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Effect of Intravenous Administration of Tramadol on the Minimum Alveolar Concentration of Isoflurane in Dogs

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Abstract : This study was aimed to evaluate the effects of tramadol hydrochloride on the minimum alveolar concentration of isoflurane (MAC_{ISO}) in dogs. Six healthy, female German shepherd dogs (aged 1-2 years) were used in this study. Anesthesia was induced by mask induction and maintained with isoflurane in oxygen. Mechanical ventilation maintained the end-tidal CO_2 partial pressure ($P_{ET}CO_2$) from 35 to 45 mmHg throughout the study. A baseline MAC_{ISO} ($MAC_{ISO}B$) was determined starting 45 minutes after induction of anesthesia by clamping a pedal digit until gross purposeful movement was detected. After $MAC_{ISO}B$ determination, dogs received a tramadol loading dose of 3 mg/kg followed by a continuous rate infusion (CRI) of 2.6 mg/kg/h. The determination of MAC_{ISO} after administration of tramadol ($MAC_{ISO}T$) began 20 min after the start of the CRI. Arterial blood pressure and heart rate were recorded continuously and arterial blood samples for blood gas analysis were collected at the end of the equilibration period. Mean ± SD values for the $MAC_{ISO}B$ and $MAC_{ISO}T$ were 1.33 ± 0.04% and 1.23 ± 0.04%, respectively. The $MAC_{ISO}B$ decreased significantly by 7.5 ± 0.2% ($P < 0.05$) after administration of tramadol. The mean heart rate and arterial blood pressure of six dogs were not changed significantly after tramadol administration. The blood gas levels remained constant during the study. In conclusion, tramadol could significantly reduce MAC_{ISO} without depression of cardiorespiratory function. Thus, the use of tramadol on inhalation anesthesia with isoflurane in dogs can improve the stability of anesthesia and the quality of recovery.

Key words **:** tramadol, isoflurane, minimum alveolar concentration, CRI, dog.

Introduction

Tramadol hydrochloride has been licensed for use in humans in Korea since 1981 and it is an opioid analgesic that commonly used in veterinary medicine. Since the drug is not controlled by Drug Enforcement Administration and costs less, it makes it appealing for use in animals.

Based on human studies, tramadol has shown its effectiveness, just like morphine, for moderate pain, but it is shown to be less effective when it comes to dealing with severe acute pain. One advantage of tramadol for chronic pain treatment over many other opioids is the absence of strict regulatory measures with regards to its use (14). In addition, tramadol has less potential for abuse, possess no clinically relevant respiratory depression or cardiovascular effects, lacks pharmacodynamic tolerance, has little effect on gastrointestinal side effect than conventional opioids, and is well tolerated with a low incidence of adverse effects in human (23,25,32). Thus, tramadol is one of the most preferable analgesic agents in human.

Similarly, tramadol has been used in veterinary medicine for postoperative analgesia. Based on the previous studies, tramadol showed significant effects on postoperative pain control after abdominal (15) and orthopedic surgery (7) in dogs and intercostal thoracotomy in cats (1). In addition, epidural administration of tramadol shows long-term analgesia with no adverse effects in horses (21). Results of several studies in rats suggest that the drug is also an effective analgesic in acute and neuropathic pain (2,8,9).

The minimum alveolar concentration (MAC), a standard of inhalational anesthetic potency, was first defined in 1963 by Eger and Merkel (4). When calculated for an individual animal, the MAC is the arithmetic mean of the end-tidal concentrations of an inhalational anesthetic that prevents and allow purposeful movement in response to a supramaximal noxious stimulus (4,22,31). The MAC is useful in evaluating objective changes in inhalant anesthetic requirements caused by drugs used during anesthesia (22). In the previous studies, tramadol had a significant reduction of the MAC of isoflurane in rats (3) and rabbits (5). Moreover, Seddighi et al. (26) reported that administration of tramadol significantly reduced the MAC of sevoflurane in dogs.

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Thus, this study was aimed to investigate the effects of tramadol on the MAC of isoflurane (MAC_{ISO}) and the cardiorespiratory system in dogs.

Materials and Methods

Animals

Six healthy, adult (aged 1-2 years) female German shepherd dogs with a body weight of 19.3 ± 3.2 kg were used in this study. Health status was assessed by means of physical examination, CBC, measurement of venous blood gases, and serum biochemical analyses. All experiments started at 2:00 PM. Food was withheld for 12 h prior to anesthesia, but access to water was unrestricted at all times. This study was approved by the Animal Care and Use Committee at Gyeongsang National University (approval number: GNU-LA-30).

Anesthesia and monitoring

Anesthesia was induced with isoflurane (Ifran, Hana Pharm., Korea) in 100% oxygen (2 L/min) delivered via a mask from a circle system. After endotracheal intubation, anesthesia was maintained with isoflurane in 100% oxygen (2 L/min) using a rebreathing, closed anesthetic circuit (Multiplus, Royal Medical Co., Korea). Dogs were positioned in left lateral recumbency and mechanically ventilated to prevent hypercapnia. Ventilator (Vent-V, Royal Medical Co., Korea) settings were varied by adjusting to maintain the end-tidal CO_2 partial pressure ($P_{ET}CO_2$) at approximately 35-45 mmHg. $P_{ET}CO_2$ and the inspired and end-tidal isoflurane concentrations (ETiso) were monitored with a calibrated multigas monitor (Capnomac Ultima, Datex Division Instrumentarium Corp., Finland). The body temperature and electrocardiogram were monitored (AS3, Datex-Ohmeda Division Instrumentarium Corp., Finland) during the procedure. Throughout the study, the body temperature was maintained at 37.5-38.5°C with a circulating water blanket and a forced warm air blanket. In addition, 0.9% normal saline was administered intravenously during the procedure at a rate of 5 mL/kg/h. Heart rate and arterial blood pressure were monitored continuously. In order to measure direct arterial blood pressure and obtain arterial blood sample for arterial blood gas analysis, a sterile 24-gauge catheter was inserted aseptically via a cut down incision into the dorsal pedal artery. The arterial catheter was connected to a blood pressure transducer (Transpac IV Monitoring Kit, Abbott Critical Care Systems, USA) and a pressure line filled with heparinized saline, which was connected to a monitor (AS3, Datex-Ohmeda Division Instrumentarium Corp., Finland) for heart rate and direct blood pressure monitoring. The values of blood pressure were set to zero to the atmospheric pressure at the level of the heart. Oxyhemoglobin saturation was also monitored continuously with a pulse oximeter.

Minimum alveolar concentration determination

Prior to the determination of baseline MAC_{ISO} ($MAC_{ISO}B$), the ETiso held constant at 1.5% for a minimum of 20 min to assure equilibration within 45 min after induction of the anesthesia. The $MAC_{ISO}B$ was determined using a method described in a previous study (31). At the end of equilibration period, a pedal digit was clamped with a with 24 cm sponge forceps until gross purposeful movement (jerking or twisting motion of the head or running motion of the extremities) was detected or 60 s had elapsed (22). Non-purposeful movement such as coughing, straining, stiffening, chewing, and changes of the respiratory pattern were not considered. When purposeful movement occurred, the ETiso was increased by 0.1%; otherwise, it was decreased by 0.1%, and the stimulus was reapplied following a 20 min equilibration period. The mean value between the highest concentration that allowed movement and the lowest concentration that prevented movement was determined as the $MAC_{ISO}B$ (22).

After $MAC_{ISO}B$ determination, tramadol (Tramadol HCL inj.®, Huons, Korea) loading dose (LD) of 3 mg/kg was administered, followed immediately by a continuous rate infusion (CRI) of 2.6 mg/kg/h intravenously. The loading and infusion doses were mixed up to a final volume of 10 and 50 ml, respectively in normal saline. Then, by using a syringe pump (JMS Syringe Pump SP-500, JMS co., Japan), it was delivered through the cephalic vein. The drug dosage was based on previously described method (26). The LD was administered over 5 min, and the CRI was started immediately afterwards. Twenty min after start of the CRI, MAC of isoflurane after administration of tramadol ($MAC_{ISO}T$) was measured with a similar fashion of $MAC_{ISO}B$ determination.

Evaluation of cardiorespiratory function

After $MAC_{ISO}B$ and $MAC_{ISO}T$ determination, equilibration period for 20 min was applied respectively. While this period, heart rate and arterial blood pressure were measured at the interval of 1 min. The mean data of the variables measured throughout this period were recorded. At the end of the equilibration period for 20 min, 0.4 ml arterial blood sample was collected for PaO_2, $PaCO_2$, pH, and HCO_3^- analysis. Blood gas analysis (Vetstat, Idexx, USA) was performed immediately after the blood was sampled. The results were automatically corrected to body temperature by using standard mammalian correction factors built into the blood gas analyzer.

Statistical analysis

The Percentage change in MAC was calculated as the following equation: $[(MAC_{ISO}T - MAC_{ISO}B)/MAC_{ISO}B] \times 100$. $MAC_{ISO}B$ and $MAC_{ISO}T$ values, times spent for $MAC_{ISO}B$ and $MAC_{ISO}T$ determination, total anesthesia time, percentage change in MAC_{ISO}, and endotracheal extubation time were presented as mean ± SD. A Wilcoxon signed rank test was used to compare $MAC_{ISO}B$ and $MAC_{ISO}T$ values. Body temperature, heart rate, arterial blood pressure, and blood gas data (PaO_2, $PaCO_2$, pH, and HCO_3^-) determined during equilibration period after $MAC_{ISO}B$ determination were compared with those determined during the equilibration period after $MAC_{ISO}T$ determination by using a paired T-test. A level of $P < 0.05$ was considered statistically significant. All the statistical tests were performed using statistical software SPSS 18.0 (SPSS Inc., USA).

Results

The total anesthesia time was 221 ± 9 min. The interval from induction of anesthesia to determination of the $MAC_{ISO}B$

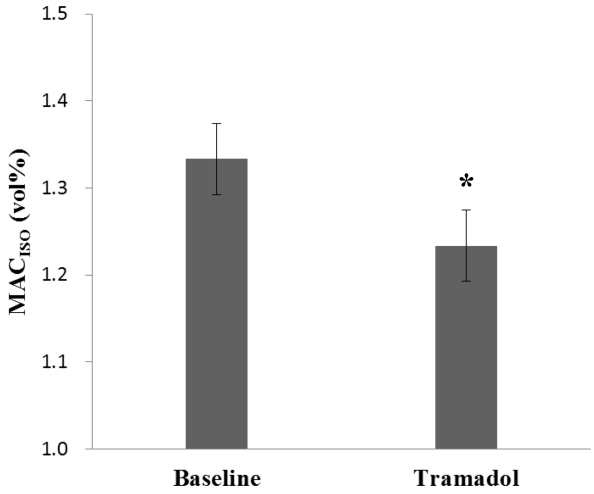

Fig 1. Effects of tramadol (3 mg/kg initial loading dose followed immediately by CRI at 2.6 mg/kg/h) on the MAC of isoflurane in dogs (n = 6). Values are mean ± SD. *Significantly different between groups ($P < 0.05$).

Table 1. Cardiorespiratory and body temperature variables measured in 6 dogs during $MAC_{ISO}B$ and $MAC_{ISO}T$ equilibration period

Variables	$MAC_{ISO}B$	$MAC_{ISO}T$
HR (beats/min)	91 ± 29	83 ± 23
SAP (mmHg)	116 ± 13	113 ± 17
MAP (mmHg)	76 ± 5	78 ± 4
DAP (mmHg)	61 ± 5	65 ± 5
PaO_2 (mmHg)	343 ± 38	292 ± 63
$PaCO_2$ (mmHg)	35 ± 2	36 ± 5
pH (units)	7.418 ± 0.033	7.418 ± 0.036
HCO_3^- (mmol/L)	21.6 ± 2.7	21.6 ± 3.4
Temp (°C)	37.9 ± 0.2	37.9 ± 0.2

Values are presented as mean ± SD
Abbreviations: $MAC_{ISO}B$ = minimum alveolar concentration of isoflurane; $MAC_{ISO}T$ = minimum alveolar concentration of isoflurane after administration of tramadol; HR = heart rate; SAP = systolic arterial blood pressure; MAP = mean arterial blood pressure; DAP = diastolic arterial blood pressure; Temp = body temperature. No variables showed significant differences between $MAC_{ISO}B$ and $MAC_{ISO}T$ equilibration period.

was 94 ± 8 min, and the interval from determination of the $MAC_{ISO}B$ to determination of the $MAC_{ISO}T$ was 77 ± 8 min. Endotracheal extubation time was 7 ± 2 min after discontinuating isoflurane.

Mean ± SD values for the $MAC_{ISO}B$ and $MAC_{ISO}T$ were 1.33 ± 0.04% and 1.23 ± 0.04%, respectively (Fig 1). Thus, the $MAC_{ISO}B$ decreased significantly by 7.5 ± 0.2% after administration of tramadol ($P = 0.031$).

The mean heart rate, arterial blood pressure, and arterial blood gas variables of six dogs were not significantly different during equilibration period following each $MAC_{ISO}B$ and $MAC_{ISO}T$ determination (Table 1). Thus, tramadol administration had no significant effects on heart rate, arterial blood pressure, and arterial blood gas. Mean arterial blood pressure was > 60 mmHg at all times during the study. Body temperature did not change after tramadol administration and hemoglobin saturation was > 98% at all times.

All of the dogs recovered from the anesthesia uneventfully and no arrhythmia was observed during the study. All of the dogs tested in this experiment were treated and put through the rehabilitation program. Complications such as vomiting or excitation during recovery were not observed.

Discussion

The present study indicated that tramdol hydrochloride significantly reduced MAC_{ISO} but it had no significant effects on heart rate, arterial blood pressure, and arterial blood gas. The mean $MAC_{ISO}B$ in this study did not differ substantially from MAC_{ISO} values reported previously in dogs: ranged from 1.27 to 1.39 (24,28,31). The MAC of inhalational anesthetics can differ substantially among animals of the same species and even among strains of the same species (16,31). Inter and intra individual variations in MAC values are commonly less than 20% and 10%, respectively (22). In this study, in order to limit potential variations owing to investigator, the one investigator has examined gross purposeful movement to minimize variation within the study. In addition, in order to eliminate potential intervention of other drugs for isoflurane sparing effect, the mask induction of isoflurane was used and any other drug was not used except tramadol.

MAC is a standard measure of potency for inhalation anesthetics and allows for comparison between different analgesic substances (4). There are two study designs for measuring MAC (27). The first method to measure MAC is the quantal study design. This method is usually used in humans. The MAC with the quantal design is determined for a population whereas the MAC values of an individual are not known. The second method to measure MAC is the bracketing study design which determines the MAC of each individual. Sonner (27) said both the quantal and bracketing study designs showed the same MAC values. Since the purpose of this study was to investigate the effects of tramadol on the MAC for each individual, the bracketing study design was used in this study.

There are several types of noxious stimuli for the use in determining the MAC for inhalation anesthesia in dogs. Commonly used methods such as supramaximal noxious stimulus for determination of the MAC in animals involve clamping techniques that clamp the tail, paw of a forelimb, or paw of a hindlimb. The stimulation site is clamped continuously for a period of 30 to 60 s elapsed or until gross purposeful movement is detected (jerking or twisting motion of the head or running motion of the extremities) (4,22,31). Another method is the use of electrical stimulation technique (50 V, 50 Hz, 10 ms through needles placed in the oral mucosa, forelimb, and hindlimb) (31). In a previous study (31), the use of clamping and electrical stimulation techniques resulted in similar MAC values in dogs anesthetized with isoflurane, and the MAC for surgical incision technique was significantly lower than the values for the other methods. In addition, the study indicated that clamping and electrical stimulation techniques were both supramaximal stimulus.

Factors that may influence MAC include age, circadian

rhythm, methodology for MAC assessment, severe hypercapnia, severe hypoxemia, changes in body temperature, severe hypotension, and acidemia or alkalemia (22). In this study, latent confounders were controlled. Six healthy, female German shepherd dogs (aged 1-2 years) were used in this study and all experiments started at the same time in order to standardize the time of anesthesia. The method for MAC determination was validated (31) and mechanically controlled ventilation with oxygen was used to prevent condition of hypercapnia, hypoxemia, acidemia or alkalemia. In addition, the esophageal temperature was maintained within reference range (37.5 to 38.5ºC) by using a supplemental heat source. A dog was temporarily hypocapnic approximately 25 mmHg due to spontaneous breathing during $MAC_{ISO}T$ determination, but it was thought that this degree of hypocarbia does not affect the MAC value. It was improbable that this variation in $PaCO_2$ could have biased MAC_{ISO} as only intense changes in $PaCO_2$ (< 10 mmHg or > 95 mmHg) reduced the MAC (6,22). Arterial blood gas data determined after $MAC_{ISO}T$ equilibration period were not changed significantly compared to those determined after $MAC_{ISO}B$ equilibration period.

Surgical procedures performed under only inhalation anesthesia without analgesic agents may result in hyperalgesia during the postoperative period on account of central sensitization of the CNS caused by the surgical trauma (18). Inhalation anesthetics inhibit autonomic outflow (33) and lead to dose-related cardiorespiratory depression (20). Intra-operative opioid infusions have been widely used as part of stabilized anesthetic management in humans and animals (12,15,30). The opioid administration method could reduce the amount of other anesthetic drugs used (10,26), postoperative pain through providing preemptive analgesia (29), the general stress response to surgery (13). The interaction between opioids and volatile anesthetics has demonstrated that opioids significantly reduced the concentration of volatile anesthetic agents required to maintain anesthesia in variety of species (12,17,21,26). There were very limited amount of studies investigating the isoflurane sparing effect of tramadol in dogs although the isoflurane sparing effect of tramadol indicated in rats (3) and rabbits (5). In accordance with the previous studies, significant MAC_{ISO} reducing effect of tramadol was found in this study.

The loading doses and infusion rate of tramadol used in this study followed the previous study (26). A previous study reported that pure μ-opioid agonists such as fentanyl decreased the MAC of enflurane to a maximum of 65-70% in dogs (19). Although the result from previous study is not directly comparable with this study, tramadol may be less effective than pure μ-opioid agonists on MAC reduction because MAC_{ISO} was decreased by 7.5 ± 0.2% after administration of tramadol. Tramadol is a weak μ-opioid agonist and has central stimulating effects (11). These characteristics of tramadol may have worked against the MAC reducing effect. In further studies, wide range of doses should be evaluated in order to detect a ceiling effect for tramadol.

In conclusion, this study investigated the effects of tramadol on the MAC_{ISO} and the cardiorespiratory system in dogs. Based on the results, tramadol has a significant effect on reducing MAC_{ISO}. In addition, any side effects associated with tramadol administration were not observed. Therefore, this study suggest that the use of tramadol on inhalation anesthesia using isoflurane in dogs can improve the stability of anesthesia and the quality of recovery by reducing MAC of isoflurane.

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개에서 트라마돌의 정맥투여가 아이소플루란의 최소폐포농도에 미치는 영향

석성훈 · 박세진 · 이승용 · 진소영 · 김영기 · 황재민 · 이희천* · 연성찬**[1]

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요 약 : 본 연구는 개에서 트라마돌의 정맥투여가 아이소플루란의 최소폐포농도 (MAC_{ISO})에 미치는 영향을 평가하기 위하여 수행되었다. 6마리의 암컷 저먼셰퍼드견이 본 실험에 사용되었다. 실험견의 마취유도는 안면마스크를 이용하여 시행되었으며 실험하는 동안 기계적 환기장치를 이용하여 호기말 이산화탄소 분압 ($P_{ET}CO_2$)을 35-45 mmHg로 유지하였다. 개에서 마취유도 후 45분이 경과한 다음 gross purposeful movement가 감지 될 때까지 후지 발가락을 클램핑하는 방법을 사용하여 baseline MAC_{ISO} ($MAC_{ISO}B$) 측정을 시작하였다. $MAC_{ISO}B$가 결정된 후, 트라마돌 3 mg/kg을 투여하였고 뒤이어 2.6 mg/kg/h으로 지속점적투여 (CRI)를 실시하였다. CRI 시작 후 20분이 경과한 다음, 트라마돌 투여 후 MAC_{ISO}값 ($MAC_{ISO}T$) 측정을 시작하였다. 동맥혈압과 심박수는 지속적으로 기록하였고 $MAC_{ISO}B$와 $MAC_{ISO}T$의 결정 후 각각 20분간 평형기간이 경과한 다음 동맥혈가스분석을 실시하였다. $MAC_{ISO}B$와 $MAC_{ISO}T$는 각각 1.33 ± 0.04% 와 1.23 ± 0.04% 로 측정되었고 $MAC_{ISO}B$는 트라마돌 투여 후 7.5 ± 0.2%의 유의적인 ($P < 0.05$) 감소효과를 나타냈다. 트라마돌 투여 후 심박수와 동맥혈압에서는 유의적인 변화가 나타나지 않았으며 동맥혈 가스분석 결과에서도 유의적인 차이가 없었다. 이상의 결과로 보아 개에서 아이소플루란을 이용한 전신마취 시 트라마돌의 투여는 심폐기능의 억압을 일으키지 않고 MAC_{ISO}값을 감소시켰으므로 마취의 안정성과 마취회복의 질을 향상시키는데 유용할 것으로 사료된다.

주요어 : 트라마돌, 아이소플루란, 최소폐포농도, 지속점적투여, 개