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Evaluation of Rocuronium Associated to Acepromazine, Propofol and Isofluorane in the Anesthesia of Female Canines Submitted to Elective Ovaryhysterectomy

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Keywords: *rocuronium, female canines, ovary hysteric tomy.*

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Index terms: rocuronium, female canines, ovary hysteric tomy.

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I. Introduction

Rocuronium bromide is a mono quartenary depolarizing muscle relaxant of intermediate-term action (Tranquili et al., 2007). Due to its low potency, rocuronium needs to be administered in high doses in order to achieve a sufficient number of molecules in the neuromuscular junction, setting its fast beginning of action (Hunter 1996, Tranquili et al., 2007). Rocuronium has minimum influence on the cardiovascular system and does not promote histamine release in horses, dogs, cats and humans (Xue et al., 1998, Neves, 2007). In high doses rocuronium may cause small increase in the heart rate and significant increase in blood pressure, probably by vagolytic action (Booij, 1997, Miranda et al., 2008). According to Dugdale et al. (2002), hypertension is transient and not followed by changes in heart frequency or rhythm.

This neuromuscular blocker presents good chemical stability and minimum liver biotransformation (McCoy et al., 1996). In men, rats and dogs, its inactive metabolite 17-deacetyl-rocuronium may be found in negligible amounts (Proost et al., 2000). This is probably an advantage over vecuronium, its precursor, which presents active metabolites that may contribute to the cumulative characteristics that follow clinical doses in healthy patients and in kidney insufficient patients. (Wright et al.,1994). The main elimination pathway is hepatic-biliary (Wierda & Proost, 1995) and occurs majorly in the first 24 hours, with 65% to 75% of the metabolites being eliminated in the feces and 9% to 25% in the urine (Proost et al., 2000).

Rocuronium has a specific cyclodextrin-based reverser, sugammadex, which favors its elimination through the kidney by making the drug more water soluble. The clearing time takes about two hours after its administration with no recurarization effect (Almeida & Locks, 2011).

The present experiment aimed to evaluate the utilization of a IV bolus 0,1 mg.Kg^{-1} rocuronium dose as a muscle relaxant in elective ovaryhysterectomy

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surgeries of female canines, in order to verify possible alterations over the respiratory and circulatory dynamics as well as the muscle relaxation effects, with the objective to help these proposed surgical techniques.

II. Material and Methods

With the approval of the ethics committee of Viçosa Federal University (UFV) (process 09/2007), 20 female canines with indication to elective ovaryhysterectomy from the UFV Veterinary Hospital routine were selected, with the owner's consent, all of them included in anesthetic risk class I, according to the *American Society of Anesthesiologists* (Futema, 2002). The animals presented medium weight of 15 ± 0,9 kg and medium age of 4 ± 1,12 years. They were randomly distributed into two groups of 10 subjects. Complete physical examination, hemogram and biochemical profile were performed for all the animals in the pre-surgical period, in order to ensure their good state of health. Only healthy animals were used in this experiment.

After 6 hours of water abstinence and 12 hours of fasting, all the subjects received acepromazine (IV 0,1 $mg.kg^{-1}$) and 10 minutes from that point the cephalic vein was catheterized and anesthetic induction was perfomed using propofol 6,0 $mg.kg^{-1}$ IV along with orotracheal intubation. Shortly after that, inhalatory anesthesia was initiated using isofluorane diluted in pure oxygen, in an anesthetic circuit with partial gas reinhalation with a calibrated vaporizer. The administered isofluorane concentration was the one necessary to maintain the anesthetic level compatible to the surgical procedure.

Immediately before the skin incision, the subjects in the GR group received rocuronium 0,1 $mg.kg^{-1}$ IV, while the subjects in the GC group received NaCl 0,9% solution in the same volume as the rocuronium solution.

The following variables were registered: respiratory frequency (FR), by the observation of the chest movement; minute-volume (V_M), by Wright's ventilometer[1]; systolic blood pressure (SBP), by a non-invasive method using a vascular doppler[2]; heart rate (HR) using a oximeter[3], with its sensor initially placed in the inguinal fold and in the tongue after anesthetic induction;

The electrocardiography, using a computer program in DII derivation[4]; arterial blood gasometry, performed in three samples collected from the femoral artery and measured by a portable blood gas analyzer[5]; blood electrolytes analysis (Cl^-, iCa,, Na^+, K^+) by the colorimetric method[6]; and muscular relaxation by questionnaire (Fig. 1).

Did the anesthetic protocol used in this surgery somehow interfered in the surgical procedures? Chose the option(s) that better represent your opinion about it.
( ) The muscular relaxation was equal to the commonly found in HOV anesthetic states for elective ovaryhysterectomy; ( ) The muscular relaxation was higher than the commonly found in HOV anesthetic states for elective ovaryhysterectomy; ( ) It was noted no difference regarding the easiness in exposing the suspensory ovaries ligaments; ( ) It was noted higher easiness in exposing the suspensory ovaries ligaments.

Figure 1 : Questionnaire on the muscular relaxation applied to the surgical staff after the experimental period

The respiratory frequency (FR) and the minute-volume (V_M) were measured before MPA (M0), 15 minutes after MPA (M1), and 2, 4, 6, 8, 10, 15, 20, 25, 30, 35 and 40 minutes after the administration of rocuronium or saline solution. The systolic blood pressure (SBP), heart rate (HR) and electrocardiography were measured before MPA (M0), 10 minutes after MPA (M1), after the setting of surgical anesthesia (M2), and, from that moment on, every 10 minutes (M3, M4, M5 e M6). A 40-minute fixed transoperative period was set for the surgeries. Blood samples were collected for gasometry at M0, M3 and M6. The anion gap $(Na^+ + K^+)$-$(Cl^- + HCO^-_3)$ and the measurable strong ion quotient $(Na^+ + K^+)$-(Cl^-) were obtained by calculation. After data collection was conducted statistical analysis, between groups was used for parametric analysis of variance (ANOVA) data and non-parametric Wilcoxon test data. For comparison along time within each group was used for parametric data and the Tukey test for non-parametric data, the Dunn's test with $p<0,05$. As for the muscular relaxation, descriptive analysis was performed.

III. Results and Discussion

The simultaneous evaluation of respiratory frequency (FR) and minute-volume (V_M) (Fig. 2) revealed similar responses in both GR and GC groups. After sedation with acepromazine, a significant decrease in these variables was noted due to the sensibility reduction of the chemoceptors in the carotid and aortic sheath and in the central nervous system facing the changes of carbon dioxide concentration in the blood (Cortopassi & Fantoni, 2002).

[1] Ferraris Mark 8 - Wright Ventilometer 100L.
[2] Portable Vascular Doppler – Medmega Industry and Medical Equipment Ltd.
[3] NPB 290 – Nellcor Puritan Bennett Europe BU.
[4] Computer ECG Acquisition Module –Brazilian Electronic Technology TEB.
[5] Portable Clinical Blood Gas Analyzer I –STAT.
[6] CELM E-225-D- Company for Modern Laboratory Equipment -São Paulo – Brazil.

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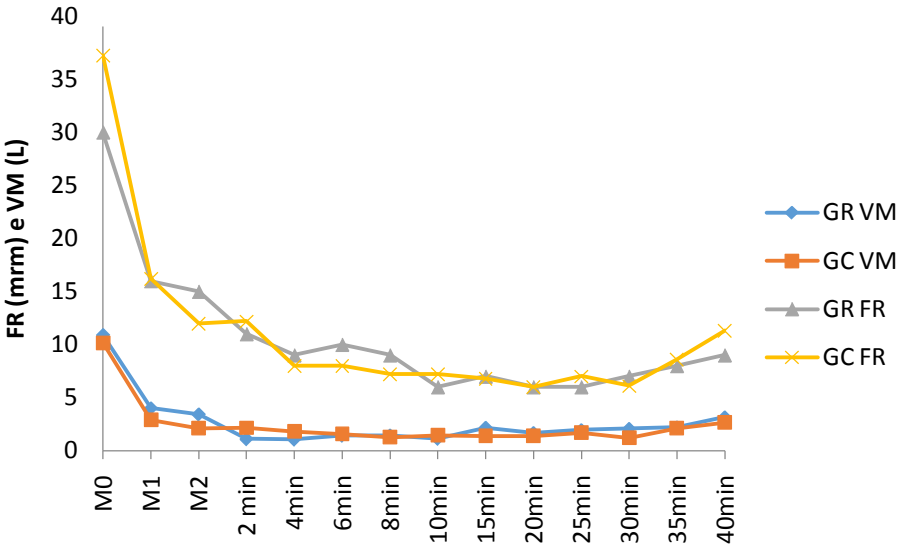

Figure 2 : Representation of FR medium values (mrm) and V_M medium values (l) featured by anesthetized female dogs with acepromazine, propofol and isofluorane, treated with rocuronium (GR) or not (GC)

*Medium values followed by equal capital letters in columns do not differ between them according to ANOVA or the non-parametric Wilcoxon test. Medium values followed by equal lowercase letters in lines do not differ between them according to Tukey's parametric test or the non-parametric Dunn's test (p<0,05). *AG (Ânion gap); **DIFm (difference between measured strong ions).*

After the administration of propofol and isofluorane for anesthetic maintenance, respectively, it was noted decrease in FR and V_M, in a dose-dependent manner, according to Short & Bufalari (1999) and Evers et al., (2006). A 0,1mg.kg^{-1} rocuronium dose did not promote respiratory arrest in any of the subjects in the GR group, nor significant reduction in FR. However, V_M was significantly and transiently affected in this group, only two minutes after the administration of rocuronium. This effect was no longer noted four minutes from the administration, demonstrating a slight reduction in intercostal muscles and/or diaphragm activities. This also demonstrates that other muscular groups were influenced by rocuronium as well, since respiratory arrest may happen when a neuromuscular blocker is administered, in a dose-dependent manner. There is a sequence of muscular paralysis beginning by facial and tail muscles, moving towards limbs and neck, followed by phonation and swallowing muscles, abdominal muscles, intercostals muscles and finally the diaphragm. Therefore, when diaphragm contraction ceases, it means that other muscular groups are under the effect of the muscular relaxant (Fuller, 2001).

The sequence of events in the recovery occurs in the reverse order of the neuromuscular blocking (Hall, 1971). Considering all that, our theory is that the dose utilized in this experiment is very close to the ideal one, if not actually ideal.

Systolic blood pressure behaved in the same manner for both groups (Tab.1). However, for the GR group, it was noted a progressive reduction nonsignificat in this variable until M4, a point where reestablishment of the values start, which may be assigned to the potentiating effect of the neuromuscular blockers on other central depressing drugs (Duke, 1995, Sano et al., 2003). The medium values of the heart rate remained stable during the whole anesthetic period in both evaluated groups, demonstrating that the protocols used in this experiment did not promote any effects on this variable. According to Xue et al. (1998) and Neves (2007), rocuronium has minimum influence on the cardiovascular system and does not lead to histamine release, which causes vascular dilation and decrease in blood pressure. Changes in pressure lead to reflex tachycardia or rhythm alterations, which were not observed in this study. Some the subjects in both experimental groups showed sinus rhythm without electrocardiogram changes during the anesthetic period.

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Table 1 : Medium values of systolic blood pressure (mmHg), heart rate (beat/min) pO_2 (mmHg), pCO2 (mmHg), pH, $cHCO^-_3$ (mmol/L) , $ctCO_2$ (mmol/L), cBase (mmol/L), Cl (mEq/L), Na (mEq/L), K (mEq/L), iCa (mEq/L), anion gap (mEq/L) and difference between measured strong íons (mEq/L) featured by female dogs anesthetized with acepromazine, propofol and isofluorane, treated with rocuronium (GR) or not (GC)

Groups		M0	M1	M2	M3	M4	M5	M6
GR	PAS	129^{A,a}	107^{A,ab}	95^{A,bc}	77^{A,c}	74^{A,c}	83^{A,bc}	99^{A,bc}
GC	PAS	145^{A,a}	143^{A,a}	118,5^{A,ab}	111,5^{A,ab}	104,5^{A,ab}	99^{A,ab}	117^{A,ab}
GR	FC	115,5^{A,a}	103,2^{A,a}	114,1^{A,a}	103,8^{Aa}	102^{A,a}	105^{A,a}	108,3^{A,a}
GC	FC	136,7^{A,a}	103,3^{A,b}	117,6^{A,ab}	107^{A,ab}	102^{A,b}	94,4^{A,b}	109,7^{A,ab}
GR	SpO_2	93,1^{A,bc}	92,8^{A,c}	96,4^{A,ab}	96,3^{A,ab}	97^{A,a}	97^{A,a}	97^{A,a}
GC	SpO_2	92,8^{A,c}	93,4^{A,bc}	99^{A,a}	97^{A,ab}	97^{A,ab}	96,3^{A,bc}	95,7^{A,abc}
GR	$pO2_{(a)}$	84,5^{A,b}			437,^{A,a}			325,8^{A,ab}
GC	$pO2_{(a)}$	74,3^{B,b}			387,^{A,a}			367,4^{A,a}
GR	$pCO_{2)}$	31,03^{A,c}			79,8^{A,a}			63,83^{A,b}
GC	$pCO_{2)}$	31,06^{A,b}			69,1^{A,a}			66,43^{A,a}
GR	$pH_{(a)}$	7,39^{A,a}			7,1^{A,c}			7,17^{A,b}
GC	$pH_{(a)}$	7,39^{A,a}			7,14^{A,b}			7,17^{A,b}
GR	$cHCO^-_{3(a)}$	18,9^{A,b}			24,4^{A,a}			22,5^{A,a}
GC	$cHCO^-_{3(a)}$	18,9^{A,b}			23,2^{A,a}			21^{A,a}
GR	$ctCO2_{(a)}$	19,8^{A,b}			26,7^{A,a}			24,4^{A,a}
GC	$ctCO2_{(a)}$	19,9^{A,b}			25,4^{A,a}			23,1^{A,a}
GR	$cBase_{(a)}$	-6,1^{A,a}			-5,3^{A,a}			-6^{A,a}
GC	$cBase_{(a)}$	-6^{A,a}			-5,8^{A,a}			-6,7^{A,a}
GR	Cl^-	122,5^{A,a}			118^{A,a}			108,3^{A,a}
GC	Cl^-	117,4^{A,a}			127^{A,a}			125,4^{A,a}
GR	Na^+	143^{A,a}			141^{A,ab}			141^{A,b}
GC	Na^+	142^{A,a}			141^{A,a}			140^{A,a}
GR	K^+	3,82^{A,a}			3,88^{A,a}			3,91^{A,a}
GC	K^+	3,75^{A,a}			3,76^{A,a}			3,7^{A,a}
GR	iCa	1,33^{A,a}			1,33^{A,a}			1,24^{A,a}
GC	iCa	1,19^{A,a}			1,29^{A,a}			1,25^{A,a}
GR	*AG	5,21^{A,a}			2,22^{A,a}			13,66^{A,a}
GC	*AG	9,86^{A,a}			5,79^{A,b}			-0,51^{A,ab}
GR	**DIFm	24,12^{A,a}			26,6^{A,a}			36,22^{A,a}
GC	**DIFm	28,73^{A,a}			17,3^{A,a}			20,72^{A,a}

*Medium values followed by equal capital letters in columns do not differ between them according to ANOVA or the non-parametric Wilcoxon test. Medium values followed by equal lowercase letters in lines do not differ between them according to Tukey's parametric test or the non-parametric Dunn's test ($p<0,05$). *AG (Ânion gap); **DIFm (difference between measured strong ions).*

Evaluation of the acid-base profile revealed that $pCO_{2(a)}$ values were not significantly different in both groups during the whole experimental period, but it was noted an increase between M0 and M3 in both groups, stating post-induction respiratory acidosis. It is known that propofol and isoflourane promote respiratory depression that leads to heart rate decrease and hypoventilation, as previously seen. By its turn there may be $pCO_{2(a)}$ increase (Ferro et al., 2005), an independent respiratory variable.

The analysis of $pH_{(a)}$ medium values indicate acidosis, once this is a dependent variable that may be altered by base concentration (metabolic component) and by $pCO_{2(a)}$ (respiratory component), being inversely proportional to this last one. Since all animals in GR and GC group showed respiratory acidosis and no alterations in base concentrations it is possible to allege that the main factor was the $pCO_{2(a)}$ increase, corroborating Ferro et al., (2007).

Increase in $pCO_{2(a)}$ lead to rising bicarbonate levels, since they are interdependent. Each 10mmHg increase in $pCO_{2(a)}$ is equivalent to an increase of 1,5mEq.L$^-$ in bicarbonate levels (Tab.1). The CO_2 concentration behaved in the same manner as bicarbonate, since it maintained 1 to 2 mEq.L$^-$ higher than bicarbonate (it also represents the CO_2 concentration dissolved in plasma) (DiBartola, 2006; Tranquili et al., 2007). While CO_2 chemical metabolites elimination processes take place in the organism, CO_2 associates to water (H_2O) and forms carbonic acid

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(H_2CO_3), which, by its turn, will form HCO^-_3 and H^+ ions, this last one's production higher since carbonic acid is weak and suffers low dissociation in bicarbonate. In addition, according to DiBartola (2006), $pCO_{2(a)}$ increase may be responsible for 50% of the blood bicarbonate level variation. Lately, the reason for this increase will be due to an attempt of kidney adaptation and respiratory acidosis, since kidneys control H^+ ions concentration in the organism excreting either acid or basic urine (DiBartola 2006).

The ions showed physiological medium values and did not differ between them (Tranquili et al., 2007), except by chloride, which presented itself elevated indicating hyperchloremia. It is suggested that the NaCl 0,9 % may have caused this effect (DiBartola 2006). The alterations were transient and similar in both groups, and did not influence in the recovery/deambulation of the subjects.

The response to the questionnaire on the muscular relaxation revealed that 80% of the animals treated with rocuronium showed appropriate relaxation and easiness in the maneuvers to expose the viscera, meanwhile, in the control group, this response was achieved in only 30% of the subjects.

From these observations, we are able to imply that abdominal musculature presented itself easy to manipulate, confirming the benefits mentioned by Hall (1971), who stated that the use of small doses of muscular relaxant might favor several surgical procedures in superficial anesthetic level.

IV. Conclusion

The administration of a 0,1 $mg.kg^{-1}$ rocuronium dose led to little alteration in the respiratory dynamics as well as to increase in the muscular relaxation level, thus presenting important benefits to surgical performance. Both utilized anesthetic protocols did not promote significant changes in heart rate, systolic blood pressure and electrocardiogram. Also both protocols promoted acidemia, respiratory acidosis and transient hyperchloremia, with no prejudice to anesthetic recovery.

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