Cardiopulmonary Effects of Medetomidine, Medetomidine-Midazolam and Medetomidine-Midazolam-Atipamezole in Dogs

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ABSTRACT. Cardiopulmonary effects of medetomidine (20 $\mu\text{g/kg}$)-midazolam (0.3 mg) (Me-Mi) were compared with those of medetomidine alone (80 $\mu\text{g/kg}$) (Me80) in dogs. The intramuscular administration of this combination caused bradycardia and transient mild pressor response. Heart rate decreased soon after the administration and remained significantly below the baseline value with average values of 50–70 beats/min. Blood pressure increased to its maximum within 5 to 10 min then decreased gradually. Cardiac index decreased corresponding the decrease in heart rate. However these changes were less profound than those of Me80 indicating significantly higher values in cardiac index and lower values in systemic vascular resistance. Effects on the respiratory function were slight. The reduction of the dose of medetomidine to one-fourth in Me-Mi was effective to reduce the adverse effect of medetomidine, especially in peripheral vasoconstriction. Atipamezole effectively reversed cardiopulmonary effects induced by medetomidine-midazolam. Heart rate and cardiac index increased and systemic vascular resistance decreased significantly after administration of atipamezole. The possible use of an antagonist as a reversal agent might enhance the value and availability of medetomidine-midazolam as a chemical restraint agent in dogs.—**KEY WORDS:** atipamezole, cardiopulmonary effect, canine, medetomidine, midazolam.

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As we reported previously, a combination of a low dose of medetomidine (20 $\mu\text{g/kg}$) and midazolam (0.3 mg/kg) produced more profound sedation, muscle relaxation and analgesia than those by a high dose of medetomidine (80 $\mu\text{g/kg}$) alone in dogs [5].

However, medetomidine has been reported to produce hemodynamic changes such as bradycardia, sinus arrhythmia, atrioventricular blocks, hypertension and decrease in cardiac output through central and peripheral actions [1, 9]. It has also been reported that these changes were relatively mild when a low dose of medetomidine was used [11].

Midazolam, a water-soluble, rapid and short acting benzodiazepine, produces minimal cardiovascular depression at clinical doses in dogs [7]. Accordingly, the profound sedation induced by the combination in relatively low doses, medetomidine — midazolam, could be expected with less cardiovascular changes than those by a high dose of medetomidine alone.

Atipamezole is a highly selective and specific α_2 -adrenoceptor antagonist. Atipamezole has been reported to have the ability to reverse the effects of medetomidine [10, 12, 13], even if medetomidine is used with midazolam in dogs [6]. If the cardiovascular effects can also be reversed quickly and smoothly, this combination should be safer and more widely available as a sedative method in dogs.

The purpose of this study was to evaluate the cardiopulmonary effects of medetomidine-midazolam as compared with those by a high dose of medetomidine administered alone in dogs. This study was also designed to evaluate the antagonistic effects of atipamezole on the hemodynamic changes induced by medetomidine-midazolam.

MATERIALS AND METHODS

Animals: Fifteen beagle dogs of either sex, 9.6 kg (range 7.6 to 11.8 kg) of average body weight, 13.5 months old (range 10 to 18 months) of average age, were used in this study. These animals were divided into three groups of five dogs each for three drug regimens. Food was withheld at least 12 hr before the experiment, but dogs were allowed free access to water.

Animal preparations: At least seven days before the experiment, a 14G heparin-coated polyvinyl chloride catheter (Anthon, Toray Medical Co., Japan) was placed into the left common carotid artery, to measure arterial blood pressure (AP) and collect arterial blood samples for measurements of arterial blood gases and pH. Isoflurane was used for anesthesia for the procedure.

Before the experiment, the skin was anesthetized with lidocaine hydrochloride. Then a 6-Fr introducer (SI-5600, Arrow International Inc., U.S.A.) was inserted into the right jugular vein percutaneously to introduce a 5 Fr Swan-Ganz catheter (model 93-132-5F, Baxter Healthcare Corporation, U.S.A.). The Swan-Ganz catheter was advanced into the pulmonary artery, to measure pulmonary arterial pressure (PAP), right atrial pressure (RAP), pulmonary arterial wedge pressure (PAWP), cardiac output (CO) and pulmonary arterial temperature (PT), and to collect mixed venous blood samples.

Experimental protocol: The dogs were kept undisturbed on a restraining table in a quiet room to stabilize. Following the measurements of baseline values in the conscious state, each dog was given 80 $\mu\text{g/kg}$ of medetomidine (Me80), 20 $\mu\text{g/kg}$ of medetomidine (Domitor: Farnos Group Ltd., Finland) and 0.3 mg/kg of midazolam

(Dormicum: Yamanouchi Pharmaceutical, Japan) (Me-Mi), or Me-Mi and 80 $\mu\text{g/kg}$ of atipamezole (Antisedan: Farnos Group Ltd., Finland) which was administered 40 min after Me-Mi. Drug or drug combination mixed in a syringe was injected intramuscularly in the hind limb.

Cardiopulmonary measurements: The following measurements were recorded before and after drug administration. Cardiovascular measurements: heart rate (HR), electrocardiogram (ECG), phasic and mean AP and PAP, RAP, PAWP, and CO. Respiratory measurements: arterial and mixed venous blood pH, partial pressure of oxygen (PO_2), and partial pressure of carbon dioxide (PCO_2).

Blood pressure was measured using a pressure transducer (TNF-R, Spectramed Medical Products, U.S.A.) connected to a multi-function monitor (BSM-8301, Nihon Kohden, Japan). HR, ECG and wave form were also recorded by this monitor. PT was measured using the Swan-Ganz catheter connected to the multi-function monitor. CO was measured by a thermal dilution method using the multi-function monitor at least twice, and the average was recorded as CO value. In dogs given Me80 and Me-Mi, these measurements were recorded before and 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 min after drug(s) administration. CO was not measured 5 and 15 min after Me80 or Me-Mi. In dogs given Me-Mi-Ati, measurements before Me-Mi administration were recorded as baseline values, and measurements before atipamezole administration (40 min after Me-Mi administration) were recorded as pre-atipamezole values. The measurements were repeated 5, 10, 15, 20, 30, 40, 50, 60 and 80 min after administration of atipamezole. CO was not measured 5 and 15 min after atipamezole.

Arterial and mixed venous blood samples for the analysis of pH and blood gases were collected anaerobically into heparinized syringes, stored in iced water and analyzed using pH/blood gas analyzer (ILsystem-1303, Instrumentation Laboratory, U.S.A.). All gas measurements were corrected to PT. Base excess (BE) and bicarbonate concentration ($[\text{HCO}_3^-]$) were calculated from these measurements. These measurements were recorded before and 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 min after the drug administration in dogs given Me80 or Me-Mi, and before Me-Mi. In dogs given Me-Mi-Ati these measurements were recorded before atipamezole and 5, 10, 15, 20, 30, 40, 50, 60 and 80 min after administration of atipamezole.

From these measurements, the following values were also calculated. Cardiovascular parameters: cardiac index (CI)= $1000 \cdot \text{CO} / \text{BW}$ ($\text{ml/min} \cdot \text{kg}$), stroke volume (SV)= CI / HR (ml/kg), systemic vascular resistance (SVR)= $(\text{APm} - \text{RAP}) / \text{CO} \cdot \text{BW}$ ($\text{mmHg} \cdot \text{kg} \cdot \text{min/l}$), pulmonary vascular resistance (PVR)= $(\text{PAPm} - \text{PAWP}) / \text{CO} \cdot \text{BW}$ ($\text{mmHg} \cdot \text{kg} \cdot \text{min/l}$), rate pressure product (RPP)= $\text{APs} \cdot \text{HR}$ (mmHg/min). Respiratory parameters: arterial O_2 saturation (SaO_2) (%), venous O_2 saturation (SvO_2) (%), arterial oxygen content (CaO_2)= $1.39 \cdot \text{Hb} \cdot \text{SaO}_2 / 100 + 0.0031 \cdot \text{PaO}_2$ (ml/blood 100

ml), venous oxygen content (CvO_2)= $1.39 \cdot \text{Hb} \cdot \text{SvO}_2 / 100 + 0.0031 \cdot \text{PvO}_2$ (ml/blood 100 ml) (Hb: hemoglobin (gm/dl)), delivery O_2 (DO_2)= $\text{CaO}_2 \cdot \text{CI} / 100$ ($\text{ml/min} \cdot \text{kg}$), oxygen consumption (VO_2)= $(\text{CaO}_2 - \text{CvO}_2) \cdot \text{CI} / 100$ ($\text{ml/min} \cdot \text{kg}$), and oxygen utilization ratio (UO_2)= $\text{DO}_2 / \text{VO}_2$.

Statistical analyses: The values of cardiopulmonary parameters after drug administration were compared with baseline values using repeated measured ANOVA and Scheffe's multiple comparison procedure, and differences between drug groups were analyzed by one way ANOVA and Scheffe's multiple comparison procedure. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS

The effects of Me80 and Me-Mi on cardiovascular system are summarized in Table 1. HR decreased markedly within soon after Me80 and Me-Mi administration, and remained the levels significantly below the baseline values throughout the recording period, with average values of 50–70 beats/min. There was no significant difference in HR between Me80 and Me-Mi.

AP rapidly increased to the maximum level within 5 min then decreased gradually, however the change in AP of Me-Mi was less profound than that in Me80. Mean AP value of Me80 was significantly higher than that of Me-Mi at 5 min. Mean AP of Me-Mi returned to the level not significantly different from base line value after 20 min and decreased slightly below baseline value, while mean AP values of Me80 were significantly higher than baseline value until 60 min. RAP and PAWP rapidly increased significantly above baseline value after Me80 and Me-Mi administration, however RAP and PAWP values of Me-Mi were significantly lower than those of Me80. PAP of Me-Mi increased initially for 10 min after the administration then decreased gradually to baseline value, which was not significant change.

SVR increased significantly above baseline values in both Me80 and Me-Mi for the entire 120 min recording period, however SVR values of Me-Mi were significantly lower than those of Me80 throughout the experiment. PVR increased moderately in both Me80 and Me-Mi.

CI decreased rapidly and remained significantly lower than baseline values in both Me80 and Me-Mi, however CI values of Me-Mi were significantly higher than those of Me80 throughout the experiment. SV decreased slightly in Me80 and Me-Mi, however the decrease in Me-Mi was less than that of Me80 with a significant difference at 10 min. RPP decreased in both Me80 and Me-Mi significantly below baseline value for the entire 120 min recording period.

The effects of Me-Mi-Ati on cardiovascular system are summarized in Table 3. After atipamezole administration, HR increased rapidly almost to baseline value, and remained constant level significantly above pre-atipamezole value. AP, RAP, PAP and PAWP decreased initially for approximately 10 min after atipamezole

Table 1. Cardiovascular consequences of medetomidine-midazolam (Me-Mi) and medetomidine (Me80) administrations in dogs^{a)}

		Time after administration of drug (min)								
Measurements		Baseline	5	10	20	30	40	60	80	120
HR	Me-Mi	106.8±12.4	62.0±13.2*	61.0±13.1*	63.2±14.3*	62.6±16.3*	62.4±14.9*	63.4±18.5*	60.8±15.4*	59.8±18.6*
(/min)	Me80	95.8±10.7	61.0±11.4*	59.8±7.0*	63.4±23.3*	60.2±8.2*	58.4±6.7*	57.4±9.6*	57.4±5.8*	52.8±8.3*
APm	Me-Mi	120.4±7.4	140.8±10.7* [#]	139.6±13.4	133.2±7.6	132.2±10.7	124.6±10.0	111.4±11.9* [#]	110.2±7.6 [#]	113.6±7.7
(mmHg)	Me80	115.2±7.6	170.8±21.9*	152.2±13.6*	138.8±11.2*	135.8±8.9*	132.2±7.1*	128.4±5.9*	124.2±10.8	119.0±8.2
RAP	Me-Mi	1.2±1.3	5.4±1.9* [#]	5.6±2.1* [#]	4.0±1.9* [#]	3.8±1.9* [#]	3.8±1.9* [#]	3.2±2.8 [#]	2.6±1.8 [#]	2.4±1.7 [#]
(mmHg)	Me80	1.8±1.5	9.4±2.3*	9.2±1.9*	8.2±1.9*	7.6±1.7*	7.2±2.2*	6.8±1.5*	6.4±2.1*	5.4±1.8*
PAPm	Me-Mi	16.2±4.4	17.6±4.6	18.8±5.4	17.4±4.8	16.4±4.0	14.6±2.7	15.4±4.8	14.2±6.5	14.2±6.0
(mmHg)	Me80	15.6±2.6	18.6±5.5	19.0±2.7*	17.2±2.7*	16.6±2.2	15.8±1.5	15.0±1.2	15.6±1.8	16.0±3.7
PAWP	Me-Mi	5.0±3.2	10.0±2.6* [#]	11.8±4.6*	10.0±3.7*	9.8±2.9*	9.4±3.0*	7.8±3.9*	7.4±4.2*	7.4±3.8*
(mmHg)	Me80	5.4±1.9	14.6±2.9*	14.0±3.0*	13.8±4.3*	12.6±2.3*	11.8±1.9*	10.4±0.9*	9.8±1.3*	9.6±3.1*
SVR	Me-Mi	569±14	ND ^{b)}	1356±336* [#]	1432±269* [#]	1337±272* [#]	1295±362* [#]	1135±289* [#]	1187±255* [#]	1167±364* [#]
(mmHg·min·kg/l)	Me80	660±153	ND	2042±242*	1873±212*	1838±260*	1749±204*	1668±153*	1695±212*	1566±168*
PVR	Me-Mi	54±10	ND	72±33	82±21*	69±23	56±17	80±25*	76±44	70±27
(mmHg·min·kg/l)	Me80	59±19	ND	73±21	52±35	59±18	56±13	64±16	84±32*	89±25
CI	Me-Mi	209±9	ND	103±24* [#]	92±15* [#]	98±16* [#]	99±31* [#]	99±22* [#]	93±16* [#]	101±24* [#]
(ml/min·kg)	Me80	179±44	ND	71±15*	71±11*	71±13*	72±11*	73±8*	70±5*	73±8*
SV	Me-Mi	2.0±0.2	ND	1.8±0.5 [#]	1.5±0.3*	1.6±0.4	1.7±0.6	1.7±0.7	1.6±0.4	1.8±0.6
(ml/kg)	Me80	1.9±0.6	ND	1.2±0.2	1.2±0.3*	1.2±0.4	1.3±0.3	1.3±0.3	1.2±0.1	1.4±0.3
RPP	Me-Mi	16211±2376	10636±2721*	10834±2541*	10207±1775*	9703±2388*	9205±1607*	8676±2075*	7907±1835*	7903±2073*
(mmHg/min)	Me80	13976±2275	12929±3161	1126±2310	10893±4922	10021±1881*	9407±1617*	8996±1512*	8758±728*	7906±1472*

a) Data were expressed as mean±standard deviation, n=5. HR=heart rate, AP=arterial blood pressure, m=mean, RAP=right atrial pressure, PAP=pulmonary arterial pressure, PAWP=pulmonary arterial wedge pressure, SVR=systemic vascular resistance, PVR=pulmonary vascular resistance, CI=cardiac index, SV=stroke volume, and RPP=rate pressure product.

b) Not done.

* Significantly (p<0.05) different from baseline.

[#] Significantly (p<0.05) different from Me80.

Table 2. Respiratory consequences of medetomidine-midazolam (Me-Mi) and medetomidine (Me80) administrations in dogs^{a)}

		Time after administration of drug (min)								
Measurements		Baseline	5	10	20	30	40	60	80	120
PaO ₂	Me-Mi	110.1±8.2	107.5±19.0	99.9±10.4 [#]	104.6±3.4 [#]	105.5±8.8 [#]	113.2±9.2	111.4±7.3	112.2±4.5	109.9±4.7 [#]
(mmHg)	Me80	109.6±4.1	109.1±8.9	116.2±6.8	120.0±8.7*	121.5±8.2*	117.5±6.9 [†]	118.7±5.6*	119.2±5.9*	124.1±6.1*
PaCO ₂	Me-Mi	31.7±4.1	31.3±3.4	31.0±1.1	31.2±1.1	30.0±2.3	30.0±1.4	27.8±1.5	29.5±1.6	30.1±2.6
(mmHg)	Me80	35.4±1.6	32.0±4.0	29.6±3.7*	30.4±6.1	27.9±4.9*	28.1±3.3*	28.7±2.4*	27.7±1.8*	26.5±3.6*
pHa	Me-Mi	7.37±0.02	7.36±0.04	7.36±0.03	7.36±0.04	7.37±0.03	7.37±0.03	7.38±0.02	7.38±0.03	7.36±0.06
	Me80	7.34±0.05	7.33±0.05	7.34±0.06	7.35±0.06	7.35±0.07	7.35±0.05	7.33±0.06	7.35±0.03	7.38±0.06
[HCO ₃] _a	Me-Mi	14.3±5.8	17.5±1.1	17.3±1.4	17.5±1.0	17.0±1.5	17.2±1.4	16.7±1.3	17.4±1.2	17.0±1.2
(nmol/l)	Me80	18.8±1.5	16.6±1.6*	15.6±1.7*	15.4±1.6*	15.2±2.1*	15.2±1.9*	15.4±1.4*	15.4±1.9*	15.6±1.2*
BEa	Me-Mi	-9.2±4.9	-7.5±1.3	-7.9±1.5	-7.7±1.4	-8.1±1.5	-7.9±1.6	-8.4±1.3	-8.0±1.4	-8.7±1.9
(nmol/l)	Me80	-6.8±2.2	-9.1±2.0*	-9.9±2.3*	-9.9±2.3*	-10.1±2.6*	-10.2±2.5*	-10.2±1.9*	-10.0±2.3*	-9.4±1.8*
DO ₂	Me-Mi	257±103	ND ^{b)}	129±76*	112±65*	121±56*	120±54 [†]	118±38 [†]	112±38*	119±37*
(ml/kg·min)	Me80	303±124	ND	130±50*	129±42*	128±34*	131±34*	131±25*	125±22*	130±18*
VO ₂	Me-Mi	54±19	ND	46±9	34±8	37±6 [#]	38±7 [#]	37±7 [#]	35±9*	40±3 [#]
(ml/kg·min)	Me80	68±5	ND	63±27	56±21	54±13	53±13	53±11*	48±11*	48±6*
UO ₂	Me-Mi	0.21±0.04	ND	0.41±0.11*	0.34±0.11*	0.34±0.10*	0.34±0.08*	0.34±0.10*	0.32±0.09*	0.36±0.11*
	Me80	0.23±0.07	ND	0.48±0.03*	0.43±0.04*	0.43±0.04*	0.41±0.04*	0.41±0.06*	0.38±0.06*	0.37±0.05*
PT	Me-Mi	39.4±0.8	39.6±0.8	39.6±0.9	39.3±0.9	39.0±1.1	38.7±1.1*	37.8±1.1*	37.4±1.1*	37.0±1.1*
(°C)	Me80	39.0±0.3	39.2±0.3*	39.3±0.4*	39.3±0.4*	39.2±0.4	39.1±0.4	38.8±0.5	38.6±0.5	38.0±0.7*

a) Data were expressed as mean±standard deviation, n=5. PaO₂, PaCO₂, pHa, [HCO₃]_a and BEa=arterial blood PO₂, PCO₂, pH, bicarbonate concentration and base excess. DO₂=delivery O₂, VO₂=oxygen consumption, UO₂=oxygen utilization ratio. PT=pulmonary arterial temperature.

b) Not done

* Significantly (p<0.05) different from baseline.

[#] Significantly (p<0.05) different from Me80.

Table 3. Cardiopulmonary consequences of medetomidine-midazolam-atipamezole (Me-Mi-Ati) administration in dogs^{a)}

Measurements	Time after administration of atipamezole (min)							
	Baseline	0 ^{b)}	5	10	20	30	40	60
HR (/min)	106.2±16.7	62.4±10.6*	90.2±15.2 [#]	101.4±38.3 [#]	108.4±19.9 [#]	103.4±15.5 [#]	112.2±22.2 [#]	111.8±27.5 [#]
APm (mmHg)	115.2±7.3	116.8±9.6	105.4±11.7 [#]	104.2±10.2	109.8±13.8	115.4±10.9	119.6±9.0	123.6±3.6
RAP (mmHg)	1.2±1.2	3.2±2.1	0.6±0.8 [#]	0.2±0.4 [#]	0.8±0.7 [#]	0.4±0.5 [#]	0.8±1.0	1.2±1.6
PAPm (mmHg)	15.2±1.0	14.6±2.3	12.2±2.6 [#]	11.4±2.4 [#]	12.4±2.1 [#]	13.0±1.4	13.8±1.6	15.6±2.7
PAWP (mmHg)	5.2±1.2	8.0±1.7*	4.4±1.9 [#]	4.0±1.4 [#]	4.6±2.1 [#]	4.8±1.6 [#]	5.4±2.2 [#]	5.2±2.8 [#]
SVR (mmHg·min·kg/l)	575±124	1077±111*	ND ^{c)}	804±79 [#]	634±193 [#]	699±168 [#]	662±196 [#]	717±232
PVR (mmHg·min·kg/l)	50±14	63±25	ND	56±16	44±14	47±9	45±8	56±8
CI (ml/min·kg)	210±58	106±4*	ND	130±16 [#]	183±36 [#]	180±33 [#]	194±51 [#]	189±59
SV (ml/kg)	2.0±0.6	1.7±0.3	ND	1.4±0.3	1.7±0.3	1.7±0.2	1.7±0.3	1.7±0.4
RPP (mmHg/min)	15088±2025	8961±1731*	11275±2194 [#]	12397±5391	13776±1874 [#]	13831±2497 [#]	15592±3006 [#]	15946±3508 [#]
DO ₂ (ml/kg min)	207±24	94±12*	ND	144±65	186±32 [#]	182±21 [#]	191±20 [#]	184±20 [#]
VO ₂ (ml/kg min)	51±13	32±5*	ND	33±9	56±24	62±21	80±31	81±19 [#]
UO ₂	0.2±0.1	0.3±0.0*	ND	0.2±0.0 [#]	0.3±0.1	0.3±0.1	0.4±0.1	0.5±0.1*
PT (°C)	39.7±0.5	38.6±0.9	37.6±1.0*	37.7±0.8*	37.7±0.9*	37.8±0.7*	38.0±0.5	38.6±0.6

a) Data were expressed as mean±standard deviation, n=5. HR=heart rate, AP=arterial blood pressure, m=mean, RAP=right atrial pressure, PAP=pulmonary arterial pressure, PAWP=pulmonary arterial wedge pressure, SVR=systemic vascular resistance, PVR=pulmonary vascular resistance, CI=cardiac index, SV=stroke volume, and RPP=rate pressure product. DO₂=delivery O₂, VO₂=oxygen consumption, UO₂=oxygen utilization ratio. PT=pulmonary arterial temperature.

b) Atipamezole was administered 40 min after administration of medetomidine-medazolam.

c) Not done.

* Significantly (p<0.05) different from baseline value.

Significantly (p<0.05) different from pre-atipamezole value.

administration to slightly below baseline values, and remained constant or gradually returned to baseline values.

After atipamezole administration, SVR and PVR decreased to the baseline values and remained constant thereafter. CI and RPP started to increase just after atipamezole administration and reached almost to baseline values at 20 min. SV slightly decreased for 10 min after atipamezole administration however remained constant.

The effects of Me80, Me-Mi and Me-Mi-Ati on respiratory system are summarized in Tables 2 and 3. There were no depression in the respiratory function after Me-Mi administration. DO₂ and VO₂ decreased and remained constant, and UO₂ increased initially then remained significantly higher level than baseline value.

Changes in PO₂, PCO₂, BE and [HCO₃⁻] after atipamezole administration were minimal (data are not shown). DO₂ increased after atipamezole administration to baseline values corresponding the increase in CI. VO₂ increased after atipamezole administration. UO₂ decreased initially for 10 min after atipamezole administration then increased gradually for following 40 min.

PT increased slightly for 10 min after drug(s) administration and decreased gradually to the level significantly below baseline value in Me80 and Me-Mi. PT decreased rapidly in 5 min after atipamezole administration and remained the level significantly below pre-atipamezole value for 30 min, then increased gradually, however it did not recover the similar level to baseline value until 50 min after atipamezole administration.

DISCUSSION

In this study, simultaneous administration of medetomidine and midazolam caused a change of the similar trend to that of medetomidine alone in cardiopulmonary effects, however its change was less profound than that of a higher dose of medetomidine alone. Administration of medetomidine-midazolam caused a decrease in HR to the same extent of Me80. CI also decreased, however CI of Me-Mi were significantly higher than that of Me80. The decrease in CI is attributed to decreases in HR and/or SV. In this study, the significant higher values in CI of Me-Mi than those of Me80 were due to the differences in SV. The decrease in SV was thought to be mainly induced by central sympatholytic effects and increase in afterload which was represented by SVR, because medetomidine has been reported to have little direct action on the myocardium [3] and preload which was represented by RAP and PAWP did not decrease after administration in this study. It has been known that medetomidine peripherally activates the vascular α₂-adrenoceptors and consequently induces vasoconstriction [14]. Increases in SVR of both Me-Mi and Me80 were probably a result of the direct vasoconstrictive actions of medetomidine, as midazolam has been demonstrated to have a minimal cardiovascular effect [7]. The reduction of medetomidine to one-fourth in Me-Mi might be effective to reduce sympatholytic action, vasoconstriction and depression in CI.

Administration of medetomidine-midazolam caused a mild pressor response, characterized by mild but rapid

increase in AP, then it decreased gradually to baseline. However this change was smaller than that of Me80 with a significant difference in mean AP at 5 min after administration. This effect was thought to be mainly induced by medetomidine, because medetomidine alone exerted the similar changes in dogs [9] and midazolam has been demonstrated to have a minimal cardiovascular effect as mentioned above. These changes were not accompanied by increases in CO but correlated well to the changes in SVR or PVR, therefore they may be mediated mainly through systemic and pulmonary vasoconstriction. Differences in AP between Me-Mi and Me80 were attributed to significantly different SVR. Me-Mi induced less change in SVR and thereby blood pressure by reducing the dose of medetomidine.

RPP correlates with myocardial oxygen consumption. RPP decreased as the result of decreased HR, although arterial blood pressure increased. This suggested Me80 and Me-Mi could provide enough oxygen supply to myocardium as oxygen demand decreased [2].

The effects of medetomidine-midazolam on respiratory system were minimal. Although DO_2 decreased due to decrease in CI, UO_2 increased slightly. This increase in UO_2 was attributed to decrease in VO_2 . The decrease in oxygen consumption is thought to be mainly due to sedation, continued suppression of norepinephrine release, and direct action on brain stem respiration center induced by medetomidine [8]. After Me-Mi administration, oxygen supply was thought to be maintained.

Atipamezole is a potent and highly selective and specific α_2 -adrenoceptor antagonist which produces a effective antagonism of the sedation induced by medetomidine-midazolam in dogs [6]. This study demonstrated that cardiopulmonary effects induced by Me-Mi could also be antagonized by atipamezole. Although cardiopulmonary effects of this combination are milder than those of higher doses of medetomidine alone [4], HR and CI decreased significantly below base line values and SVR increased significantly above baseline value 40 min after Me-Mi administration (before atipamezole administration). However, soon after atipamezole administration these values recovered not significantly different levels to baseline values. Atipamezole effectively reversed the cardiovascular changes induced by Me-Mi.

The effective antagonism of atipamezole suggests that cardiopulmonary changes induced by Me-Mi are mainly due to the effect of medetomidine. Therefore intramuscular administration of 80 $\mu\text{g}/\text{kg}$ of atipamezole seems to be adequate to antagonize the effects induced by Me-Mi. The results of this trial could assure the availability and safety of use of this combination.

In conclusion, medetomidine-midazolam caused bradycardia and mild pressor response, however these changes were less profound than a higher dose of medetomidine alone indicating significantly lower values in SVR and AP and higher values in CI. The reduction of the dose of medetomidine seemed to be effective especially to peripheral effects of medetomidine, consequently reduced

the adverse side effects of medetomidine. The combination of medetomidine and midazolam could produce much more potent sedation than a higher dose of medetomidine alone [5] with less depression on cardiopulmonary function. Cardiopulmonary effects induced by a combination of medetomidine and midazolam could be reversed quickly and smoothly by atipamezole. This reversal action was obtained at a dose of 80 $\mu\text{g}/\text{kg}$, which was four times the dose of the preceding medetomidine. The possible use of an antagonist as a reversal agent might enhance the value and availability of medetomidine-midazolam as a chemical restraint agent in dogs.

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