J Vet Clin 20(1) : 33-41(2003)

Comparison of Tiletamine/Zolazepam, Xylazine-Tiletamine/Zolazepam and Medetomidine-Tiletamine/Zolazepam Anesthesia in Dogs

Young-Sam Kwon, Jae-Hoon Jeong and Kwang-Ho Jang[1]

Department of Veterinary Medicine, Kyungpook National University

Abstract : The cardiopulmonary and anesthetic effects of tiletamine/zolazepam(TZ, 10 mg/kg IV), xylazine-tiletamine /zolazepam(XTZ, X: 1.1 mg/kg IM, TZ: 10 mg/kg IV) and medetomid-ine-tiletamine/zolazepam(MTZ, M: 30 μg/kg IM, TZ: 10 mg/kg IV) were evaluated to 15 healthy mongrel dogs (4.16± 0.65 kg). These dogs were randomly assigned to the three treatment groups(Control, XTZ, MTZ) with 5 dogs in each group. All experimental animals were premedicated with atropine(0.03 mg/kg, IM). Xylazine or medetomidine were administered to dogs in XTZ group and MTZ group 10 minutes after atropine injection. TZ was administered 20 minutes after atropine injection in all groups. The loss of pain response at pedal reflex and ear pinching tests in XTZ and MTZ groups were significantly extended when compared with that of Control group($P < 0.05$). Mean arousal time, mean sternal recumbency time and mean walking time in XTZ and MTZ groups were much longer compared with those of Control group($P < 0.01$). All dogs in this study showed head rocking and hypersalivation during recovery time. Body temperature decreased progressively during experimental period in all groups, but it was not significant. After TZ injection, heart beat rate significantly increased 10 and 20 minutes in Control group, and 20 and 40 minutes in XTZ group($P < 0.05$). Respiratory rate significantly decreased 0, 10, 20 and 40 minutes after TZ injection in XTZ and MTZ groups. In Control group, systolic arterial pressure (SAP) 20 minutes. diastolic arterial pressure(DAP) 10 minutes and mean arterial pressures (MAP) 10 and 20 minutes after TZ injection significantly decreased($P < 0.05$). In XTZ group, SAP, DAP and MAP significantly decreased 20 and 40 minutes after TZ injection($P < 0.05$). Thus, it was considered that XTZ and MTZ were useful in a canine surgical treatment that requires long anesthetic duration and deep analgesia.

Key words : Xylazine, medetomidine, tiletamine/zplazepam, dog

Introduction

Tiletamine [2-(ethylamino)-2-(2-thienyl) cyclohexanone hydrochloride] was first reported in 1969[27]. It is a dissociative anesthetic agent with similar pharmacologic properties to those of ketamine, but its potency and duration of action is in the midpoint between the long-acting phencyclidine and the short-acting ketamine[3,5,12,24,26-29]. The CNS effects induced by tiletamine are highly species specific. In rats and mice tiletamine causes excitation and ataxia even at low dose. This effect is not as marked in other species. Catalepsy occurs in all species when tiletamine is given in moderate doses[5,27,28].

Zolazepam [4-(o-fluorophenyl)-6,8-dihydro-1,3,8-trimethylpyrzolo[3,4-e] [1,4] diazepine-7(1H)-one] is a benzodiazepine derivative with similar pharmacologic properties to those of diazepam[3,5,12,24,26-,29]. Benzodiazepines have effects including production of amnesia, minimal depression of cardiorespiratory function, strong anticonvulsant action. It is relatively safe even when overdosed and rarely causes significant tolerance or physical dependence[27]. Zolazepam was first investigated for use in humans and is the only benzodiazepine approved by the FDA for use in animals when combined with tiletamine[32].

Zoletil®(Virbac®, France) as Telazol®(A H Robins®) is a 1 : 1 mixture by weight of tiletamine and zolazepam and a nonnarcotic, nonbarbiturate injectable anesthetic and immobilizing agent used in dogs, cats, other domestic and wild animals[24,27]. Intramuscular or intravenous administration of tiletamine-zolazepam to dogs and cats results in smooth induction and recovery from anesthesia, excellent skeletal muscle relaxation and retention of pharyngeal and palpebral reflexes. Tachycardia, however, may be a common effect and may last for 30 minutes in dogs. Other adverse effects include transient apnea, vocalization, erratic and/or prolonged recovery, involuntary muscular twitching, hypertonia, cyanosis, cardiac arrest pulmonary edema, muscle rigidity and either hypertension or hypotension[27,32].

Some α_2-agonists are used as sedatives and analgesics by veterinarians. Xylazine hydrochloride was the first reported α_2-agonist. It was synthesized in Germany in 1962 for use as an antihypertensive but was found to have potent sedative effects in animals. In the early 70's, reports of xylazine's utility as an anesthetic adjunct began appearing in American and European veterinary literature[36]. Xylazine is currently approved for use in dogs, cats, horses, deer, and elk in the United States[32].

Medetomidine is a selective and potent α_2-agonist which exerts marked sedative and analgesic effects in laboratory animals, cats and dogs. It is lipophilic, rapidly eliminated and possesses more potency and efficacy than other α_2-agonist. As with xylazine, higher doses do not result in more sedation but increase the duration of effect. Medeto-

Corresponding author.
E-mail : khojang@knu.ac.kr

midine is commonly used as a preanesthetic prior to ketamine, barbiturate, or mask induction with an inhalation anesthetic[2,34,36,41].

Lately tiletamine/zolazepam combination substitute for ketamine that commonly used for an injectable anesthetic for dogs and cats. So, this experiment is carried out to evaluate the anesthetic effects of tiletamine/zolazepam, xylazine-tiletamine/zola-zepam and medetomidine-ti-letamine/zolazepam and to assess the most useful anesthetic combination.

Materials and Methods

Animals

Fifteen healthy adult, mixed-breed dogs of either sex, weighing from 3.45 to 5.25 kg(mean±SD, 4.21±0.55 kg) were studied. They were vaccinated (Vangard puppy®, Pfizer Co., France) 1 month before the experiment. They were housed individually and fed a commercial dry food (Biomill®, Woosung Feed Co Ltd, Korea). Food and water were withheld for 12 hrs prior to the experiment. Dogs were randomly allotted to one of three groups(n = 5); tiletamine/zolazepam(Control), xylazine-tileta-mine/zola-zepam(XTZ) and medetomidine-tiletamine/zolazepam(MTZ).

Treatment

Hair was clipped at both catheter and needle electrodes inserted site. All experimental animals were premedicated with atropine(Atropine sulfate®, Dong-A Pharm Co. Ltd., Korea, 0.03 mg/kg, IM). Xylazine(Rumpun®, Bayer Korea, Korea, 1.1 mg/kg, IM) or medetomidine(Domitor®, Orion Co, Finland, 30 μg/kg, IM) were administered to dogs in XTZ group and MTZ group 10 minutes after atropine injection. TZ(Zoletil50®, Virbac, France, 10 mg/kg, IV) was administered 10 minutes after the preanesthetics injection in XTZ and MTZ groups, and 20 minutes after atropine injection in Control group.

Dogs were positioned dorsal recumbency. A catheter inserted into the femoral artery after surgical approach with routine methods was connected to a tube filled with heparin. The tube was connected to a polygraph(Model 7P1, Grass instrument Co., USA) for measuring blood pressure.

Measurements

1) Pedal reflex and ear pinching test: The interdigital region and an ear was grasped with a mosquito forcep for 5 seconds, every 10 minutes from 10 minutes after TZ injection till showing pain response. Pain response was judged by bending the hind leg and shaking head.

2) Duration of anesthesia: From the time of TZ injection, arousal time until dog lifted its head, sternal recumbency time until the dog positioned sternal recumbency, and walk time until the dog could hold up its body and take a step on a nonskid surface were measured.

3) Body temperature, heart beat rate, and respiratory rate: These were recorded before experiment, 0(right before TZ injection), 10, 20, 40, and 60 minutes after TZ injection till the dog lifted its head. Body temperature with a electrothermometer, respiratory rate with stethoscope, and heart beat rate with the polygraph of electrocardiography were measured .

4) Arterial blood pressure: Via the femoral artery, systolic arterial pressure(SAP), diastolic arterial pressure(DAP) and mean arterial pressure(MAP) were measured with the polygraph during 30 seconds. These were recorded after catheter inserted into the femoral artery, 0, 10, 20, 40, and 60 minutes after TZ injection till the dog lifted its head.

5) Blood gas analysis: Via the tube that was connected to the catheter inserted into the femoral artery, 1.5 ml of arterial blood was collected and pH, PaO_2, $PaCO_2$ were measured with blood gas analyzer(AVL compact 1 Blood Gas Analyzer, AVL Scientific Co.) at same time point of measuring arterial blood pressure.

6) Complete blood count(CBC), and blood chemistry test: Blood(1.5 ml) samples were collected from the jugular vein on day-1(before experiment), 0(40 minutes after TZ injection), 1, 3 and 7 after experi-ment. Blood urea nitrogen (BUN), creatinine, serum alanine aminotransfer-ase(SALT), serum aspartate aminotrasferase(SAST), and total protein were measured with auto dry chemistry analyzer (SPOTCHEM SP-4410, Kyoto DAIICHI KAGAGU Co. Ltd., Japan) and CBC was evaluated with auto blood cell analyzer(HEMA VET 850, CDC Technologies Inc.).

Statistical analysis

All data were expressed as mean±standard deviation (SD). The comparisons for statistical significance among groups were performed with the Student's *t*-test and *P* values < 0.05 were considered significant.

Results

Duration of analgesia

The absence of pain response lasted for 10±0.0(mean± SD) minutes in Control group, 38±4.5 minutes in XTZ group and 44±8.9 minutes in MTZ group based on pedal reflex, and 18±4.5 minutes in Control group, 40±12.2 minutes in XTZ group and 56±12.2 minutes in MTZ group based on ear pinching test. The absence of pain reflex in XTZ and MTZ groups in both tests were significantly extended, compared with those in Control group($P < 0.05$) (Fig 1).

Duration of anesthesia

Mean arousal time(MAT) was 23.4±8.8(mean±SD) minutes in Control group, 50.5±3.4 minutes in XTZ group and 67.3±7.0 minutes in MTZ group. In XTZ and MTZ group, MAT was significantly extended compared with Control group ($P < 0.01$). Mean sternal recumbency time(MST) was 34.4±9.7 minutes in Control group, 58.3±6.0 minutes in XTZ group and 73.1±6.4 minutes in MTZ group. In XTZ

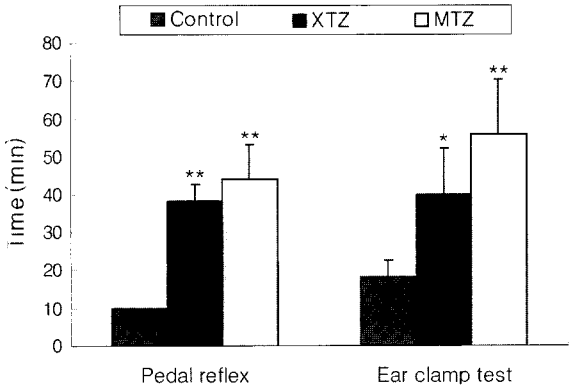

Fig 1. Comparison of analgesic time in dogs anesthetized with tiletamine/zolazepam
Control: tiletamine/zolazepam only(10 mg/kg, IV)
XTZ: xylazine(1.1 mg/kg,IM)-tiletamine/zolazepam(10mg/kg, IV)
MTZ: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV)
* P<0.05 compared with TZ
**: P<0.01 compared with TZ

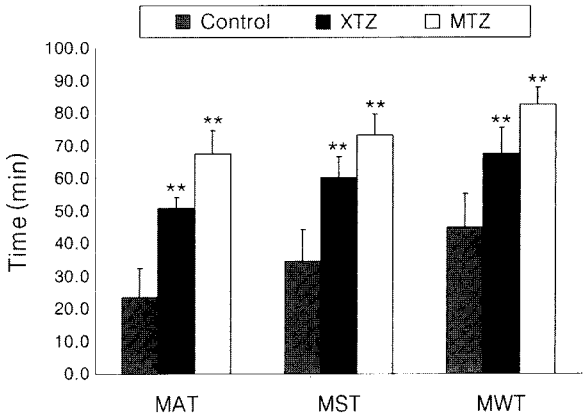

Fig 2. Comparison of analgesic time in dogs anesthetized with tiletamine/zolazepam
*: P<0.01 compared with TZ

and MTZ group, time to dogs seated sternal recumbency was significantly extended compared with that in control group($P < 0.01$). Mean walking time(MWT) was 44.8±10.2 minutes in Control group, 67.3±8.0 minutes in XTZ group and 82.3±5.4 minutes in MTZ group. In XTZ and MTZ groups, mean walking time was significantly extended compared with that in Control group ($P < 0.01$) (Fig 2). In Control group, all dogs showed head rocking and hypersalivation, and a dog showed circling movement. Dogs in XTZ and MTZ groups also showed head rocking and hypersalivation, but their recovery was more smooth than those of Control group. In Control group, all dogs showed excitation, shaking their head and neck rocking or circling movement and salivation when recovery period. In XTZ group, 3 dogs vomited after xylazine administration and all dogs showed shaking their head and salivation in recovery period, but more smoothly recovered than those of Control group. In MTZ group, any dogs did not vomit but showed their head and neck rocking and salivation in recovery period, but more weaker than those of Control group.

Body temperature, heart rate, and respiratory rate

Body temperature did not change significantly over time in all groups. Body temperature, however, progressively decreased in anesthetic period and increased in reversal period. Heart beat rate significantly increased 10 minutes and 20 minutes in Control group, but significantly decreased 20 minutes and 40 minutes in XTZ group($P < 0.05$) after TZ injection, respectively. In MTZ group, heart beat rate didn't change significantly over time. Respiratory rate significantly

Table 1. Values of temperature, heart rates, and respiratory rates obtained in each recording stages in dogs anesthetized with tiletamine/zolazepam (mean ± SD)

Group	Variables	Time after tiletamine/zolazepam injection (minutes)					
		-10	0	10	20	40	60
Control	BT	39.3±0.6	39.3±0.4	39.1±1.0	39.1±1.3		
	HR	136.4±20.6	129.3±4.1	220.0±33.5*	226.7±23.1*		
	RR	30.5±7.9	28.0±4.3	24.0±5.9	28.7±11.0		
XTZ	BT	39.0±0.5	38.8±0.8	38.7±0.8	38.3±0.9	38.2±0.8	
	HR	109±19.1	104.1±21.9	91.0±33.5	84.0±21.7*	84.0±16.7*	
	RR	37.2±17.8	20.4±12.4*	15.6±9.1*	16.4±5.0*	30.4±15.6*	
MTZ	BT	39.1±0.7	39.2±0.4	39.1±0.8	38.3±1.0	38.8±0.8	38.4±0.6
	HR	115.2±11.8	108.0±11.0	104.0±21.9	108.0±17.9	96.0±26.1	105.1±10.0
	RR	34.0±4.2	21.6±6.8*	17.2±7.0*	17.4±4.4**	24.8±5.0*	31.0±3.5

BT: Body temperature(°C)
HR: Heart rates(beats/min),
RR: Respiratory rates(breaths/min)
*: $P < 0.05$ compared with values of before atropine injection
**: $P < 0.01$ compared with values of before atropine injection

Table 2. Values of arterial blood pressures in dogs anesthetized with tiletamine/zolazepam (mean ± SD)

Group	Variables	Time after tiletamine/zolazepam injection (minutes)					
		-10	0	10	20	40	60
Control	SAP	275.0± 6.2	275.4± 8.7	256.7±17.5*	258.5± 4.0*		
	DAP	220.3±15.8	219.1±19.1	175.1±34.3*	171.8±35.9*		
	MAP	245.8±10.0	245.1±12.7	213.0±24.1*	215.1±19.9*		
XTZ	SAP	270.4± 7.3	249.0±23.4	235.2±23.2*	221.0±18.8*	204.2±18.3**	
	DAP	205.2±25.1	176.1±46.7	168.6±23.2*	141.4±27.3*	125.1±20.9**	
	MAP	237.8±15.6	212.6±35.0	201.9±22.5*	181.2±22.7**	164.7±19.3**	
MTZ	SAP	263.8± 5.4	266.2± 2.8	263.4± 4.4	260.0± 5.4	241.9±18.4	244.1±15.1
	DAP	180.0±27.5	208.5±12.1	215.0±24.1	198.5±24.4	178.6±26.4	180.5±17.1
	MAP	222.1±16.0	236.9± 6.8	239.3±12.3	229.5±13.8	211.8±18.9	170.8±96.4

SAP: Systolic arterial pressure(mmHg)
DAP: Diastolic arterial pressure(mmHg)
MAP: Mean arterial pressure(mmHg)
*: $P < 0.05$ compared with -10
**: $P < 0.01$ compared with -10

Table 3. Values of arterial blood analysis after tiletamine/zolazepam injection in dogs (mean ± SD)

Group	Variables	Time after tiletamine/zolazepam injection (minutes)					
		-10	0	10	20	40	60
Control	pH	7.360±0.091	7.302±0.072	7.271±0.047	7.277±0.076		
	$PaCO_2$	26.8±6.7	28.9±3.2	26.4±3.9	21.8±3.2		
	PaO_2	108.5±22.6	118.5±21.2	134.7±15.4	136.0±21.1		
XTZ	pH	7.407±0.045	7.307±0.068	7.215±0.137	7.233±0.162	7.343±0.065	
	$PaCO_2$	26.9±4.7	26.1±4.3	27.9±4.1	25.5±4.6	25.8±2.2	
	PaO_2	112.0±21.9	145.4±12.4	121.5±34.2	131.9±23.7	131.8±21.8	
MTZ	pH	7.391±0.045	7.355±0.056	7.272±0.098	7.303±0.109	7.340±0.035	7.332±0.056
	$PaCO_2$	27.3±3.0	23.3±4.5	25.8±7.5	20.8±4.6	27.2±4.2	23.1±2.9
	PaO_2	124.6±20.7	123.8±28.9	96.7±14.8	113.9±25.4	133.1±28.5	132.1±19.4

$PaCO_2$: Arterial partial pressure of carbon dioxide (mmHg)
PaO_2: Arterial partial pressure of oxygen(mmHg)

decreased 0, 10, 20 and 40 minutes after TZ injection in XTZ and MTZ groups. In Control group, however, respiratory rate did not change significantly(Table 1).

Arterial blood pressure

Arterial blood pressure progressively decreased over time in all groups(Table 2).

After TZ injection, SAP, DAP and MAP significantly decreased 10 and 20 minutes later ($P < 0.05$) in Control group, 20 and 40 minutes later ($P < 0.05$) in XTZ group. In MTZ group, they did not change significantly.

Blood gas analysis

Insignificant changes in pH, PaO_2 and $PaCO_2$ levels were seen in all groups(Table 3).

Complete blood count and blood chemistry

Insignificant changes in CBC levels were seen in all groups, except WBC level in XTZ group on day 1 after experiment. It increased significantly($P < 0.05$)(Table 4). The levels of SALT, SAST, BUN, creatinine and total protein were in normal ranges and did not significantly change in all groups(Table 5).

Discussion

The choice of anesthetic agents in veterinary practice is influenced by many factors including patient's condition, familiarity with a specific anesthetic regimen, cost, personnel, record keeping, training of the veterinarian and caseload of the practice[31]. In view of training of the veterinarian and caseload of the practice, ketamine is the most commonly

Table 4. Changes in complete blood count in dogs anesthetized with tiletamine/zolazepam (mean ± SD)

Groups	Variables	Time after experiment (day)				
		-1	0	1	3	7
Control	WBC	15.90±3.09	16.05±5.70	20.00±6.08	16.52±5.49	15.70±1.88
	RBC	8.23±1.23	7.45±0.82	6.53±1.80	6.82±1.01	6.89±1.82
	PLT	416±91	396±44	403±56	417±35	371±69
	PCV	45.9±4.7	41.1±6.0	42.7±3.8	44.1±4.9	44.6±5.6
XTZ	WBC	13.82±1.04	15.03±3.79	22.76±4.17*	15.83±1.44	13.34±1.70
	RBC	8.07±1.14	7.14±0.55	7.34±1.53	7.99±1.38	9.33±1.19
	PLT	439±95	426v38	431±64	388±38	372±92
	PCV	47.4±4.2	44.3±4.1	45.6±3.9	46.1±2.4	47.2±0.9
MTZ	WBC	13.44±2.60	13.79±4.20	17.92±6.90	14.57±5.39	15.79±1.94
	RBC	7.67±0.54	6.68±0.78	6.84±1.82	6.95±0.93	6.77±1.23
	PLT	428±117	388±92	417±82	367±90	365±65
	PCV	49.6±4.7	45.6±4.1	44.4±3.1	47.9±2.4	46.2±2.9

WBC: white blood cell(K/μl)
RBC: red blood cell(M/μl)
PLT: platelet(K/μl)
PCV: packed cell volume(%)
* $P < 0.05$

Table 5. Changes in Serum chemistry values in dogs anesthetized with tiletamine/zolazepam (mean ± SD)

Groups	Variables	Recording stage(day)				
		-1	0	1	3	7
Control	SALT	22.0±12.7	25.4±17.6	24.4±12.2	16.8±11.2	17.4±5.7
	SAST	12.4±4.7	15.2±7.4	13.0±8.9	13.4±6.7	15.0±4.9
	BUN	17.4±3.4	14.6±3.0	15.2±4.0	12.6±5.2	12.8±5.5
	Cre	0.7±0.1	0.7±0.1	0.7±0.1	0.6±0.2	0.5±0.2
	T-Pro	6.6±0.4	6.3±0.4	6.3±0.5	6.5±0.4	6.8±0.7
XTZ	SALT	17.2±11.3	18.4±10.8	16.4±7.1	13.6±6.5	12.4±6.1
	SAST	10.8±4.0	11.8±6.3	10.0±1.4	11.0±2.8	9.2±0.4
	BUN	20.2±6.7	13.4±4.0	16.4±5.8	19.4±8.5	16.8±5.6
	Cre	0.8±0.4	0.8±0.1	0.7±0.1	0.7±0.1	0.8±0.1
	T-Pro	5.5±0.8	5.6±0.1	6.2±0.5	6.4±0.3	6.8±0.6
MTZ	SALT	22.0±12.7	25.4±17.6	24.4±12.2	16.8±11.2	17.4±5.7
	SAST	11.2±2.2	10.0±1.7	13.0±3.8	10.0±1.4	9.8±1.8
	BUN	19.2±4.9	20.6±8.2	13.6±4.6	13.8±3.5	21.0±6.9
	Cre	0.7±0.2	0.7±0.1	0.7±0.1	0.6±0.1	0.7±0.2
	T-Pro	7.1±0.6	7.2±1.2	6.2±0.8	6.3±0.9	7.3±1.5

SALT: serum alanine aminotransfer-ase(IU/L)
SAST: serum aspartate aminotrasferase(IU/L)
BUN: blood urea nitrogen(mg/dl)
Cre: creatinine(mg/dl)
T-Pro: total protein(g/dl)

used dissociative injectable anesthetic agent for animal anesthesia[32,41,44].

Zoletil® is a nonopioid, nonbarbiturate injectable anesthetic agent. It consists of a 1:1(weight:weight) combination of tiletamine and zolazepam. The pharmacodynamics of tiletamine, a dissociative anesthetic agent, are similar to those of ketamine, but tiletamine has a longer duration of action and greater analgesic effect than does ketamine[10,24-29,37]. Tiletamine is only approved for use in combination with a benzodiazepine derivative, zolazepam[27].

Xylazine and medetomidine are α_2-adrenergic agonists commonly used as preanesthetics with dissociative anesthetics. These α_2-adrenergic agonists can mediate analgesia, anxiolysis, sedation, sympatholysis, and control of hypertension. Xylazine has adverse effects including vomiting, hypersalivation, hyperurination, hyperglycemia, arrythmia, and bradycar-dia[19,20,21,30,32,36,41].

Emesis may occur in dogs and cats soon after xylazine is administered[13,36]. It was reported that medetomidine also induced emesis in dogs(30-40 μg/kg) and cats(80-110 μg/kg)[40], but no emesis was observed in any dogs treated medetomidine(30 μg/kg, IM) in this study. Xylazine and TZ can cause hypersalivation. Atropine or glycopyrrolate has been recommended to be used with xylazine and TZ to control this problem[33,37]. Although all dogs were premedicated with atropine, they showed hypersalivation during recovery time in this study.

Other side effects including head rocking and muscle tremor were observed. The dogs of Control group showed rougher recovery than those in XTZ and MTZ groups. When TZ combination is used, there is a shorter duration of tranquilization than anesthesia due to the longer duration of tiletamine than that of zolazepam[32]. In XTZ and MTZ groups, the dogs showed smooth recovery and it was supposed that xylazine and medetomidine offered longer duration of tranquilizing effect.

Pedal reflex, limb flexing in response to painful stimulation on the digits or interdigital region and ear pinching test, head shaking in response to ear pinching are useful guide to assess the depth of anesthesia in dogs, cats, rabbits, guinea pigs and rats[35]. However, other studies have reported that laryngeal, pharyngeal, and pedal reflex were maintained when TZ administered alone[16,25,31]. In this study, pedal reflex was shown in all dogs of Control group 10 minutes after TZ administration. Tiletamine offered sufficient analgesic effect but duration was short whereas zolazepam offered strong muscle relaxation and anticonvulsant action with unsatisfactory analgesic effect. The duration showing no response to pedal reflex and ear pinching test in XTZ group were 38±4.5(mean±SD) and 40±12.2 minutes, and 44±8.9 and 56±12.2 minutes in MTZ group. These significantly increased when compared to those of Control group ($P < 0.01$). This is relevant to a previous study that reported medeto-midine(20 μg/kg, IM) elevated pressure response thresholds for 30 minutes and thermal response threshold for 180 minutes after administration in beagle dogs[2].

The dogs of Control group showed the shortest anesthetic period(23.4±8.8 minutes) and those of MTZ group showed the longest anesthetic period(67.3±7.0 minutes) in this study. The dogs in XTZ and MTZ groups had a significantly longer period of anesthesia than those in Control group ($P < 0.01$). Chang *et al.* have observed the similar study[10]. Although the duration of anesthetic period was extended significantly when TZ combined with xylazine or medetomidine, the time difference among MAT, MST and MWT of each group showed little difference. Therefore, it is supposed that xylazine and medetomidine extend anesthetic period only.

Changes of body temperature were not significant but consistently decreased during the experimental period in all groups. One study with polar bears had reported that most anesthetized bears remained stable across a wide range of ambient temperatures[6] and another study with black bears treated MTZ has reported similar result[8]. However, Booker et al. has reported that hypothermia was induced after TZ injection in *Rhesus macaque*[27]. Little changes of body temperature in this study was probably due to the temperature of the table, which was maintained at 38°C. Hypothermia may occur after TZ injection as a result of profound muscle relaxation and it seems to be related to size or weight of animal[12].

Respiratory rate increases in most species following TZ injection[27], but xylazine and medetomidine can reduce respiratory rate in dogs[4,21]. Cullen et al. have reported that respiratory rates were significantly increased after TZ administered alone in dogs[12] and Trace *et al.* have also reported that tachypnea was observed in dogs and cats, administered TZ intramusculary and intravenously[37], but Booker et al. have reported that respiratory rates were not changed significantly in *Rhesus macaque*[27]. In this study, respiratory rates of control group were significantly increased($P < 0.05$). Respiratory rates of XTZ and MTZ groups were significantly decreased($P < 0.05$) 0, 10, 20 and 40 minutes after TZ injection. Although it is considered that TZ is related to increasing respiratory rate, respiratory rates were significantly decreased in XTZ and MTZ groups. However, the pH, $PaCO_2$, and PaO_2 were not changed significantly. When TZ(2-4 mg/kg) was given intravenously to dogs without any premedication, the dogs showed apnea for about 1 minute followed by irregular, slow and shallow breathing but $PaCO_2$ remained nearly normal[14]. Although respiratory rate decreases with the administration of xylazine at clinically recommended dose, the pH, $PaCO_2$ and PaO_2 values remain virtually unchanged in dogs[21]. However, one study has reported that the pH, $PaCO_2$ and PaO_2 were significantly changed at some recording point in sheep treated with TZ[24], and similar result has been reported in horses[18]. Cullen *et al.* has reported that $PaCO_2$ was significantly increased 3, 5 and 10 minutes after TZ administered without a significant reduction in arterial PaO_2 in dogs[12]. Wood bison treated with XTZ and MTZ showed significant increase in pH and $PaCO_2$, and significant decrease in PaO_2[7].

The cardiovascular depressant effects of TZ in dogs and cats are dose dependent[31]. Xylazine induced such effect has been linked to central α_2-adrenoceptor activation. Three of five dogs showed arrhythmia in this study. Several studies in dogs have reported that the ventricular arrhythmogenic action of xylazine alone or in combination with other anesthetic agent[15,20-22,30,38,39,43]. And medetomidine also induced

arrhythmia and bradycardia[34]. Reduction of heart beat rate is caused by xylazine significantly enhancing vagal tone[1,19]. This effect is reduced by injection of antichol-inergic drugs[34,36]. Although the dogs of XTZ group were premedicated with atropine, heart beat rates significantly decreased ($P < 0.05$) 20 and 40 minutes after TZ administered in this study. In sheep[24] and cats[41], TZ caused insignificant changes in heart beat rate, but it significantly reduced heart beat rate 10 minutes after the injection in monkeys[28]. Tracy *et al.*, however, have reported that TZ raised heart beat rate in dogs and cats[37]. Other studies in dogs have reported that significant increase of heart beat rate has also been observed in dogs given TZ[12,17,37]. In this study, dogs of control group also showed significant increase of heart beat rate. The increase in heart beat rate is attributed to direct central nervous system(CNS) stimulation leading to increased sympathetic tone and perhaps decreased vagal tone[27]. However, heart beat rate of the XTZ group were significantly decreased($P < 0.05$) 20, 40 minutes after TZ administration and those of MTZ group were insignificatnly changed. This was considered as a result of vagal tone being enhanced by xylazine and medetomidine.

Changes in arterial blood pressure induced by TZ are characterized by a decrease followed by an increase after intravenous injection in dogs[17]. Tiletamine given to the dog induces tachycardia and hypertension in dogs[11], and TZ also induces tachycardia but decrease in blood pressure in dogs[42]. Thus, an increase in blood pressure at a brief period after TZ administration seems to be caused by tiletamine and a long-lasting decrease caused by zolazepam in dogs. In this study, SAP, DAP and MAP of TZ group were significantly decreased 10 and 20 minutes. The effect of xylazine on blood pressure is similar to that of TZ[44]. This effect is observed in nearly all species. Kuusela *et al.*, however, have reported that there was no significant change of SAP and DAP in dogs treated with medetomidine(40 μg/kg)[23]. Therefore, it is considered that MTZ is more useful than XTZ for patients with hypotension.

In CBC and serum chemistry, no significant change was observed except for WBC of XTZ group on day 1 after the experiment. WBC values of all groups increased on day 1 after recovery from anesthesia. This is considered as the result of inflammatory response to the surgical procedure.

Although relatively low dose of TZ was used in this study, XTZ and MTZ combinations showed safe and good anesthetic effects. But, prolonged duration of recovery period after TZ injection is considered to be the problem to be solved. One study has reported that Ro 15-1788 has shortened duration of recovery period in TZ injected dogs, but this induced side effects including continuous or semi-continuous padding and whining[3].

The duration of loss of pain reflex was long in XTZ and MTZ groups, but we don't know whether this was the real loss of perception of pain or only immobilization due to muscle relaxation. Further studies using electroencephalography need to be performed for accurate evaluation of this result.

The results from our study indicate that xylazine(1.1 mg/kg) -TZ(10 mg/kg) and medetomidine(30 μg/kg)-TZ(10 mg/kg) are considered to be useful in canine operation that requires long anesthetic duration and strong analgesic effect.

References

1. Antonaccio MJ, Robson RD, Kerwin L. Evidence for increased vagal tone and enhancement of baroreceptor reflex activity ater xylazine (2-(2,6-dimethylphe-nylamino)4-H-5,6-dihydro-1,3-thia-zine) in anesthetized dogs. Eur J Pharmacol 1973; 23: 311-315.
2. Barnhart MD, Hubbell JAE, Muir WW. Evaluation of the analgesic properties of acepromazine maleate, oxymorphone, medetomidine and a combination of acepromazine-oxymorphone. Vet Anaesth Analg 2000; 27: 89-96.
3. Bendnarski RM, Muir WW, Tracy CH. The effects of tolazoline, doxapram, and Ro 15-1788 on the depressant action of Telazol. Vet Med 1989; 84: 1016-1022.
4. Bergström K. Cardiovascular and pulmonary effects of a new sedative/analge-sic(medetomidine) as a preanesthetic drugs in the dog. Acta Vet Scand 1988; 29: 109-116.
5. Booker JL Jr., Erickson HH, Fitzpatrick EL. Cardiodynamics in the rhesus macaque during dissociative anesthesia. Am J Vet Res 1982; 43: 671-675.
6. Cattet MRL, Caulkett NA, Polischuk SC, Ramsay MA. reversible immoilization of free-ranging polar bears with medetomi-dine-zolazepam-tiletamine and atipamezole. J Wildlife Disease 1997; 33: 611-617.
7. Caulkett NA, Cattet MRL, Cantwell CS, Cool N, Olsen W. Anesthesia of wood bison with medetomidine-zolazepam/tiletamine and xylazine-zolazepam/tiletamine combinations. Can Vet J 2000; 41: 49-53.
8. Caulkett NA, Cattet MRL. Physiological effects of medetomidine-zolazep-am-tiletamine immobilization in black bears. J Wildlife Diseases 1997; 33: 616-622.
9. Celly CS, Mcdonell WN, Young SS, Black WD. The comparative hypoxaemic effect of four 2 adrenoceptor agonists (xylazine, romifidine, detomidine and med-etomidine) in sheep. J Vet Pharmacol Therap 1997; 20: 464-471.
10. Chang HS, Jang IH. Comparison of tiletamine-zolazepam, tiletamine-zolazep-am-xylazine and ketamine-xylazine anesthesia in dogs. Korean J Vet Res 1998; 38: 401-412.
11. Chen G, Ensor CR, Bohner B. The pharmacology of 2-(ethylamino)-2-(2-thie-nyl)-cyclohexanone HCL (CI-634). J Pharmacol Exp Ther 1969; 168: 171-179.
12. Cullen LK, Reynoldson JA. Effects of tiletamine/zolazepam premedication on propofol. Vet Rec 1997; 140: 363-366.
13. Cullen LK. Xylazine and medetomidine in small animals: these drugs should be used carefully. Aust Vet J 1999; 77: 722-723.
14. Donaldson LL, McGrath CJ, Tracy CH. Testing low doses of intravenous Telazol in canine practice. Vet Med 1989; 84: 1202-1207.
15. Haskins SC, Peiffer RR Jr., Stowe RM. A clinical comparison of CT1341, ketamine, and xylazine in cats, Am J Vet Res 1975; 36: 1537-1543.

16. Hatch RC, Clark JD, Jernigan AD. Searching for a safe, effective antagonist to Telazol overdose. Vet Med 1988; 83: 112-117.
17. Hellyer P, Muir WW, Hubbell JAE, Sally J. Cardiorespiratory effects of the intravenous administration of tiletamine-zolazepam to dogs. Vet Surg 1989; 18: 160-166.
18. Hubbell JAE, Bednarski RM, Muir WW. Xylazine and tiletamine-zolazepam anesthesia in horses. Am J Vet Res 1989; 50: 737-742.
19. Jang HS, Jang KH, Lee MG, Jang IH, Effects of yohimbine and Atipamezole in dogs anesthetized with xylazine-ketamine combination on EEG. J Vet Clin 2002; 19: 174-185.
20. Kirkpatrick RM. Use of xylazine and ketamine as a combination anesthetic. Canine Practice 1978; 5: 32-57.
21. Klide AM, Calderwood HW, Soma LR. Cardiopulmonary effects of xylazine in dogs. AM J Vet Res 1975; 36: 931-935.
22. Kolata RJ, Rawlings CA. Cardiopulmonary effects of intravenous xylazine, ketamine, and atropine in the dog. Am J Vet Res 1982; 43: 2196-2198.
23. Kuusela E, Raekallio M, Anttila M, Falck I, Mölsä S, Vainio O. Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Therap 2000; 23: 15-20.
24. Lagutchik MS, Januszkiewicz AJ, Dodd KT, Martin DG. Cardiopulmonary effects of a tiletamine-zolazepam combination in sheep. Am J Vet Res 1991; 52: 1441-1447.
25. Lin HC, Thurmon JC, Benson GJ. Telazol - a review of its pharmacology and use in veterinary medicine. J Vet Pharmacol Ther 1993; 16: 383-418.
26. Lin HC, Thurmon JC, Tranquilli WJ, Benson GJ, Olson WA. Hemodynamic response of calves to tiletamine-zolazepam-xy-lazine anesthesia. Am J Vet Res 1991; 52: 1606-1610.
27. Lin HC. Dissociative anesthetics. In: veterinary anesthesia, 3rd ed. Baltimore: Williams & Wilkins. 1996: 241-296.
28. McNamara JA, Jr., Sly DL, Cohen BJ. Effects of CI 744 on skeletal muscle activity in monkeys(*Macaca mulatta*). Am J Vet Res 1974; 35: 1089-1091.
29. Millspaugh JJ, Brundige GC, Jenks JA, Tyner CL, Hustead DR. Immobilization of rocky mountain elk with Telazol and xylazine hydrochloride, and antagonism by yohimbine hydrochloride. J Wildlife Diseases 1995; 31: 259-262.
30. Muir WW, Werner LL, Hamlin RL. Effects of xylazine and acetylpromazine upon induced ventricular fibrillation in dogs anesthetized with thiamylal and halothane. Am J Vet Res 1975; 36: 1299-1303.
31. Pablo LS, Bailey JE. Etomidate and telazol. Vet Clin North Am Small Anim Pract 1999; 29: 779-792.
32. Plumb DC, Veterinary drug handbook, 3rd ed. Iowa: Iowa State University Press. 1999: 394-651.
33. Short CE, Talking about Telazol, Roundtable. Vet Med 1989; 84: 1-8.
34. Short CE. Effects of anticholinergic treatment on the cardiac and respiratory systems in dogs sedated with medetomidine. Vet Rec 1991; 129: 310-313.
35. Thurmon JC, Tranquilli WJ, Benson GJ. History and outline of animal anesthesia. In: veterinary anesthesia, 3rd ed. Baltimore: Williams & Wilkins. 1996: 2-61.
36. Thurmon JC, Tranquilli WJ, Benson GJ. Preanesthetics and anesthetic adjuncts. In: veterinary anesthesia, 3rd ed. Baltimore: Williams & Wilkins. 1996: 183-209.
37. Tracy CH, Short CE, Clark BC. Comparing the effects of intravenous and intramuscular administration of Telazol. Vet Med 1988; 83: 104-111.
38. Tranquilli WJ, Thurmon JC, Benson GJ, Davis LE. Alteration in the arrythmogenic dose of epinephrine (ADE) following xylazine administration to halothane-anesthetized dogs, J Vet Pharm Ther 1986; 9: 198-203.
39. Tranquilli WJ, Turmon JC, Benson GJ. Alterations in epinephrine-induced arrhythmogenesis after xylazine and subsequent yohimbine administration in isoflurane anesthetized dogs. Am J Vet Res 1988; 49: 1072-1075.
40. 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.
41. Vähä-Vahe T. The clinical efficacy of medetomidine. Acta Vet Scand 1989; 85: 193-197.
42. Ward GS, Johnsen DO, Roberts CR. The use of CI-744 as an anesthetic for laboratory animals. Lab Anim Sci 1974; 24: 737-742.
43. Wright M, Heath RB, Wingfield WE. Effects of xylazine and ketamine on epinephrine induced arrythmia in the dog. Vet Surg 1987; 16: 398-403.
44. Wright M. Pharmacologic effects of ketamine and its use in veterinary medicine. J Am Vet Med Asoc 1982; 180: 1462-1471.

개에서 Tiletamine/Zolazepam, Xylazine-Tiletamine/Zolazepam과 Medetomidine-Tiletamine/Zolazepam의 마취효과

권영삼 · 정재훈 · 장광호[1]
경북대학교 수의과대학

요 약 : 건강한 잡종견(4.16±0.65 kg, mean±SD) 15두를 tiletamine/zolazepam(TZ) 투여군(대조군), xylazine-tiletamine/zolazepam(XTZ) 투여군 및 medetomidine -tiletamine/ zolazepam(MTZ) 투여군으로 구분하고 마취 효과와 심폐계 영향을 평가하였다. Atropine(0.03 mg/kg, IM)투여 10분 후 xylazine(1.1 mg/kg IM) 또는 medetomidine (30 μg/kg IM)을 투여하였으며, atropine 투여 20분 후에 TZ(10 mg/kg IV)를 해당 실험군에 투여하였다. Pedal reflex와 ear pinching test 시 TZ군과 비교하여 XTZ군과 MTZ군에서 통증반응의 소실이 유의성 있게 증가하였다 ($P<0.05$). TZ 투여 직후부터 실험견이 머리를 들기까지 걸리는 평균시간과 실험견이 흉와 자세를 유지하기까지 걸리는 평균 시간, 실험견이 완전히 걸을 수 있을 때까지의 소요시간 역시 TZ군에 비해 XTZ군과 MTZ군에서 유의적인 증가를 나타내었다($P<0.01$). 본 실험에 사용된 모든 실험견은 회복기에 머리를 심하게 흔들고, 과도한 유연을 나타내었다. 체온은 전 실험군에서 점차 감소하였으나, 유의성은 나타나지 않았다. 대조군에서 심박수는 TZ 투여 후 10분과 20분에서 유의성 있게 증가하였으며, XTZ군에서는 TZ 투여 후 20분과 40분에 심박수가 유의성 있게 감소하였으나($P<0.05$) MTZ군에서는 유의성 있는 변화가 관찰되지 않았다. 호흡수는 XTZ군과 MTZ군에서 xylazine 또는 medetomidine 투여 후 10분, TZ 투여 후 10, 20, 40분에 유의성 있는 감소가 나타났다. 대조군에서는 TZ 투여 10분 후의 이완기 혈압, 20분후의 수축기 혈압, 그리고 10분과 20분 후의 평균혈압이 유의성 있게 감소하였다 ($P<0.05$). XTZ군에서는 모든 혈압이 TZ 투여 후 20분과 40분에서 유의성 있게 감소하였다($P<0.05$). 본 실험 결과, XTZ와 MTZ의 병용은 개에서 강한 진통작용과 긴 마취시간을 필요로 하는 외과 처치시 유용한 마취조합으로 사료된다.

주요어 : xylazine, medetomidine, tiletamine/zolazepam, dog