J Vet Clin 28(2) : 211-218 (2011)

Journal of Veterinary Clinics
www.ksvc.or.kr

Antagonistic Effects of Atipamezole and Yohimbine on Medetomidine-Midazolam-Ketamine Anesthesia in Beagle Dogs

Hag-Kyun Hwang, Jae-Yeon Lee, Seong-Mok Jeong and Myung-Cheol Kim[1]

Research Institute of Veterinary Medicine, College of Veterinary Medicine, Chungnam National University, Daejeon 305-764, Korea

(Accepted: April 04, 2011)

Abstract : The aims of this study were to investigate the anesthetic effects of medetomidine-midazolam-ketamine (MMK) combination and to compare antagonistic effects of atipamezole and yohimbine in dogs anesthetized with MMK. Eighteen adult male healthy beagles were used in this study. All dogs were anesthetized with intramuscular (IM) administration of medetomidine (0.04 mg/kg), midazolam (0.2 mg/kg) and ketamine (5 mg/kg) in one syringe. Intravenous (IV) administration of atipamezole (0.24 mg/kg, MMKA), yohimbine (0.2 mg/kg, MMKY) or saline solution (0.1 ml/kg, MMK) was administered 20 minutes after MMK combination anesthesia. Induction and recovery times, scores of sedation and analgesia, heart rate, blood pressure, rectal temperature, respiratory rate and blood gases were determined and recorded for each dog. Mean anesthesia times, sternal recumbency times, standing times and walking times in the MMKA and MMKY groups were significantly shorter than those in the MMK group. But there were not significantly different between MMKA and MMKY groups. In all groups, MMK administration produced a satisfactory sedation and analgesia for all dogs. However, after administration of atipamezole or yohimbine the scores for posture and response to noxious stimuli were significantly lower in the MMKA or MMKY group than those in the MMK group. MMK produced good sedation and anesthesia effects, and atipamezole or yohimbine can be used as a safe and effective agent for antagonizing the MMK anesthesia in dogs.

Key words **:** atipamezole, medetomidine, midazolam, ketamine, yohimbine.

Introduction

In recent years various drug combinations, such as ketamine-medetomidine, ketamine-xylazine and medetomidine-midazolam have been used to anesthetize dog (8). The dissociative anesthetic ketamine, in combination with an α_2-adrenergic agonist, medetomidine, has been more effective for sedation in dogs than medetomidine alone in dogs. This anesthetic combination produces a deep sedation, which is sufficient enough for minor operation (13).

A medetomidine-midazolam combination may be used as a premedication before ketamine anesthesia in dogs. The combination of midazolam or medetomidine with ketamine has been successfully used in dogs (6). However, to the best of our knowledge there are no reports on medetomidine-midazolam-ketamine (MMK) combination for anesthesia in dogs.

Antagonism may be required when the anesthetized animals showed profound depression of vital signs, adverse effects of the given agents, and delayed recovery from anesthesia. Anesthesia with combinations of agents-each of which can be antagonized by specific antagonists has potential advantage. In combination anesthesia each component may potentiate each other's actions, lower individual dose requirements, and therefore produce surgical anesthesia more safely (15). It is therefore very important to determine a suitable antagonist for the fast recovery of anesthetized veterinary clinic fields. Alpha adrenergic antagonists such as atipamezole and yohimbine have been used effectively for antagonizing the anesthetic effects of alpha-adrenoceptor agonist-based combination (14). The actions of medetomidine can be reversed by α_2- adrenoceptor antagonists, such as, the highly specific receptor atipamezole or the less specific yohimbine (13).

There are many established intramuscular anesthetic combinations in dogs. An antagonist to reverse MMK induced anesthesia in cats has been reported (4,12). However, there is little information available on the effects of MMK combination and its antagonistic effects in dogs.

The purpose of this study is to investigate the anesthetic effects of MMK combination and to compare antagonistic effects of atipamezole and yohimbine in beagle dogs anesthetized with MMK.

Materials and Methods

Experimental animals

Eighteen adult male healthy beagles, with a mean age of 2.8 ± 0.7 years and mean body weight of 7.2 ± 0.9 kg were used in

[1]Corresponding author.
E-mail : mckim@cnu.ac.kr

the study. All dogs were raised in appropriate animal management facilities and fed a standard commercial dry canine food (Science Diet® Adult, Hill's Pet Nutrition, Inc, Topeka, USA). Routine hematological tests were performed before the experiment commenced. All values were within the normal physiological range. This experiment was conducted under the supervision of the Chungnam National University Animal Care and Use Committee. The dogs were fasted for 12 hours before the experiment, and water was withheld for 2 hours before anesthesia in order to prevent any possible adverse effects, such as vomiting during anesthesia or recovery periods.

Experimental group

All dogs were anesthetized with intramuscular (IM) administration of medetomidine (Domitor®, Orion Pharma, Espoo, Finland, 0.04 mg/kg), midazolam (Dormicum®, F. Hoffmann-La Roche Ltd, Basel, Switzerland, 0.2 mg/kg) and ketamine (Ketamine 50®, Yuhan Co, Seoul, Korea, 5 mg/kg) in one syringe. Intravenous (IV) administration of atipamezole (Antisedan®, Orion Pharma, Espoo, Finland, 0.24 mg/kg, MMKA), yohimbine (Yobin®, Lloyd Laboratories, Iowa, USA, 0.2 mg/kg, MMKY) or saline solution (0.1 ml/kg, MMK) was administered 20 minutes after MMK combination anesthesia. After drugs administration of the test dose, animals were positioned in right lateral recumbency, and analgesia and cardiopulmonary data were determined and recorded.

Instrumentation and drugs administration

Before experimentation, a sterile 22-gauge arterial catheter (BD IV Catheter®, Becton Dickinson Korea Ltd, Seoul, Korea) was inserted percutaneously into the left dorsal pedal artery of each dog masked down by isoflurane (Forane®, Choong Wae Pharma Corp, Seoul, Korea) anesthesia for few minutes, for the measurement of the arterial blood pressure and to obtain arterial blood samples. The catheter was flushed with heparinized saline (2 IU/ml), secured in place, and connected to a pressure transducer with a noncompliant tube. The transducer was attached to a physiological monitor (Pulscan- Component®, Scionic, Seoul, Korea). After inserting the catheter, isoflurane was discontinued, and then the dogs were allowed to recover for 60 minutes prior to administration of the treatment drugs. Dogs were restrained for collecting arterial blood samples and measuring baseline data. Each of the 18 dogs received three different treatments at the rate of one treatment per 14 days in a randomized order.

Induction and recovery

Induction time, anesthesia time, sternal recumbency time, standing time and walking time were recorded for each dog. Induction time was the time from MMK administration to complete immobilization. Complete immobilization was defined as the lack of response to handling. Anesthesia time was the time interval between complete immobilization and the first attempt made by the animal to lift its head a few centimeters above the ground. Sternal recumbency time was the time from MMK, MMKA or MMKY administration to when the dogs achieved sternal recumbency. Standing time was the time from MMK, MMKA or MMKY administration to when the dogs stood up

Table 1. Subjective criteria used to score levels of sedation and response to noxious stimulus in dogs treated with medetomidine/midazolam/ketamine (MMK), medetomidine/midazolam/ketamine-atipamezole (MMKA) and medetomidine/midazolam/ketamine-yohimbine (MMKY)

Variable	Score	Criteria
Sedative score	0-5	
Spontaneous posture		
	0	Normal
	1	Being able to stand or sit on their hind legs
	2	Keeping the position of ventral recumbency
	3	Lateral recumbency with apparent spontaneous movement (head lifting or struggling)
	4	Lateral recumbency with subtle spontaneous movement (ear and nose twitching or blink)
	5	Lateral recumbency without spontaneous movement
Score of response to noxious stimulus	0-3	
Pedal withdrawal response to pinching of a digit or interdigital web		
	0	Hypersensitive or normal
	1	Slightly impaired
	2	Clearly weak
	3	Absent

without assistance for longer than 10 seconds. Walking time was the time from MMK, MMKA or MMKY administration to when the dogs were able to walk with no knuckling.

Heart rate, blood pressures and rectal temperature

These variables were measured at time 0 (pre-injection) and at 5, 10, 20, 30, 40, 50, 60 and 70 minutes after drug administration. The heart rate (HR) was measured by the transducer attached to a physiological monitor. The mean arterial pressure (MAP), systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were measured by using a patient monitor and were recorded. Calibration of blood pressure device was done in each experiment for the accurate measurement of blood pressure. The left scapulohumeral joint was used as the zero reference point for MAP measurement. Rectal temperature (RT) was continuously recorded using a digital thermometer with the thermocouple probe (Pulscan-Component®, Scionic, Seoul, Korea) that was placed deep into the rectum.

Respiratory rate and blood gases

These variables were also measured at time 0 (pre-injection) and at 5, 10, 20, 30, 40, 50, 60 and 70 minutes after drug administration. The respiratory rate (RR) was measured by observation of thoracic movement. Arterial blood samples were collected anaerobically and analyzed immediately using a portable analyzer (i-STAT® Portable Clinical Analyzer, Abbott Laboratories, Illinois, USA). The analyzer calculated sample arterial pH, carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure (PaO_2) and arterial oxygen saturation (SaO_2).

Evaluation of sedation and analgesia

The levels of sedation (spontaneous posture) and analgesia (pedal withdrawal) were assessed each designated times during anesthesia according to the criteria of Table 1.

Statistical analysis

Immobilization characteristics were compared by using a paired *t*-test. Two-way analysis of variance (ANOVA) for repeated measures was used to compare physiological responses between treatments. One-way ANOVA for repeated measures was used to compare physiological parameters over time. A Bonferroni correction for multiple comparisons was used to determine when significant differences occurred. The significance level for this study was set at $P < 0.05$.

Results

Induction and recovery

Duration of induction, anesthesia, sternal recumbency, standing and walking were shown in Table 2. Mean induction times were not significantly different among MMK, MMKA and MMKY groups (1.0 ± 0.0 min, 1.4 ± 0.9 min and 1.4 ± 0.6 min, respectively). Mean anesthesia times in the MMKA and MMKY groups (26.6 ± 5.7 min and 24.6 ± 2.6 min, respectively) were significantly shorter than those in the MMK group (88.8 ± 9.7 min). But there were not significantly different between MMKA and MMKY groups. Mean sternal recumbency times in the MMKA and MMKY groups (30.6 ± 4.3 min and 32.0 ± 2.6 min, respectively) were significantly shorter than those in the MMK group (98.0 ± 11.3 min). But there were not significantly different between MMKA and MMKY groups. Mean standing times in the MMKA and MMKY groups (35.8 ± 5.9 min and 34.6 ± 2.7 min, respectively) were significantly shorter than those in the MMK group (108.6 ± 9.5 min). But there were not significantly different between MMKA and MMKY groups. Mean walking times (MWT) in the MMKA and MMKY groups (39.0 ± 5.5 min and 36.0 ± 2.6 min, respectively) were significantly shorter than those in the MMK group (117.6 ± 12.3 min). But there were not significantly different between MMKA and MMKY groups.

Table 2. Time for induction, duration of anaesthesia and recovery times in dog after administration of medetomidine/midazolam/ketamine (MMK), medetomidine/midazolam/ketamine-atipamezole (MMKA) and medetomidine/midazolam/ketamine-yohimbine (MMKY)

	MMK	MMKA	MMKY
Induction time	1.0 ± 0.0	1.4 ± 0.9	1.4 ± 0.6
Duration of anesthesia	88.8 ± 9.7	26.6 ± 5.7*	24.6 ± 2.6*
Time to sternal recumbency	98.0 ± 11.3	30.6 ± 4.3*	32.0 ± 2.6*
Time to standing	108.6 ± 9.5	35.8 ± 5.9*	34.6 ± 2.7*
Time to walking	117.6 ± 12.3	39.0 ± 5.5*	36.0 ± 2.6*

Data are expressed as mean ± SD (n = 6).
*Significantly different ($p < 0.05$) from MMK.

Evaluation of sedation and analgesia

In all groups, the administration of MMK produced a satisfactory sedation and analgesia in all dogs. However, after administration of atipamezole or yohimbine in the MMKA or MMKY group the scores for posture and response to noxious stimuli were significantly lower than those in the MMK group (Table 5).

Heart rate, blood pressures and rectal temperature

Data of heart rate, blood pressures and rectal temperature were shown in Table 3. In all groups, the heart rate significantly decreased after MMK administration. In the MMK group, the heart rate significantly decreased within 5 minutes after MMK administration and remained consistently below the baseline value for 70 minutes. In the MMKA and MMKY groups, the heart rate decreased for 20 minutes, but after administration of atipamezole or yohimbine they were recovered to baseline value. There were significantly different in heart rate between the MMKA or MMKY and MMK groups.

In all groups, the blood pressures (MAP, SAP and DAP) significantly increased after MMK administration. In the MMK

Table 3. Heart rate, blood pressures and rectal temperature in dogs after administration of medetomidine/midazolam/ketamine (MMK), medetomidine/midazolam/ketamine-atipamezole (MMKA) and medetomidine/midazolam/ketamine-yohimbine (MMKY)

	Groups	Pre	5 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min
HR (beats/min)	MMK	114 ± 6	76 ± 22[a]	82 ± 27[a]	70 ± 21[a]	59 ± 27[a]	58 ± 14[a]	56 ± 15[a]	52 ± 14[a]	58 ± 23[a]
	MMKA	109 ± 5	81 ± 12[a]	79 ± 11[a]	68 ± 8[a]	119 ± 12[b]	NT	NT	NT	NT
	MMKY	119 ± 11	83 ± 23[a]	87 ± 12	79 ± 8[a]	114 ± 27[b]	NT	NT	NT	NT
SAP (mmHg)	MMK	128 ± 16	179 ± 39[a]	171 ± 37[a]	166 ± 20[a]	161 ± 25[a]	157 ± 24[a]	159 ± 20[a]	152 ± 20	148 ± 17
	MMKA	130 ± 23	179 ± 16[a]	167 ± 17[a]	160 ± 18[a]	149 ± 25	NT	NT	NT	NT
	MMKY	116 ± 14	180 ± 17[a]	176 ± 13[a]	159 ± 12[a]	128 ± 16	NT	NT	NT	NT
MAP (mmHg)	MMK	80 ± 11	131 ± 30[a]	128 ± 31[a]	119 ± 19[a]	112 ± 22[a]	106 ± 18	109 ± 20	101 ± 13	98 ± 16
	MMKA	77 ± 9	142 ± 16[a]	133 ± 19[a]	120 ± 13[a]	99 ± 15	NT	NT	NT	NT
	MMKY	71 ± 16	143 ± 13[a]	139 ± 15[a]	117 ± 15[a]	92 ± 15	NT	NT	NT	NT
DAP (mmHg)	MMK	62 ± 10	113 ± 28[a]	110 ± 26[a]	97 ± 24[a]	92 ± 21[a]	87 ± 14	81 ± 14	80 ± 9	79 ± 12
	MMKA	55 ± 18	127 ± 15[a]	118 ± 18[a]	104 ± 13[a]	76 ± 15	NT	NT	NT	NT
	MMKY	52 ± 14	126 ± 10[a]	123 ± 16[a]	100 ± 19[a]	78 ± 19	NT	NT	NT	NT
RT (°C)	MMK	37.0 ± 1.3	37.1 ± 1.2	37.1 ± 1.2	37.2 ± 1.3	37.1 ± 1.4	37.1 ± 1.4	37.1 ± 1.4	37.0 ± 1.4	37.1 ± 1.4
	MMKA	37.8 ± 0.5	37.8 ± 0.6	37.7 ± 0.8	37.8 ± 0.7	37.5 ± 0.8	NT	NT	NT	NT
	MMKY	37.6 ± 0.6	37.7 ± 0.6	37.7 ± 0.6	37.8 ± 0.7	37.1 ± 0.5	NT	NT	NT	NT

Data: mean ± SD (n = 6). HR, heart rate; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; RT, rectal temperature; NT, not tested;
MMK, medetomidine-midazolam-ketamine combination;
MMKA, medetomidine-midazolam-ketamine combination followed 20 minutes later by atipamezole;
MMKY, medetomidine-midazolam-ketamine combination followed 20 minutes later by yohimbine.
[a]significantly different ($P < 0.05$) from baseline value.
[b]significantly different ($P < 0.05$) from MMK.

Table 4. Respiratory rates and blood gases in dogs after administration of medetomidine/midazolam/ketamine (MMK), medetomidine/midazolam/ketamine-atipamezole (MMKA) and medetomidine/midazolam/ketamine-yohimbine (MMKY)

	Groups	Pre	5 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min
RR (beats/min)	MMK	16 ± 8	17 ± 9	17 ± 7	18 ± 9	19 ± 9	20 ± 11	21 ± 10	22 ± 10	23 ± 9
	MMKA	20 ± 5	25 ± 14	20 ± 7	21 ± 7	25 ± 5	NT	NT	NT	NT
	MMKY	15 ± 3	19 ± 9	15 ± 60	15 ± 3	29 ± 13	NT	NT	NT	NT
pH	MMK	7.3 ± 0.1	7.3 ± 0.1	7.2 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	7.3 ± 0.7	7.3 ± 0.1	7.3 ± 0.1
	MMKA	7.3 ± 0.0	7.3 ± 0.1	7.2 ± 0.1	7.3 ± 0.0	7.4 ± 0.1	NT	NT	NT	NT
	MMKY	7.3 ± 0.0	7.3 ± 0.1	7.2 ± 0.0	7.3 ± 0.0	7.4 ± 0.0	NT	NT	NT	NT
$PaCO_2$ (mmHg)	MMK	56.4 ± 9.6	56.1 ± 18.3	61.6 ± 28.3	50.8 ± 10.3	48.7 ± 7.6	48.6 ± 15.1	45.2 ± 11.5	41.1 ± 8.0	41.1 ± 9.3
	MMKA	44.6 ± 2.0	44.1 ± 10.6	46.2 ± 6.4	45.0 ± 5.6	43.6 ± 5.3	NT	NT	NT	NT
	MMKY	51.3 ± 5.6	50.6 ± 10.3	56.8 ± 10.2	50.6 ± 7.6	42.1 ± 9.4	NT	NT	NT	NT
PaO_2 (mmHg)	MMK	108.6 ± 19.4	73.6 ± 17.0[a]	63.6 ± 14.4[a]	73.0 ± 15.5[a]	83.8 ± 16.7[a]	96.0 ± 12.2	98.2 ± 9.2	100.0 ± 12.5	102.4 ± 9.8
	MMKA	102.6 ± 46.9	63.6 ± 11.6[a]	65.8 ± 10.8[a]	85.2 ± 9.4[a]	108.0 ± 16.1	NT	NT	NT	NT
	MMKY	102.3 ± 35.2	58.4 ± 11.7[a]	55.2 ± 6.8[a]	79.0 ± 3.4[a]	105.4 ± 10.0	NT	NT	NT	NT
SaO_2 (%)	MMK	100.0 ± 0.0	90.6 ± 6.4[a]	86.4 ± 6.8[a]	90.8 ± 5.2[a]	90.6 ± 10.5[a]	96.2 ± 1.9	97.2 ± 0.5	97.6 ± 0.6	97.6 ± 0.6
	MMKA	100.0 ± 0.0	87.0 ± 8.0[a]	86.4 ± 9.7[a]	94.6 ± 1.1[a]	98.0 ± 0.7	NT	NT	NT	NT
	MMKY	99.8 ± 0.5	83.0 ± 12.7[a]	80.8 ± 5.9[a]	93.2 ± 1.1[a]	97.8 ± 0.8	NT	NT	NT	NT

Data: mean ± SD (n = 6). RR, raspiratory rate; $PaCO_2$, carbon dioxide partial pressure; PaO_2, arterial oxygen partial pressure; SaO_2, arterial oxygen saturation; NT, not tested;
MMK, medetomidine-midazolam-ketamine combination;
MMKA, medetomidine-midazolam-ketamine combination followed 20 minutes later by atipamezole;
MMKY, medetomidine-midazolam-ketamine combination followed 20 minutes later by yohimbine.
[a] Significant different ($P < 0.05$) from baseline value.

Table 5. Scores of sedation (spontaneous posture) and response to noxious stimulus (pedal withdrawal) after the administration of medetomidine/midazolam/ketamine (MMK), medetomidine/midazolam/ketamine-atipamezole (MMKA) and medetomidine/midazolam/ketamine-yohimbine (MMKY)

	Groups	Pre	5 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min
Spontaneous posture	MMK	0.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0
	MMKA	0.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	1.8 ± 0.5[a,b]	NT	NT	NT	NT
	MMKY	0.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	5.0 ± 0.0	2.2 ± 0.5[a,b]	NT	NT	NT	NT
Response to noxious stimulus	MMK	0.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0
	MMKA	0.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.00	1.0 ± 0.0[a,b]	NT	NT	NT	NT
	MMKY	0.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	1.0 ± 0.0[a,b]	NT	NT	NT	NT

Data: mean ± SD. NT: not tested; MMK: medetomidine-midazolam-ketamine combination,
MMKA: medetomidine-midazolam-ketamine combination followed 20 minutes later by atipamezole,
MMKY: medetomidine-midazolam-ketamine combination followed 20 minutes later by yohimbine.
[a]significantly different from baseline value ($P < 0.05$).
[b]significantly different from MMK ($P < 0.05$).

group, the blood pressures significantly increased within 5 minutes after MMK administration and remained consistently above the baseline value for 70 minutes. In the MMKA and MMKY groups, the blood pressures increased for 20 minutes, but after administration of atipamezole or yohimbine they were recovered to baseline value. There were not significantly different in blood pressures between groups. Rectal temperature did not change significantly at all time points in all groups.

Respiratory rate and blood gases

Respiratory rate and blood gas analysis were shown in Table 4. Respiratory rate was increased after MMK administration, but there were not significantly different over times and among groups. In all three groups, the arterial pH decreased during the first 10 minutes and then gradually increased. But the arterial pH tended to be higher in the MMKA or MMKY group than those in the MMK group at 30 minutes. The carbon dioxide partial pressure ($PaCO_2$) increased during the first 10 minutes and then decreased. But the $PaCO_2$ tended to be lower in the MMKA or MMKY group than those in the MMK group at 30 minutes. The arterial oxygen partial pressure (PaO_2) and arterial oxygen saturation (SaO_2) significantly decreased within 5 minutes following MMK administration and remained consistently below the baseline value for 70 minutes in the MMK group, but after administration of atipamezole or yohimbine they were recovered to baseline value in the MMKA and MMKY groups.

Discussion

Alpha-agonists have proved very effective as sedative-analgesic adjuncts when co-administered with dissociatives, benzodiazepines or opioid agonists (11,13). The combining of low doses of α_2-agonist, dissociative and benzodiazepine results in a synergic anesthetic effect while minimizing the undesirable side effects of these three classes of drugs. Based on the previous findings described above, we determined intramuscular doses of 0.04 mg/kg medetomidine, 0.5 mg/kg midazolam and 5 mg/kg ketamine for this study. This study showed that MMK at the given doses used produced good anesthesia with excellent muscle relaxation and analgesia for 70 minutes in dogs.

Ebner *et al* reported that cats with 0.02 mg/kg medetomidine, 0.5 mg/kg midazolam and 2.0 mg/kg ketamine combination intramuscularly in one syringe had been immobilized for 68 ± 11 min (5). The doses of 0.5 mg/kg midazolam, combined with 0.02 or 0.03 mg/kg medetomidine, and 2 or 3 mg/kg ketamine was suitable as a repeatable IM immobilization method for non-invasive procedures in healthy cats (5). Present result (dogs with 0.04 mg/kg medetomidine, 0.2 mg/kg midazolam and 5 mg/kg ketamine combination in one syringe) revealed that dogs had been anesthetized for 88.8 ± 9.7 min, possible for general surgical procedures such as dental prophylaxis, ovariohysterectomy or castration.

Complete reversal of sedative, analgesic and cardiovascular effects of medetomidine is achieved when atipamezole or yohimbine was administered intravenously in this study. The previous study demonstrated that atipamezole alone did not markedly antagonize MMK anesthesia. However, this study revealed that atipamezole or yohimbine administration was effective in antagonizing the anesthesia induced by MMK combination.

Lee *et al* reported that they inserted arterial catheter into left dorsal metatarsal artery of each pig masked down by isoflurane. After inserting the catheter, isoflurane was discontinued, and then the pigs were allowed to recover for 60 minutes prior to administration of the anesthesia treatment drugs (10). In this study, we inserted arterial catheter into the dorsal pedal artery of each dog masked down by isoflurane. After inserting the catheter, we followed Lee *et al* (10).

In this study, all dogs tested were constantly induced to a deep sedation, and there were little variance of induction time or degree of sedation induced between each dog. Administra-

tion of atipamezole or yohimbine quickly reversed the effects induced by MMK, and recumbency, standing and anesthesia times were significantly reduced as compare with MMK group. In this study, the atipamezole dose of 0.24 mg/kg was selected for reversal of 0.04 mg/kg medetomidine, because the effective reversal dose of atipamezole in dogs has been found to be four to six times that of medetomidine (9). Dose calculation of yohimbine is made based on agonist/antagonist ratio of approximately 10:1 for dogs. Therefore, if the initial dose of xylazine is 1.1 to 2.2 mg/kg IM or SC for dogs, then yohimbine would be given IV at a dose of 0.11 to 0.22 mg/kg (1). In this study, the yohimbine dose of 0.2 mg/kg was determined.

In dogs, atipamezole effectively reversed sedation and significantly shortened arousal time and total recovery time without apparent side effects produced by medetomidine-midazolam or medetomidine-ketamine. Atipamezole also effectively reversed changes in heart rate, respiratory rate and body temperature (14). In this study, a significant shortening of the recovery period was obtained when atipamezole was used. Curro *et al.* reported that Siberian tigers were able to stand 21 ± 2 minutes after MMK anesthesia (0.05 mg/kg medetomidine, 1.0 mg/kg midazolam and 2.5 mg/kg ketamine) that was reversed by 0.25 mg/kg atipamezole intramuscularly (3).

Yohimbine is used as a selective α_2-adrenoceptor antagonist of the sedative and cardiovascular effects of xylazine in dogs and cats (1). Yohimbine present all four pharmacological subtypes of the α_2- adrenoceptor (A, B, C and D) in ligand affinity, and has a approximately 60 times more selective for the α_2- than the α_1- adrenoceptor (13). The administration of 0.2 mg/kg yohimbine showed noticeable effects on recovery from MMK anesthesia in this study.

In this study, there were significant decreases in heart rate, cardiac arrhythmias and hypertension after MMK administration. On the other hand, the heart rate in the MMKA and MMKY groups were recovered to baseline values, probably as a result of the reversal of the MMK-induced effect by atipamezole or yohimbine. A significant decrease of heart rate in the MMK group is considered to be classic response after the administration of α_2-adrenoceptor agonist in animals. The pharmacological effects of medetomidine include depression of central nervous system (CNS), peripheral and cardiac vasoconstriction, bradycardia, respiratory depression and hypothermia (13). Effects on blood pressure are variable. While hypotension occurs frequently, higher doses of medetomidine can raise the blood pressure due to an effect on peripheral receptors (2). In this study, reversal of bradycardia and hypertension is mainly due to atipamezole or yohimbine.

Respiratory rate in all dog increased (but not significantly) following MMK administration and the pattern become more regular. The most significant finding in the respiration and gas exchange portion of this study was hypoxemia following the administration of MMK. The PaO_2 and SaO_2 in the MMK group decreased with time, and were significantly lower than the baseline value at 5, 10, 20 and 30 minutes. On the other hand, the PaO_2 and SaO_2 were recovered to baseline value after administration of atipamezole or yohimbine in the MMKA and MMKY groups. Improvement in hypoxemia occurred after administration of atipamezole or yohimbine. Therefore, atipamezole and yohimbine appears to have minimal effects on cardiopulmonary function in dogs in this study.

In this study, the administration of atipamezole or yohimbine was considered to be effective in antagonizing the anesthesia and reversing adverse effects induced by MMK in dogs. Atipamezole or yohimbine alone reversed effectively the anesthesia, hypoxemia, bradycardia and hypertension produced by MMK. Therefore, atipamezole or yohimbine can be widely and practically applied to clinics by shortening recovery time after administration of clinical dose of MMK in dogs. Also the atipamezole or yohimbine can be used for antagonizing overdosage of MMK.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (No.2010-0024553).

References

1. Andréjak M, Ward M, Schmitt H. Cardiovascular effects of yohimbine in anaesthetized dogs. Eur J Pharmacol 1983; 94: 219-228.
2. Cullen LK. Medetomidine sedation in dogs and cats: a review of its pharmacology, antagonism and dose. Br Vet J 1996; 152: 519-535.
3. Curro TG, Okeson D, Zimmerman D, Armstrong DL, Simmons LG. Xylazine-midazolam-ketamine versus medetomidine-midazolam-ketamine anesthesia in captive Siberian tigers (Panthera tigris altaica). J Zoo Wildl Med 2004; 35: 320-327.
4. Ebner J, Wehr U, Baumgartner C, Erhardt W, Henke J. Partial antagonization of midazolam-medetomidine-ketamine in cats-atipamezole versus combined atipamezole and flumazenil. J Vet Med A Physiol Pathol Clin Med 2007; 54: 518-521.
5. Ebner J, Wehr U, Busch R, Erhardt W, Henke J. A comparative clinical study of three different dosages of intramuscular midazolam- medetomidine-ketamine immobilization in cats. J Vet Med A Physiol Pathol Clin Med 2007; 54: 418-423.
6. Hellyer PW, Freeman LC, Hubbell JA. Induction of anesthesia with diazepam-ketamine and midazolam-ketamine in greyhounds. Vet Surg 1991; 20: 143-147.
7. Jalanka H, Skutnabb K, Damstén Y. Preliminary results on the use of medetomidine-ketamine combinations in the dog. Acta Vet Scand Suppl 1989; 85: 125-127.
8. Ko JC, Fox SM, Mandsager RE. Sedative and cardiorespiratory effects of medetomidine, medetomidine-butorphanol, and medetomidine-ketamine in dogs. J Am Vet Med Assoc 2000; 216: 1578-1583.
9. Kwon YS, Joo EJ, Jang KH. The clinical effectiveness of atipamezole as a medetomidine-tiletamine/zolazepam antagonist in dogs. J Vet Clin 2003; 20: 286-293.
10. Lee JY, Jee HC, Jeong SM, Park CS, Kim, MC. Comparison of anaesthetic and cardiorespiratory effects of xylazine or

medetomidine in combination with tiletamine/zolazepam in pigs. Vet Rec 2010; 167: 245-249.
11. Tranquilli WJ, Benson GJ. Advantages and guidelines for using alpha-2 agonists as anesthetic adjuvants. Vet Clin North Am Small Anim Pract 1992; 22: 289-293.
12. Ueoka N, Hikasa Y. Antagonistic effects of atipamezole, flumazenil and 4-aminopyridine against anaesthesia with medetomidine, midazolam and ketamine combination in cats. J Feline Med Surg 2008; 10: 47-54.
13. Verstegen J, Fargetton X, Donnay I, Ectors F. An evaluation of medetomidine/ketamine and other drug combinations for anaesthesia in cats. Vet Rec 1991; 128: 32-35.
14. Verstegen J, Fargetton X, Zanker S, Donnay I, Ectors F. Antagonistic activities of atipamezole, 4-aminopyridine and yohimbine against medetomidine/ketamine-induced anaesthesia in cats. Vet Rec 1991; 128: 57-60.
15. Verstegen J, Petcho A. Medetomidine-butorphanol-midazolam for anaesthesia in dogs and its reversal by atipamezole. Vet Rec 1993; 132: 353-357.

비글견에서 medetomidine-midazolam-ketamine 마취에 대한 atipamezole과 yohimbine의 길항효과

황학균 · 이재연 · 정성목 · 김명철[1]

충남대학교 수의과대학

요 약 : 개에서 많은 주사용 마취제가 있고, 그 부작용을 줄이기 위해 다양한 약물들을 혼합하여 사용한다. 개에서 medetomidine-midazolam-ketamine (MMK) 합제에 대한 마취효과를 알아보고, 이 합제에 대한 atipamezole과 yohimbine의 길항효과를 비교하였다. 18마리 수컷 비글견을 사용하였고, 모든 개에서 medetomidine (0.04 mg/kg), midazolam (0.2 mg/kg) 및 ketamine (5 mg/kg)을 근육주사하고, 20분 후 atipamezole (0.24 mg/kg, MMKA), yohimbine (0.2 mg/kg, MMKY) 또는 생리식염수(0.1 ml/kg, MMK)를 정맥주사하였다. 유도 및 회복시간, 진정 및 진통점수, 심박수, 혈압, 직장온도, 호흡수, 동맥혈액가스를 측정하였다. 평균마취, 흉와, 기립 및 보행시간은 MMKA와 MMKY군에서 MMK군보다 유의성있게 짧았다. 그러나 MMKA군과 MMKY군 간의 유의적인 차이는 없었다. 모든 군에서 MMK 투여는 개에서 만족스런 진정 및 진통을 일으켰다. 그러나 atipamezole이나 yohimbine 투여 후 자세점수 및 유해자극반응은 MMK군에 비해 MMKA나 MMKY군에서 유의성있게 감소하였다. 본 실험 결과 MMK는 양호한 진정 및 마취효과를 나타냈고, atipamezole과 yohimbine은 개에서 MMK 마취를 길항하는 데 안전하고 효과적으로 사용될 수 있을 것으로 사료된다.

주요어 : atipamezole, medetomidine, midazolam, ketamine, yohimbine