

## Clinical evaluation of the sedative properties of acepromazine-xylazine combinations with or without atropine and their effects on physiologic values in dogs

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### ABSTRACT

The purpose of this study was to clinically evaluate the sedative effects of different doses of acepromazine-xylazine combinations with or without atropine in dogs. One hundred and twenty dogs of various breeds and both sexes were used in a prospective randomized, blinded clinical study. Dogs, presented to the Veterinary Clinic for various diagnostic and surgical procedures, were randomly divided into four groups (n=30/group) and received the following drug combinations intramuscularly: Group AX: acepromazine (0.05 mg kg<sup>-1</sup>) + Xylazine (0.5 mg kg<sup>-1</sup>), Group AXA: Acepromazine (0.05 mg kg<sup>-1</sup>) + Xylazine (0.5 mg kg<sup>-1</sup>) + Atropine (0.04 mg kg<sup>-1</sup>) Group LA-HX: Acepromazine (Low dose: 0.03 mg kg<sup>-1</sup>) + Xylazine (High dose: 0.8 mg kg<sup>-1</sup>), Group HA-LX: Acepromazine (High dose: 0.08 mg kg<sup>-1</sup>) + Xylazine (Low dose: 0.3 mg kg<sup>-1</sup>). Heart and respiratory rates, electrocardiogram and rectal temperature were recorded before drug injection (baseline) and during maximum sedation. Sedation was scored using descriptive categories. Heart rate significantly decreased from the baseline following sedation in the AX, LA-HX and HA-LX groups. A significant reduction in respiratory rate was observed in all treatment groups. The median sedation score did not differ significantly between the groups; however, the quality of sedation was enhanced when atropine was added to the acepromazine-xylazine combination and a higher number of dogs were assigned score 3 in AXA group. No adverse effects were recorded during the study. The acepromazine-xylazine combination, particularly with atropine, can be used effectively for sedation and premedication before general anaesthesia in healthy dogs.

**Key words:** acepromazine, atropine, dog, sedation, xylazine

### Introduction

Tranquilizers and sedatives are commonly used in veterinary practice to facilitate handling and as premedication before general anaesthesia in small animals. Phenothiazine

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agents and  $\alpha_2$  agonists are often used to reduce anxiety and produce sedation in dogs (LEMKE, 2007).

Acepromazine, a phenothiazine derivative, is a potent neuroleptic agent with relatively low toxicity. It induces mild to moderate tranquilization, muscle relaxation and a decrease in spontaneous activity attributable principally to central dopaminergic antagonism. Acepromazine possesses antiemetic, anticonvulsant, antispasmodic, hypotensive and hypothermic properties (LEMKE, 2007). Although acepromazine is generally avoided in dogs with histories of seizures, no evidence is available to confirm that it lowers the convulsive seizure threshold in dogs (TOBIAS et al., 2006). Acepromazine effectively prevents cardiac dysrhythmia and ventricular fibrillation in dogs during barbiturate and halothane anaesthesia (MUIR et al., 1975; DYSON and PETTIFER, 1997).

Xylazine was the first  $\alpha_2$ -adrenergic agonist to be used as a sedative and analgesic in veterinary practice. Its sedative and analgesic activities are related to CNS depression mediated by stimulation of  $\alpha_2$ -adrenergic receptors (HSU et al., 1985). Sedative doses of xylazine cause heart rate and cardiac output to decrease significantly in dogs, while blood pressure and peripheral vascular resistance initially increase, followed by a longer lasting hypotension (KLIDE et al., 1975; MUIR and PIPER., 1977; ILBACK and STALHANDSKE, 2003). Emesis may occur in dogs and cats after xylazine administration by either the IM or SC route, which may be caused by activation of central  $\alpha_2$  receptors (LEMKE, 2007).

Atropine, an anticholinergic agent, blocks muscarinic receptors at the postganglionic terminations of cholinergic fibers in the autonomic nervous system. Atropine increases the incidence of cardiac dysrhythmia and sinus tachycardia in dogs (MUIR, 1978). Anticholinergics have been used to prevent bradycardia caused by administration of  $\alpha_2$ -agonists in dogs (SHORT, 1991; KO et al., 2001).

Excited or aggressive dogs are not good candidates for acepromazine administration, because phenothiazines produce only mild sedation and are not effective in these circumstances. A higher dose of acepromazine does not increase sedation, but prolongs the side effects. Acepromazine is not reversible and does not provide analgesia. For these reasons, it is best to administer acepromazine in conjunction with opioid analgesics as part of a balanced regimen (STEPIEN et al., 1995; BARNHART et al., 2000). However, opioids are controlled substances and may not be readily available in some private practices.

A combination of acepromazine and xylazine has been used in horses (MUIR et al., 1979; NILSFORS et al., 1988; HUBBELL et al., 1999) and dogs (CRONIN et al., 1983). This combination is reported to produce rapid and better quality sedation in horses compared to when either drug is used alone (MUIR et al., 1979). The combination of acepromazine and xylazine, that exert different mechanisms of action, can increase sedative effects, yet decrease the side effects of these drugs. For example, acepromazine has antiemetic and antiarrhythmic effects, while xylazine can cause vomiting and cardiac arrhythmias

(LEMKE, 2007). Unlike acepromazine, xylazine has both profound sedative and some analgesic properties and can be used in excited and restless dogs. Its effects are reversible with the selective  $\alpha_2$  adrenergic antagonists (GROSS, 2001; LEMKE, 2007). The peak effects of xylazine occur within 15 min, while 30 to 60 min should be allowed for maximal sedative effects to occur after SC or IM injection of acepromazine. This drug combination may result in more predictable and effective sedation and analgesia and fewer side effects due to the lower doses required.

To our knowledge, no clinical evaluation of the sedative and cardiorespiratory effects of the acepromazine and xylazine drug combination in dogs has been published. The purpose of the study reported here was to evaluate the sedative and cardiopulmonary effects of clinical doses of acepromazine-xylazine combinations with or without atropine in conscious dog.

#### Materials and methods

One hundred and twenty,  $2.0 \pm 1.8$  [range: 0.25-11] year old client-owned dogs of various breeds and both sexes (74 males, 46 females), weighing  $18.1 \pm 8.6$  [range: 3.2-47] kg that were presented to the Veterinary Clinic for a variety of diagnostic and surgical procedures, were included in this study. Based on physical examination and medical history, dogs were all classed as ASA (American Society of Anesthesiologists) I-II. This study was approved by the Research Animal Care and Use Committee of the School of Veterinary Medicine, Shiraz University. The animals were randomly divided into four groups ( $n = 30$ ) and received the following drug combinations intramuscularly. Each dog was randomly assigned to one of four groups to receive equal volumes of different combinations:

Group 1 (AX): Acepromazine maleate (Castran, Interchemie, Holland) ( $0.05 \text{ mg kg}^{-1}$ ) + Xylazine hydrochloride (Alfasan, Woerden, Holland) ( $0.5 \text{ mg kg}^{-1}$ )

Group 2 (AXA): Acepromazine ( $0.05 \text{ mg kg}^{-1}$ ) + Xylazine ( $0.5 \text{ mg kg}^{-1}$ ) + Atropine (Alfasan, Woerden, Holland) ( $0.04 \text{ mg kg}^{-1}$ )

Group 3 (LA-HX): Acepromazine (Low dose:  $0.03 \text{ mg kg}^{-1}$ ) + Xylazine (High dose:  $0.8 \text{ mg kg}^{-1}$ )

Group 4 (HA-LX): Acepromazine (High dose:  $0.08 \text{ mg kg}^{-1}$ ) + Xylazine (Low dose:  $0.3 \text{ mg kg}^{-1}$ ).

All drugs were mixed in the same syringe before use and injected intramuscularly into the thigh muscles. The final volume of drug combination was corrected to a standardized volume so that each dog received the same volume of  $0.1 \text{ mL kg}^{-1}$  (or  $1 \text{ mL } 10 \text{ kg}^{-1}$ ). Following drug administration, the animals were left undisturbed for 15-20 minutes in a calm environment.

Heart rate (HR), respiratory rate (RR), rectal temperature and electrocardiogram (ECG) were recorded before drug administration and during maximal sedative effects; i.e., 15-20 min after drug administration. During ECG recording, dogs were placed in right lateral recumbency. The three standard bipolar limb leads, I, II and III were recorded on paper with an electrocardiograph (Cardiostat 701, Simens, Germany). The paper speed and sensitivity were set to 50 mm/sec and 1 mV, respectively. Heart rate (HR) was counted from the ECG recording, and respiratory rate (RR) was measured by observing thoracic excursions. Bradycardia was defined as a heart rate of less than 70 beats minute<sup>-1</sup> and sinus tachycardia was defined as a heart rate of greater than 160 (in large breeds) or 180 (in small breeds) beats minute<sup>-1</sup> (TILLEY, 1992).

The degree of sedation was assessed on a simple descriptive scale of 0-3 (Table 1). A person unaware of the treatment was responsible for assessing objective and subjective data throughout the study.

Table 1. Description of sedation score categories

Category	Description
0	Not sedated. No signs of depression, drowsiness or ataxia
1	Slightly sedated. Mild signs of depression, drowsiness or ataxia. Decreased reaction to stimuli
2	Moderate sedation. Sever ataxia, reluctant to move, may attain sternal recumbency
3	Deep sedation. Depressed, drowsy and sleepy, no resistance to positioning on lateral recumbency

*Data analysis.* Data distribution for physiologic parameters was tested for normality using Shapiro-Wilks testing. One-way ANOVA and Tukey's test were used for comparison of mean values for age, body mass, HR, RR, temperature and onset of recumbency between four treatment groups. A paired *t*-test was used for comparison of measured parameters before and after drug injection in each group. A Chi square was used to compare the incidence of cardiac dysrhythmias and vomiting. Sedation score was compared between the groups by use of the Mann-Whitney test for nonparametric data. All data were presented as mean  $\pm$  SD or Median (25-75<sup>th</sup> percentile range). Statistical analysis was undertaken using the SPSS Version 10 for Windows (SPSS, MicroMaster, Richboro, PA, USA) and values of  $P < 0.05$  were considered significant.

## Results

There were no significant differences between groups for age, body mass and breed (Table 2). All drug combinations produced sedation within 20-30 minutes. The median sedation score did not differ significantly between the groups; however, the number of

dogs assigned score 3 were significantly higher in AXA ( $P < 0.05$ ). Eight dogs that received AXA had deep sedation (score 3), whereas only one dog in AX and LA-HX, and 3 dogs in HA-LX were assigned score 3. The onset of recumbency (min) tended to be faster in AX and AXA treated dogs compared to the other two groups; however, the differences were not significant (Table 2). Since some dogs underwent general anaesthesia and surgery afterwards, it was not possible to record the duration of sedation.

Table 2. Patient characteristics, type of arrhythmias, sedation score and onset of recumbency in dogs receiving Acepromazine-xylazine combination with or without atropine. Data presented as mean  $\pm$  SD or median (25-75<sup>th</sup> percentile range).

Treatment	AX	AXA	LA-HX	HA-LX
Age, yrs	1.8 $\pm$ 0.3	2.3 $\pm$ 0.4	2.3 $\pm$ 0.4	1.3 $\pm$ 0.2
Body mass, kg	15.5 $\pm$ 7.9	18.3 $\pm$ 7.3	20.9 $\pm$ 8.1	17.5 $\pm$ 10.1
Breed				
Large-mixed breed	14	13	18	12
German Shepherd	5	10	7	7
Terrier	5	1	4	7
Spitz	2	3	-	2
Dobermann Pinscher	2	1	-	-
Great Dane	-	-	1	2
Others	2	2	-	-
Sex (M:F)	17:13	21:9	18:12	18:12
Type of arrhythmia				
First-degree AV block	11	4	6	7
Second-degree AV block	-	1	2	1
Sinoatrial block	1	-	1	-
Ventricular tachycardia	1	-	1	2
Sedation score (Median, 25-75 <sup>th</sup> percentile range)	1 (1-2)	2 (1-3)	2 (1-2)	2 (1-2)
Onset of recumbency, min	14.1 $\pm$ 5.4	15.7 $\pm$ 5.8	20.0 $\pm$ 8.1	20.3 $\pm$ 7.6
Defecation/urination	2/1	3/1	4/1	6/3

AX: Acepromazine (0.05 mg/kg) + Xylazine (0.5 mg/kg); AXA: Acepromazine (0.05 mg/kg) + Xylazine (0.5 mg/kg) + Atropine (0.04 mg/kg); LA-HX: Acepromazine (Low dose: 0.03 mg/kg) + Xylazine (High dose: 0.8 mg/kg); HA-LX : Acepromazine (High dose: 0.08 mg/kg) + Xylazine (Low dose: 0.3 mg/kg)

Table 3. Mean  $\pm$  SD heart rate, respiratory rate and rectal temperature

Treatment	AX	AXA	LA-HX	HA-LX
HR (beats minutes <sup>-1</sup> )				
before	109 $\pm$ 28	111 $\pm$ 27	94 $\pm$ 32	116 $\pm$ 33
after	76 $\pm$ 29*	126 $\pm$ 35 <sup>†</sup>	72 $\pm$ 23*	89 $\pm$ 38*
RR (breaths minutes <sup>-1</sup> )				
before	36 $\pm$ 23	45 $\pm$ 27	42 $\pm$ 39	53 $\pm$ 39
after	20 $\pm$ 10*	20 $\pm$ 12*	30 $\pm$ 22*	31 $\pm$ 18*
Rectal temperature (°C)				
before	38.9 $\pm$ 0.7	39.4 $\pm$ 0.7	39.4 $\pm$ 0.8	39.3 $\pm$ 0.5
after	38.5 $\pm$ 0.7*	38.6 $\pm$ 0.7*	39.2 $\pm$ 0.9	38.8 $\pm$ 0.7*

\*significant differences from before drug injection; <sup>†</sup> significant differences from other treatments (P<0.05).

The data for HR, RR and rectal temperature before and after the administration of drug combinations are summarized in Table 3. The mean values of HR, RR and rectal temperature did not differ before drug administration between the treatments. Following drug administration, HR decreased in AX, LA-HX and HA-LX (P<0.05). Heart rate was significantly higher in dogs receiving AXA compared to the other groups. Bradycardia (HR<70 beats minutes<sup>-1</sup>) was observed in 6, 13 and 15 dogs in HA-LX, LA-HX and AX, respectively. Only one dog in the AXA group had bradycardia.

Before drug administration, positioning in right lateral recumbency and ECG recording was possible in only 31 dogs (28.5%), whereas 112 dogs (93.3%) allowed ECG recording after drug administration. First-degree AV block was present in one dog in each group, except AXA, and two dogs in HA-LX group showed bradycardia or tachycardia before drug injection. The incidence of cardiac arrhythmia during maximal sedation was similar for all treatments (Table 2). Cardiac arrhythmias were self-correcting with time and no treatment was necessary. A significant decrease (28-44%) in RR was observed in all treatment groups (P<0.05). There was no apnea or cyanosis in any groups.

Rectal temperature decreased significantly in AX, AXA and HA-LX treatments during maximum sedation (P<0.05). The change in rectal temperature was not significant in LA-HX. Vomiting was observed in all treatments within 10 minutes after drug injection, in 5 dogs in AX, 2 dogs in AXA, 1 dog in LA-HX and 4 dogs in HA-LX. Defecation and urination were observed in some cases (Table 2). No adverse events were observed during the study and all dogs recovered quietly and uneventfully.

### Discussion

In this study, identical volumes of drug combinations were given as single IM injections in order to avoid distress caused by multiple injections. In the clinical setting,

intramuscular injection is the preferred route of drug administration for sedation and premedication before general anaesthesia, because minimal restraint is required. Besides, cardiovascular responses are attenuated when anticholinergics and  $\alpha_2$ -agonists are administered intramuscularly (VAINIO and PALMU, 1989).

Although the sedative and hemodynamic effects of acepromazine and xylazine have been reported previously, the sedative effect of simultaneous administration of acepromazine and xylazine in conscious dogs has not been studied to our knowledge. When used in combination, the adverse actions of both drugs may be diminished due to the lower doses required. Combinations of acepromazine and xylazine and the effects of 4-aminopyridine and yohimbine, as reversal agents, have been studied in dogs (CRONIN et al., 1983). However, the doses of acepromazine and xylazine (0.5 and 2.2 mg kg<sup>-1</sup>, respectively) were much higher than the standard dose and not recommended clinically. In healthy dogs, intramuscular doses of acepromazine and xylazine range from 0.05 to 0.2 mg kg<sup>-1</sup> and 0.5 to 1.0 mg.kg<sup>-1</sup>, respectively (LEMKE, 2007). The acepromazine-xylazine combination has been reported to produce better quality sedation than when either drug is used alone in horses (MUIR et al., 1979). Administration of acepromazine-xylazine, at twice the standard dose, has been used successfully to produce sedation in exercised horses, without increasing the untoward effects (HUBBELL et al., 1999). Although the number of dogs assigned score 3 were significantly higher in AXA, there were no significant differences between the four groups with respect to the degree of final sedation. A more sensitive scoring system to assess the level of sedation would improve the chances of detecting differences.

The principal advantage of the acepromazine-xylazine combination is its reversibility by administration of selective antagonists (HSU et al., 1985; LEMKE, 2007). Yohimbine and 4-aminopyridine, alone or in combination, significantly reduced recovery time following acepromazine-xylazine administration in dogs; re-sedation was not observed in any dogs (CRONIN et al., 1983). Reversal with a selective  $\alpha_2$ -adrenoceptor antagonist (i.e., atipamezole) is recommended in situations of inadvertent overdose, when significant cardiopulmonary complications occur or residual sedation is undesirable (LEMKE, 2007). Complete antagonism of the  $\alpha_2$  agonists will reverse both the analgesic and sedative effects.

Acepromazine and  $\alpha_2$  agonists are frequently used as premedication before general anesthesia. Acepromazine administration (0.2 mg kg<sup>-1</sup>, IM) in dogs anesthetized with halothane or isoflurane decreased the MAC by 28% and 48%, respectively (WEBB and O'BRIEN, 1988). Preanesthetic administration of acepromazine (0.02 or 0.2 mg.kg<sup>-1</sup> i.m.) also decreases MAC by 34% and 44% in dogs anesthetized with halothane, respectively (HEARD et al., 1986). Xylazine premedication also decreases induction and maintenance anesthetic requirements dramatically in dogs (TRANQUILLI et al., 1984). Intravascular



administration of xylazine (0.8 mg/kg) decreases the dose of propofol required to induce anesthesia in dogs by >50%. The MAC of halothane decreases following xylazine administration (1.1 mg kg<sup>-1</sup> IV) by 38% (LEMKE, 2007). Although the anesthetic sparing effect of acepromazine-xylazine combination is not known, a significant reduction in the doses of injectable and inhalational anesthetics is recommended. Clinically, we have noticed a 50% reduction in the induction dose of diazepam-ketamine or thiopental, following premedication with this drug combination in dogs undergoing general anesthesia.

The clinical efficacy of atropine was tested in one group in order to assess the reversibility of the xylazine-induced bradycardia. It seems that the concurrent administration of atropine with the acepromazine-xylazine combination enhances the degree of sedation. Concurrent drug administration can influence the pharmacodynamic and pharmacokinetics of drugs. The reason for the higher sedation level in dogs receiving AXA can probably be attributed to the marked cardiovascular effects of atropine. Atropine, as a small unionized molecule, crosses the blood-brain barrier and may have a mild sedative effect when administered at therapeutic doses (LEMKE, 2007).

The heart rate decreased significantly after AX, LA-HX and HA-LX administration, but increased insignificantly after administration of AXA. Decreased HR after administration of  $\alpha_2$ -agonist agents has been attributed to augmentation of vagal tone. Development of sinus bradycardia and AV block are common after xylazine administration (HASKINS et al., 1986; ILBACK and STALHANDSKE, 2003). Anticholinergics have been administered with  $\alpha_2$ -agonists to prevent bradycardia.

Bradycardia was almost completely prevented by concurrent administration of atropine; however, because HR was recorded 15-20 minutes after drug injection, earlier bradycardia may have been missed. Atropine inhibits the action of acetylcholine on the muscarinic cholinergic receptors and would be a drug of choice when severe bradycardia is presented secondary to increased vagal tone (LEMKE, 2007). However, excessive doses of atropine may cause sinus tachycardia. It has been reported that prior administration of atropine only partially reverses xylazine-induced bradycardia (KLIDE et al., 1975; HSU et al., 1985). The complete reversal of bradycardia in the present study could be attributed to the combined effects of atropine and acepromazine. Increases in heart rate may be observed in some patients following IV administration of acepromazine in response to peripheral vasodilation (LEMKE, 2007). Administration of the acepromazine-xylazine combination at very high doses resulted in a slight, insignificant increase in HR in dogs premedicated with atropine (CRONIN et al., 1983). Due to a possible increase in myocardial oxygen demand, combinations of anticholinergics and xylazine are probably best reserved for use in young healthy animals and should be avoided in dogs with preexisting myocardial diseases (ALIBHAI et al., 1996). However concurrent administration of acepromazine,



a potent peripheral vasodilator, may offset the  $\alpha_2$ -agonist-induced increase in blood pressure from vasoconstriction. In this situation, it may make physiological sense to treat bradycardia with an anticholinergic.

Although arterial blood pressure was not measured in the present study, a decrease in blood pressure is expected following the acepromazine-xylazine combination, because of the combined vasodilatory and negative chronotropic effects of acepromazine and xylazine, respectively. In conscious dogs, IV administration of acepromazine ( $0.1 \text{ mg kg}^{-1}$ ) decreases mean arterial pressure by 20% to 25% for at least 2 hours (STEPIEN et al., 1995). Intravenous or intramuscular administration of xylazine induces biphasic blood pressure response (hypertension followed by hypotension) in dogs (KLIDE et al., 1975; HASKINS et al., 1986; ILBACK and STALHANDSKE, 2003); however, the cardiovascular effects observed after IM administration of xylazine are less dramatic as compared to IV injection (LEMKE, 2007). Cardiac output (CO) and mean arterial blood pressure (ABP) decreased after IV administration of a acepromazine ( $0.05 \text{ mg kg}^{-1}$ )-xylazine ( $0.55 \text{ mg kg}^{-1}$ ) combination in horses, but were not significantly different from values obtained after acepromazine ( $0.09 \text{ mg kg}^{-1}$ ) or xylazine ( $1.1 \text{ mg kg}^{-1}$ ) alone (MUIR et al, 1979). In fact, these values for the drug combination were midway between the values for either drug alone (CO: Acp>Acp-Xyl>Xyl; ABP: Xyl>Acp-Xyl>Acp).

Interestingly, two other studies have shown an increase in arterial blood pressure in dogs and exercised horses given the acepromazine-xylazine combination (CRONIN et al., 1983; HUBBELL et al., 1999). The authors concluded that the lack of hypotensive response might be associated with the predominance of the vasoconstrictive effects of xylazine or prior atropine administration. The exact mechanism of this unexpected response is unknown and deserves further investigation.

The incidence of cardiac arrhythmia was not statistically significant among treatments (Table 2). Because ECG was not recorded until maximum sedation was reached (at least 15 minutes after drug injection), one study limitation is the possible failure to record cardiac arrhythmias that may have occurred within minutes of drug administration. Although high doses of xylazine appear to sensitize the myocardium to epinephrine-induced arrhythmias in halothane anesthetized dogs (MUIR et al., 1975; TRANQUILLI et al., 1986), more recent studies have shown that administration of lower doses of xylazine may even attenuate the development of epinephrine-induced arrhythmias in dogs anesthetized with halothane or isoflurane (LEMKE et al., 1993a,b). Acepromazine premedication also prevents the development of ventricular arrhythmias in halothane-anesthetized dogs (MUIR et al., 1975; DYSON and PETTIFER, 1997). The effect of the acepromazine-xylazine combination on an arrhythmogenic dose of epinephrine is not known.

In the present study, the mean respiratory rate decreased markedly by 28-44% in dogs treated with the acepromazine-xylazine combination; however, no signs of apnea or cyanotic mucous membranes were observed in any of the dogs. In conscious dogs, respiratory rate decreases, but arterial pH, partial pressure of carbon dioxide ( $PCO_2$ ), partial pressure of oxygen ( $PO_2$ ) and hemoglobin saturation do not change after IV administration of acepromazine (STEPIEN et al., 1995). Blood gas values did not change significantly following intravenous ( $1-1.1 \text{ mg kg}^{-1}$ ) or intramuscular ( $2.2 \text{ mg kg}^{-1}$ ) administration of xylazine, in spite of significant decreases (by 68%) in respiratory rate (KLIDE et al., 1975, HASKINS et al., 1986). The decreased respiratory rate may be attributable to sedation and reduced anxiety; however, blood gas values may remain unchanged due to increased tidal volume and decreased  $O_2$  consumption and  $CO_2$  production (HASKINS et al., 1986; STEPIEN et al., 1995). Administration of acepromazine-xylazine combination at very high doses resulted in 63% reduction in respiratory rate in dogs (CRONIN et al., 1983). No data is available regarding the effects of acepromazine-xylazine combination on blood gas values.

During maximum sedation, body temperature decreased in the four groups though not statistically significantly in the treatment LA-HX. The administration of sedatives and tranquilizers generally depress the basal metabolic rate and induce muscle relaxation, resulting in lowered body temperature (LEMKE, 2007). Phenothiazines cause peripheral vasodilation, which may exaggerate hypothermia (GROSS, 2001). Hypothermia may be much more profound in smaller patients due to their larger body surface area to body mass ratio. The hypothalamic thermoregulatory center is also affected by phenothiazine administration, leading to the loss of thermoregulatory control. The hypothermic effects of  $\alpha_2$ -agonists are mediated by activation of the  $\alpha_{2C}$  receptor subtype (LEMKE, 2007). However,  $\alpha_2$ -agonists may reduce cutaneous heat losses by peripheral vasoconstriction and central redistribution of blood, resulting in preservation of body temperature. The insignificant reduction of body temperature in the LA-HX group may be due to the lower dose of acepromazine ( $0.03 \text{ mg kg}^{-1}$ ) used.

The incidence of vomiting ranged from 3.3 to 16.7 percent and there were no significant differences between the four treatment groups. Nausea and vomiting associated with IM xylazine administration are caused by activation of the central  $\alpha_2$  receptors and prior administration of  $\alpha_2$ -antagonists can prevent emesis (HIKASA et al., 1986). Premedication with acepromazine produces an antiemetic effect, which is attributed to the blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. In dogs, prior but not simultaneous, administration of acepromazine lowers the incidence of opioid-induced vomiting (VALVERDE et al., 2004). In the present study, the incidence of vomiting was lower (though not statistically significant) in AXA and LA-HX groups. The lower incidence of vomiting may be attributable to acepromazine, atropine, or both (LEMKE,

2007). It was expected that fewer dogs would vomit in the HA-LX group because of the higher dose of acepromazine and lower dose of xylazine; however, the frequency of vomiting may be affected by recent feeding in some dogs. Prior administration of acepromazine may lower the incidence of xylazine -induced vomiting.

The results of the present study suggested that the acepromazine-xylazine combination could be useful for sedation, anxiolysis, muscle relaxation, and premedication in healthy dogs. Atropine can be administered simultaneously to prevent the development of severe bradycardia and heart blocks. Following the present study, the combination of acepromazine-xylazine-atropine has been used for sedation or as premedication before general anesthesia in more than 250 dogs in our clinic without any adverse effects. However, further studies are required to evaluate the cardiopulmonary effects of this drug combination in detail.

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**VESAL, N., A. A. SARCHAHI, B. NIKAHVAL, A. KARAMPOUR: Klinička prosudba sedativnih svojstava acepromazin-ksilazina u kombinaciji s atropinom i njihov učinak na fiziološke vrijednosti temperature, bila i disanja u pasa. *Vet. arhiv* 81, 485-498, 2011.**

**SAŽETAK**

Svrha ovog rada bila je klinički procijeniti sedativne učinke različitih doza acepromazin-ksilazina u kombinaciji s atropinom u pasa. Istraživanje je bilo provedeno na 120 nasumce odabranih pasa različitih pasmina obaju spolova s dvostruko slijepim probama. Psi su bili klinički obrađivani na jednoj veterinarskoj klinici zbog potrebe za različitim dijagnostičkim i kirurškim pregledima. Za potrebe istraživanja bili su podijeljeni u četiri skupine (30 pasa po skupini), a po skupinama su intramuskularno dobivali sljedeće kombinacije lijekova: skupina AX dobivala je acepromazin (0,05 mg kg<sup>-1</sup>) i ksilazin (0,5 mg kg<sup>-1</sup>), skupina AXA dobivala je acepromazin (0,05 mg kg<sup>-1</sup>), ksilazin (0,5 mg kg<sup>-1</sup>) i atropin (0,04 mg kg<sup>-1</sup>), skupina LA-HX dobivala je acepromazin (malu dozu od 0,03 mg kg<sup>-1</sup>) i ksilazin (veliku dozu od 0,8 mg kg<sup>-1</sup>), a skupina HA-LX acepromazin (veliku dozu od 0,08 mg kg<sup>-1</sup>) i ksilazin (malu dozu od 0,3 mg kg<sup>-1</sup>). Vrijednosti bila, frekvencije disanja, elektrokardiograma i rektalne temperature bile su izmjerene prije davanja sedativa te za vrijeme maksimalne sedacije. Sedacija je bila bodovana opisno. Vrijednosti bila značajno su se smanjile nakon sedacije u pasa skupina AX, LA-HX i HA-LX. Značajno smanjena frekvencija disanja bila je zabilježena u svim skupinama. Srednji broj bodova sedacije nije se značajno razlikovao među skupinama, ali je kvaliteta sedacije bila bolja kada je atropin bio dodan kombinaciji acepromazin-ksilazin te su tri boda bila dodijeljena većem broju pasa u skupini AXA. Nuspojave

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nisu bile zabilježene. Kombinacija acepromazin-ksilazin, osobito s atropinom, može se rabiti za učinkovitu sedaciju i premedikaciju prije opće anestezije u zdravih pasa.

**Ključne riječi:** acepromazin, atropin, pas, sedacija, ksilazin

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