

## Comparison of the effects of romifidine and an emulsion of amitraz on sedation and spontaneous locomotor activity of horses

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### Abstract

Amitraz (AM) and romifidine (RMF), two alpha-2 adrenoceptor agonists, produce sedative effect and decrease spontaneous locomotor activity (SLA) of horses. The behavioral effects and sedation after intravenous injection of RMF (0.06mg/kg) or AM 0.1mg/kg (AM 0.1) or AM 0.4mg/kg (AM 0.4) were compared in horses. RMF caused head ptosis (HP) until 45 min. The lower AM dose induced HP from 45 to 60 minutes and from 120 to 150 minutes, and the higher dose induced HP until 180 minutes. Data concerning changes in SLA were not conclusive. RMF or AM 0.4 caused a greater sedation than AM 0.1 until 20 min. After 20 minutes, the sedation caused by AM 0.4 was greater than that of RMF or AM 0.1. Romifidine caused consistent sedation until 45 minutes. The amitraz emulsion produced a dose-dependent sedation until 180 minutes. Comparing to romifidine, the emulsion of amitraz induced a more substantial sedation. At dosages and dilution applied, amitraz is an effective sedative for horses.

### Key words:

Amitraz.  
Romifidine.  
Sedation.  
Spontaneous  
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Horses.

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### Introduction

Restraining horses in small rooms stimulates exploratory behaviors that can be defined as spontaneous locomotor activity.<sup>1</sup> Tobin et al.<sup>2</sup> developed a study method on behavioral stalls in order to measure the effects of stimulant or sedative substances on the spontaneous locomotor activity of horses, which was improved by Kamerling et al.<sup>3</sup>

The sedative effects of alpha-2 adrenoceptor agonists on horses include bradypnea, head ptosis, dropping of the upper eyelids and of the lower lip, ataxia and also penis exposition. Frequently, hypertension occurs because of increased peripheral vascular resistance and subsequently bradycardia, hypotension and decrease of cardiac output<sup>4,5</sup> are observed. Drugs from this group have affinity and specificity for subtypes of alpha-2 receptors that grant them diverse extent of effects, intensity of sedation and analgesia.<sup>6</sup>

Romifidine, as xylazine and

detomidine, is an alpha-2 adrenoceptor agonist that produces cardiovascular changes<sup>7</sup>, including bradycardia, second-degree atrioventricular block and hypertension followed by hypotension<sup>8</sup>. In horses, romifidine at doses varying from 0.4 to 1 mg/kg induces dose-dependent sedation.<sup>9,10,11</sup>

Amitraz showed central effects of alpha-2 adrenoceptor agonist, inducing similar ataxia, intestinal stasis, behavioral, cardiovascular, muscular and diuretic effects.<sup>12,13,14,15,16,17</sup> These effects could provide an indication for the use of amitraz for sedation practices in veterinary medicine, and this might be particularly appealing in horses because of its low price and its potential analgesic and muscle relaxing effects.<sup>18</sup>

Considering the well known effects of romifidine on horses, mediated by its highly specific action on alpha-2 adrenoceptors, this behavioral study proposes to compare its sedative effects with those induced by an emulsion of amitraz, in order to determine the possibility of using this drug as a sedative for horses.

## Material and Method

Six adult, male horses, between three and ten years of age were used, all in good clinical conditions and not exposed to amitraz for at least six months. During the adaptation period, horses were fed a commercial diet twice a day, water and grass hay *ad libitum* and conditioned to the behavioral stalls. Each horse was submitted to all treatments in time intervals of at least 15 days. Thus each animal was considered as a control of itself, which configures a repeated measures study.

In order to quantify the spontaneous locomotor activity (SLA), were used two 4x4 meters behavioral stalls with a smoked-glass window each, directed towards the observing room, and avoiding interaction of the horses with the outside environment. Each behavioral stall was equipped with four pairs of photoelectric sensors (Banner Engineering Corp. - Minneapolis, MN-USA) that emitted infrared beams composing nine virtual squares. An electric pulse was created each time one beam was interrupted. The number of pulses were counted at five minute intervals and recorded in a data logger (Data Logger, Campbell Scientific, Inv. Logan, UT-USA) connected to a computer.<sup>19</sup> SLA was calculated from data registered in the computer as the mean of interruptions every 10 minutes.

Head ptosis (HP) was used to evaluate the sedation intensity by quantifying the distance between the lower lip and the floor measured in centimeters, confronting the lower lip with the metric length unit painted on the walls of the stalls.<sup>20</sup> In the statistical analysis these data were converted to percentage relating the observed value at the respective moment and the mean basal value (measured before the drug administration).

At each observation moment, the position of the horses in the stall was checked in relation to the virtual squares composed by the infrared beams referred above. This could indicate if the horses were searching for some kind of outside contact, as well as the interference of the manipulation in their

behavior.

In the afternoon preceding the experiments, horses were placed inside the behavioral stalls (one per stall) receiving grass hay and water *ad libitum*. On the experiment day, the hay was removed from the stalls at 6:30 am and at 7:00 am the sensors were turned on and the basal values for SLA were measured for one hour. During this period, HP was measured at fifteen minute intervals.

For drug injection, the horses were kept inside the stalls and handled in the softest way, in order to minimize behavioral interferences. At 8:00 am, romifidine (Sedivet – Boehringer De Angeli Química e Farmacêutica Ltda. - Itapecerica da Serra, SP-Brazil) (0.06mg/kg) or amitraz (Amitraz - Laboratório Sintesul SA. - Pelotas, RS-Brazil) emulsion (0.1mg/kg or 0.4mg/kg) was injected in the external jugular vein. Amitraz emulsion was prepared as described by Farias<sup>21</sup> and the applied doses were based on previous studies with this emulsion on horses<sup>22,23</sup>.

Initially, HP was evaluated at ten minute intervals (T10, T20 e T30), followed by fifteen minute intervals (T45 e T60) for the first hour and then at thirty minute intervals (T90, T120, T150 e T180) until the third observation hour. The same schedule was applied to define the horse's location inside the stall. The SLA was measured for 6 hours (T10 a T360) using five minute intervals. After the experimental period the horses were removed from the stalls and taken back to the pastures.

The HP and SLA data were analyzed using the non-parametric Wilcoxon's test for repeated measures in order to compare each observation moment to the basal values. Comparisons among treatments were carried out using a non-parametric Friedman's test for repeated measures, followed by the Student-Newman-Keuls' test (SNK). The results were considered significantly different when  $P < 0.05$ . Data concerning the location of the horses were submitted to subjective analysis for frequencies of occurrence.

## Results

Tables 1 and 2 show data related to HP and SLA, and the comparisons between the observation moments after drug administration and basal values for each treatment. Figure 1 show the comparison among treatments for HP. Figure 2 show the comparison for SLA between observation moments among treatments after drug administration and basal values for each treatment.

Romifidine induced intense HP ( $P < 0.05$ ) over 45 minutes; amitraz induced HP ( $P < 0.05$ ) over 180 minutes for the higher dose. The lower dose of amitraz produced HP from 45 to 60 and from 120 to 150 minutes after its administration. During 20

minutes HP induced by romifidine or amitraz 0.4mg/kg were greater than amitraz 0.1mg/kg ( $P < 0.05$ ). After 20 minutes, the sedation caused by amitraz at the dose of 0.4mg/kg was greater than that of romifidine or amitraz 0.1mg/Kg ( $P < 0.05$ ).

## Discussion

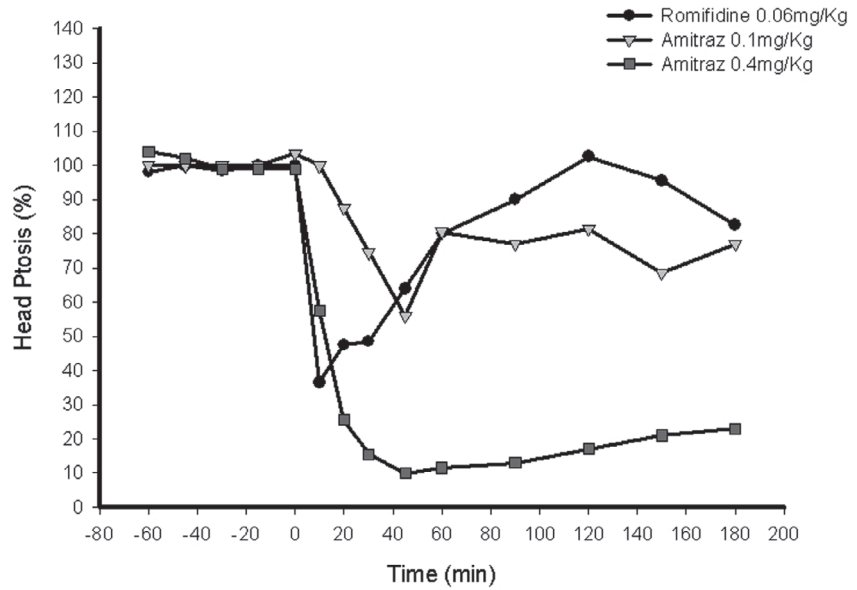
Despite several authors' statements that amitraz is an alpha-2 agonist drug<sup>12,13,14,17,18</sup>, there are no pharmacological studies that establish its specificity to this receptor. Thus, a clinical comparison between amitraz and romifidine, which is a potent alpha-2 agonist<sup>24,25</sup>, is proposed as an efficient method to establish possibilities of using amitraz as an intense and long lasting

**Table 1** - Head ptosis (percentage from basal values) observed in horses treated with intravenous injection of romifidine (0.06mg/kg) or amitraz (0.1 or 0.4mg/kg). Basal values were considered 100%. T10 to T180 indicate checking at respective moments (in minutes) after drug administration. HP: head ptosis. RMF: romifidine. AM 0.1: amitraz 0.1mg/kg. AM 0.4: amitraz 0.4mg/kg. Data presented as median, minimum and maximum values. \*: Significant differences when compared to basal values, Wilcoxon's test ( $P < 0,05$ ). Jaboticabal-SP, 2006

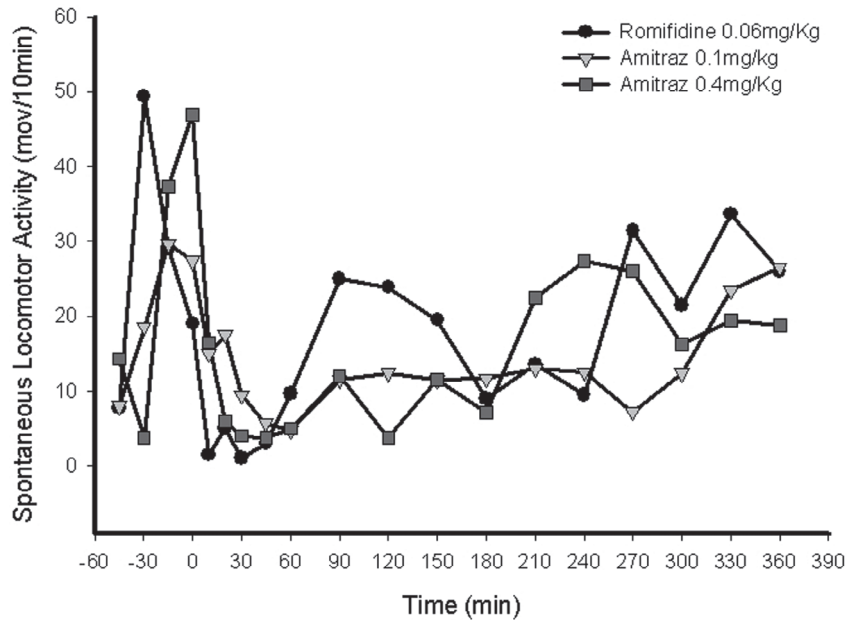
DRUGS	HP								
	T10	T20	T30	T45	T60	T90	T120	T150	T180
RMF	36.5* (25-97)	47.5* (10-75)	48.5* (38-61)	64* (58-75)	80 (35-100)	90 (67-105)	102.5 (67-138)	95.5 (77-116)	82.5 (48-116)
AM 0.1	100 (71-107)	87.5 (67-100)	74.5 (39-100)	56* (48-90)	80.5* (39-95)	77 (53-107)	81.5* (53-93)	68.5* (46-89)	77 (48-100)
AM 0.4	57.5* (25-73)	25.5* (13-31)	15.5* (6-25)	10* (6-13)	11.5* (6-21)	13* (5-31)	17* (5-37)	21* (5-50)	23* (9-42)

**Table 2** - Spontaneous locomotor activity observed in horses treated with intravenous injection of romifidine (0.06mg/kg) or amitraz (0.1 or 0.4mg/kg), presented as movements every 10 minutes, at each observation moment. BASAL indicates checking before drug administration. T10 to T360 indicate checking at respective moments (in minutes) after drug administration. SLA: spontaneous locomotor activity. RMF: romifidine. AM 0.1: amitraz 0.1mg/kg. AM 0.4: amitraz 0.4mg/kg. Data presented as median, minimum (min) and maximum (max) values. \*: Significant differences when compared to basal values, Wilcoxon's test ( $P < 0,05$ ). Jaboticabal-SP, 2006

DRUGS	SLA															
	BASAL	T10	T20	T30	T45	T60	T90	T120	T150	T180	T210	T240	T270	T300	T330	T360
RMF	33.1	1.5	5	1	3	9.7	25	23.9	19.5	9*	13.5	9.5*	31.4	21.5	33.7	26
(min)	12.2	0	0	0	0	0	2.3	7	3	0	0	0.7	1.3	2	13	11
(max)	65.7	33	20	30	17.3	27.3	54.3	47.3	41.3	46	31	37.7	97	52.7	53.3	54.3
AM 0.1	23	15	17.5	9.5	5.7*	4.7*	11.5	12.4	11.5	11.7	13	12.5	7.2	12.4	23.5	26.5
(min)	8.3	2	0	0	0.7	0	0	0	5.3	1	0	0	3.7	1.3	1	3.3
(max)	55.8	223	106	22	16.7	12.7	17.3	30.7	42.0	51.7	31.7	92.7	35.3	30.7	64.7	57.7
AM 0.4	22.4	16.5	6	4	3.7	5	12	3.8	11.5	7.2	22.5	27.4	26	16.2	19.5	18.7
(min)	2.2	0	0	1	0.7	0.7	4	0	0.3	0	1	1.3	5.7	1.3	2.3	5.3
(max)	197	81	26	11	16.7	58.7	26.3	24	63.3	30	87	72.7	97.7	55.3	41.3	50.3



**Figure 1** - Head ptosis observed in horses treated with intravenous injection of romifidine (0.06mg/kg) or amitraz (0.1 or 0.4mg/kg), presented as a percentage relation between the observed value of the distance between the lower lip and the floor at the respective moment and the basal value. The arrow indicates the moment of drug administration. Data presented as median. \*: Significant differences when comparing amitraz 0.1mg/kg and amitraz 0.4mg/kg (SNK's test;  $P < 0.05$ ). #: Significant differences when comparing amitraz 0.4mg/kg and romifidine (SNK's test;  $P < 0.05$ ). D: Significant differences when comparing amitraz 0.1mg/kg and romifidine (SNK's test;  $P < 0.05$ ). Jaboticabal-SP, 2006



**Figure 2** - Spontaneous locomotor activity observed in horses treated with intravenous injection of romifidine (0.06mg/kg) or amitraz (0.1 or 0.4mg/kg), presented as movements in 10 minutes, between each observation moment. The arrow indicates the moment of drug administration. There were no differences among treatments. Data presented as median. \*: Significant differences when comparing to basal values, for romifidine 0.06mg/Kg (Wilcoxon's test;  $P < 0.05$ ). #: Significant differences when comparing to basal values, for amitraz 0.1mg/Kg (Wilcoxon's test;  $P < 0.05$ ). Jaboticabal-SP, 2006

sedative for horses.

The comparison between the amitraz 0.1 and 0.4mg/kg shows stronger effects at the higher dose. These dosages of amitraz, prepared in the same emulsion, were previously used<sup>22</sup> and showed similar dose-dependent effects in horses.

Dimetilformamide<sup>26, 27</sup> and DMSO<sup>28, 29, 30</sup> are organic excipients used in amitraz suspensions because of the low hydrosolubility of amitraz, which also occurs with other apolar substances. Dimetilformamide or DMSO excipients increase the plasmatic disposal of amitraz and probably also its plasma availability<sup>21</sup>.

It is believed that the lipid excipient used in this research creates an emulsion that, when in contact with blood, decreases the plasmatic disposal of amitraz thereupon injection. A first passage through the liver would be needed in order to increase the availability of the drug. Thus the amitraz levels available to interact with the adrenoceptors in the central nervous system would be smaller in the first half hour, which explains its relatively long latency of sedative effects. This could also explain the lower sedative effect observed when using the lipid excipient in the same dose described with other excipients, as the intravenous injections of amitraz 0.1mg/kg diluted in dimetilformamide<sup>18</sup>, for example.

Although romifidine presented sedation equivalent to that of amitraz 0.4mg/kg during the first 20 minutes, a substantial and long lasting sedative effect of amitraz with this dosage was observed, which remained until the end of the observation time (180 minutes). This suggests that the intensity of amitraz sedation is dose-dependent and that the lipid excipient was determinant for the long lasting effect. These results and the fact that the sedative effect was more intense with amitraz at 0.4mg/kg than at 0.1mg/kg confirm what was reported by Costa et al.<sup>31</sup>, who described the duration and intensity of the effects of amitraz as dose-dependent.

Statistics shows that romifidine

reduced SLA ( $P < 0.05$ ) at 180 and 240 minutes, and amitraz 0.1mg/Kg had the same effect from 45 to 60 minutes after its administration, while amitraz 0.4mg/Kg did not reduce SLA. These results are not consistent with the observed for HP.

The large range observed in basal values for all treatments may have covered real effects, since the medians themselves showed other tendencies. Besides, it was already described that romifidine indeed induced ataxia in horses<sup>10, 32</sup>, what would result in reduced SLA. Harkins et al.<sup>26</sup> observed a reduction of SLA of horses for 120 minutes after intravenous injection of amitraz. However, it must be also considered that these authors used dimetilformamide as excipient for amitraz and that it has distinct pharmacological properties from the lipid emulsion used in the present study. Therefore, it seems that the sample must be increased for this kind of evaluation to be reliable in this study.

Before the drugs administration, the horses were mainly placed in front of the observation window of the stall; from 10 to 180 minutes after the administration of drugs, they were mainly placed in front of the door. This observation shows that, although relatively isolated from the outside environment, the horses kept on searching for some kind of contact with the exterior of the stall even during the sedation periods.

## Conclusion

The amitraz emulsion produced a dose-dependent sedation for 180 minutes. Romifidine at this dosage caused a substantial sedation for 45 minutes. Comparing to romifidine, the emulsion of amitraz induced a more substantial sedation. At dosages and dilution applied, amitraz is an effective sedative for horses.

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## Comparação dos efeitos da romifidina e de uma emulsão de amitraz na sedação e na atividade locomotora espontânea de eqüinos

### Resumo

Os agonistas de receptores adrenérgicos do tipo alfa-2 amitraz (AM) e romifidina (RMF) produzem efeito sedativo e reduzem a atividade locomotora espontânea (ALE) em eqüinos. Compararam-se os efeitos sedativos e comportamentais da injeção intravenosa de RMF (0,06mg/kg) ou AM 0,1mg/kg (AM 0,1) ou 0,4mg/kg (AM 0,4) em cavalos. RMF provocou ptose de cabeça (PC) por 45 minutos. O amitraz provocou PC entre 45 e 60 e entre 120 e 150 minutos com a dose menor, e por 180 minutos com a dose maior. Os dados relacionados à ALE não foram conclusivos. RMF ou AM 0,4 causaram sedação mais intensa que AM 0,1 até 20 minutos. Após 20 minutos, a sedação provocada pelo AM 0,4 foi mais intensa que para a RMF ou o AM 0,1. A romifidina causou sedação por 45 minutos. A emulsão de amitraz provocou sedação dose-dependente por 180 minutos. Em relação à romifidina, o amitraz produziu uma sedação mais consistente. Nas doses e na diluição aplicada, o amitraz é eficaz como sedativo para cavalos.

### Palavras-chaves:

Amitraz.  
Romifidina.  
Sedação.  
Atividade Locomotora Espontânea.  
Eqüinos.

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