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Evaluation of Sedative and Cardiovascular Effects Following Administration of Medetomidine, Dexmedetomidine and their Combination with Acepromazine, Atropine and Methadone in Dogs

Mozhdeh Shamshiri, Bahman Mosallanejad, Hadi Imani Rastabi ✉

Department of Clinical Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran

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ABSTRACT

Pre-anesthetic drugs used for sedation have several effects on the cardiovascular system. Even in minor procedures, they may cause significant cardiac depression and hemodynamic instability. The present study evaluated the effects of medetomidine, or dexmedetomidine, combined with acepromazine and atropine with and without methadone on dogs' sedation scores and cardiovascular system. Forty stray dogs were randomly divided into four groups of ten. Each dog was intramuscularly given one of the compounds of acepromazine (0.05 mg/kg) + dexmedetomidine (5 µg/kg) + atropine (0.03 mg/kg) (Group A); acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg) (Group B); acepromazine + medetomidine (10 µg/kg) + atropine (Group C) and acepromazine + medetomidine + atropine + methadone (Group D). Sedation scores, heart rate, respiratory rate, blood pressure, and body temperature were evaluated and recorded at baseline, 5 and 20 minutes after the drug injection. Electrocardiograms (ECG) were also taken at predetermined intervals. The sedation scores in group A were significantly higher at 5 minutes than the baseline. In groups B, C, and D, the sedation scores were significantly higher at 5 and 20 minutes than the baseline. There was no significant difference in the sedation scores during evaluation times between the groups. Heart rate was decreased in all groups after injection. R wave height was increased in all groups. Bradycardia, sinus arrest, and 1st and 2nd-degree heart block were observed in all groups. In conclusion, moderate to deep sedation was achieved in all groups. Heart rate was decreased in all groups, although it returned to baseline earlier in the medetomidine-contained treatments. Occurrences of arrhythmias should be considered when these combinations are used.

Introduction

Sedation is usually used for various purposes, such as vascular access, placing a urinary catheter, bandaging, imaging, creating post-operative analgesia, reducing the anesthetic dose, facilitating anesthesia recovery, controlling excitement, and reducing parasympathetic side effects and anesthesia complications.[1] In anesthesiology, sedation and analgesia are two essential pillars in examinations, sampling, and surgery, which are associated with challenges. Drugs that are used as analgesics, sedatives, or anesthetics affect the cardio-respiratory system and hemodynamics of the body, creating varying degrees of risks to animals. Therefore, general care of the patent's vital systems is an undeniable necessity.[2]

Medetomidine is a potent α-2 adrenergic receptor

✉ Corresponding author. Email: h.imani@scu.ac.ir

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agonist and stimulates the receptors centrally to produce dose-dependent sedation and analgesia.[3] It causes significant adverse effects on the cardiovascular system, including primary peripheral vasoconstriction, increased blood pressure, bradycardia, and bradyarrhythmia.[4] Dexmedetomidine is another α-2 adrenergic receptor agonist widely used in veterinary medicine due to its sedative, analgesic, and muscle relaxant properties.[5] Since medetomidine and dexmedetomidine have significant adverse impacts on the cardiovascular system, they are often used with other drugs to decrease or limit the unpleasant effects.

Acepromazine is a mild to moderate phenothiazine sedative in dogs. This drug can reduce the dose of injectable and inhaled anesthetics and has antiemetic and antiarrhythmic properties.[6] Atropine is used before anesthesia and during anesthesia in small animals to prevent the muscarinic effects of acetylcholine.[7] Methadone is a complete mu (μ) receptor agonist and acts as an n-methyl-di-aspartate receptor antagonist and also inhibits the reuptake of norepinephrine and serotonin in the brain and spinal cord. In addition to the analgesic benefits of methadone, there are fewer adverse effects, such as vomiting and impulsive behavior, compared with other mu agonists.[8] These advantages have led to the use of methadone as a pre-drug before general anesthesia in dogs.[9]

Since no study was found evaluating the effects of medetomidine or dexmedetomidine combined with acepromazine and atropine, with or without methadone, on dogs, the present study aimed to assess the impacts of such combinations on sedation scores and cardiovascular changes in dogs.

Materials and Methods

Forty healthy Indigenous dogs with an average weight of 17.1 ± 3.1 kg, 20 male and 20 female, aged 1-3 years old (using a dental formula), were trapped and collected from the surrounding areas of Ahvaz. The dogs were randomly divided into four equal groups of ten. Each dog was given one of the medicinal compounds intramuscularly (IM): group A: acepromazine (0.05 mg/kg; Neurotranq, Alfasan, Netherland) + dexmedetomidine (5 μg/kg; Precedex, Hospira, USA) + atropine (0.03 mg/kg; Caspian Tamin, Iran), Group B: acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg; Darou Pakhsh, Iran), Group C: acepromazine + medetomidine (10 μg/kg; Dorbene vet, Syva, Spain) + atropine, and group D: acepromazine + medetomidine + atropine + methadone. For a few days before carrying out the project, they were examined in terms of history and underwent a complete clinical examination. They were all classified as classes I and II according to ASA classification score. The meaning of minor disease is some non-infectious and superficial diseases, such as a brief injury to the skin caused by trauma and a slight abdominal hernia, which are classified in category II of the ASA system.[10] Also, this project did not use old, immature, and pregnant animals. All experiment protocols used in this research were approved by the Animal Care Ethics Committee of the Shahid Chamran University of Ahvaz (EE/1401.2.24.226059/scu.ac.ir).

On the day of the experiment, the animal was placed on the right side of the recumbency on a surgery table. After soaking the shaved areas (at the elbow and stifle joints) with alcohol, the electrocardiograph (ECG) clamps were attached to the skin of the determined regions. The ECG device was set to be at 50 mm/s and ten mV. The base ECG was taken after obtaining the appropriate rhythm of the ECG. In this case, the ECG included leads I, II, III, aVR, aVF, aVL, and long lead II. The heart rate (HR), respiratory rate (RR), and body temperature (BT) were also recorded, then. To measure blood pressure, the cuff of the vital sign device (Burtons PM-9000-2, UK) was placed above the left tarsal joint, and the given systolic, mean, and diastolic blood pressures were recorded. After recording the baseline data, the drug was injected IM into the bulk of the hamstring muscles. At 5 minutes and 20 minutes after the drug administration, the data were re-recorded, and the ECG was taken. Also, the animal was evaluated in terms of the level of sedation. Sedation was scored as 0- no sedation, 1- mild sedation (calm and alert), 2- moderate sedation (sleepy and able to walk), 3- deep sedation (severely sleepy and unable to walk), and 4- profound sedation (lack of full consciousness).[11] The ECG was assessed regarding the height and length of the P wave, QRS complex, T wave, PR interval, Q-T interval, and the S-T segment. ECGs were also analyzed and interpreted to determine the type of arrhythmia. After completing the experiment, the animal was placed in a quiet environment to recover and gain full ability to move, and then the animal was returned to the kennel.

Statistical Analysis

GraphPad Prism 9.0.0 software was used for statistical evaluation. The Shapiro-Wilk test was used to check the normality of the data. Kruskal-Wallis non-parametric tests were used to compare sedation scores between, and Friedman's test was used to compare within groups. One-way ANOVA and Duncan's test were used between the groups to compare HR, blood pressure, RR, BT, and ECG parameters. A variance test with repeated measures (repeated measure for ANOVA) with Dunnett's Test was used to compare HR, blood pressure, RR, BT, and ECG factors within the groups. $p < 0.05$ was considered statistically significant. Parametric data are shown as mean ± standard deviation (SD), and non-parametric data are shown as median (minimum-maximum).

Results

The scores for sedation are presented in Table 1. The sedation scores in group A were significantly higher in the 5th minute compared to the baseline ($p < 0.05$). In groups B, C, and D, the sedation scores were significantly higher at 5 and 20 minutes compared to the baseline ($p < 0.05$). No significant difference was observed in terms of sedation scores during evaluation time points between groups ($p > 0.05$).

The heart rate showed a significant decrease in groups A and B at 5 and 20 minutes compared to the baseline ($p < 0.05$). The rectal temperature in group A, at 20 minutes, was significantly lower than 5 minutes ($p < 0.05$). There were no significant changes in other parameters within or between treatments ($p > 0.05$) (Table 2).

The QRS amplitude was significantly higher in group A at 5 minutes compared with the baseline ($p < 0.05$). In group C, the QRS amplitude was significantly higher at 5 and 20 minutes compared to the baseline ($p < 0.05$). The T wave amplitude in group D was significantly higher at 20 minutes compared with baseline and 5 minutes ($p < 0.05$). In group B, the T wave amplitude at 5 minutes was significantly higher than in group A ($p < 0.05$). The P-R interval in group D was significantly higher at 20 minutes than the baseline ($p < 0.05$). The R-R interval in group B was significantly higher at 5 and 20 minutes compared to the baseline ($p < 0.05$). In groups C and D, the R-R interval in 5 minutes was significantly higher than the baseline ($p < 0.05$). The Q-T interval in group B at 20 minutes was

Table 1. Scores related to sedation (range 0-4) in dogs (n = 40) received acepromazine (0.05 mg/kg) + dexmedetomidine (5 µg/kg) + atropine (0.03 mg/kg) (group A), acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg) (group B), acepromazine + medetomidine (10 µg/kg) + atropine (group C), and acepromazine + medetomidine + atropine + methadone (groups D).

Groups	Baseline	5 min	20 min
A	0 ^{A}	3 (0-4) ^{B}	2 (0-4) ^{A}
B	0 ^{A}	2 (1-4) ^{B}	3 (1-4) ^{B}
C	0 ^{A}	2.5 (1-4) ^{B}	2 (1-4) ^{B}
D	0 ^{A}	3 (1-4) ^{B}	3 (1-4) ^{B}

Different uppercase letters indicate significant differences within the groups ($p < 0.05$).

Table 2. Mean ± SD of heart rate, systolic, diastolic, and mean blood pressures (SAP, DAP, MAP, respectively), respiratory rate, and body temperature in dogs (n = 40) received acepromazine (0.05 mg/kg) + dexmedetomidine (5 µg/kg) + atropine (0.03 mg/kg) (group A), acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg) (group B), acepromazine + medetomidine (10 µg/kg) + atropine (group C), and acepromazine + medetomidine + atropine + methadone (groups D).

Parameter		Group	Baseline	5 min	20 min
Heart rate (per minute)		A	82 ± 22^{A}	53 ± 20^{B}	54 ± 14 ^{B}
		B	87 ± 24^{A}	59 ± 19^{B}	55 ± 15 ^{B}
		C	81 ± 22	57 ± 27	71 ± 22
		D	63 ± 14	50 ± 12	63 ± 28
Blood pressure (mmHg)	SAP	A	147 ± 41	125 ± 51	131 ± 34
		B	134 ± 44	122 ± 48	122 ± 27
		C	150 ± 35	146 ± 42	120 ± 43
		D	140 ± 38	155 ± 51	165 ± 49
	DAP	A	89 ± 24	78 ± 34	84 ± 25
		B	77 ± 31	74 ± 35	62 ± 17
		C	88 ± 26	90 ± 45	79 ± 31
		D	78 ± 22	92 ± 40	95 ± 38
	MAP	A	103 ± 25	89 ± 34	99 ± 29
		B	101 ± 37	88 ± 34	83 ± 26
		C	102 ± 25	107 ± 43	92 ± 38
		D	95 ± 23	116 ± 36	121 ± 35
Respiratory rate (per minute)		A	27 ± 14	11 ± 18	14 ± 5
		B	26 ± 15	16 ± 6	20 ± 12
		C	20 ± 4	19 ± 6	11 ± 18
		D	44 ± 24	25 ± 14	22 ± 30
Body temperature (°C)		A	39.1 ± 0.6	39.1 ± 0.5 ^{A}	0.39 ± 0.1 ^{B}
		B	39.1 ± 0.3	39.1 ± 0.2	39.0 ± 0.6
		C	39.0 ± 0.6	39.0 ± 0.5	39.0 ± 0.5
		D	39.0 ± 0.5	39.0 ± 0.5	39.0 ± 0.6

Different uppercase letters indicate significant differences within the groups ($p < 0.05$).

Table 3. Mean ± SD of ECG parameters in dogs (n = 40) received acepromazine (0.05 mg/kg) + dexmedetomidine (5 µg/kg) + atropine (0.03 mg/kg) (group A), acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg) (group B), acepromazine + medetomidine (10 µg/kg) + atropine (group C), and acepromazine + medetomidine + atropine + methadone (groups D).

Parameter	Groups	Base	5 min	20 min
QRS amplitude (mv)	A	0.9 ± 0.4 [A]	0.3 ± 1.2 [B]	1.2 ± 0.3
	B	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4
	C	0.3 ± 0.1 [A]	0.4 ± 1.1 [B]	0.4 ± 1.1 [B]
	D	1 ± 0.3	1.1 ± 0.3	1.2 ± 0.3
T-wave amplitude (mv)	A	0.2 ± 0.1	05 ± 0.2 [A]	0.2 ± 0.1
	B	0.2 ± 0.2	0.3 ± 0.2 [B]	0.3 ± 0.1
	C	0.2 ± 0.06	0.2 ± 0.1	0.2 ± 0.1
	D	0.2 ± 0.1 [A]	07 ± 0.2 [A]	05 ± 0.3 [B]
P-R interval (s)	A	0.03 ± 0.1	0.2 ± 0.04	0.2 ± 0.07
	B	0.02 ± 0.1	0.02 ± 0.1	0.04 ± 0.1
	C	0.2 ± 0.2	0.2 ± 0.02	0.2 ± 0.06
	D	02 ± 0.1 [A]	0.2 ± 0.05	03 ± 0.2 [B]
RR interval (s)	A	0.7 ± 0.2	1 ± 0.6	1 ± 0.3
	B	0.6 ± 0.2 [A]	1 ± 0.5 [B]	0.3 ± 1.2 [B]
	C	0.7 ± 0.2 [A]	0.5 ± 1.2 [B]	1 ± 0.5
	D	0.8 ± 0.2 [A]	1.6 ± 0.5 [B]	1 ± 0.5
QT interval (s)	A	0.4 ± 0.6	0.3 ± 0.02	0.3 ± 0.07
	B	04 0.2 ± 0.2 [A]	0.2 ± 0.05	03 ± 0.3 [B]
	C	0.2 ± 0.03	0.3 ± 0.03	0.3 ± 0.03
	D	03 ± 0.2 [A]	03 ± 0.3 [B]	03 ± 0.3 [B]

Different uppercase letters indicate significant differences within the groups ($p < 0.05$).

Table 4. The number of dogs showed arrhythmias after administration of acepromazine (0.05 mg/kg) + dexmedetomidine (5 µg/kg) + atropine (0.03 mg/kg) (group A), acepromazine + dexmedetomidine + atropine + methadone (0.5 mg/kg) (group B), acepromazine + medetomidine (10 µg/kg) + atropine (group C), and acepromazine + medetomidine + atropine + methadone (groups D).

Group	Time	Sinus arrest	Bradycardia (ECG)	1st degree AV block	2nd degree AV block	Hypotension
A	Baseline	0	0	0	0	1
	5 min	7	1	3	2	1
	20 min	7	2	3	4	1
B	Baseline	1	0	0	0	0
	5 min	5	2	1	0	2
	20 min	6	5	3	1	0
C	Baseline	0	0	0	0	0
	5 min	4	3	1	1	0
	20 min	6	3	4	3	2
D	Baseline	1	0	0	0	1
	5 min	4	7	4	2	0
	20 min	5	3	9	2	0

significantly higher than the baseline ($p < 0.05$). In group D, the Q-T interval at 5 and 20 minutes was significantly higher than the baseline ($p < 0.05$) (Table 3).

The occurrence of arrhythmia (sinus arrest (Figure 1-4) and 1st and 2nd AV blocks), bradycardia (below 40 beats per minute), and hypotension (below 65 mmHg) in the four groups is given in Table 4.

Discussion

The results showed that the amount of sedation increased significantly in all groups at 5 and 20 minutes after the injection compared with the baseline, and no significant difference was seen between the groups. It has been shown that the maximum amount of sedation after

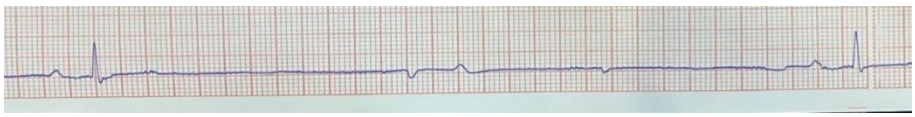

Figure 1. 2nd degree atrioventricular (AV) block in dog No.35 after the administration of acepromazine-dexmedetomidine-atropine (group A) at 20 minutes (lead II).

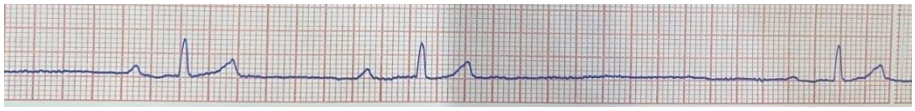

Figure 2. 1st degree atrioventricular (AV) block after the administration of acepromazine-dexmedetomidine-atropine-methadone (group B) at 5 minutes (lead II).

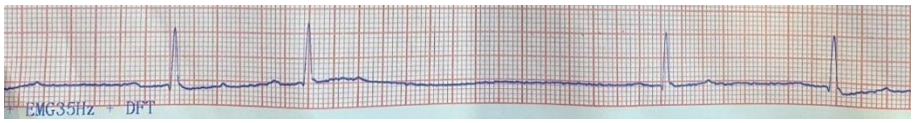

Figure 3. Sinus arrest in dog No.20 after the administration of acepromazine-medetomidine-atropine (group C) at 5 minutes (lead II).

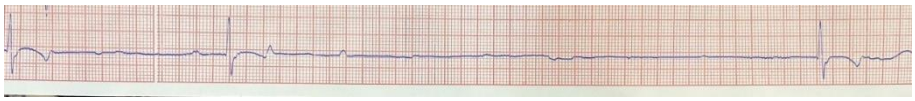

Figure 4. Sinus arrest and 1st and 2nd degree atrioventricular (AV) block in dog No.20 after administration of acepromazine-medetomidine-atropine-methadone (group D) at 20 minutes (lead II).

injection of medetomidine and dexmedetomidine in dogs was achieved at 20 minutes, and the sedation provided by the medetomidine was significantly higher than that offered by the dexmedetomidine.[12] Acepromazine can provide better sedation and analgesia when combined with other sedation drugs. This phenothiazine sedative also has antiemetic and antiarrhythmic properties.[13] In this study, acepromazine was used in all groups. All dogs tolerated the sedation process well, and vomiting was observed in only two cases after 20 minutes.

Administering the combination of dexmedetomidine and methadone or morphine to conscious dogs significantly improved the sedation rate compared with the results when dexmedetomidine was administered alone.[14] In the current study, the amount of sedation in the groups with methadone was not significantly different from the groups without methadone, which could be due to the inappropriate dose or insufficient time of investigation, although in general, adding narcotics to the sedation combination is part of an effort to manage pain around surgery; therefore, it is possible that the addition of methadone, although it did not increase sedation in the studied groups, is effective in reducing the pain of animals.

In a study in dogs, no significant difference has been observed in the HR reduction between the two groups of medetomidine and dexmedetomidine.[15] In the present study, in groups C and D (groups containing medetomidine), the HR decreased at 5 minutes compared with the baseline and returned to baseline at 20 minutes, but in groups A and B (groups containing dexmedetomidine), the HR showed a reduction at both 5 and 20 minutes compared with the baseline. Therefore, it seems that, the HR returned to the baseline faster in the groups containing medetomidine, while in the other two groups, it remained for a longer period at lower rate than the baseline values.

It has been stated that, the effect of α-2 agonists on arterial blood pressure is biphasic, and at first, they cause a transient increase in blood pressure, and after a while, hypotension with long-term bradycardia occurs.[16] The study of Boström *et al.* (2003) on dogs showed that the blood pressure in the group that used acepromazine 30 minutes before anesthesia decreased compared with the group that used physiological saline.[17] In the present study, the MAP in groups A and B decreased at 5 and 20 minutes compared to the baseline, probably due to acepromazine. The MAP in groups C and D increased at 5 minutes after the injection compared with the baseline, possibly due to vasoconstriction and increased blood pressure caused by medetomidine injection. By comparing four treatments in the current study, it showed that the blood pressure in groups A and B, where dexmedetomidine was used, dropped at the 5 and 20 minutes. Still, in groups C and D, where medetomidine was used, blood pressure increased at the 5 minutes.

Previous studies have shown the effects of medetomidine and dexmedetomidine on the respiratory system.[18] Accordingly, in the present study, the number of breaths decreased in all four groups. In the study of Ansah *et al.* (1998) on cats with three different doses of medetomidine and dexmedetomidine, in both medetomidine and dexmedetomidine groups, in all doses, there was an initial decrease in rectal temperature, which showed a trend toward normalization until the end of the experiment.[19] In the study of Monteiro *et al.* (2009) on dogs, it was also shown that the BT decreased after the injection of acepromazine and narcotics such as methadone.[20] In the current investigation, the BT decreased in groups A and B. In group A, the body

temperature at 20 minutes significantly decreased compared with the 5 minutes and the baseline. However, no significant difference in BT was observed in groups C and D.

A prolonged P-R interval indicates first-degree AV block. The normal P-R interval is between 0.06 and 0.11 seconds, and it is considered normal up to 0.13 seconds.[21] In the present study, the P-R interval increased in all groups and was out of the normal range in almost all treatments, which indicates first-degree AV block. The Q-T interval is the sum of ventricular depolarization and repolarization and represents ventricular systole, and its normal interval is between 0.15-0.27 seconds.[22] In the present study, Q-T interval was also outside the normal range in all groups after drug administration. In a study, after the injection of atropine, the HR increased, and the R-R interval decreased, which indicates an inverse relationship between the HR and the R-R interval.[23] In the present study, the R-R interval increased in all groups as the HR decreased. The R-R interval in group B was significantly higher at 5 and 20 minutes than the baseline, and in groups C and D, the R-R interval at 5 minutes was significantly higher than the baseline.

In one study in dogs, the most prominent changes in the ECG rhythm caused by medetomidine were bradycardia and sinus arrhythmia. 2nd-degree AV block was also observed 15 minutes after the injection of medetomidine in doses of 80 and 160 µg/kg.[24] In another study, in the groups receiving medetomidine, widespread sinus arrests were observed in the 15th minute, and 2nd-degree AV block was observed in 4 cases of the medetomidine protocol; it was also shown that acepromazine prevents heart blocks caused by medetomidine.[25] it has been shown that, by suppressing the Vagus nerve, atropine can prevent cardiac arrest caused by parasympathomimetic drugs.[26] In the present study, bradycardia, sinus arrest, and 1st-degree and 2nd-degree AV block were observed in all groups after injection.

It was concluded that using the medetomidine or dexmedetomidine combined with acepromazine and atropine, with or without methadone, caused moderate to deep sedation in dogs. Heart rate decreased in all groups, although it returned to baseline faster in medetomidine-containing treatments. Mean blood pressure decreased in the groups containing dexmedetomidine and increased in those containing medetomidine in the 5th minute after administration. Various arrythmias and AV blocks were observed after injection.

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Conflict of Interest

None to declare.

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