• Arq. Bras. Med. Vet. Zootec. 52 (1) • Feb 2000 •

https://doi.org/10.1590/S0102-09352000000100008

Effect of amitraz and xylazine on some physiological variables of horses

Efeitos do amitraz e da xilazina sobre algumas características fisiológicas de cavalos

Abstracts

The effect of the intravenous injection of amitraz (0.1mg/kg) to horses on cardiac activity, respiratory rate, intestinal motor activity, rectal temperature, sweating and masticating was evaluated and compared to the effect of intravenous administration of xylazine (1mg/kg, iv) on heart rate, respiratory rate and intestinal activity. Amitraz caused a significant decrease in heart activity, respiratory rate and intestinal movements, but these effects were not as pronounced as those caused by xylazine. Amitraz also caused a significant relaxation of the rectal smooth muscle, and an apparent increase in sweating and in the frequency of horses found masticating hay. Rectal temperature was not influenced by amitraz. The results indicated that amitraz, at the dose used, did not cause severe side effects in horses.

Horse; Amitraz; xylazine; cardiac activity; respiratory activity; intestinal activity

Avaliaram-semos os efeitos das injeções intravenosas (iv) de amitraz (0,1mg/kg) e xilazina (1mg/kg), em cavalos, sobre a atividade cardíaca, freqüência respiratória, atividade motora intestinal, temperatura retal, sudorese e freqüência de apreensão de alimentos. O amitraz causouuma diminuição significativa da atividade cardíaca, da freqüência respiratória e da movimentação intestinal, mas esses efeitos não foram tão pronunciados quanto os causados pela xilazina. O amitraz causou, também, um relaxamento significativo da musculatura lisa retal, e um aparente aumento da sudorese e da freqüência de cavalos flagrados mastigando feno. A temperatura retal não foi influenciada pelo amitraz. Os resultados

indicam que o amitraz, na dose utilizada, não causou efeitos colaterais severos em cavalos.

Cavalo; amitraz; xilazina; atividade cardíaca; atividade respiratória; atividade intestinal

Effect of amitraz and xylazine on some physiological variables of horses

(Efeitos do amitraz e da xilazina sobre algumas características fisiológicas de cavalos)

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Recebido para publicação, após modificação, em 29 de julho de 1999.

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ABSTRACT

The effect of the intravenous injection of amitraz (0.1mg/kg) to horses on cardiac activity, respiratory rate, intestinal motor activity, rectal temperature, sweating and masticating was evaluated and compared to the effect of intravenous administration of xylazine (1mg/kg, iv) on heart rate, respiratory rate and intestinal activity.

Amitraz caused a significant decrease in heart activity, respiratory rate and intestinal movements, but these effects were not as pronounced as those caused by xylazine. Amitraz also caused a significant relaxation of the rectal smooth muscle, and an apparent increase in sweating and in the frequency of horses found masticating hay. Rectal temperature was not influenced by amitraz. The results indicated that amitraz, at the dose used, did not cause severe side effects in horses.

Keywords: Horse, Amitraz, xylazine, cardiac activity, respiratory activity, intestinal activity

RESUMO

Avaliaram-semos os efeitos das injeções intravenosas (iv) de amitraz (0,1mg/kg) e xilazina (1mg/kg), em cavalos, sobre a atividade cardíaca, freqüência respiratória, atividade motora intestinal, temperatura retal, sudorese e freqüência de apreensão de alimentos. O amitraz causouuma diminuição significativa da atividade cardíaca, da freqüência respiratória e da movimentação intestinal, mas esses efeitos não foram tão pronunciados quanto os causados pela xilazina. O amitraz causou, também, um relaxamento significativo da musculatura lisa retal, e um aparente aumento da sudorese e da freqüência de cavalos flagrados mastigando feno. A temperatura retal não foi influenciada pelo amitraz. Os resultados indicam que o amitraz, na dose utilizada, não causou efeitos colaterais severos em cavalos.

Palavras-chave: Cavalo, amitraz, xilazina, atividade cardíaca, atividade respiratória, atividade intestinal

INTRODUCTION

Amitraz [N-methyl-N'-2,4-xylyl-N-(N-2,4-xylylformimidyl) formamide] (AMZ) is an acaricidal formamidine widely used to control ectoparasites in veterinary medicine. One of the first studies reporting the use of AMZ in domestic animals was published by Harrison et al. (1973), showing that this drug is a good alternative for the control of ectoparasites in cattle, especially for the treatment of tick strains resistant to organochlorine and organophosphorus pesticides.

The use of AMZ in horses appears contraindicated (Smith, 1994) because of the common occurrence of severe colic when the animals are sprayed with this acaricide. Nevertheless, AMZ continues to be extensively applied to horses in tropical countries, Brazil among them, because it is a highly effective and economically interesting tick killer. Thus, the Veterinary Hospital of the Faculty of Agrarian and Veterinary Sciences, Jaboticabal Campus, commonly treats horses intoxicated with this drug.

In addition of having an excellent acaricidal and insecticidal activity, AMZ has a highly complex pharmacological activity in mammals, that can be related to the ability of formamidines to inhibit monoaminooxidase (Aziz & Knowles, 1973), to block prostaglandin E_2 synthesis (Yim et al.,1978), to have a local anesthetic effect (Chinn et al., 1977) and, most important, to stimulate a_2-adrenergic receptors (Costa & Murphy, 1987).

In 1979, the first report of AMZ toxicity in horses was published (Roberts & Seawright, 1979). In a later work the same authors (Roberts & Seawright, 1983) induced colic in horses and ponies by administering AMZ at the dose of 1mg/kg (iv). A rapid arrest of abdominal sounds, stasis and extensive impaction and tympanism were observed in the entire large bowel. According to these investigators, the action of AMZ on horses is not clear, possibly affecting both fluid transport and the action of neuromodulators that coordinate the myoelectric activity of pacemakers supposedly existing in the large bowel.

Auer et al. (1984) reported a case of AMZ intoxication in horses in which 3 of 4 animals sprayed with a 0.025% aqueous solution (mass/volume) presented typical signs of central nervous system (CNS) depression (tranquillization, ataxia, and lack of muscle coordination) and impaction colic that lasted up to 6 days. The authors suggested as a possible aggravating factor was the fact that a certain amount of the same product prepared weeks earlier was mixed with the freshly prepared AMZ. It seems that the AMZ present in the old solution hydrolyzed to N-3,5-dimethylphenyl N-methyl formamide, a more toxic metabolite. On the other hand, Harkins et al. (1997) suggested that there is a similarity in the mode of action of amitraz, xylazine and detomidine, since those drugs

cause decrease in locomotor activity, in horses, and in a separate experiment, yohimbine administration immediately reversed the sedative effect of amitraz. More recently Queiroz-Neto et al. (1998) concluded that amitraz, at the dose of 0.1mg/kg iv, present a marked, long lasting and powerful sedative effect in horse compared to xylazine.

The objective of the present study was to determine the side effects of iv administration of 0.10mg/kg AMZ to horses on cardiac activity, respiratory rate, intestinal motor activity, rectal temperature, sweating and reaching for food in English Thoroughbred horses and compare with those caused by xylazine on the cardiac activity, respiratory rate and intestinal sounds.

MATERIAL AND METHODS

The study was conducted on 11 English Thoroughbred mares belonging to the experimental herd of the Department of Veterinary Sciences, University of Kentucky, Lexington, KY, USA, and on 8 mares of the same breed from the herd of the Faculty of Agrarian and Veterinary Sciences of Jaboticabal, UNESP, Brazil.

For the evaluation of the effects of AMZ and xylazine on tyhe physiological variablesparameters, the mares were injected with dimethylformamide (control-vehicle) or with AMZ [Sintesul - Pelotas, RS, Brazil] (0.10mg/kg) or xylazine[Rompun - Bayer S.A. Saúde Animal- Porto Alegre, RS] (1mg/kg), with an interval of at least 7 days between administrations. The animals were placed in the stalls the afternoon before the day of the experiments. At 7:00am of the day of the experiment they were fed with 3kg of commercial ration (12% protein) and "coast-cross" hay *ad libitum*. At 9:00am and temperature around 26° C, tThe following variables were analyzed after AMZ orand xylazine injection: heart rate (HR), electrocardiogram (ECG), respiratory rate (RR) and intestinal sounds (IS). After AMZ administration were also analyzed, rectal muscle contractility (RC), rectal temperature (RT), sweating (SW) and reaching for food (RF). RC was measured with the aid of a bulb dynamometer [Christy Company, Pleasantown, CA, USA]. HR and IS were measured with a stethoscope.

Before the administration of vehicle, AMZ or xylazine, the above variables were measured three times at 10 minute intervals in order to establish baseline values for each animal. After the injections, the variables were evaluated at 5, 15, 30, 60, 190, 180, 240 and 300 minutes.

Data were analyzed by the Student t-test for paired samples (HR, RR, RT, RC, IS).

RESULTS AND DISCUSSION

The effect of AMZ on the heart can be observed in Figure 1 which shows a significant decrease in heart rate in horses injected iv with 0.10mg/kg AMZ, which started 15 minutes after drug administration and lasted 90 min. Although the literature consulted did not show specific data about heart rate in horses treated with AMZ, many authors have reported cardiocirculatory collapse in horses intoxicated with this pesticide (Roberts & Seawright, 1983; Auer et al., 1984). However, decreased heart rate after AMZ administration has been frequently observed in other animal species (Bonsall & Turnbull, 1983; Hsu & Hopper, 1986; Cullen & Reinoldson, 1990). The bradycardia-producing effect observed after the injection of a $_2$-adrenergic agonists is common and has been reported for various animal species. Some of the more recent papers that cite this effect are those by Aantaa et al. (1991) using dexmedetomidine in humans, Browning & Collins (1994) with romifidine in horses, Hamm et al. (1995) with romifidine and detomidine in horses, and Mohammad et al. (1995) with medetomidine in sheep.

The cardiac effects of AMZ observed in the present study were similar to those seen with xylazine and may have been less intense (considering the first 30 min after drug injection) on heart rate than those obtained with the latter drug. Similarly, electrocardiogram studies (data not shown) demonstrated the occurrence of atrioventricular block after administration of both drugs, an effect that lasted approximately 30 minutes, with a tendency to normalization thereafter.

It can be seen that both AMZ and xylazine caused a fall in the respiratory rate of horses (Figure 2). This agrees with data reported by Butelman & Woods (1993) and Mohammad et al. (1995) who also described this effect. Xylazine appeared to have a more pronounced, but shorter effect on this parameter. The decreased respiratory rate may be explained by reduced CNS activity or by the fact that the animals under the effect of AMZ required a lower oxygen supply since they remained practically motionless throughout the period in question.

Another matter to be considered with respect to the respiratory activity of animals under the effect of a_2-adrenergic agonists is the ability of these drugs to promote bronchodilation. Watney & Hall (1988) reported that xylazine provokes bronchodilation in healthy ponies, so, the reduced respiratory rate observed after the administration of AMZ and xylazine may be explained as a reflex response to the higher capacity for pulmonary ventilation.

Figure 3 shows that the depressive effect of xylazine on intestinal sounds appeared to be more intense than the effect of AMZ. The depressive effect of xylazine on the intestinal motility of horses was reported in a study on ponies, in which, the intramuscular xylazine administration at the dose of 2.2mg/kg reduced the propulsive motility of the distal jejunum, cecum and pelvic flexure of healthy ponies for up to 140 minutes (Adams et al., 1984).

Figure 4 shows that vehicle administration did not cause changes in rectal muscle tonus, whereas AMZ caused a clear relaxation, the effect being significant 5, 15 and 30 minutes after administration.

As previously discussed, one of the more evident and characteristic effects of AMZ is the reduced intestinal motor activity which may lead to severe colic and, not infrequently, to death, especially among horses (Roberts & Seawright, 1983; Auer et al., 1984; Roberts & Argenzio, 1986). However, analysis of Figures 3 and 4 suggests that the effect of the AMZ dose used (0.10mg/kg) was transitory and did not differ significantly from that observed for xylazine. These results reveal that, at doses that cause sedation,

AMZ did not provoke alterations in intestinal motility that would justify the contraindication of its use in horses.

The rectal temperature of horses in the group treated with AMZ (0.10mg/kg, iv) did not differ from control (data not shown). This result disagrees with data reported by Roberts & Seawright (1983), who observed hypothermia after iv administration of AMZ to ponies, and by Bonsall & Turnbull (1983) who reported a decrease in temperature after animal intoxication with AMZ preparations. These investigators, however, pointed out that part of the effects observed in these cases may be due to the vehicle(s) used, which in many preparations are mainly represented by xylene. This observation seems to be pertinent, even if it does not explain the results obtained with the ponies, since in the present experiments and in those reported by Mohammad et al. (1995), rectal temperature was not affected by the administration of a_2-adrenergic agonists.

AMZ (0.10mg/kg) increased sweating in all animals (data not shown), with the effect being quite strong in 4 of the total of 5 animals tested in this experiment, from 30 to 120 minutes after administration, and with profuse sweating occurring in 3 of them. This effect was previously described by Roberts & Seawright (1983) for AMZ in horses and seems to be shared by other a_2-adrenergic agonists, having been reported for detomidine in horses (Kohn & Muir, 1988) and more recently for romifidine, also in horses (Browning & Collins, 1994).

Another interesting factor was the much more frequent masticating activity of the horses treated with AMZ compared to those treated with vehicle. This observation is graphically presented in Figure 5, where the percentage of animals found masticating food is given on the abscissa and the observation times on the ordinate.

Pfister & Yim (1978) in a study of the effect of AMZ on rats, reported a considerable increase in food consumption caused by the agent. This is a very important fact in cases of horse intoxication caused by the pesticide since the increased food consumption is definitely a complicating factor that favors the development of

impaction colic. Analysis of Figure 5 suggests that AMZ increased the frequency of animals found masticating food, in agreement with the data reported by the above authors. However, food consumption itself was not evaluated. Thus, there are no sufficient data to support this statement for horses. Similarly, data reported by Hamm et al. (1995) do not provide evidence that food ingestion indeed was increased. The authors reported that, after injection of detomidine at doses of 20µg/kg or higher, the animals presented head ptosis together with a lip movement behavior similar to mastication, or even the maintenance of food in the mouth without mastication, but this behavior did not imply an increased food ingestion.

The present results allow to conclude that the intravenous administration of AMZ at the dose of 0.1mg/kg did not cause severe side effects on English Thoroughbred horses.

ACKNOWLEDGEMENTS

This work was supported by Fundação de Amparo a Pesquisa do Estado de São Paulo - FAPESP and Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq, Brazil.

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Publication Dates

» **Publication in this collection**
14 Aug 2000

» **Date of issue**
Feb 2000

History

» **Received**
29 July 1999

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FIGURES

Figures (5)

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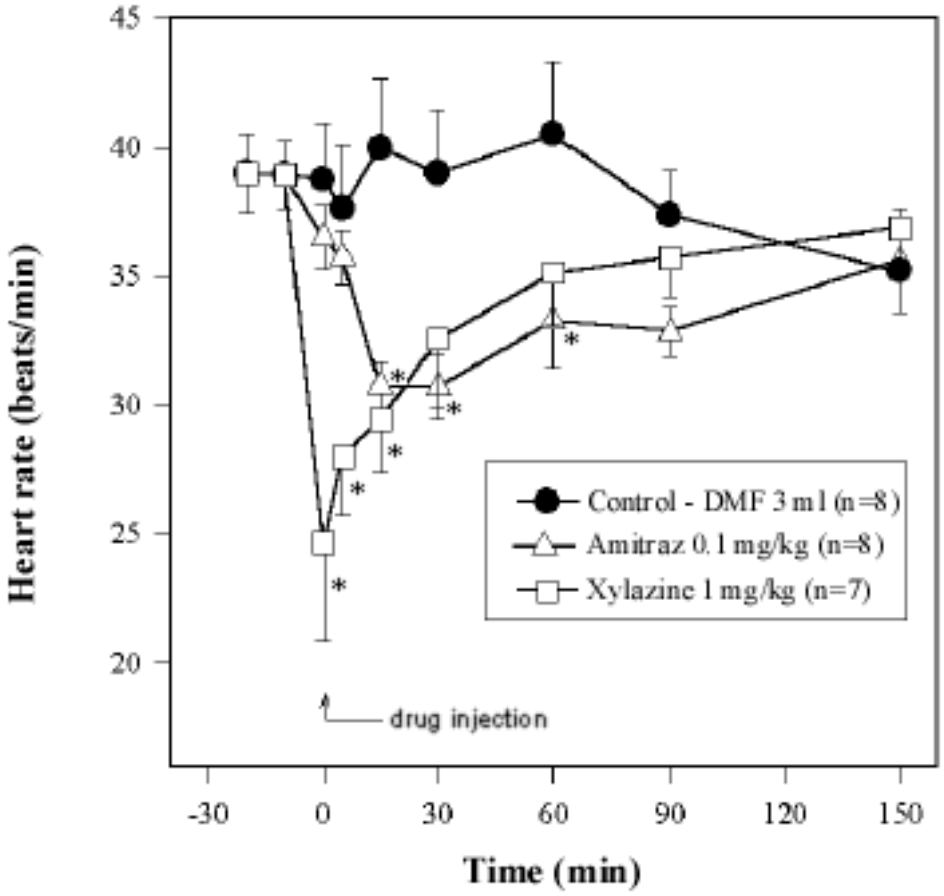

Figure 1. Effect of intravenous injection of dimethylformamide (control), amitraz (0.1mg/kg) and xylazine (1mg/kg) on the heart rate of horses. The vertical bars indicate the standard error of the means. * Significantly different from control (P<0.05)

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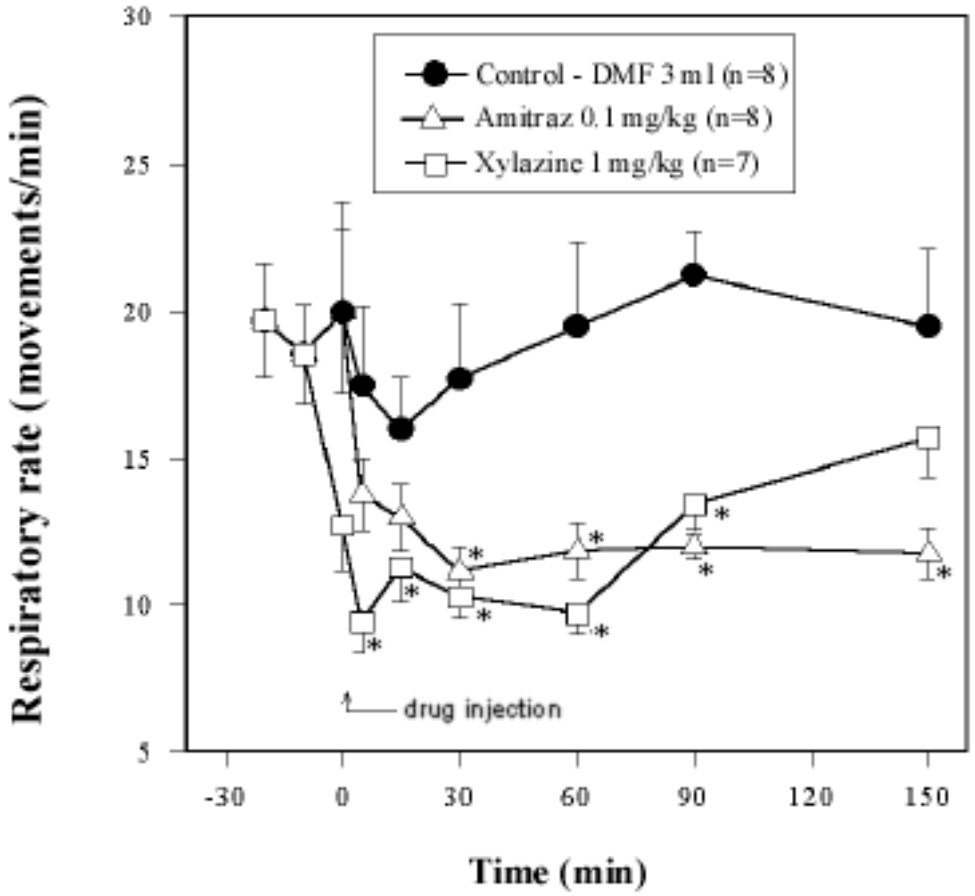

Figure 2. Effect of intravenous injection of dimethylformamide (control), amitraz (0.1mg/kg) and xylazine (1mg/kg) on the respiratory rate of horses. The vertical bars indicate the standard error of the means. * Significantly different from control ($P<0.05$)

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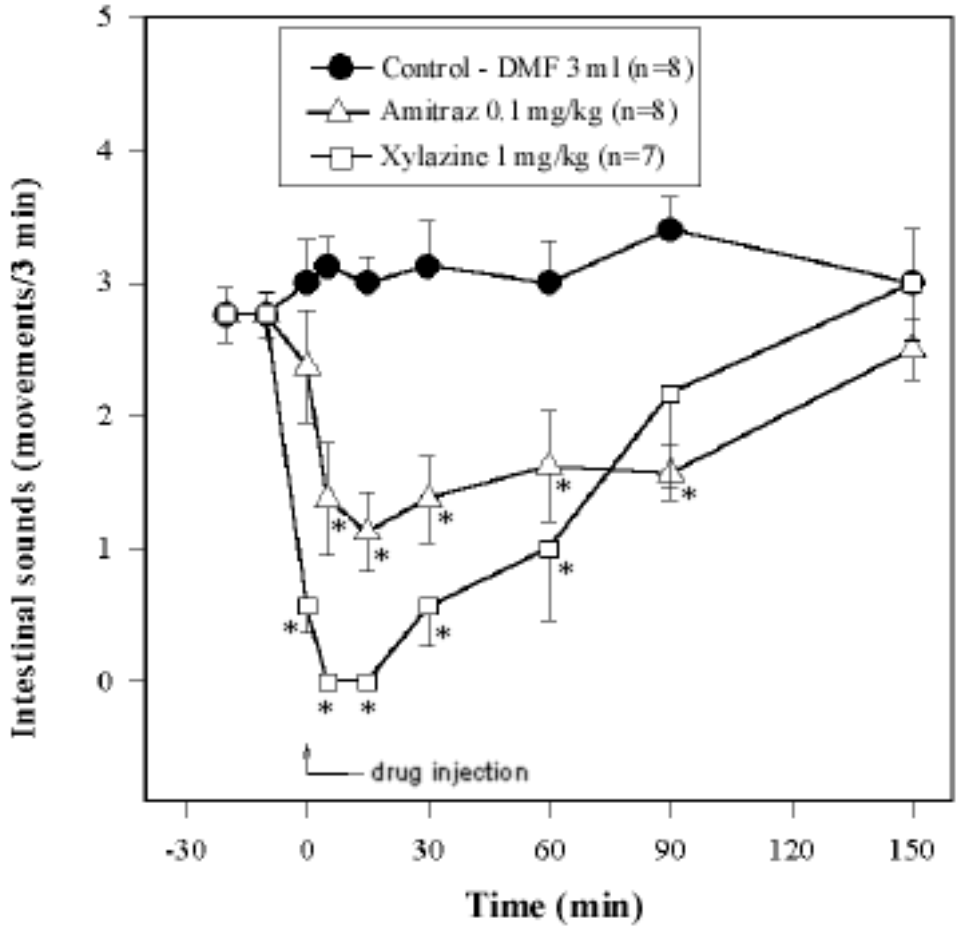

Figure 3. Effect of intravenous injection of dimethylformamide (control), amitraz (0.1mg/kg) and xylazine (1mg/kg) on the intestinal movements of horses. The vertical bars indicate the standard error of the means.
* Significantly different from control ($P<0.05$)

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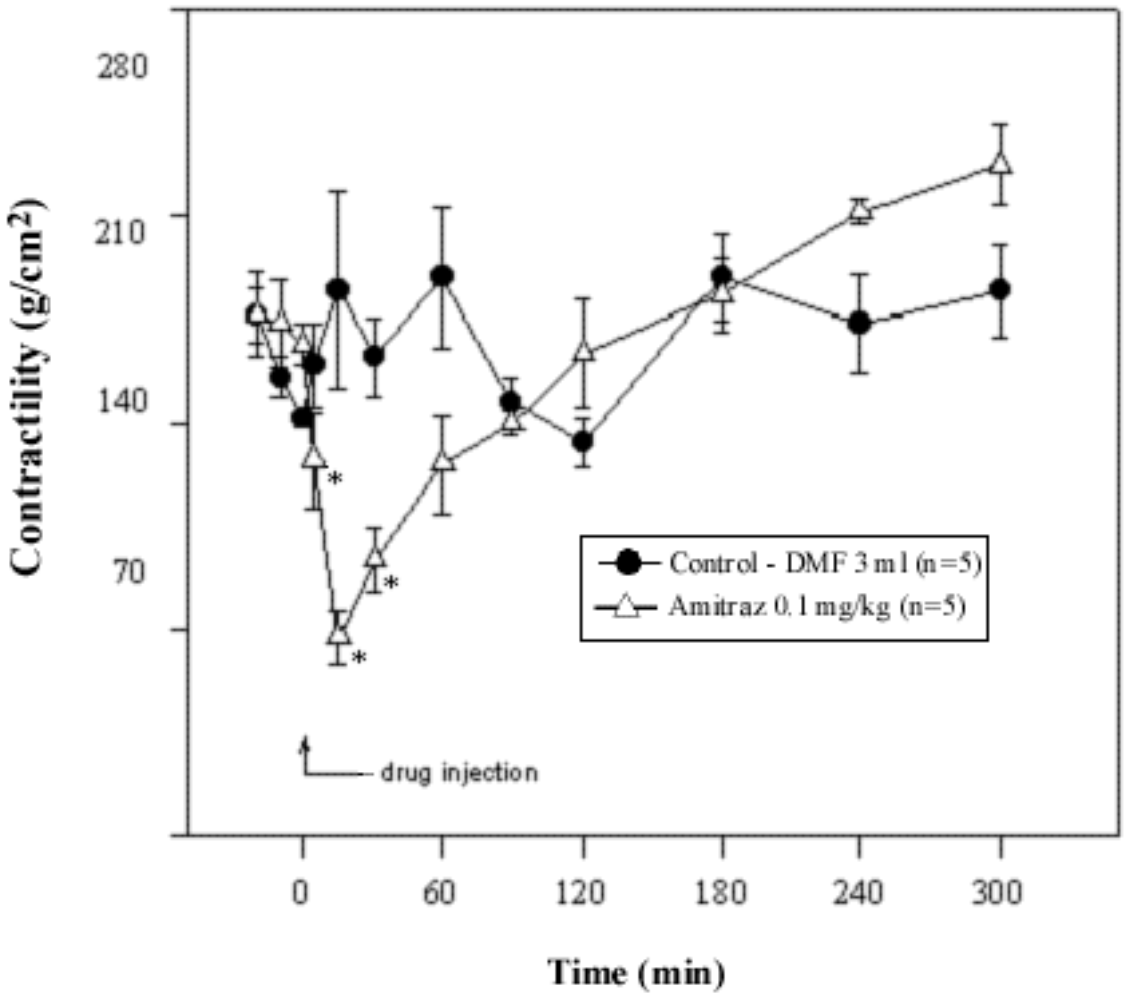

Figure 4. Effect of intravenous injection of dimethylformamide (control), amitraz (0.1mg/kg) and xylazine (1mg/kg) on the rectal muscle contractility of horses. The vertical bars indicate the standard error of the means. * Significantly different from control ($P<0.05$)

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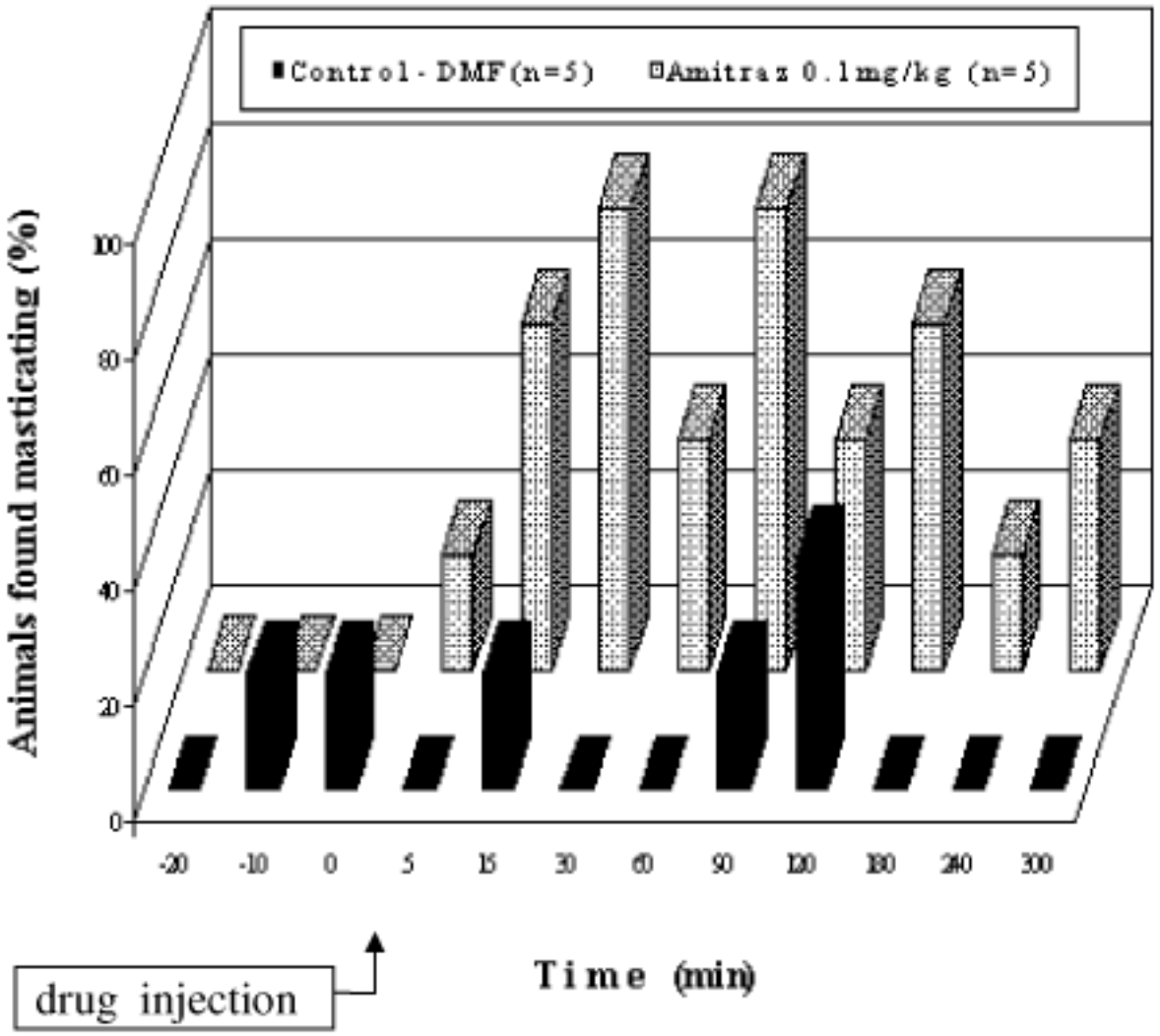

Figure 5. Effect of intravenous injection of dimethylformamide (control) and amitraz (0.1mg/kg) on the willingness of horses to reach for food (alfalfa hay).

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HOW TO CITE

Queiroz-Neto, A. et al. Effect of amitraz and xylazine on some physiological variables of horses. Arquivo Brasileiro de Medicina Veterinária e Zootecnia [online]. 2000, v. 52, n. 1 [Accessed 25 August 2023], pp. 27-32. Available from: <https://doi.org/10.1590/S0102-09352000000100008>. Epub 14 Aug 2000. ISSN 1678-4162. https://doi.org/10.1590/S0102-09352000000100008.

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