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

Jun TAMURA1), Takaharu ITAMI1), Tomohito ISHIZUKA1), Sho FUKUI1), Norihiko OOYAMA1), Kenjiro MIYOSHI1), Tadashi SANO2) and Kazuto YAMASHITA1)*

1)Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069–8501, Japan
2)Department of Veterinary Nursing Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069–8501, Japan

(Received 24 January 2013/Accepted 21 August 2013/Published online in J-STAGE 4 September 2013)

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.

KEYWORDS: canine, MAC-BAR, robenacoxib, sevoflurane.

doi: 10.1292/jvms.13-0042; J. Vet. Med. Sci. 76(1): 113–117, 2014

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 perioradicular 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 minimum alveolar concentration for blunting adrenergic response (MAC-BAR) as 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 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-
produces 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 robenacoxib 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™ 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 CO₂ (EtCO₂) 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 (SpO₂,%), EtCO₂ (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 adaptable respirator (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 capnography and anesthetic agent monitor were used to determine respiratory rate, EtCO₂ 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 CO₂ (PaCO₂) and EtCO₂.

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

| Dogs | Age (years) | Sex | Sevoflurane MAC-BAR (%) | Rate of variability (%) |
|------|-------------|-----|------------------------|-------------------------|
| 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).
Table 2. Esophageal temperature, heart rate, respiratory rate, mean arterial blood pressure (MABP), oxygen saturation by pulse oximetry (SpO2) and end-tidal concentration of CO2 (EtCO2) at the determination of the sevoflurane MAC-BAR in dogs

|                  | Control | RBCX  | P-value |
|------------------|---------|-------|---------|
| Esophageal temp. (°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   |
| SpO2 (%)          | 99 ± 1  | 99 ± 1  | 0.438   |
| EtCO2 (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.

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 E2 and I2 [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 cardiovascular 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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