Journal of Animal and Veterinary Advances 14 (4): 95-99, 2015
ISSN: 1680-5593


# Dose-Dependent Isoflurane-Sparing Effect of Maropitant in Dogs Undergoing Ovariohysterectomy

[1]Kimiyoshi Okano, [2]Taro Kimura and [3]Kazuya Edamura
[1]Okano Animal Hospital, 234-0054 Kanagawa, Japan
[2]Kimura Animal Hospital, 162-0045 Tokyo, Japan
[3]Laboratory of Veterinary Surgery, Department of Veterinary Medicine,
College of Bioresource Sciences, Nihon University, 252-0880 Kanagawa, Japan

**Abstract:** The dose-dependent isoflurane-sparing effect of maropitant in dogs undergoing Ovariohysterectomy (OHE) was investigated. Thirty six female dogs undergoing OHE were randomly divided into 3 groups. The MAR-1 group dogs were premedicated with 1 mg $kg^{-1}$ maropitant and 0.5 mg $kg^{-1}$ morphine (n = 12). The MAR-5 group dogs were premedicated with 5 mg $kg^{-1}$ maropitant and 0.5 mg $kg^{-1}$ morphine (n = 12). The MOR group dogs received saline and 0.5 mg $kg^{-1}$ morphine (n = 12). The intraoperative isoflurane-sparing effect was compared among the groups. The mean intraoperative isoflurane requirements during the surgery were 1.88±0.10, 1.76±0.13 and 1.69±0.16% in the MOR, MAR-1 and MAR-5 groups, respectively. The requirements of the MAR-1 and MAR-5 groups were significantly lower than that of the MOR group. The mean intraoperative isoflurane requirement during the surgery of the MAR-5 group was the lowest of all 3 groups. The isoflurane requirement at 40 min after the start of surgery of the MAR-5 group was significantly lower than that of the MAR-1 group. Preoperative administration of maropitant effectively reduces the intraoperative isoflurane requirement in a dose-dependent manner.

**Key words:** Dog isoflurane-sparing effect, maropitant, ovariohysterectomy, morphine, group

## INTRODUCTION

Maropitant prevents vomiting by inhibiting binding between substance P and Neurokinin 1 (NK1) receptors that are distributed in the vomiting center and Chemoreceptor Trigger Zone (CTZ) (Benchaoui *et al*., 2007a; Hickman *et al*., 2008; Sedlacek *et al*., 2008). Substance P, a ligand of the NK1 receptor is also involved in pain transmission (Alvaro and Di Fabio, 2007). Substance P is released from primary afferent nerves in response to peripheral painful stimulation (Otsuka and Yoshioka, 1993). Substance P then transmits pain-related information to the secondary afferent nerves, mainly through NK1 receptors in the dorsal horn of the spinal cord (Mantyh and Yaksh, 2001; Alvaro and Di Fabio, 2007; Duncan, 2012). Considering these findings, we expected that inhibition of binding between substance P and NK1 receptors would have an analgesic effect. A previous study by Lembeck *et al*. (1981) using a pain model in which a rat was stimulated by heat reported that NK1 receptor antagonists produced an analgesic effect.

Boscan *et al*. (2011) reported that administration of maropitant reduced the Minimum Alveolar Concentration (MAC) of sevoflurane in a dose-dependent manner in dogs undergoing laparoscopic Ovariohysterectomy (OHE) under general anesthesia with sevoflurane. Alvillar *et al*. (2012) reported that administration of maropitant reduced the MAC of sevoflurane by 16% in dogs receiving noxious stimulation using the Tail-Clamp Method. These results suggest that administration of maropitant reduces the MAC of sevoflurane in dogs experiencing painful stimulation.

Unfortunately, to the best of our knowledge, there have been no reports on the effect of maropitant administration on isoflurane requirement in dogs, although, isoflurane is the inhalation anesthesia most widely used in canine clinical practice. Further, it has not been determined whether administration of maropitant reduces the inhalational anesthetic requirement in a dose-dependent manner in dogs undergoing surgery with an abdominal incision. In the present study, we investigated the dose-dependent isoflurane-sparing effect of maropitant premedication in small-breed dogs undergoing OHE. In addition, we also investigated the effect of maropitant on the respiratory and cardiovascular systems under general anesthesia with isoflurane.

**Corresponding Author:** Kazuya Edamura, Laboratory of Veterinary Surgery, Department of Veterinary Medicine, College of Bioresource Sciences, Nihon University, 1866 Kameino, Fujisawa, Kanagawa, Japan

## MATERIALS AND METHODS

**Study population:** Thirty six small-breed dogs that were brought to Okano Animal Hospital for the purpose of OHE from March 2012 through August 2013 were used in this study. This study was conducted with the approval of the director of the hospital and all owners of dogs used in this study consented to the collection of data for research purposes. All dogs were classified as American Society of Anesthesiologists (ASA) status I (Ament, 1979) according to age, general condition, physical examination, complete blood count, blood chemical analysis and electrocardiography. Subject dogs were randomly allocated into 3 premedication groups. The MAR-1 group (n = 12) received maropitant citrate (1 mg $kg^{-1}$; Cerenia; Zoetis, Japan, Tokyo, Japan) and morphine hydrochloride (0.5 mg $kg^{-1}$; Morphine hydrochloride, Shionogi, Shionogi & Co. Ltd., Osaka, Japan). The MAR-5 group (n = 12) received maropitant (5 mg $kg^{-1}$) and morphine (0.5 mg $kg^{-1}$). The MOR group (n = 12) received saline (normal saline, Terumo Co., Tokyo, Japan) and morphine (0.5 mg $kg^{-1}$). In all subject dogs, OHE were performed according to routine surgical methods through a midline abdominal incision.

**Premedication, induction and maintenance of anesthesia:** In the MAR-1 and MAR-5 groups, maropitant was injected Intravenously (IV) at 1 and 5 mg $kg^{-1}$, respectively 1 h before the start of inhalation anesthesia. In the MOR group, saline was injected IV at 0.1 mL $kg^{-1}$, 1 h before the start of inhalation anesthesia. In all groups, morphine and atropine sulfate (Atropine Sulfate Injection, Fuso Pharmaceutical Industries Ltd., Osaka, Japan) were injected subcutaneously at 0.5 and 0.05 mg $kg^{-1}$, respectively 15 min before the start of inhalation anesthesia.

Anesthesia was induced by IV injection of propofol (4-6 mg $kg^{-1}$; Rapinovet, Intervet K.K., Tokyo, Japan) while allowing the dogs to inhale 100% oxygen through a mask connected to an inhalation anesthesia apparatus (A.D.S. 1000 Model: 2000, Shin-Ei Industries, Inc., Saitama, Japan). When the spontaneous breathing weakened, consciousness disappeared and laryngeal reflex was sufficiently suppressed, a cuffed endotracheal tube (PVC soft endotracheal tube, standard cuff type, Fuji Systems Co., Tokyo, Japan) was inserted into the trachea. Following intubation, inhalation anesthesia was initiated by controlling the vapor volume of isoflurane (ISOFUL®, Dainippon Sumitomo Pharma Co. Ltd., Osaka, Japan) with an isoflurane vaporizer (ISOREX I-200, Shin-Ei Industries). At the start of surgery, the End-Tidal isoflurane concentration (Etiso) was set at 2.0% and the isoflurane concentration was reduced by 0.2% every 10 min thereafter. ETiso was measured using a veterinary patient monitor (AM-120, Fukuda M-E Kogyo Co. Ltd., Tokyo, Japan) that was calibrated with 2.0% isoflurane calibration gas following the manufacturer's recommendation once every 3 months. If spontaneous breathing was confirmed or HR and blood pressure became remarkably elevated because of surgical invasion, the isoflurane concentration was increased. Anesthesiologists controlling the concentration of isoflurane were blinded to the details of the premedication administered to subject dogs. During anesthesia, breathing was controlled by artificial ventilation with 100% oxygen. The ventilator parameters were set as follows: breathing frequency, 8 breaths $min^{-1}$; tidal volume, 15-20 mL $kg^{-1}$; Inspiratory to Expiratory time (I/E) ratio, 1:2 and End-Tidal Carbon Dioxide concentration ($ETCO_2$), 35-40 mmHg. During surgery, a heat pad (T/Pump TP-401, Gaymar Industries Inc., New York, NY, USA) was used to maintain body temperature. In all groups, IV infusion (10 mL/kg/h) of lactated Ringer's solution (SOLULACT®, Terumo Co., Tokyo, Japan) was started at induction of anesthesia and continued throughout surgery. After completing the sutures, 2.0 mg $kg^{-1}$ of bupivacaine (Marcain Injection®, AstraZeneca, Osaka, Japan) diluted in 3-5 mL saline was infiltrated locally around the surgical incision for postoperative analgesia. In addition, meloxicam (Metacam®, Boehringer Ingelheim Japan Inc., Tokyo, Japan) was injected subcutaneously at 0.2 mg $kg^{-1}$ prior to terminating isoflurane inhalation anesthesia. Finally, the endotracheal tube was removed when the laryngeal reflex recovered.

**Monitoring of anesthesia:** Perioperative body temperature, HR, peripheral oxygen saturation ($SpO_2$), $ETCO_2$, ETiso and non-invasive Mean Arterial blood Pressure (MAP) were measured using a veterinary patient monitor (AM-120, Fukuda M-E Kogyo Co. Ltd., Tokyo, Japan) and recorded every 5 min. The times between anesthesia induction and termination of inhalation anesthesia (anesthesia time), preparation for the operation and skin incision (patient preparation time), skin incision and completion of sutures (surgery time) and termination of isoflurane inhalation and removal of the endotracheal tube (tube removal time) were also measured.

**Statistical analysis:** The results of this study are reported as mean±SD. Statistical analysis of the data was performed using the StatMate IV Software package

(ATMS, Tokyo, Japan). One-way ANOVA was used for comparison of variables including age, body weight, subject monitoring results, anesthesia time, patient preparation time, surgery time and tube removal time. Post hoc analysis was conducted using Tukey's test to compare groups in which significant differences were detected. Differences were considered significant when the $p<0.05$.

## RESULTS

In all dogs used in this study, anesthesia induction, endotracheal tube insertion, OHE and recovery were routine. No significant differences were observed in age, body weight, anesthesia time, patient preparation time, surgery time and tube removal time among the groups (Table 1).

None of the dogs experienced bradycardia or respiratory depression due to subcutaneous morphine injection. In the MAR-1 and MAR-5 groups, vomiting after injection of morphine tended to be less frequent than in the MOR group. In all groups, the values for $SpO_2$, $ETCO_2$, HR and MAP during the surgery were maintained as follows: approximately 99%, 31-33 mmHg, 101-111 beats $min^{-1}$ and 88-96 mmHg, respectively. Intraoperative body temperature was maintained between 37.6 and 38.1°C, although, it tended to decline as time elapsed following induction of anesthesia. No significant difference was observed in these values among the groups (Table 2).

The mean intraoperative isoflurane requirements during the surgery in the MOR, MAR-1 and MAR-5 groups were 1.88±0.10, 1.76±0.13 and 1.69±0.16%, respectively. The values for the MAR-1 and MAR-5 groups were significantly lower than the value for the MOR group (Table 3). Compared with the mean isoflurane requirement of the MOR group, the mean isoflurane requirements during the surgery in the MAR-1 and MAR-5 groups were reduced by 6.12 and 10.20%, respectively. The mean intraoperative isoflurane requirement during the surgery of the MAR-5 group was significantly lower than that of the MAR-1 group, indicating a dose-dependent isoflurane-sparing effect (Table 3).

The isoflurane requirements at 30 and 40 min after the start of surgery of the MAR-1 group and at 20, 30 and 40 min after the start of surgery of the MAR-5 group were significantly lower than those of the MOR group (Table 3). At 40 min after the start of surgery, the isoflurane requirement of the MAR-5 group was significantly lower than that of the MAR-1 group, showing a reduction of the isoflurane requirement by as much as 7.81% (Table 3).

Table 1: Age, body weight, patient preparation time, surgery time, anesthesia time and time to extubation in 36 dogs anesthetized with isoflurane for ovariohysterectomy. Dogs were premedicated with morphine (0.5 mg $kg^{-1}$) alone (group MOR; n = 12), morphine and maropitant (1 mg $kg^{-1}$; group MAR-1; n = 12) or morphine and maropitant (5 mg $kg^{-1}$; group MAR-5; n = 12)

| Groups | Age (month) | Body weight (kg) | Patient preparation time (min) | Surgery time (min) | Anesthesia time (min) | Tube removal time (min) |
|---|---|---|---|---|---|---|
| MOR | 10.1±3.8 | 2.6±1.0 | 23±3 | 51±5 | 74±7 | 8.4±1.6 |
| MAR-1 | 9.5±4.9 | 2.5±0.9 | 24±3 | 49±6 | 74±8 | 8.4±1.4 |
| MAR-5 | 9.3±4.3 | 2.6±1.3 | 23±2 | 50±7 | 73±8 | 8.5±2.0 |

Mean±SD

Table 2: Physiologic variables measured in 36 dogs anesthetized with isoflurane for ovariohysterectomy. Dogs were premedicated with morphine (0.5 mg $kg^{-1}$) alone (group MOR; n = 12), morphine and maropitant (1 mg $kg^{-1}$; group MAR-1; n = 12) or morphine and maropitant (5 mg $kg^{-1}$; group MAR-5; n = 12)

| | | Minutes after start of surgery | | | | |
|---|---|---|---|---|---|---|
| Variables | Groups | 0 | 10 | 20 | 30 | 40 |
| $SpO_2$ (%) | MOR | 99.3±0.9 | 99.3±0.8 | 99.4±0.8 | 99.1±0.8 | 98.9±0.9 |
| | MAR-1 | 99.2±0.8 | 99.1±0.7 | 99.2±0.6 | 99.1±0.7 | 99.1±0.5 |
| | MAR-5 | 99.2±0.4 | 99.0±1.0 | 99.1±0.8 | 99.1±0.9 | 99.1±0.7 |
| $ETCO_2$ (mmHg) | MOR | 32±3 | 31±3 | 33±3 | 32±3 | 32±2 |
| | MAR-1 | 31±3 | 33±4 | 33±4 | 31±4 | 31±3 |
| | MAR-5 | 32±4 | 33±5 | 32±5 | 32±4 | 32±4 |
| HR (beats $min^{-1}$) | MOR | 102±10 | 104±14 | 105±7 | 107±6 | 103±10 |
| | MAR-1 | 107±6 | 104±14 | 111±9 | 106±7 | 111±24 |
| | MAR-5 | 102±6 | 102±17 | 105±9 | 112±13 | 105±8 |
| MAP (mmHg) | MOR | 94±11 | 91±18 | 85±12 | 97±14 | 93±13 |
| | MAR-1 | 95±12 | 93±15 | 89±9 | 94±12 | 95±11 |
| | MAR-5 | 97±12 | 92±14 | 94±11 | 98±12 | 99±12 |
| Temp (°C) | MOR | 38.0±0.6 | 37.8±0.7 | 37.7±0.6 | 37.6±0.6 | 37.5±0.6 |
| | MAR-1 | 37.9±0.6 | 37.8±0.6 | 37.7±0.6 | 37.6±0.6 | 37.5±0.7 |
| | MAR-5 | 38.1±0.6 | 37.9±0.5 | 37.7±0.5 | 37.7±0.6 | 37.6±0.6 |

Mean±SD: $SpO_2$: Hemoglobin oxygen saturation; $ETCO_2$: End-Tidal Carbon dioxide pressure; HR: Heart Rate; MAP: Non-invasive Mean Arterial Pressure; Temp: Esophageal Temperature

Table 3: Mean end-tidal isoflurane concentrations (%) required for 36 dogs anesthetized with isoflurane for ovariohysterectomy. Dogs were premedicated with morphine (0.5 mg $kg^{-1}$) alone (group MOR; n = 12), morphine and maropitant (1 mg $kg^{-1}$; group MAR-1; n = 12) or morphine and maropitant (5 mg $kg^{-1}$; group MAR-5; n = 12)

| | Minutes after start of surgery | | | | |
|---|---|---|---|---|---|
| Groups | 10 | 20 | 30 | 40 | Average during surgery |
| MOR | 1.93±0.07 | 1.89±0.11 | 1.86±0.11 | 1.83±0.09 | 1.88±0.10 |
| MAR-1 | 1.89±0.09 | 1.81±0.12 | 1.70±0.07* | 1.64±0.05* | 1.76±0.13* |
| MAR-5 | 1.86±0.09 | 1.73±0.11* | 1.64±0.14* | 1.55±0.11*† | 1.69±0.16*† |

Mean±SD; *Significant difference versus MOR group ($p<0.05$); †Significant difference versus MAR-1 group ($p<0.05$)

## DISCUSSION

OHE in dogs is one of the most frequently conducted operations and is characterized by mild to moderate pain levels (Cheryl, 2007). For that reason, use of opioids, including morphine is encouraged for preemptive analgesia. Combination of an opioid with other analgesics is adopted for perioperative pain management and dose reduction of inhalational anesthetics (Cheryl, 2007; Boel, 2012; Duncan, 2012). Maropitant, an NK1 receptor antagonist is marketed as an antiemetic drug in veterinary medicine (Benchaoui *et al*., 2007b; Hickman *et al*., 2008; Sedlacek *et al*., 2008). However, because the NK1 receptor and its ligand, substance P are also involved in pain transmission, blocking the transduction pathway with an NK1 receptor antagonist has become an important subject in the field of pain control (Lembeck *et al*., 1981; Hill, 2000; Mantyh and Yaksh, 2001; Alvaro and Di Fabio, 2007; Duncan, 2012). The sevoflurane-sparing and analgesic effects of maropitant administration in dogs have been reported in several articles (Alvillar *et al*., 2012; Boel, 2012). However, to the best of our knowledge, there have been no reports on the effect of preoperative maropitant administration on the requirement of isoflurane, the inhalational anesthetic most widely used in canine clinical practice.

In the present study, the mean intraoperative isoflurane requirements during the surgery of the MAR-1 and MAR-5 groups injected with maropitant were significantly lower than those of the MOR group. These results suggest that maropitant may possess an isoflurane-sparing effect in dogs. Opioid analgesics including morphine are known to suppress the release of neurotransmitters such as substance P (Duncan, 2012). For that reason, we speculated that the combination of maropitant and morphine would reduce the isoflurane requirement because of the additive effect of morphine's suppression of release of neurotransmitters and maropitant's inhibition of neurotransmitter binding.

In the present study, the reductions in the inhalational anesthetic requirements were smaller than previously reported (Boscan *et al*., 2011; Alvillar *et al*., 2012). Boscan *et al*. (2011) reported a 24 and 30% decrease in MACs of sevoflurane in dogs undergoing laparoscopic ovariectomy when maropitant was administered to the dogs by intravenous injection at doses of 1 and 5 mg $kg^{-1}$, respectively. Alvillar *et al*. (2012) reported a 16% reduction in the MAC of sevoflurane after intravenous injection of 5 mg $kg^{-1}$ maropitant in dogs receiving noxious stimulation by the tail-clamp method under general anesthesia with sevoflurane. The smaller reduction in isoflurane requirement in the present study compared with the previous investigations might have been due to differences in the type of inhalational anesthetic and surgical or pain-induction method.

Two concentrations of maropitant administered IV were used to investigate any isoflurane-sparing effect, referring to the report by Boscan *et al*. (2011). As a result, the mean intraoperative isoflurane requirement during the surgery of the MAR-5 group was significantly lower than that of the MAR-1 group. In addition, the isoflurane requirement at 40 min after the start of surgery of the MAR-5 group was significantly lower than that of the MAR-1 group. These results revealed that maropitant's isoflurane-sparing effect is dose dependent.

The maximum drug concentration time (Tmax) and half-life (T1/2) of maropitant in dogs in the case of subcutaneous injection at 1 mg $kg^{-1}$ are reported to be 0.75 and 7.75 h, respectively (Benchaoui *et al*., 2007a). The pharmacokinetics in the present study might have differed slightly from those in previous reports because our subject dogs received intravenous injections of maropitant. However, we deemed that the blood concentration of maropitant had reached a sufficient level at the time of skin incision in all dogs because maropitant was injected 1 h before the initiation of inhalation anesthesia. In this investigation, an isoflurane-sparing effect was observed in the maropitant groups at time points during 40 min after the start of surgery. Generally, the T1/2 of drugs tends to be shorter with intravenous than subcutaneous injection. However, blood concentrations of maropitant are likely to be maintained at effective levels during surgeries lasting several hours or less.

Further, investigations are required to determine whether the isoflurane-sparing effect of maropitant can be obtained in surgeries associated with higher pain levels,

such as orthopedic surgery and leg amputation. In addition, we must verify whether a similar effect can be obtained when maropitant is combined with other opioids such as fentanyl and remifentanil, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), N-Methyl-D Aspartate (NMDA) receptor antagonists including ketamine and alpha-2 adrenergic receptor agonists including medetomidine. The results of these further investigations will help establish indications and protocols for usage of maropitant as preanesthetic medication in dogs.

## CONCLUSION

In the present study, preoperative administration of maropitant provided a dose-dependent isoflurane-sparing effect without causing serious adverse reactions. These results suggest that maropitant may prove useful for preanesthetic medication in canine clinical practice.

## REFERENCES


Alvaro, G. and R. Di Fabio, 2007. Neurokinin 1 receptor antagonists-urrent prospects. Curr. Opin. Drug Discov. Devel., 10: 613-621.

Alvillar, B.M., P. Boscan, K.R. Mama, T.H. Ferreira, J. Congdon and D.C. Twedt, 2012. Effect of epidural and intravenous use of the neurokinin-1 (NK-1) receptor antagonist maropitant on the sevoflurane Minimum Alveolar Concentration (MAC) in dogs. Vet. Anaesth. Analg., 39: 201-205.

Ament, R., 1979. Origin of the ASA classification. Anesthesiology, 51: 179-179.

Benchaoui, H.A., S.R. Cox, R.P. Schneider, J.F. Boucher and R.G. Clemence, 2007a. The pharmacokinetics of maropitant, a novel neurokinin type-1 receptor antagonist, in dogs. J. Vet. Pharmacol. Ther., 30: 336-344.

Benchaoui, H.A., E.M. Siedek, V.A. De La Puente-Redondo, N. Tilt, T.G. Rowan and R.G. Clemence, 2007b. Efficacy of maropitant for preventing vomiting associated with motion sickness in dogs. Vet. Rec., 161: 444-447.

Boel, A.F., 2012. Ovaries and Uterus. In: Veterinary Surgery: Small Animal, 1st Edn., Tobias, K. and S. Johnston (Eds.). Elsevier Saunders, St. Louis, MO., pp: 1871-1890.

Boscan, P., E. Monnet, K. Mama, D.C. Twedt, J. Congdon and E.P. Steffey, 2011. Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. Am. J. Vet. Res., 72: 1576-1579.

Cheryl, S.H., 2007. Surgery of the Reproductive and Genital Systems. In: Small Animal Surgery Textbook, 3rd Edn., Fossum, T.W. (Ed.). Mosby, St. Louis, MO., pp: 702-774.

Duncan, X.L., 2012. Surgical Pain: Pathophysiology, Assessment and Treatment Strategies. In: Veterinary Surgery: Small Animal, 1st Edn., Tobias, K. and S. Johnston (Eds.). Elsevier Saunders, St. Louis, MO., pp: 237-247.

Hickman, M.A., S.R. Cox, S. Mahabir, C. Miskell, J. Lin, A. Bunger and R.B. McCall, 2008. Safety, pharmacokinetics and use of the novel NK-1 receptor antagonist maropitant (Cerenia) for the prevention of emesis and motion sickness in cats. J. Vet. Pharmacol. Ther., 31: 220-229.

Hill, R., 2000. $NK_1$ (substance P) receptor antagonists-why are they not analgesic in humans? Trends Pharmacol. Sci., 21: 244-246.

Lembeck, F., K. Folkers and J. Donnerer, 1981. Analgesic effect of antagonists of substance P. Biochem. Biophys. Res. Commun., 103: 1318-1321.

Mantyh, P.W. and T.L. Yaksh, 2001. Sensory neurons are PARtial to pain. Nat. Med., 7: 772-773.

Otsuka, M. and K. Yoshioka, 1993. Neurotransmitter functions of mammalian tachykinins. Physiol. Rev., 73: 229-308.

Sedlacek, H.S., D.S. Ramsey, J.F. Boucher, J.S. Eagleson, G.A. Conder and R.G. Clemence, 2008. Comparative efficacy of maropitant and selected drugs in preventing emesis induced by centrally or peripherally acting emetogens in dogs. J. Vet. Pharmacol. Ther., 31: 533-537.