NOTE *Surgery*

Sparing Effect of Robenacoxib on the Minimum Alveolar Concentration for Blunting Adrenergic Response (MAC-BAR) of Sevoflurane in Dogs

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ABSTRACT. Robenacoxib is a newer nonsteroidal anti-inflammatory drug approved for dogs and cats. This study was designed to evaluate the effect of robenacoxib on the minimum alveolar concentration for blunting adrenergic response (MAC-BAR) of sevoflurane in dogs. Sevoflurane MAC-BAR was determined by judging dogs' response to a noxious electrical stimulus (50 V, 50 Hz and 10 msec) for 10 sec in 6 beagle dogs on two occasions at least a 7-day interval. In each occasion, saline (0.1 ml/kg) or robenacoxib (2 mg/kg) was administered subcutaneously at 1 hr prior to the MAC-BAR determination. Robenacoxib significantly decreased the sevoflurane MAC-BAR (3.44 ± 0.53% for saline vs. 2.84 ± 0.38% for robenacoxib, P=0.039). These results suggest that subcutaneous robenacoxib provides a clinically relevant sparing effect on anesthetic requirement.
KEY WORDS: canine, MAC-BAR, robenacoxib, sevoflurane.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) produce analgesic and anti-inflammatory effects by inhibiting arachidonate cyclooxygenase (COX), thereby inhibiting the production of prostaglandins. The COX primary appears in 2 isoforms: COX-1, which is a constitutive isoform and is mainly responsible for the synthesis of prostaglandins that protect organs, and COX-2, an inducible isoform related to inflammatory stimulation and pathological conditions [13]. Robenacoxib is a newer coxib-group NSAID and approved for dogs and cats as a perioperative analgesic drug in some countries including Japan. Robenacoxib is a highly selective COX-2 inhibitor that has been shown to produce analgesic effects with minimal side effects in dogs [9, 10]. It has been reported that preoperative administration of robenacoxib has a similar efficacy to those of meloxicam for the management of perioperative pain and inflammation in dogs undergoing orthopedics surgery [6].

Sevoflurane is a volatile anesthetic drug with a relatively low blood/gas solubility coefficient resulting in rapid induction and recovery from anesthesia [19]. Because of these strong points, sevoflurane has become a popular inhalation anesthetic in veterinary practice. However, it should be remembered that sevoflurane causes dose-dependent hypotension, hypoventilation, impaired cardiac contractility and hypothermia in dogs [19]. A sparing effect on anesthetic requirement provided by the preemptive administration of analgesic drugs is expected to convey the advantage of preserving cardiovascular function in patients anesthetized with sevoflurane.

The potency of inhalation anesthetics traditionally has been evaluated by use of the concept of minimum alveolar concentration to prevent movements (MAC), which is the alveolar concentration of inhalation anesthetic agent at 1 atmosphere that prevents movement in 50% of population exposed to a noxious stimulation [5]. Several studies provide evidence that volatile inhalant anesthetic agents act primarily within the spinal cord to decrease movement in response to a noxious stimulation [1, 20] and produce immobility mainly by acting on the spinal ventral horn [2, 8]. Therefore, the MAC could reflect the suppression of motor neurons at the ventral horn in the spinal cord [8]. On the other hand, minimum alveolar concentration for blunting adrenergic response (MAC-BAR) is defined as the minimum anesthetic concentration that prevents an autonomic response to a noxious stimulation [21]. It is well known that heart rate and arterial blood pressure might increase in response to surgical stimulation, despite of immobility. Absence of responses to noxious stimulation and cardiovascular stability during surgery are desirable, because increases in heart rate and blood pressure reflect activation of the neuroendocrine stress response [23]. MAC-BAR is a useful measure of an anesthetic effect on autonomic pathways in the subcortical centers (spinal cord and brainstem) and may provide important information to diminish the intraoperative neuroendocrine stress response [21].

Perioperative administration of ketrolac, a NSAID, re-

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Table 1. Minimum alveolar concentration for blunting adrenergic response (MAC-BAR) of sevoflurane in both groups and the rate of variability of the sevoflurane MAC-BAR in dogs

Dogs	Age (years)	Sex	Sevoflurane MAC-BAR (%)		Rate of variability (%)
			Control	RBCX	
No. 1	1	female	3.50	3.35	−4.3
No. 2	3	female	4.25	2.70	−36.5
No. 3	3	female	3.25	2.90	−10.8
No. 4	1	male	3.83	3.03	−20.9
No. 5	1	male	3.03	2.88	−5.0
No. 6	2	male	2.80	2.20	−21.4
Mean ± SD	1.8 ± 1.0		3.44 ± 0.53	2.84 ± 0.38*	−16.5 ± 12.3

*Significantly difference from the value in Control group detected by paired *t*-test (P=0.039).

duces the requirement for isoflurane during surgery by an amount similar to that observed following administration of opioid in people [18]. In dogs, a little information is available on a sparing effect on anesthetic requirement for prevent movement of NSAIDs during anesthesia [11, 12, 24]. As far as I know, the effect of NSAIDs including robencaoxib on sevoflurane MAC-BAR in dogs has not been reported. A sparing effect on inhalants provided by the preemptive administration of robenacoxib is expected to convey the advantage of preserving cardiovascular function in patients anesthetized with sevoflurane. Therefore, it is important for veterinary practitioners to confirm the effect of robenacoxib on the sevoflurane requirement in dogs. The purpose of this study was to evaluate the sparing effects of robenacoxib on the MAC-BAR of sevoflurane in dogs. We hypothesized that a preemptive administration of robenacoxib would reduce the sevoflurane MAC-BAR in dogs.

Six intact adult beagle dogs (3 males and 3 females), 1 to 3 years of age [1.8 ± 1.0 (mean ± standard deviation) years old] and weighing from 8.0 to 12.5 kg (10.4 ± 1.4 kg), were anesthetized with sevoflurane twice with a minimum 7-day washout period. In each occasion, robenacoxib (RBCX group) or saline (Control group) was administered at 1 hr prior to the determination of sevoflurane MAC-BAR. The dogs were judged to be in good to excellent health based upon a physical examination. Food was withheld from the dogs for 12 hr before anesthesia, but allow free access to water. 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. The Animal Care and Use Committee of Rakuno Gakuen University approved this study.

Anesthesia was induced by mask induction using sevoflurane (Sevoflo, DS Pharma Animal Health Co., Ltd., Osaka, Japan) in oxygen. All dogs were orotracheally intubated after the induction of anesthesia and anesthetized with oxygen and sevoflurane in left lateral recumbency. The cephalic vein and the dorsal pedal artery were catheterized with a 22-guage catheter (Supercath, Medikit Co., Ltd., Tokyo, Japan). Arterial blood pressure was directly measured by connecting this arterial catheter to a pressure transducer (BD DTX^{TM} Plus DT-4812, Japan Becton, Dickinson and Co., Fukushima, Japan) placed and zeroed at the level of the mid-sternum. During anesthesia, end-tidal concentration of CO_2 ($EtCO_2$) 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 at a rate of 10 ml/kg/hr intravenously through the cephalic vein. Esophageal temperature was maintained between 37.5 and 38.5°C using a heating pad and a warm air blanket in all dogs.

Esophageal temperature (°C), heart rate (beats/min), lead II of the electrocardiogram, respiratory rate (breathes/min), arterial blood pressure (mmHg), oxygen saturation by pulse oxymetry (SpO_2;%), $EtCO_2$ (mmHg) and end-tidal concentration of sevoflurane (EtSEV;%) were monitored using a veterinary patient monitoring system (BP-608V, Omron Colin Co., Ltd., Tokyo, Japan). The esophageal temperature was measured using an electric thermometer probe placed orally into the thoracic esophagus. A commercially available adaptor (Air way adaptor L-shape, Omron Colin Co., Ltd.) modified with an 8-Fr feeding tube (Atom Indwelling Feeding Tube, Atom medical Co., Ltd., Tokyo, Japan) was placed at the Y-piece of the breathing circuit. The feeding tube passed through the endotracheal tube so that its tip rested in the thoracic portion of the trachea. Gas samples were drawn from the proximal end of the endotracheal tube using the feeding tube at a rate of 200 ml//min. A side stream capnograghy and anesthetic agent monitor were used to determine respiratory rate, $EtCO_2$ and EtSEV. The anesthetic agent monitor was calibrated at the start of experiment. Arterial blood sample was collected at approximately 30 min before the first MAC-BAR determination from the arterial catheter into a syringe containing heparin to correct the gradient between partial pressure of arterial CO_2 ($PaCO_2$) and $EtCO_2$.

Following the instrumentation, dogs were received a subcutaneous injection of robenacoxib 2 mg/kg (Onsior, Novartis Animal Health Inc., Tokyo, Japan) or the same volume of saline (0.1 ml//kg). MAC-BAR determination began, after the dogs were allowed to equilibrate for 60 min at EtSEV 3.0%. The MAC-BAR of sevoflurane was determined by judging the dogs' response to a noxious electrical stimulus (50 V, 50 Hz and 10 msec) [25] applied to their right upper gingival. The electrical stimulus was applied for 10 sec using

Table 2. Esophageal temperature, heart rate, respiratory rate, mean arterial blood pressure (MABP), oxygen saturation by pulse oxymetry (SpO_2) and end-tidal concentration of CO_2 ($EtCO_2$) at the determination of the sevoflurane MAC-BAR in dogs

	Control	RBCX	*P*-value
Esophageal temperature (°C)	37.9 ± 0.3	37.9 ± 0.2	0.740
Heart rate (beats/min)	108 ± 15	112 ± 17	0.297
Respiratory rate (breaths/min)	12	12	-
MABP (mmHg)	65 ± 22	64 ± 17	0.399
SpO_2 (%)	99 ± 1	99 ± 1	0.438
$EtCO_2$ (mmHg)	38 ± 1	37 ± 5	0.310

Data are expressed as mean ± standard deviation for 12 observations from 6 dogs. Data from 2 observations recorded immediately prior to electrical stimulation that produced changes in response to stimulation were obtained from each dog.

an electrical stimulator (SEN3301, Nihon Koden Co., Tokyo, Japan). Positive response for the MAC-BAR determination was fixed an increased either heart rate or mean arterial blood pressure (MABP) over 15% above the value recorded at 1 min before applying the electrical stimulus during a 30-sec observation period. When the dog exhibited the positive response, 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 the positive response, the EtSEV was decreased by 10 to 20%, and the dog was rested after 20 min of re-equilibration. The MAC-BAR of sevoflurane was defined as the mean of the EtSEV that did or did not prevent the positive response and was determined in duplicate. The data were reported as mean ± standard deviation and analyzed by use of the paired *t*-test. The level of significance was set at $P<0.05$.

It took 162.7 ± 35.3 min and 190.2 ± 65.5 min to obtain the duplicate data for sevoflurane MAC-BAR after the administration in RBCX and Control groups, respectively. There was no significant difference in the duration required to determine the MAC-BAR between both groups ($P=0.343$). The sevoflurane MAC-BAR was 2.84 ± 0.38% and 3.44 ± 0.53% in RBCX and Control groups, respectively. The subcutaneous administration of robenacoxib (2 mg/kg) produced significant reduction in the sevoflurane MAC-BAR ($P=0.039$) by 16.5 ± 12.3% (Table 1). In Control group, the sevoflurane MAC-BAR was 3.67 ± 0.52% in 3 females and 3.22 ± 0.54% in 3 males.

Esophageal temperature and cardio-respiratory parameters immediately prior to the determination of MAC-BAR are summarized in Table 2. In the present study, normothermia was achieved by using a heating pad and a warm air blanket in all dogs. Good oxygenation and eucapnia were also achieved by both oxygen inhalation and IPPV. MABP was close to clinically lower limit (60 mmHg) during MAC-BAR determination in both groups. There was no statistically significant difference in the esophageal temperature ($P=0.426$), heart rate ($P=0.079$), respiratory rate (12 breathes/min in all dogs), MABP ($P=0.423$), SpO_2 ($P=0.065$) and $EtCO_2$ ($P=0.530$) between groups.

In the present study, the sevoflurane MAC-BAR after administration of saline for the dogs was 3.44 ± 0.53% and is similar to the MAC-BAR value for middle aged (9 to 11 years old) intact female dogs (3.33%) [25]. On the other hand, the sevoflurane MAC-BAR values for intact male dogs reported by Love *et al.* [16] and Seddighi *et al.* [22] (2.77% and 2.50%, respectively) are lower than that in the present study. Love *et al.* [16] mentioned that their sevoflurane MAC-BAR was lower than expected value based on their previous canine study using the same methodology, documented a sevoflurane MAC-BAR of 3.21% (Wilson *et al.* 2008. Determination of MAC and MAC derivatives for isoflurane and sevoflurane. Proceedings of the American College of Veterinary Anesthesiologists, Scottsdale, AZ, pp.4–5). Differences in study design and individual animal may account for variability in the MAC-BAR results.

It was reported that clinical pre-anesthetic subcutaneous dose of carprofen (4 mg/kg) or meloxicam (0.2 mg/kg) decreased the sevoflurane MAC by 11.3 ± 8.3% or 12.9 ± 10.2%, respectively [24]. However, Ko *et al.* [12] failed to demonstrate significant sparing effect of preoperative oral administration of carprofen (2.2 mg/kg) on isoflurane MAC in dogs, despite of the MAC reduction by 6.24 ± 3.42%. In the present study, the clinical pre-anesthetic subcutaneous dose of robenacoxib produced a significant reduction in the sevoflurane MAC-BAR by 16.5 ± 12.3% in dogs. Electrical stimulus is categorized into noxious mechanical stimulation and may stimulate 2 different types of peripheral nociceptors. The nociceptors of C-fibers respond to noxious mechanical, chemical and thermal stimuli [4], whereas the nociceptors of Aδ-fibers respond to mechanical and thermal stimuli [3]. NSAIDs inhibit the expression of peripheral COX-2 in injured tissues that produce prostaglandins E_2 and I_2 [13]. Therefore, NSAIDs could prevent the sensitization in peripheral nociceptors of the C-fibers responding chemical stimuli coupled with enhanced pain transmission [13]. Also, there are some evidences suggesting about the central analgesic effects of NSAIDs in laboratory animals [17] and human beings [14]. It was reported that COX-2 was constitutively expressed in the dorsal horn of the spinal cord in rats [17] and prostaglandins distributed throughout all regions of the central nervous system in dogs [7]. In addition, Lizarraga *et al.* [15] reported that intravenous administration of ketoprofen produced hypoalgesia in the absence of inflammation, and its effects were prevented by intrathecal administration of naloxone or atipamezole in sheeps. Therefore, NSAIDs

might produce central analgesic effects by activating inhibitory descending opioidergic and adrenergic mechanisms as well as COX inhibition. Although plasma concentration and cerebrospinal fluid concentration of robenacoxib were not determined in the present study, it is surmised that these central analgesic effects of robenacoxib in spinal cord might be associated with its sparing effect on the sevoflurane MAC-BAR. Further investigation is necessary to confirm the mechanisms for the sparing effect of robenacoxib and other NSAIDs on the MAC and/or MAC-BAR in dogs.

Mutoh *et al.* [19] reported that arterial blood pressure and systemic vascular resistance decreased in a dose-dependent manner in dogs anesthetized with 1.0, 1.5 and 2.0 MAC of sevoflurane. In the present study, heart rate was within normal values for dogs during anesthesia, however, MABP was close to clinically lower limit (60 mmHg) in both groups during the MAC-BAR determination. The end-tidal concentration of sevoflurane that prevents an autonomic response to a noxious stimulation (i.e., MAC-BAR) is higher than that prevents movements (i.e., MAC), and it was reported that the ratio of MAC-BAR/MAC was 1.61 MAC for sevoflurane in dogs [25]. Because sevoflurane produces the cardiovascular depression in a dose-dependent manner, the concentration required for blocking the autonomic response can induce considerable cardiovascular depression in dogs. In the present study, we did not detect any significant difference in MABP between groups, despite the fact that sparing effect on the sevoflurane MAC-BAR was observed in the dogs received subcutaneous robenacoxib. Yamashita *et al.* [24] reported that increase in blood pressure associated with a sparing effect on the sevoflurane MAC was observed in the dogs treated with carprofen or meloxicam. We considered that the failure to observe any beneficial effects on cardiopulmonary function associated with the sparing effect on the sevoflurane MAC-BAR in the present study may have been a result of the high concentration of sevoflurane required for blocking the autonomic response and significant, but not much decrease in the sevoflurane MAC-BAR after robenacoxib administration. A combination of NSAIDs and opioid produces additive effect on MAC reduction in dogs [11, 12, 24]. Because higher concentration of sevoflurane MAC-BAR induced considerable cardiovascular depression and a sparing effect on the sevoflurane MAC-BAR of robenacoxib was significant but not enough to convey the advantage of preserving cardiovascular function in the present study, it is preferable to combine robenacoxib with other analgesic, such as opioid, in order to diminish the hemodynamic suppression at higher sevoflurane concentration.

In conclusion, the preoperative subcutaneous administration of robenacoxib produced a clinical relevant sparing effect of the MAC-BAR on sevoflurane in dogs. Further investigation is necessary to confirm the mechanisms for the sparing effect of robenacoxib on the sevoflurane MAC-BAR in dogs.

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