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Hematological Values in Equines Sedated with Different Doses of Romifidine

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Abstract: The hematological values in equines sedated with different doses of romifidine were assessed. Total 15 h were randomly distributed into three groups of five animals each. The groups were denominated GI (romifidine 60 mcg/kg), GII (romifidine 80 mcg/kg) and GIII (romifidine 100 mcg/kg), given intravenously. Venous blood samples were collected prior to the drug administration (T_0), 30 (T_{30}), 60 (T_{60}) and 90 (T_{90}) min after the drug administration. The parameters evaluated included Red Blood Cells count (RBC), Packed Cell Volume (PCV), hemoglobin, mean corpuscular volume, total leukocytes, total protein and fibrinogen. The results showed a decrease of RBCs in the moments T_{30}, T_{60} and T_{90} in comparison to T_0, however, with no significant changes. PCV decreased significantly in GI at the moments T_{30}, T_{60} and T_{90} in comparison to T_0 ($p<0.05$). Hemoglobin showed a significant increase in GII in comparison to GI in all the times and decreased values in GIII when compared to GII values. Mean corpuscular volume, total leukocytes, total protein and fibrinogen showed no significant difference between groups and the times studied.

Key words: Romifidine, hematology, sedation, equine, GII comparison, significant

INTRODUCTION

Romifidine is an alpha-2 adrenergic agonist sedative for isolated or combined usage with opioids in equines. It's sedative and analgesic properties are dose dependents and the utilized doses for those effects range from 40-120 mcg/kg (Gasthuys *et al*., 1987; Diamond *et al*., 1993; Hamm *et al*., 1995; Freeman and England, 2000; Spinosa *et al*., 2006).

After administration of those drugs many changes can occur such as hematological and biochemical. Those changes can influence the homeostasis of the body which can bring prejudicial effects to the patient such as decrease in packed cell volume, dose-dependent hyperglycemia, secretion of antidiuretic hormone, secretion of adrenocorticotropic hormone and cortisol (Gasthuys *et al*., 1987; Muir and Hubbell, 1991; Wagner *et al*., 1991; Wood *et al*., 1992; Kullmann *et al*., 2014).

Complete blood count has an importance as a preoperative exam, for it can determine changes in red and white blood cells count, showing a decreased capacity of oxygen transportation to the tissues (Short, 1987; Hall *et al*., 2013). The acute inflammatory process response can be measured by fibrinogen dosage in equines. Elevated values assures an inflammatory process while decreased values reflects a consultative coagulation process, specially in disseminated intravascular coagulation processes (Meyer *et al*., 1995).

Drugs that induce changes to packed cell volume and total solids are reportedly being used followed by administration of alpha-2 adrenergic agonists (xylazine, detomidine, medetomidine) but there are only a few studies done with romifidine (Daunt *et al*., 1993; Kullmann *et al*., 2014). The objective of this study is to evaluate the hematological values in equines sedated with different doses of romifidine.

MATERIALS AND METHODS

Animals: Total 15 h (males, adults, mix breed, non-castrated) weighing 402.5±38.3 kg and ageing 6.3±2.6 (mean±standard deviation), from Univesity of Uberaba Teaching Farm were utilized. The study was approved by the Ethics Committee in Animal Experimentation of University of Uberaba (CEEA 0100/2009) and belongs to risk category 1 and 2.

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Study design; the animals were distributed into three groups: Group 1 received 60 mcg/kg, group 2 80 mcg/kg and group 3 100 mcg/kg of romifidine (Sedivet 1%; Boehringer Ingelheim, Randburg, RSA) given intravenously. All the experimental procedures were performed during the morning period with the horses individually restrained, allowing minimum managing. The equines had access to tifton hay and water ad libitum untill 30 min before the drug administration and then, it was removed until the end of the observation period. The equines were taken to the stalls 24 h before the experiment for acclimatization.

Instrumentation and blood sampling: A 14 G (2.1×83 mm), poly tetra fluor oethylene catheter (BD-Becton, Dickinson and Company, New Jersey, USA) was aseptically placed in the left jugular vein on the morning of each treatment day and removed immediately after collection of the final blood sample. After 60 min to allow recovery from catheterization, baseline measurements were recorded and the initial blood sample was collected (T_0).

To study the hematological profile (red blood cells count, packed cell volume, hemoglobin, mean corpuscular volume, total leukocytes, total protein and fibrinogen) venous blood samples were collected prior to romifidine administration (T_0) and at 30 (T_{30}), 60 (T_{60}) e 90 (T_{90}) after the injection. About 10 mL of blood was collected and discarded before each sample draw (5-15 mL) and the catheter was flushed with 10 mL of 0.9% heparinized saline after each blood sample draw. The blood samples were immediately refrigerated at 5°C until processing, which occured in a maximum of 45 min after the samples were collected. Erythrogram and leukogram values in blood with EDTA anticoagulant were obtained by previoulsy calibrated routine hematology (ABCVET; Horiba, Northampton, UK). Packed cell volume values were obtained by centrifugation 11.800 rpm (14.000×g) for 5 min, using a microhematocrit centrifuge (LB-116/30, BENFER, Sao Paulo, Brazil) utilizing microcapillary tubes cointaining 1 μL of total blood drawn from the tubes containing EDTA.

To determine the total proteins and fibrinogen, a refractometer (RTP12, Instrutherm Instrumentos de Medicao Ltda, Sao Paulo, Brazil) was utilized by using the blood serum from the microcapillary tube, obtained from plasma separation after centrifugation. The equipment was calibrated with distilled water prior to measurements. All measurements were performed twice and mean values were utilized.

Statistical analysis: Repeated measures Analysis of Variance (ANOVA) was used to test for differences in outcome variables among treatments over time using simple contrasts with baseline values set as the reference. Post-hoc tests were performed using the bonferroni correction for multiple comparisons. Analysis were performed using commercially available software (Bioestat 5.3, Tefe, Amazonas, Brazil) and results were interpreted at the 5% level of significance.

RESULTS AND DISCUSSION

It was possible to perform the blood colletion in all animals due to sedation. More pronounced characteristics were observed in animals that received larger doses of romifidine (GIII).

The results concerning the hematological parameters are described in Table 1. There was a reduction of total erythrocyte count at the moments T_{30}, T_{60} and T_{90} in comparison to T_0, however, with no significant changes ($p<0.05$). As to the packed cell volume, there was an important reduction in GI at the moments T_{30}, T_{60} and T_{90} in comparison to T_0 ($p<0.05$). There were no significant changes among groups.

Hemoglobin values had no significant changes at the moments T_{30}, T_{60} and T_{90} in comparison to T_0. From the same variable a significant increase in GI and GII was observed in all treatments over time among groups comparison. After a peak value, the hemoglobin values significantly decreased in GIII when compared to GII in all studied moments.

Mean corpuscular volume and total leukocytes showed no significant changes among groups and times studied. Relatively to the biochemical variables (total protein and fibrinogen) (Table 2), there was no significant difference among evaluated groups in none of the parameters.

Several drugs can be used as preanesthetic medication in equines, however, they can produce undesirable effects on hematological parameters (Fantoni *et al*., 1999). Determination of hematological values are often requested by veterinarians that dedicate themselves to equine medicine with the objective of evaluating the health conditions of their patient (Fan *et al*., 1982). Thus, caution is advised while administering drugs in patients that already show previous changes in those variables which can lead to and enhanced effect, reducing the hemodynamic variables and consequently to a decompensation of cardiovascular system and tissue oxygenation (Ballard *et al*., 1982).

The most important finding of this study was the decrease of packed cell volume with the dose of 60 mcg/kg (GI) and the increase in hemoglobin with the dose of 80 mcg/kg (GII) (Table 1). Although, the

Table 1: Mean values±SD of total erythrocytes (million/mm^3, packed cell volume (%), hemoglobin (gd/L), mean corpuscular volume (μ^3) and total leukocytes ($\times10^3/\mu L$) of equines sedated with romifidine

Parameters(groups)	T_0	T_{30}	T_{60}	T_{90}
Total erythrocytes				
GI	6.39±0.92	5.31±0.76	5.04±0.78	5.27+0.48
GII	6.94±1.15	5.93±0.89	6.06±0.65	5.72±0.28
GIII	6.21±0.92	5.77±0.64	5.30±0.55	5.18±0.70
Packed cell volume				
GI	30.20±1.92	24.20±3.42*	23.00±2.82*	23.60±1.51*
GII	31.20±2.38	26.40±1.34	26.60±3.20	25.60±2.07
GIII	31.60±4.21	29.80±2.58	27.00±1.22	27.00±2.34
Hemoglobin				
GI	10.12±0.72[a]	7.720±1.51[a]	7.68±1.09[a]	7.80±0.88[a]
GII	13.60±1.67[b]	12.90±1.94[b]	11.24±0.52[b]	12.24±1.82[b]
GIII	10.70±1.64[a]	10.30±0.71	9.26±0.26[a]	9.08±0.54[a]
Mean corpuscular volume				
GI	48.03±7.47	47.60±8.65	43.02±4.39	48.16±6.25
GII	45.60±5.19	45.24±6.70	44.25±7.19	44.82±4.37
GIII	51.00±2.22	51.80±3.29	51.21±3.32	52.39±3.50
Total leukocytes				
GI	11.54±2.82	11.41±2.78	9.04±2.51	10.84±3.03
GII	13.26±1.67	13.48±2.13	13.56±1.22	12.12±1.58
GIII	8.020±2.42	7.40±2.25	6.90±1.67	7.08±1.46

*Based on repeated measures ANOVA comparing T_0 versus T_{30}, T_{60}, T_{90} administration of romifidine ($p<0.05$; [a, b]Based on repeated measures ANOVA comparing the within subject treatment effect. Means withim columns with superscripts differ significantly at $p<0.05$ between groups based on bonferroni adjustment for multiple pairwise comparisons; T_o

Table 2: Mean values±SD of total protein (g/dL) and fibrinogen (mg/dL) of equines sedated with romifidine

Parameters (groups)	T_0	T_{30}	T_{60}	T_{90}
Total protein				
GI	7.48±0.74	7.0±0.67	6.8±0.70	6.9±0.68
GII	7.48±0.72	7.04±0.58	6.84±0.57	7.04±0.43
GIII	7.08±0.71	6.72±0.68	6.56±0.69	6.72±0.83
Fibrinogen				
GI	400±141.42	280±109.54	240±89.44	300±141.42
GII	420±286.35	360±89.442	220±109.54	200±0
GIII	280±109.54	280±109.54	320±109.54	280±109.54

T_0 before romifidine administration; T_{30} 30 min; T_{60} 60 min; T_{90} 90 min after romifidine administration

changes in hematological values after administration of alpha-2 agonist has been reported, statistically relevant data for romifidine hasn't been described like this study. These changes have clinical importance and should be considered when horses that received romifidine are being evaluated.

Postulated mechanisms to explain these changes after alpha-2 agonist administration includes a change of extravascular fluid to the intravascular space in response to hipotension caused by the adrenergic alpha receptors and spleen blood sequestration due to splenic vasodilation (Kullmann *et al*., 2014).

Gasthuys *et al*. (1987), Muir and Hubbell (1991) and Wagner *et al*. (1991) reports that alpha-2 agonists derivatives (detomidine, xylazine) can produce decreased mean corpuscular volume. In this study with the use of romifidine there was no difference among the studied groups.

Total leukocytes values are minimally influenced by sedative and tranquilizer drugs. Usually, the reduction is related to cell marginalization along vascular wall. The increase is due to cortisol increase which is accompanied by the increase in neutrophiles release (Muir, 2009; Lacerda *et al*., 2010). In this study, the results were kept in the reference values and there was no significant changes in all treatments.

Although, in studies with xylazine and detomidine there are decreased total protein and fibrinogen values due to intravascular influx of fluids, proving the plasmatic volume expansion and hemodilution hypothesis (Young *et al*. 1993; Tiburcio *et al*., 2014) in this study, romifidine did not influence the values of total proteins and fibrinogen, remaining without significant changes.

Patients with anemia, hypovolemia or with different forms of hepatopathies may show important changes in tissue oxygenation or the inability to biotransform the administered drugs (Muir, 2007). In healthy equines, romifidine can be indicated for utilization, given that the results fo this study does not show important reduction of the hematologial values. Thus, new studies are suggested through longer periods of evaluation and with repeated doses with the objective of elucidating the limits of the hematological changes.

CONCLUSION

Romifidine produces alterations in hematological variables, specially in hemoglobin values using the dose of 80 mcg/kg and packed cell volume using the dose of 60 mcg/kg. Changes in total leukocytes, total proteins and fibrinogen with the three studied doses are temporary and have no clinical significance.

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