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Effects of Medetomidine and Tramadol Administration on the Minimum Alveolar Concentration of Isoflurane in Dogs

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Abstract : This study was to evaluate the effects of tramadol and medetomidine administration on minimum alveolar concentration (MAC) of isoflurane in dogs. MAC of isoflurane was determined in four occasions; 1 ml saline (Control), 2 μg/kg medetomidine (M2), 4 mg/kg tramadol (T4), 2 μg/kg medetomidine-4 mg/kg tramadol combination (M2T4). Heart rate, blood pressure, respiratory rate, end-tidal carbon dioxide concentration, saturation of hemoglobin with oxygen and body temperature were recorded. After administration of M2 (0.81 × 0.18%), T4 (0.81 × 0.14%) and M2T4 (0.62 × 0.12%), less isoflurane was required than the control value (1.13 × 0.19%). Significantly lower heart rate than the control value was detected after treatment of M2, T4, and M2T4. When only M2T4 was administered, blood pressure was significantly higher than the control value. In conclusion, administrations of tramadol, medetomidine and medetomidine-tramadol combination decreased the MAC of isoflurane in dogs. Especially, medetomidine-tramadol combinations could be useful as a premedication because of the anesthetic sparing effect and moderate changes in cardiovascular system.

Key words **:** medetomidine, tramadol, minimum alveolar concentration (MAC), isoflurane, dog.

Introduction

Premedication allows anesthesia to be induced and maintained in a gentle manner so recently the number of studies about preanesthetic combination has been growing steadily. It is important to select an appropriate drug combination since it can have a radical effect on patient's physiological condition during anesthesia (13,18,20,24).

Medetomidine is a sedative analgesic that is potent and specific to the α_2-adrenoreceptor (4). Medetomidine is commonly used in conjunction with opioids for minor surgery, procedures and premedication for general anesthesia because it improves anesthesia stability (15,24). The major complication of medetomidine is a bradycardia, in the form of an increase in systemic vascular resistance related to reduction in cardiac output. The increases in arterial blood pressure are associated with the dose of the medetomidine administration (12,24). Many clinicians are concerned about applying medetomidine with patients that have cardiovascular problems, although they are using medetomidine at the recommended dose. Therefore, it is recommended to administer at a low dose of medetomidine intramuscularly for the prevent excessive hypertension (29). Medetomidine also has injectable and inhalant anesthetics sparing effect (1,4,10,14,22,24). Medetomidine dramatically decreases the minimum alveolar concentration (MAC) of the inhalant anesthetics and this effect can be reversed with atipamezole (9).

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Tramadol is an atypical centrally acting opioid analgesic, which has one-tenth the potency of morphine (2,3,8,35). Tramadol has been used to control moderate pain in humans for decades in many countries but veterinarians have recently become interested in tramadol to control postoperative pain. Tramadol and its metabolites, *O*-desmethyltramadol, are μ-opioid receptor agonists that have central analgesic effects. They have 200 times higher affinity than tramadol to the μ-opioid receptor. Tramadol also inhibits reuptake of norepinephrine and promote release of serotonin, which contribute to the reduction of nociceptive transmission in the spinal cord (4,6,17,19,21).

It has been suggested that tramadol was not an appropriate premedication for inhalant anesthesia. The risk of awareness during general anesthesia associated with insufficient sedative activity was considered as the main drawback of tramadol as an intraoperative analgesic. It was thought that insufficient sedative activity would be related to its effects on monoaminergic pathways and supplementary studies were needed to estimate tramadol for using it as an intraoperative analgesic (2,3,8,34). However, the reports about the inhalant sparing effect of tramadol for various species verified that tramadol turned out to reduce MAC of inhalants. The effect of 10 mg/kg tramadol was similar to 1 mg/kg morphine in rats and that of 8.6~11.6 mg/kg tramadol surpasses 0.1 mg/kg hydromorphone in cats (11,28,34).

Many small animal clinicians have considered applying analgesic and/or sedative agents in order to use less inhalant without complications (9,33). Not only requirement of inhalants but dose of injectable anesthetics for the induction can be

decreased with drug combinations. Administration of medetomidine and butorphanol reduced amounts of thiopental and isoflurane required for anesthesia (22). Ko *et al.* reported that 1 μg/kg of medetomidine reduced propofol dosage for endotracheal intubation and the effects were similar to those of high-dose diazepam (14). In another study, cats administered with medetomidine and buprenorphine required significantly less isoflurane. However they appeared to be in cardio respiratory depression (10).

The purpose of this study was to evaluate the effects of medetomidine, tramadol and their combination on the MAC of isoflurane, cardiovascular and respiratory system in dogs.

Materials and Methods

Animals

Eight mixed-breed dogs aged 1~3 years were used in this study. The mean standard body weight was 10.3 ± 3 kg. No dogs showed any abnormal finding in the physical examinations, serum chemistry analysis and complete blood count. All dogs were vaccinated and negative to the test for the heartworm detection.

Experimental Design

Dogs were studied using randomized complete-block design. The MAC of isoflurane was determined on four occasions; saline (Control), 2 μg/kg medetomidine (M2), 4 mg/kg tramadol (T4), 2 μg/kg medetomidine-4 mg/kg tramadol combination (M2T4). For the baseline MAC determination, dogs received 1 ml of saline intravenously and determined baseline MAC value. Then, dogs were given 2 μg/kg of medetomidine (Domitor®, Pfizer, USA) and allowed to re-equilibrate for 15 minutes. After equilibration time, the MAC of M2 was determined. All dogs had clearance time of a week and were studied with another treatment.

After 1 week, at the beginning of anesthesia, the dogs received 4 mg/kg of tramadol (Toranzin®, Samsung Pharm, Korea) intravenously and were evaluated at MAC of T4. In the same manner as with the first treatment, after determining MAC of T4, the dogs were given 2 μg/kg of medetomidine intramuscularly. After allowing the dogs to re-equilibrate for 15 minutes, the MAC of M2T4 was estimated. The anesthesia and procedure time were completed within 5 hours of tramadol administration since it is shorter than the action time of tramadol. Following the administration of medetomidine, the procedure was completed within 2 hours.

Anesthesia and MAC determination

Anesthesia was induced using 5% isoflurane, via a facemask, using an anesthetic machine (Royal Delta-88X, Royal medical, Korea). The endotracheal tube was placed and maintained with isoflurane in oxygen. All dogs were heated to maintain body temperature (BT). The heart rate (HR), respiratory rate (RR), end-tidal carbon dioxide concentration ($EtCO_2$), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), oxygen saturation of hemoglobin (SpO_2) and BT were monitored with the anesthesia monitor (S/5™, Datex-Ohmeda, Finland). After intubation of the endotracheal tube, all dogs were allowed to equilibrate in 1.5% end-tidal isoflurane for at least 20 minutes. The modified tail clamp method was used to measure MAC of the isoflurane (7,16,25). The two single stimulus, clamping the tail with a Backhaus towel clamp for 20 seconds, were delivered in 10 second intervals. Purposeful movement was defined as movement of head or extremities but did not consider increased respiratory rate and effort. If the purposeful movement occurred in response to tail clamping, the end-tidal isoflurane concentration was increased by 0.1%~0.2% and the dog was re-estimated after 10~15 minutes of re-equilibration. Otherwise it was decreased by 0.1%~0.2% and retested following a 10~15 minutes equilibration. The MAC was determined in duplicated and the mean value was taken as MAC. If the difference between the two MAC values was larger than 10%, a third procedure was performed and averaged with other two MAC values.

Statistical Analysis

MAC value and cardio respiratory data were analyzed using ANOVA for repeated measures followed by a Tukey post test. The percentage change in MAC was calculated as $[(MAC_{treatment} - MAC_{control})/MAC_{control}] \times 100$. Statistical significance was achieved if the probability was less than 5% ($P < 0.05$).

Results

The MACs in M2, T4 and M2T4 were significantly lower than the baseline MAC value ($P < 0.05$). After administration M2 (0.81 ± 0.18%) and T4 (0.81 ± 0.14%), less isoflurane was required than control (1.13 ± 0.19%). Percent changes of M2 and T4 were 28.0 ± 11% and 27.3 ± 15.3%, respectively. The MAC following M2T4 administration was 0.62 ± 0.12% and the percentage change was 44.5 ± 13.9%. The MAC of M2T4 was also significantly lower than that of M2 and T4 ($P < 0.05$) (Fig 1).

A significantly lower HR was detected after the treatment of

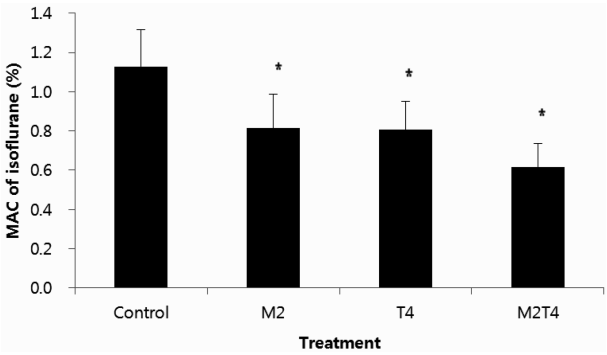

Fig 1. Effects of medetomidine and tramadol on the MAC of isoflurane in dogs. M2: 2 μg/kg medetomidine, T4: 4 mg/kg tramadol, M2T4: 2 μg/kg medetomidine and 4 mg/kg tramadol combination. *significantly different from the control value ($P < 0.05$).

Table 1. Cardiovascular and pulmonary data over the anesthetic period after administration of various treatments

	Control	M2	T4	M2T4
HR (beats/min)	118.8 ± 24.9	90.6 ± 21.2*	104.4 ± 19.5*	85.8 ± 21.6*†
SPB (mm Hg)	120.9 ± 21.3	133.2 ± 18.3	129.6 ± 24.7	139.6 ± 21.6*
MBP (mm Hg)	81.9 ± 14.4	91.4 ± 17.9	89.9 ± 25.2	98.6 ± 13.3*
DBP (mm Hg)	62.1 ± 14.9	68.8 ± 20.5	71.6 ± 23.3	79.5 ± 10.9*
RR (breaths/min)	23.5 ± 13.5	26.8 ± 14.8	23.7 ± 13.5	26 ± 11.7
$EtCO_2$ (mmHg)	37.5 ± 8.3	37.2 ± 4.2	40.7 ± 7.3	38.4 ± 6.3
SpO_2 (%)	96.3 ± 2.5	95.4 ± 2.2	96 ± 2.9	96.4 ± 2.3
BT (°C)	37.8 ± 0.8	37.5 ± 0.5	37.7 ± 0.6	37.6 ± 0.4

M2: 2 mg/kg medetomidine, T4: 4 mg/kg tramadol, M2T4: 2 mg/kg medetomidine and 4 mg/kg tramadol combination. *significantly different from the control value ($P < 0.05$), †significantly different from T4 value ($P < 0.05$).

M2 (90.6 ± 21.2 beats/min), T4 (104.4 ± 19.5 beats/min), and M2T4 (85.8 ± 21.4 beats/min) than the control value (118.8 ± 24.9 beats/min). The HR of M2T4 presented significant differences compared with control and T4 ($P < 0.05$). When only M2T4 was administered, SBP was significantly higher than the control value ($P < 0.05$). DBP and MBP followed the same pattern as SBP. HR and BP were not influenced by time. There was no considerable change in RR, $EtCO_2$, SpO_2 and BT in all treatments (Table 1).

Discussion

It is of vital importance that veterinary clinicians perform stable anesthesia with the safety of animals in mind. A number of researchers have studied physical changes which patients undergo according to administration of anesthetic agents and have suggested numerous ways of concurrent drug use.

Previous studies reported that the MAC of isoflurane was 1.28 ± 0.06% and 1.18 ± 0.11% in dogs (9,30). The baseline MAC value of isoflurane in this study (1.13 ± 0.19%) was slightly lower but was fairly consistent with previous reports. The variation of MACs is the result of inconsistency in stimulus methods, anatomical sites, the subjectivity of researchers and individual differences (31). In order to minimize variation during this experiment, we restricted the observer to one person throughout the research period and stimuli were applied to the same anatomical site using one instrument.

Administration of α_2-agonist during the inhalant anesthesia decreased MACs in various species (9,20,22). In the present study, even though lower than recommended doses of medetomidine have been used, reduced MAC of M2 (0.81 ± 0.18%) was detected. This result was not exactly consistent with prior studies, which explained that lower doses of medetomidine than 5 μg/kg had no affect on the requirement of isoflurane (22). However, recent studies demonstrated that it unexpectedly had anesthetic sparing and sedative effects at lower doses medetomidine (1 and 2 μg/kg) (15,24). In our preliminary unpublished research, the MAC of isoflurane in dogs that administered 1 μg/kg medetomidine and 2 mg/kg tramadol combination as a premedication also decreased by 20.5%.

Tramadol is a centrally acting synthetic analogue of codeine, which has been known to be as effective as morphine for moderate pain (3). As described previously, it used to be questionable whether tramadol was an appropriate preoperative analgesic or not because of risk of awareness during anesthesia (2,6,19). However, Wolff *et al.* (1999) reported that tramadol turned out to reduce the MAC of isoflurane from 1.38% to 1.22% in rats (34). In addition, an amount of tramadol decreased the MAC of sevoflurane by 36 ± 12% in dogs and from 2.45% to 1.48% in cats. The result of this study supports those proposals which mention that tramadol decreased MAC of inhalants in a variety of animals. In addition, previous studies show that administration of naloxone fully reversed the tramadol-induced reduction of the MAC of inhalants. These results supported that tramadol decreased the requirement of inhalants related to opioid receptor (14,26).

The HR of M2 was significantly different from the baseline measurement and BP increased moderately ($P = 0.074$). This result is similar to the report, which evaluated hemodynamic effects of various doses of medetomidine. Medetomidine makes BP biphasic condition, with an initial increase followed by a decrease whereas low doses of medetomidine (1 and 2 μg/kg) showed an insignificant increase in the early period and bradycardia was also less marked. That's because higher doses produced a more intense stimulation of peripheral adrenoreceptors. This report suggested that the reduction of administered dosage weakened cardiovascular effects, since it was thought to be dose dependent (20,24). In the same manner, cardiovascular signs of M2 and M2T4 were comparatively stable with slight changes throughout the anesthesia. These features might not be considered as clinically drastic changes for small animal clinicians.

Lower HR and slightly higher BP in T4 were detected compared with those of the control value. This hemodynamic change was attributable to peripheral and pulmonary vascular resistance (23). Pulmonary depression such as a decrease in RR and a rise in $EtCO_2$ was not noticed in T4. This characteristic, which has no clinically relevant respiratory depression, is considered to be one of the main advantages of tramadol along

with less complication compared to other opioids and non-steroidal anti-inflammatory drugs (NSAIDs) (6,21).

There were various suggestions about opioids, NSAIDs and sedatives alone and in combinations for the reduction of the MAC of inhalants. The effects of drugs on the MAC of inhalants were very different from each treatment. Opioids clearly reduced the concentration of volatile agents (5,13,18,26,32,34). In the case of NSAIDs, the anesthetic sparing effect of them is still debatable. Yamashita *et al*. reported the administration of NSAIDs, carprofen and meloxicam, significantly decreased the MAC of sevoflurane in dogs (36). But carprofen administration in dogs and flunixin meglumine in goats did not decrease the MAC of isoflurane (5,16).

When applying the combination drugs, the interactions between drugs do not always yield consistent results (18,27,33). One study demonstrated that the sevoflurane sparing effect of the combination of carprofen and meloxicam with butorphanol in dogs were additive (36). But in other study, it was not evident that an additional reduction in MAC when tramadol was administered with butorphanol and hydromorphone in cats (11). The results of this study indicate that medetomidine enhanced the inhalant sparing effect without an alteration in effect of tramadol. Inhalant sparing effect of M2T4 was proved as 44.5 ± 13.9% reduction and range of MAC reduction is from 22.2% up to 61%.

Different from our hypothesis, considerable changes in the cardiovascular system were found in M2T4 administration that, at the same time, did not bring respiratory changes. This result indicates that M2T4 produced clinically substantial side effects in cardiovascular and respiratory systems. As a matter of course, we detected minor complications involving bradycardia, hypertension, tachypnea and salivation that were all mild and temporary. Although the effect of the M2T4 combination on the cardiovascular system was statistically significant, this data would not be clinically important for clinicians. Therefore, the M2T4 combination could be an effective preoperative and intraoperative medication devoid of major complications. Another advantage of the M2T4 combination is that actions of medetomidine and tramadol can be reversed with atipamezole and naloxone, respectively. Atipamezole could be used to reverse the desirable MAC reduction of isoflurane and undesirable effects of medetomidine. The inhalant sparing effect of tramadol can be also returned with naloxone, as previously explained. (4,6,9,11,34).

The M2, T4 and M2T4 combination significantly decreased the MAC of isoflurane in dogs. Intraoperative M2 surprisingly decreased the requirement of isoflurane more than expected. The M2T4 combination produced significant changes in the cardiovascular system but variations are clinically acceptable to apply as a premedication for isoflurane anesthesia. Supplementary research would be required to find out improved drug combination.

In conclusion, administrations of medetomidine, tramadol and medetomidine-tramadol combinations decrease the requirement of isoflurane in dogs. Even though effects of medetomidine-tramadol combinations on heart rate and blood pressure are statistically significant, medetomidine-tramadol combinations could be useful as a premedication because of the anesthetic sparing effect and moderate changes in cardiovascular system.

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Medetomidine과 Tramadol이 개에서 Isoflurane의 최소 폐포 농도에 미치는 영향

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요 약 : 본 연구는 tramadol과 medetomidine이 개에서 isoflurane의 최소폐포농도에 미치는 영향에 대해 알아보고자 하였다. Isoflurane의 최소폐포농도는 1 ml의 생리식염수(control), 2 μg/kg의 medetomidine (M2), 4 mg/kg의 tramadol (T4), 2 μg/kg medetomidine과 4 mg/kg tramadol (M2T4)의 투여 네 가지 경우에 따라 측정되었다. 실험 중 심박수, 혈압, 호흡수, 호기말 이산화탄소분압, 혈중산소포화도, 체온을 측정하였다. M2, T4, M2T4 투여 후 isoflurane의 최소폐포농도는 각각 0.81 ± 0.17%, 0.81 ± 0.14%, 0.62 ± 0.13%로 대조군1.13 ± 0.19% 에 비해서 낮았다. 심박수는 M2, T4, M2T4 투여 시 낮았고 혈압은 M2T4투여 시에만 유의적으로 높았다. Tramadol 과 medetomidine의 투여 및 두 약물의 혼합투여는 isoflurane의 최소폐포농도를 유의적으로 낮추었다. 특히 tramadol과 medetomidine의 혼합투여는 마취제의 절감효과와 심혈관계에 있어 변화가 적기 때문에 전마취제로서 유용하게 사용될 수 있을 것이다.

주요어 : medetomidine, tramadol, 최소폐포농도, isoflurane, 개