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The Clinical Effectiveness of Atipamezole as a Medetomidine-Tiletamine/Zolazepam Antagonist in Dogs

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Abstract : The cardiopulmonary and antagonistic effects of atipamezole to medetomidine (30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV) were determined. Twelve healthy mongrel dogs (4.00±0.53 kg, mean±SD) were randomly assigned to the four experimental groups (control, A30; atipamezole 30 μg/kg, A60; atipamezole 60 μg/kg, A150; atipamezole 150 μg/kg) with 3 dogs in each group. Atropine (0.03 mg/kg, IM), medetomidine, and tiletamine/zolazepam (TZ) were injected 10 minute intervals. Atipamezole was injected intravenously 15 minutes after TZ injection. Mean arousal time (MAT) was 52.50±4.98, 43.06±2.60, 32.83±8.13, and 14.36±1.60 minutes in control, A30, A60, and A150 groups respectively. In A150 group, MAT was significantly reduced ($P<0.05$). but mean walking time (MWT) was similar to that in control group. In recovery period, the higher doses of atimapezole, the rougher recovery including head rocking, hypersalivation, and muscle twitching. Five of twelve dogs vomited within 5 minutes after medetomidine injection. In Control group, heart rate significantly decreased in all recording stages except 15 minutes after TZ injection, 10 minutes after medetomidine injection in all groups, and 40 minutes after atipamezole injection in A30 group ($P<0.05$). In A150 group, atipamezole reversed the respiratory depression induced by medetomidine. Arterial blood pressure was significantly decreased 10minutes after medetomidine injection and 15 minutes after TZ injection in almost dogs in this study ($P<0.05$). From 10 minutes after atipamezole injection to arousal time, arterial blood pressure was progressively increased in A60 and A150 group. Any value of blood gas analysis and CBC, and serum chemistry values were not significantly changed except pH of A150 at 10 minutes after medetomidine injection. As shown in present study, atipamezole(150 μg/kg) is considered to exert a useful reversal effect in dogs anesthetized with medetomidine-tiletamine/zolazepam combination.

Key words **:** Medetomidine, tiletamine, zolazepam, atipamezole, dog

Introduction

Xylazine and medetomidine, α_2-adrenoceptor agonists, are commonly used sedative analgesics and preanesthetics in veterinary medicine.

Medetomidine[4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole] is a specific α_2-adrenoceptor agonist and sedavitve-analgesic intended for use in dogs, cats and other mammalian species[1,14,26,30,34,36]. It is commonly used as a preanesthetic prior to ketamine, barbiturate or mask induction with an inhalation anesthetic[30]. The adverse effects reported with medetomidine are an extension of its pharmacologic effects including bradycardia, occasional AV blocks, decreased respiration, hypothermia, urination, vomiting and hyperglycemia[25].

Atipamazole [4-(2-ethyl-2,3-dihydro-1H-inden-2-yl)-1H-imidazole] was synthesized in the course of a project to find a potential medetomidine antagonist for use in veterinary practice[32]. It is a specific and competitive α_2-antagonistic drug which is able to counteract the sedative, analgesic and other effects of medetomidine[19,34,36,38]. The α_2/α_1 selectivity ratio of atipamezole is 200 to 300 times higher than either idazoxan or yohimbine[34,37].

Tiletamine[2-(ethylamino)-2-(2-thienyl) cyclohexanone hydrochloride] was first reported in 1969[22]. It is a dissociative anesthetic agent with pharmacologic properties similar to those of ketamine, but its potency and duration of action intermediate between the long-acting phencyclidine and the short-acting ketamine[15,21-23].

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 pharmacologic properties similar to those of diazepam[4,22,31]. Benzodiazepine has effects include production of amnesia, minimal depression of cardiorespiratory function, strong anticonvulsant action, relative safety even if overdosed and rare development of significant tolerance or physical dependence[22].

Zoletil®(Virbac, France) is a 1 : 1 mixture by weight of tiletamine and zolazepam. It is a nonnarcotic, nonbarbiturate injectable anesthetic and immobilizing agent for use in dogs, cats, other domestic and wild animals[2,17,22,29].

The muscular clonus, body rigidity, and convulsive movements produced by tiletamine alone were absent when combined with zolazepam. The bizarre behavior including fear reaction, territorial exploration and jumping-climbing resulted from zolazepam alone was also absent when cats awoke from tiletamine/zolazepam anesthesia[22].

Tachycardia in dogs has been reported following intravenous and intramuscular tiletamine/zolazepam combination (TZ) injection[13]. And other adverse effects include transient apnea,

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vocalization, erratic and/or prolonges recovery, involuntary muscular twitching, hypertonia, cyanosis, cardiac arrest pulmonary edema, muscle rigidity and either hypertension or hypotension[22,25].

The purpose of the present study was to evaluate the ability of atipamezole, with different doses, antagonizing medetomidine-tiletamine/zolazepam (MTZ) induced anesthesia in dogs.

Materials and Methods

Experimental Design

Twelve healthy adult, mongrel dogs of either sex (4.00 ± 0.53 kg) were used in this study. They were vaccinated (Vangard puppy®, Pfizer Co., France) 1 month before experiment. They were fed a commercial dry food (Biomill®, Woosung Feed Co Ltd, Korea). Food and water were withheld for 12 hrs prior to the experiments. The dogs were divided into four groups (n = 3): the control group in which the dogs were treated with only medetomidine-tiletamine/zolazepam (MTZ) combination, the A30 group in which the dogs were treated with MTZ and atipamezole (30 μg/kg, IV), the A60 group in which the dogs were treated with MTZ and atipamezole (60 μg/kg, IV) and the A150 group in which the dogs were treated with MTZ and atipamezole (150 μg/kg, IV).

All dogs were premedicated with atropine (Atropine sulfate®, Dong-A Pharma Co Ltd, Korea, 0.03 mg/kg, IM) 10 minute before medetomidine (Domitor®, Orion Pharma, Finland, 30 μg/kg, IM) injection, tiletamine/zolazepam (TZ, Zoletil50®, Virbac, France, 10 mg/kg, IV) was injected 10 minutes after medetomidine injection. Atipamezole (Antisedan®, Orion Pharma, Finland) was injected 15 minutes after TZ injection.

The site for both a catheter and needle electrodes insertion was clipped. The dogs were positioned in dorsal recumbency. Before cannulation the skin over the artery was desensitised with a subcutaneous injection of lidocaine(2% Lidocaine HCl®, Gwang-myung Pharma Co Ltd, Korean). The cannula was connected via a tube filled with heparine. The tube was connected to a polygraph(Model 7P1, Grass instrument Co., USA) for measuring blood pressure and electrocardiography.

Recordings and Evaluations

Duration of anesthesia and observation of behavior changes. Arousal time was measured from the time of the atipamezole injection (in control group, 15 minutes after TZ injection) to the time when the dog could lift or hold up its head. Sternal rcumbency time was measured from the time of the atipamezole injection (in control group, 15 minutes after TZ injection) to the time when the dog could position sternal recumbency. Walk time was measured from atipamezole injection (in control group 15 minutes after TZ injection) until the dog could hold up its body and take a step on a non-skid surface.

Body temperature, heart rate and respiratory rate. Heart beat rate was measured by electrocardiography via the polygraph. Body temperature was measured with a electro-thermometer and respiratory rate was measured with a stethoscope.

Timepoints for body temperature, heart beat rate, and respiratory rate were before experiment, 10 minutes after medetomidine injection, 15 minutes after TZ injection, 5, 10, 20 and 40 minutes after atipamezole injection.

Arterial blood pressure and blood gas analysis. Via the femoral artery, systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were evaluated with the polygraph during 30 seconds.

Blood samples were collected from the arterial catheter via a three-way-stopcock. A waste sample was first withdrawn prior to the timed samples, and afterwards the catheter was flushed with heparin matching the amount of blood removed (1.5 ml). Blood gas samples were withdrawn anaerobically in heparin syringes and measured immediately by an automatic analyser (AVL compact 1 Blood Gas Analyzer, AVL Scientific Co., USA). pH, PaO_2 and $PaCo_2$ were measured.

Timepoints for arterial blood pressure and blood gas analysis were right before medetomidine injection, 10 minutes after medetomidine injection, 15 minutes after TZ injection, 5, 10, 20 and 40 minutes after atipamezole injected. These recordings were stopped when dogs lifted its heads.

CBC and serum chemistry. The Blood samples(1.5 ml) were collected from the jugular vein into EDTA tubes for CBC and heparine tubes for serum chemistry test. Blood urea nitrogen (BUN), creatinine, serum alanine aminotransferase (SALT), serum aspartate aminotrasferase (SAST) and total protein were measured by an auto dry chemistry analyzer (SPOTCHEM™, SP-4410®, Kyoto DAIICHI KAGAGU Co., Ltd.) and CBC was measured by an auto blood cell analyzer (HEMA VET 600®, CDC Technologies Inc.)

CBC was evaluated on day -1 (before experiment), 0 (10 minutes after atipamezole injection), 1, 3, and 7 after experiment.

Statistical Analysis

All data were expressed as mean ± satndard 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

Observation of behavior changes

Mean arousal time (MAT) was 52.50 ± 4.98 (mean ± SD) minutes in Control group, 43.06 ± 2.60 minutes in A30 group, 32.83 ± 8.13 minutes in A60 group and 14.36 ± 1.60 minutes in A150 group. Mean sternal recumbency time (MST) was 62.29 ± 6.44 minutes in Control group, 50.76 ± 0.65 minutes in A30 group, 46.30 ± 9.06 minutes in A60 group and 42.02 ± 4.64 minutes in A150 group. Mean walking time (MWT) was 73.32 ± 3.84 minutes in Control group, 72.95 ± 5.57 minutes in A30 group, 66.00 ± 6.01 minutes in A60 group and 62.52 ± 4.13 minutes in A150 group. Significant

decrease of MAT and MST were only observed in A150 group compared with those in Control group ($P < 0.05$). Difference of MWT among groups was not observed (Fig 1).

All dogs in this study showed head rocking and hypersalivation. The most serious side effects were observed in A150 group.

Body Temperature, Heart Beat Rate, and Respiratory Rate

Body temperature, heart beat rate and respiratory rate were summarized in Table 1. Body temperature was insignificantly changed at all time points in all groups. However it was progressively decreased. Heart beat rate was significantly decreased 10 minutes after medetomidine injection in all groups, compared with 25 minutes before atipamezole injection ($P < 0.05$). In Control group, heart beat rates were significantly decreased every recording stage except 10 minutes after TZ injection atipamezole injection($P < 0.05$). In A30 group, heart beat rates also significantly decreased 40 minutes after atipamezole injection. Medetomidine induced respiratory depression, but it was insignificant. In A150 group, atipamezole reversed the depressed respiratory rate.

Arterial Blood Pressure and Blood Gas Analysis

In most dogs, the arterial pressure was significantly decreased 10minutes after medetomidine injection and 15 minutes after TZ injection 10, 20 and 40 minutes after recovered atipamezole injection ($P < 0.05$) (Table 2), the level of

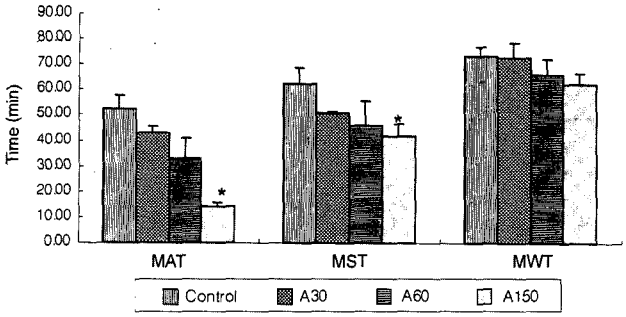

Fig 1. Comparison of mean head up time (MAT), mean sternal recumbency time (MST), and mean walking time (MWT) after atipamezole injections in dogs anesthetized with medetomidine-tiletamine/zolazepam.
Control: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV) only
A30: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV) + atipamezole(30 μg/kg, IV)
A60: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV) + atipamezole(60 μg/kg, IV)
A150: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam (10 mg/kg, IV) + atipamezole(150 μg/kg, IV)
*: $P < 0.05$ compared with Control

Table 1. Values in body temperature, heart beat rate, and respiratory rate in dogs anesthetized with tiletamine/zolazepam in dogs (mean ± SD)

Groups	Variables	Time after atipamezole injection(minutes)						
		-25†	-15‡	0	5	10	20	40
Control	T	39.5± 0.6	39.7± 0.6	39.6± 0.7	39.0± 0.9	39.0± 0.9	38.9± 1.0	38.9± 1.3
	P	129.3± 2.3	73.3± 23.1*	86.7± 23.1	86.7± 11.5*	86.7± 11.5*	86.7± 11.5*	80.0± 0.0**
	R	34.0± 12.5	22.3± 3.8	17.3± 1.2	16.0± 3.5	22.0± 6.9	24.7± 7.0	0.7± 9.2
A30	T	38.9± 0.9	39.3± 0.9	38.8± 1.1	38.6± 1.0	38.4± 1.1	38.2± 1.2	37.8± 1.2
	P	142.0± 24.2	96.7± 20.8*	106.7± 11.5	113.3± 11.5	93.3± 11.5	86.7± 11.5	93.3± 11.5*
	R	34.0± 5.3	22.7± 10.1	22.0± 9.2	25.3± 12.7	24.0± 10.4	29.3± 11.0	32.0± 9.2
A60	T	38.9± 1.1	39.6± 0.9	39.4± 1.3	38.9± 1.4	38.7± 1.5	38.6± 1.5	
	P	122.0± 19.3	80.0± 20.0*	120.0± 20.0	113.3± 11.5	113.3± 41.6	120.0± 40.0	
	R	26.7± 7.6	22.7± 2.3	19.3± 3.1	18.0± 6.0	22.0± 3.5	28.0± 6.9	
A150	T	39.1± 0.2	39.6± 0.5	39.7± 0.6	39.4± 0.7	39.3± 0.7		
	P	127.3± 21.2	88.7± 33.8*	120.0± 34.6	160.0± 40.0	173.3± 41.6		
	R	28.0± 6.9	19.3± 2.3	22.0± 9.2	40.0± 21.1	54.7± 9.2*		

Control: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam(10 mg/kg, IV) only
A30: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam(10 mg/kg, IV) + atipamezole(30 μg/kg, IV)
A60: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam(10 mg/kg, IV) + atipamezole(60 μg/kg, IV)
A150: medetomidine(30 μg/kg, IM)-tiletamine/zolazepam(10 mg/kg, IV) + atipamezole(150 μg/kg, IV)
T: body temperature(°C)
P: heart beat rate(beats/min)
R: respiratory rate(breath/min)
†: before medetomidine injection
‡: before tiletamine/zolazepam injection
*: $P < 0.05$ compared with -25
**: $P < 0.01$ compared with -25

Table 2. Values of arterial blood pressure obtained in each recording stages after atipamezole injection in dogs anesthetized with medetomidine-tiletamine/zolazepam (mean ± SD)

Groups	Variables	Time after atipamezol injection (minutes)						
		-25	-15	0	5	10	20	40
Control	SAP	260.3± 14.5	237.3± 3.1*	225.0± 5.0*	216.7± 7.6*	212.0± 2.6*	213.3± 10.4**	211.3± 7.6*
	DAP	188.3± 25.7	153.3± 15.3	154.0± 10.6	146.7± 14.6	142.7± 11.7	143.3± 22.5	152.3± 15.0*
	MAP	34.0± 12.5	231.3± 9.3	198.7± 8.5	184.3± 7.8*	181.7± 8.5*	85.7± 4.9*	187.7± 11.7
A30	SAP	262.3± 2.1	239.7± 2.9**	225.7± 4.5*	236.0± 20.8	243.3± 11.5	240.7± 22.1	246.7± 15.3
	DAP	208.3± 16.1	189.0± 9.5*	174.3± 8.1*	145.0± 13.2*	156.3± 3.25*	163.3± 10.4	163.3± 17.6**
	MAP	235.0± 8.7	212.7± 8.7*	198.7± 8.1**	190.0± 17.3*	193.7± 3.2	201.7± 16.5	209.0± 7.9**
A60	SAP	262.7± 4.0	237.3± 9.0	222.7± 15.5*	209.3± 26.8	240.3± 17.6	244.3± 22.7	
	DAP	190.0± 15.0	169.0± 10.1*	153.3± 16.1*	124.3± 18.9	150.7± 17.9	170.0± 15.0	
	MAP	226.0± 9.5	200.0± 4.0*	188.7± 9.8*	166.3± 22.8	195.3± 17.6	207.0± 19.1	
A150	SAP	268.0± 5.3	244.3± 6.0**	229.0± 3.5**	221.7± 28.9	260.3± 6.7		
	DAP	210.0± 5.0	182.7± 2.5*	166.7± 9.1*	156.7± 32.1	204.7± 21.0		
	MAP	230.3± 13.3	208.3± 11.5**	193.0± 11.8**	188.7± 24.6*	233.0± 15.9		

SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure
*: $P < 0.05$ compared with -25
**: $P < 0.01$ compared with -25

Table 3. Values of arterial blood analysis obtained in each recording stages after atipamezole injection in dogs anesthetized with medetomidine-tiletamine/zolazepam (mean ± SD)

Groups	Variables	Time after atipamezole injection (minutes)						
		-25	-15	0	5	10	20	40
Control	pH	7.355.± 0.047	7.259± 0.059	7.289± 0.043	7.269± 0.014	.324± 0.067	7.303± 0.040	7.344± 0.053
	$PaCO_2$	24.20± 5.50	23.97± 5.59	21.67± 6.60	25.27± 5.63	21.67± 4.48	24.60± 6.20	27.23± 3.61
	PaO_2	147.53± 14.42	120.77± 20.07*	124.73± 32.77	129.53± 3.40	28.73± 0.60	151.57± 10.84	148.07± 16.29
A30	pH	7.452± 0.047	7.264± 0.079	7.234± 0.093	7.281± 0.068	7.182± 0.120	7.207± 0.081	7.063± 0.255
	$PaCO_2$	27.83± 4.71	28.23± 0.83	23.87± 5.81	30.43± 2.51	22.80± 6.62	25.83± 6.33	23.57± 2.72
	PaO_2	155.07± 2.30	155.77± 1.93	151.47± 5.90	134.80± 2.86	136.30± 22.81	129.10± 15.49	156.97± 6.06
A60	pH	7.363± 0.083	7.256± 0.157	7.247± 0.141	7.286± 0.040	7.159± 0.105	7.259± 0.153	
	$PaCO_2$	25.80± 2.65	20.97± 3.14	26.27± 7.27	22.87± 5.20	20.43± 8.30	21.83± 3.33	
	PaO_2	126.20± 36.44	115.20± 27.35	118.36± 34.58	150.10± 23.52	137.33± 28.06	152.50± 18.37	
A150	pH	7.395± 0.056	7.228± 0.036*	7.267± 0.123	7.325± 0.040	7.233± 0.098		
	$PaCO_2$	22.00± 3.66	24.07± 4.80	25.20± 7.30	24.17± 2.55	20.47± 3.18		
	PaO_2	139.07± 26.03	130.90± 27.13	107.40± 9.58	127.73± 25.06	162.83± 5.53		

$PaCO_2$: partial oxygen pressure(mmHg), PaO_2: partial carbon dioxide pressure(mmHg)
MAP: mean arterial pressure(mmHg)
*: $P < 0.05$, compared with -25

arterial pressure was progressively recovered as level of 25 minutes before atipamezole injection in A30, A60 and A150 group.

PaO_2 was decreased transiently by medetomidine in Control and pH was decreased by medetomidine in A150 group. pH, $PaCO_2$ and PaO_2 were not significantly changed other recording stages (Table 3).

CBC and Serum Chemistry

The values of WBC, RBC, platelet, and packed cell volume were summarized in Table 4. 1 day after experiment in Control and A30 group and 3 days after experiment in A60 group, WBC were significantly increased ($P<0.05$). Other values were not changed significantly in all groups.

Chemical Changes of Venous Blood

SALT, SAST, BUN, creatinine and total protein were in normal ranges, and did not changed in all groups (Table 5).

Table 4. Values of complete blood counts obtained in each recording stages after atipamezole injection in dogs anesthetized with medetomidine-tiletamine/zolazepam (mean ± SD)

Groups	Variables	Recording stage (day)				
		-1	0	1	3	7
Control	WBC	12.25± 1.10	13.08± 1.97	17.34± 1.51*	16.32± 2.28	5.01± 1.41
	RBC	7.46± 0.98	6.79± 0.44	7.74± 1.06	7.08± 0.90	8.52± 1.79
	PLT	435.0± 60.5	434.7± 11.2	463.7± 61.8	418.3± 20.6	405.3± 11.6
	PCV	44.6± 2.49	47.0± 4.06	46.2± 3.61	43.5± 2.37	45.6± 1.53
A30	WBC	11.80± 0.75	12.00± 1.86	17.87± 1.12**	13.90± 2.86	14.36± 1.81
	RBC	8.02± 1.66	7.06± 1.86	4.95± 1.12	6.23± 2.86	5.79± 1.81
	PLT	505.0± 64.6	417.7± 85.2	420.0± 63.8	400.7± 63.0	395.0± 91.3
	PCV	44.5± 0.55	46.8± 2.37	43.0± 0.41	47.2± 1.79	47.0± 1.40
A60	WBC	12.14± 1.38	12.10± 1.04	15.32± 3.19	18.78± 1.32*	14.55± 2.18
	RBC	8.39± 1.03	7.51± 0.39	8.55± 0.28	8.43± 1.69	8.49± 1.09
	PLT	481.0± 103.9	379.3± 21.4	405.3± 56.3	367.7± 67.1	325.3± 69.5
	PCV	44.4± 4.03	40.1± 6.47	42.4± 5.69	43.1± 4.86	43.4± 5.54
A150	WBC	11.52± 1.90	12.41± 0.97	17.94± 2.10	13.69± 2.97	12.55± 1.57
	RBC	8.12± 0.49	8.04± 0.59	6.46± 2.08	7.88± 0.27	8.21± 0.78
	PLT	389.0± 62.1	399.7± 58.5	418.3± 49.0	418.0± 24.9	318.0± 18.2
	PCV	47.0± 2.43	41.4± 3.82	45.4± 1.52	44.2± 4.22	44.2± 3.60

WBC: white blood cell(K/μl), RBC: red blood cell(M/μl), PLT: platelet(K/μl), PCV: packed cell volume(%)
*: $P < 0.05$, compared with -1
**: $P < 0.01$, compared with -1

Table 5. Values of blood chemical test obtained in each recording stages after atipamezole injection in dogs anesthetized with medetomidine-tiletamine/zolazepam (mean ± SD)

Groups	Variables	Recording stage (day)				
		-1	0	1	3	7
Control	SALT	23.3± 13.2	22.3± 11.7	25.3± 8.7	22.7± 13.5	20.0± 5.2
	SAST	15.0± 5.2	15.7± 7.0	9.7± 1.2	11.0± 3.5	10.0± 1.7
	BUN	20.7± 7.0	13.7± 4.6	16.7± 8.3	17.3± 15.3	19.7± 5.7
	Cre	0.83± 0.51	0.83± 0.06	0.67± 0.06	0.63± 0.06	0.67± 0.06
	T-pro	5.97± 0.75	5.77± 0.25	6.23± 0.12	6.30± 0.40	6.63± 0.84
A30	SALT	14.7± 9.8	12.0± 3.6	15.0± 6.0	12.7± 3.2	12.0± 5.2
	SAST	12.7± 1.2	9.3± 0.6	10.7± 2.9	10.0± 1.7	10.3± 2.3
	BUN	20.3± 4.0	21.7± 3.2	18.7± 1.5	17.7± 0.6	18.3± 13.6
	Cre	0.63± 0.15	0.61± 0.24	0.67± 0.12	0.43± 0.25	0.67± 0.06
	T-pro	7.43± 0.51	7.24± 1.37	6.47± 0.61	6.77± 0.45	7.77± 1.45
A60	SALT	15.7± 6.5	14.7± 6.0	19.0± 8.7	11.3± 4.0	12.0± 3.0
	SAST	10.0± 1.7	11.7± 4.6	12.3± 5.8	10.7± 2.9	10.3± 1.5
	BUN	18.3± 7.4	12.3± 3.5	14.7± 2.1	16.3± 3.2	14.3± 2.5
	Cre	0.63± 0.12	0.63± 0.06	0.60± 0.10	0.60± 0.10	0.67± 0.15
	T-pro	5.90± 1.04	5.70± 0.26	6.07± 0.65	6.67± 0.25	6.90± 0.26
A150	SALT	18.7± 15.0	23.0± 12.2	18.0± 9.0	19.3± 11.1	14.0± 8.7
	SAST	9.3± 0.6	11.3± 4.0	10.0± 1.7	15.3± 3.5	13.7± 4.0
	BUN	18.3± 4.9	15.3± 3.1	13.7± 5.1	12.7± 0.6	16.3± 3.8
	Cre	0.73± 0.21	0.77± 0.15	0.77± 0.12	0.70± 0.10	0.60± 0.40
	T-pro	6.33± 0.31	6.43± 0.40	6.10± 0.26	6.03± 0.42	6.40± 0.70

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

Discussion

In this study, MTZ combination was effective for anesthetizing dogs, and atipamezole in A150 group was effective for shortening MAT and MST by this combination. However, atipamezole, doses of A30 and A60 groups, was not effective for shortening MAT. Although MAT and MST were shortened by atipamezole in A150 group, MWT was similar to that of Control group. In the study of Vaha-Vahe, The most appropriate dose of atipamezole was four to six folds higher than the preceding medetomidine dose in dogs38 and higher doses of atipamezole induced smoother recovery. In wood bison, 180 μg/kg of atipamezole is able to reverse the effects of MTZ (medetomidine 60 μg/kg, TZ 1.2 mg/kg) combination[7]. In these two studies, side effects during recovery time was rare, but in this study, adverse effects including head rocking, tremors, and hypersalivation, during recovery period of A150 group was stronger than those of other groups. This was probably due to the fact that the effects of tiletamine were incompletely antagonised by atipamezole.

In this study, MAT of A150 group was 14.36± 1.60 (mean± SD) minutes. In cats, reversed from medetomidine-ketamine combination by atipamezole, MAT was 5.8 to 7.0 minutes[36], and wood bison were also reversed within 10 minutes[7]. Similar result was observed in the study with polar bear[6].

In A30, A60 and A150 groups, the heart beat rate which had been depressed by MTZ combination was increased by atipamezole. However, in A30 and A60 groups, heart beat rate was increased after atipamezole injection in 5 minutes, but the initial effect was not maintained and the secondary decrease in the heart beat rate was observed. In A150 group, the dogs showed tachycardia 5 and 10 minutes after atipamezole injection. In the study of Vainio *et al.*, similar result was observed[33]. The heart beat rate of all groups was significantly decreased 10 minutes after medetomidine injection ($P < 0.05$). The heart beat rate was insignificantly decreased 15 minutes after TZ injection in all groups. In the study of Ewing KK *et al.*, heart beat rate was decreased by medetomidine during isoflurane anesthesia in dogs[14], and similar results were shown in other studies with various animal species[7,8,20,27,28,32,34-36]. The insignificant decrease of heart beat rate 15 minutes after TZ injection was considered to be due to effect of it. Other studies have reported that TZ might induce tachycardia[13,24,25]. Respiratory rate was significantly increased 10 minutest after atipamezole injection in A150 group. In this study, respiratory rate was insignificantly decreased 10 minutes after medetomidine injection in all groups. These results are different from those of previous studies in several animal species[3,34,36]. The result of present study was probably due to the effect of atropine. Apnea, transiently occurring right after medetomidine injection, was not observed in this study. One study showed that apnea was disappeared in dogs that sedated with medetomidine and premedicated atropine[28].

Body temperature was not changed significantly in this study. Although medetomidine and TZ may induce hypothermia[15,36], it did not occur in this study. This was probably due to temperature of the table, which was maintained at 38°C.

Following medetomidine injection, in all groups, significant decrease of arterial blood pressure was observed ($P < 0.05$). The arterial blood pressure became lower after TZ injection. It was maintained until 40 minutes after atipamezole injection in Control and A30 groups. The arterial blood pressure temporarily incresed right after atipamezole injection then increased after 5 min in A60 and A150 groups. It reached the level before medetomidine injection after 10 minutes and it was maintained until arousal time. A similar result has been reported in other study[34]. Medetomidine also induced hypotension in sheep[9]. In black bear, anesthetized with medetomidine-TZ combination, arterial blood pressure was decreased[8]. Medetomidine showed a biphasic pressure response, i.e. an initial hypertension followed by an eventual return to normal blood pressure, or significant decrease[9]. Hellyer *et al.* have reported that the arterial systolic pressure of dogs transiently decreases then returns to slightly above resting levels following intravenous injection of TZ(6.6 mg/kg)[16]. All doses of TZ caused a biphasic blood pressure response as medetomidine did, but blood pressure was first decreased after increased. The initial decrease of blood pressure could be caused in large part by the rate of injection[22]. Therefore, medetomidine-TZ combination has to be carefully used for patients with cardiac problem[18].

In this study, pH of arterial blood was not changed significantly except at 10 minutes after medetomidine injection in A150 group. However, pH was decreased from post medetomidine injection to pre atipamezole injection. $PaCO_2$ and PaO_2 were not changed significantly in this study, except PaO_2 10 minutes after atipamezole injection in control group, PaO_2 of this stage was significantly decreased ($P < 0.05$). When a dose of 2 to 4 mg/kg is given intravenously to dogs without premedication, the ventilatory pattern is characterized by a short period of apnea (about 1 minute) followed by irregular, slow and shallow breathing. This is accompanied by slight hypoxemia, but the $PaCO_2$ remains near normal[13]. Although PaO_2 was increased in dogs treated with TZ, PaO_2 was decreased in dogs treated with propofol-TZ combination in other study[11]. In black bears treated with MTZ combination, pH, $PaCO_2$, and PaO_2 were normal, but one bear showed a sign of hypoxemia ($PaO_2 < 60$ mmHg)[8]. TZ has been shown to produce hypoventilation as evidenced in increased $PaCO_2$ in sheep[21]. In ruminants, although hypoventilation would have contributed to hypoxemia, the major cause of hypoxemia was probably ventilation-perfusion mismatch[7].

There was no significant change in CBC,, and blood chemistry in this study. Only WBC increased at 1 day and 3 days after experiment, it was probably due to the inflammatory response to the surgical procedure. TZ induced renal toxicity in white rabbit[5,12], and rabbits treated with TZ at dose of 64 mg/kg, glomerular necrosis was observed histologically.

Since increase of BUN or creatinine is observed when over 70% of nephrons are destroyed, normal BUN and creatinine values are not the indices of renal funcion. Therefore, histological evaluation should be performed to evaluate renal toxicity[10].

In conclusion, the results of this study showed that atipamezole at 5-fold dose of medetomidine was effective antagonist for MTZ combination. Higher dose of atipamezole was more effective in reducing the anesthetic time, but induced rougher recovery. A further study needs to be performed to evaluate the effects of higher dose of atipamezole to MTZ combination.

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개에서 Medetomidine-Tiletamine/Zolazepam 마취에 대한 Atipamezole의 길항 효과

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요 약 : Medetomidine (30 μg/kg IM) - tiletamine/zolazepam (10 mg/kg IV) 합제를 사용하여 마취한 잡종견(4.00±0.53 kg) 12두에서 atipamezole의 심폐계 영향과 길항효과에 대하여 평가하였다. 4개의 실험군에 각각3두씩 임의로 배당하였다 (대조군: atipamezole 처치를 하지 않은 군, A30군: atipamezole 30 μg/kg, A60: atipamezole 60 μg/kg, A150: atipamezole 150 μg/kg). 모든 실험견은 medetomidine 투여 10분 전 atropine (0.03 mg/kg, IM)으로 전처치하였으며, medetomidine 투여 10분 후 tiletamine/zolazepam (TZ)를 투여하였다. TZ 투여 15분 후 atipamezole을 정맥으로 투여하였다. 실험견이 머리를 들 때까지의 평균시간은 대조군 43.06±2.60분, A30군 43.06±2.60분, A60군 32.83±8.13분, A150군 14.36±1.60분으로 대조군과 비교할 때 A150군에서 유의성 있게 감소하였으나 ($P<0.05$) 완전한 보행을 보일 때까지의 평균시간에는 유의성이 나타나지 않았다. 회복기에 보이는 두부의 진전, 과도한 유연, 근육 경련과 같은 부작용은 atipamezole의 용량이 증가할수록 심하게 나타났다. 12두의 실험견중 5두가 medetomidine 투여 후 5분 이내에 구토를 하였다. 대조군에서 심박수는 TZ 투여 후 15분을 제외하고, 모든 측정시간대에서 유의성 있는 감소를 나타내었으며, 전 실험군에서 medetomidine 투여 10분 후, A30군에서 atipamezole 투여 후 40분에 심박수의 유의성 있는 감소가 나타났다 ($P<0.05$). A150군에서는 atipamezole 투여 10분 후 심계 항진 및 호흡 항진이 나타났다. 대다수 실험견에서 동맥혈압은 medetomidine과 tiletamine/zolazepam 투여 후 유의성 있게 감소하였으나 ($P<0.05$) A60군과 A150군에서는 atipamezole 투여 후 점차적으로 회복되었다. 혈액가스검사와 총 혈구계산치는 유의성 있는 변화가 관찰되지 않았다. 본 실험의 결과로 atipamezole 150 μg/kg은 MTZ 병용 마취견 각성에 뛰어난 효과를 나타낸다고 사료된다.

주요어 : medetomidine, tiletamine, zolazepam, atipamezol, 개