

Effects of Carprofen and Meloxicam with or without Butorphanol on the Minimum Alveolar Concentration of Sevoflurane in Dogs

Kazuto YAMASHITA¹*, Yoshihiko OKANO¹, Maiko YAMASHITA¹, Mohammed A. UMAR¹, Tokiko KUSHIRO¹ and William W. MUIR²

¹Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069–8501 Japan and ²Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210–1089, U.S.A.

(Received 19 February 2007/Accepted 11 September 2007)

ABSTRACT. Sparring effects of carprofen and meloxicam with or without butorphanol on the minimum alveolar concentration (MAC) of sevoflurane were determined in 6 dogs. Anesthesia was induced and maintained with sevoflurane in oxygen, and MAC was determined by use of a tail clamp method. The dogs were administered a subcutaneous injection of carprofen (4 mg/kg) or meloxicam (0.2 mg/kg), or no medication (control) one hour prior to induction of anesthesia. Following the initial determination of MAC, butorphanol (0.3 mg/kg) was administered intramuscularly, and MAC was determined again. The sevoflurane MACs for carprofen alone ($2.10 \pm 0.26\%$) and meloxicam alone ($2.06 \pm 0.20\%$) were significantly less than the control ($2.39 \pm 0.26\%$). The sevoflurane MACs for the combination of carprofen with butorphanol ($1.78 \pm 0.20\%$) and meloxicam with butorphanol ($1.66 \pm 0.29\%$) were also significantly less than the control value after the administration of butorphanol ($2.12 \pm 0.28\%$). The sevoflurane sparing effects of the combinations of carprofen with butorphanol and meloxicam with butorphanol were additive.

KEY WORDS: canine, carprofen, meloxicam, minimum alveolar concentration (MAC), sevoflurane.

J. Vet. Med. Sci. 70(1): 29–35, 2008

Preemptive analgesia (i.e., treatment using analgesic drugs before pain occurs) reduces the amount of anesthetic drug required to produce and maintain surgical anesthesia, helps to stabilize anesthesia, reduces the total amount of analgesic drugs required to control pain both intraoperatively and postoperatively, and decreases overall patient morbidity associated with surgery and anesthesia [23]. Preemptive opioid administration decreases the amount of volatile anesthetic agent required to produce general anesthesia, as evidenced by a decrease in the minimum alveolar concentration (MAC) of volatile anesthetics [13, 21, 25, 27]. Perioperative administration of ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), reduces the requirement for isoflurane during surgery by an amount similar to that observed following administration of opioid analgesics in humans [21].

The combination and administration of analgesic drugs that act by different mechanisms, “multimodal therapy”, is often advocated to maximize analgesic drug effects [23]. The administrations of two major analgesics, NSAIDs and opioids, have long been used for pain management in dogs and other animals [2, 6, 33]. Carprofen and meloxicam are NSAIDs that have been shown to produce analgesic effects with minimal side effect in dogs [6, 34]. Butorphanol is an opioid agonist-antagonist frequently administered either intramuscularly or intravenously as preanesthetic medication to manage pain in dogs [12, 33, 35–37]. The co-administration of oral carprofen and intravenous butorphanol

produces additive decreases in the minimum alveolar concentration (MAC) of isoflurane in dogs [16]. Potential benefits of decreasing the amount of inhalant anesthetic required to maintain anesthesia include decrease in dose-related cardiorespiratory depression, inhalant anesthetic pollution, and cost of anesthesia. It is expected that the preoperative administration of carprofen or meloxicam combined with butorphanol would provide these benefits in dogs.

Sevoflurane is a volatile anesthetic with a relatively low blood/gas solubility coefficient resulting in rapid induction and recovery from anesthesia [24]. The effect of carprofen or meloxicam administered alone on sevoflurane MAC in dogs has not been reported. Furthermore, the interaction between carprofen or meloxicam and butorphanol on sevoflurane in dogs has not been evaluated. The purpose of the study reported here was to evaluate the sparing effects of carprofen and meloxicam with or without butorphanol on the MAC of sevoflurane in dogs.

MATERIALS AND METHODS

Experimental animals: Six beagle dogs aged 2 years and weighing between 9.4–12.0 kg were used for this study. The dogs were cared for according to the principles of the “Guide for the Care and Use of Laboratory Animals” prepared by Rakuno Gakuen University. All dogs were judged to be in good to excellent health based upon a physical examination, complete blood cell count, and serum biochemical analysis. Food and water were withheld for 12 hr before beginning the experiment. All six dogs were anesthetized with sevoflurane on three occasions (*Experimental*

* CORRESPONDENCE TO: YAMASHITA, K., Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069–8501, Japan.
e-mail: yamasita@rakuno.ac.jp

treatments-A, B, and C) with randomized crossover study design, separated by a minimum of 7 days.

Experimental treatment-A: One hour prior to induction of anesthesia, dogs were administered carprofen (Rimadyl Injectable, Pfizer Japan, Tokyo, Japan) at a dose of 4 mg/kg subcutaneously (SC). The MAC of sevoflurane was determined (carprofen alone) and butorphanol (Vetorphale, Meiji Seika Co., Tokyo, Japan), 0.3 mg/kg intramuscularly (IM), was administered and MAC was redetermined (carprofen with butorphanol).

Experimental treatment-B: One hour prior to induction of anesthesia, dogs were administered meloxicam (Metacam 0.5 % Injectable, Boehringer-Ingelheim Vetmedica Japan, Kawanishi, Japan) at a dose of 0.2 mg/kg SC. The MAC of sevoflurane was determined (meloxicam alone) and butorphanol, 0.3 mg/kg IM, was administered and MAC was redetermined (meloxicam with butorphanol).

Experimental treatment-C: The MAC of sevoflurane was determined without prior drug administration (control). Butorphanol 0.3 mg/kg IM was administered and MAC was redetermined (control with butorphanol).

Anesthesia and instrumentation: Anesthesia was induced by mask induction using sevoflurane (Sevoflo, Dainippon-Sumitomo Pharma, Osaka, Japan) in oxygen. A 33-Fr cuffed endotracheal tube (Phicon, Fuji Systems Co., Tokyo, Japan) was positioned in the trachea and the dogs were placed in right lateral recumbency. Anesthesia was maintained with sevoflurane in oxygen (2 L/min) delivered via a circle anesthetic rebreathing system (Beaver 20, Kimura Medical Instrument Co., Tokyo, Japan) with an out-of-circuit vaporizer (Sevotech III, Ohmeda, Datex-Ohmeda, Tokyo, Japan). The end-tidal partial pressure of CO₂ (PETCO₂) was maintained between 35 and 40 mmHg by intermittent positive pressure ventilation (IPPV) using a time-cycled ventilator (Nuffield Anesthesia Ventilator Series 200, Penlon, Abingdon Oxon, U.K.). All dogs were administered lactated Ringer's solution (Solulact, Terumo, Tokyo, Japan) at a rate of 10 ml/kg/hr intravenously (IV) through a 22-gauge catheter (Happycath Z, Medikit Co., Tokyo, Japan) placed in the left cephalic vein. Esophageal temperature was maintained between 37.5 and 38.0°C, using a heating pad (Micro-Temp II, Cincinnati Sub-Zero Products, Cincinnati, U.S.A.) and a warm air blanket (FK-CL3, Sanyo Electric, Moriguchi, Japan).

Esophageal temperature (°C), heart rate (beats/min), cardiac rhythm, respiratory rate (breaths/min), PETCO₂ (mmHg), end-tidal concentration of sevoflurane (ETSEV; %), indirect blood pressure (mmHg), and saturation of hemoglobin with oxygen (SpO₂; %) 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. Heart rate and cardiac rhythm were monitored by visual inspection of Lead II of the electrocardiogram. Blood pressure was determined by the oscillometric method. The SpO₂ was measured by pulse oximetry. A commercially available adaptor (Airway adap-

tor L-shape, Omron Colin Co.) modified with an 8-Fr feeding tube (Safeed feeding tube, Terumo) was placed at the Y-piece of the breathing circuit. The tube passed through the endotracheal tube so that its tip rested in the thoracic portion of the trachea. A side-stream capnograph and anesthetic agent monitor was used to determine respiratory rate, PETCO₂, and ETSEV. The anesthetic agent monitor was calibrated immediately prior to each sevoflurane MAC determination, using a commercial calibration kit (AG calibration gas and adaptor set, Omron Colin Co.).

MAC determination: The MAC of sevoflurane was determined by use of the tail clamp method [10, 16], with minor modifications. Briefly, dogs were allowed to equilibrate for 30 min at ETSEV 2.4%. The hair was clipped from a section of the tail with a diameter approximately equivalent to the diameter of a standard Backhaus towel clamp. After the equilibration, a towel clamp was then 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. Purposeful movement was defined as substantial movement of the head or extremities and did not include coughing, chewing, swallowing, or an increased respiratory effort. The clamp circumscribed the tail and did not puncture the skin of the dog thereby producing a blunt force on the tail [16].

If the dog exhibited any purposeful movement in response to tail clamping, the ETSEV was increased by 10–20%, and the dog was retested after 20 min of re-equilibration. If the dog did not exhibit any purposeful movement in response to tail clamping, ETSEV was reduced by 10–20%, and the dog was retested after 20 min of re-equilibration. Testing continued until the lowest ETSEV at which the dog did not demonstrate purposeful movement in response to tail clamping was determined. The MAC was calculated as the mean of the ETSEV at which the dog did not demonstrate purposeful movement and the next lower concentration tested (i.e., the highest concentration at which the dog still demonstrates purposeful movement in response to tail clamping). The MAC for each dog was determined in triplicate. Cardiorespiratory data were collected immediately before MAC determinations. The observer was not aware of the group allocation of each dog.

After the determination of sevoflurane MAC, dogs received the intramuscular injection of butorphanol and allowed to equilibrate for 20 min at the ETSEV equal to the determined sevoflurane MAC in each dog before the administration of butorphanol. Then, the MAC was redetermined and cardiorespiratory data were collected in similar manner.

Statistical analysis: Data are reported as mean ± standard deviation. The cardiorespiratory data and MAC were compared between carprofen alone, meloxicam alone, and control, and between carprofen with butorphanol, meloxicam with butorphanol, and control with butorphanol. These data were analyzed by use of one-way factorial ANOVA and Fisher's PLSD test.

Percentage MAC reductions were also compared between carprofen alone and meloxicam alone, and between

carprofen with butorphanol and meloxicam with butorphanol. The percentage MAC reduction was calculated as: Percentage MAC reduction = (MAC of control - MAC of treatment without butorphanol) / MAC of control \times 100 or (MAC of control with butorphanol - MAC of treatment with butorphanol) / MAC of control with butorphanol \times 100. These data were analyzed by use of one-way factorial ANOVA.

A drug interaction of carprofen and butorphanol or meloxicam and butorphanol was evaluated as to whether the changes in cardiorespiratory data and MAC values produced by the administration of butorphanol departed from those of control. The changes observed in dogs treated with carprofen or meloxicam were compared with those observed in control dogs by use of two-way repeated-measures ANOVA. If a significant difference was obtained with a significant interaction, the drug interaction between carprofen and butorphanol or between meloxicam and butorphanol was judged to be synergistic or antagonistic. If a significant difference was obtained without any significant interaction, the drug interaction was judged to be additive. For all analyses, values of $P < 0.05$ were considered significant.

RESULTS

It took 177.2 ± 21.1 min, 161.3 ± 9.5 min, or 148.3 ± 21.1 min after the induction of anesthesia to get the triplicate data of sevoflurane MAC in dogs that received preanesthetic treatment with carprofen, dogs that received preanesthetic treatment with meloxicam, or control dogs that received no preanesthetic treatment, respectively (Fig. 1). The MAC determinations were completed in less than 180 min after the induction of anesthesia, although there was a statistically significant difference in the duration of MAC determination between the dogs pretreated with carprofen and the control dogs ($P = 0.005$). On the other hand, the triplicate MAC determinations were completed at 165.2 ± 29.0 min, 168.3 ± 24.7 min, or 168.5 ± 13.5 min after the administration of butorphanol in dogs pretreated with carprofen, dogs pretreated with meloxicam, or the control dogs, respectively. There was no significant difference between treatments.

The preanesthetic treatment with carprofen or meloxicam significantly decreased the MAC of sevoflurane (carprofen alone: $2.10 \pm 0.26\%$, $P = 0.031$; meloxicam alone: $2.06 \pm 0.20\%$, $P = 0.016$), compared to the control value ($2.39 \pm 0.26\%$). The administrations of carprofen with butorphanol ($1.78 \pm 0.20\%$, $P = 0.047$) and meloxicam with butorphanol ($1.66 \pm 0.29\%$, $P = 0.009$) significantly decreased sevoflurane MAC, compared to the control with butorphanol ($2.12 \pm 0.28\%$). There was no significant difference in the sevoflurane MAC values between carprofen alone and meloxicam alone ($P = 0.741$) and between carprofen with butorphanol and meloxicam with butorphanol ($P = 0.420$). The percentage MAC reductions were $11.3 \pm 8.3\%$ in carprofen alone, $12.9 \pm 10.2\%$ in meloxicam alone, $14.9 \pm 9.4\%$ in carprofen with butorphanol, and $21.3 \pm 11.4\%$ in meloxicam with butorphanol. There was no significant dif-

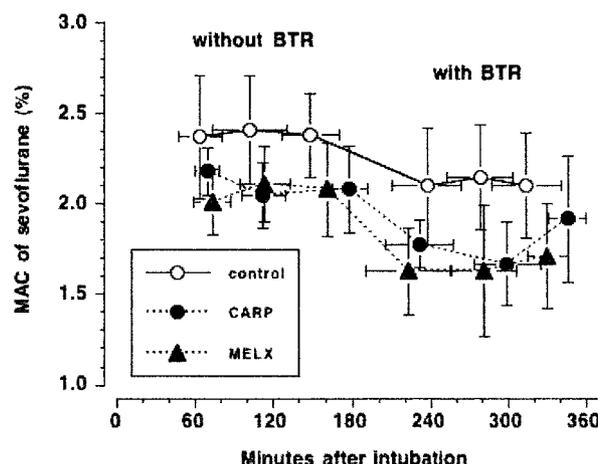


Fig. 1. Minimum alveolar concentration (MAC) of sevoflurane and duration of MAC determination following no preanesthetic drug (control) and a subcutaneous injection of carprofen 4 mg/kg (CARP) or meloxicam 0.2 mg/kg (MELX) in dogs. The MAC was determined in triplicate without (without BTR) and with an intramuscular injection of butorphanol 0.3 mg/kg (with BTR). Plots and error bars represent mean values and standard deviations, respectively for 6 dogs. The MAC determinations without BTR were completed in less than 180 min after the induction of anesthesia. There was a significant difference in the duration of MAC determination between CARP and control ($P = 0.005$). The MAC determinations with BTR were completed in less than 180 min after the administration of butorphanol in all treatments with no significant difference. The preanesthetic treatment with CARP ($2.10 \pm 0.26\%$, $P = 0.031$) or MELX ($2.06 \pm 0.20\%$, $P = 0.016$) significantly decreased the MAC, compared to control ($2.39 \pm 0.26\%$). The administrations of CARP with BTR ($1.78 \pm 0.20\%$, $P = 0.047$) and MELX with BTR ($1.66 \pm 0.29\%$, $P = 0.009$) significantly decreased the MAC, compared to control with BTR ($2.12 \pm 0.28\%$).

ference in the percentage MAC reductions between carprofen alone and meloxicam alone ($P = 0.764$) and between carprofen with butorphanol and meloxicam with butorphanol ($P = 0.207$).

Throughout the present study, the heart rate and indirect mean blood pressure (IMBP) collected immediately before the determination of sevoflurane MAC were within the normal values for dogs in all dogs (Table 1). Normothermia and eucapnea were achieved by incubation and IPPV, respectively. Before the administration of butorphanol, IMBP was significantly higher in dogs pretreated with carprofen and dogs pretreated with meloxicam than control dogs ($P = 0.033$ or $P = 0.029$, respectively). After the administration of butorphanol, significant difference in IMBP was not detected between experimental treatments. Significant differences in SpO_2 were detected but were not of clinical importance.

Changes in IMBP and MAC produced by the administration of butorphanol were significantly different between the control dogs and the dogs pretreated with carprofen ($P = 0.016$ and $P = 0.029$, respectively) and between the con-

Table 1. Cardiorespiratory data collected immediately before the determination of minimum alveolar concentration (MAC) of sevoflurane following administration of no preanesthetic drug (control), carprofen, and meloxicam with or without the administration of butorphanol in dogs

Valuable	Treatments	
	Without butorphanol	With butorphanol 0.3 mg/kg IM
Esophageal temperature (°C)		
Control	37.9 ± 0.1	37.8 ± 0.1
Carprofen 4 mg/kg SC	37.9 ± 0.1	37.9 ± 0.1
Meloxicam 0.2 mg/kg SC	37.9 ± 0.1	37.9 ± 0.1
Heart rate (beats/min)		
Control	132 ± 11	118 ± 13
Carprofen 4 mg/kg SC	125 ± 16	108 ± 20
Meloxicam 0.2 mg/kg SC	124 ± 13	109 ± 25
IMBP (mmHg)		
Control	88.3 ± 9.2	81.6 ± 7.5
Carprofen 4 mg/kg SC	97.8 ± 7.1*	84.3 ± 8.1
Meloxicam 0.2 mg/kg SC	100.2 ± 9.8*	86.5 ± 7.5
SpO ₂ (%)		
Control	99.1 ± 1.6	99.8 ± 0.2
Carprofen 4 mg/kg SC	99.0 ± 0.7	99.1 ± 0.8†
Meloxicam 0.2 mg/kg SC	99.1 ± 0.6	99.9 ± 0.2
Respiratory rate (breaths/min)		
Control	11.9 ± 0.5	12.1 ± 0.3
Carprofen 4 mg/kg SC	11.9 ± 0.1	12.3 ± 0.8
Meloxicam 0.2 mg/kg SC	12.7 ± 1.3	13.1 ± 2.4
PETCO ₂ (mmHg)		
Control	37.6 ± 0.7	37.5 ± 0.3
Carprofen 4 mg/kg SC	37.8 ± 0.3	37.9 ± 0.7
Meloxicam 0.2 mg/kg SC	37.2 ± 1.4	37.4 ± 1.3

Data are expressed as mean ± standard deviation for 6 dogs. SC: subcutaneous injection, IM: intramuscular injection, SpO₂: saturation of hemoglobin with oxygen, IMBP: indirect mean blood pressure, PETCO₂: end-tidal partial pressure of carbon dioxide. Significantly different from control value: * $P < 0.05$. Significantly different from control value with the administration of butorphanol: † $P < 0.01$.

control dogs and the dogs pretreated with meloxicam ($P=0.034$ and $P=0.020$, respectively). The statistical interactions of the change in IMBP were significant between the control dogs and the dogs pretreated with carprofen ($P < 0.001$) and between the control dogs and the dogs pretreated with meloxicam ($P < 0.001$). Therefore, it indicates that effects of the combinations of carprofen with butorphanol and meloxicam with butorphanol on the improvement of blood pressure were antagonistic (Fig. 2a). The statistical interactions of the change in MAC were not significant between the control dogs and the dogs pretreated with carprofen ($P=0.676$) and between the control dogs and the dogs pretreated with meloxicam ($P=0.263$). Therefore, it indicates that sparing effects of the combination carprofen with butorphanol and meloxicam with butorphanol on MAC were additive (Fig. 2b).

DISCUSSION

In the present study, the control value of sevoflurane MAC was $2.39 \pm 0.26\%$, which is similar to the MAC of sevoflurane reported by Kazama and Ikeda [14] for a larger group of unmedicated dogs ($2.36 \pm 0.46\%$, $n=18$). The

administration of carprofen or meloxicam alone slightly but significantly reduced the MAC of sevoflurane. The combinations of carprofen with butorphanol and meloxicam with butorphanol provided additive sevoflurane-sparing effects without causing severe cardiac depression in dogs.

NSAIDs produce analgesic, anti-inflammatory, and antipyretic effects by nonspecifically inhibiting various isoforms of arachidonate cyclooxygenase (COX), thereby inhibiting the production of prostaglandins [6]. The COX appears in 2 isoforms: COX-1, which is observed under physiological conditions and is responsible for the synthesis of prostaglandins that protect the organism, and COX-2, the isoform induced by inflammatory stimuli and pathological conditions [6]. NSAIDs are classified depending on the activity of each isoform as nonselective COX inhibitors and COX-2 selective inhibitors [6]. Carprofen and meloxicam are COX-2 selective inhibitors that have been shown to produce analgesic effects with minimal side effect in dogs [5, 6, 15, 34]. Their preoperative administration to dogs undergoing ovariohysterectomy has been reported to produce a greater analgesic effect in the early postoperative period than does postoperative administration [18, 19]. Also carprofen and meloxicam have been reported to relieve signs of

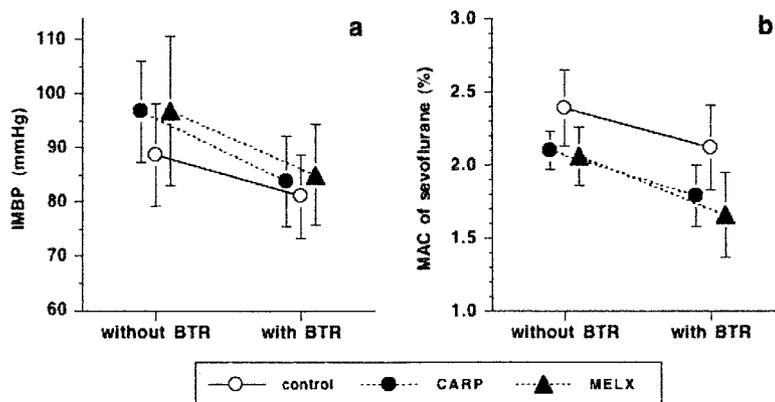


Fig. 2. Changes in indirect mean blood pressure (IMBP) and minimum alveolar concentration (MAC) of sevoflurane in dogs treated with no preanesthetic drug (control), a subcutaneous injection of carprofen 4 mg/kg (CARP), or meloxicam 0.2 mg/kg (MELX) before and after an intramuscular injection of butorphanol 0.3 mg/kg (BTR). Plots and error bars represent mean values and standard deviations, respectively for 6 dogs. Effects of both combinations of carprofen with butorphanol and meloxicam with butorphanol on the improvement of blood pressure were antagonistic (a). Sparing effects of these combinations on sevoflurane MAC were additive (b).

pain for up to 24 hr in dogs undergoing orthopaedic surgery [7, 17].

However, it is unclear whether preoperative administration of carprofen or meloxicam reduces inhalant anesthetic requirements. Alibhai and Clarke [1] reported that carprofen minimally influenced the MAC of halothane in dogs. On the other hand, Ko *et al.* [16] reported that preoperative oral administration of carprofen alone produced $6.24 \pm 3.42\%$ of the percentage MAC reduction, but the isoflurane-MAC values were not significantly different from control ($0.90 \pm 0.21\%$ vs $1.03 \pm 0.22\%$, $P=0.069$). In the present study, the preoperative subcutaneous administration of carprofen or meloxicam alone produced $11.3 \pm 8.3\%$ or $12.9 \pm 10.2\%$ reduction of the percentage MAC, respectively, that were significantly different compared to control. The MAC of sevoflurane is approximately 1.6 to 1.8 and 2.2 to 2.7 times greater than that for isoflurane and halothane, respectively, in dogs [14, 24]. Therefore, the differences in MAC values between control and carprofen or meloxicam alone were numerically larger and it may be due to satisfactory detection of statistical significances. Our result suggests that the preoperative administration of carprofen or meloxicam alone can provide a mild sparing effect on sevoflurane requirement in dogs.

Combinations of analgesic drugs have long been used in human patients to provide and enhance analgesia [2]. The combination of 2 or more analgesics with different mechanisms of action (i.e., multimodal therapy) may produce supra-additive (synergistic) effects [2, 23]. A synergistic sparing effect of a combination aspirin, a nonselective COX inhibitor, with morphine on isoflurane MAC has been observed in rats [28]. The mechanism of action of this effect has been identified as a synergistic synaptic interaction

between opioids and NSAIDs [32]. Activation of μ -opioid receptors in the periaqueductal gray (PAG) causes a presynaptic inhibition of γ -aminobutyric acid (GABA) release that is mediated by activation of a voltage-dependent K^+ channel via 12-lipoxygenase metabolites of arachidonic acid [32]. Furthermore, the action of μ -receptor agonists in the PAG is potentiated by inhibitors of COX and 5-lipoxygenase [32]. In the present study, however, the administration of carprofen or meloxicam in combination with butorphanol provided only additive sevoflurane-sparing effects in dogs. Similar results have been observed in dogs after administration of butorphanol in combination with carprofen [16] and rabbits after administration of butorphanol in combination with meloxicam [30]. There is conflicting information in the literature regarding the effect of butorphanol on the MAC of inhalant anesthetics in dogs [16, 25, 27]. One study [27], in which butorphanol was administered in doses up to 0.8 mg/kg IV, was unable to demonstrate alterations in halothane MAC values, whereas other studies demonstrated significant decreases in enflurane MAC values by $15 \pm 4\%$ after the administration of butorphanol up to 0.3 mg/kg IV [25] and in isoflurane MAC values by $20.26 \pm 12.91\%$ after the administration of 0.4 mg/kg IV butorphanol [16]. Butorphanol appears to be less effective than morphine on enflurane-MAC reduction in dogs [25]. Butorphanol is a synthetic opioid believed to exert its effects mainly at κ -opioid receptors and has minimal effect at μ -opioid receptors [33]. Possible explanations for the lack of a synergistic effect include the fact that morphine is a μ -opioid agonist, whereas butorphanol is a κ -opioid agonist [33].

Sevoflurane has dose-dependent depressant effects on cardiorespiratory function in dogs [26]. In the present study, heart rate and IMBP were within normal range in all

dogs during MAC determination. In addition, improvements in blood pressure associated with the sevoflurane-sparing effect were observed in both groups of dogs treated with carprofen and meloxicam alone, compared to control. However, these improvements of blood pressure were offset by the administration of butorphanol. It has been also reported that small but significant decreases in heart rate and arterial blood pressure occurred after the intravenous injection of butorphanol in dogs [29]. Renal dysfunction caused by decreases in renal perfusion may occur following the administrations of any NSAID and is a consequence of prostaglandin inhibition [6]. Although the intravenous injection of carprofen (4 mg/kg) or meloxicam (0.2 mg/kg) does not cause clinically important alterations of renal function when administered 1 hr before onset of anesthesia and surgery in young healthy dogs [9], decrease in blood pressure after the administration of butorphanol could impair renal blood flow and function in anesthetized dogs that are simultaneously treated with an NSAID. Arterial blood pressure should be monitored and maintained within a normal range during anesthesia when carprofen or meloxicam are administered with butorphanol as premedication for dogs.

Both clinical doses of carprofen and meloxicam provide effective postoperative analgesia when preoperatively administered [17–19], although meloxicam has higher in vitro selectivity of COX-2 inhibition than carprofen in dogs [5, 15]. We also did not find any difference in sevoflurane-sparing effect between the treatments with carprofen alone and meloxicam alone, and between carprofen with butorphanol and meloxicam with butorphanol in dogs. On the other hand, some differences in side effects between carprofen and meloxicam have been reported [3, 20]. A long-term oral administration of carprofen (4 mg/kg daily for 90 days) induces less frequency of gastrointestinal adverse effects than that of meloxicam (0.1 mg/kg daily for 90 days) in dogs [20]. Oral administration of meloxicam (0.1 mg/kg daily for 10 days) affects platelet function minimally in dogs with osteoarthritis whereas carprofen (4 mg/kg daily for 10 days) decreases clot strength and platelet aggregation [3]. The differences in side effects between carprofen and meloxicam should be considered when they are used preoperatively in dogs.

In conclusion, the pre-anesthetic administration of carprofen or meloxicam in combination with or without butorphanol decreased sevoflurane MAC values in dogs. The sparing effects of carprofen with butorphanol and meloxicam with butorphanol were additive. Preoperative administration of carprofen or meloxicam combined with butorphanol could provide clinically useful multimodal analgesia in dogs.

REFERENCES

- Alibhai, H. I. K. and Clarke, K. W. 1996. Influence of carprofen on minimum alveolar concentration of halothane in dogs. *J. Vet. Pharmacol. Ther.* **19**: 320–321.
- Beaver, W. T. 1984. Combination analgesics. *Am. J. Med.* **77**: 38–53.
- Brainard, B. M., Meredith, C. P., Callan, M. B., Budsberg, S. C., Shofer, F. S., Drissen, B. and Otto, C. M. 2007. Changes in platelet function, hemostasis, and prostaglandin expression after treatment with nonsteroidal anti-inflammatory drugs with various cyclooxygenase selectivities in dogs. *Am. J. Vet. Res.* **68**: 251–257.
- Breder, C. D., Dewitt, D. and Kraig, R. P. 1995. Characterization of inducible cyclooxygenase in rat brain. *J. Comp. Neurol.* **355**: 296–315.
- Brideau, C., Van Staden, C. and Chan, C. C. 2001. *In vitro* effects of cyclooxygenase inhibitors in whole blood of horses, dogs, and cats. *Am. J. Vet. Res.* **62**: 1755–1760.
- Budsberg, S. 2002. Nonsteroidal anti-inflammatory drugs. pp. 184–198. *In: Handbook of Veterinary Pain Management* (Gaynor, J. S. and Muir, W. W. 3rd. eds.), Mosby, St. Louis.
- Budsberg, S. C., Cross, A. R., Quandt, J. E., Pablo, L. S. and Runk, A. R. 2002. Evaluation of intravenous administration of meloxicam for perioperative pain management following stifle joint surgery in dogs. *Am. J. Vet. Res.* **63**: 1557–1563.
- Christie, M. J., Connor, M. A., Vaughan, C. W., Ingram, S. L. and Bagley, E. E. 2000. Cellular actions of opioids and other analgesics: implications for synergism in pain relief. *Clin. Exp. Pharmacol. Physiol.* **27**: 520–523.
- Crandell, D. E., Mathews, K. A. and Dyson, D. H. 2004. Effect of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation. *Am. J. Vet. Res.* **65**: 1384–1390.
- Eager, E. I. 2nd, Saidman, L. J. and Brandstater, B. 1965. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. *Anesthesiology* **26**: 756–763.
- Grimm, K. A., Tranquilli, W. J., Thurmon, J. C. and Benson, G. J. 2000. Duration of nonresponse to noxious stimulation after intramuscular administration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. *Am. J. Vet. Res.* **61**: 42–47.
- Hosgood, G. 1990. Pharmacologic features of butorphanol in dogs and cats. *J. Am. Vet. Med. Assoc.* **196**: 135–136.
- 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.
- Kazama, T. and Ikeda, K. 1988. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. *Anesthesiology* **68**: 435–437.
- Kay-Mugford, P., Benn, S. J., LaMarre, J. and Conlon, P. 2000. *In vitro* effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. *Am. J. Vet. Res.* **61**: 802–810.
- Ko, J. C., Lange, D. N., Mandsager, R. E., Payton, M. E., Bowen, C., Kamata, A. and Kuo, W. C. 2000. Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. *J. Am. Vet. Med. Assoc.* **217**: 1025–1028.
- Laredo, F. G., Belda, E., Murciano, J., Escobar, M., Navarro, A., Robinson, K. J. and Jones, R. S. 2004. Comparison of the analgesic effects of meloxicam and carprofen administered preoperatively to dogs undergoing orthopaedic surgery. *Vet. Rec.* **155**: 667–671.
- Lascelles, B. D., Cripps, P. J., Jones, A. and Waterman-Pearson, A. E. 1998. Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Vet. Surg.* **27**: 568–582.
- Leece, E. A., Brearley, J. C. and Harding, E. F. 2005. Comparison of carprofen and meloxicam for 72 hours following ovari-

- ohysterectomy in dogs. *Vet. Anaesth. Analg.* **32**: 184–192.
20. Luna, S. P., Basilio, A. C., Steagall, P. V., Machado, L. P., Moutinho, F. Q., Takahira, R. K. and Brandao, C. V. 2007. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. *Am. J. Vet. Res.* **68**: 258–264.
 21. Matthews, N. S. and Lindsay, S. L. 1990. Effect of low-dose butorphanol on halothane minimum alveolar concentration in ponies. *Equine Vet. J.* **22**: 325–327.
 22. Moss, J. T., Baysinger, C. L., Boswell, G. W. and Sayson, S. 1992. Possible intraoperative anesthetic-sparing effect of parenteral ketorolac. *Ann. Pharmacother.* **26**: 922–924.
 23. Muir, W. W. 3rd. 2002. Choosing and administering the right analgesic therapy. pp. 329–345. *In: Handbook of Veterinary Pain Management* (Gaynor, J. S. and Muir, W. W. 3rd. eds.), Mosby, St. Louis.
 24. Muir, W. W. 3rd, Hubbell, J. A. E., Skarda, R. T. and Bednarski, R. M. 2002. Inhalation anesthesia. pp. 154–163. *In: Handbook of Veterinary Anesthesia* 3rd ed. (Muir, W. W. 3rd et al. eds), Mosby, St. Louis.
 25. Murphy, M. R. and Hug, C. C. Jr. 1982. The enflurane sparing effect of morphine, butorphanol, and nalbuphine. *Anesthesiology* **57**: 489–492.
 26. Mutoh, T., Nishimura, R., Kim, H. Y., Matsunaga, S. and Sasaki, N. 1997. Cardiopulmonary effects of sevoflurane, compared with halothane, enflurane, and isoflurane, in dogs. *Am. J. Vet. Res.* **58**: 885–890.
 27. Quandt, J. E., Raffae, M. R. and Robinson, E. P. 1994. Butorphanol does not reduce the minimum alveolar concentration of halothane in dogs. *Vet. Surg.* **23**: 156–159.
 28. Santos, M., Kunkar, V., Garcia-Iturralde, P. and Tendillo, F. J. 2004. Meloxicam, a specific COX-2 inhibitor, does not enhance the isoflurane minimum alveolar concentration reduction produced by morphine in the rat. *Anesth. Analg.* **98**: 359–363.
 29. Trim, C. M. 1983. Cardiopulmonary effects of butorphanol tartrate in dogs. *Am. J. Vet. Res.* **44**: 329–331.
 30. Turner, P. V., Kerr, C. L., Healy, A. J. and Taylor W. M. 2006. Effect of meloxicam and butorphanol on minimum alveolar concentration of isoflurane in rabbits. *Am. J. Vet. Res.* **67**: 770–774.
 31. Vaughan, C. W. 1998. Enhancement of opioid inhibition of GABAergic synaptic transmission by cyclo-oxygenase inhibitors in rat periaqueductal grey neurons. *Br. J. Pharmacol.* **123**: 1479–1481.
 32. Vaughan, C. W., Ingram, S. L., Connor, M. A. and Christie, M. J. 1997. How opioids inhibit GABA-mediated neurotransmission. *Nature* **390**: 611–614.
 33. Wagner, A. E. 2002. Opioids. pp. 164–183. *In: Handbook of Veterinary Pain Management* (Gaynor, J. S. and Muir, W. W. 3rd. eds.), Mosby, St. Louis.
 34. Welsh, E. M., Nolan, A. M. and Reid, J. 1997. Beneficial effects of administering carprofen before surgery in dogs. *Vet. Rec.* **141**: 251–253.
 35. Yamashita, K., Harada, K., Yokoyama, T., Tsuzuki, K., Maehara, S., Seno, T., Izumisawa, Y. and Kotani, T. 2003. Combination of droperidol and butorphanol as premedication for inhalation anesthesia in dogs. *J. Jpn. Vet. Med. Assoc.* **56**: 325–331 (in Japanese with English summary).
 36. Yamashita, K., Ishihara, N., Tsuzuki, K., Koike, M., Isaka, M., Seno, T., Katoh, S., Izumisawa, Y., Kotani, T. and Muir, W. W. 2001. Combination of midazolam and butorphanol as premedication in dogs. *J. Jpn. Vet. Med. Assoc.* **54**: 476–482 (in Japanese with English summary).
 37. Yamashita, K., Koshi, M., Izumisawa, Y. and Kotani, T. 1999. Effect of combination of medetomidine and butorphanol for preanesthetic medication in dogs. *Jpn. J. Vet. Anesth. Surg.* **30**: 15–25 (in Japanese with English summary).