

## Romifidine or xylazine combined with ketamine in dogs premedicated with methotrimeprazine

## Romifidina ou xilazina associadas à quetamina em cães premedicados com levomepromazina

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### SUMMARY

The cardiorespiratory and analgesic effects of romifidine or xylazine combined with ketamine was investigated in dogs. Dogs were premedicated with 1.0 mg/kg of methotrimeprazine IV, followed by 0.1 mg/kg of romifidine (n = 8) or 1.0 mg/kg of xylazine (n = 8) and 15 mg/kg of ketamine IM, using a double blind randomised design. Dogs of both groups developed hypothermia, bradycardia, slight hypotension and reduction in respiratory rate and minute volume. There were minimal changes in end tidal CO<sub>2</sub> and O<sub>2</sub> saturation. There were no differences either in time or between the groups in pH, PaO<sub>2</sub>, and blood biochemistry. The reflexes to pain were reduced until 30-45 minutes of anaesthesia in both groups. Twelve bitches were divided in two groups as above and underwent ovariohysterectomy. Recovery was longer after romifidine/ketamine when compared to xylazine/ketamine in both studies. Although these anaesthetic protocols produced minimal cardiorespiratory changes, the quality of anaesthesia was not ideal for ovariohysterectomy.

**UNITERMS:** Methotrimeprazine; Xylazine; Ketamine; Dogs.

### INTRODUCTION

One of the most popular injectable anaesthesia used for small animals is the combination of  $\alpha$ -2 adrenoceptor agonists and ketamine<sup>4,7</sup>. Alpha-2 adrenoceptor agonists produce sedation, analgesia and muscle relaxation<sup>3,7,9</sup>. Other effects of  $\alpha$ -2 adrenoceptor agonists include bradycardia, arrhythmia, atrioventricular block, transitory hypertension, followed by hypotension, increase of central venous pressure, reduction of systolic volume and cardiac output, increase of vascular resistance and respiratory depression, produced by reduction of respiratory rate and minute volume<sup>7,9</sup>.

Romifidine is a potent and selective  $\alpha$ -2 adrenoceptor agonist that produces similar cardiorespiratory effects to other drugs of this group. In horses, romifidine produced a longer sedation than xylazine<sup>2</sup>. England *et al.*<sup>3</sup> compared the effect of several doses of romifidine in dogs. No difference in sedation was observed among these doses, but higher doses produced a more consistent effect.

Ketamine is a dissociative anaesthetic widely used in combination with several drugs in dogs. Ketamine produces increased motor activity, hyperreflexia and sympathetic activation<sup>12</sup>, effects which are counterbalanced when this drug

is combined with  $\alpha$ -2 adrenoceptor agonists<sup>7,12</sup>. However the use of  $\alpha$ -2 adrenoceptor agonists even combined with ketamine may produce emesis, increased secretions, arrhythmia and atrioventricular block<sup>7</sup>. Atropine may be used to prevent the xylazine-induced salivation, bradycardia and arrhythmia, but intense hypertension produced by the combination of these two drugs is an undesirable effect<sup>8</sup>. Phenothiazines are also widely used for premedication of dogs. These drugs reduce secretion and have an antiemetic and antiarrhythmic effects. Methotrimeprazine is a typical phenothiazine, with the advantage of producing a similar analgesic effect of morphine<sup>5</sup>.

The aim of this paper was to study the analgesic and cardiorespiratory effects of dogs premedicated with methotrimeprazine and anaesthetised with romifidine or xylazine, combined with ketamine.

### MATERIAL AND METHOD

This paper was divided in two studies. The first study was carried out without surgery. The cardiopulmonary effects of the combination of methotrimeprazine, xylazine and ketamine or methotrimeprazine, romifidine and

ketamine were investigated. The second study evaluated the efficacy of these combinations in order to perform ovariohysterectomy in bitches.

### Study 1 - Anaesthesia

Sixteen mongrel adult dogs weighing  $10.2 \pm 0.7$  kg and from both sexes were used in a double blind randomised study. They were starved of food for 12 hours and water was withheld 2 hours before the beginning of the experiment. Dogs were premedicated with 1 mg/kg of methotrimeprazine<sup>a</sup> intravenously. A 20 gauge catheter<sup>b</sup> was introduced in the metatarsal artery for collection of arterial blood samples and measurement of arterial blood gases. Fifteen minutes later dogs received an injection of 1 mg/kg of xylazine<sup>c</sup> combined with 15 mg/kg of ketamine<sup>d</sup> (n = 8) or 0.1 mg/kg of romifidine<sup>e</sup> combined with 15 mg/kg of ketamine (n = 8) intramuscularly. Rectal temperature<sup>f</sup>, heart rate and electrocardiogram<sup>g</sup>, indirect mean arterial blood pressure measured in the radial artery<sup>h</sup>, respiratory rate, tidal and minute volume<sup>i</sup> were measured before premedication, 15 minutes after premedication, every 15 minutes after romifidine/ketamine administration for 120 minutes. Expired CO<sub>2</sub> and haemoglobin O<sub>2</sub> saturation<sup>j</sup> and arterial blood gas analysis, glucose and electrolytes<sup>k</sup> were measured for 90 minutes only. Analgesia was investigated for 120 minutes, using a forceps clamped at the skin of the abdominal region close to the umbilicus, anal sphincter and interdigital space. Muscle relaxation was also investigated for 120 minutes. The nociceptive response was scored as "0" normal response, "1" reduced response and "2" no response. All measurements were performed only until 90 minutes after xylazine/ketamine.

Quality of recovery, onset of effect (from  $\alpha$ -2 agonists/ketamine administration until no response to clamping at the abdominal region), duration of anaesthesia (time to reduced response to clamping at the abdominal region, when nociceptive response was scored at least "1"), time to the first movement of the head, time to assume sternal and standing position were also measured.

### Study 2 - Surgery

Twelve bitches from several breeds, ranging from 6 to 120 ( $40 \pm 10$ ) months and weighing between 4 and 25 ( $10 \pm 2$ ) kg underwent ovariohysterectomy using the same protocol as previously described: methotrimeprazine/xylazine/ketamine

(n = 6) and methotrimeprazine/romifidine/ketamine (n = 6). Quality of recovery, onset of effect, duration of surgery and anaesthesia, time to assume sternal and standing position and response to surgical stimulus were measured.

### Statistical analysis

Statistical analysis was performed using an Apple Macintosh Statview software<sup>10</sup>. Analysis of variance (ANOVA) for repeated measures were used in each group for parametric variables to assess changes from control with time, followed by Dunnett's test when a significant difference was indicated<sup>1</sup>. One way ANOVA was used to compare the groups at each time point followed by Fisher's Paired Least Square Difference test when appropriate. Degree of analgesia was assessed using Friedman test in each group to assess changes from control with time and Mann Whitney test, to compare the groups at each time point. Differences were considered significant when  $p < 0.05$ . The tables and graphs are expressed in means  $\pm$  standard error of means.

## RESULTS

### Study 1

Time to onset of effect was  $6 \pm 1$  minutes in both groups, duration of anaesthesia was  $52 \pm 6$  minutes in dogs treated with methotrimeprazine/xylazine/ketamine and  $60 \pm 14$  minutes in dogs treated with methotrimeprazine/romifidine/ketamine. Time to standing position was  $95 \pm 6$  minutes in dogs treated with methotrimeprazine/xylazine/ketamine and  $132 \pm 17$  minutes in dogs treated with methotrimeprazine/romifidine/ketamine (Tab. 1).

### Methotrimeprazine/xylazine/ketamine

The anal reflex was reduced until 30 minutes and the cutaneous and interdigital reflexes until 45 minutes after administration of xylazine/ketamine (Fig. 1).

Temperature and heart rate decreased from 15 to 90 minutes after xylazine/ketamine (Tab. 3). Mean arterial blood pressure and respiratory rate reduced only at 90 minutes of anaesthesia (Tab. 3 and 4). Tidal and minute volume reduced after premedication, remaining below basal values until 60 (tidal volume) and 90 minutes (minute volume) after administration of xylazine/ketamine (Tab. 4). PaO<sub>2</sub> and

<sup>a</sup> Neozine, Rhodia, Brazil.

<sup>b</sup> Abbotth-T Plus, Brazil.

<sup>c</sup> Coopazine, Mallinkrodt Coopers, Brazil.

<sup>d</sup> Francotar, Francodex, Brazil.

<sup>e</sup> Sedivet, Boehringer, Brazil.

<sup>f</sup> Digital thermometer, Becton Dickinson, Brazil.

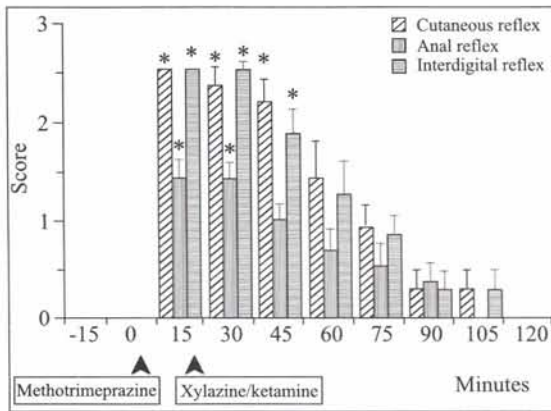
<sup>g</sup> Funbec 4-ITC/FC, Brazil.

<sup>h</sup> DX 2710, Dixtal, Brazil.

<sup>i</sup> Volumeter, Drager, Germany.

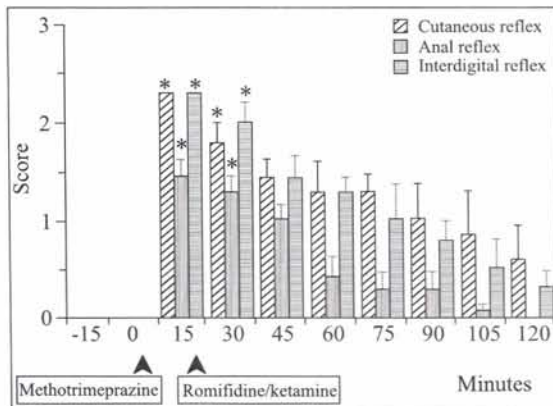
<sup>j</sup> DX 7100 ETCO<sub>2</sub>/SpO<sub>2</sub>, Dixtal, Brazil.

<sup>k</sup> Stat Profile Plus 5 Blood Gas Analyser, Nova Biomedical, USA.



**Figure 1**

Mean and Standard Error Mean of cutaneous, anal and interdigital reflexes in dogs anaesthetised with methotrimeprazine/xylazine/ketamine (n=8)–Botucatu–SP, February to May 1996. \* difference from “0” (after methotrimeprazine).



**Figure 2**

Mean and Standard Error Mean of cutaneous, anal and interdigital reflexes in dogs anaesthetised with methotrimeprazine/romifidine/ketamine (n = 8) – Botucatu – SP, February to May 1996. \* difference from “0” (after methotrimeprazine).

haemoglobin O<sub>2</sub> saturation increased at 75 and 90 minutes and blood potassium concentration decreased at 15 and 90 minutes (Tab. 3 and 4). There was no difference in pH, PaCO<sub>2</sub>, expired CO<sub>2</sub>, osmolality and blood bicarbonate, sodium, calcium and glucose concentrations (Tab. 3 and 4).

#### Methotrimeprazine/romifidine/ketamine

The anal, cutaneous and interdigital reflexes were reduced until 30 minutes after administration of romifidine/ketamine (Fig. 2).

Temperature and heart rate decreased from 30 and from 75 minutes respectively after administration of romifidine/ketamine until 120 minutes (Tab. 3). Hypotension was observed

only at 120 minutes and respiratory rate reduced from 15 to 30 and from 75 to 120 minutes after administration of romifidine/ketamine (Tab. 3 and 4). Minute volume decreased from 15 to 120 minutes after the administration of romifidine/ketamine (Tab. 4). Expired CO<sub>2</sub> reduced at 75 minutes and blood potassium concentration reduced from 75 to 90 minutes after administration of romifidine/ketamine (Tab. 3 and 4). No difference was observed for pH, PaO<sub>2</sub>, PaCO<sub>2</sub>, haemoglobin O<sub>2</sub> saturation, osmolality and blood bicarbonate, sodium, calcium and glucose concentrations (Tab. 3 and 4).

One out of eight dogs showed atrioventricular block from 25 minutes and two from 45 minutes after administration of romifidine/ketamine.

#### Comparison between groups

Sinusal arrhythmia was observed in both groups. Expired CO<sub>2</sub> was higher at 45 and 60 minutes in the dogs treated with romifidine/ketamine. Haemoglobin O<sub>2</sub> saturation was lower at 90 minutes in the dogs treated with romifidine/ketamine.

Myoclonia, shivering and muscle spasm occurred during anaesthesia in 8 out of 8 animals treated with romifidine/ketamine and 5 out of 8 animals treated with xylazine/ketamine.

#### Study 2

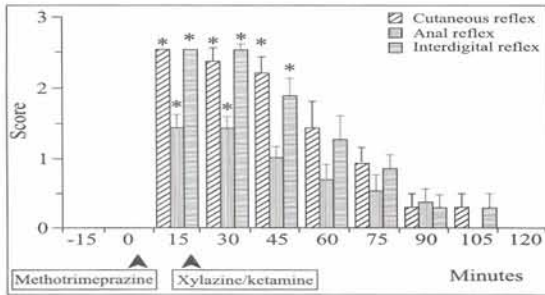
Time to onset of effect was 5 ± 1 and 3 ± 1 minutes in dogs treated with methotrimeprazine/xylazine/ketamine and methotrimeprazine/romifidine/ketamine respectively. Duration of anaesthesia was 59 ± 5 minutes in dogs treated with methotrimeprazine/xylazine/ketamine and 64 ± 6 minutes in dogs treated with methotrimeprazine/romifidine/ketamine. Time to standing position was 162 ± 30 in dogs treated with methotrimeprazine/xylazine/ketamine and 222 ± 26 in dogs treated with methotrimeprazine/romifidine/ketamine (Tab. 2). Time to assume sternal and standing position was longer in this study when compared with the same anaesthetic protocol in study 1.

Intense bleeding and tension at the ovarian pedicle was observed in three dogs treated with xylazine/ketamine. Two of these dogs needed local anaesthesia at the ovarian pedicle, followed in one of them by more 0.5 mg/kg of xylazine and 7.5 mg/kg of ketamine at 30 minutes during anaesthesia.

One dog from the romifidine/ketamine group showed muscle hypertonia, movement of the head, neck and limbs at 35 minutes during anaesthesia and received another dose of 0.05 mg/kg of romifidine and 7.5 mg/kg of ketamine. No other reaction was observed thereafter. This animal did not show a good abdominal muscle relaxation. Bleeding and tension of the ovarian pedicle was observed in this animal and in other two dogs from this group.

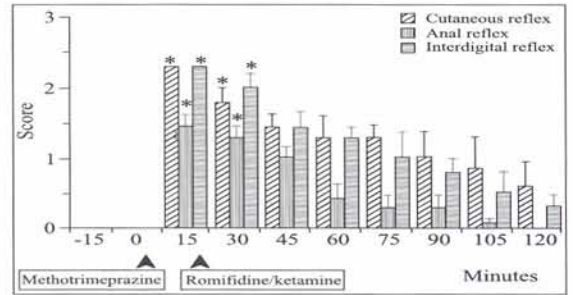
**Table 1**

Mean and Standard Error Mean (minutes) of onset of action, duration of anaesthesia, time to the first movement of the head and time to assume sternal and standing position of dogs anaesthetised with methotrimeprazine/xylazine/ ketamine and methotrimeprazine/romifidine/ketamine. There was no significant difference between the groups – Botucatu – SP, February to May 1996.



**Table 2**

Mean and Standard Error Mean (minutes) of onset of action, duration of surgery, duration of anaesthesia and time to assume sternal and standing position of dogs anaesthetised with methotrimeprazine/xylazine/ketamine and methotrimeprazine/romifidine/ketamine and submitted to ovariohysterectomy – Botucatu – SP, February to May 1996.



† difference between groups ( $p < 0.05$ ).

**Table 3**

Mean and Standard Error Mean of temperature ( $^{\circ}\text{C}$ ), heart rate (beats per minute), mean arterial blood pressure – MABP (mmHg), blood bicarbonate concentration (mEq/l), osmolality (mOsm), blood sodium (mmol/l), potassium (mmol/l), calcium (mg/dl) and glucose (mg/dl) concentrations in dogs anaesthetised with methotrimeprazine, xylazine and ketamine – MXK ( $n = 8$ ) and methotrimeprazine, romifidine and ketamine – MRK ( $n = 8$ ) – Botucatu – SP, February to May 1996.

		before	0	15	30	45	60	75	90	105	120
Temperature	MXK	39.2±0.14	38.6±0.14	38.0±0.23*	37.4±0.25*	37.0±0.25*	36.5±0.2*	36.0±0.17*	35.6±0.12*		
	MRK	38.8±0.11	38.4±0.18	37.8±0.22	37.3±0.25*	37.0±0.31*	36.7±0.35*	36.5±0.39*	36.0±0.40*	35.8±0.43*	34.9±0.27*
heart rate	MXK	104±6	89±8	72±7*	65±7*	67±7*	67±6*	68±6*	65±6*		
	MRK	109±10	89±6	83±11	81±9	81±12	81±12	78±13	66±10*	67±10*	62±8*
MABP	MXK	108±4	91±8	101±10	96±7	101±7	101±2	92±3	80±2*		
	MRK	108±8	88±5	97±11	95±14	92±15	98±11	97±10	94±9	81±6	74±4*
Bicarbonate	MXK	19.8±1.0	20.9±1.0	19.9±1.2	20.3±1.2	19.4±1.3	19.6±1.2	19.1±1.3	18.4±1.7		
	MRK	19.9±0.5	20.7±0.3	21.1±1.3	21.4±1.2	20.9±1.4	21.1±1.5	21.0±1.5	21.5±1.5		
Osmolality	MXK	282±1	284±1	286±1	286±2	286±2	286±2	284±4	284±4		
	MRK	281±3	283±2	283±3	286±1	286±1	285±3	286±3	287±3		
Sodium	MXK	141±1	145±1	145±1	146±1	145±1	145±1	144±1	144±2		
	MRK	143±2	144±1	144±1	145±1	145±1	144±1	144±1	144±1		
Potassium	MXK	3.86±0.16	3.76±0.17	3.46±0.12*	3.64±0.11	3.55±0.12	3.56±0.13	3.51±0.09	3.38±0.08*		
	MRK	4.13±0.13	3.83±0.15	3.79±0.21	3.80±0.12	3.86±0.15	3.71±0.16	3.67±0.15*	3.61±0.13*		
Calcium	MXK	3.32±0.40	3.81±0.22	3.25±0.26	4.15±0.15	3.85±0.45	3.65±0.39	3.79±0.32	3.35±0.47		
	MRK	3.58±0.26	3.97±0.24	3.84±0.41	4.04±0.4	3.97±0.27	4.09±0.34	3.60±0.30	3.72±0.23		
glucose	MXK	100±3	106±4	111±12	110±6	118±10	130±14	134±15	134±18		
	MRK	111±6	117±6	99±10	115±5	120±6	121±10	125±11	132±14		

\* difference from basal values (before) in each group ( $p < 0.05$ ). There was no difference between groups.

## DISCUSSION

Like in horses, recovery from anaesthesia was longer in dogs treated with romifidine/ketamine when compared to xylazine/ketamine in both anaesthetic and surgical groups<sup>2</sup>. Although not significant, the duration of anaesthesia was also slightly longer after romifidine/ketamine compared with xylazine/ketamine. Romifidine combined with ketamine also prolonged the time of recumbence when compared to the use of romifidine alone<sup>3</sup>. It is important to mention that recovery was longer in the surgical cases, showing that trauma inflicted by surgery may prolong recovery. Although recovery was longer after romifidine/ketamine, the longer duration of anaesthesia might be a potential advantage of

romifidine, which should be considered.

The occurrence of myoclonia, shivering and muscle spasm is a common finding when ketamine is used<sup>12</sup> and apparently xylazine produced a better muscle relaxation than romifidine. This was a similar response than that observed in horses, where romifidine produced less ataxia than xylazine<sup>2</sup>.

Hypothermia is a common finding during anaesthesia and the causes have been discussed elsewhere<sup>6,11</sup>.

Reduction of the heart rate, atrioventricular block and hypotension are usually observed after the use of  $\alpha$ -2 adrenoceptor agonists<sup>9</sup>. The concomitant use of ketamine probably delayed the arterial hypotension, which was observed only at the end of anaesthesia<sup>7,12</sup>. The use of methotrimeprazine probably also abolished the incidence of atrioventricular block

**Table 4**

Mean and Standard Error Mean of respiratory rate (breaths/minute), tidal volume/kg (ml), minute volume/kg (ml), pH, PaO<sub>2</sub> (mmHg), PaCO<sub>2</sub> (mmHg), expired CO<sub>2</sub> (mmHg) and haemoglobin O<sub>2</sub> saturation (%) in dogs anaesthetised with methotrimeprazine, xylazine and ketamine - MXK (n = 8) and methotrimeprazine, romifidine and ketamine - MRK (n = 8) - Botucatu - SP, February to May 1996.

		before	0	15	30	45	60	75	90	105	120
respiratory rate	MXK	21±2	13±1	15±1	17±3	22±3	15±1	13±1	10±1*		
	MRK	21±2	15±1	13±1*	13±1*	16±2	14±3	13±2*	12±2*	10±1*	11±3*
tidal volume/kg	MXK	21.7±1.4	18.9±1.2	13.5±0.8*	15.0±1.8*	14.5±1.9*	15.4±1.8*	16.6±1.4	16.8±1.6		
	MRK	19.8±2.1	19.9±2.7	12.9±2.0	13.9±1.7	14.0±2.4	14.9±2.4	17.3±2.5	17.7±1.6	18.1±1.7	18.0±1.4
Minute vol./kg	MXK	444±36	240±18*	199±15*	233±26*	285±39*	261±52*	245±54*	158±9*		
	MRK	400±57	321±56	166±20*	184±14*	212±17*	202±30*	223±34*	219±28*	165±17*	132±11*
PH	MXK	7.43±0.01	7.42±0.01	7.40±0.01	7.40±0.02	7.43±0.01	7.42±0.01	7.45±0.01	7.44±0.02		
	MRK	7.43±0.02	7.44±0.01	7.39±0.02	7.40±0.02	7.42±0.02	7.41±0.02	7.42±0.02	7.41±0.01		
PaO <sub>2</sub>	MXK	89.1±2.3	88.1±1.5	95.2±4.6	97.6±2.9	101.1±5.0	100.7±6.6	105.0±5.0*	107.4±3.9*		
	MRK	87.1±4.2	93.0±3.6	87.7±2.7	96.0±4.0	100.0±6.1	98.2±6.6	103.4±7.1	97.6±5.6		
PaCO <sub>2</sub>	MXK	30.1±1.1	31.4±1.0	31.8±1.5	31.7±1.6	29.2±1.7	29.7±1.9	28.4±1.7	27.5±3.1		
	MRK	30.1±0.5	30.6±0.6	34.8±1.8	34.5±1.9	31.9±2.1	33.0±2.2	31.9±1.7	33.4±2.2		
Expired CO <sub>2</sub>	MXK	38.6±0.8	37.8±0.9	40.6±1.9	38.3±1.9	34.5±1.6†	32.5±2.3†	32.3±2.1	33.3±2.4		
	MRK	42.4±2.1	37.8±0.8	45.1±1.6	43.0±1.5	39.5±1.2†	39.0±1.6†	36.8±1.3*	37.5±0.8		
O <sub>2</sub> saturation	MXK	97.2±0.2	97.1±0.12	97.3±0.39	97.6±0.3	97.9±0.4	98.2±0.2	98.5±0.1*	98.4±0.2*†		
	MRK	96.8±0.5	97.6±0.2	96.5±0.4	97.4±0.2	97.6±0.5	97.7±0.3	97.9±0.3	97.3±0.3†		

\* difference from basal values (before) in each group and † differences between groups (p < 0.05)

in dogs treated with xylazine/ketamine and minimised this finding in those dogs treated with romifidine/ketamine<sup>3</sup>.

Although respiratory rate and minute volume decreased in both groups, these changes did not produce respiratory acidosis as reported in a previous study, when xylazine/ketamine was used in dogs<sup>7</sup>. The differences in PaO<sub>2</sub>, haemoglobin O<sub>2</sub> saturation and blood potassium concentration in time in the two groups and the differences in expired CO<sub>2</sub> between the groups were minimal and did not have biological importance, as the values were within the normal range for the canine species.

Both anaesthetic techniques produced stable cardiorespiratory function and can be considered safe when this aspect is considered. Otherwise, quality of surgical anaesthesia was not ideal, as some dogs showed increased muscular tonus and also needed additional doses of the combination and even local anaesthesia at the ovarian pedicle.

#### ACKNOWLEDGEMENTS

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#### RESUMO

Investigaram-se neste estudo os efeitos cardiorrespiratório e analgésico da associação de romifidina ou xilazina com a quetamina em cães. Dezesesseis cães receberam como medicação pré-anestésica 1,0 mg/kg de levomepromazina IV, seguido de 0,1 mg/kg de romifidina (n = 8) ou 1,0 mg/kg de xilazina (n = 8) associadas a 15 mg/kg de quetamina IM, utilizando-se protocolo aleatório de seleção dos grupos, em estudo duplo cego. Os cães de ambos os grupos apresentaram hipotermia, bradicardia, leve hipotensão e redução da frequência respiratória e volume minuto. Poucas alterações foram observadas na concentração de CO<sub>2</sub> expirada e na saturação de O<sub>2</sub> na hemoglobina. Os valores de pH, PaO<sub>2</sub> e bioquímica sanguínea não apresentaram diferenças ao longo do tempo em cada grupo ou entre os grupos. Os reflexos dolorosos permaneceram reduzidos por até 30 a 45 minutos após a aplicação dos α-2 agonistas e quetamina. Doze cadelas foram divididas em dois grupos, anestesiadas como acima e foram submetidas a ovariosterectomia. A recuperação foi mais longa nas cadelas tratadas com romifidina/quetamina. Embora estes protocolos anestésicos tenham produzido mínimas alterações cardiorrespiratórias, a qualidade da anestesia não foi ideal para ovariosterectomia.

**UNITERMOS:** Metotrimeprazine; Xilazina; Ketamina; Cão.

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