aJava

Asian Journal of Animal and Veterinary Advances

Academic
Journals Inc.

www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 8 (3): 483-492, 2013
ISSN 1683-9919 / DOI: 10.3923/ajava.2013.483.492

Influence of Surgery on the Pharmacokinetics of Tramadol Following Intravenous Administration in Dogs

[1,2]S. Buhari, [3]H. Kalthum, [4]Y.M. Goh and [5]S.H.Gan

[1]Department of Veterinary Clinical Studies, Faculty of veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

[2]Department of Veterinary Surgery and Radiology, Faculty of Veterinary Medicine, Usmanu Danfodiyo University Sokoto, P.M.B.2346, Sokoto, Nigeria

[3]Faculty of Veterinary Medicine, Universiti Malaysia Kelantan, 16100 Kota Bharu Kelantan, Malaysia

[4]Department of Veterinary Preclinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

[5]Human Genome Centre, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia

Corresponding Author: Y.M. Goh, Department of Veterinary Preclinical Studies, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

ABSTRACT

Surgery and anesthesia causes fluctuations in hemodynamics which can lead to subtherapeutic drug levels and usually therapeutic failure, making postsurgical pain management difficult. The influence of surgery and anesthesia on the pharmacokinetics of intravenous tramadol in dogs was investigated. Tramadol (3 mg kg^{-1}) was administered during premedication to female dogs (n = 6) undergoing ovariohysterectomy (Group 1) and to another non-surgery group (n = 6) of female dogs (Group 2) and the pharmacokinetics were compared between the groups. The outcome of this study showed that surgery and anesthesia affected the pharmacokinetics of tramadol, as indicated by a two-fold increase in the elimination half-life (1.10±0.18 h in Group 1 compared to 0.49±0.07 h in Group 2) and a three-fold increase in the area under the curve (770.21±117.76 ng.h mL^{-1} for Group 1 compared to 117.61±85.16 ng.h mL^{-1} for Group 2). Clearance was also significantly lower (3.98±0.56 mL min^{-1} kg^{-1}) in Group 1 than in Group 2 (21.06±9.34 mL kg^{-1}). Serum levels of both interleukin-6 and β-endorphin were increased at 6 and 9 h in the surgery group which further indicates that the rapid metabolism and clearance of tramadol in dogs are correlated with postsurgical pain. Therefore, re-administration of tramadol at 3 h is necessary for pain control. This suggests that surgery has a significant effect on the pharmacokinetics of tramadol in dogs.

Key words: Tramadol, pharmacokinetic, anesthesia, ovariohysterectomy

INTRODUCTION

Control of post surgical pain is becoming increasingly important in small animal practice (Taylor, 2003). Pain recognition in humans is subjective and pain in animals can be challenging to identify because many species have evolved to mask signs of illness and distress (De Sousa *et al*., 2008). Many nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in managing post-surgical pain in dogs (Abu-Seida, 2012); however, their use is limited due to the development of unwanted side effects (Riviere and Papich, 2001). The use of opioids as a substitute for the use of NSAIDs for the management of postsurgical pain is well established in small animal practice (Waterman and Kalthum, 1989).

Tramadol is an analgesic with a dual mechanism of action. It binds to the μ_1-opioid receptor (Kukanich and Papich, 2004; Guedes *et al*., 2005) and inhibits the monoaminergic pathway, which includes the Noradrenaline (NA) and serotonin (5HT) reuptake pathways (Kubota *et al*., 2008; McMillan *et al*., 2008). For this reason, tramadol is also referred to as an "atypical opioid" and is partially inhibited by the opioid receptor antagonist naloxone (McMillan *et al*., 2008). Tramadol is widely used preoperatively for post-surgical pain control in humans (Wang *et al*., 2005) and has also been used recently in dogs (Kubota *et al*., 2008; Almeida *et al*., 2010). However, tramadol is reported to have a relatively short half-life. Therefore, there is often the need for re-administration, which may increase the incidence of collateral effects (Kukanich and Papich, 2004).

As with any other stress, surgery causes fluctuations in hemodynamics, physiological shifts, intense metabolic changes and protein catabolism, which often occur within a few hours of the surgery. Although, it has been demonstrated that the therapeutic concentration of tramadol must be attained within the plasma before the beginning of surgery, it is not clear whether the therapeutic level can be maintained throughout the whole surgical period. The potential for alterations in the pharmacokinetics of drugs following surgery should be recognized. Surgery involves a number of major stresses associated with pain, anxiety, cardiovascular instability and possibly major intraoperative hemodynamic changes, especially if there is major blood loss or cross-clamping of large vessels (Barker *et al*., 1987). These stresses trigger the release of catecholamines, corticosteroids and a range of hormones and cytokines (Kehlet, 1989). This can lead to subtherapeutic drug levels, especially when there is massive blood loss and subsequent fluid replacement (Sue *et al*., 1989; Markantonis *et al*., 2004) and usually therapeutic failure, making postsurgical pain management difficult.

To date, there are only a few reports regarding the pharmacokinetics of tramadol in dogs (Kukanich and Papich, 2004; McMillan *et al*., 2008), particularly in terms of its pharmacokinetics following surgery. Both surgery and anesthesia can influence the pharmacokinetics and pharmacodynamics of drugs (Nimmo and Peacock, 1988; Kennedy and Van Riji, 1998). Presently, the possible effects of surgery and anesthesia on the pharmacokinetics of tramadol in dogs have not been reported. The aim of this study was to evaluate the influence of elective surgery on the pharmacokinetics of tramadol following intravenous (i.v.) administration.

MATERIALS AND METHODS

The study started in the middle of 2011 and was completed within eight month. Female dogs (n = 12) between the ages of 1 and 3 years (1.95±0.65), weighing between 10.5 and 17.1 kg (13.12±1.95), were randomly selected. All dogs were judged to be healthy based on physical and clinical examinations prior to surgery. The dogs were individually housed in a kennel in a quiet and clean environment. All protocols and guidelines for the use, management and handling of animals in research were approved by the faculty of Veterinary Medicine, Universiti Putra Malaysia Animal Care and Utilization Committee (UPM/FPV/PS/3.2.1.551/AUP-R86).

Experimental procedures: The dogs were randomly divided into two groups (n = 6). They were fasted for 12 h prior to surgery but had free access to water until two hours prior to sedation. A 20 gauge 1 1/4 inch sterile catheter was placed in a cephalic vein. Group 1 underwent an ovariohysterectomy (OHE) and received 3 mg kg^{-1} tramadol intravenously (i.v.) as premedication about 15 min before the commencement of the surgery. The premedication also consisted of 0.04 mg kg^{-1} atropine and 0.50 mg kg^{-1} xylazine. Group 2 received tramadol at a similar dosage without undergoing any surgery.

Induction and surgery: Each dog in group 1 was induced with ketamine HCl (Narketan^{R} Vetoquinol SA, 70204 Lure, Cedex, France) at 10 mg kg^{-1} (i.v.) and the lungs were ventilated. After anesthesia, the ventral abdomen from the xiphoid to the pubis was clipped and aseptically prepared for OHE. An incision was made through the skin and subcutaneous tissue to expose the linea alba, just caudal to the umbilicus in the cranial third of the caudal abdomen. A stab incision was made into the abdominal cavity and extended cranially and caudally. The ovaries were identified, double ligated using 2-0 chromic catgut and transected in between. Both uterine horns were traced to the uterine body and ligated cranial to the cervix, then transected at the uterine body. Finally the abdominal wall was apposed in three layers (rectus fascia, subcutaneous tissue and skin).

Sample collection: Three milliliters of blood was taken at baseline and at 2.0, 5.0, 10.0, 15.0, 30.0 and 45.0 min and 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 9.0 h post-administration of tramadol from each dog in both groups. Prior to drawing blood samples for pharmacokinetic analysis, blood (1 mL) was drawn from the jugular catheter and discarded. The catheters were flushed with 1 mL of sterile saline following each sampling. Samples were placed in a plain tube (Becton Dickinson, Franklin Lanes, New Jersey, USA), allowed to stand at room temperature for 30 min for clotting and were subsequently placed on ice. Samples were carefully labeled using a permanent marker. Blood samples were centrifuged at 1000 X g for 10 min. The separated sera were kept frozen at -80°C until analysis within six months.

To determine the levels of β-endorphins and interleukin-6 (IL-6), blood samples (2 mL) were collected at baseline and at 1.0, 2.0, 3.0, 6.0 and 9.0 h after tramadol administration. The blood samples were allowed to clot for 30 min before centrifugation for 15 min at 1000 X g. The separated sera were kept frozen at -80°C until analysis using commercially available Enzyme-linked Immunosorbent Assay (ELISA) kits (Cusabio Biotech Co., Ltd., Wuhan P.R. China) specific for canine β-endorphin and IL-6. A wavelength of 450 nm was selected for Optical Density (OD) measurements on an ELISA microplate reader (Bio-Rad model 680, Bio-Rad Laboratories Inc., Tokyo, Japan).

Extraction of tramadol using the solid phase extraction (SPE) method: The extraction process was based on the method developed previously (Gan *et al*., 2002).

Determination of serum tramadol concentrations by HPLC: The HPLC system consisted of a quaternary pump, degasser, automated sampler and UV detector that were set at 218 nm. The analytical column was Agilent Zobax reverse phase (RP-C18) (5 μm; 4.6×250 mm). The control of the HPLC system and data collection were achieved with an IBM-compatible computer equipped with Agilent LC ChemStation software (Agilent Technologies©, 32-bit version, Hewlett-Packard-Strasse 8 76337 Waldbronn, DE Germany).

Serum tramadol concentrations were detected by reverse phase HPLC with ultraviolet (UV) detection based on the method described (Gan and Ismail, 2001) with some slight modifications. Briefly, the mobile phase was a mixture of 70% phosphate buffer (0.01 M), 30% acetonitrile and 0.1% triethylamine (v/v) and the final mixture was adjusted to pH 5.9. The phosphate buffer ($KHPO_4$) was prepared fresh daily by dissolving 1.36 g of $KHPO_4$ (HPLC grade, Fisher Scientific Loughborough, Leicestershire LE11 5RG UK) into 1000 mL of ddH_2O. The final mixture was filtered through a 0.45 μm cellulose filter (Sartorius, Germany) under vacuum followed by

sonication for 20 min to remove any residual gas bubbles. A flow-rate of 0.75 mL min^{-1} was used throughout. Each reconstituted sample was injected (25 μL) into the column, which was heated to 40°C.

Pharmacokinetic analysis: Tramadol's pharmacokinetic parameters were calculated using a pharmacokinetic computer software program (WinNonlin Version 5.3, Pharsight Corp., Mountain View CA, USA). The best fit model for compartmental analysis was determined by residual plots and Aikake's information criterion. An open two-compartment model with a central compartment best described the decline in the tramadol plasma concentration following i.v. administration. The total body clearance (Cl), volume of distribution (Vd), area under the plasma concentration curve (AUC), plasma distribution half-life ($\alpha T_{1/2}$), plasma clearance half-life (β $T_{1/2}$), intercept of the distribution phase (A), intercept of the elimination phase (B), rate constant associated with distribution (alpha) and rate constant associated with elimination (beta) were derived.

Statistical analysis: Statistical analysis was performed using the SPSS program (IBM® SPSS software Inc. version 16, New York, USA). The results are expressed as the means±SD. The pharmacokinetic parameters were compared using an independent t-test between two groups. A p-value of less than 0.05 is considered to be statistically significant.

RESULTS

No adverse effects were observed after administration of tramadol HCl at 3 mg kg^{-1}. All dogs appeared mildly sedated after administration and one dog exhibited nausea (salivating), which stopped after 5 min. A female dog from group 2 became very aggressive and was removed from the study. This dog was substituted with a randomly selected dog. The serum concentration over time was then plotted for both Groups 1 and 2 (Fig. 1).

The pharmacokinetics of tramadol are presented in Table 1. The plasma concentration reflected in the mean AUC value was four times higher in animals from Group 1 than that of Group 2, while the average Cl was approximately five times lower in Group 1 than in Group 2 (21.06±9.34 mL min^{-1} kg^{-1}). The mean serum β-endorphin levels were significantly higher in Group 1 at 6 and 9 h than those of Group 2 (Fig. 2). Similarly, there was also a significant increase

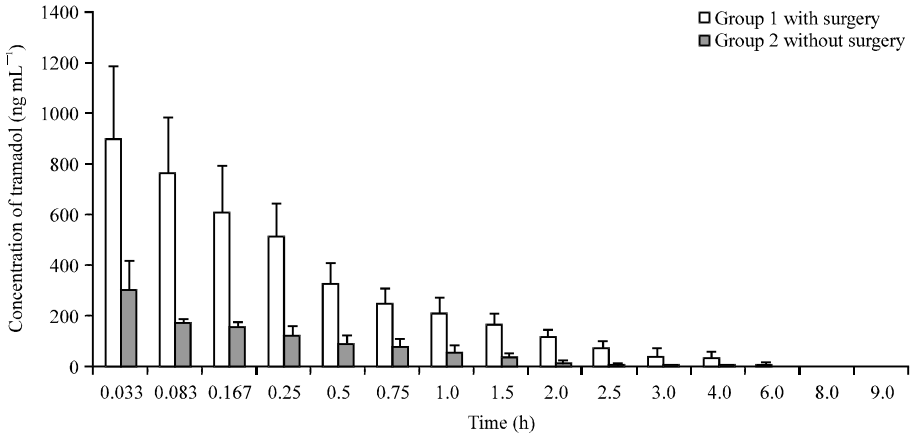

Fig. 1: Serum concentration of tramadol vs time

Table 1: Pharmacokinetic profile of tramadol

Pharmacokinetic parameters	Group 1 (n = 6)	Group 2 (n = 6)
A (ng.h mL^{-1})	666.20±469.08	657.30±462.5
B (ng.h mL^{-1})	347.93±144.59[a]	148.68±47.28
α (L h^{-1})	6.16±3.46[a]	45.61±39.19
β (L h^{-1})	0.55±0.18[a]	1.12±0.20
$t_{1/2\alpha}$ (h)	0.15±0.07[a]	0.04±0.04
$t_{1/2\beta}$ (h)	1.07±0.48	0.64±0.11
λz (L h^{-1})	0.65±0.12[a]	1.43±0.21
$t_{1/2}$λz (h)	1.10±0.18[a]	0.49±0.07
MRT (h)	1.59±0.26[a]	0.76±0.18
Cl_T (ml/min kg^{-1})	3.98±0.56[a]	21.06±9.34
$Vd_{(ss)}$ (L kg^{-1})	6.27±1.01[a]	14.37±4.96
AUC_{0-8} (h*ng) mL^{-1}	770.21±117.76[a]	177.61±85.16
$AUMC_{0-8}$ (h*h*ng) mL^{-1}	1245.40±351.73[a]	140.01±75.25
C_0 (ng mL^{-1})	917.00±290.75[a]	333.00±120.48
K10 (L h^{-1})	1.18±0.47[a]	4.33±2.10
K12 (L h^{-1})	3.36±2.78	13.34±12.58
K21 (L h^{-1})	1.20±0.87[a]	6.12±1.46
K10 $t_{1/2}$ (h)	0.58±0.18[a]	0.17±0.10
V1 (L kg^{-1})	3.46±1.34	3.30±2.93
V2 (L kg^{-1})	2.90±1.99[a]	8.92±2.81

λz: First-order rate constant, t½ λz: Half-life of the terminal portion of the curve, MRT: Mean residence time, Cl_T: Total body clearance, Vdss: Volume of distribution at steady state, AUC_0-8: Area under the curve from 0 to infinity, $AUMC_0$-8: Area under the first moment curve from 0 to infinity, C_0: Concentration at time 0, t½α: Distribution half-life, t½β: Elimination half-life, α: Rate constant associated with distribution, β: rate constant associated with elimination; A: Intercept for the distribution phase, B: Intercept for the elimination phase, K10: Elimination rate from compartment 1, K12: Rate of movement from compartment 1 to compartment 2, K21: Rate of movement from compartment 2 to compartment 1, K10 $t_{1/2}$: Half-life of the elimination phase; V1: Volume of compartment 1, V2: Volume of compartment 2, Group 1: Surgery group, Group 2: Non surgery group, [a]Means with superscript differ significantly at $p<0.05$ between groups

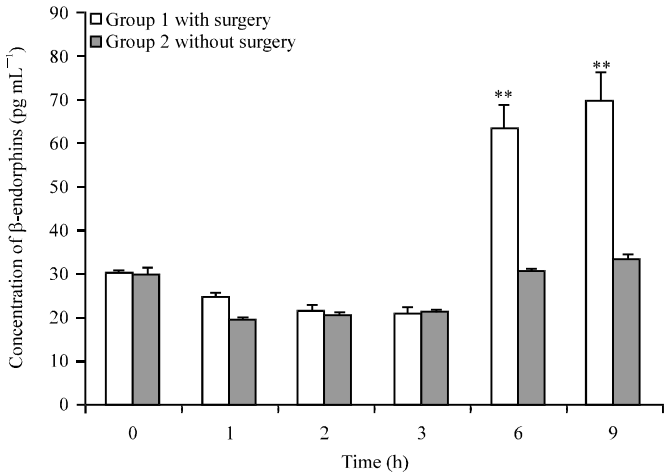

Fig. 2: Serum concentration of beta endorphins vs time. **Means with superscript (asterisks) differ significantly at $p<0.05$ between groups

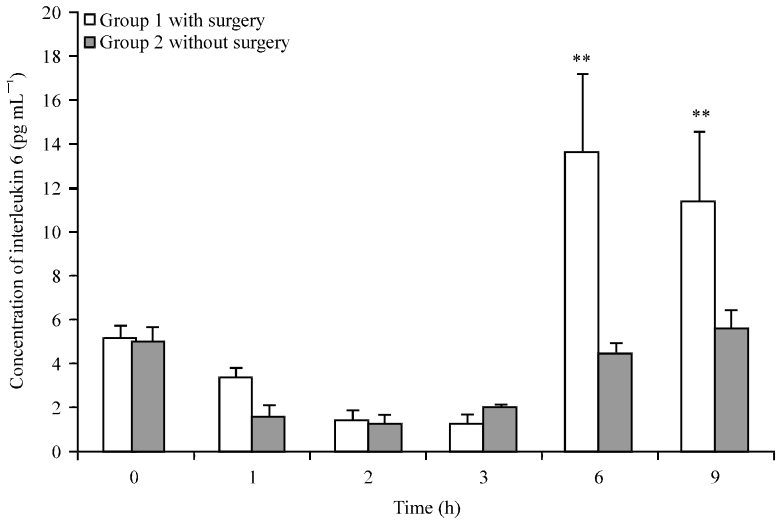

Fig. 3: Serum concentration of interleukin 6 vs time. **Means with superscript (asterisks) differ significantly at $p<0.05$ between groups

in mean serum IL-6 concentrations in Group 1 at 6 h (Fig. 3), indicating that tramadol had similar effects in controlling pain for both groups.

DISCUSSION

The present study was undertaken in light of the limited information available regarding tramadol's pharmacokinetics in dogs. This study is the first to show that surgery significantly affects several pharmacokinetic parameters of tramadol when administered to dogs intravenously. The pharmacokinetic parameters that were significantly affected included the $t_{1/2á}$, Cl_T, $Vd_{(ss)}$, AUC_{0-8} and $C_{0.}$

In this study, it was found that a two-compartmental model best fit the plasma tramadol concentrations when administered intravenously, as also reported by Dayer *et al.* (1994), Kukanich and Papich (2004) and McMillan *et al.* (2008). However, even though Kukanich and Papich (2004) reported that the metabolite concentrations are best represented by a non-compartmental model, (McMillan *et al.*, 2008) stated that the plasma concentration of the active metabolite is too low to be reliably measured in dogs, as is also the case in humans (Gan *et al.*, 2007). Similarly, it was found that the metabolite concentration was lower than the detection limit of our machine and was therefore, not measured.

The liver tends to show increased activity in the post-surgical period (Kennedy and Van Riji, 1998). It is reported that serum albumin increases post-surgically, leading to changes in binding characteristics and subsequent decreases in albumin concentrations (Kennedy and Van Riji, 1998). Although, the protein binding of tramadol is relatively low (20%) Dayer *et al.* (1994), this binding may lead to a decrease in the serum concentration of tramadol post-surgically.

In this study, the plasma concentration of tramadol following i.v. administration in non-surgery dogs declined very rapidly, with a $t_{1/2}\,\alpha$ between 0.006 and 0.12 h (mean 0.04±0.04 h) compared to between 0.06 and 0.22 h (mean 0.15±0.07 h) observed among the surgery group. A slightly higher

$t_{1/2}\alpha$ (0.32 h) was reported by Kukanich and Papich (2004) following i.v. administration of 4 mg kg^{-1} tramadol in beagle dogs. De Sousa *et al.* (2008) reported a $t_{1/2}\alpha$ of 0.18 h in dogs undergoing routine ovariohysterectomy and a $t_{1/2}\alpha$ of 0.12 hr following 2 mg kg^{-1} i.v. tramadol administration to cats has also been reported (Cagnardi *et al.*, 2011).

The $Vd_{(ss)}$ following i.v. administration of tramadol to young healthy volunteers was 203 L, indicating that tramadol has a high tissue affinity (Lee *et al.*, 1993). However, the Vd in dogs is lower than in humans. Furthermore, during surgery, blood volume may be altered due to blood loss, venous pooling, co-morbidity or shock, thus affecting the size of the compartments into which the drug is delivered. In this study, the size of the second compartment (V2) as well as the $Vd_{(ss)}$ significantly decreased in animals that underwent surgery as opposed to the non-surgical group. The decrease in Vd may further be compounded by alterations in cardiac function that occur postoperatively (Moffat and Milne, 1983).

Reduction in cardiac output and hepatic blood flow caused by the anesthesia and surgery slowed drug distribution from the central compartment to the immediate peripheral tissues and subsequently impaired hepatic elimination of the drug (Sue *et al.*, 1989; Cagnardi *et al.*, 2011). This may explain why in our study, both the $Vd_{(ss)}$ and Cl were significantly reduced in Group 1. A reduction in Vd tends to decrease the time required for recovery after drug administration (Shafer and Vavel, 1991). Cagnardi *et al.* (2011) observed a significant decrease in tramadol's Vd among cats undergoing ovariohysterectomy compared with the distributional values reported by De Sousa *et al.* (2008) in cats not undergoing surgery.

The decrease in Vd may lead to an increase in tramadol concentration, as reflected in the AUC and C_0 values, thus exposing the animals to toxicity, especially in the initial stages. However, none of the animals from either group showed any adverse effects from tramadol, perhaps due to the relatively low dose used (3 mg kg^{-1}). Choi *et al.* (2011) administered tramadol to dogs at three different doses (1, 2 and 4 mg kg^{-1}) and reported no adverse effects seen in any of the animals except for those receiving 4 mg kg^{-1}, where the animals were reported to be sedated at 15 min after administration. Kukanich and Papich (2004) administered tramadol at a higher dose (4.4 mg kg^{-1}) and observed that some of the animals exhibited signs of nausea, including salivation and increased swallowing. Furthermore, the initial tramadol concentrations varied considerably (range 190-1350 g mL^{-1}), indicating that there is high inter-individual variability in plasma concentrations. This could be attributed to using mixed-breed animals as opposed to using only purebred dogs, as did Kukanich and Papich (2004).

The Cl of the drug from the body could be a reflection of the drug's elimination half-life. However, this may vary because other pharmacokinetic parameters such as Vd may be involved. Clearance, as opposed to the rate of Cl, is nevertheless independent of such variables. The rate of clearance of tramadol from the plasma is decreased among dogs undergoing surgery (3.98±0.56 ml/min kg^{-1}) in comparison with the non-surgery groups (21.06±9.34 ml/min kg^{-1}). This could be attributed to the longer $t_{1/2}$ for Group 1. Similarly, lower tramadol Cl were observed by Cagnardi *et al.* (2011) in cats undergoing surgery under general anesthesia, contrary to the values reported by Pypendop and Ilkiw (2008) in experimental cats under normal laboratory conditions.

Blood loss due to surgery may alter kidney function and subsequently affect renal elimination, hence slowing the Cl of the drug as reported by Sue *et al.* (1989). Following oral administration of carbon 14-labelled tramadol to humans, approximately 90% of the drug was excreted by the kidneys, with the remaining 10% appearing in the feces (Lee *et al.*, 1993). It has also been reported that short operations are usually followed by increased activity of hepatic drug metabolizing

enzymes as a consequence of enzyme induction (Kennedy and Van Riji, 1998). This may contribute to the lower Cl values and the reduction in Cl which tend to increase the time required for recovery from surgery (Shafer and Vavel, 1991).

Liver hypoxia may also occur due to impaired hepatic blood flow, impaired oxygen carrying capacity of the blood or impaired delivery of blood oxygen (Jones *et al*., 1989). Phase I enzymes are susceptible to low oxygen tensions, although some enzymes in the cyctochrome P450 (CYP) family are more tolerant than others to hypoxia (Kennedy and Van Riji, 1998). In humans, tramadol is metabolized by cytochrome P450 (CYP) 2D6 or CYP2D6, which are highly polymorphic (Gan *et al*., 2002). However, in animals, particularly in dogs, other genes may be involved. For example, the CYP1A, 2C, 2D and 3A subfamilies have been reported to correlate with the oxidative metabolism of many drugs in animal species (Shah *et al*., 2007), with CYP1A showing high polymorphic activities in dogs (Mise *et al*., 2008; Aretz and Geyer, 2011). It has also been reported that increased levels of cytokines can decrease the activity of CYP in humans (Young *et al*., 1998). However, we did not measure cytokine levels in our study to confirm this fact. The influence of the gene expression and cytokine levels need to be investigated in future studies.

The lower Cl values of tramadol after surgery also resulted in a longer t½, indicating that there is a higher chance of tramadol toxicity following surgery, especially when higher tramadol doses are used. Reduced Cl after surgery, as seen in this study, may also indicate the liver's reduced capacity to biotransform tramadol following surgery. It has been reported that the body's response to stress is usually hypermetabolism and the liver is the major site for this activity (Kennedy and Van Riji, 1998). In addition to secreting products such as albumin, the liver is also involved in the synthesis of many products, including IL-6. In this study, IL-6 levels were significantly elevated at six hours post-surgery. This is not surprising because it has been reported that IL-6 is the major progenitor of the hepatic acute-phase response to stress (Kennedy and Van Riji, 1998). Young *et al*. (1998) reported that IL-6 levels increase from undetectable levels preoperatively to 73.6±32.8 ng L^{-1} on the first day after operation in humans.

In this study, β-endorphin levels were also significantly elevated at six and nine hours post-surgery, perhaps because serum tramadol concentrations were already decreased by this time and therefore the animals may have been in pain. β-endorphin is an indicator of painful stimuli in humans, where its concentrations were found to be elevated much longer in the presence of pain stimuli as opposed to non-painful stimuli (Rasmussen and Farr, 2009). De Riu *et al*. (1989) observed that in severely injured dogs, serum β-endorphin levels were increased over time and exceeded the levels in moderately traumatized dogs. These results indicate a significant role for β-endorphin as an objective biomarker of pain (Sommer and Kress, 2004; Rasmussen and Farr, 2009) and as a modulator in acute traumatic conditions such as surgery (Shahed and Shoskes, 2001). Therefore, tramadol may need to be re-adiministered after three hours. It has also been reported that circulating catecholamines tend to increase as part of the endocrine response associated with surgery (Udelsman and Holbrook, 1994). However, serum catecholamines are not measured in this study.

CONCLUSION

The results from this study provide pharmacokinetic information about tramadol for future consideration when this drug is required as an analgesic agent in dogs during surgery and anesthesia. The pharmacokinetic parameters for i.v. tramadol were significantly different in dogs undergoing surgery in comparison with non-surgery dogs.

ACKNOWLEDGMENT

This study was supported by a Research University Grant (1001/PPSP/815073), Universiti Sains Malaysia and Research University Grant 91465 University Putra Malaysia.

REFERENCES

Abu-Seida, A.M.A., 2012. Efficacy of diclofenac sodium either alone or together with cefotaxime sodium, for control of postoperative pain, in dogs undergoing ovariohysterectomy. Asian J. Anim. Vet. Adv., 7: 180-186.

Almeida, R.M., A. Escobar and S. Maguilnik, 2010. Comparison of analgesia provided by lidocaine, lidocaine-morphine or lidocaine-tramadol delivered epidurally in dogs following orchiectomy. Vet. Anaesth. Analgesia, 37: 542-549.

Aretz, J.S. and J. Geyer, 2011. Detection of the CYP1A2 1117C > T polymorphism in 14 dog breeds. J. Vet. Pharmacol. Ther., 34: 98-100.

Barker, S.J., D.M. Gamel and K.K. Tremper, 1987. Cardiovascular effects of anesthesia and operation. Crit. Care Clin., 3: 251-268.

Cagnardi, P., R. Villa, A. Zonca, M. Gallo and M. Beccaglia *et al.*, 2011. Pharmacokinetics, intraoperative effect and postoperative analgesia of tramadol in cats. Res. Vet. Sci., 90: 503-509.

Choi, W., H.S. Jang, H.S. Yun, J.S. Park, Y.S. Kwon and K.H. Jang, 2011. Effect of tramadol on medetomidine and ketamine anesthesia in dogs. Pak. Vet. J., 31: 99-104.

Dayer, P., L. Collart and J. Desmeules, 1994. The pharmacology of tramadol. Drugs, 47: 3-7.

De Riu, P., V. Petruzzi, G. Palmieri, C. Gentili and F. Melis *et al.*, 1989. Beta-endorphin in experimental canine spinal ischemia. Stroke, 20: 253-258.

De Sousa, A.B., A.C.D. dos Santos, J.C. Florio and H.S. Spinosa, 2008. Pharmacokinetics of tramadol administered by intravenous and intramuscular routes to female dogs submitted to ovariohysterectomy. Braz. J. Vet. Res. Anim. Sci., 45: 239-247.

Gan, S.H. and R. Ismail, 2001. Validation of a high-performance liquid chromatography method for tramadol and o-desmethyltramadol in human plasma using solid-phase extraction. J. Chromatogr. B: Biomed. Sci. Appl., 759: 325-335.

Gan, S.H., R. Ismail, W.A. Wan Adnan and W. Zulmi, 2007. Impact of CYP2D6 genetic polymorphism on tramadol pharmacokinetics and pharmacodynamics. Mol. Diagn. Ther., 11: 171-181.

Gan, S.H., R. Ismail, W.A. Wan Adnan and Z. Wan, 2002. Method development and validation of a high-performance liquid chromatographic method for tramadol in human plasma using liquid-liquid extraction. J. Chromatogr. B, 772: 123-129.

Guedes, A.G.P., C.C. Natalini, E.P. Robinson, S.D.L. Alves and S.T. Oliveira, 2005. Epidural administration of tramadol as an analgesic technique in dogs submitted to stifle surgery. Int. J. Applied Res. Vet. Med., 3: 351-359.

Jones, D.P., T.Y. Aw and X.Q. Shan, 1989. Drug metabolism and toxicity during hypoxia. Drug Metab. Rev., 20: 247-260.

Kehlet, H., 1989. The stress response to surgery: Release mechanisms and the modifying effect of pain relief. Acta Chir. Scand. Suppl., 550: 22-28.

Kennedy, J.M. and A.M. Van Riji, 1998. Effects of surgery on the pharmacokinetic parameters of drugs. Clin. Pharmacokinetics, 35: 293-312.

Kubota, R., T. Komiyama, Y. Miwa, T. Ide, H. Toyoda, F. Asanuma and Y. Yamada, 2008. Pharmacokinetics and postoperative analgesia of epidural tramadol: A prospective, pilot study. Curr. Ther. Res., 69: 49-55.

Kukanich, B. and M.G. Papich, 2004. Pharmacokinetics of tramadol and the metabolite O-desmethyl tramadol in dogs. J. Vet. Pharmacol. Therap., 27: 239-246.

Lee, C.R., D. McTavish and E.M. Sorkin, 1993. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in acute and chronic pain states. Drugs, 46: 313-340.

Markantonis, S.L., G. Kostopanagiotou, D. Panidis, V. Smirniotis and D. Voros, 2004. Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. Clin. Ther., 26: 271-281.

McMillan, C.J., A. Livingston, C.R. Clark, P.M. Dowling, S.M. Taylor, T. Duke and R. Terlinden, 2008. Pharmacokinetics of intravenous tramadol in dogs. Can. J. Vet. Res., 72: 325-331.

Mise, M., T. Hashizume and S. Komuro, 2008. Characterization of substrate specificity of dog CYP1A2 using CYP1A2-deficient and wild-type dog liver microsomes. Drug Metab. Dispos., 36: 1903-1908.

Moffat, J.A. and B. Milne, 1983. Pharmacokinetics in anaesthesia. Can. J. Anesthesia, 30: 300-307.

Nimmo, W.S. and J.E. Peacock, 1988. Effect of anaesthesia and surgery on pharmacokinetics and pharmacodvamics. Br. Med. Bull., 44: 286-301.

Pypendop, B.H. and J.E. Ilkiw, 2008. Pharmacokinetics of tramadol and its metabolite O-desmethyl-tramadol, in cats. J. Vet. Pharmacol. Ther., 31: 52-59.

Rasmussen, N.A. and L.A. Farr, 2009. Beta-endorphin response to an acute pain stimulus. J. Neurosci. Methods, 177: 285-288.

Riviere, J.E. and M.G. Papich, 2001. Potential and problems of developing transdermal patches for veterinary applications. Adv. Drug Delivery Rev., 50: 175-203.

Shafer, S.L. and J.R. Vavel, 1991. Pharmacokinetics, pharmacodynamics and rational opioid selection. Anesthesiology, 74: 53-63.

Shah, S.S., S. Sanda, N.L. Regmi, K. Sasaki and M. Shimoda, 2007. Characterization of cytochrome P450-mediated drug metabolism in cats. J. Vet. Pharmacol. Ther., 30: 422-428.

Shahed, A.R. and D.A. Shoskes, 2001. Correlation of β-endorphin and prostaglandin e2 levels in prostatic fluid of patients prostatitis with diagnosis and with chronic treatment response. J. Urol., 166: 1738-1741.

Sommer, C. and M. Kress, 2004. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci. Lett., 361: 184-187.

Sue, D., T.A. Salazar, K. Turley and B.J. Guglielmo, 1989. Effect of surgical blood loss and volume replacement on antibiotic pharmacokinetics. Ann. Thoracic Surg., 47: 857-859.

Taylor, P., 2003. Pain management in dogs and cats-More causes and locations to contemplate. Vet. J., 165: 186-187.

Udelsman, R. and N.J. Holbrook, 1994. Endocrine and molecular responses to surgical stress. Curr. Prob. Surg., 31: 662-720.

Wang, G., Y. Weng, Y. Ishiguro, H. Sakamoto and S. Morita, 2005. The effect of tramadol on serum cytokine response in patients undergoing pulmonary lobectomy. J. Clin. Anesthesia, 17: 444-450.

Waterman, A. and W. Kalthum, 1989. Pharmacokinetics of intramuscularly administered pethidine in dogs and the influence of anaesthesia and surgery. Vet. Rec., 124: 293-296.

Young, A.B., L.G. Ott, D. Beard, R.J. Dempsey, P.A. Tibbs and C.J. McClain, 1998. The acute-phase response of the brain-injured patient. J. Neurosurg., 69: 375-380.