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Pharmacological Effects of Intramuscularly Administration of Xylazine or Romifidine in Calves Raised on Pasture

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Abstract: To compare the effects of two alpha-2 adrenergic receptors agonist's drugs, xylazine and romifidine intramuscularly, using 12 randomly selected Nelore calves.The animals were divided into two groups of 6 and submitted to two treatments. Treatment 1 received 0.2 mg kg^{-1} of xylazine (XYL; mean dose 1.45 mL) of body weight, and treatment 2 received 0.04 mg kg^{-1} of romifidine (ROM; mean dose 0.56 mL) of body weight. Heart and respiratory rates, arterial pressure (systolic, diastolic, and mean), rectal temperature, and ruminal movements were measured before treatments (baseline) and at 15, 30, 45, 60, 90 120 and 150 min after drug injection. Blood for glucose was collected from the jugular vein before sedation and at 30, 60, 120 and 180 min Degree of analgesia was evaluated by introducing a sterile needle subcutaneously between the ribs and interdigitally. It was evaluated latency period (time from drug administration to recumbency), analgesia period and recovery time (from first spontaneous movements to standing). Latency period was 9±3 min and 20±8 min (mean±SD) and analgesic period was 75±8 min and 90±5 min to xylazine or romifidine, respectively. Sialorrhea and reticulum-ruminal atony were similar in both treatments. Heart and respiratory rates decreased significantly ($p<0.05$) in both treatments. In calves, romifidine caused the previously published and widely known alpha-2 agonists effects including bradycardia, bradypnea, hyperglycaemia, sedation and analgesia. The use of 0.04 mg kg^{-1} of romifidine (5 times less than xylazine) produced a greater duration of analgesia with similar cardiorespiratory effects than xylazine and appeared to be a good alternative to xylazine in calves raised on pasture, although its cost was higher.

Key words: Pharmacological effects, xylazine, romifidine, calves

INTRODUCTION

Some routine procedures in calves raised under extensive pasture management conditions, such as castration, dehorning and umbilical hernia, need to be performed with animal sedation and regional or local anesthesia. General anesthesia is used in restrict circumstances because of the ruminants anatomic and physiologic characteristics. Under deep sedation, when ruminants adopt lateral recumbency, the incapacity to belch gas, during a long time can result in tympany, regurgitation and aspiration pneumonia. Passive regurgitation is seen at deeper levels of anesthesia and is characterized by a continual stream of stomach fluid draining from the mouth. The anaesthetic agent can also influence the amount of passive regurgitation that occurs. This problem does not occur when the animal is positioned in sternal recumbency.

The alpha-2 agonists drugs induce a sedative and/ or rapid tranquillisation effects, with low dose and some drugs may reduce central effects[1]. Sedation following the use of alpha-2 agonists can be reversed by alpha-2 adrenoceptor antagonists, yohimbine, tolazoline, atipamazole, and idazoxan[2-5]. Xylazine is the most common alpha-2 agonist drug used in veterinary medicine to obtain sedation or, in higher doses, restraint (recumbency and light planes of general anesthesia) in cattle or calves[6] with sedation duration for approximately one hour. Romifidine is an alpha-2 agonist drug that was used initially to promote sedation or as a preanesthetic drug in horse. Later, its analgesic utility was researched in cattle. Romifidine dose, ten times less than xylazine provided similar analgesic period[7].

The objective of this study was to compare analgesic, sedation, cardiovascular and respiratory effects, reticular motility, and glucose levels of the xylazine and romifidine intramuscularly administered in raised-pasture calves.

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MATERIALS AND METHODS

The Ethics Committee approved this prospective randomised trial; at the Federal University of Mato Grosso do Sul State. The study was carried out on 12 healthy raised-pasture calves weighing 137±21 kg (Mean±SD), aging 14 to 16 months, of a Nelore breed. All calves were fasted for 24 h and deprived of water for 8-12 h. All animals were maintained in stalls during the experimental period. Each calve was used only once. Xylazine and romifidine were injected intramuscularly. The animals were randomly assigned into one of two treatments: xylazine treatment (XYL): 6 calves weighing 110to180 kg (mean 135 kg^{-1}) received 0.2 mg kg^{-1} of body weight of 2% xylazine (mean dose 1.45 mL; Dorcipec: Vallée, Veterinary Products Ltda, Brazil) and romifidine treatment (ROM): 6 calves weighing 120 to 176 kg (mean 141 kg) received 0.04 mg kg^{-1} of body weight of 1% romifidine (mean dose 0.56 mL; Sedivet: Boehringer De Angell, Química e Farmacêutica Ltda, Brazil). The venipuncture and catheterisation of the jugular vein and the place of the insertion of a catheter was clipped and the skin was surgically scrubbed with povidone iodine. Each drug was injected over a period of 30 sec with 16-gauge catheter.

Heart Rate (HR), Respiratory Rate (RR), arterial pressures (systolic-SAP; diastolic-DAP, and mean–MAP), Rectal Temperature (RT), Reticular Motility (RM), analgesia and sedation were determined before drug administration (baseline), at 15, 30, 45, 60 min after drug administration, and at 30 min intervals thereafter. Blood samples (5 mL) for glycemia were collected from the jugular vein before administration and 30, 60, 120 and 180 min. The whole procedure usually lasted no more than 30 Sec. Degree of analgesia was evaluated by needle-prick subcutaneously between the ribs and interdigitally. The following scale was used: 1) normal response to a painful stimulus (i.e. a strong positive response to a noxious stimulus); 2) mild analgesia; 3) analgesia and 4) complete analgesia. Central effects produced by the drugs rated depth of sedation. The scale was: 1) no sedative effect; 2) reduced alertness with no other signs; 3. drowsiness and slight drop of the head, and 4. marked drowsiness and recumbency. It was evaluated the latency period (time from drug administration to recumbency), analgesia period and recovery time (from the first spontaneous movement to standing). Arterial pressure was measured through a cardiac monitor EMAI-RX. 300[A] (Transmai Equipamentos Médicos Hospitalares, São Paulo, Brazil), by using a non-invasive device with its cuff attached to the third metacarpal in order to measure the pressure in the digital palmar common artery. Heart rate was measured as for beats min, respiratory rate as for number of chest movements/min and rectal temperature with a digital thermometer. Sialorrhoea, ruminal movements, response to noise and sudden movements of personnel were also recorded.

Analysis statistics: Data were analysed using the Statistical Analysis System (SAS 6.12, SAS Institute Inc., Cary, NC, USA). A Randomised Block Design was used for each drug, with time as treatment and each of the six animals as a block. For the dependent variables HR, SAP, DAP, MAP, RR, RM, glucose and RT Analysis Of Variance differed from baseline (time 0). For analgesia and sedation dependent variables, the non-parametric Friedman test was used, followed by multiple data comparison. The Dunnett Rank test was also applied, with time 0 being considered as baseline. In each analysis, differences were considered significant if $p<0.05$.

RESULTS

Both alpha-2 adrenergic drugs used in raised-pasture calves in this experiment, xylazine and romifidine intramuscularly, produced analgesia, sedation, bradycardia, decrease in the respiratory rate, hyperglycaemia and abolition of the ruminal movements. Xylazine treatment induced hypotension.

After intramuscular injection of xylazine or romifidine, the latency period was 9±3 min (Mean±SD) and 20±8 min, respectively ($p<0.05$). Analgesic period was 75±min for xylazine and 90±5 min for romifidine (not significantly

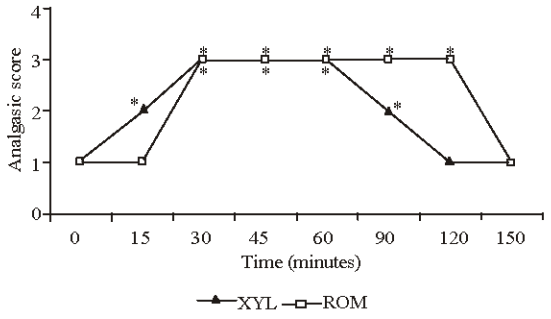

Fig. 1: Analgesia. Response to a standard noxious stimulus in the regions tested after intramuscular administration of xylazine (XYL; 0.2 mg kg^{-1}) or romifidine (ROM; 0.04 mg kg^{-1}) in six calves. Analgesic score was as follows: (1) normal response to a painful stimulus, (2) mild analgesia, (3) analgesia, and (4) complete analgesia. Each point represents the median (Md) of six animals. (*) Denotes statistical significance from baseline ($p<0.05$)

Table 1: Cardiovascular effects, respiratory rate and rectal temperature values in 6 calves after intramuscular injections of xylazine, or romifidine (Mean ± SD)

Variable	Treatments	Time (min.) Basal	15	30	45	60	90	120	150
HR	XYL	63±5	48±5*	45±6*	44±7*	44±8*	49±4*	47±5*	47±6*
	ROM	61±6	39±9*	34±6*	34±6*	36±6*	35±8*	35±7*	37±6*
SAP	XYL	147±13	134±18	135±11	130±7	133±13	140±14	138±11	139±4
	ROM	159±17	151±13	137±19	150±12	147±9	144±17	147±23	150±16
DAP	XYL	105±9	97±9	91±4*	91±5*	86±7*	95±10	96±7	99±5
	ROM	105±18	101±22	97±18	111±13	105±15	99±18	96±18	105±15
MAP	XYL	121±9	112±11*	109±3*	107±5*	109±9*	115±10*	113±8*	113±5*
	ROM	125±10	122±15	112±17	126±9	121±11	118±14	116±12	120±11
RR	XYL	22±3	22±2	18±2	18±3	17±4*	16±3*	16±3*	15±2*
	ROM	26±2	21±5*	16±3*	19±3*	15±3*	15±4*	17±3*	15±3*
RT	XYL	38.8±0.4	39.3±0.4	39.2±0.3	39.2±0.4	38.7±0.5	38.9±0.5	38.9±0.5	38.9±0.6
	ROM	39±0.5	39.3±0.4	39.3±0.4	39.2±0.5	39.3±0.5	39.3±0.6	39.1±0.7	39.2±0.7

HR: Heart Rate, beats/min.; SAP: Systolic Arterial Pressure, mm Hg; DAP: Diastolic Arterial Pressure, mm Hg; MAP: Mean Arterial Pressure, mm Hg; RR: Respiratory Tate, breaths/min.; RT: Rectal Temperature, °C; XYL: Xylazine, 0.2 mg kg^{-1}; ROM: romifidine, 0.04 mg kg^{-1}.
*Statistical significance from baseline ($p<0.05$)

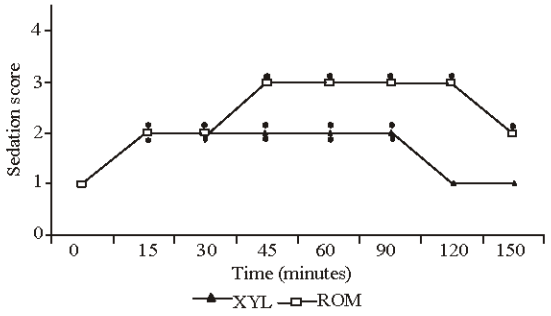

Fig. 2: Sedation. Sedation scores for six calves after intramuscular administration of xylazine (XYL; 0.2 mg kg^{-1}) or romifidine (ROM; 0.04 mg kg^{-1}). Sedative score indicates (1) no sedative effect, (2) reduced alertness with no other signs, (3) drowsiness and slight drop of the head, and (4) marked drowsiness and recumbency. Each point represents the median (Md) of six animals. (*) Denotes statistical significance from baseline ($p<0.05$)

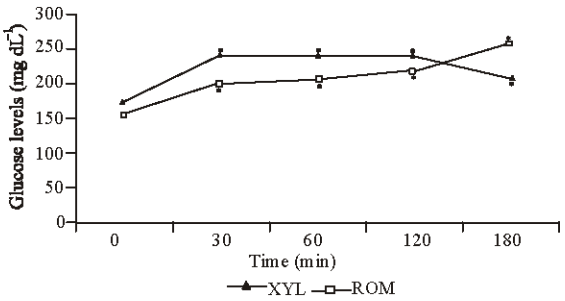

Fig. 3: Mean ± SD of glucose levels (mg/dl) in six calves after administration of xylazine (XYL; 0.2 mg kg^{-1}) or romifidine (ROM; 0.04 mg kg^{-1}). (*) Denotes statistical significance from baseline ($p<0.05$).

different; Fig. 1). Recovery time was>80 min for xylazine and>120 min for romifidine. Intramuscular xylazine and romifidine induced variable degrees of sedation, with the XYL treatment causing moderate drowsiness (score 2) and full tranquillisation in the ROM treatment (score 3; Fig. 2). Xylazine and romifidine treatments induced a significant decrease ($p<0.05$) in the heart rate that began at 15 min remaining unchanged until the end of the study. Significant decreases in DAP at 30-60 min and in MAP at 15 min up to the end were observed in the XYL treatment. The arterial pressures (SAP, DAP and MAP) did not show significant alterations after ROM when compared to the basal value. There was a significant decrease ($p<0.05$) in respiratory frequency in the XYL and ROM treatments compared to baseline. The XYL treatment from 60 to 180 min being that such decrease lasted longer in the romifidine treatment, from 15 to 180 min. The rectal temperature did not alter significantly in both treatments although the experimental period. Heart and respiratory rates, arterial pressures and rectal temperature are shown in the Table 1. Glucose levels increased significantly from 30 min ($p<0.05$) until the end of the experimental period (Fig. 3). Ruminal movements were totally abolished for 120 min in both treatments. Sialorrhea and slight tympanism occurred in all animals in both treatments.

DISCUSSION

The alpha-2 agonist drugs are frequently used in ruminants to perform immobilization, sedation, superficial anesthesia and they can assistant local or regional anaesthetic blocks. Calves have been shown to be more sensitive to alpha-2 agonist drugs than adult cattle. These substances act on both pre- and postsynaptic alpha-2 receptors, in the Central Nervous System (CNS), which decrease interneuronal transmission of norepinephrine and promote sedative and analgesic effects[3]. Both alpha-2 agonist drugs used in this study, xylazine or romifidine, produced sedation and analgesia in calves raised on pasture with different times, but not

significative. Analgesic period was shorter than the sedative one but ROM treatment produced sedative and analgesic time longer with dose 5 times less than xylazine. Similar results obtained in other study with adult cattle[7].

The alpha-2 adrenergic drugs promote sympatic nervous system depresses and consecutive increase in the parasympatic activity, reducing HR and promoting sinusal bradycardia or 1st to 2nd degree atrioventricular block[8]. This effect can increase in cattle when submitted to fasting and water restriction[9]. Bradycardia found in present experiment is in agreement with results reported by Massone *et al.*[7] who used intramuscular injection of xylazine (0.2 mg kg^{-1}) and romifidine (0.02 mg kg^{-1}). Present study, xylazine treatment produced a significant decrease in the DAP and MAP, but no significant alteration in the arterial pressures (SAP, DAP and MAP) in the romifidine treatment. A study with four alpha-2 adrenergic drugs (xylazine, romifidine, detomidine, and medetomidine) in sheep (intramuscularly), demonstrated that the romifidine and detomidine treatments increase the MAP, and xylazine and medetomidine treatments decrease it significantly[10]. Initially, alpha-2 adrenergic drugs stimulate alpha-1 and alpha-2 adrenoceptors, causing increase in arterial pressures, but later, when sympathic release decreases in the CNS, it remains below normal values[8]. In present results, MAP decreased in XYL treatment and continued low even at the 150 m, probably because we used high dose in young calves. The alpha-2 adrenergic receptors are involved in several cardiopulmonary effects. The alpha-2 agonist drugs induce respiratory rate decrease in dogs, cats, and horses, without changes significantly $PaCO_2$, pH, or PaO_2 [11]. Unlikely, it increased $PaCO_2$ in cattle or sheep[4,10-12]. Marked decrease in PaO_2 with only a slight increase in $PaCO_2$ was observed in cattle after xylazine intramuscular administration. Probably, this occurred due to recumbency or hypoventilation[13]. Xylazine-ketamine combinations were found to have minimal hemodynamic effects on calves[14], although significant respiratory effects were noted, including markedly increase respiratory rate and $PaCO_2$ concentrations and significantly decreased PaO_2 concentrations[12,15]. In present study, gasometria was not monitored but none of the calves' demonstrated signals of hypoxemia. Both treatments decreased significantly respiratory rate in all animals but it was more evident and prolonged in the romifidine treatment. Respiratory depression induced by alpha-2 agonists drugs is dose-dependent, and xylazine also produced changes in the rhythm and respiratory rate decrease[16].Theses effects are mediated by alpha-2 receptors but they do not occur with alpha-1 receptors. Idazoxan (alpha-2 antagonist drug) may abolish these effects in sheep, however this not occurs with prazocin (alpha-1 antagonist drug)[4]. Recumbency post-anaesthetics is another important factor in ruminants. This position can cause hypoxia due to decrease in pulmonary capacity, hypoventilation, and ventilation and perfusion mismatching[17]. Healthy animals tolerate these effects better than sick ones; which can present pulmonary haemorrhage, oedema, hypoxia and death[17].

In this study, ruminal atony occurred with all calves in the xylazine and romifidine treatments. Ruminal atony has begun since 30 min and continued until the end of the experimental period. In previous study, ultrasonographic evaluation of reticular motility with xylazine intramuscular in cows, demonstrated results similar time of the abolition of the ruminal movements (32-108 min)[18]. This effect is induced by alpha-2 agonist drugs in goats[1], sheep and cattle[19]. Several experimental studies of the pharmacological control of the reticulum-rumen revealed two major central inhibitory pathways: an adrenergic system, which inhibits the magnitude of reticulum-ruminal movements and involves alpha-2 receptors, and inhibitory opioid system, which modulates contractions rates[20]. The inhibition of the ruminal contractions induced by alpha-2 agonists drugs is partially antagonized for the injection of atipamazole, an alpha-2 antagonist drug[1]. These facts demonstrated a direct involvement of these drugs in the changes in the ruminal contractions.

Alpha-2 agonists drugs (xylazine or romifidine) suppress insulin release, stimulating the presynaptic alpha-2 receptors in the pancreas, inducing an increase of the glucose plasmatic concentration[8]. Intravenous injection of xylazine induced a dose-dependent hyperglycaemia and hypoinsulemia for 3-4 h[21]. A study suggests that hyperglycaemia and hypoinsulemia induced by alpha-2 agonists drugs are mediated by alpha-2 adrenergic receptors situated in β-pancreatic islet that inhibit the insulin release[21]. These facts support our results in Nelore pasture-raised calves. In this experiment, all animals in both treatments produced sialorrhea and this result was similar to results in other study with cattle[7]. Ruminants produce a large volume of saliva, which continues to flow during anesthesia. The saliva volume produced in this experiment was slight when compared to other anaesthetic agents or the recumbency, besides the sedation period.

CONCLUSIONS

We concluded that intramuscular romifidine in pasture-raised calves causes analgesic and sedative effects similar to those produced by xylazine. Both drugs induced bradycardia, decrease in the respiratory rate, hyperglycaemia and abolition of the ruminal movements. Romifidine, with dose 5 times lower than xylazine,

produced a higher analgesic period in pasture-raised calves, although its cost was greater.

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