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Effect of Glycopyrrolate on Cardiovascular System in Dogs Sedated with Medetomidine-Midazolam Combination

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Abstract : This study was performed to evaluate the effect of intravenous administration of glycopyrrolate on cardiovascular and respiratory system in dogs given intravenous medetomidine (20 μg/kg) and intramuscular midazolam (0.3 mg/kg) (MM). Prior to administration of MM, glycopyrrolate was administered intravenously at doses of 5 μg/kg (Gly-5), 10 μg/kg (Gly-10) or 20 μg/kg (Gly-20), respectively. For the control group saline was administered intravenously. In the cardiovascular system, HR, BP, RAP, PAWP, CI, SI, SVR, and PVR were measured. RR, V_T, P_{ETCO2}, and arterial blood gas analysis were measured for respiratory system. Although rapid and satisfied depth of sedation was obtained by MM, life-threatening bradycardia, the outstanding side-effect on cardiovascular system in dogs were observed. This combination also decreased CO and increased SVR, RAP, and PAWP significantly. The bradycardia could be prevented in all the glycopyrrolate treated groups, but tachycardia was observed in Gly-10 and Gly-20 groups. Significant increases in blood pressure were shown in glycopyrrolate treated groups. Also, tachycardia depends on dose of glycopyrrolate, compensating the CO. However, these were not fully reserved. In conclusion, MM combination could induce rapid and satisfied depth of sedation but was not the suitable method for the deep sedation of dogs with cardiovascular or circulatory problems.

Key words **:** medetomidine, midazolam, glycopyrrolate, cardiovascular, dog.

Introduction

Application of anesthetics or sedatives in veterinary medicine is to control animal's movement, reduce pain and making the patient unconsciously for the favorable diagnostic and therapeutic procedure. It is also important for protecting veterinarians themselves from the animal. First use of anesthetic agents has started in the sixteenth century (29). Injectable anesthesia and its method, began in the late nineteenth century, have been widely accepted as safe and effective way for various purposes (29). Recently, for diagnostic procedure or simple treatment like radiography, oral examination, biopsy or splint application, necessity of short-term sedation or anesthesia is increasing (26). Since such procedures does not require much time or produce great pain, physical restraint or deep anesthetic depths are not needed. In addition, excessive restraint or anesthesia are improper for precise examination and adequate treatment, as well as animal welfare. In this regard, method for short-term sedation or anesthesia and fast recovery is getting more important (28).

Medetomidine is a α_2-adrenergic receptor agonist, which has been used for sedative or preanesthetic agent in veterinary medicine (1, 8, 22, 30). Medetomidine is preferred as combined anesthetic agent than sole agent, for inducing deep sedation or light anesthesia. Medetomidine is also used as induction agent in gas anesthesia and possible combining agents include ketamine, butorphanol, acepromazine and midazolam (11, 12, 14, 21).

Midazolam is a water-soluble benzodiazepine derivative, used as sedative in human medicine. However, considering unsatisfactory sedative action and side effects like ataxia or confusion when used as sole agent, using medetomidine/midazolam combination is better for adequate sedation effect (4,6,14). Moreover, by giving atipamezole, medetomidine antagonist, fast and smooth recovery is achievable after the procedure is over (4,7).

Because medetomidine produces severe cardiovascular side effects such as bradycardia, arrhythmia or vasoconstriction, many studies about reducing them by using atropine or glycopyrrolate are reported (2,5,13,25,26,31). Since atropine takes 10 to 20 minutes to be absorbed when injected intramuscularly or subcutaneously, it should be administrated 20 minutes before sedative or anesthetic injection. Atropine induces bradycardia when intravenously injected because it passes blood-brain barrier (BBB). On the other hand, glycopyrrolate is highly polarized so that it does not go through BBB. Subsequent intravenous injection of glycopyrrolate is possible. When it is administered in intramuscular or subcutaneous route, peak effect is expected after 20 minutes (8,18). Reducing cardiovascular side effects of medetomidine with glycopyrrolate has been reported (9,19).

Medetomidine/midazolam combination is appropriate for sim-

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ple procedure that induces mild pain or as combination with other Injectable anesthetic agent. Though it is used as induction agent in gas anesthesia, it can be less popular if induction time is prolonged, in spite of having antagonist (7).

Intravenous medetomidine and intramuscular midazolam combination brings rapid sedation but causes profound cardiovascular depression. This study is performed to evaluate cardiovascular effect of intravenous glycopyrrolate in dogs treated with rapid sedation protocol of medetomidine/midazolam combination.

Materials and Methods

Animals

This study was approved by Chungnam National University Animal Care and Use Committee. Sixteen clinically healthy beagles weighting 8.4 kg (5.9 kg, 11.6 kg) [mean (minimum, maximum)] were used. Dogs were acclimated 1 month before the experiment and undergone physical examination, blood examination and radiographic examination to make sure of their health status. Food was given 2 times a day and free water was supplied. Dogs for experimental study were selected randomly, in no order.

Catheterization

Animals were fasted for 12 hours and lactated Ringer's solution was continuously infused at the rate of 10 ml/hour through IV catheter on cephalic veins. Anesthesia monitor (S-5 Anesthesia Monitor®, Datex-Ohmeda, Finland) was connected, followed by gas induction through face mask with gas anesthetic machine (Royal-77®, Royal Medical Co, Korea). After intubation, animals were positioned in left lateral recumbency and anesthesia was maintained with 1.5 MAC isoflurane under pure oxygen.

Under anesthesia, 21-gauge 2-inch indwelling catheter (D&B Cath®, Sindongbang Medical Co, Korea) was inserted in dorsal pedal artery of right hind limb. Pressure transducer (Transpac®, IV Monitoring Kit, USA) was connected to IV catheter and anesthesia monitor. Through left jugular vein, 5-french 90 cm flow-directed thermo-dilution catheter (BIOTRAY TD1504HD, LEUR®, Biosensors International Ltd, Singapore) was inserted until the tip of catheter positioned in main pulmonary artery.

After all catheters were placed, anesthetic gas supply was stopped and only 100% oxygen was given, waiting to recover from anesthesia. When anesthetic gas concentration dropped by 0.5% or less, cardiovascular parameters were measured so as to use for baseline value (27). Oxygen supply was kept on until the end of procedure.

Administration of drugs

Five minutes after measuring cardiovascular parameters, drugs were administrated. For control group, 1 ml of normal saline was injected, followed by 20 μg/kg medetomidine (Domitor®, Orion Pharma, Finland) intravenous injection, 0.3 mg/kg midazolam (Vascam®, Hana Pharm, Co, Korea) intramuscular injection. Glycopyrrolate (Glycopyrrolate inj.®, Reyon Pharm, Co, Korea) administration group was separated according to the dose; 5 μg/kg (Gly-5), 10 μg/kg (Gly-10) and 20 μg/kg (Gly-20) were injected intravenously. Medetomidine and midazolam were administrated same as control group immediately after glycopyrrolate injection.

Measurement of parameters

Cardiovascular system

Cardiovascular parameters were measured and recorded at each time; before and, 2, 5, 10, 20 and 30 minutes after administration. Heart rate (HR), blood pressure [(BP); systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP)], right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), were directly measured by anesthesia monitor; cardiac output (CO) was measured 3 times by thermo-dilution method and took an average.

By parameters obtained above, values were calculated: cardiac index (CI) = CO/BW, stroke index (SI) = CI/HR, systemic vascular resistance (SVR) = (MAP-RAP)/CO × 79.9 and pulmonary vascular resistance (PVR) = (PAP-PAWP)/CO × 79.9.

Respiratory system

Respiratory rate (RR), tidal volume (V_T) and end-tidal PCO_2 (P_{ETCO2}) were directly assessed by anesthesia monitor.

Arterial pH, PaO_2, $PaCO_2$, T_{CO2} and HCO_3^- were measured by arterial blood gas analyzer (i-STAT®, Heska Co, USA) at each time: before and, 5, 10, 20 and 30 minutes after administration. Arterial blood samples were obtained from catheter on dorsal pedal artery.

Catheter removal and recovery

After final measurement at 30 minutes after administration was done, antibiotic was given. Arterial catheter was removed; compression hemostasis and bandage were applied. Atipamezole (Antisedan®, Orion Pharma, Finland), medetomidine antagonist, was given by intravenously route at a dose of 0.2 μg/kg.

Statistical analysis

All statistics were performed using a computer statistical package (SPSS for Windows, Release 12.0.1, SPSS Inc, USA).

Cardiopulmonary parameters of each group were compared by Friedman's test to verify statistical significance. If significant ($P < 0.05$), each variable was undergone Wilcoxon's signed rank test. To prove significance of certain time between the groups, Two-way ANOVA was conducted ($P < 0.05$).

Results

Pronounced sedation was shown immediately after medetomidine-midazolam injection.

Cardiovascular parameters

Administrating glycopyrrolate, In Gly-10 and Gly-20 groups, HR, ABP, PAP and PAWP were significantly increased and different from control group. Otherwise, there were no significant differences in Gly-5 group (Table 1).

Table 1. Effect of intravenous administration of glycopyrrolate on cardiovascular parameters in dogs given medetomidine and midazolam

Variable	Group	Time after administration of medetomidine and midazolam (minute)					
		Pre	2	5	10	20	30
HR (bpm)	Control	109 ± 18	32 ± 5*	31 ± 6*	43 ± 11*	34.5 ± 8*	37 ± 1*
	Gly-5	107 ± 17	81 ± 46	93 ± 28a	93 ± 24a	82 ± 16a	80 ± 10a
	Gly-10	99 ± 19	137 ± 18a	174 ± 41*,a	154 ± 27*,a	129 ± 19a,b	121 ± 36a,b
	Gly-20	109 ± 10	179 ± 18*,a,c	172 ± 17*,a,b	162 ± 13*,a,b	129 ± 13a,b	115 ± 13a,b
SAP (mmHg)	Control	140 ± 17	15 ± 14	164 ± 22	156 ± 15	149 ± 13	142 ± 15
	Gly-5	121 ± 8	197 ± 48	189 ± 29*	192 ± 44	187 ± 42	175 ± 34
	Gly-10	129 ± 6	229 ± 17*,a	206 ± 18*	203 ± 10*,a	211 ± 9*,a	201 ± 15*,a
	Gly-20	123 ± 10	242 ± 22*,a	258 ± 50*,a	228 ± 20*,a	196 ± 21*,a	179 ± 26*
MAP (mmHg)	Control	102 ± 15	117 ± 13	121 ± 16	117 ± 13	107 ± 10	103 ± 10
	Gly-5	80 ± 8	159 ± 45*	157 ± 24*	157 ± 33*	149 ± 32*	136 ± 26*
	Gly-10	84 ± 4	199 ± 17*,a	182 ± 25*,a	174 ± 10*,a	181 ± 13*,a	174 ± 18*,a
	Gly-20	86 ± 11	189 ± 9*,a	200 ± 35*,a,b	186 ± 13*,a	162 ± 10*,a	146 ± 14*,a
DAP (mmHg)	Control	83 ± 16	97 ± 17	100 ± 15	98 ± 16	86 ± 11	84 ± 11
	Gly-5	60 ± 8	140 ± 44*	141 ± 21*	140 ± 28*	129 ± 26*	113 ± 22*
	Gly-10	61 ± 5	192 ± 7*,a,b	170 ± 28*,a	160 ± 10*,a	166 ± 16*,a	160 ± 19*,a,b
	Gly-20	68 ± 12	167 ± 10*,a,c	182 ± 46*,a	165 ± 16*,a	145 ± 10*,a	130 ± 12*,a
RAP (mmHg)	Control	-1.2 ± 1.0	6.3 ± 1.5*	6.8 ± 1.7*	6.0 ± 2.2*	5.0 ± 1.4*	4.8 ± 1.0*
	Gly-5	-1.2 ± 2.2	5.3 ± 3.3*	7.0 ± 4.4*	6.2 ± 3.5*	5.8 ± 3.5*	4.8 ± 3.3*
	Gly-10	-1.3 ± 1.5	4.5 ± 1.7*,a	6.0 ± 2.2*	5.8 ± 1.7*	4.5 ± 2.1*	3.3 ± 2.1*
	Gly-20	-2.8 ± 1.3	4.0 ± 2.2*,a	4.5 ± 1.9*	3.5 ± 1.3*	2.5 ± 1.0*	2.5 ± 1.7*
PAP (mmHg)	Control	9.3 ± 1.0	10.5 ± 3.3	10.8 ± 3.6	10.3 ± 3.3	9.5 ± 3.3	8.5 ± 3.1
	Gly-5	10.0 ± 1.4	22.0 ± 9.8	22.2 ± 7.5*	21.0 ± 7.9	17.3 ± 5.4	13.2 ± 3.6
	Gly-10	9.8 ± 2.2	23.2 ± 8.0*,a	27.8 ± 5.7*,a	25.0 ± 4.1*,a	21.8 ± 4.1*,a	18.5 ± 3.9*,a
	Gly-20	7.8 ± 2.9	29.2 ± 7.5*,a	24.0 ± 8.4*,a	25.0 ± 4.9*,a	19.0 ± 7.2*	14.8 ± 7.0
PAWP (mmHg)	Control	1.5 ± 1.7	NE	9.0 ± 2.7*	8.0 ± 2.0*	6.5 ± 2.7*	6.8 ± 1.7*
	Gly-5	0.8 ± 1.5		18.5 ± 7.4*	16.5 ± 6.6*	13.0 ± 4.1*	9.8 ± 3.3*
	Gly-10	2.0 ± 2.8		23.3 ± 8.2*,a	21.3 ± 6.2*,a	17.0 ± 5.5*,a	14.5 ± 5.0*
	Gly-20	1.0 ± 2.2		21.0 ± 8.2*,a	19.5 ± 7.9*,a	16.0 ± 8.0*,a	12.5 ± 7.0*
CI (ml/kg/min)	Control	261.07 ± 35.60	NE	8.60 ± 16.92*	78.03 ± 13.12*	86.15 ± 9.70*	87.43 ± 18.31*
	Gly-5	207.00 ± 51.63		62.83 ± 11.44*	70.60 ± 11.18*	77.60 ± 20.02*	80.30 ± 24.80*
	Gly-10	264.59 ± 85.27		84.01 ± 12.84*	84.60 ± 17.70*	101.00 ± 22.30*	107.32 ± 24.95*
	Gly-20	285.19 ± 61.07		120.65 ± 26.26*,a,b	170.00 ± 90.91a,b	161.02 ± 56.42a,b	132.09 ± 17.59*,a,b
SI (ml/kg)	Control	2.46 ± 0.62	NE	2.22 ± 0.69	2.55 ± 0.56	2.15 ± 0.65	2.70 ± 0.97
	Gly-5	1.95 ± 0.41		1.18 ± 1.12	0.79 ± 0.19*	0.85 ± 0.18*,a	0.99 ± 0.28*,a
	Gly-10	2.62 ± 0.40		0.63 ± 0.17*,a	0.53 ± 0.26*,a	0.69 ± 0.29*,a	0.87 ± 0.33*,a
	Gly-20	2.60 ± 0.34		0.69 ± 0.21*,a	1.03 ± 0.66*,a	1.01 ± 0.41*	1.03 ± 0.15*,a
SVR (dyness/cm^5)	Control	4117 ± 570	NE	17981 ± 3853*	15162 ± 3630*	12395 ± 1879*	12006 ± 2364*
	Gly-5	3671 ± 259		22088 ± 3259*	19603 ± 3279*	17241 ± 3893*	15433 ± 4435*
	Gly-10	3341 ± 869		20748 ± 3909*	20156 ± 4777*	17797 ± 4897*	16377 ± 5233*
	Gly-20	3194 ± 683		16546 ± 3959*	12700 ± 5748*	10753 ± 3708*	10900 ± 1558*
PVR (dyness/cm^5)	Control	313 ± 74	NE	279 ± 183	285 ± 168	347 ± 252	214 ± 190
	Gly-5	417 ± 56		554 ± 96	574 ± 77	487 ± 91	393 ± 51
	Gly-10	294 ± 108		517 ± 267	394 ± 305	474 ± 192	342 ± 165
	Gly-20	252 ± 122		235 ± 192	335 ± 208	231 ± 222	177 ± 226

Data are expressed as mean ± SD (n = 04)
*Significantly different from pre value ($p < 0.05$)
[a]Significantly different from control group ($p < 0.05$)
[b]Significantly different from Gly-5 group ($p < 0.05$)
[c]Significantly different from Gly-10 group ($p < 0.05$)
NE: Not examined

SVR and RAP were increased in all groups. However, there were no significant differences among groups (Table 1).

CI was significantly decreased in all groups, but in Gly-20 group, the degree of CI decrease was lesser than in other groups. There was significant difference from control and other treatment groups. SI was significantly decreased in glycopyrrolate treatment groups (Gly-5, Gly-10 and Gly-20) (Table 1).

PVR showed no significant difference in all groups, while in control group, tendency of decrease with no significance was observed (Table 1).

Respiratoryparameters

V_T increased with significant difference only in Gly-10 group. Arterial pH of Gly-5 group was low with significant difference at 5, 10 and 20 minutes than baseline value (Table 2).

There were no significant differences in other parameters.

Discussion

Major effects of α_2-adrenergic agonists includes: CNS depression by stimulating both presynaptic and postsynaptic α_2-adrenoceptors, dose-dependent sedation, muscle relaxation and

Table 2. Effect of intravenous administration of glycopyrrolate on respiratory parameters in dogs given medetomidine and midazolam

Variables	Group	Time after administration of medetomidine and midazolam (minute)					
		Pre	2	5	10	20	30
RR (breath/min)	Control	24 ± 9	7 ± 3*	12 ± 7	13 ± 8	16 ± 6	18 ± 5
	Gly 5	18 ± 9	4 ± 5	10 ± 3	12 ± 3	14 ± 3	14 ± 3
	Gly 10	32 ± 11	12 ± 12	16 ± 9	17 ± 9	18 ± 9	16 ± 6
	Gly 20	23 ± 10	18 ± 9	20 ± 10	19 ± 7	17 ± 7	15 ± 5
V_T (ml)	Control	127 ± 30	107 ± 30	119 ± 31	109 ± 38	113 ± 15	115 ± 6
	Gly 5	133 ± 33	168 ± 40	125 ± 17	130 ± 18	135 ± 19	135 ± 19
	Gly 10	90 ± 14	185 ± 90*	150 ± 63*	144 ± 39*	143 ± 35*	150 ± 28*
	Gly 20	138 ± 50	159 ± 66	167 ± 59	155 ± 44	138 ± 50	140 ± 61
P_{ETCO2} (mmHg)	Control	43 ± 3	38 ± 2	49 ± 4	49 ± 3	48 ± 1	45 ± 2
	Gly 5	45 ± 2	23 ± 25	53 ± 2*	52 ± 1*	48 ± 1	47 ± 1
	Gly 10	37 ± 12	40 ± 6	46 ± 5	45 ± 4	44 ± 3	43 ± 2
	Gly 20	46 ± 2	44 ± 2	47 ± 1	49 ± 1	50 ± 2	49 ± 3
pH	Control	7.33 ± 0.05	NE	7.29 ± 0.05	7.27 ± 0.06	7.28 ± 0.05	7.29 ± 0.05
	Gly 5	7.30 ± 0.01		7.25 ± 0.01*	7.24 ± 0.02*	7.25 ± 0.02*	7.28 ± 0.02
	Gly 10	7.31 ± 0.02		7.26 ± 0.03	7.27 ± 0.02	7.28 ± 0.01	7.28 ± 0.01
	Gly 20	7.31 ± 0.03		7.29 ± 0.04	7.28 ± 0.03	7.29 ± 0.04	7.30 ± 0.03
PaO_2 (mmHg)	Control	581 ± 53	NE	611 ± 27	601 ± 34	576 ± 84	567 ± 149
	Gly 5	574 ± 35		560 ± 68	576 ± 64	569 ± 21	597 ± 67
	Gly 10	572 ± 40		577 ± 30	590 ± 55	596 ± 35	612 ± 22
	Gly 20	514 ± 40		551 ± 20	549 ± 46	491 ± 94	540 ± 68
$PaCO_2$ (mmHg)	Control	49 ± 4	NE	54 ± 5	56 ± 7	49 ± 12	45 ± 15
	Gly 5	52 ± 3		58 ± 4*	57 ± 4	53 ± 4	50 ± 3
	Gly 10	39 ± 24		57 ± 9	54 ± 7	52 ± 5	53 ± 4
	Gly 20	46 ± 3		50 ± 4	50 ± 2	49 ± 7	48 ± 6
T_{CO2} (mEq/L)	Control	28 ± 2	NE	28 ± 2	27 ± 1	25 ± 4	23 ± 9
	Gly 5	27 ± 1		27 ± 2	26 ± 3	26 ± 1	25 ± 2
	Gly 10	26 ± 3		28 ± 3	27 ± 3	26 ± 2	27 ± 1
	Gly 20	24 ± 1		26 ± 1	25 ± 2	26 ± 2	25 ± 2
HCO_3^- (mEq/L)	Control	26.4 ± 2.1	NE	26.0 ± 1.9	25.4 ± 1.2	24.5 ± 2.7	21.9 ± 7.9
	Gly 5	25.4 ± 1.2		25.8 ± 2.0	24.4 ± 2.3	23.8 ± 0.8	23.8 ± 1.6
	Gly 10	24.9 ± 2.8		25.6 ± 2.5	24.7 ± 2.4	24.3 ± 2.2	25.1 ± 1.5
	Gly 20	22.9 ± 1.1		24.3 ± 04	23.7 ± 1.7	24.0 ± 1.4	23.6 ± 1.3

Data are expressed as mean ± SD (n=4)
*Significantly different from pre value ($p < 0.05$)
NE: Not examined

analgesia in peripheral nerve system (18). Medetomidine is α_2-adrenergic agonist with high affinity, usually used for minor surgical procedure or induction agent for inhalation anesthesia in veterinary practice (18).

Demonstrated by previous studies, more remarkable sedation was produced with medetomidine/midazolam combination than with medetomidine alone (5). Previous studies found that the significant sedation after IM injection of medetomidine (30 μg/kg) are evident within 5 minutes and persists for 1 to 2 hours (32). In this study, IV medetomidine injection (20 μg/kg) and IM midazolam (0.3 μg/kg) caused immediate and profound sedative effect. Also, subsequent decrease of HR and CO and increase of RAP and SVR were observed.

Several cardiovascular changes after giving medetomidine were reported; bradycardia decreased CO and increased SVR by vessel contraction due to peripheral α_2-adrenoreceptor stimulation (8). Various research articles have demonstrated that the drop in CO is not due to direct negative action of the α_2-agonist on myocardial contractility, but is secondary to increased SVR and reduced HR (3,20,24). Arterial pressure can be increased due to SVR increase but significant difference was not shown in the present study (10). Previous study showed that administration of high doses of medetomidine can stimulate peripheral adrenergic receptor, inducing increase of blood pressure, but with low doses, such effects are insignificant (23).

To prevent bradycardia after medetomidine administration, anticholinergic agent is used. Intramuscular injection of atropine, 10 minutes before giving medetomidine, can inhibit bradycardia (10). Peak effects of atropine are induced within 5 minute with IV injection, compared to 10-20 minutes with IM injection.

Glycopyrrolate also has similar pharmacokinetic property to atropine, but does not pass BBB (8). Based on such characteristics, IV injection of glycopyrrolate with medetomidine IV injection is expected to prevent bradycardia and CI decrease, which was observed in this study. Besides, tachycardia occurred in Gly-10 and Gly-20 groups. But in Gly-20 group significant decrease of CI was only observed at 5 and 30 minutes after administration. And, in Gly-20 group CI was significantly different from those of control and Gly-5 groups.

CO is largely connected with SVR and HR. In this study, statistically significant decrease of SI in both Gly-10 and Gly-20 groups was observed, which is thought to be occurred due to increase of SVR after medetomidine and increase of HR after anticholinergic injection. Consequent synergetic effect appeared as arterial pressure increase (16). Increase of arterial pressure was also observed in other studies about effects of anticholinergics, when given before medetomidine (10). In all groups, SVR progressively increased with significant difference, but significant difference was not present between control group and Gly groups. Therefore, anticholinergic administration doesn't seem to influence SVR; CI increase is seems to be influenced by HR increase.

Central venous pressure (CVP), representing equilibrating state between CO and venous return (17), is measured by estimating RAP. In this study, RAP increased with significant difference in all groups with time, except in Gly-10 and Gly-20, which showed RAP decrease in 2 minutes after administration of medetomidine/midazolam combination. Our results correspond to previous reports that showed α_2-agonist induces CVP increase by peripheral vascular contraction and anticholinergics-induced HR increase result in CVP decrease (17).

Based on the results, PAP and PAWP of Gly-10 and Gly-20 groups showed statistically significant increase in 2, 5, 10 and 20 minutes after administration of medetomidine/midazolam combination. Because PVR did not show significant difference, medetomidine-induced peripheral vascular contraction and glycopyrrolate-induced HR increase seems to be related to PAP and PAWP changes in Gly-10 and Gly-20 groups.

Medetomidine administration has little effect on pulmonary function. In this study RR and pH showed decreasing tendency although Gly-10 group had significant difference. Such change seems to be occurred by decreased sensitivity of respiratory center after medetomidine IV administration. In one study, IV administration of medetomidine decrease the neurorespiratory response to increases in P_{CO2}; decrease tidal volume and respiratory rate with an overall decrease in minute volume when administered in large dosages IV (15,17). However, these do not alter arterial blood gas values insignificantly and produces less depression of ventilatory drive than dose isoflurane (1 MAC) in dogs (8). But from other studies, respiratory suppression after medetomidine administration with 20-80 μg/kg were reported (31). In this study, statistically significant decrease of RR was observed for 2 minutes in control group, which was absent in Gly groups. This seems to be due to bronchodilating effect of anticholinergics, but significant difference was not shown in this study.

In conclusion, IV administration of medetomidine, followed by intramuscular injection of midazolam in dogs, brings immediate and sufficient sedative depth but many cardiovascular side effects come after. Therefore, animals with cardiovascular or circulatory disorder should be excluded from using such anesthetic protocol. Additionally, simple increase in HR by anticholinergic administration might not be helpful for medetomidine/midazolam combination anesthesia in dogs. Therefore, further studies are needed related to administration order and route and to reducing SVR for the use of medetomidine/midazolam combination in small animal practice.

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개에서 Medetomidine과 Midazolam 병용 투여 시 Glycopyrrolate가 심맥관계에 미치는 영향

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요 약 : 이 연구는 혈관 내로 medetomidine (20 μg/kg)을 투여하고, 근육 내로 midazolam (0.3 mg/kg)을 투여한 개에서 혈관 내로 glycopyrroate를 투여하였을 때 심혈관계와 호흡기계에 미치는 영향을 평가하기 위해 실시하였다. 임상적으로 건강한 16마리의 중성화 하지 않은 비글견 (BW: 평균 8.35 kg)이 사용되었다. 혈관 내로 medetomidine과 근육 내로 midazolam을 투여하기 전에 glycopyrrolate를 5 μg/kg (Gly-5), 10 μg/kg (Gly-10), 또는 20 μg/kg (Gly-20)의 용량으로 혈관 내로 투여하고, 대조군은 생리식염수를 혈관 내로 투여하였다. 심박수, 혈압(수축기 동맥압, 이완기 동맥압, 평균 동맥압), 우심방 동맥압, 폐동맥압, 폐동맥 쐐기압, 호흡수, 일회호흡량, 호기말 이산화탄소 분압을 환축감시기를 통해 직접 측정하였다. 심박출량을 측정하고, 계산공식으로 심박출계수, 일회심박출지수, 전신혈관 저항, 폐혈관 저항을 산출했다. 동맥혈을 채취하여 동맥혈 가스를 분석기로 분석하였다. Medetomidine/midazolam병용 투여의 부작용으로 심혈관계에서 서맥이 나타나고, 심박출량 감소와 전신혈관저항, 우심방압, 폐동맥 쐐기압은 증가 현상을 보였다. 서맥은 glycopyrrolate를 투여한 군에서는 나타나지 않았다. 그러나 Gly-10, Gly-20군에서는 빈맥이 관찰되었다. 전반적으로 glycopyrrolate를 투여한 군에서는 혈압은 상승하였으나, Gly-5 군의 경우 대조군과 유의적인 차이는 없었다. 심박출량 지수는 Gly-20군을 제외한 모든 군에서 medetomidine/ midazolam병용 투여 10분과 20분에 큰 차이는 보이지 않았다. 이상의 결과로 medetomidine/midazolam병용 투여는 빠르고 만족할 만한 진정을 보여주나, 현저한 심혈관 부작용이 관찰되고 혈관 내로 glycopyrrolate를 투여에 의해서도 큰 역전을 보이지 않는다. 이러한 결과로 medetomidine/midazolam병용 투여는 심폐기능 변화에 적응할 수 있는 건강한 개에서만 고려될 수 있는 방법이라고 생각된다.

주요어 : 메데토미딘, 미다졸람, 글라이코필로레이트, 심맥관계, 개