-squared tests and Mann–Whitney post hoc tests for between group comparisons. Parametric data (age, weight, duration of surgery, duration of anaesthesia and time for sternal recumbency) were tested between groups with one-way analysis of variance (ANOVA) followed by Student–Newmann–Kleus test. The rescue analgesia data were analyzed using Fisher's exact tests. A value of $P < 0.05$ was considered significant.

Results

All cats completed the study without any major complications. There were no differences in bodyweight (GB 3.5 ± 0.4 kg; GR 3.7 ± 0.5 kg; GRB 3.5 ± 0.5 kg), age (GB 19.7 ± 7.4 months; GR 18.1 ± 6.1 months; GBR 20.5 ± 3.1 months), duration of surgery (GB 34.6 ± 12.3 min; GR 38.6 ± 9.3 min; GBR 39.5 ± 13.2 min), duration of anaesthesia (GB 49.6 ± 9.2 min; GR 52.1 ± 11.3 min; GBR 54.2 ± 9.3 min) and time to sternal recumbency (GB 30.4 ± 6.6 min; GR 31.3 ± 9.5 min; GBR 33.4 ± 9.2 min) between groups. Anaesthesia and surgery were uneventful and no additional anaesthetic/analgesic drugs were administered.

Pain score was higher in GB at 2, 3, 4, 6 and 8 h compared to baseline in the same group and compared to GBR at the same study times. Pain score was also higher in GB compared to GR at 2, 3, 4 and 6 h (Table 2; Fig. 1). Sedation score at 1 and 2 h was higher than baseline values in all groups (Table 2; Fig. 2). The proportion of cats that required rescue analgesia was higher in GB (9/10) than in GR (2/10) or GRB (3/10). The proportion of cats that required more than one dose of rescue analgesia was significantly higher in GB (3/10) than in GR (0/10) or GBR (0/10). The mean number of doses administered during the observation time (24 h) was higher in GB (1.2 doses) than in GR (0.2 doses) and GBR (0.3 doses). The total amount of buprenorphine administered over the 24 h study period was higher in GB (24 μ g/kg/24 h) than in GR (4 μ g/kg/24 h) or GBR (6 μ g/kg/24 h). The time of the first rescue analgesia administration was similar in all groups (GB: 4 h; GR: 4.5 h; GBR: 3 h).

Discussion

The results of this study demonstrate that robenacoxib alone or in combination with buprenorphine provides a better postoperative analgesia than buprenorphine alone in cats undergoing ovariohysterectomy, anaesthetised with ketamine, medetomidine, propofol and isoflurane.

The need to provide adequate analgesia for cats has been increasingly recognized (Robertson, 2008), but there are relatively few analgesic drugs licensed for feline use. In particular, there are few NSAIDs licensed for cats and their usage is generally limited to administration over a short period of time. The paucity of toxicological data together with relatively low safety margins could explain

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