FULL PAPER *Surgery*

Cardiovascular Effects of Tramadol in Dogs Anesthetized with Sevoflurane

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ABSTRACT. Cardiovascular effects of tramadol were evaluated in dogs anesthetized with sevoflurane. Six beagle dogs were anesthetized twice at 7 days interval. The minimum alveolar concentration (MAC) of sevoflurane was earlier determined in each dog. The dogs were then anesthetized with sevoflurane at 1.3 times of predetermined individual MAC and cardiovascular parameters were evaluated before (baseline) and after an intravenous injection of tramadol (4 mg/kg). The administration of tramadol produced a transient and mild increase in arterial blood pressure (ABP) (P=0.004) with prolonged increase in systemic vascular resistance (SVR) (P<0.0001). Compared with baseline value, mean ABP increased significantly at 5 min (119% of baseline value, P=0.003), 10 min (113%, P=0.027), and 15 min (111%, P=0.022). SVR also increased significantly at 5 min (128%, P<0.0001), 10 min (121%, P=0.026), 30 min (114%, P=0.025), 45 min (113%, P=0.025) and 60 min (112%, P=0.048). Plasma concentrations of tramadol were weakly correlated with the percentage changes in mean ABP (r=0.642, P<0.0001) and SVR (r=0.646, P<0.0001). There was no significant change in heart rate, cardiac output, cardiac index, stroke volume, pulmonary arterial pressure, right atrial pressure and pulmonary capillary wedge pressure. In conclusion, the administration of tramadol produces a prolonged peripheral vascular constriction in dogs anesthetized with sevoflurane, which is accompanied with a transient and mild increase in arterial blood pressure. It also indicated that the degree of vasoconstriction might depend on the plasma concentration of tramadol.

KEY WORDS: canine, cardiovascular effects, sevoflurane, tramadol.

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Treatment with analgesic drugs reduces the amount of anesthetics required to produce surgical anesthesia, helps to stabilize anesthesia, and decreases overall patient morbidity associated with surgery and anesthesia [17]. Opioid administration decreases the amount of volatile anesthetics required to produce general anesthesia, as evidenced by decreases in the minimum alveolar concentration (MAC) of volatile anesthetics [10, 19].

Tramadol is a centrally acting 'atypical' opioid analgesic and widely used in humans for control of acute and chronic pain [6, 25]. Tramadol is less likely to induce tolerance in animals and humans compared with morphine because of its non-opioid mechanism of action [15]. Use of tramadol in dogs has gained popularity among veterinarians because the drug is perceived to be an effective analgesic, in easily administered, and has a longer duration of action and fewer adverse effects than most other opioids. It was demonstrated that tramadol administration decreased in the MAC of volatile anesthetics [28] and its preoperative administration provided an early pain control after ovariohysterectomy in dogs [13]. Tramadol produces a synergistic analgesic effect provided by a μ-opioid receptor affinity coupled with inhibitions of synaptic reuptake of monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT) and norepinephrine [8, 25]. In addition, one of its active metabolites, *O*-desmethyltramadol (M1), also has a weak agonistic effect to μ-opioid receptor [2, 9]. M1 has a 200 times higher μ-opioid receptor binding activity than tramadol [8, 25] and its formation is important for the anti-nociceptive effects of tramadol [24]. In dogs, M1 production from the parent compound has been also demonstrated [11, 33]. Therefore, M1 probably contributes to anti-nociceptive effects of tramadol in dogs.

Sevoflurane is a volatile anesthetic drug with a relatively low blood/gas solubility coefficient resulting in rapid induction and recovery from anesthesia [29]. Because of these strong points, sevoflurane has become a popular inhalation anesthetic in veterinary practice. Sevoflurane is minimally metabolized and easily cleared in animals; however, it should be remembered that sevoflurane causes dose-dependent hypotension, hypoventilation, impaired cardiac contractility and hypothermia [20]. Therefore, a sparing effect on anesthetic requirement provided by the preoperative administration of tramadol is expected to convey the advantage of preserving cardiovascular function in patients anesthetized with sevoflurane. On the other hand, it has been suggested that tramadol is a mild myocardial depressant in dogs [23]. Therefore, it is important for veterinary practitioners to confirm interactions between sevoflurane and tramadol on the cardiovascular function in dogs. To our knowledge, however, there is no published report evaluating the cardiovascular effect of tramadol in dogs during anesthesia.

The purpose of the present study was to evaluate the cardiovascular effects of tramadol in dogs anesthetized with sevoflurane. We also evaluated plasma concentrations of

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tramadol and M1 to confirm relationship with the cardiovascular function in dogs.

MATERIALS AND METHODS

Experimental animals: Six beagle dogs aged from 8 to 10 years (9.7 ± 0.8 years of mean ± SD, 3 males and 3 females) and weighing from 9.4 to 15.4 kg (11.6 ± 2.3 kg) were used for this study. The dogs were judged to be in good to excellent health based upon the results of a physical examination, complete blood cell count and serum biochemical analysis. The dogs were owned by the university and cared for according to the principles of the "Guide for the Care and Use of Laboratory Animals" prepared by Rakuno Gakuen University. The Animal Care and Use Committee of Rakuno Gakuen University approved the study. Food and water were withheld from dogs for 12 hr before experiment. All dogs were anesthetized twice at 7 days interval. The MAC of sevoflurane was earlier determined in each dog. The dogs were then anesthetized with 1.3 times concentration of individual predetermined sevoflurane MAC and cardiovascular effects of tramadol were evaluated.

Determination of sevoflurane MAC: The MAC of sevoflurane was determined by the tail clamp method [29]. Anesthesia was induced by mask induction using sevoflurane (Sevoflo, Dainippon-Sumitomo Pharma. Osaka, Japan) in oxygen. All dogs were orotracheally intubated after the induction of anesthesia and positioned in left lateral recumbency. Anesthesia was maintained with sevoflurane in oxygen (2 *l*/min) delivered via a circle rebreathing system and anesthetic machine (Beaver 20, Kimura Medical Instrument Co., Tokyo, Japan) with an out-of-circuit vaporizer (Sevotech III, Ohmeda, Datex-Ohmeda, Tokyo, Japan). After the dogs were allowed to equilibrate for 30 min at 2.4% of end-tidal concentration of sevoflurane (ETSEV), a 13-cm standard Backhaus towel clamp (Backhaus Towel Clamp, Mizuho, Tokyo, Japan) was placed around the tail and closed to the third ratchet. The clamp was left in place for 60 sec or until gross purposeful movement was evident. The gross purposeful movement was defined as substantial movement of head or extremities and did not include coughing, chewing, swallowing, or an increasing respiratory effort. When the dog exhibited the purposeful movement, the ETSEV was increased by 10 to 20%, and the dog was retested after 20 min of re-equilibration. When the dog did not exhibit any purposeful movement, the ETSEV was decreased by 10 to 20%, and the dog was retested after 20 min of re-equilibration. The MAC was determined as the mean of the ETSEV at which the dog did not demonstrate any purposeful movement and next lower concentration tested (i.e., the highest concentration at which the dog demonstrated purposeful movements in response to the tail clamping). The MAC for each dog was determined in triplicate by the same person (K.Y.).

During the MAC determination, the dogs were mechanically ventilated (12 breaths/min of respiratory rate and 1:2 of inspiratory and expiratory ratio) using a time-cycled ventilator (Nuffield Anesthesia Ventilator Series 200, Penlon, Abingdon Oxon, U.K.) to maintain end-tidal partial pressure of carbon dioxide ($PETCO_2$) between 35 and 40 mmHg. All dogs received lactated Ringer's solution at a rate of 10 m*l*/kg/hr intravenously through a 22-gauge catheter placed in the right cephalic vein. Esophageal temperature was maintained between 37.5 and 38.5°C, using a heating pad and a warm air blanket. Esophageal temperature, $PETCO_2$, and ETSEV were monitored using a veterinary patient monitoring system (BP-508V, Omron Colin Co., Tokyo, Japan). Esophageal temperature was measured using an electric thermometer probe placed orally into the thoracic esophagus. A side-stream capnometer and anesthetic agent monitor was used to determine respiratory rate, $PETCO_2$, and ETSEV. The anesthetic agent monitor was calibrated immediately prior to each sevoflurane MAC determination.

Evaluation of cardiovascular effects of tramadol: Seven days later since the MAC determination, all dogs were orotracheally intubated following a mask induction with sevoflurane and connected to an anesthetic machine with a built-in ventilator (ACOMA BLANDA-STD, Acoma Medical Industry Co., Tokyo, Japan). Then, the dogs were anesthetized with 1.3 times of individual sevoflurane MAC in right lateral recumbency. During anesthesia, the dogs were mechanically ventilated to maintain arterial partial pressure of carbon dioxide ($PaCO_2$) between 40 and 45 mmHg and administered lactated Ringer's solution at a rate of 10 m*l*/kg/hr intravenously through a 22-gauge catheter placed in the left cephalic vein.

Left neck and right interior femoral region were clipped and aseptically prepared. Then, approximately 0.5 m*l* of 2% lidocaine (Xylocaine, Astra-Zeneca, Osaka, Japan) was injected subcutaneously at each catheter site. A 6-Fr catheter introducer (Catheter Introducer, Medikit Co., Tokyo, Japan) was transcutaneously placed in the left jugular vein. A 5-Fr thermodilution catheter (TC-504, Nihon Koden Co., Tokyo, Japan) was advanced into the pulmonary artery through the introducer. The desensitized area of the right interior femoral region was surgically incised and bluntly dissected to place a 22-gauge catheter into the right femoral artery.

Cardiac output (CO) was determined by thermodilution method [31]. A volume of 3 m*l* of iced 5% dextrose (Terumo) was injected into the right atrium through the thermodilution catheter. Temperature fluctuation was detected by the thermo-sensor placed in the pulmonary artery. The CO was measured three times and a mean value was used as CO (*l*/min). Arterial blood pressure (ABP; mmHg), pulmonary arterial pressure (PAP; mmHg), right atrial pressure (RAP; mmHg), and pulmonary capillary wedge pressure (PWP; mmHg) was determined by connecting the catheters to pressure transducers (CDX-A90, Cobe Laboratories, Tokyo, Japan) and zeroed at the level of the mid-sternum. Esophageal temperature (°C), heart rate (HR; beats/min), electrocardiogram by a lead II, ABP, PAP, RAP, PWP and CO were recorded by a multi-parameter anesthetic monitoring system (DS-5300, Fukuda Denshi Co., Tokyo, Japan).

Cardiac index (CI; m*l*/min/kg) was calculated from the body weight and CO, stroke volume (SV; m*l*/beat) was calculated from the HR and CO, and systemic vascular resistance (SVR; dynes·sec·cm^{-5}) was calculated determined from the mean ABP (MABP), CO, and the mean RAP (MRAP). CI, SV and SVR were calculated by inserting values into formulas below [16].

CI (m*l*/min/kg) = CO / Body Weight × 1,000
SV (m*l*/beat) = CO / HR
SVR (dynes·sec·cm^{-5}) = 80 × (MABP – MRAP) / CO

After the animals were instrumented and stabilized, baseline values for HR, ABP, RAP, PAP, CO, arterial partial pressure of oxygen (PaO_2) and $PaCO_2$ were recorded. Then, the dogs were intravenously (IV) administered 4 mg/kg of tramadol (Tramal, Nippon Shinyaku Co., Kyoto, Japan) through a 22-gauge catheter placed in the left cephalic vein. After tramadol administration, cardiopulmonary parameters were measured at 5, 10, 15, 30, 45, 60, 90 and 120 min. Simultaneously, arterial blood samples (2 m*l*) were anaerobically collected from the 22-gauge catheter placed into the femoral artery and mixed with heparin sodium (30 units per 1 m*l* of blood) to determine PaO_2 and $PaCO_2$ using a blood gas analyzer (Rapidlab 348, Bayer Medical Co., Tokyo, Japan). Another heparinized arterial blood samples (2 m*l*) were also collected to analyze the plasma concentration of tramadol and M1. These blood samples were immediately centrifuged (1,000 × *g* for 10 min) to separate plasma. The plasma samples were stored at –80°C until high performance liquid chromatography (HPLC) analysis.

Measurement of plasma concentrations of tramadol and M1: Each plasma sample (200 μl) was mixed with 100% methanol (400 μl) and the top clear layer (300 μl) was obtained by centrifugation (1,400 × g for 5 min). Another 100 % methanol (400 μl) was mixed with the precipitate and the top clear layer (300 μl) was also obtained by centrifugation. These 2 layers were combined in a tube as an extract. The extract (200 μl) was mixed with purified water (600 μl) and filtrated with protein precipitation filter (HLK-DISC for ion-chromato, Kanto Kagaku, Tokyo, Japan) and stored at –80°C until HPLC analysis.

The plasma concentration of tramadol and M1 were determined by HPLC consisting of dual pump (DP-8020, Toso, Tokyo, Japan), auto-sampler (AS-8020, Toso), reversed-phase column (Unison UK-C18, Toso), integration software (LC-8020, Toso), degasser (AG-12, Toso) and intelligent fluorescence detector (FS-8020, Toso). Tramadol within each extract sample was separated with the reversed-phase column using a linear gradient mobile phase from methanol-water-ammonium acetate (24:75.94:0.06) to 100% methanol delivered at 0.3 m*l*/min and detected by the fluorescence detector set at 270 nm (excitation) and 304 nm (emission). M1 within each extract sample was also separated with same column using a linear gradient mobile phase from methanol-water-ammonium acetate (5:94.94:0.06) to 100% methanol delivered at 0.3 m*l*/min and detected by same sets. The limits of detection were 5.0 *n*g/m*l* for tramadol and 5.0 *n*g/m*l* for M1.

Statistical analysis: Data were reported as mean ± SD. Firstly, changes in cardiovascular parameters were analyzed by one-way repeated measure ANOVA. Secondly, the values collected after the administration of tramadol were compared with the baseline value using students paired *t*-test when a statistically significant change was detected in the parameter by the ANOVA. In addition to this, relationships between the percentage changes to the baseline value in the parameter and plasma concentrations of tramadol and M1 were evaluated using a linear regression and Pearson's correlation coefficient (*r*). The level of significance was set at $P<0.05$.

RESULTS

MAC of sevoflurane: It took 155 ± 45 min after the mask induction to obtain the triplicate data for determination of sevoflurane MAC. The average sevoflurane MAC was 1.86 ± 0.29% in the dogs. Consequently, we adopted 2.42 ± 0.38% (1.3 MAC) of ETSEV to anesthetize the dogs during the estimation of cardiovascular effects of tramadol.

Plasma concentration of tramadol and M1: Changes in plasma concentration of tramadol and its metabolite, M1, are shown in Fig. 1. The plasma concentration of tramadol gradually decreased over time, and their mean values at 5, 10 and 15 min were 1,893, 1,334 and 1,102 *n*g/m*l*, respectively. The plasma concentration of M1 showed a peak at 15 min after tramadol administration and then gradually decreased over time, and their mean values at 5, 10 and 15 min were 202, 287 and 332 *n*g/m*l*, respectively.

Cardiovascular effects of tramadol: It took 100 min [SD13] after the mask induction for the instrumentations of

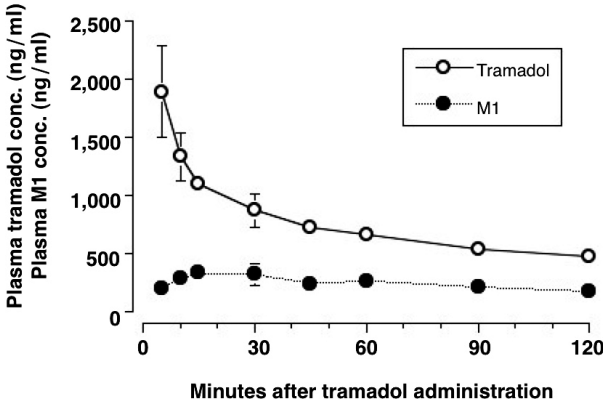

Fig. 1. Plasma concentration vs. time curves for tramadol and M1 following intravenous injection of tramadol (4 mg/kg) to 6 dogs. Plots and error bars represent mean values and standard deviations (SD) of plasma concentration of tramadol (○) and M1 (●). The plasma concentration of tramadol gradually decreased over time. The plasma concentration of M1 showed a peak at 15 min after tramadol administration and then gradually decreased.

Table 1. Changes in cardiovascular parameters after an intravenous injection of tramadol (4 mg/kg) in dogs anesthetized sevoflurane

	Minutes after the administration of tramadol								
	Base line	5	10	15	30	45	60	90	120
HR (beats/min)	126 ± 14	130 ± 22	129 ± 22	127 ± 22	121 ± 22	117 ± 21	116 ± 22	113 ± 20	112 ± 20
MABP (mmHg)†	98 ± 16	117 ± 24**	111 ± 20*	109 ± 19*	105 ± 21	102 ± 20	102 ± 21	99 ± 18	101 ± 18
MPAP (mmHg)	15 ± 2	17 ± 2	7 ± 2	16 ± 2	16 ± 2	16 ± 2	16 ± 2	16 ± 2	17 ± 3
MRAP (mmHg)	4 ± 3	5 ± 3	4 ± 3	5 ± 3	4 ± 3	4 ± 3	4 ± 3	4 ± 2	4 ± 3
MPWP (mmHg)	6 ± 1	7 ± 1	7 ± 2	7 ± 2	7 ± 2	7 ± 1	7 ± 2	7 ± 2	7 ± 3
Esophagus temperature (°C)	36.6 ± 0.5	36.5 ± 0.4	36.5 ± 0.4	36.5 ± 0.5	36.5 ± 0.5	36.5 ± 0.6	36.5 ± 0.6	36.4 ± 0.7	36.4 ± 0.7
CO (*l*/min)	2.10 ± 0.57	1.98 ± 0.63	2.02 ± 0.65	2.10 ± 0.63	2.01 ± 0.66	1.99 ± 0.71	2.02 ± 0.80	2.00 ± 0.77	2.10 ± 0.87
CI (ml/min/kg)	180 ± 24	169 ± 34	173 ± 43	180 ± 42	171 ± 38	169 ± 42	171 ± 46	169 ± 41	176 ± 47
SV (ml/beat)	16.6 ± 3.2	15.1 ± 3.6	15.4 ± 3.4	16.3 ± 3.4	16.5 ± 4.0	16.7 ± 3.8	17.1 ± 4.4	17.5 ± 4.8	18.5 ± 5.6
SVR (dynes·sec/cm^5)†	3,651 ± 488	4,667 ± 661**	4,403 ± 658*	4,102 ± 597	4,169 ± 680*	4,128 ± 617*	4,105 ± 801*	4,108 ± 1,033	4,026 ± 1,156

Data was shown in mean ± SD. HR: heart rate, MABP: mean arterial blood pressure, MPAP: mean pulmonary artery pressure, MRAP: mean right atrial pressure, MPWP: mean pulmonary capillary wedge pressure, CO: cardiac output, CI: cardiac index, SV: stroke volume, SVR: systemic vascular resistance. † Significant change detected by one-way repeated measure ANOVA (P<0.01). Significant difference from the baseline value detected by paired t-test:* P<0.05, ** P<0.01.

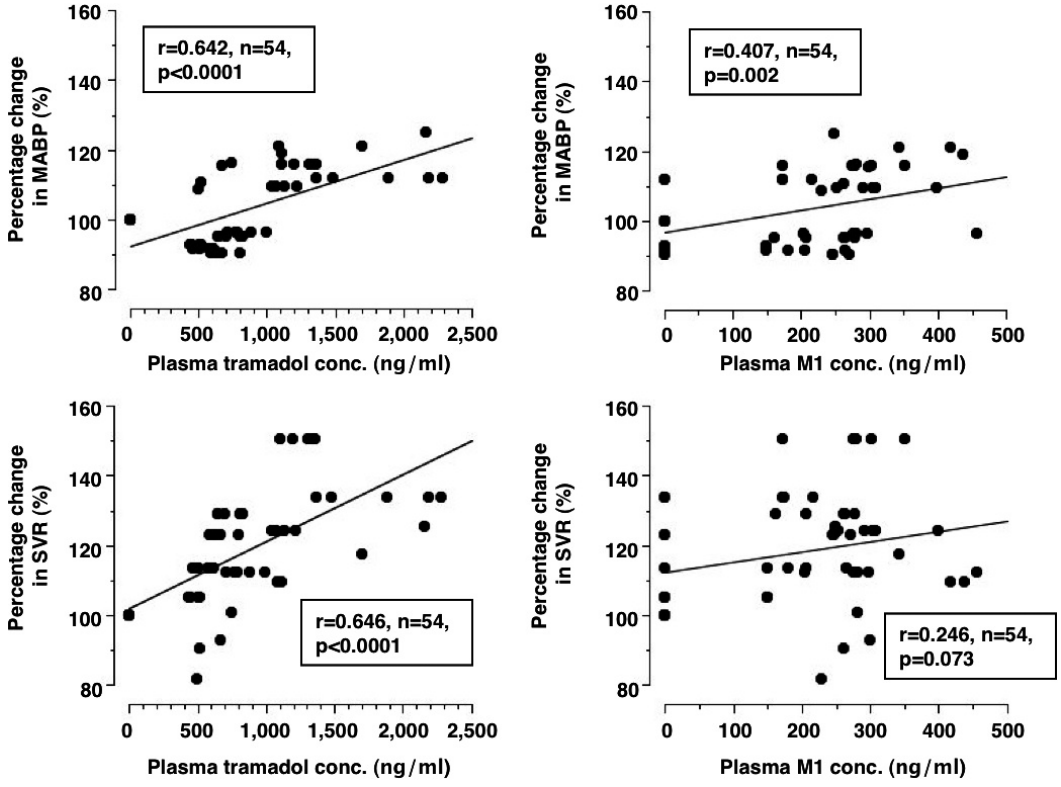

Fig. 2. Relationship between percentage change in mean arterial blood pressure (MABP) and Plasma tramadol concentration (upper left), percentage change in MABP and plasma *O*-desmethyltramadol (M1) concentration (upper right), percentage change in systemic vascular resistance (SVR) and plasma tramadol concentration (lower left), and percentage change in SVR and plasma M1 concentration (lower right).

the catheters. Changes in cardiovascular parameters after the administration of tramadol are summarized in Table 1. The administration of tramadol produced a mild increase in ABP (P=0.004) and SVR (P<0.0001). Compared with baseline value, mean ABP was significantly increased at 5 min (119% of baseline value, P=0.003), 10 min (113%, P=0.027), and 15 min (111%, P=0.022) after the administration of tramadol. SVR was also significantly increased at 5 min (128%, P<0.0001), 10 min (121%, P=0.026), 30 min (114%, P=0.025), 45 min (113%, P=0.025) and 60 min (112%, P=0.048) after the tramadol administration. Plasma concentrations of tramadol were weakly correlated with the percentage changes in MABP and SVR (r=0.642 and r=0.646, respectively; P<0.0001) (Fig. 2). There was no significant change in HR, CO, CI, SV, PAP, RAP and PWP.

DISCUSSION

In the present study, an IV injection of tramadol (4 mg/kg) produced a prolonged increase in systemic vascular resistance in dogs anesthetized with sevoflurane, which was accompanied with a transient and mild increase in arterial blood pressure. These cardiovascular changes were correlated weakly with the plasma concentrations of tramadol, but not with those of M1. It was indicated that tramadol induced a mild but prolonged vasoconstriction and its degree might depend on the plasma concentration of tramadol in dogs.

We adopted the dosage of tramadol (4 mg/kg IV) based on previous reports on pharmacokinetics of an IV injection of tramadol [11, 14], a clinical study [13] and our clinical investigations (data was not shown) in dogs. On the other hand, we adopted the dosage of sevoflurane (1.3 MAC) for two reasons: 1) the MAC is a useful concept for comparing effects of inhalation anesthetics on vital organs, and 2) the MAC corresponds to the median effective dose (ED_{50}) and the dose that corresponding the ED_{95} is 1.2 to 1.4 MAC [29]. In a single species the variability of the MAC is generally small and not substantially influenced by gender, duration of anesthesia, variation in $PaCO_2$ and/or PaO_2 metabolic alkalosis or acidosis, moderate anemia, or moderate hypotension [29]. However, some factors influence the value of MAC including increasing age [29, 30]. In fact, the sevoflurane MAC (1.86 ± 0.29%) for the dogs aged from 8 to 10 years in the present study was lower than that for the dogs aged from 10 to 19 months old in the previous study (2.09 ± 0.13%) [20]. Therefore, MAC values were initially determined for individual dog and the cardiovascular measurements made during anesthesia using an individual 1.3 MAC of end-tidal concentration of sevoflurane. This additional experimental step helped to minimize individual variability as a source of error to establish the relation ship between changes in cardiovascular parameters and plasma concentration of tramadol and M1.

Nishioka [23] observed that tramadol (5 mg/kg IV) induced a significant reduction of cardiac contractility at 5 and 10 min after its administration in awaking dogs and he suggested that tramadol was a mild myocardial depressant in dogs. Müller and Wilsmann *et al.* [18] reported that tramadol (1 and 4.64 mg/kg IV) induced a slight increase in heart rate (about 105–107% of the baseline value) and arterial blood pressure (about 110% of the baseline value) without influencing cardiac output in rabbits anesthetized with urethane and α-chloralose. It was also reported that tramadol (2 and 4 mg/kg IV) induced a mild increase in arterial blood pressure (about 110% of the baseline value) and a mild decrease in heart rate (about 92 to 98% of the baseline value) in rats anesthetized with intraperitoneal injection of pentobarbital [21]. On the other hand, Egger *et al*. [4] reported that tramadol (4.4 mg/kg IV) induced a transient but significant decrease in heart rate (about 84% of the baseline value) immediately after its administration in rabbits anesthetized with isoflurane. In the present study, we observed a transient increase in arterial blood pressure after the tramadol administration (4 mg/kg IV). This is consistent with previous reports in rabbits [18] and rats [21]. The cardiovascular change in dogs was only mild increase in arterial blood pressure caused by peripheral vascular constriction. The increase in arterial blood pressure lasted 15 min after the tramadol administration. We also observed a mild and prolonged vasoconstriction evidenced by statistically significant increase in systemic vascular resistance at 5, 10, 30, 45 and 60 min after the tramadol administration. The peak systemic vascular resistance recorded at 5 min was 4,667 ± 667 dynes·sec·cm^{-5}. This is similar to the systemic vascular resistance determined in conscious dogs [20]. It is thought that tramadol has a mild cardiovascular effect in dogs. However, further investigations may be necessary to confirm the negative effect of its prolonged vasoconstriction.

The analgesic effects of tramadol are produced by agonistic action to the μ-opioid receptor [9] and inhibiting reuptakes of norepinephrine [7] and 5-HT [1]. Several investigators have reported that tramadol inhibits reuptake of neurotransmitter monoamines released from nerve endings and regulates the extraneural norepinephrine concentration [3, 26]. Norepinephrine produces a constriction of the vascular smooth muscles in most tissue via α_1-adrenergic receptors [16]. 5-HT also produces a constriction of the vascular smooth muscles via 5-HT_2 receptors [22]. Nagaoka *et al.* [21] showed that a bolus IV injection of tramadol (2 mg/kg) induced an increase in arterial blood pressure and serum norepinephrine concentration in rats. It is suggested that the inhibition of norepinephrine and/or 5-HT reuptake by tramadol may induce increases in circulating norepinephrine and then may result in the peripheral vasoconstriction [21]. Although we did not measure circulating concentrations of norepinephrine and 5-HT, it is conjectured that the increases in their circulating concentrations resulted from the inhibition of reuptake by tramadol may contribute to the mild increases in arterial blood pressure and systemic vascular resistance observed in the present study.

Sevoflurane has dose-dependent cardiovascular depressant effects [29]. It was reported that systemic vascular resistance decreased with increasing anesthetic depth, which accompanied by dose dependent decrease in arterial blood pressure in dogs anesthetized with sevoflurane at 1.0, 1.5 and 2.0 MAC [20]. In the present study, the dogs were anesthetized with 1.3 MAC of sevoflurane throughout the experiment. It was reported that the cardiovascular function had been maintained over 2 hr in horses anesthetized with 1.3 MAC of sevoflurane [32] and in dogs anesthetized 1.5 MAC of isoflurane [12]. This sevoflurane concentration might be high enough to induce decreases in systemic vascular resistance [20]. However, we observed a prolonged increase in systemic vascular resistance after the tramadol administration, which was accompanied by a transient and mild increase in arterial blood pressure. It was indicated that the vasoconstriction induced by tramadol might moderately overcome the vasodilation induced by sevoflurane. This

interaction between tramadol and sevoflurane may have an advantage to maintain cardiovascular function in dogs anesthetized with sevoflurane. Again, further investigations may be necessary to confirm the negative effect of its prolonged vasoconstriction.

Pharmacokinetic profiles for tramadol were reported in beagle dogs [5, 11] and mixed breed dogs [14]. These dogs have a rapid elimination rate for tramadol [5, 11, 14] as compared to humans [27]. The changes in the plasma concentration of tramadol in our dogs almost concurred with those in previous reports in awaking dogs [11, 14]. In our dogs, tramadol produced a prolonged increase in systemic vascular resistance that was accompanied with a transient and mild increase in arterial blood pressure. These cardiovascular changes were correlated weakly with the plasma concentrations of tramadol, but not with those of M1. It was indicated that tramadol induced a mild but prolonged vasoconstriction and that the degree of vasoconstriction induced by tramadol might be depending on its plasma concentration in dogs.

In conclusion, the administration of tramadol produces a prolonged peripheral vascular constriction in dogs anesthetized with sevoflurane, which accompanied with a transient and mild increase in arterial blood pressure. The vasoconstriction may increase depending on the plasma tramadol concentration and may be useful for overcoming the vasodilation induced by sevoflurane.

REFERENCES

1. Bamigbade, T. A., Davidson, C., Langford, R. M. and Stamford, J. A. 1997. Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus. *Br. J. Anaesth.* **79**: 352–356.
2. Berrocoso, E., De Benito, M. D. and Mico, J. A. 2007. Role of serotonin 5-HT1A and opioid receptors in the antiallodynic effect of tramadol in the chronic constriction injury model of neuropathic pain in rats. *Psychopharmacology (Berl.)* **193**: 97–105.
3. Driessen, B., Reimann, W. and Giertz, H. 1993. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. *Br. J. Pharmacol.* **108**: 806-811.
4. Egger, C. M., Souza, M. J., Greenacre, C. B., Cox, S. K. and Rohrbach, B. W. 2009. Effect of intravenous administration of tramadol hydrochroride on the minimum alveolar concentration of isoflurane in rabbits. *Am. J. Vet. Res.* **70**: 945–949.
5. Giorgi, M., Del Carlo, S., Saccomanni, G., Łebkowska-Wieruszewska, B. and Kowalski, C. J. 2009. Pharmacokinetics of tramadol and its major metabolites following rectal and intravenous administration in dogs. *N. Z. Vet. J.* **57**: 146–152.
6. Haeseler, G., Foadi, N., Ahrens, J., Dengler, R., Hecker, H. and Leuwer, M. 2006. Tramadol, fentanyl and sufentanil but not morphine block voltage-operated sodium channels. *Pain* **126**: 234–244.
7. Halfpenny, D. M., Callado, L. F., Hopwood, S. E., Bamigbade, T. A., Langford, R. M. and Stamford, J. A. 1999. Effects of tramadol stereoisomers on norepinephrine efflux and uptake in the rat locus coeruleus measured by real time voltammetry. *Br. J. Anaesth.* **83**: 909–915.
8. Hennies, H. H., Friderichs, E. and Schneider, J. 1988. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. *Arzneimittelforschung* **38**: 877–880.
9. Ide, S., Minami, M., Ishihara, K., Uhl, G. R., Sora, I. and Ikeda, K. 2006. Mu opioid receptor-dependent and independent components in effects of tramadol. *Neuropharmacology* **51**: 651–658.
10. Ilkiw, J. E., Pascoe, P. J. and Tripp, L. D. 2002. Effects of morphine, butorphanol, buprenorphine, and U50488H on the minimum alveolar concentration of isoflurane in cats. *Am. J. Vet. Res.* **63**: 1198–1202.
11. Kukanich, B. and Papich, M. G. 2004. Pharmacokinetics of tramadol and the metabolite O-desmethyltramadol in dogs. *J. Vet. Pharmacol. Ther.* **27**: 239–246.
12. Martinez, E. A., Hartsfield, S. M., Melendez, J. D., Matthews, N. S. and Slater, M. R. 1997. Cardiovascular effects of buprenorphine in anesthetized dogs. *Am. J. Vet. Res.* **58**: 1280–1284.
13. Mastrocinque, S. and 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.
14. McMillan, C. J., Livingston, A., Clark, C. R., Dowling, P. M., Taylor, S. M., Duke, T. and Terlinden, R. 2008. Pharmacokinetics of intravenous tramadol in dogs. *Can. J. Vet. Res.* **72**: 325–331.
15. Miranda, H. F. and Pinardi, G. 1998. Antinociception, tolerance, and physical dependence comparison between morphine and tramadol. *Pharmacol. Biochen. Behav.* **61**: 357–360.
16. Muir, W. W. 2007. Cardiovascular system. pp. 61–116. *In*: Lumb and Jones' Veterinary Anesthesia and Analgesia, 4th ed. (Tranquilli, W. J., Thurmon, J. C. and Grimm, K. A. eds.), Blackwell Publishing, Iowa.
17. Muir, W. W. 2002. Choosing and administering the right analgesic therapy. pp. 329–345. *In*: Handbook of Veterinary Pain Management (Gaynor, J. S. and Muir, W. W. eds.), Mosby, St. Louis.
18. Müller, B. and Wilsmann, K. 1984. Cardiac and hemodynamic effects of the centrally acting analgesics tramadol and pentazocine in anaesthetized rabbits and isolated guinea-pig atria and papillary muscles. *Arzneimittelforschung* **34**: 430–433.
19. Murphy, M. R. and Hug, C. C. Jr. 1982. The enflurane sparing effect of morphine, butorphanol, and nalbuphine. *Anesthesiology* **57**: 489–492.
20. Mutoh, T., Nishimura, R., Kim, H. Y., Matsunaga, S. and Sasaki, N. 1997. Cardiopulmonary effects of sevoflurane, compaired with halothane, enflurane, and isoflurane, in dogs. *Am. J. Vet. Res.* **58**: 885–890.
21. Nagaoka, E., Minami, K., Shiga, Y., Uezono, Y., Shiraishi, M., Aoyama, K. and Shigematsu, A. 2002. Tramadol has no effect on cortical renal blood flow—despite increased serum catecholamine levels—in anesthetized rats: implications for analgesia in renal insufficiency. *Anesth. Analg.* **94**: 619–625.
22. Nishihira, K., Yamashita, A., Tanaka, N., Moriguchi-Goto, S., Imamura, T., Ishida, T., Kawashima, S., Yamamoto, R., Kitamura, K. and Asada, Y. 2008. Serotonin induces vasoconstriction of smooth muscle cell-rich neointima through 5-hydroxytryptamine2A receptor in rabbit femoral arteries. *J. Thromb. Haemost.* **6**: 1207–1214.
23. Nishioka, K. 1979. The effect of non-narcotic analgesic, tramadol, on cardiac contractility in dog. *Tohoku J. Exp. Med.* **128**: 401–402.

24. Poulsen, L., Arendt-Nielsen, L., Brosen, K. and Sindrup, S. H. 1996. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin. Pharmacol. Ther.* **60**: 636–644.
25. Raffa, R. B., Friderichs, E., Reimann, W., Shank, R. P., Codd, E. E. and Vaught, J. L. 1992. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J. Pharmacol. Exp. Ther.* **260**: 275–285.
26. Reimann, W. and Hennies, H. H. 1994. Inhibition of spinal noradrenaline uprake in rats by the centrally acting analgesic tramadol. *Biochem. Pharmacol.* **47**: 2289–2293.
27. Scott, L. J. and Perry, C. M. 2000. Tramadol: A review of its use in perioperative pain. *Drugs* **60**: 139–176.
28. Seddighi, M. R., Egger, C. M., Rohrbach, B. W., Cox, S. K. and Doherty, T. J. 2009. Effects of tramadol on the minimum alveolar concentration of sevoflurane in dogs. *Vet. Anaesth. Analg.* **36**: 334–340.
29. Steffey, E. P. and Mama, K. R. 2007. Inhalation anesthetics. pp. 355–393. *In*: Lumb and Jones' Veterinary Anesthesia and Analgesia, 4th ed. (Tranquilli, W. J., Thurmon, J. C. and Grimm, K. A. eds.), Blackwell Publishing, Iowa.
30. Yamashita, K., Iwasaki, Y., Umar, M. A. and Itami, T. 2009. Effect of age on minimum alveolar concentration (MAC) of sevoflurane in dogs. *J. Vet. Med. Sci.* **71**: 1509–1512.
31. Yamashita, K., Ueyama, Y., Miyoshi, K., Igarashi, R., Kushiro, T., Umar, M. A. and Muir, W. W. 2007. Minimally invasive determination of cardiac output by transthoracic bioimpedance, partial carbon dioxide rebreathing, and transesophageal Doppler echocardiography in beagle dogs. *J. Vet. Med. Sci.* **69**: 43–47.
32. Yamashita, K., Satoh, M., Umikawa, A., Tsuda, A., Yajima, Y., Tsubakishita, S., Seno, T., Katoh, S., Izumisawa, Y. and Kotani, T. 2000. Combination of continuous intravenous infusion using a mixture of guaifenesin-ketamine-medetomidine and sevoflurane anesthesia in horses. *J. Vet. Med. Sci.* **62**: 229–235.
33. Wu, W. N., McKown, L. A., Gauthier, A. D., Jones, W. J. and Raffa, R. B. 2001. Metabolism of the analgesic drug, tramadol hydrochloride, in rat and dog. *Xenobiotica* **31**: 423–441.