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Original research paper

Postoperative pain in dogs undergoing hemilaminectomy: Comparison of the analgesic activity of buprenorphine and tramadol

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ABSTRACT

The objective of this study was to compare the analgesic activity of buprenorphine and tramadol for the management of postoperative pain after hemilaminectomy because of acute intervertebral disc extrusion in dogs. This is a randomized, blinded, and prospective clinical trial. The study was carried out on 50 dogs undergoing hemilaminectomy. After diagnosis, the dogs were divided randomly into 2 groups: group A (n = 25 dogs) received 3 mg/kg^{-1} of tramadol intramuscularly and group B (n = 25 dogs) received 0.02 mg/kg^{-1} of buprenorphine intramuscularly 10-15 minutes before the end of surgery and, then, every 8 and 6 hours, respectively, for 48 hours. Using the short form of the Glasgow Composite Pain Scale at 4 time points (before and 2, 12, and 24 hours after surgery), the dogs were clinically monitored and scored by the same operator who was blinded to the treatment. Data were analyzed using Mann-Whitney *U* tests. Significance was set at $P < 0.05$. Both drugs showed a good analgesic activity. There were significant differences between the 2 groups with regard to the short form of the Glasgow Composite Pain Scale scores: buprenorphine showed a faster and greater analgesic effect. None of the 2 molecules showed any side effects, such as respiratory depression. Buprenorphine and tramadol can be used safely and effectively to control postoperative pain in dogs undergoing hemilaminectomy for acute disc extrusion, thus contributing to animal welfare. Buprenorphine might be better than tramadol during the first stage of hospitalization, but tramadol might represent a good alternative for the pursuance of the treatment, considering its lower incidence of side effects, both contributing to improve animal welfare.

Introduction

The veterinary practitioner has an ethical obligation to alleviate animal pain. Nociception is a physiological process that involves transduction, transmission, modulation, and perception of the noxious stimuli. Chemical mediators are important components of the nociceptive reflex and offer a target for pharmacologic modulation. Assessment of pain in animals is the most important step for its successful management. Choosing an appropriate method of pain control would depend on the type of procedure followed, severity of pain, and economic considerations for each specific circumstance.

Acute intervertebral disc extrusion is characterized by a chondroid degeneration of the nucleus pulposus. It starts at about 6-8 months of age, especially in chondrodystrophic breeds (e.g., dachshund, Pekinese, shih tzu, beagle, cocker spaniel), but it is also described in medium-large breeds (e.g., sheepdogs) (Cudia and Duval, 1997).

The degree of pain experienced during acute disc extrusion is usually between severe and terrible (Carroll and Martin, 2007). At first, the degeneration is asymptomatic until the nucleus pulposus, flooded with hyaline cartilage, protrudes through a slot of the annulus fibrosus.

Symptomatology and pain, during an intervertebral disc extrusion, are caused by the compression of the meninges and nerve roots, but they are actually the final representation of a slow disc

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degeneration, which started months or, more often, many years before. It is still debated whether pain is caused also by the receptor stimulation in the annulus fibrosus and in the dorsal longitudinal ligament. The symptomatology depends on the amount of herniated material and the ratio between the diameter of the medulla and the vertebral canal. As a result of the initial mechanical event and persistent compression of the spinal cord, a cascade of secondary injury mechanisms, which exacerbate the degree of tissue destruction, occurs. These processes include free radical formation, cellular ionic imbalance, cell membrane lipid peroxidation, release of excitotoxic glutamate, and vascular phenomena, such as vasospasm and perfusion-reperfusion injury (Wilson and Fehlings, 2011).

The onset of clinical signs is generally acute, after a jump or a sudden movement while the dog is running or playing. Clinical manifestations begin from 2 to 6 years, and the most common site of injury is the thoracolumbar region, especially from T11 to L3.

Clinical diagnosis is based on the history and clinical data collected during the general physical and neurologic examination. The final diagnosis is achieved by myelography and advanced diagnostic imaging. Computed tomography (CT) allows observation of the section of the medullary parenchyma so as to detect even lateral compressions and the early parenchymal abnormalities of myelomalacia. Magnetic resonance imaging, unlike CT, allows a comprehensive view of the spine, with a high definition display of the soft tissues (Cooper et al., 2014).

The therapy of choice is hemilaminectomy surgery, performed as early as possible to prevent the onset of irreversible spinal cord damage (Tator and Fehlings, 2010). Surgery has the goal of decompressing the spinal cord and restoring spinal stability. Although a consensus regarding the optimal timing of surgical decompression has not been reached yet, most of the preclinical and clinical evidences in human and animal models support performing early surgery (<24 hours) (Wilson and Fehlings, 2011).

Buprenorphine, a partial μ-opioid receptor agonist, has a very high affinity with this type of receptor, which leads to the formation of a virtually unbreakable bond. It showed good analgesic properties, and this makes it a good choice for alleviation of mild to moderate pain (Slingsby et al., 2006; Shih et al., 2008). It has a fairly long-lasting action (6-8 hours) (Andaluz et al., 2009), and the maximum effect is reached about 20 minutes after intramuscular (IM) administration. Previous studies showed a decreased incidence of ceiling and side effects, such as respiratory depression (Dahan et al., 2005). Recent evidences suggest that the submaximal response to buprenorphine at high doses may be because of the interaction with the non-μ class of opioid receptor-like (ORL1) receptors, which, when upregulated, may attenuate the analgesic effects of buprenorphine (Lutfy et al., 2003; Lufty and Cowan, 2004).

Tramadol provides pain relief through different levels of action, especially the inhibition of norepinephrine and serotonin uptake. Its primary metabolite, O-desmethyl-tramadol, shows an affinity with μ receptors 20-200 times higher than tramadol itself. Compared with other opioids, it appears to cause less respiratory depression and not cause problems of tolerance and abuse, except in a very limited way. It has a half-life of about 4-6 hours, and the onset of the analgesic effect is achieved after 10-20 minutes. Administered orally and parenterally in humans and animals, it seems to have a good analgesic activity on different types of pain (Perez-Jimenez et al., 2016). Side effects include dysphoria and sedation especially in cats and reduced seizure threshold in humans. Tramadol is often used in dogs for postoperative pain control because of its nonaddictive effect and relatively low cost. In the United States, tramadol is classified as a narcotic drug, requiring a narcotic type prescription; however, in other countries, it is still considered a non-narcotic drug, so represents a good compound for short-term treatment at home.

Some studies have evaluated the analgesic effects of these drugs in dogs undergoing ovariohysterectomy (Shih et al., 2008; Moll et al., 2011; Morgaz et al., 2013) or other surgical procedures (Bosmans et al., 2007; Slingsby et al., 2011; Linton et al., 2012), but there is a lack of report on neuropathic pain after spinal surgery.

The aim of this work was to compare the effectiveness of tramadol and buprenorphine in postoperative pain management in dogs undergoing hemilaminectomy surgery because of acute intervertebral disc extrusion.

Materials and methods

This study was carried out in a private veterinary clinic specialized in neurosurgery between January 2012 and August 2014. During this period, all the dogs diagnosed with an acute disc extrusion undergoing hemilaminectomy were enrolled. Animals suffering from pre-existing diseases were excluded.

Fifty dogs of different breeds (21 dachshunds, 6 mongrel dogs, 3 beagles, 2 miniature poodles, 2 Chihuahuas, 2 Jack Russell terriers, 2 Beijingers, 1 Yorkshire terrier, 1 rottweiler, 1 Staffordshire, 1 Dalmatian, 1 English bulldog, 1 Maltese, 1 Zwergpinscher, 1 German shepherd, 1 schnauzer, and 1 shih tzu), sex (34 males and 16 females), age (range, 18 months-14 years; mean ± standard deviation [SD], 5.7 ± 2.8 years), and body weight (2.5-45 kg; mean ± SD, 10.4 ± 8.6 kg) met the criteria required. Each dog was subjected to clinical and neurologic examinations, hematological and hematochemical profiles, radiographs of the spine, CT (Toshiba Asteion VR; Toshiba America Medical Systems, Tustin, California, USA), and mielo-CT to obtain a definitive diagnosis of acute disc extrusion at the thoracolumbar region (T13-L3).

All the animals underwent hemilaminectomy as early as possible.

Perioperative narcosis and analgesia were obtained in all patients with the same anesthetic protocol: acepromazine (Prequillan; Fatro SpA, Ozzano Emilia, BO, Italy) 0.02 mg/kg^{-1} IM for the premedication, propofol (Rapinovet; Bayer SpA, Milan, Italy) 3 mg/kg^{-1} intravenously (IV), and fentanyl (Fentanest; Pfizer Italia Srl, Latina, Italy) 0.004 mg/kg^{-1} IV for the induction, and isoflurane (Isoflurane Vet; Merial Italia SpA, Noventa Padovana, PD, Italy), oxygen, and fentanyl 0.004 mg/kg^{-1} h^{-1} IV in constant rate infusion for the maintenance. A broad-spectrum antimicrobial therapy was started. The surgery lasted approximately 60 minutes.

The dogs were randomly divided into 2 groups to receive different postoperative analgesic treatment. Group A dogs (n = 25) were treated with tramadol (Altadol; Formevet SpA, Milan, Italy) 3 mg/kg^{-1} IM every 6 hours (total of 8 doses), whereas group B dogs (n = 25) were treated with buprenorphine (Bupaq Multidose; Richter Pharma AG, Wels, Austria) 0.02 mg/kg^{-1} every 8 hours (total of 6 doses). About 10-15 minutes before the end of the surgery, constant rate infusion of fentanyl was interrupted, and the first IM administration of the chosen analgesic was performed by an operator who was unaware of the contents of the syringes. To guarantee the welfare of dogs already stressed by surgery, all patients were monitored until fully awake and then hospitalized for 48 hours. Dogs were housed in an air-conditioned and quiet intensive care unit with soft lights and natural photoperiod. External stimuli that could have worsened the dogs' stress because of their painful condition were minimized. Dogs were hospitalized in specific cages of adequate dimensions for each dog size to restrict movement on a soft and comfortable surface. Fluid balance, antibiotic administration, gastrointestinal motility, nutrition, nursing care, and wound care were managed.

The short form of the Glasgow Composite Pain Scale (GCPS-SF) was used for the evaluation of the degree of pain in all patients (Reid et al., 2007).

The short form of the Glasgow Composite Measure Pain Scale (GCMPS-SF) comprises 6 behavioral categories with associated descriptive expressions (items): section A—(1) vocalization (score, 0-3) and (2) attention to wound (score, 0-4); section B—(3) mobility (score, 0-4); section C—(4) response to touch (score, 0-5); and section D—(5) demeanor (score, 0-4) and (6) posture/activity (score, 0-4). Items are placed in increasing order of pain intensity and numbered accordingly. The operator chooses that item within each category that best describes the dog's behavior, and ranked scores are summed (total score: 1 + 2 + 3 + 4 + 5 + 6); the maximum pain score is 24 or 20 if mobility is impossible to assess.

The compilation of questionnaires was performed by the same operator, who was unaware of group allocation, to avoid a possible interobserver variability and to minimize the effect of subjective bias. Pain was evaluated during the preoperative and, then, at 2, 12, and 24 hours after surgery. Forty-eight hours after surgery, the patients were discharged.

This study and procedures were approved by the Ethics Committee of the Department of Veterinary Sciences, University of Messina, Italy.

The research was carried out in a high standard veterinary referral clinic, and client-owned dogs were enrolled after the informed consent had been provided by the owners.

The drugs administered in this trial are registered for use in dogs.

Data analysis

Pain scores obtained using GCPS-SF were reported as mean ± SD, median, and range. Data were tested for normality using the Shapiro-Wilk normality test. Data did not result to be normally distributed ($P < 0.05$) and were analyzed using the Mann-Whitney U test for nonparametric analysis. Significance was set at $P < 0.05$.

No difference in scores between the 2 groups was taken as the null hypothesis.

All data collected during the trial were entered into a spreadsheet (Microsoft Excel); the statistical test was performed using the STATISTICA 7 software (Stat Soft, Inc, Tulsa, OK; 2003).

Results

Section B (mobility) of GCPS-SF was not carried out as a result of the animals' physical condition, so that the total score was out of 20 rather than 24.

No statistically significant difference in GCPS-SF scores between the 2 groups was recorded before surgery ($P > 0.8$), showing homogeneity of the sample, characterized by a high degree of pain (group A, 15.92 ± 1.58; median, 16; range, 12-18 and group B, 15.84 ± 1.62; median, 16; range, 13-18).

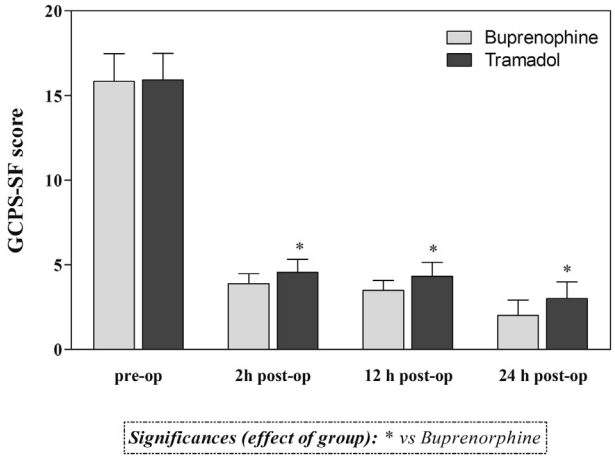

Figure 1. The short form of the Glasgow Composite Pain Scale (GCPS-SF) score evaluated in group A (tramadol) and group B (buprenorphine) before surgery (preoperatively) and during postoperative period (2 hours postoperatively, 12 hours postoperatively, and 24 hours postoperatively) with the respective significance found between groups. Preop, preoperatively; postop, postoperatively.

The Table shows the descriptive statistic of GCPS-SF scores calculated for group A and group B. In particular, statistical analysis showed a significant effect of time both within and between the groups. Both in group A (tramadol) and group B (buprenorphine), GCPS-SF score was significantly higher preoperatively compared with all other time points of the postoperative period ($P < 0.001$), with lowest score values at 12 hours postoperatively and 24 hours postoperatively compared with 2 hours postoperatively (Figure 1). The statistical analysis also showed a significant effect of medication, with GCPS-SF scores lower in dogs treated with buprenorphine than in those treated with tramadol ($P = 0.049$, $P = 0.016$, and $P = 0.003$ at 2 hours postoperatively, 12 hours postoperatively, and 24 hours postoperatively, respectively) (Figure 2).

In detail, during the period of monitoring, group B dogs showed greater comfort, with less tendency to impatience, less spinal stiffness, and higher tolerance of handling than those of group A, as soon as 2 hours postoperatively after surgery. Similarly, after 12 hours postoperatively and 24 hours postoperatively, both groups responded positively to the treatment, but group B animals were found to be more manageable; they had a less capricious appetite (were less choosy with food), less tendency to nervousness, and kyphosis was rarely present.

During the postoperative period, the GCPS-SF scores did not exceed 5 of 20 in group B (mean ± SD, 3.12 ± 1.08; median, 3; range, 1-5), whereas 2 dogs at 2 hours postoperatively and 1 dog at 12 hours postoperatively of group A scored 6 of 20 (mean ± SD, 3.96 ±

Table
Descriptive statistic of GCPS-SF scores calculated for group A and group B (mean, SD, median, minimum, maximum, lower and upper quartiles, and variances) during the preoperative period (preop) and 2 (2 hours postop), 12 (12 hours postop), and 24 (24 hours postop) hours after surgery

Groups	Time	Mean	SD	Median	Minimum	Maximum	Lower quartile	Upper quartile	Variance
A	Preop	15.92	1.58	16	12	18	15	17	2.49
	2 h postop	4.56	0.77	5	3	6	4	5	0.59
	12 h postop	4.32	0.83	4	3	6	4	5	0.68
	24 h postop	3	0.99	3	2	5	2	3	0.98
B	Preop	15.84	1.62	16	13	18	15	17	2.64
	2 h postop	3.88	0.59	4	3	5	3.5	4.2	0.34
	12 h postop	3.48	0.59	3	2.5	4.5	3	4	0.34
	24 h postop	2	0.92	2	1	4	1	2.5	0.85

GCPS-SF, the short form of the Glasgow Composite Pain Scale; SD, standard deviation.

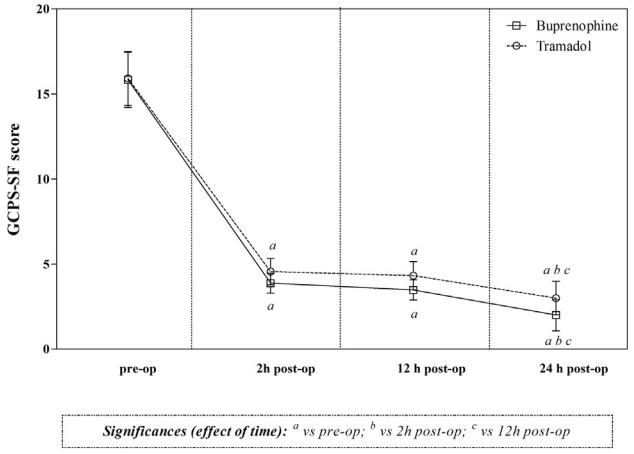

Figure 2. The short form of the Glasgow Composite Pain Scale (GCPS-SF) score evaluated in group A (tramadol) and group B (buprenorphine) before surgery (preoperatively) and during postoperative period (2 hours postoperatively, 12 hours postoperatively, and 24 hours postoperatively) with the respective significances found within each group. Preop, preoperatively; postop, postoperatively.

1.10; median, 4; range, 2-6), considered as a possible analgesic intervention level (Reid et al., 2007).

Discussion

The control of pain is part of a veterinarian's duty of care toward their patients to ensure good welfare. Painful sensations determine alterations of various body systems, including cardiovascular, respiratory, gastroenteric, and immune systems, and slow the tissue healing process. Pain is also known to impair decision making and mental processing as may neuter the behavior resulting in vocalization, anxiety or depression, aggressiveness, and automutilation of the affected area. Behavioral changes that result in aggression and anxiety are potentially dangerous for the veterinarian, making it more difficult to manage and examine the dog, and may lead to a drastic reduction of animal welfare and an impairment of patient's capability to cope in stressful conditions.

Although the importance related to the alleviation of pain in companion animals is increasing, recent surveys suggest that the use of analgesic drugs in small animal veterinary practice is suboptimal (Reid et al., 2007). In fact, pain management is a real challenge in veterinary medicine because it requires special skills of the clinician in recognizing, as objectively as possible, its different aspects in nonverbal patients.

The GCMPS is a validated behavior-based composite scale, developed using psychometric methodology, to assess acute pain in dogs. This scale measures pain to a level of precision suitable for clinical trials (Morton et al., 2005). Indeed, the application of a scaling model is particularly important in quantitative studies of analgesia, for example, in pre-, peri-, and postoperative settings. A short form of the GCMPS-SF was developed for routine clinical use, where the emphasis is on speed, ease of use, and guidance for analgesia provision (Reid et al., 2007).

Although many researchers (Lascelles and Waterman, 1997) support the need to include, in analgesic drug studies, a control group without treatment, we decided not to use a comparison group for ethical reasons related to the professional code of ethics that ensures, first of all, the physical and mental welfare of the animal. In fact, it is widely recognized that disc pathologies and surgeries are characterized by moderate to severe pain (Carroll and Martin, 2007), as confirmed by the high scores achieved during the preoperative evaluation of our sample. Likewise, other authors compared the effect of morphine and buprenorphine (Brodbelt et al., 1997) and tramadol and morphine (Mastrocinque and Fantoni, 2003) administered for postoperative pain in dogs, without entering a control group.

In the present study, both analgesics showed good efficacy in controlling acute postoperative pain resulting from hemilaminectomy, as evidenced by the rapid and significant improvement of the GCPS-SF scores. However, buprenorphine showed a higher and more rapid analgesic effect than tramadol.

Although tramadol has a lower affinity for the μ receptors, several studies in humans have shown an analgesic effect of tramadol similar to that of morphine (Matrocinque and Fantoni, 2003; Neves et al., 2012; Kongara et al., 2013). However, some studies carried out in the canine species suggest a lower efficacy than in man. Particularly, in beagle dogs, a limited production of the metabolite M1, which has a high affinity for μ-opioid receptors, and of spinal serotonin receptors, has been proven (Wu et al., 2001). Even in rats, tramadol showed an analgesic efficacy lower than buprenorphine (McKeon et al., 2011).

At the dosage and condition of administration used in our study, both molecules showed no side effects; in particular, no depressant effects were observed on the respiratory function, as recorded in other studies performed in dogs with tramadol and morphine (Mastrocinque and Fantoni, 2003).

The advantages of treatment with buprenorphine include a greater plasma half-life (from 6 to 8 hours), with a lower frequency of administration, good analgesic effect, and different routes of administration. Disadvantages include the ceiling effect, the difficulties of antagonization, and the administration subjected to the restriction for the narcotic drugs.

The advantages of the use of tramadol include a lower occurrence of adverse respiratory, gastrointestinal, and immunomodulatory effects compared with other opioid drugs, and an anti-inflammatory effect, albeit moderate (Buccellati et al., 2000).

Conclusions

The results obtained in the present study show that both buprenorphine and tramadol can be used safely in controlling postoperative pain in dogs treated for acute intervertebral disc extrusion, although buprenorphine has shown a faster and higher analgesic effect.

Buprenorphine might be better than tramadol during the first stage of hospitalization, but tramadol might represent a good alternative for continued treatment, considering its lower incidence of side effects. Use of both medications can contribute to improve animal welfare.

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Ethical considerations

Protocols of animal husbandry and experimentation were reviewed in accordance with the standards recommended by the *Guide for the Care and Use of Laboratory Animals* and Directive 2010/63/European Union for animal experiments and approved by the Ethics Committee of the Department of Veterinary Sciences, of the University of Messina (record number, 007/2016).

Authorship

The idea for the article was conceived by E. Giudice and C. Crinò. The experiments were designed by S. Di Pietro, A. Alaimo, and C.

Crinò. The experiments were performed by G. Barillaro and A. Alaimo. The data were analyzed by S. Di Pietro and F. Macrì. The article was written by C. Crinò and E. Giudice.

Conflict of interest

The authors disclaim any financial support or relationships that may pose conflict of interest.

References

Andaluz, A., Moll, X., Abellán, R., Ventura, R., Carbò, M., Fresno, L., García, F., 2009. Pharmacokinetics of buprenorphine after intravenous administration of clinical doses to dogs. Vet. J. 181, 299–304.

Bosmans, T., Gasthuys, F., Duchateau, L., de Bruin, T., Verhoeven, G., Polis, I., 2007. A comparison of tepoxalin-buprenorphine combination and buprenorphine for postoperative analgesia in dogs: a clinical study. J. Vet. Med. 54, 364–369.

Brodbelt, D.C., Taylor, P.M., Stanway, G.W., 1997. A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs. J. Vet. Pharmacol. Ther. 20, 284–289.

Buccellati, C., Sala, A., Ballerio, R., Bianchib, M., 2000. Tramadol anti-inflammatory activity is not related to a direct inhibitory action on prostaglandin endoperoxide synthases. Eur. J. Pain 4, 413–415.

Carroll, L.G., Martin, D.D., 2007. Trauma and critical patients. In: Tranquilli, W.J., Thurmon, J.C., Grimm, K.A. (Eds.), Lamb and Jones' Veterinary Anaesthesia and Analgesia, 4th ed. Blackwell Publishing Professional, Ames, IA, pp. 969–984.

Cooper, J.J., Young, B.D., Griffin, J.F., Fosgate, G.T., Levine, J.M., 2014. Comparison between noncontrast tomography and magnetic resonance imaging for detecting and characterization of thoracolumbar myelopathy caused by intervertebral disk herniation in dogs. Vet. Radiol. Ultrasound 55, 182–189.

Cudia, S.P., Duval, J.M., 1997. Thoracolumbar intervertebral disk disease in large, nonchondrodystrophic dogs: a retrospective study. J. Am. Anim. Hosp. Assoc. 33, 456.

Dahan, A., Yassen, A., Bijl, H., Romberg, R., Sarton, E., Teppema, L., Olofsen, E., Danhof, M., 2005. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br. J. Anaesth. 94, 825–834.

Kongara, K., Chambers, J.P., Johnson, C.B., Dukkipati, V.S., 2013. Effects of tramadol or morphine in dogs undergoing castration on intra-operative electroencephalogram responses and post-operative pain. N. Z. Vet. J. 61, 349–353.

Lascelles, D., Wateman, A., 1997. Analgesia in cats. In Pract. 19, 203–213.

Linton, D.D., Wilson, M.G., Newbound, G.C., Freise, K.J., Clark, T.P., 2012. The effectiveness of a long-acting transdermal fentanyl solution compared to buprenorphine for the control of postoperative pain in dogs in a randomized, multicentered clinical study. J. Vet. Pharmacol. Ther. 35, 53–64.

Lutfy, K., Cowan, A., 2004. Buprenorphine: a unique drug with complex pharmacology. Curr. Neuropharmacol. 2, 395–402.

Lutfy, K., Eitan, S., Bryant, C.D., Yang, Y.C., Saliminejad, N., Walwyn, W., Kieffer, B.L., Takeshima, H., Carroll, F.I., Maidment, N.T., Evans, C.J., 2003. Buprenorphine-induced antinociception is mediated by the μ-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. J. Neurosci. 23, 10331–10337.

Mastrocinque, S., Fantoni, D.T., 2003. A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. Vet. Anaesth. Analg. 30, 220–228.

McKeon, G.P., Pacharinsak, C., Long, C.T., Howard, A.M., Jampachaisri, K., Yeomans, D.C., Felt, S.A., 2011. Analgesic effects of tramadol, tramadol–gabapentin, and buprenorphine in an incisional model of pain in rats (*Rattus norvegicus*). J. Am. Assoc. Lab. Anim. Sci. 50, 192–197.

Moll, X., Fresno, L., García, F., Prandi, D., Andaluz, A., 2011. Comparison of subcutaneous and transdermal administration of buprenorphine for pre-emptive analgesia in dogs undergoing elective ovariohysterectomy. Vet. J. 187, 124–128.

Morgaz, J., Navarrete, R., Muñoz-Rascón, P., Domínguez, J.M., Fernández-Sarmiento, J.A., Gómez-Villamandos, R.J., Granados, M.M., 2013. Postoperative analgesic effects of dexketoprofen, buprenorphine and tramadol in dogs undergoing ovariohysterectomy. Res. Vet. Sci. 95, 278–282.

Morton, C., Reid, J., Scott, E., Holton, L.L., Nolan, A.M., 2005. Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. Am. J. Vet. Res. 66, 2154–2166.

Neves, C.S., Balan, J.A., Pereira, D.R., Stevanin, H., Cassu, R.N., 2012. A comparison of extradural tramadol and extradural morphine for postoperative analgesia in female dogs undergoing ovariohysterectomy. Acta. Cir. Bras. 27, 312–317.

Perez-Jimenez, T.E., Mealey, K.L., Grubb, T.L., Greene, S.A., Court, M.H., 2016. Tramadol metabolism to O-desmethyl tramadol (M1) and N-desmethyl tramadol (M2) by dog liver microsomes: species comparison and identification of responsible canine cytochrome P-450s (CYPs). Drug Metab. Dispos. 44, 1963–1972.

Reid, J., Nolan, A.M., Hughes, J.M.L., Lascelle, D., Pawson, P., Scott, E.M., 2007. Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. Anim. Welf. 16, 97–104.

Shih, A., Robertson, S., Isaza, N., Pablo, L., Davies, W., 2008. Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy. Vet. Anaesth. Analg. 35, 69–79.

Slingsby, L.S., Taylor, P.M., Murrell, J.C., 2011. A study to evaluate buprenorphine at 40 μg Kg^{-1} compared to 20 μg Kg^{-1} as a post-operative analgesic in the dog. Vet. Anaesth. Analg. 38, 584–593.

Slingsby, L.S., Taylor, P.M., Waterman-Paerson, A.E., 2006. Effects of two doses of buprenorphine four or six hours apart on nociceptive thresholds, pain and sedation in dogs after castration. Vet. Rec. 159, 705–711.

Tator, C.H., Fehlings, M.G., 2010. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. J. Neurosurg. 112, 15–26.

Wilson, J.R., Fehlings, M.G., 2011. Emerging approaches to the surgical management of acute traumatic spinal cord injury. Neurotherapeutics 8, 187–194.

Wu, W.N., McKown, L.A., Gauthier, A.D., Jones, W.J., Raffa, R.B., 2001. Metabolism of the analgesic drug, tramadol hydrochloride, in the rat and dog. Xenobiotica 31, 423–441.