Comparison of the effects of different doses of acepromazine-xylazine on the electrocardiogram in dogs

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Summary

Seventy seven adult large mixed breed dogs of either sex were included in this study. The animals were randomly divided into four groups and received the following drug combinations intramuscularly: Group 1 xylazine (0.5 mg/kg) and acepromazine (0.05 mg/kg), Group 2 xylazine (0.8 mg/kg) and acepromazine (0.03 mg/kg), Group 3 xylazine (0.3 mg/kg) and acepromazine (0.08 mg/kg) and Group 4 xylazine (0.5 mg/kg) acepromazine (0.05 mg/kg) and atropine (0.04 mg/kg). Results showed no significant differences in the P-wave and QRS complex durations, PR interval and R waves among the 4 groups. QT interval significantly decreased following drug administration in group 4 compared to groups 1 ($P = 0.03$) and 3 ($P = 0.004$). There were significant increases in the QT interval in groups 1 ($P = 0.001$) and 3 ($P = 0.01$) after drug injections. Heart rate (HR) significantly decreased in groups 1, 2 and 3 after drug injections ($P = 0.004$, 0.01 and 0.03, respectively). There was a significant negative correlation between HR, PR and QT intervals, and a positive correlation between HR and P-wave amplitude. There were no significant differences between all groups in the incidence of first and second degree AV blocks.

Key words: Acepromazine, Atropine, Dog, Electrocardiogram, Xylazine

Introduction

Tranquilizers are used in veterinary practices, primarily to relieve anxiety. In addition they may be used to quiet a patient for physical examination or transport and prevent animals from licking wounds or chewing bandages and splints (Thurmon *et al*., 1996).

Acepromazine, a phenothiazine derivative, is a potent neuroleptic agent with relatively low toxicity (Thurmon *et al*., 1996). Xylazine was the first α_2-adrenergic agonist to be used as a sedative and analgesic in veterinary practice (Thurmon *et al*., 1996). Concerns over the cardiodepressant and arrhythmogenic effects of xylazine have prevented some veterinarians from embracing its use (Klide *et al*., 1975; Muir *et al*., 1975; Kirkpatrick, 1978; Kolata and Rawlings, 1982; Haskins *et al*., 1986). Atropine, an anticholinergic agent, increases the incidence of cardiac dysrhythmias and sinus tachycardia in dogs. Second-degree atrioventricular block is the most frequent dysrhythmia in dogs associated with atropine (Rishniw *et al*., 1996; Ko *et al*., 2001).

Electrocardiogram (ECG) is a key examination when evaluating the effects of drugs on the cardiovascular system and is performed routinely in toxicity and pharmacology studies. It provides critical information on a number of changes in the electrophysiological function, in particular the effects of a test compound on cardiac rhythmicity, conduction, depolarization and repolarization, which can not be assessed by other methods and which have no morphological correlates visible at histopathological examination (Detweiler, 1981).

A combination of acepromazine and xylazine produce a rapid effect and better

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quality sedation than is seen with either drug alone (Cronin *et al*., 1983). A combination of acepromazine and xylazine, that exert different mechanisms of action, can increase tranquilization effects, yet decrease some side effects of these drugs. For example, acepromazine has antiemetic and antiarrhythmic effects, while xylazine can cause vomiting and cardiac arrhythmias (Klide *et al*., 1975; Dunkle *et al*., 1986; Green and Thurmon, 1988; Hikasa *et al*., 1992; Dyson and Pettifer, 1997; Liu *et al*., 2007). On the other hand, xylazine is a potent tranquilizer and can be used in excited and restless dogs, but low sedative effect and the relatively long time from administration of acepromazine until peak effects precludes its use as a sole agent in some situations (Hatch *et al*., 1983; Raiha *et al*., 1989).

No works have been published on the effects of the acepromazine and xylazine combination on the electrocardiograph P-QRS-T parameters in dogs. These measurements are of value in electrocardiography because they are affected by abnormalities in the cardiac conduction system, depolarization and repolarization (Tilley, 1992). Changes in heart rate, PR interval, QT interval and T-wave can all indicate changes in sympathetic and parasympathetic tone (Tilley, 1992). Thus this study was designed to compare the electrocardiographic effect of different dosages of acepromazine-xylazine combinations with or without atropine in dogs.

Materials and Methods

This study was performed on 77 adult large mixed breed dogs of both sexes which were referred to the Veterinary Teaching Hospital, School of Veterinary Medicine, Shiraz University, Iran, for different diagnostic and surgical procedures. They were judged to be healthy based on history and physical examination. ECGs were taken from 29 dogs before drug administration but of the others, ECG could not be taken before drug administration due to the animal's anxiety and restlessness. The animals were randomly divided into four groups (Table 1).
Group I: Xylazine hydrochloride (Alfasan, Woerden, Holland) (0.5 mg/kg) + Acepromazine maleate (Castran, Interchemie, Holland) (0.05 mg/kg).
Group II: Xylazine hydrochloride (High dose: 0.8 mg/kg) + Acepromazine maleate (Low dose: 0.03 mg/kg).
Group III: Xylazine hydrochloride (Low dose: 0.3 mg/kg) +Acepromazine maleate (High dose: 0.08 mg/kg).
Group IV: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg) + Atropine (Alfasan, Woerden, Holland) (0.04 mg/kg).

Furthermore, dilutions of drug combinations were made so that each animal received 0.1 ml/kg (or 1 ml per 10 kg). All injections were done by intramuscular (IM) route into the semitendinosus or semimembranosus muscles. Drug injections were being performed in a free distraction area where there was no additional stimulation to the animals. After drug injection the animals were left in a quiet area until the maximum sedation (lateral recumbency) was achieved. The maximum sedation was assessed when the animals were assumed lateral recumbency within 14.17 ± 1.12 (group 1), 19.96 ± 1.69 (group 2), 20.35 ± 1.49 (group 3) and 15.79 ± 1.10 (group 4) min after drug injections. At this time post-injection ECGs were taken. During ECG recording, dogs were placed in right lateral recumbency. The three standard bipolar limb leads I, II and III, and the three augmented unipolar leads aVR, aVL and aVF were recorded on paper with a Simens Cardiostat 701 electrocardiograph. The paper speed and sensitivity were set to 50 mm/sec and 10 mm/mV, respectively. Heart rate, P and

Table 1: Experimental design

Group	Number		Age (months)	Weight (kg)	Total number
	Male	Female			
1	8	9	23.4±20	20.8±5	17
2	14	8	28.0±26	23.2±7	22
3	10	8	21.6±8	23.5±8	18
4	14	6	31.0±28	21.5±5	20

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QRS duration, PR and QT intervals, P and R amplitude in lead II were measured.

Statistical analysis

Analysis of variance (ANOVA) and Tukey's test were used for comparison of measured parameters between the four groups. Paired t-test was used for comparison of measured parameters before and after drug injection. In order to investigate the correlation between HR and PR and QT intervals and P-wave amplitude, Pearson's correlation test was used. Chi-square was used to study the cardiac dysrhythmias. Numeric data were presented as mean ± SE. Values were considered to be statistically significant at $p<0.05$.

Results

Statistical analysis for comparison of age in study groups showed no significant difference. The comparison of mean ECG parameters before and after the administration of drug combinations is summarized in Table 2. Also, the

Table 2: Comparison of mean (±SE) ECG parameters recorded before and after administration of different drug groups

Parameter[a]	Group[b]	n	Before	After	P-value
P-wave duration (ms)	1	6	35 (2)	40 (0)	0.08
	2	7	40 (0)	38 (4)	0.69
	3	8	41 (1)	40 (0)	0.35
	4	8	40 (3)	41 (1)	0.60
P-wave amplitude (mv)	1	6	0.108 (0.02)	.092 (0.02)	0.36
	2	7	0.125 (0.02)	.090 (0.16)	0.10
	3	8	0.125 (0.16)	.100 (0.19)	0.27
	4	8	0.134 (0.03)	.150 (0.02)	0.43
PR interval (ms)	1	6	111.7 (7)	130 (9)	0.07
	2	7	113.3 (15)	143.3 (15)	0.27
	3	8	123.9 (19)	152.5 (15)	0.21
	4	8	105 (6)	120 (8)	0.09
R amplitude (mv)	1	6	1.383 (0.1)	1.367 (0.10)	0.61
	2	7	1.083 (0.12)	1.083 (0.17)	0.30
	3	8	1.300 (0.2)	1.269 (0.22)	0.62
	4	8	1.175 (0.17)	1.331 (0.24)	0.08
QRS duration (ms)	1	6	46.7 (2)	41.7 (2)	0.08
	2	7	51.7 (3)	53.3 (6)	0.79
	3	8	51.3 (2)	48.7 (4)	0.52
	4	8	51.3 (3)	52.5 (5)	0.68
QT interval (ms)	1	6	213.3 (12)	253.3 (8)	0.001
	2	7	200 (7)	230 (25)	0.34
	3	8	220 (11)	245 (12)	0.01
	4	8	213.8 (8)	220 (7)	0.28
Heart rate (bpm)	1	6	102 (10)	56.33 (4)	0.004
	2	7	99.17 (11)	60.00 (4)	0.01
	3	8	111.25 (17)	75.38 (10)	0.006
	4	8	114.63 (12)	135.00 (8)	0.25
Mean electrical axis (d)	1	6	72.1 (5)	83.7 (3)	0.03
	2	7	81.4 (9)	87.3 (6)	0.57
	3	8	74.6 (5)	77.4 (2)	0.58
	4	6	74.3 (3)	68.7 (6)	0.44

a: ms = Millisecond, mv = Milivolt, d = Degree, bmp = Beats per minute and n = Number of cases. b: Group I: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg); Group II: Xylazine hydrochloride (High dose: 0.8 mg/kg) + Acepromazine maleate (Low dose: 0.03 mg/kg); Group III: Xylazine hydrochloride (Low dose: 0.3 mg/kg) +Acepromazine maleate (High dose: 0.08 mg/kg) and Group IV: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg) + Atropine (0.04 mg/kg)

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comparison of different ECG parameters between groups of dogs after drug injection is shown in Table 3.

None of the test groups showed any significant effects on P-wave duration, PR interval, QRS duration and R amplitude.

Table 3: ECG parameter values in different groups after drug administration

Parameter[a]	Group[b]	Number	Mean	SE
P-wave duration (ms)	1	17	40	0
	2	22	39	2
	3	18	38	1
	4	20	43	2
P-wave amplitude (mv)	1	17	0.13[ab]	0.01
	2	22	0.15[ab]	0.01
	3	18	0.10[a]	0.01
	4	20	0.16[b]	0.01
PR interval (ms)	1	17	124	6
	2	22	132	8
	3	18	137	8
	4	20	126	7
R amplitude (mv)	1	17	1.18	.14
	2	22	1.25	0.1
	3	18	1.40	0.1
	4	20	1.38	0.1
QRS duration (ms)	1	17	49	2
	2	22	56	3
	3	18	51	3
	4	20	54	2
QT interval (ms)	1	17	232[a]	6
	2	22	229[ab]	9
	3	18	239[a]	6
	4	20	205[b]	5
Heart rate (bpm)	1	17	77.1[a]	10
	2	22	72.8[a]	5
	3	18	79.6[a]	5
	4	27	128.2[b]	6
Mean electrical axis (d)	1	10	83.5	2
	2	22	84.0	3
	3	18	76.1	3
	4	12	77.1	4

a: ms = Millisecond, mv = Milivolt, d = Degree, bmp = Beats per minute and n = Number of cases. b: Group I: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg); Group II: Xylazine hydrochloride (High dose: 0.8 mg/kg) + Acepromazine maleate (Low dose: 0.03 mg/kg); Group III: Xylazine hydrochloride (Low dose: 0.3 mg/kg) +Acepromazine maleate (High dose: 0.08 mg/kg) and Group IV: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg) + Atropine (0.04 mg/kg). The different letters in columns show significant differences ($P<0.05$)

There was a variability in the amplitude of the P-wave, ranging from 0.5 to 3 mV. The P-wave amplitude was significantly greater after drug injection in group 4 compared to 3 ($P = 0.01$). There were no statistical differences in P-wave amplitude in all other groups, and before and after injection.

QT interval significantly decreased following drug administration in group 4 compared to groups 1 ($P = 0.03$) and 3 ($P = 0.004$). QT interval significantly increased after injection in group 1 and 3 (Table 3).

Heart rate (HR) significantly decreased after drug injection in group 1, 2 and 3, but there was no significant difference among the groups. HR increased in group 4 but this change was not significant.

Mean electrical axis (MEA) was not significantly different among the 4 groups. In group 1, MEA significantly decreased after injection ($P = 0.03$), but changes of MEA in other groups after injection were not significant. MEA ranged from 50° to 117° (Mean 75°) in normal dogs.

The amplitude of the T-wave showed no significant change in any of the groups. A positive T-wave was seen predominantly in most of the animals. However, a change in the polarity of the T-wave was seen in a few of the animals.

There was a statistically significant negative correlation between HR and PR ($r = -0.24$, $P = 0.03$) and QT ($r = -0.58$, $P<0.0001$) intervals, and a positive correlation between HR and P-wave amplitude ($r = 0.25$, $P = 0.03$). There were no significant differences in the incidence of the first and second degree heart blocks between the groups. The incidence of sinus bradycardia in group 4 significantly decreased compared to groups 1 and 2 ($\chi2 = 8.1$, $P = 0.004$ and $\chi2 = 10.3$, $P = 0.001$, respectively) and incidence of sinus tachycardia in group 4 significantly increased compared to group 2 and 3 ($\chi2 = 7.8$, $P = 0.005$, $\chi2 = 9.1$, $P = 0.002$, respectively) (Table 4). In the present study no treatment was necessary to reverse the side effects of the injected drugs.

Discussion

In the present study the post injection measurements were obtained as soon as the animals reached a depth of tranquilization determined by the recumbency of the animals. The ECGs were recorded at this time. Time from the administration of drugs to time of maximal sedation varied among

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Table 4: Frequency of cardiac arrhythmias after drug administration in different groups

Group	Number	Arrhythmia											
		FDAVB		SDAVB		Sinus arrest		Ventricular tachycardia		Sinus bradycardia		Sinus tachycardia	
		Freq	%	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
1	18	5	27.78	0	0	1	5.56	1	5.56	8	44.44	3	16.67
2	22	4	18.18	2	9.09	1	4.55	0	0	11	50	1	4.55
3	18	6	33.33	1	5.56	0	0	0	0	4	22.22	0	0
4	20	8	40	0	0	0	0	0	0	1	5	8	40

FDAVB = First degree AV block, SDAVB = Second degree AV block, and Freq = Frequency. Group I: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg); Group II: Xylazine hydrochloride (High dose: 0.8 mg/kg) + Acepromazine maleate (Low dose: 0.03 mg/kg); Group III: Xylazine hydrochloride (Low dose: 0.3 mg/kg) +Acepromazine maleate (High dose: 0.08 mg/kg) and Group IV: Xylazine hydrochloride (0.5 mg/kg) + Acepromazine maleate (0.05 mg/kg) + Atropine (0.04 mg/kg)

the animals.

The absence of noteworthy differences in ECG parameters between sexes is consistent with the literature (Eckenfels and Trieb, 1979; Hanton and Rabemampianina, 2006) and allows the combination of values from males and females for the interpretation of data in pharmacology studies, thereby increasing the power of the statistical analysis for comparison of treated and control groups.

The drugs used did not change the duration of the P-wave, QRS and PR interval, or the amplitude of the P and R waves, indicating that these drugs had no effect on the atrial and ventricular depolarization time and area.

There was high inter-animal variability in the PR interval in normal dogs. It is therefore difficult to establish a threshold above which a first degree atrioventricular block (AVB1) could be diagnosed (Hanton and Rabemampianina, 2006). Detweiler (1981) considers that AVB1 is present when PR intervals are above 150 ms; Hanton and Rabemampianina (2006) reported that the values of PR interval up to 169 ms may occur in healthy beagle dogs. In the present study the PR interval above 130 ms was considered as AVB1 (Tilley, 1992). However, for the evaluation of the effects of a drug on atrioventricular conduction, instead of using an arbitrary value for the diagnosis of an AVB1, it would be better to compare the changes in the PR interval with contemporary controls or to pre-dose values (Hanton and Rabemampianina, 2006).

The QT intervals increased in all groups; however only in groups 1 and 3 these increases were significant. The increased QT interval suggests slow repolarization of ventricles (Thomsen *et al*., 2006). Tilley (1992) mentioned that HR and QT intervals are governed separately by sympathetic neurons, and these may or may not be activated together. Further, the increased QT intervals might be due to a decrease in heart rate and a corresponding decrease in the oxygen requirement of the heart (Haskins *et al*., 1986) as a result of xylazine administration.

As expected, a correlation was found between the HR and QT interval (r = -0.58, P<0.0001) (Osborne and Leach, 1971; Ganz and Knappen, 1976; Eckenfels and Trieb, 1979). This relationship is considered to result from a complex interplay of autonomic influences since QT interval and HR are governed by different autonomic pathways, which are generally activated simultaneously during physiological adaptation (Davidowski and Wolf, 1984; Tilley, 1992; Huang *et al*., 1995).

There was also a significant correlation between the HR and PR interval (r = -0.24, P = 0.03), although it was less marked than the correlation between HR and QT, as indicated by a lower coefficient of correlation for the relation between PR and HR. These findings are consistent with those of Grauwiler (1970), Osborne and Leach (1971), Ganz and Knappen (1976), Eckenfels and Trieb (1979) and Hanton and Rabemampianina (2006). The relationship between HR and PR probably originates mainly from the dependence of both parameters on the autonomic system. The sympathetic system increases the HR and velocity of atrioventricular conduction, and therefore shortens the PR interval, whereas

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the parasympathetic system has the opposite effects (O'Toole *et al*., 1984; Nayebpour *et al*., 1992; Furukawa *et al*., 1997). However, an increase in HR results in a prolongation of atrioventricular conduction time due to an increase in the atrioventricular nodal refractoriness (Warner and Loeb, 1986). The relationship between PR and HR is therefore the net result of these complex opposite effects, which explains the rather poor statistical correlation between these parameters.

Based on the current analysis, a positive correlation is clear between HR and the amplitude of P-wave (r = 0.25, P = 0.03), but (Hanton and Rabemampianina, 2006), as the coefficient of correlation is low, it is probable that the amplitude of the P-wave depends mainly on factors other than HR (Hanton and Rabemampianina, 2006).

According to Tables 2 and 3, the HR significantly decreased in groups 1, 2 and 3 after drug administration. In group 4, the HR shows some increases that are not significant compared to before drug administration. The HR in group 4 after drug injection showed a significant increase compared to the other 3 groups (P<0.01). The decrease in heart rate in groups 1, 2 and 3 might be due to the effects of xylazine and acepromazine. The decrease in heart rate after xylazine injection can be attributed to one or more of the following mechanisms: inhibition of sympathetic tone, prevention of norepinephrine release from adrenergic endings, activation of vagus nerve in response to primary blood vessel contractions and increase in acetylcholine release from cardiac parasympathetic nerves (Muir *et al*., 1975; Greene *et al*., 1995; Ilbäck and Stalhandske, 2003). The significantly higher HR in group 4 (128.22 ± 6.49) compared to other groups can be due to atropine use in this group (Table 3). Atropine blocks transmission of vagal impulses to the heart and causes HR increases and sinus rhythmia (Rishniw *et al*., 1996; Ko *et al*., 2001).

According to Table 4, there were no significant differences in the incidence of the first and second degree heart blocks between the groups and the incidence of more important cardiac abnormalities including 2nd degree AV blocks, sinus arrest and ventricular tachycardia, are low with the acepromazine-xylazine combination compared to xylazine alone. The arrhythmias observed in the present study might be due to vagal stimulation by these drugs. Sinoatrial block and AV blocks probably occur due to increased vagal activity caused by the vasopressor effects of α_2-agonists (Knight, 1980). These effects have also been reported in horses (Skarda and Muir, 1996). Dyson *et al*. (1998) reported that the incidence of cardiac arrest is higher after xylazine compared to the combination of ketamine-acepromazine. This shows that xylazine has greater effects on the heart compared to acepromazine.

In the present study, the rate of sinus bradycardia significantly decreased in group 4 compared to groups 1 and 2; and the rate of sinus tachycardia significantly increased in group 4 compared to group 2 and 3. Bradycardia was defined as a heart rate of less than 60 beats/min and sinus tachycardia was defined as a heart rate of greater than 170 beats/min (Tilley, 1992). These results indicate that high doses of xylazine cause more bradycardia. In group 4 in which the dose of xylazine is the same as group 1, bradycardia was prevented by atropine.

Thus, on the basis of these findings, it is recommended to administer atropine after acepromazine-xylazine administration, in order to prevent xylazine-induced bradycardia, heart blocks and sinus arrest. However, it should be remembered that atropine may cause tachycardia or 2nd degree AV blocks in some cases (Rishniw *et al*., 1996). Further studies need to be conducted to evaluate the effects of co-administration of atropine with acepromazine-xylazine combination on cardiac output, blood pressure and tissue perfusion in dogs.

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