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BEHAVIORAL AND SEDATIVE EFFECTS OF XYLAZINE AND ACEPROMAZINE ADMINISTERED INTRANASALLY IN DONKEYS

EFEITOS COMPORTAMENTAIS E SEDATIVOS DA XILAZINA E ACEPROMAZINA POR VIA INTRANASAL EM ASININOS

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ABSTRACT

The study evaluated the sedative or tranquilizing effect of acepromazine and xylazine administered intranasally, associated or not, in donkeys. Twenty-four healthy, male, young animals were distributed into three groups of eight animals each. Group 1 (G1) received acepromazine (0.1 mg/kg), group 2 (G2) received xylazine (1 mg/kg) and group 3 (G3) received xylazine (1 mg/kg) associated with acepromazine (0.1 mg/kg), intranasally. Baseline parameters (t0) were evaluated and every 10 minutes (t1-t6) after drug administration. Sneezing was observed immediately after intranasal administration in 19 animals (79%), eight in G1 (33%), six in G2 (25%) and five in G3 (21%). Head swing movements were noted in four animals (16%), three from G1 (12%) and one from G3 (4%). Two animals from G1 (8%) and three animals from G3 (12%) rubbed their heads or noses on their feet or on the restraint. Nibbling or chewing was observed in 11 animals (46%), three in G1 (12%) and four in G2 (17%) and G3 (17%). Twelve animals (50%) raised the upper lip, four from G1 (17%), three from G2 (12%) and five from G3 (21%). There was statistical difference in respiratory rate between groups. The animals showed no signs of sedation or tranquilization in any of the groups. The administration of acepromazine associated or not with xylazine intranasally was not effective under the conditions presented by the study.

Keywords: horses, phenothiazines, hypnotics and sedatives, preanesthetic medication

INTRODUCTION

Donkeys (*Equus asinus*), popularly known in Brazil as *jumentos*, are rustic animals that were domesticated more than 5000 years ago (KIMURA et al., 2010), and present great social, ecological, cultural, and economic importance due to its use (OUDMAN, 2004). It is a neglected species due to its particularities, whether in the morphophysiological and behavioral or pharmacological perspective (LIZARRAGA et al., 2004). This situation on several occasions invalidates its comparison in anesthetic practice since these animals biotransform different drugs quickly with doses and intervals similar to those used in other species (BURDEN and THIEMANN, 2015).

In view of these particularities, some studies have been carried out to verify the effects of preanesthetic medications on donkeys (NADDAF et al., 2015; LIZARRAGA et al., 2017), with intravenous and intramuscular application routes that have reduced latency time, increased bioavailability and fast absorption (PINHEIRO et al., 2016; MASSONE, 2017).

Since the routes of application can cause pain, discomfort and infection, alternatives have been sought for drug administration in different animal species. The intranasal approach is widely used in Human Medicine for sedation of children (GRASSIN-DELYLE et al., 2012) and in Veterinary Medicine in sedation of birds (SCHAFFER et al., 2017). It is interesting because of the effectiveness and short latency that is enhanced by the rich vascularization of the region, which allows high permeability.

Due to the lack of studies related to anesthetic protocols in donkeys, the present study aimed to evaluate the sedative or tranquilizing effect of the intranasal administration of acepromazine and xylazine, associated or not, in donkeys.

MATERIAL AND METHODS

The research project was submitted to the Ethics Committee on the Use of Animals at the Federal University of Western Bahia (UFOB) and approved under protocol No. 007/2018. Twenty-four healthy, male and young animals that were not subjected to water or food fasting were used. The animals were clinically evaluated to confirm their health prior to the experiment. Animals in conditions of mistreatment or with abnormalities were not included in the study.

For drug administration, a device was devised, and a maximum volume of 3 mL was defined to be infused in both nostrils simultaneously, to allow maximum absorption without the liquid draining (FIGURE 1). Body weight was estimated through thoracic perimeter circumference with a tape measure for equines to determine the volume to be infused intranasally.

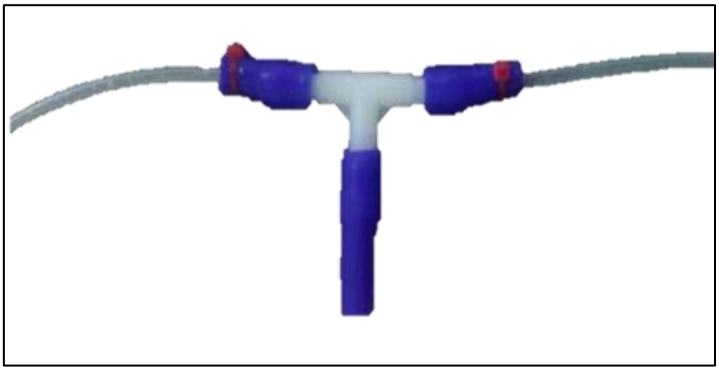

Figure 1. Device for the application of drugs intranasally. Source: Personal Archive

Prior to the study, 3 ml of saline solution was administered intranasally to eight animals to identify possible behavioral changes arising from the contact of the liquid with the nasal cavity (FIGURE 2).

Figure 2. Intranasal drug administration in donkeys. Source: Personal Archive

Of the 24 animals that received drugs intranasally, eight received acepromazine (0.1 mg/kg) (G1); eight received xylazine (1 mg/kg) (G2); and eight received xylazine (1 mg/kg) associated with acepromazine (0.1 mg/kg) (G3). The animal's head was kept elevated for one minute after administration of the drug to allow the liquid to remain in contact with the nasal

mucosa. The latency time was recorded between the time of intranasal administration until the presentation of signs of sedation or tranquilization.

The animals were subjected to physical restraint for baseline evaluation (t0) and later received the drug intranasally. Every 10 minutes after application, heart rate, respiratory rate, pulse, color of mucosa and capillary filling time were recorded. The total evaluation time was 60 minutes (t0-t6). Changes were assessed on cardiopulmonary auscultation, body temperature, presence of ataxia, decubitus, eyelid ptosis, labial ptosis, alertness, neck relaxation with lowering of the head, sneezing, nibbling, swallowing, blowing or any adverse behavioral signs other than usual for the species.

For non-parametric data (behavioral changes) descriptive statistical analysis was used. Parametric data (heart rate, respiratory rate and body temperature) were submitted to the Shapiro-Wilk normality test and analysis of variance followed by design with the Tukey test for comparison between the means ($p<0.05$).

RESULTS AND DISCUSSION

The average weight of the animals was 180 ± 23.6 kg. On clinical examination there was an absence of lymphatic reactivity, capillary filling time equal to or less than 1.5 seconds, normal colored mucosa, normohydrate, heart and respiratory rate within normal values, which for the species varies between 31 to 53 beats per minute and 13 to 31 movements per minute (BURDEN and THIEMANN, 2015) respectively, strong and synchronous pulse.

After application of saline solution in eight animals, six presented sneeze or blew (75%), a movement of the head (12.5%) and three raised the upper lip (37.5%).

In the 24 animals evaluated, a few minutes after intranasal drug administration, the presence of sneeze or blew was observed in 19 animals (79%), eight of the (G1) (33%), six of the (G2) (25%) and five of the (G3) (21%). Head swing movements were noted in four animals (16%), three belonging to G1 (12%) and one to G3 (4%). It was also observed that two animals from G1 (8%) and three animals from G3 (12%), rubbed their heads or nostrils on their feet or at the containment site, as if they scratched the region, which may be related to the irritation caused by the contact of the drug or its vehicles with the nasal mucosa once in intravenous or intramuscular application using acepromazine (LIZARRAGA et al., 2017), xylazine or the

associated drugs (CASTILLO et al., 2018), changes such as sneezing or blew, head shake or rubbing the head or nostrils were not observed.

In 11 animals (46%), there was a reflex of nibbling or chewing, three from G1 (12%) and four (17%) in each of the other groups. Twelve animals (50%) showed elevation of the upper lip (similar to Flehmen reflex), four from G1 (17%), three from G2 (12%) and five from G3 (21%). The Flehmen reflex is described with the purpose of differentiating odors where the elevation of the upper lip provides the closing of the nostrils and the raised head promotes a pressure difference capable of directing substances to the vomeronasal organ, which results in behavioral changes generally related to the identification of estrus (SILVA, 2011).

During the assessment period (every 10 minutes) (t1-t6) the animals from the three groups showed slight changes in heart and respiratory rates, and in temperature (TABLE 1). Capillary filling time, mucosal color and pulse did not change. No ataxia, decubitus, eyelid and labial ptosis, neck relaxation with lowering of the head were identified.

Table 1. Mean values ± standard deviation of heart rate in beats per minute, respiratory rate in respiratory movements per minute and body temperature of donkeys submitted to acepromazine administration (0.1 mg/kg) and xylazine (1 mg/kg), associated or not, intranasally, being monitored for 60 minutes. Mean values with different capital letters in the same column are significantly different ($p < 0.05$) in the Tukey test.

PHYSIOLOGICAL VARIABLES	EXPERIMENTAL GROUPS	EVALUATION TIME (MEAN ± STANDARD DEVIATION)						
		T0 (X ± S)	T1 (X ± S)	T2 (X ± S)	T3 (X ± S)	T4 (X ± S)	T5 (X ± S)	T6 (X ± S)
HEART RATE	G1	50.7 ± 6.27	50.00 ± 6.68	50.25 ± 6.47	50.50 ± 5.66	50.37 ± 6.78	49.87 ± 6.01	50.50 ± 6.12
	G2	47.75 ± 13.80	45.75 ± 14.94	46.25 ± 14.80	47.25 ± 13.00	44.87 ± 15.00	46.00 ± 13.21	46.50 ± 12.36
	G3	46.12 ± 4.26	45.50 ± 5.34	46.62 ± 3.58	46.25 ± 4.20	47.00 ± 3.96	46.37 ± 3.66	45.75 ± 4.23
RESPIRATORY RATE	G1	39.25 ± 2.37 A	41.75 ± 3.77 A	41.37 ± 2.39 A	41.50 ± 0.92 A	41.62 ± 1.06 A	41.37 ± 1.19 A	41.25 ± 1.03 A
	G2	31.25 ± 6.92 A	30.50 ± 6.12 B	29.50 ± 6.57 B	30.00 ± 6.21 B	28.75 ± 5.52 B	31.12 ± 5.72 B	31.50 ± 4.63 B
	G3	53.25 ± 10.36 B	48.87 ± 6.92 A	48.00 ± 3.16 C	49.75 ± 1.98 C	50.62 ± 3.02 C	52.12 ± 3.31 C	51.00 ± 2.07 C
TEMPERATURE (ºC)	G1	37.45 ± 0.49	37.46 ± 0.38	37.51 ± 0.37	37.51 ± 0.34	37.56 ± 0.38	37.59 ± 0.32	37.55 ± 0.36
	G2	37.25 ± 0.69	37.19 ± 0.51	37.31 ± 0.53	37.70 ± 0.30	37.74 ± 0.31	37.72 ± 0.20	37.89 ± 0.22
	G3	37.40 ± 0.42	37.41 ± 0.39	37.50 ± 0.40	37.55 ± 0.41	37.54 ± 0.23	37.66 ± 0.31	37.85 ± 0.32

Only the respiratory rate showed a statistical difference between groups. This finding is correlated with the increase in environmental temperature during the experiment. It should be noted that the variations found in the physiological parameters of the animals in the present study are within the normal range for species and although it presents statistical significance between treatments, clinically, the animals did not show any sign of sedation or tranquilization regardless of the group.

The absence of sedation or tranquilization may have occurred due to several possibilities, such as the dose is still low for the species, the route is not suitable for drug administration in the form that are commercially available, or due to underestimation of weight, because there is no standard tape for donkeys. The substitution of xylazine for another alpha 2 adrenergic agonists may enable sedation or tranquilization of these animals, since in a study conducted with the use of dexmedetomidine intranasally in brachycephalic dogs, signs of sedation and sternal decubitus were evidenced (CASTRO et al., 2019).

The use of acepromazine causes a temporary increase in heart rate, probably related to reduction of systemic vascular resistance and blood pressure, which consequently establishes a compensatory tachycardia (ARAÚJO et al., 2014). On the other hand, xylazine favors bradycardia due to response of the baroreceptors to increase in transient blood pressure, as described in other studies, since such drug will act on the alpha 1 and 2 receptors (RANKIN, 2015).

In a study that evaluated the sedative or tranquilizing effects of acepromazine associated or not with xylazine, intravenously in donkeys, in a lower dose than the present study, it was found that acepromazine (0.05 mg/kg) did not promote sedative or tranquilizer effect. In addition, the association of acepromazine with xylazine (0.5 mg/kg) did not provide an ideal state for performing short-term procedures (CASTILLO et al., 2018). It is suggested the association of xylazine in low dose (0.5 mg/kg) with drugs of the opioid group, intravenously, since there is interaction of synergisms between the groups which potentiates the effects and these associated drugs should be used when it is necessary to increase the duration and depth of sedation since the animal remains standing and the procedure to be performed is minimally invasive (LIZARRAGA and CASTILLO-ALCALA, 2015).

Acepromazine promotes muscle relaxation and one of the characteristic signs of its effectiveness is penile prolapse, as observed by Araújo et al. (2014) when administering this drug (0.1 mg/kg), in donkeys, intravenously, and the latency time is reduced when associating

diazepam, in the same dose and route, showing synergisms between the drugs used. However, in the present study none of the animals submitted to the treatment of acepromazine alone or associated with xylazine showed a satisfactory result since no sedation or tranquilization was observed.

When evaluating the efficacy of the intranasal route in dogs with the use of dexmedetomidine (0.02 mg/kg), deep sedation was observed with slight bradycardia when compared to intramuscular administration, proving to be an adequate route for sedation of dogs (MICIELI et al., 2017). In canaries, to assess the quality of intranasal sedation, midazolam and xylazine were used, and these drugs produced adequate sedation in canaries. However, unlike midazolam, xylazine did not allow the animal to be supine (VESAL and ZARE, 2006). Midazolam alone or associated with butorphanol also proved to be satisfactory in the sedation of birds (SILVA et al., 2017; DOSS et al., 2018). Thus, it is worth mentioning that anatomical and physiological differences in vascularization and innervation of the nasal region of different species can alter the diffusion of drugs (GRAFF and POLLACK, 2005).

CONCLUSION

Administration of acepromazine associated or not with xylazine intranasally was not effective for sedation or tranquilization under the conditions presented by the study. However, further studies are needed to determine whether factors related to the application device, application site, total infused volume, concentration and drug vehicle were determinant for the absence of pharmacological effects or whether the route is ineffective in donkeys.

Ethical approval

The study was submitted to and approved by the Ethics Committee on the Use of Animals at the Federal University of Western Bahia (UFOB) under protocol No. 007/2018.

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