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Comparison of tramadol and buprenorphine analgesia for continuous intravenous propofol anaesthesia in dogs undergoing dental prophylaxis

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ABSTRACT: The objective of this study was to compare, in client-owned patients, the analgesic effects of the centrally acting analgesics tramadol and buprenorphine in continuous intravenous anaesthesia (TIVA) with propofol. The study included forty dogs aged two to seven years and weighing 6–27 kg undergoing prophylactic dental treatment. The animals were classified into ASA (American Society of Anaesthesiologists) I. and II. risk groups. One group of dogs received intravenous administration of tramadol (2 mg/kg) and the second one buprenorphine (0.02 mg/kg) 30 min prior to sedation induced by midazolam (0.3 mg/kg) and xylazine (0.5 mg/kg) *i.v.* General anaesthesia was induced by propofol (2 mg/kg) and maintained by a 120-minute propofol infusion (0.2 mg/kg min). Arterial blood pressure, heart rate, respiratory rate, saturation of haemoglobin with oxygen, body temperature and deep pain sensation elicited by haemostat forceps pressure on the fingers were recorded at ten minute intervals. The tramadol group of dogs showed significantly better blood pressure values ($P < 0.001$), minimal tendency to bradycardia ($P < 0.05$) and respiratory rate ($P < 0.001$), without any negative effects on oxygen saturation. Significantly better deep pain sensation was achieved in the tramadol group ($P < 0.001$). Blood gas/acid base profile analysis showed a non-significant increase in the tramadol group of dogs. In conclusion, in comparison with buprenorphine, tramadol provided significantly better results with respect to degree of analgesia, as well as the tendency towards cardiopulmonary complications arising during anaesthesia. Significantly better analgesia and a lower depressive effect of tramadol on vital functions allows better control and management of the continuous intravenous propofol anaesthesia.

Keywords: dog; analgesics; side effects; continuous propofol anaesthesia

Tramadol is marketed as a racemic mixture of both R and S stereoisomers. This is because the two isomers complement each other's analgesic activity (Brayfield 2014). Tramadol is metabolised to O-desmethyltramadol, a significantly more potent opioid (Raffa et al. 2012*).* Tramadol is a weak mu-opioid receptor agonist; it can be addictive and it has been shown that it weakly inhibits the reuptake of norepinephrine and serotonin (Reimann and Schneider 1998). It is thought that these effects on central catecholaminergic pathways contribute significantly to the drug´s analgesic effects (Stoelting 1999). Tramadol is recommended for the management of chronic and acute pain of moderate-to-severe intensity (Grond and Sablotzki 2004). Duthie (1998) claimed that the analgesic potency of tramadol administered intravenously is the same as that of meperidine and one-tenth that of morphine. Mastrocinque and Fantoni (2003) compared tramadol and morphine administered preoperatively with the aim of assessing early postoperative pain during canine ovariohysterectomy. No differences were found between the two groups with regard to analgesia, sedation, haemoglobin oxygen saturation (SpO_2), pH and blood gases, cardiovascular variables, glucose, catecholamine and cortisol concentrations. Significantly higher end tidal carbon dioxide concentrations were

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measured 30 min following morphine injection. Tramadol (1 mg/kg), administered after induction of anaesthesia, provided equivalent post-operative pain relief, and similar recovery times and post-operative patient-controlled analgesia (PCA) as the administration of 0.1 mg/kg morphine. These results also suggest that pre-surgical exposure to systemic opioid analgesia may not provide clinically significant benefits (Ungulec et al. 2003). Siddiqui and Chohan (2007) compared tramadol and nalbuphine in total intravenous anaesthesia for obstetric dilatation and evacuation and found no statistically significant differences in the measured cardiopulmonary parameters. They found statistically a significantly lower sedating effect with nalbuphine as well as a shorter recovery period. Buprenorphine is a semi-synthetic partial opioid agonist that is used to treat opioid addiction in higher dosages, to control moderate acute pain in non-opioid-tolerant individuals in lower dosages and to control moderate chronic pain in even smaller doses (Grond and Sablotzki 2004). Due to its excellent analgesic properties, buprenorphine is a drug that finds broad clinical applications for cats, dogs, exotic species and laboratory animals. It provides analgesia for the management of pre-operative/post-operative pain, as well as painful joint injuries, fractures, tissue inflammation due to infection, tissue necrosis and trauma resulting from wounds (Roughan and Flecknell 2002). Paul-Murphy et al. (1999) compared the analgesic effects of butorphanol and buprenorphine in parrots. They confirmed a significantly increased threshold to electrical stimuli in the case of butorphanol. At the dosage used, buprenorphine did not change the threshold to electrical stimulus. Butorphanol elicited an analgesic response in half of the birds tested. Buprenorphine should be used with caution in animals with head trauma, compromised cardiovascular function, liver disease and in geriatric or severely debilitated animals. A slowed respiratory rate is a possible side-effect of buprenorphine in some dogs, so it should not be used to treat dogs with heart failure, head trauma or respiratory issues (Dohoo and Dohoo 1996). Common adverse drug reactions associated with the use of buprenorphine are similar to those of other opioids and include nausea and vomiting, drowsiness, dizziness, headache, memory loss, cognitive and neural inhibition, perspiration, itchiness, dry mouth, miosis, hypotension and urinary retention. Constipation and CNS effects are seen less frequently with buprenorphine than with morphine (Budd and Raffa 2005). Due to the fact that elimination is mainly hepatic, there is no risk of accumulation in patients with renal impairment (Moody et al. 2009). The objective of this study was to compare the analgesic effects of buprenorphine and tramadol and their possible side-effects in dogs pre-medicated with midazolam, xylazine *i.v.*, in long-term total intravenous anaesthesia maintained by propofol.

MATERIAL AND METHODS

Forty dogs undergoing dental prophylactic treatment (first two stages of periodontitis not including tooth extractions) with no other diseases were used in the study. The age of dogs ranged from 2–7 years (mean 4.16) with weight ranging from 6–27 kg (mean 12.6). The dogs under examination were classified into the ASA (American Society of Anaesthesiologists) groups I and II They were divided into two buprenorphine and tramadol groups (B group and T group) with twenty animals in each group. The study was approved by the local Ethics Committee and the owners were informed and gave theirconsent to participation in this study.

Intravenous catheters were placed into *v. cephalica antebrachii sinistra* and *dextra*, one for constant rate infusion-based total intravenous anaesthesia and the second for blood collection. In the buprenorphine group (B), a 0.02 mg/kg *i.v.* dose was administered 30 min before the sedation protocol. In the tramadol group (T), tramadol in a dose of 2 mg/kg *i.v.* was used before sedation in place of buprenorphine. The sedating effects of the compared analgesics were assessed according to the American Society of Anaesthesiologists as mild, moderate, deep or general anaesthesia. All dogs were sedated using 0.3 mg/kg midazolam administered intravenously, in three partial doses administered in three two-minute intervals followed by 0.5 mg/kg xylazine *i.v.* Anaesthetic induction with 2 mg/kg propofol was followed by a 120 min 0.2 mg/kg/min propofol infusion using an infusion system IPB 2050 (Polymed, CZ). After reaching adequate muscle relaxation and reflex depression patients were intubated and were allowed to breathing room air. The ambient temperature was kept at 26 °C by a fan heater. Dogs were monitored throughout the anaesthetic and recovery periods. Venous blood was sampled from the *vena cephalica*

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antebrachii into glass heparinised capillaries and examined for blood pH (pH), partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), concentration of actual bicarbonates (HCO_3^-) and base excess (BE). The analysis was performed on an automated ABL 5 analyser (Radiometer Copenhagen, Denmark). Blood samples collected 30 min (pH 30) following analgesic administration and at the end of propofol infusion (pH 120) were compared between groups. Oscillometric arterial blood pressure (ABP), ECG heart rate (HR), respiratory rate (RR), oximetry saturation of haemoglobin with oxygen (SpO_2) and core body temperature (BT) were recorded using a Patient Monitor-9000Vet (Hamburg, DE). Pain reactions were recorded in ten minute intervals. Pain sensation was induced by intermittent haemostat pressure on the periosteum of second phalanges over the course of one minute. Pain sensation was classified into three grades. Grade 1 – no pain reaction, grade 2 – increased heart and respiratory rate and grade 3 – movement. In the case of a decreased depth of anaesthesia (increased palpebral reflex), propofol in a dose of 2 mg/kg *i.v.* was administered. In the case of an increased plane of anaesthesia, propofol infusion was stopped. Bradycardia (less than 60 heart beats per minute) developing during anaesthesia was corrected by administration of 0.015 mg/kg *i.v.* atropine. During the recovery period, time of extubation following appearance of the swallowing reflex, the ability to lift up the head, take a sternal position and first walk were recorded.

Statistical analysis used mean values ($\bar{x}$) and standard deviation (SD). Observed mean parameters were statistically analysed using one way analysis of variance (ANOVA). The level of significance was assessed at 0.001. Analyses were done in the MS Excel program.

RESULTS

Buprenorphine (Group B) produced deeper sedation as measured by unstable gait and lying within 5-8 minutes following administration compared to tramadol following *i.v.* administration. In 50% of dogs in the B group the degree of muscle relaxation and reflex depression allowed intubation before induction of general anaesthesia with propofol with no or minimal tracheal irritation during the procedure. This phenomenon was not seen in the tramadol (T) group of dogs. In this group, the dogs experienced some degree of incoordination following midazolam administration, which disappeared after dosing with xylazine. Dogs in the T group could be intubated only following propofol administration. The average mean blood pressure values showed significant differences between groups ($P < 0.001$) with higher blood pressure values in the T group (Table 1). Heart rate did not differ significantly between the groups (Table 2).

However, this result was obtained using atropine at a dose of 0.01 mg/kg *i.v.* in eight patients (40%) of group B with the aim of correcting developing. In four dogs, it was necessary to administer bradycardia twice and in another four, three times during anaesthesia. In dogs of the T group bradycardia occurred in one patient immediately after propofol induction. A single dose of atropine adjusted the

Table. 1. Changes in mean blood pressure in the evaluated groups of dogs (means ± SD)

Analgesic		0	10	20	30	40	50	60	70	80	90	100	110	120
T group*	$\bar{x}$	92.7	98.0	93.8	89.5	88.3	84.8	83.5	90.0	90.3	90.3	92.3	88.8	90.3
	SD	8.1	13.6	11.2	6.2	6.7	5.6	7,9	15.1	12.3	11.7	9,3	5.3	3.9
B group	$\bar{x}$	89.0	94.2	87.2	82.0	71.7	78,7	75.8	74.0	86.5	79.2	75.3	86.8	76.5
	SD	27.7	17.6	13.7	11.1	18.2	17.1	20.1	13.8	17.1	14.4	18.4	13.3	15.4

*statistically significant differences between the groups ($P < 0.001$)

Table 2. Changes in mean heart rate in the evaluated groups of dogs (means ± SD)

Analgesic		0	10	20	30	40	50	60	70	80	90	100	110	120
T group	$\bar{x}$	64.5	89	79	75.7	75	74.7	75.3	72.7	75.2	74	70.3	71.3	71.3
	SD	14.6	43.2	25.9	17.7	10.8	7.0	6.1	12.2	12.1	13.1	7.8	7.4	7.9
B group	$\bar{x}$	68.5	75	86.8	78.7	71.3	74.7	72.5	71.2	82	74.8	79.3	66.8	64.2
	SD	10.3	19.7	45.9	25	13.5	12.1	8.8	9.6	32.1	22.4	16.6	11.1	12.4

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heart rate for the remainder of the anaesthesia. A significant difference was confirmed between the T and B group ($P < 0.05$) in relation to the frequency of the use of atropine to correct developing bradycardia. In six dogs in the B group tachypnoea ranging between 45 and 120 breaths per minute was observed after buprenorphine administration. During TIVA these dogs also showed episodes of costal type tachypnoea in the range of 28–122 breaths per minute. The other 14 dogs in this group exhibited a tendency towards bradypnoea with respiratory rates in the range of seven to nine breaths per minute. Statistical analysis of average respiratory rates confirmed a significant difference between groups ($P < 0.001$, Table 3). SpO_2 ranged from 87–98 % without a significantly lower saturation in the B group. The nociceptive response showed better results in the T group, where during the first 30 min of anaesthesia no pain reactions were noted (Table 4). Statistically better analgesia was achieved in the T group ($P < 0.001$). Blood gases, pH, base excess and bicarbonate values were within the physiological ranges in both groups (Table 5). The measured parameters showed only non-significant differences. In the recovery period the average time of extubation was 10 min and 50 s in the B group and 13 min in the T group. The appearance of head movement (17.3 vs 18.5 min), sternal position (25 vs 30.3 min) and walking (27.7 vs 32.3 min) were faster in the T group. Body temperature did not show significant changes during general anaesthesia. The difference in the recovery times between the groups was not statistically significant.

DISCUSSION

The main aim of this study was to compare the pre-operative analgesic effects of buprenorphine and tramadol. Buprenorphine is regulated by the Drug Enforcement Agency while tramadol is not, which was an additional reason to compare these two analgesics. While buprenorphine is employed

Table. 3. Changes in respiratory rate in the evaluated groups of dogs (means ± SD)

Analgesic		0	10	20	30	40	50	60	70	80	90	100	110	120
T group*	$\bar{x}$	14.7	11.7	14.2	14.7	14.5	15.8	15.7	16.3	18.8	15.8	16.2	16.2	17.0
	SD	4.8	3.7	5.2	5.9	5.0	3.9	5.4	6.9	6.2	6.9	6.0	6.0	5.8
B group	$\bar{x}$	15.2	16.0	15.3	15.8	29.3	25.2	28.2	23.8	26.0	21.5	22.3	22.7	26.3
	SD	12.6	12.5	9.5	10.0	33.8	30.3	38.0	24.8	29.4	20.4	21.1	23.6	29.6

*statistically significant differences between the groups ($P < 0.001$)

Table. 4. Changes in pain reaction in the evaluated groups of dogs (means ± SD)

Analgesic		0	10	20	30	40	50	60	70	80	90	100	110	120
T group*	$\bar{x}$	1	1	1	1	1.3	1.3	1.5	1.5	1.8	1.7	1.2	1.2	1.8
	SD	0	0	0	0	0.5	0.5	0.5	0.5	0.8	0.8	0.4	0.4	0.4
B group	$\bar{x}$	1.3	1.8	1.8	1.8	2.2	2.2	2.2	2.2	2.0	2.2	2.2	2.0	2.8
	SD	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0	0.4	0.4	0.0	0.4

*statistically significant differences between the groups ($P < 0.001$)

Table. 5. Blood gas/acid base profile differences between the evaluated groups of dogs (means ± SD, *P*)

Analgesic		pH 30	pH 120	pCO_2 30	pCO_2 120	pO_2 30	pO_2 120	HCO_3 30	HCO_3 120	BE 30	BE 120
T group*	$\bar{x}$	7.36	7.34	5.34	5.37	6.37	9.63	21.86	20.86	–2.57	–3.00
	SD	0.05	0.03	0.50	1.18	1.55	5.25	1.46	4.30	1.72	2.24
B group	$\bar{x}$	7.33	7.33	5.64	6.34	5.58	7.14	21.60	22.80	–3.80	–3.40
	SD	0.04	0.06	0.19	0.84	2.02	1.15	1.82	1.79	2.17	1.82
	P	0.232	0.724	0.193	0.129	0.486	0.264	0.801	0.311	0.327	0.740

*statistically significant differences between the groups ($P < 0.001$); *P* = significance of the differences between the groups of dogs

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for pre-operative analgesia in veterinary medicine, in humans it is only used in regional epidural anaesthesia. Tramadol is a much weaker pain medication when compared to morphine; it is about 10 times less potent. Studies have also shown that tramadol does not cause breathing problems (Grond and Sablotzki 2004). For moderate pain its effectiveness is equivalent to that of morphine, while for severe pain it is less effective than morphine. Ungulec et al. (2003) confirmed that tramadol (1 mg/kg), administered after induction of anaesthesia offered equivalent post-operative pain relief, and similar recovery times and post-operative patient-controlled analgesia as 0.1 mg/kg morphine. These results also suggest that pre-surgical exposure to systemic opioid analgesia may not result in clinically significant benefits. Lee et al. (1993) found that tramadol was not a suitable analgesic for use in human balanced anaesthesia because of problems with increased intra-operative awareness. Khan (2009) concluded that although the use of *i.v.* tramadol as a pre-induction agent is associated with a low risk of side-effects, due to its potential to cause seizure activity (found in 0.33% of 600 patients), it is best avoided in environments where adequate resuscitative measures are not available. There is still controversial data regarding the convulsant effects of tramadol *in vitro.* For example, it has been demonstrated that tramadol has anticonvulsant effects in mice (Manocha et al. 2005). Meanwhile, Spiller et al. (1997) claimed that seizures in humans were reported in patients receiving the drug in overdose and, rarely at the recommended dose unless it was taken by people with epilepsy or taken together with other drugs that reduced the seizure threshold. Our results did not confirm the seizure-promoting effect of tramadol in the used dose. While Mastrocinque and Fantoni (2003) found no differences between groups with regard to analgesia, sedation, SpO_2, pH and blood gases, cardiovascular variables, glucose, catecholamine and cortisol concentrations when comparing tramadol and morphine our results showed increased sedation and decreased analgesia in the case of buprenorphine. Our experience with tramadol in balanced intravenous anaesthesia has not confirmed any of the side-effects described in humans. The dogs in the T group had significantly better parameters of blood pressure, respiratory rate and analgesia in comparison with the B group. The dogs receiving tramadol did not show any clinical signs of sedation. Buprenorphine produced overt sedation shortly after administration in some patients accompanied by tachypnoea. The potentiating effect of buprenorphine to xylazine was confirmed as it was possible to intubate 50% of dogs without propofol induction. This was not observed in the T group where intubation was possible only following propofol induction. The dogs in the B group had significantly higher episodes of bradycardia corrected by anticholinergic atropine. In a study comparing tramadol and buprenorphine for the relief of cancer pain, Bono and Cuffari (1997) confirmed a better tolerance and fewer and milder adverse reactions in the case of tramadol than buprenorphine. Tramadol, although theoretically less potent, brought about as much pain relief as did buprenorphine. In conclusion, for this class of drug, tramadol provided an excellent balance between efficacy and tolerability, confirming preliminary studies (Lee et al. 1993). In an experimental study, Kogel et al. (2014) could not confirm the anti-nociceptive effects of tramadol in beagles, which was explained by the marginal amounts of the M1 metabolite of tramadol in some breeds of dogs. According to our clinical results, in balanced anaesthesia in dogs the use of tramadol resulted in significantly enhanced values for the monitored parameters in comparison with that of buprenorphine. In this study buprenorphine produced sedation, but the analgesic effect was inferior to tramadol as could be seen from the results. Taylor and Houlton (1984) also found that buprenorphine produced more sedation than morphine in dogs and considered that this could affect analgesia assessment. Whereas in general anaesthesia there is a loss of consciousness, the sedative effect of analgesics does not play as important a role in pain assessment as in animals that are awake in the post-operative period. While in the T group we did not find signs of pain perception within the first 30 min in the B group, some dogs reacted to painful stimuli with increased heart and respiratory rate from the beginning of anaesthesia. Studies in human medicine also report a significantly better analgesic effect of oral tramadol in human cancer patients suffering from strong/unbearable pain (Brema et al. 1996; Bono and Cuffari 1997). The time of recovery did not differ significantly between the groups, both needing approximately 30 min to stand up and walk. It can be concluded that balanced continuous propofol anaesthesia with tramadol as an analgesic, achieved significantly better endpoints in relation to analgesia and the frequency of corrective interventions to maintain the observed parameters in the

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physiological range. None of the side-effects observed in humans have been confirmed in dogs. The results describe a safe long-term intravenous anaesthesia without the need of oxygen support. The rapid recovery time is comparable with inhalation anaesthesia.

REFERENCES

Bono AV, Cuffari S (1997): Effectiveness and tolerance of tramadol in cancer pain. A comparative study with respect to buprenorphine. Drugs, 53 (Suppl 2), 40–49.

Budd K, Raffa RB (2005): Buprenorphine – The Unique Opioid Analgesic. 1st ed. Thieme Stuttgard, New York. 132 pp.

Brayfield A (2014): Tramadol hydrochloride. In: Brayfield A (ed.): Martindale: The Complete Drug Reference. Pharmaceutical Press, London. 4688 pp.

Brema F, Pastorino G, Martini MC, Gottlieb A, Luzzani M, Libretti A, Sacca L, Gigolari S (1996): Oral tramadol and buprenorphine in tumour pain. An Italian multicentre trial. International Journal of Clinical Pharmacology Research 16, 109–116.

Dohoo SE, Dohoo IR (1996): Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. Canadian Veterinary Journal 37, 552–556

Duthie DJR (1998): Remifentanil and tramadol: recent advances in opioid pharmacology. British Journal of Anaesthesia 81, 51–57.

Grond S, Sablotzki A (2004): Clinical pharmacology of tramadol. Clinical Pharmacokinetics 43, 879–923.

Khan TH (2009): Safety of tramadol as a pre-induction agent. Anaesthesia Pain and Intensive Care 13, 57–60.

Kogel B, Terlinden R, Schneider J (2014): Characterisation of tramadol, morphine and tapentadol in an acute pain model in Beagle dogs. Veterinary Anaesthesia and Analgesia 41, 297–304.

Lee CR, McTavish D, Sorkin EM (1993): Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs 46, 313–340.

Manocha A, Sharma KK, Mediratta PK (2005): On the mechanism of anticonvulsant effect of tramadol in mice. Pharmacology Biochemistry and Behavior 82, 74–81.

Mastrocinque S, Fantoni DT (2003): A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. Veterinary Anaesthesia and Analgesia 30, 220–228.

Moody DE, Fang Lin SN, Weyant DM, Strom SC, Omiecinski CJ (2009): Effect of rifampin and nelfinavir on the metabolism of methadone and buprenorphine in primary cultures of human hepatocytes. Drug Metabolism and Disposition 37, 2323–2329.

Paul-Murphy JR, Brunson DB, Miletic V (1999): Analgesic effects of butorphanol and buprenorphine in conscious African grey parrots (Psittacus erithacus erithacus and Psittacus erithacus timneh). American Journal of Veterinary Research 60, 1218–1221.

Raffa RB, Buschmann H, Christoph T, Eichenbaum G, Englberger W, Flores CM, Hertrampf T, Kogel B, Schiene K, Straßburger W, Terlinden R, Tzschentke TM (2012): Mechanistic and functional differentiation of tapentadol and tramadol. Expert Opinion on Pharmacotherapy 13, 1437–1449.

Reimann W, Schneider F (1998): Induction of 5-hydroxytryptamine release by tramadol, fenfluramine and reserpine. European Journal of Pharmacology 349, 199–203.

Roughan JV, Flecknell PA (2002): Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Laboratory Animals 36, 322–343.

Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage, MM, Anderson DL (1997): Prospective multi-center evaluation of tramadol exposure. Journal of Toxicology: Clinical Toxicology 35, 361–364.

Siddiqui KM, Chohan U (2007): Tramadol versus Nalbuphine in total intravenous anaesthesia for dilatation and dvacuation. Journal of Pakistan Medical Association, 57, 67–70.

Stoelting RK (1999): Opioid agonists and antagonists. In: Stoelting RK (ed.): Pharmacology and Physiology in Anesthetic Practice. Lippincott Williams & Wilkins, Philadelphia. 77–112

Taylor PM, Houlton JEF (1984): Postoperative analgesia in the dog – a comparison of morphine, buprenorphine and pentazocine. Journal of Small Animal Practice 25, 437–451.

Ungulenc H, Ozalevli M, Gunes Y, Guler T, Isik G. (2003): Pre-emptive analgesic efficacy of tramadol compared with morphine after major abdominal surgery. British Journal of Anaesthesiology 91, 209–213.

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