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Pharmacokinetics, intraoperative effect and postoperative analgesia of tramadol in cats

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ABSTRACT

Tramadol is a synthetic codeine analogue used as an analgesic in human and veterinary medicine, but not approved for use in cats. Tramadol (2 mg/kg) was administered intravenously (IV) as preoperative analgesic in 12 cats (6 males) undergoing surgical gonadectomy. The pharmacokinetic profile of the drug and its *O*-desmethyl metabolite were determined in 8 animals (4 males), while intraoperative effects and postoperative analgesia, estimated by subjective pain score (0–24), were evaluated in all. Mean intraoperative isoflurane consumption was reduced, but hypoventilation was not observed. Sex-related differences were not observed, particularly in terms of postoperative analgesia: rescue analgesic was never administered. Concentrations of the active *O*-desmethyl metabolite were persistently high in all the animals. Considering the results obtained in this study, tramadol, at the dose of 2 mg/kg IV, did not produce any evident intraoperative cardiorespiratory side effects and with additional investigation may prove to be an appropriate intraoperative analgesic in cats undergoing gonadectomy.

1. Introduction

Tramadol is a synthetic codeine analogue that acts centrally as an analgesic. It was registered in 1977 in Germany, in 1994 in the UK, in 1995 in the USA (Grond and Sablotzki, 2004) and recently authorized for use in dogs in Europe (for example in Italy as Altadol, Formevet). The drug is supplied as a racemic mixture of the hydrochloride salts which are more effective than either enantiomer alone (Scott and Perry, 2000). The analgesic effects of tramadol result from complex interactions with opiate receptors and activation of descending inhibitory pathways (Scott and Perry, 2000). The stimulation of periaqueductal grey matter, nucleus raphe magnus, nucleus reticularis gigantocellularis and locus coeruleus inhibits norepinephrine and serotonin reuptake by neurons projecting from these nuclei to the spinal cord (Mayer, 1984); as a result, the activity of these neurons is increased, and pain transmission is modulated at the level of the dorsal horn. Tramadol inhibits neuronal norepinephrine and serotonin reuptake thereby increasing the activity of these pathways (Kayser et al., 1992; Raffa et al., 1992). Tramadol has no demonstrated affinity for δ or κ opioid receptors (Raffa et al., 1992) and its affinity for μ opioid receptors is about 10 times lower than that of codeine and about 6000 times lower than that of morphine (Grond and Sablotzki, 2004). However, the *O*-demethylated metabolite (*O*-desmethyl tramadol or M1) has a 300-fold greater affinity for μ opioid receptors than tramadol and thus contributes significantly to the analgesic effect of tramadol (Hennies et al., 1988; Frink et al., 1996; Gillen et al., 2000). In humans, tramadol is mainly metabolized to glucuronides and sulphates via *O*- and *N*-demethylation and conjugation reactions. Both tramadol and M1 are mainly excreted via the kidney (Scott and Perry, 2000). Hepatic demethylation to M1 occurs at different rates in dogs, goats, cats and horses (Kukanich and Papich, 2004; Vettorato et al., 2006; Zonca et al., 2006; Giorgi et al., 2007; Shilo et al., 2008; De Sousa et al., 2008; Pypendop and Ilkiw, 2008; Vettorato et al., 2010). As far as we are aware, limited information are available on how tramadol is metabolised in the cat. Previous studies (Cagnardi et al., 2006; Pypendop and Ilkiw, 2008) showed a high persistence of M1 and this seems to be related to cats' poor ability to glucuronidate compounds. Moreover the metabolite was present at levels over 0.01 μg/ml, i.e. above the lowest concentration associated with therapeutic efficacy in humans (Lehmann et al., 1990).

In humans, the analgesic effect of tramadol following parenteral administration is about 10% that of morphine (Grond and Sablotzki, 2004). Although the analgesic properties of tramadol

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have been investigated in laboratory conditions in various animals such as rat (Guneli et al., 2007; Kamerman et al., 2007), horse (Natalini and Robinson, 2000) and cat (Steagall et al., 2008; Pyendop et al., 2009; Castro et al., 2009), only few clinical trials have been published. The analgesic efficacy of tramadol has been studied in dogs after intravenous (IV) and extradural administration (Mastrocinque and Fantoni, 2003; Vettorato et al., 2010), and in cats after subcutaneous (SC) administration (Brondani et al., 2006, 2009a,b).

The present study reports (a) the pharmacokinetic profile of tramadol and its M1 metabolite in cats after IV administration at 2 mg/kg prior to surgical gonadectomy, and (b) a clinical evaluation of the efficacy of tramadol as postoperative analgesic. The aim of the study was to generate data for the rational dosing of this substance in cats.

2. Materials and methods

2.1. Animals

The study was performed on 12 healthy domestic shorthair cats, age 0.5–1.5 years, 6 males and 6 females, weighing between 2.5 kg and 4.3 kg, undergoing gonadectomy at the Department of the Clinical Veterinary Sciences, University of Milan. All animals were judged healthy (ASA status I) on the basis of physical examination and results of routine blood tests, and were enrolled in the study after written consent from their owners, as required by Italian law (D.L. 116/1992). Subsequently, the protocol was approved by the Ethical Committee of the University of Milan.

2.2. Anaesthetic and surgical procedures

All animals received atropine sulphate (0.03 mg/kg) and acepromazine maleate (0.05 mg/kg) intramuscularly (IM), as pre-anaesthetic medications. Anaesthesia was induced with isoflurane in oxygen (100%) using an anaesthetic chamber. After intubation anaesthesia was maintained with the same gases, delivered by a non-rebreathing system (Mapleson C). Tramadol (2 mg/kg) was administered IV as a bolus over 15 s through a cephalic catheter (22 gauge) 5 min after intubation and 20 min prior to beginning surgery. During surgery lactated Ringer's solution was administered at 5 ml/kg/h through the same catheter. Female cats underwent ovariectomy and the males underwent orchiectomy according to standard surgical procedures. During surgery, heart rate, electrocardiogram (lead II), respiration rate, oxyhaemoglobin saturation, end tidal carbon dioxide (CO_2), mean non-invasive arterial blood pressure, and end tidal isoflurane concentration were recorded every 5 min using a UT4000F Pro monitor (Goldway Inc.).

After extubation subjective pain scores were assessed by a trained observer using a method modified after Smith et al. (2004). The method involves assessment of behavioural indicators of pain (comfort, movement, appearance, unprovoked behaviour, interactive behaviour and vocalization) assigning a score of 0–4 for each. Thus a score of 24 indicates maximum pain and a score of zero no pain. Pain was assessed every 30 min up to 6 h. Buprenorphine (10 μg/kg IM) was administered if the pain score was 9 or above.

2.3. Collection, purification and analysis of serum samples

For 8 animals (4 males and 4 females), venous blood samples (2 ml) were collected into non-heparinized tubes from a jugular vein catheter: before tramadol administration (time 0) and 5, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h after tramadol administration. The samples were centrifuged (1500*g*, 10 min at room temperature) soon after collection and the serum stored at −80 °C pending assay.

Serum samples were purified by solid phase extraction on Isolute SPE C2 (100 mg/ml) cartridges (International Sorbent Technology Ltd., UK) previously activated with 2 ml of methanol followed by 2 ml of 0.05 M sodium chloride. Five hundred μl of 0.05 M sodium hydrogen phosphate dodecahydrate solution was added to 500 μl of serum and briefly vortexed. The sample was then loaded onto the cartridge followed by washing with 2 ml of 0.05 M sodium chloride. The compounds were eluted with 1 ml of methanol. The eluate was evaporated to dryness under nitrogen at 45 °C and the residue dissolved in 100 μl of mobile phase.

Residues were analysed for tramadol and M1 by HPLC. The apparatus included a binary pump, auto sampler, Peltier column oven (all Perkin–Elmer Series 200, Italy) at 20 °C, and a fluorescence detector (Perkin–Elmer LC240, Italy) with excitation and emission wavelengths 200 nm and 301 nm, respectively. The column was an ODS Hypersil C18 250 × 4.6 mm 5 μm column with Hypersil 5 μm 4.6 mm pre-column (Supelco, Italy). The mobile phase was 15 mM aqueous sodium hydrogen phosphate dodecahydrate with 45 mM triethylamine pH 3 and acetonitrile (82:18, v:v). Flow rate was 1.0 ml/min and injection volume was 50 μl.

Solutions for the calibration curve were prepared diluting stock solutions of tramadol and M1 (1 mg/ml) to obtain concentrations in the range 0.05–10 μg/ml in blank cat serum.

HPLC retention times were 11.5 min for tramadol and 5.4 min for M1. The HPLC method was validated in our laboratory and found to be specific, linear (in the range 0.05–10 μg/ml) precise (CV 2.05–7.4% for tramadol and 3.8–9.6% for M1) and accurate (−13% to +0.1% for tramadol and −0.02% to +2.5% for M1), with limit of quantification 0.05 μg/ml and limit of detection 0.0008 μg/ml for both compounds investigated. The mean recoveries for tramadol and M1 were 98.6 ± 6.86% and 92.9 ± 4.6%.

Serum binding of tramadol and M1 in the range 0.5–1 μg/ml was determined in vitro. The serum-bound molecules were removed by ultrafiltration (Villa et al., 1994, 1997) using a disposable device (Amicon, Millipore, Italy) and free substances in the filtrate were analyzed by HPLC as described above.

Tramadol hydrochloride was kind gift from Formevet; M1 was purchased from Sigma. Other reagents and solvents were purchased from J.T. Baker (Italy).

2.4. Pharmacokinetic analysis

Pharmacokinetic parameters were deduced from serum concentration–time data using the WinNonLin 5.2.1 software (Pharsight Corporation, USA) which allows compartmental and non-compartmental analyses of the experimental data. Minimum information criterion estimates (MAICE; Yamaoka et al., 1978) were used to choose the model that best fitted the data. All data points were weighted by the inverse square of the fitted value. Serum concentrations after IV tramadol administration were fitted to a standard bi-exponential curve (Gibaldi and Perrier, 1982) describing a two-compartment model with elimination from the central compartment.

Parameters estimated from the model were used to calculate pharmacokinetic variables for each animal. The volume of distribution in the central compartment (V_c) was calculated as:

$$V_c = Dose/C_0 \quad (1)$$

where *Dose* is dose of tramadol and C_0 is the extrapolated serum concentration of tramadol at time 0. The kinetics of M1 was determined by non-compartmental analysis. Mean residence time (MRT), body clearance (ClB) and volume of distribution at steady state (V_{dss}) were determined from the following equations (Gibaldi and Perrier 1982):

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$$MRT = AUMC/AUC \quad (2)$$

$$Cl_B = Dose/AUC \quad (3)$$

$$V_{dss} = Cl_B * MRT \quad (4)$$

where AUMC is area under the moment curve and AUC is area under serum concentration–time curve.

2.5. Statistical methods

Means and standard deviations (SD) of intraoperative variables and pain scores were calculated for male and female cats separately. The *t*-test and the Mann–Whitney rank sum test were used to estimate the significance of differences, with $P < 0.05$ considered significant. The analyses were carried out with the GLM-SigmaStat 2.03 software.

Pharmacokinetic parameters were reported as means (SD); harmonic means with pseudo-standard deviations were calculated for half lives using a jack-knife technique (Lam et al., 1985). To assess sex-related differences, kinetic parameters for tramadol and M1 in male and female animals were compared by unpaired *t*-test with Welch correction (variances unequal); differences with $P < 0.05$ were considered significant.

3. Results

3.1. Intra-anaesthetic evaluation and postoperative analgesia

Mean age, body weight, duration of surgery, selected surgical variables, and subjective pain scores are shown in Table 1. The mean duration of surgery was 14.5 ± 3.7 min for males and 28.5 ± 3.4 min for females. No significant differences between males and females in terms of cardiovascular and respiratory variables during the surgery were found. Although the mean isoflurane requirement in female cats (1.5 ± 0.4%) was higher than in males (1.3 ± 0.3%), the difference was not significant. Normocapnia (end tidal CO_2 in range 35–45 mm Hg) and spontaneous ventilation were maintained in all animals throughout the procedure.

The results of the subjective pain evaluations over the 6 h after extubation are shown in Fig. 1. In no case did pain score exceed the level required for the rescue analgesia administration and differences between males and females were never statistically significant. Nevertheless, female cats had a higher pain score at first observation than males (7.5 in females versus 5.7 in males) which decreased rapidly to 2 by 0.5 h. Pain score decreased less rapidly in males, with mean scores of 4.8 at 0.5 h and 3.5 at 1 h. For the remaining postoperative period the two pain score curves were very similar, with scores very close to 2. No side-effects were observed during the observation period.

Table 1
Mean (±SD) values of general characteristics, selected surgical variables, and subjective pain score in 12 cats undergoing surgical gonadectomy.

	Males ($n = 6$)	Females ($n = 6$)	Males + females ($n = 12$)
Age (months)	11 ± 4.5	10 ± 4.6	10 ± 4.4
Body weight (kg)	3.6 ± 0.7	2.8 ± 0.2	3.7 ± 1.1
Surgery time (min)	14.5 ± 3.7	28.5 ± 3.4	21.5 ± 8
Time from tramadol injection to start of surgery (min)	20	20	20
Heart rate (per minute)	120.3 ± 13.6	134.9 ± 16.3	128.7 ± 16.7
Respiration rate (per minute)	37.6 ± 8.1	30.6 ± 12.2	33.6 ± 11.2
End tidal CO_2 (mm Hg)	41.5 ± 2.5	41.6 ± 2.3	41.5 ± 2.4
Mean non-invasive blood pressure (mm Hg)	67.2 ± 4.2	66.7 ± 6.8	66.9 ± 5.4
Oxyhemoglobin saturation (%)	>98	>98	>98
End tidal isoflurane (%)	1.3 ± 0.3	1.5 ± 0.4	1.4 ± 0.4
Subjective pain score	2.7 ± 1.2	2.6 ± 1.5	2.6 ± 1.4

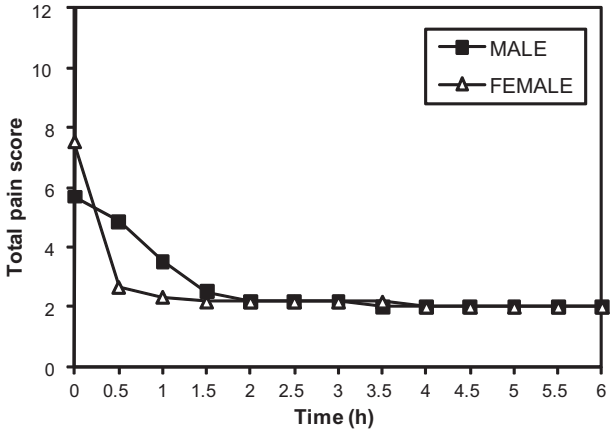

Fig. 1. Total pain scores in males ($n = 6$) and females ($n = 6$) assessed at various times after extubation obtained using a subjective pain scoring method modified after Smith et al. (2004).

3.2. Serum concentrations

Mean serum concentrations of tramadol and M1 after IV administration are shown in Fig. 2. Mean tramadol concentration in serum was 2.08 ± 0.64 μg/ml at first sampling (0.08 h), decreased to 0.58 ± 0.14 μg/ml at 1 h post-treatment, and subsequently declined more slowly to 0.07 ± 0.05 μg/ml at 7 h. The mean peak concentration of M1 (0.81 ± 0.23 μg/ml) occurred at 0.25 h. M1 decline was slower than for tramadol and at last sampling (8 h) was 0.11 ± 0.01 μg/ml, while tramadol was below the limit of quantification (0.05 μg/ml). The mean percentages of protein binding were 15% for tramadol and 17% for M1. In Fig. 3 pain scores and serum concentrations of tramadol and M1 are plotted versus time.

3.3. Pharmacokinetics

The time courses of tramadol after IV administration was described by a two-compartment open model and a non-compartmental model was applied to M1 serum concentrations. Table 2 shows pharmacokinetic variables for the two sexes separately. No sex-related differences for these variables were found and therefore, the means for males plus females are reported and discussed. Mean AUC values for tramadol and M1 were 2.53 ± 0.87 h μg/ml and 3.61 ± 1.28 h μg/ml, respectively, and mean MRT values 2.40 ± 0.87 h and 5.73 ± 2.82 h for tramadol and M1 respectively. Distribution and elimination half-lives for tramadol were 0.15 ± 0.12 h and 1.86 ± 0.66 h, while the terminal half-life for M1 was 3.54 ± 1.17 h. Tramadol C_0 was 2.60 ± 0.64 μg/ml and M1 C_{max} and T_{max} were 0.81 ± 0.23 μg/ml and 0.25 ± 0, respectively.

4. Discussion

The purpose of this study was to provide pharmacokinetic data about tramadol and its M1 metabolite in cats administered before surgery at the dose of 2 mg/kg (IV) and to evaluate the clinical efficacy of tramadol as postoperative analgesic.

Tramadol, as used in this study, did not cause respiratory depression but can reduce the isoflurane requirement and produce postoperative analgesia in cat undergoing gonadectomy. No difference in the pharmacokinetic behaviour were detected between sexes.

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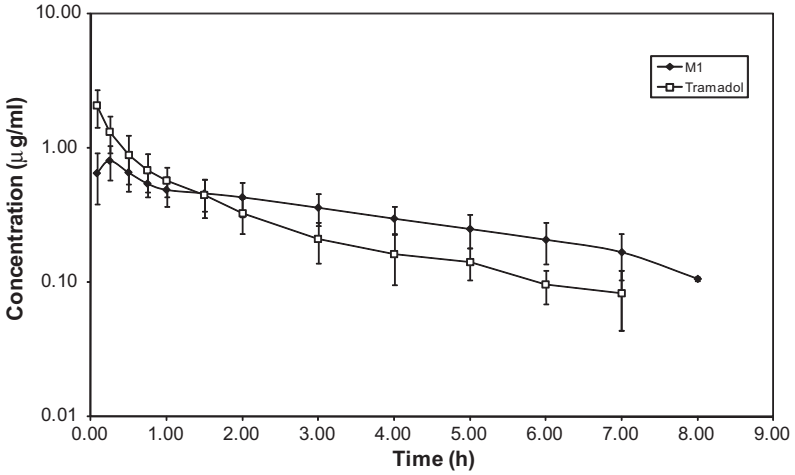

Fig. 2. Mean (±SD) serum concentrations (µg/ml) of tramadol and M1 in cats ($n = 8$) after IV administration of tramadol at 2 mg/kg.

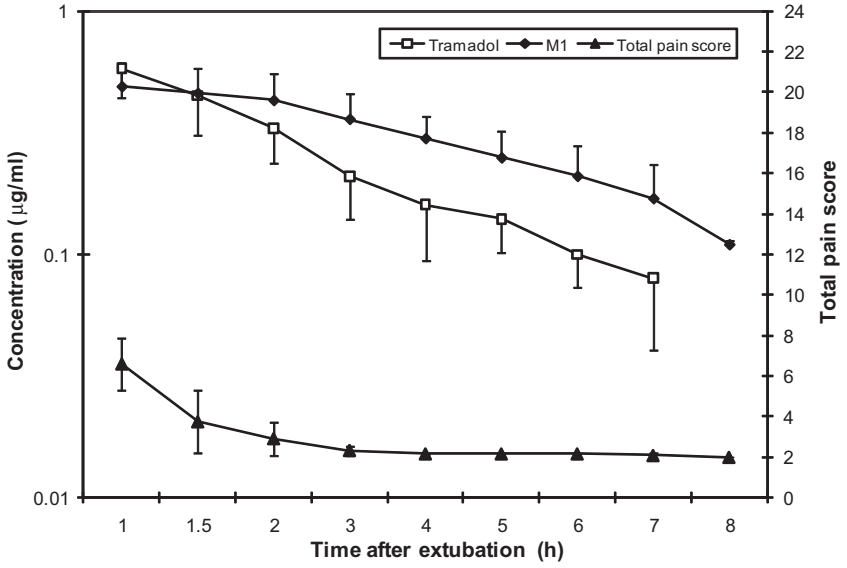

Fig. 3. Mean (±SD) serum concentrations (µg/ml) of tramadol and M1 in cats after IV administration of tramadol at 2 mg/kg with mean (±SD) pain score (males + females) plotted versus time after extubation.

Table 2
Pharmacokinetic parameters (mean ± SD) of tramadol and *O*-desmethyl tramadol (M1) after IV administration in 8 cats at the dose of 2 mg/kg.

Parameter (units)	Tramadol mean ± SD			M1 mean ± SD		
	Males ($n = 4$)	Females ($n = 4$)	Males + females	Males ($n = 4$)	Females ($n = 4$)	Males + females
$t_{1/2\lambda z}$ (h)	n.d. [b]	n.d. [b]	n.d. [b]	3.32 ± 1.18	3.85 ± 1.1	3.54 ± 1.17[a]
AUMC (h h µg/ml)	4.46 ± 2.71	8.72 ± 5.05	6.59 ± 4.39	21.88 ± 16.8	23.81 ± 21.02	22.85 ± 17.35
$MRT_{(0-\infty)}$ (h)	1.86 ± 0.37	2.94 ± 0.92	2.40 ± 0.87	5.38 ± 2.83	6.07 ± 2.55	5.73 ± 2.82
$AUC_{(0-\infty)}$ (h µg/ml)	2.25 ± 1.02	2.82 ± 0.71	2.53 ± 0.87	3.72 ± 1.32	3.47 ± 1.44	3.61 ± 1.28
$t_{1/2\lambda 1}$ (h)	0.12 ± 0.09	0.21 ± 0.16	0.15 ± 0.12[a]	n.d.	n.d.	n.d.
$t_{1/2\lambda 2}$ (h)	1.54 ± 0.4	2.35 ± 0.9	1.86 ± 0.66[a]	n.d.	n.d.	n.d.
C_0 (µg/ml)	2.87 ± 0.74	2.23 ± 0.46	2.60 ± 0.64	n.d.	n.d.	n.d.
V_{dss} (ml/kg)	1831.78 ± 515.26	2075.13 ± 322.54	1953.65 ± 418.68	n.d.	n.d.	n.d.
V_c (ml/kg)	736.59 ± 206.2	844.60 ± 157.38	810.60 ± 187.34	n.d.	n.d.	n.d.
Cl_B (ml/h kg)	1052.08 ± 473.94	738.53 ± 153.21	895 + 30 ± 366.62	n.d.	n.d.	n.d.
C_{max} (µg/ml)	n.d.[b]	n.d.[b]	n.d.[b]	0.89 ± 0.31	0.72 ± 0.09	0.81 ± 0.23
T_{max} (h)	n.d.[b]	n.d.[b]	n.d.[b]	0.25 ± 0.0	0.25 ± 0.0	0.25 ± 0.0

$t_{½\lambda z}$ = elimination half-time; AUMC = area under moment curve; $MRT_{(0-\infty)}$ = mean residence time; $AUC_{(0-\infty)}$ = area under serum concentration–time curve; $t_{½\lambda 1}$ = distribution half-time; $t_{½\lambda 2}$ = elimination half-time; C_0 = serum concentration at time 0; V_{dss} = volume of distribution at steady state; V_c = volume of distribution in central compartment; Cl_B = body clearance; C_{max} = maximum concentration; T_{max} = observed time for C_{max}; n.d. = not done for non-compartmental model.

[a] Harmonic mean ± pseudo SD.

[b] n.d. = not done for bi-compartmental model.

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The dose of tramadol administered in this study (2 mg/kg IV) was chosen on the basis of previous studies on cats (Brondani et al., 2006; Pypendop and Ilkiw, 2008; Brondani et al., 2009a) and in consideration that the veterinary product used (Altadol, Formevet, Italy) is authorized in Italy for use in dogs by IV, IM or oral administration at the same dosage.

Because spontaneous ventilation, normocapnia and high oxyhaemoglobin saturation were maintained throughout the procedure in all animals (Table 1, individual data not shown) we conclude that preoperative IV administration of a single dose of tramadol to cats undergoing elective gonadectomy did not cause clinically significant hypoventilation. Tramadol reduces total ventilatory CO_2 sensitivity by acting on μ opioid receptors in the human brainstem, but does not depress the hypoxic ventilatory response (Grond and Sablotzki, 2004). Postoperative respiratory depression leads to hypercapnia and if severe may also lead to hypoxaemia (Grond and Sablotzki, 2004). Clinical studies in humans indicate absence of significant respiratory depression at analgesic doses of tramadol compared to traditional opioid drugs (Houmes et al., 1992; Vickers et al., 1992; Tarkkila et al., 1997, 1998). This important difference is exploited in pediatric medicine and adults with compromised cardiopulmonary function or contra-indicated for non-opioid analgesics (Grond and Sablotzki, 2004).

The ability of tramadol to reduce the minimum alveolar concentration (MAC) of inhalational anaesthetics has been previously reported in rats (De Wolff et al., 1999) and cats (Ko et al., 2008). In our study, mean end tidal isoflurane was 1.36% (±0.37) with no significant difference between males (1.31 ± 0.32%) and females (1.47 ± 0.43%). These concentrations are lower than those suggested as necessary to maintain "surgical" anaesthesia in cats when no analgesics are administered (Steffey and Mama, 2007). However, acepromazine might have contributed to the sparing effect of isoflurane and might have produced an antinociceptive effect as described by Steagall et al. (2008).

Pain assessment in cats is challenging because of the limited information available on the severity of postoperative pain, behavioural indicators of pain and effects of surgery on well-being (Ilkiw, 2003; Robertson, 2005). Further, unlike dogs (Buback et al., 1996; Conzemius et al., 1997; Holton et al., 1998; Firth and Haldane, 1999; Reid et al., 2007), no scales have been validated for pain assessment in the feline species. However, according to Lascelles and Waterman (1997), observation of behaviour is the best means of assessing the pain experienced by cats. A composite rating scale was adopted by Brondani et al. (2006, 2009a) where the subcutaneous administration of tramadol (2 mg/kg) in cats provided significantly superior analgesia and decreased the requirement of rescue analgesia compared to placebo. For these reasons we also employed a composite rating scale (Smith et al., 2004) in which comfort, movement, appearance, unprovoked and interactive behaviour and vocalisation were assessed by a single observer every 30 min up to 6 h after extubation. For all animals, scale scores were always below the threshold chosen for the administration of rescue analgesia (Fig. 1) suggesting that tramadol was able to produce sufficient postoperative analgesia in cats undergoing gonadectomy.

Initial tramadol concentrations varied considerably between animals (range 1.2–3.2 μg/ml) and thus high inter-individual variability was found for both tramadol and consequently M1 (C_{max} 0.6–1.3 μg/ml at 0.25 h). Nevertheless M1 concentrations peaked at just under 1 μg/ml at 0.25 h after tramadol administration and remained high (>0.01 μg/ml) for the entire observation period (Fig. 2). Since 0.01 μg/ml is the lowest concentration associated with therapeutic efficacy in humans (Lehmann et al., 1990) this could suggest that M1 has contributed to tramadol analgesia in cats. However, the lowest concentration associated to an analgesic effect in the feline species is unknown and from the results here obtained it is not possible to identify an efficacious serum concentration of M1 in cat (Fig. 3).

At extubation (corresponding to 1 h after tramadol administration) maximum pain was recorded (6.59 ± 1.29) but tramadol and M1 concentrations were already decreased to 0.58 ± 0.14 and 0.49 ± 0.12 μg/ml, respectively. During the rest of the recovery the pain scores were decreased to 2, while tramadol and M1 concentration gradually and constantly decreased to 0.08 ± 0.04 and 0.17 ± 0.06 μg/ml, respectively. The negative correlation between plasma concentration and pain could simply represent an indirect relationship – hysteresis – which cannot be identified with parenteral administration. All the animals in our study were comfortable and they did not require rescue analgesia at any time. The higher pain score soon after extubation might be associated with increased loco-motor activity due to post-anaesthetic excitation or possible euphoria/dysphoria. According to Steagall et al. (2008) subcutaneous administration of tramadol (1 mg/kg) produced dysphoric effect in two over eight pain free cats. Further, one of those cats did not become tranquillized even when tramadol was combined with acepromazine. In our study all the animals underwent surgery; however, it can be speculated that orchiectomy is less invasive and then less painful than ovariectomy. Therefore, same serum concentration of tramadol and M1 might have produced excitatory behavioural effect in male cats but not in females because of different levels of pain. However, no statistically significant differences were detected in the postoperative period between the two gender and none of the cats appeared to be in distress and required sedation or more analgesia. The lack of sensitivity of the scoring system used and the restricted number of animals studied should also be taken into consideration. However, as mentioned above, no pain scoring system has been validated in the feline species yet. Clinical observations and a lack of a need for further analgesic intervention suggest that perioperative tramadol provided analgesia in the postoperative period.

The pharmacokinetic parameters we derived for tramadol differ somewhat to those recently published by Pypendop and Ilkiw (2008) in female cats. Our results showed higher values for tramadol AUC (2.53 ± 0.87 h μg/ml versus 1.79 ± 0.25 h μg/ml) and C_0 (2.60 ± 0.64 μg/ml versus 1.3 ± 0.09 μg/ml), and consequently lower values for V_{dss} (1953.65 ± 418.68 ml/kg versus 3000 ± 100 ml/kg) and Cl (895.30 ± 366.62 ml/h kg versus 1248 ± 192 ml/h kg). However, pharmacokinetic data for M1 were consistent between the two studies, particularly in terms of M1 concentration that at about 2 h after tramadol administration was higher than the parent compound. The lower clearance of tramadol in our study is likely due to the fact that our cats were anaesthetized and undergoing neutering, while those of Pypendop and Ilkiw (2008) were experimental cats under laboratory conditions; in addition, our animals were less homogenous in terms of weight and age. The fact that Pypendop and Ilkiw (2008) studied only female cats is unlikely to be significant, since our data indicate no sex-related differences in tramadol pharmacokinetics.

Like Pypendop and Ilkiw (2008), we found that the M1:tramadol AUC ratio was >1 in cats, whereas in dogs this ratio is about 0.3 (Kukanich and Papich, 2004; Vettorato et al., 2006, 2010), indicating considerably greater M1 production in cats than in dogs, even though the higher AUC of M1 in cats may have been influenced by its slower elimination. In human, the analgesic efficacy of tramadol administration is correlated to the probably synergistic effect of tramadol itself and M1 and the contribution of M1 in cats may deserve an accurate revision. In a recent paper, Pyendop et al. (2009) reported that M1 plays a minor role in thermal analgesia of cats. Further, when administered orally, tramadol doses ⩾2 mg/kg were required to induce a significant and sustained effect. According to the same authors, a dose of 4 mg/kg administered every 6 h may maintain analgesia close to the tramadol maximum effect. In

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our trial, when 2 mg/kg were administered IV, serum tramadol and M1 concentrations were comparable to those obtained by Pyendop et al. (2009) with the oral dose of 4 mg/kg and no respiratory depression was observed. However, a repeated administration study would be advocated to better define an appropriate and long term dosage scheme for tramadol in the feline species.

In humans, M1 seems mainly produced by the 2D6 isoenzyme of cytochrome P-450 (CYP2D6) and its production varies in relation to the presence of different polymorphisms of the isoenzyme (Poulsen et al., 1996). A recent study (Shah et al., 2007) suggested that cytochrome P450 2D activities were similar in dogs and female cats, but lower in male cats, and higher in male and female cats than humans, while Chauret et al. (1997) reported that there were no marked sex-related differences in the metabolism of the different catalytic activity markers tested in human, dog, horse and cat. Moreover, in our study, although carried out on only four animals of each sex, there were no pharmacokinetic differences between the sexes. The persistent M1 we found in cats could be due to slow glucuronidation and consequently slow M1 elimination, since M1 elimination is reported to require glucuronidation in humans (Overbeck and Blaschke, 1999; Allegaert et al., 2006).

Comparison of our present results with those obtained in dogs using the same tramadol dose (2 mg/kg) under similar conditions (Vettorato et al., 2010) shows that M1 levels were maintained for a longer period in cats than dogs (C_{max} 0.81 ± 0.23 μg/ml versus 0.31 ± 0.17 μg/ml), with mean concentrations of 0.1 μg/ml in cats and 0.05 μg/ml in dogs 8 h after administration, hence greater AUC in cats than dogs (3.61 ± 1.28 h μg/ml versus 1.24 ± 0.16 h μg/ml) and a consequent higher M1:tramadol AUC ratio in cats. It is not possible to compare the efficacy evaluations between the two studies due to the differences in surgical procedures (gonadectomy versus tibial plateau levelling osteotomy). Since tramadol administration leads to M1 formation also in the feline species, the potential analgesic effect of M1 in this species needs to be better elucidated.

5. Conclusions

Preoperative administration of tramadol (2 mg/kg IV) to 12 cats undergoing gonadectomy did not cause clinically significant hypoventilation, decreased the isoflurane requirement and, according to the pain scoring system used, produced sufficient postoperative analgesia. These findings, together with the positive kinetic behaviour, suggest that 2 mg/kg of tramadol IV might be useful as intra and postoperative analgesic in cat sedated with acepromazine and undergoing gonadectomy. However, further studies are advocated to better understand the analgesic property and the appropriate dosage of tramadol in the feline species.

Conflict of interest statement

None declared.

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