Journal of Animal and Veterinary Advances 17 (3): 82-86, 2018
ISSN: 1680-5593
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# Isoflurane-Sparing Effect of Maropitant in Cats Undergoing Ovariohysterectomy

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**Abstract:** Maropitant exerts antiemetic effects and is also effective in reducing the inhalational anesthetic requirement. In this study, 20 Japanese domestic cats that were brought to a private animal hospital to be spayed were divided into two groups: one group was administered a combination of Maropitant and Buprenorphine (MAR group, n = 10) and the other group was administered saline solution and buprenorphine (control group, n = 10). In all cases, ovariohysterectomy was performed under general anesthesia using isoflurane. The isoflurane concentration was measured in both groups at the following stages: at 15 min after initiating inhalational anesthesia ($T_0$), during skin incision ($T_1$), left ovary retraction stimulation ($T_2$), right ovary retraction stimulation ($T_3$), uterus retraction stimulation ($T_4$), start of abdominal closure ($T_5$) and start of skin suture ($T_6$). The isoflurane requirements in the MAR group were significantly lower than those in the control group at $T_4$-$T_6$ ($p<0.05$) and the requirement decreased at $T_6$ by approximately 5.5%. These results suggest that maropitant might have an isoflurane-sparing effect in cats undergoing ovariohysterectomy.

**Key words:** Cat, isoflurane, laparotomy, maropitant, ovariohysterectomy, concentration, administered

## INTRODUCTION

Maropitant is a Neurokinin 1 (NK1) receptor antagonist and acts as an antiemetic by inhibiting the binding of Substance P (SP) to NK1 receptors which are distributed in the vomiting center and chemoreceptor trigger zone. Because of this effect, maropitant is used for the prevention and treatment of acute vomiting and motion sickness in dogs (Benchaoui *et al*., 2007b; Hickman *et al*., 2008; Sedlacek *et al*., 2008; Trepanier, 2015; Martin-Flores *et al*., 2016).

SP and NK1 receptors are also deeply involved in pain transmission. SP is released from the primary afferent nerve following peripheral stimulation and transmits pain signals to the secondary afferent nerve via. the NK1 receptors of the dorsal horn of the spinal cord (Mantyh and Yaksh, 2001; Alvaro and Di Fabio, 2007; Duncan, 2012). Hence, NK1 receptor antagonists are suggested to have an analgesic effect (Lembeck *et al*., 1981). Some reports have even documented that the administration of maropitant reduces the inhalational anesthetic requirements in dogs (Boscan *et al*., 2011; Alvillar *et al*., 2012; Okano *et al*., 2015).

Recently, the antiemetic effect of maropitant has also been reported in cats (Hickman *et al*., 2008; Trepanier, 2015) and maropitant has been approved for the treatment of vomiting in cats in Japan. In a previous study on cats, pretreatment with maropitant was reported to lower the sevoflurane requirement during laparoscopic ovarian traction stimulation (Niyom *et al*., 2013). Thus, maropitant not only shows an antiemetic effect, but also exhibits an inhalational anesthetic-sparing effect during pain stimulation in cats (Niyom *et al*., 2013). However, to the best of our knowledge, no study has reported that maropitant reduces the requirements of isoflurane which is the most common inhalational anesthetic in cats. In addition, no study has investigated the inhalational anesthetic-sparing effect of maropitant during laparotomy.

In the present study, isoflurane was selected for Ovario Hyst Erectomy (OHE) via. laparotomy in cats to investigate the inhalational anesthetic-sparing effect of maropitant and its effects on the respiratory and cardiovascular systems during anesthesia.

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## MATERIALS AND METHODS

**Patients:** The 20 Japanese domestic cats that were brought to Okano Animal Hospital for OHE between April, 2013 and August, 2014 were used in this study. This study was conducted with the approval of the director of the hospital and all owners of the cats used in this study consented to the collection of data for research purposes. These cats were evaluated as class 1 according to the American Society of Anesthesiologists classification system (Ament, 1979), based on age, weight, general condition, physical examination, complete blood count, blood chemical analysis and electrocardiography. They were randomlydivided into two groups a control group (n = 10 age, 6.8±0.9 months weight, 2.6±0.3 kg) and a maropitant (MAR) group (n = 10; age, 7.2±1.1 months weight, 2.4±0.3 kg).

**Premedication and induction of anesthesia:** An indwelling catheter (Supercath 24 G, Medikit Inc., Tokyo, Japan) was placed in the right or left cephalic vein of all 20 cats at 15 min before induction of general anesthesia. Maropitant (Cerenia®, Zoetis Japan Inc., Tokyo, Japan) was slowly administered intravenously at 1 mg/kg$^{-1}$ (0.1 mL/kg$^{-1}$) to the MAR group whereas physiological saline (Otsuka Physiological Saline, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was administered intravenously at 0.1 mL/kg$^{-1}$ to the control group. In addition, both groups received atropine sulfate (Atropine Sulfate, Fuso Pharmaceutical Industries Ltd., Osaka, Japan) subcutaneously at 0.05 mg/kg$^{-1}$, followed by buprenorphine (Lepetan® injection, Otsuka Pharmaceutical Co., Ltd.) and cefazolin (Rasenazolin® injection, Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan), administered intravenously at 0.02 mg/kg$^{-1}$ and 25 mg/kg $^{-1}$ respectively.

Anesthesia was induced by administering propofol (Rapinovet®, Intervet K.K., Tokyo, Japan) intravenously at 4-6 mg kg$^{-1}$ while 100% oxygen was inhaled through a mask. Once spontaneous breathing became weak with loss of consciousness and adequate suppression of laryngeal reflex, a cuffed endotracheal tube (PV soft endotracheal tube, standard cuffed type, Fuji Systems Co., Ltd., Tokyo, Japan) was inserted into the trachea of the cats. Following intubation, inhalational anesthesia was initiated by controlling the vapor volume of isoflurane (ISOFLU®, DS Pharma Animal Health Co., Ltd., Osaka, Japan) with an isoflurane vaporizer (IsoRex I-200, Shin-Ei Industries Inc., Saitama, Japan).

**Perioperative management of respiration, temperature and circulation:** All 20 cats received 100% oxygen for respiratory management during anesthesia. The ventilator parameters were set as follows: respiratory rate at 8 times min$^{-1}$, tidal volume at 15-20 mL/kg$^{-1}$, inspiratory/expiratory ratio = 1:2 and End-Tidal Carbon dioxide concentration ($ETCO_2$) at 35-40 mmHg. A warm water recirculator (T-pump TP-401, IMI Co., Ltd., Saitama, Japan) and heating pad were used to maintain body temperature perioperatively. Once anesthesia was induced, lactated Ringer's solution (SOLULACT®, Terumo Co., Tokyo, Japan) was administered via. intravenous infusion (10 mL/kg$^{-1}$/h$^{-1}$) to both groups and the flow rate of the solution was maintained evenly throughout the surgery. If any circulatory abnormality was observed, appropriate circulatory treatment was performed in both groups.

**Monitoring of anesthesia:** The heart rate, peripheral oxygen saturation ($SpO_2$), non-invasive Mean Arterial Blood Pressure (MABP), $ETCO_2$, End-Tidal isoflurane concentration ($ET_{ISO}$), and body temperature were measured using a veterinary patient monitor (AM-120_CFukuda M-E Kogyo Co., Ltd., Tokyo, Japan). In this study, esophageal temperature was measured as an index of body temperature. The results obtained at 15 min after initiating inhalational anesthesia were set as the baseline values (Time 0, $T_0$). The respective measurements were repeated at the following time points: during skin incision ($T_1$), left ovarian traction stimulation ($T_2$), right ovarian traction stimulation ($T_3$), uterine traction stimulation ($T_4$), start of abdominal closure ($T_5$) and start of skin suture ($T_6$). The time from induction of anesthesia to the end of isoflurane inhalation (anesthesia time), the time from the induction of anesthesia to the skin incision (surgery preparation time), the time from the skin incision to the end of abdominal closure (total surgery time), the duration of each period from $T_0$-$T_6$ (each surgery time) and the time from stopping isoflurane inhalation to recovery of laryngeal reflex and endotracheal tube removal (extubation time) were also measured.

**Method of adjusting isoflurane concentration:** The $ET_{ISO}$ displayed on the veterinary patient monitor was used as the index for isoflurane concentration. At $T_0$, isoflurane concentration was set at 2.0%. In the period from $T_1$-$T_6$, the concentration was reduced in a stepwise manner by 0.1% each time (to a maximum reduction of 1.5%). If the heart rate increased by = 20% from $T_0$, isoflurane concentration was temporarily increased. If an increase in isoflurane concentration resulted an increase in heart rate by = 10% from $T_0$, the isoflurane concentration was returned to the level at last time when the increase in heart rate was observed and the surgery was restarted. The number of cats with a heart rate that increased by = 20% from $T_0$ was also recorded.

**Surgical procedure:** The abdomen was opened using a routine procedure through a midline incision approach ($T_1$). First, the left ovarian ligament was grasped using mosquito forceps and the left ovary was pulled up from the abdominal cavity ($T_2$). After the ovarian ligament was cut, the ovarian artery and vein were ligated using absorbable sutures (VICRYL®, Johnson and Johnson K.K., Tokyo, Japan) and these vessels were cut using surgical scissors. The same procedure was performed for the right ovary ($T_3$). After the broad ligament of the uterus was isolated, it was pulled up from the abdominal cavity ($T_4$). The caudal uterine body was then ligated with an encircling ligature, using the same absorbable sutures, followed by resection of the uterine body. Thus, the ovaries and entire uterus were extracted (Cheryl, 2007; Fransson, 2012). Subsequently, the abdominal cavity was closed ($T_5$), followed by closure of the subcutaneous tissue and skin ($T_6$).

**Postsurgical management:** After the abdominal cavity was closed, bupivacaine (Marcaine®, AstraZeneca K.K., Osaka, Japan) which was diluted with 1-2 mL of saline solution was administrated locally around the suture wound at a concentration of 1 mg/kg$^{-1}$ for postoperative analgesia. Furthermore, meloxicam (Metacam®, Beohringer Ingelheim Vetmedica Japan Inc., Tokyo, Japan) was administered at 0.3 mg/kg$^{-1}$ subcutaneously and the isoflurane inhalational anesthetic was then discontinued. Once the laryngeal reflex recovered, the endotracheal tube was removed.

**Statistical analysis:** The measured values of this study were expressed as mean±standard deviation. Statistical analysis of the data was performed using the StatMate IV Software package (ATMS Co., Ltd., Tokyo, Japan). Welch's t-test was used to compare age, weight, measurement values obtained from the veterinary patient monitor, anesthesia time, surgery preparation time, total surgery time, each surgery time and extubation time between the two groups. Fisher's exact probability test was used to compare the number of cats with a heart rate that increased by ≥20% from T0. In this study, a p value below 0.05 was considered statistically significant.

## RESULTS AND DISCUSSION

**Patient data and each surgery time during anesthesia:** No significant difference was observed in the age, weight, surgery preparation time, total surgery time, each surgery time, anesthesia time and extubation time between the two groups (Table 1). Induction of anesthesia, endotracheal intubation, OHE and awakening were uneventful in all cats.

Table 1: Patient data and each time during anesthesia

| Description | Control | MAR |
|---|---|---|
| Age (months) | 6.8±0.9 | 7.2±1.1 |
| Weight (kg) | 2.6±0.3 | 2.4±0.3 |
| Surgery preparation time (min) | 22.5±3.6 | 21.6±3.1 |
| Total surgery time (min) | 33.1±4.3 | 31.8±4.1 |
| Each surgery time | | |
| T1: Skin incision (min) | 0.00 | 0.00 |
| T2: Left ovarian traction stimulation (min) | 5.3±1.4 | 4.4±2.1 |
| T3: Right ovarian traction stimulation (min) | 10.0±2.4 | 8.7±2.3 |
| T4: Uterine traction stimulation (min) | 14.1±2.4 | 12.8±2.3 |
| T5: Abdominal closure (min) | 20.7±4.3 | 19.3±3.7 |
| T6: Skin suture (min) | 27.4±4.3 | 25.5±3.5 |
| Anesthesia time (min) | 55.6±7.3 | 53.4±4.5 |
| Extubation time (min) | 8.3±2.0 | 8.7±1.8 |

Table 2: Changes in isoflurane requirement during each surgery time and the number of cats with increased heart rate

| | $ET_{ISO}$ (%) | | Number of cats with increased heart rate | |
|---|---|---|---|---|
| Parameters | Control | MAR | MAR | Control |
| $T_1$ | 2.00 | 2.00 | 2 | 1 |
| $T_2$ | 1.92±0.04 | 1.91±0.03 | 6 | 1* |
| $T_3$ | 1.88±0.06 | 1.82±0.06 | 3 | 1 |
| $T_4$ | 1.81±0.07 | 1.74±0.06 | 1 | 0 |
| $T_5$ | 1.72±0.07 | 1.64±0.06* | 0 | 0 |
| $T_6$ | 1.62±0.07 | 1.53±0.06* | 0 | 0 |
| Average | 1.83±0.14 | 1.77±0.16* | | |

*Indicates a significant difference with the control group ($p<0.05$)

**Changes in isoflurane requirement and number of cats with increased heart rate:** The mean isoflurane requirements from $T_1$ and $T_6$ were 1.83±0.14 and 1.77± 0.16% in the control and MAR groups, respectively. The isoflurane requirement was reduced by 3.2% due to administration of maropitant, although no significant difference was observed (Table 2). The isoflurane requirements in the MAR group were significantly lower than those in the control group at $T_4$, $T_5$ and $T_6$ ($p< 0.05$), and the requirement decreased by approximately 5.5% at $T_6$ (Table 2). The number of cats with a heart rate that increased by = 20% from $T_0$ was the highest at $T_2$; this was observed in 6 of the 10 cats (60%) in the control group but in only 1 of the 10 cats (10%) in the MAR group ($p<0.05$) (Table 2).

**Effect of the respiratory and circulatory systems:** During surgery, the values for heart rate, $SpO_2$, MABP and $ETCO_2$ were maintained at 130-150 beats min, 98-100 %, 80-110 mmHg and 28-32 mmHg, respectively (Table 3). Because the heart rate did not decrease to ≤80 beats minute$^{-1}$ in either of the groups in this study, circulatory intervention such as atropine administration was not performed. Body temperature varied in the range of 37.7-38.2°C; however, body temperature tended to decrease with the passage of time from the induction of anesthesia (Table 3). The statistical analysis results showed no significant difference in these values between the two groups.

Table 3: Effect on the respiratory and circulatory systems

| | HR (beats minute$^{-1}$) | | $SpO_2$ (%) | | MABP (mmHg) | | $ETCO_2$ (mmHg) | | Temp (°C) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameters | Control | MAR | Control | MAR | Control | MAR | Control | MAR | Control | MAR |
| $T_0$ | 149.5±12.1 | 148.3±9.60 | 98.9±0.7 | 99.0±0.8 | 96.2±15.1 | 97.2±14.6 | 31.9±3.1 | 31.3±2.8 | 38.2±0.5 | 38.1±0.5 |
| $T_1$ | 153.5±14.1 | 150.6±9.50 | 99.1±0.8 | 99.4±0.7 | 97.2±12.1 | 97.7±13.0 | 32.0±2.1 | 30.8±2.9 | 38.1±0.6 | 38.0±0.6 |
| $T_2$ | 161.2±10.1 | 154.3±8.10 | 99.2±0.7 | 99.2±0.6 | 98.7±11.3 | 99.2±13.9 | 31.6±2.4 | 33.3±4.2 | 38.0±0.6 | 38.0±0.6 |
| $T_3$ | 155.2±13.4 | 151.9±12.5 | 99.3±0.8 | 99.1±0.5 | 97.7±13.4 | 98.2±14.6 | 32.2±3.0 | 32.8±3.3 | 37.9±0.7 | 37.9±0.7 |
| $T_4$ | 151.5±11.7 | 149.3±7.20 | 99.0±0.8 | 98.9±0.5 | 98.4±12.6 | 97.0±12.2 | 31.5±3.4 | 30.9±2.8 | 37.9±0.7 | 37.9±0.7 |
| $T_5$ | 150.5±12.8 | 148.7±10.7 | 98.7±0.8 | 98.9±0.3 | 97.8±17.4 | 97.3±18.6 | 31.2±2.1 | 30.9±3.6 | 37.8±0.6 | 37.8±0.6 |
| $T_6$ | 149.1±10.0 | 148.3±10.9 | 98.8±0.9 | 99.2±0.4 | 98.7±13.0 | 97.2±14.0 | 33.1±4.3 | 31.1±3.9 | 37.7±0.7 | 37.8±0.8 |

HR, heart rate; $SpO_2$, peripheral oxygen saturation; MABP, non-invasive mean arterial pressure; $ETCO_2$, the end-tidal carbon dioxide concentration; Temp, esophageal temperature

OHE is a surgical procedure that is performed on a daily basis in cats and the pain level ranges from mild to moderate (Cheryl, 2007; Gaynor and Muir, 2009; Fransson, 2012). Therefore, use of opioids such as buprenorphine and butorphanol is also recommended for preemptive analgesia in cats. Hence, these opioids are generally used in perioperative pain management for OHE in cats (Gaynor and Muir, 2009; Clarke and Trim, 2014). In the present study, buprenorphine was selected as the opioid and used for perioperative pain management for OHE in both groups. In addition to buprenorphine maropitant which is an NK1 receptor antagonist was administered in the MAR group. Consequently, maropitant significantly reduced the isoflurane requirements of the cats undergoing OHE. These results suggest that maropitant might exert an isoflurane-sparing effect in cats.

Neither a decrease in the inhalational anesthetic requirement nor an analgesic effect can be observed in humans even when NK1 receptor antagonists are administered (Hill, 2000). Conversely, several studies have reported that maropitant reduces the inhalational anesthetic requirement and exerts an analgesic effect in dogs (Boscan *et al*., 2011; Alvillar *et al*., 2012). In our previous study, maropitant significantly reduced the isoflurane requirement in dogs undergoing OHE via. laparotomy (Okano *et al*., 2015). Similarly, the isoflurane requirement could also be reduced by the inhibitory effect of maropitant on the binding of SP to NK1 receptors in cats. In addition, opioids such as buprenorphine are known to inhibit the release of neurotransmitters such as SP (Duncan, 2012). Hence, the isoflurane requirement might be reduced by both the inhibition of SP release by buprenorphine and the inhibition of binding between SP and NK1 receptors by maropitant.

In the present study, the isoflurane requirement at $T_6$ in the MAR group decreased by approximately 5.5% compared to that in the control group. However, the degree of decrease in the inhalational anesthetic requirement tended to be smaller than that in previous study using cats. In a previous study on ovarian traction stimulation via. a laparoscopic procedure after the administration of maropitant at 1 mg/kg$^{-1}$, the sevoflurane requirement decreased by 15% (Niyom *et al*., 2013). The decrease in the inhalational anesthetic requirement in the present study might have been lower than that in the aforementioned report because of differences in the type of inhalational anesthetic and surgical procedures used. In other words, the decrease in the inhalational anesthetic requirement may have been low because of study design. In the present study, the isoflurane concentration was reduced by 0.1% at each time point in a stepwise manner, and the concentration was not reduced to 1.5%. For the MAR group, the concentration could likely have been reduced to 1.4% or lower. However, this study was not conducted on experimental animals but on clinical cases, and from the viewpoint of pain management for cats, a maximum reduction in the isoflurane concentration of 1.5% was the limit of this study.

In this study, the percentage of cats with increased heart rates at the $T_2$ was 60% in the control group but only 10% in the MAR group. The significant difference in this percentage between the two groups may have been caused by the analgesic effect of maropitant, although, heart rate may not be suitable as an analgesic index during general anesthesia in cats. Niyom *et al*. (2013) reported that ovarian traction stimulation model is useful for visceral stimulation in cats. As such it is suggested that ovarian traction stimulation induces pain in OHE. In the present study, the isoflurane requirement at $T_3$ in the MAR group was also significantly lower than that at $T_3$ in the control group and ovary retraction occurred at $T_2$ and $T_3$. On the basis of these results, maropitant might be effective in inhibiting the pain associated with ovarian traction stimulation.

Few studies have been conducted on the use of maropitant in cats compared with those on dogs. In a study on xylazine-induced emesis, maropitant was more effective in intravenous administration than in subcutaneous administration (Hickman *et al*., 2008). It has been reported that the half-life of plasma drug concentration following intravenous administration in

cats ranges from 13-17 h which is longer than that in dogs (Benchaoui *et al*., 2007a; Hickman *et al*., 2008). When administering maropitant intravenously, it is important to injection over 1-2 min. If maropitant is administered intravenously as a premedication of anesthesia, it is necessary to know this information.

In the present study, no cats exhibited a major clinical adverse reaction associated with the intravenous administration of maropitant. These findings demonstrate that maropitant is a drug that can be safely used perioperatively in cats. In addition, the fact that an isoflurane-sparing effect and antiemetic effect could be seen, suggests that maropitant is likely to be clinically useful as a premedication drug.

## CONCLUSION

In the present study, the preoperative administration of maropitant exerted an isoflurane-sparing effect without causing severe adverse reactions. These results suggest that maropitant may prove useful as a premedication drug in cats in clinical practice.

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