COMPARISON OF THE SEDATIVE AND/OR ANTINOCICEPTIVE EFFECTS OF ACEPROMAZINE, LEVOMEPROMAZINE AND AZAPERONE IN HORSES

COMPARAÇÃO DOS EFEITOS SEDATIVOS E/OU ANTINOCICEPTIVOS DOS TRANQUILIZANTES ACEPROMAZINA, LEVOMEPROMAZINA E AZAPERONE EM EQUINOS

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SUMMARY

The aim of this study was to investigate the sedative and antinociceptive effects of three dopaminergic blockers often used in veterinary medicine. The study was conducted on 10 Thoroughbred mares. Sedation was evaluated by determining the spontaneous locomotor activity (SLA) in automated individual behavior stalls and by measuring head ptosis (HP). The intravenous injection of acepromazine (0.05; 0.08 and 0.11 mg/kg) and azaperone (0.25; 0.5 and 1.0 mg/kg) did not induce significant changes on SLA. In contrast, intramuscular injection of levomepromazine caused an increase in SLA at the dosages of 0.75 and 1.0 mg/kg, but not at 0.5 mg/kg. Significant head ptosis occurred with all dosages and drugs. Antinociception was determined utilizing a heat projection lamp to record the hoof withdrawal reflex latency (HWRL) and skin twitch reflex latency (STRL). Acepromazine (0.08 mg/kg) and levomepromazine (0.75 mg/kg) did not induce significant changes on both HWRL and STRL, but azaperone (0.5 mg/kg) produced a significant increase in both HWRL and STRL . The data were evaluated by analysis of variance (ANOVA) and Tukey test ($P<0.05$). The results indicate the antinociceptive effect of azaperone, and the tranquilizer effect of acepromazine and levomepromazine, in horses.

KEY-WORDS: Head height. Locomotor activity. Hoof withdrawal reflex. Skin twitch reflex.

RESUMO

O objetivo do presente estudo foi investigar o efeito sedativo e antinociceptivo de três bloqueadores dopaminérgicos usados em medicina veterinária. Utilizou-se 10 éguas Puro Sangue Inglês. A sedação foi avaliada determinando-se a atividade locomotora espontânea (ALE) e altura da cabeça (AC) em baia comportamental automatizada. A injeção iv de acepromazina (0,05; 0,08 e 0,11 mg/kg) e azaperone (0,25; 0,5 e 1,0 mg/kg) não induziu mudanças significantes na ALE. A injeção im de levomepromazina causou um aumento em ALE nas dosagens de 0,75 e 1,0 mg/kg. Com relação a AC, observou-se diferença significativa ($P<0,05$) em todas as dosagens e drogas. Antinocicepção foi avaliada pela mensuração dos tempos para ocorrer a latência do reflexo de retirada do membro (LRRM) e a latência do reflexo do frêmito cutâneo (LRFC) com o auxílio de uma lâmpada de projeção de calor (estímulo doloroso) direcionado, respectivamente para a falange proximal do membro torácico e região da cernelha. A acepromazina (0,08 mg/kg) e a levomepromazina (0,75 mg/kg) não induziram mudanças significantes em LRRM e LRFC, o azaperone (0,5 mg/kg) causou aumento significativo da LRRM e LRFC. Os dados foram analisados por análise de variância (ANOVA) e teste de Tukey ($P<0,05$). A acepromazina e o azaperone mostraram efeito sedativo relevante. No que se refere ao efeito antinociceptivo, apenas o azaperone mostrou-se eficiente.

PALAVRAS-CHAVE: Altura da cabeça. Atividade locomotora. Reflexo de retirada do membro. Reflexo do frêmito cutâneo.

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INTRODUCTION

The studied tranquilizers have a common mechanism of action, that is, the antagonism of dopaminergic receptors. Acepromazine and levomepromazine are phenothiazine derivatives, which act in the thalamic nuclei, hypothalamus, afferent sensory pathways, limbic structure and motor system. They are also able to act on the periphery, affecting the autonomous nervous system (HATTA et al., 2000). Their primary action mechanism is mainly related to its antagonism in dopamine D2 receptors, but has additional effects related to the blockage of α_1 adrenergic and muscarinic cholinergic receptors (PAWSON, 2010).

Acepromazine is used as sedative and pre-anesthetic in animals, since it induces reduction of cortical activity, sedation and muscle relaxation (MARROUM et al., 1994) and blocks peripheral adrenergic receptors resulting in decreased peripheral vascular resistance with consequent reduction of blood pressure (HALL et al., 2001). In addition to these characteristics, acepromazine has also immunomodulatory, antioxidant and anti-inflammatory action (SANDERSEN, 2011).

Levomepromazine has several beneficial effects to humans. It can be used as antipsychotic, anxiolytic, sedative (GREEN, 2004), antiemetic (EISENCHLAS et al., 2005) and to treat schizophrenia as well (SIVARAMAN et al., 2011).

The azaperone is a butyrophenone acid derivative, with action mechanism similar to phenothiazines, widely used in pigs (MUIR & HUBBEL, 2001), but rarely reported in equine medicine. There are reports of its use as doping at lower dosages than that of tranquilizer (SAMS et al., 1996).

The objective of this study is to compare, in Thoroughbred English horses, the sedative effect of levomepromazine, acepromazine and azaperone, by measuring head ptosis (HP) and spontaneous locomotor activity (SLA) in behavioral stalls, and to evaluate also their antinociceptive effect by means of two tests of motor response latency to thermal stimuli.

MATERIAL AND METHODS

Ten adult Thoroughbred English mares, weighing between 450 and 550 kg, were used. The mares belonged to the experimental herd of the Departamento de Morfologia e Fisiologia Animal, Faculdade de Ciências Agrárias e Veterinárias, Unesp, Jaboticabal.

The possible sedative effect of the drugs was evaluated at the following dosages: acepromazine[2] (0.05; 0.08 and 0.11 mg/kg IV), levomepromazine[3] (0.5; 0.75 and 1.0 mg/kg IM), azaperone[4] (0.25; 0.5 and 1.0 mg/kg IV), and saline solution as control.

Sedation was assessed by measuring spontaneous locomotor activity (SLA) and head ptosis (HP), before and after the drugs, according to the modified method described by Kamerling *et al.* (1988), at the following times: -45, -30, -15, 0 (time of injection), 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270 and 300 minutes.

Antinociception was evaluated for the following drugs and doses: acepromazine (0.08 mg/kg IV), levomepromazine (0.75 mg/kg IM), azaperone (0.5 mg/kg IV), and saline (control). The relationship between time and dose-response for the various drugs were determined using an adapted heat projection lamp as described by Kamerling et al. (1985) and built by the Department of Electrical Engineering at the University of Kentucky, USA.

A quick exposure to the heat projection lamp was used as a painful stimulus. The light was directed, in independent trials, towards the following body parts:

- region of the proximal phalanx of the forelimb to trigger the classical reflex of the limb and to measure Hoof Withdrawal Reflex Latency (HWRL), defined as the time elapsed between the application of the heat lamp and withdrawal of the hoof.

- region of the horse´s withers to measure Skin Twitch Reflex Latency (STRL), defined as the time elapsed between painful stimulus and the twitching of the skin. In both trials, the painful stimulus was interrupted, invariably, when time exposure reached 10 seconds ("cut off time") to prevent tissue injury.

HWRL and STRL were always measured 30 minutes and immediately before the IV injection of saline (control) and the drugs and, at 5, 15, 30, 45, 60, 90, 120 and 240 minutes after the drugs were administered.

Mean values of control and treatment groups within each time were analyzed by ANOVA and compared by Tukey test at 5% significance level. The results are presented as mean ± SD.

RESULTS

Figure 1A shows that for the 0.05 mg/kg IV dose of acepromazine, SLA values were virtually the same as the control group. Figure 1B shows that the 0.05 mg/kg IV dose of acepromazine caused a slight decrease of HP. This effect was different ($P<0.05$) for the 5 and 30 minute times compared to the control group. The dose of 0.08 mg/kg did not increase locomotor activity, although in some animals SLA increased significantly between 10 and 30 minutes compared to the control group. Figure 1B shows drug effect on head ptosis. It can be observed that acepromazine effect at this dosage was similar to that presented at 0.05 mg/mg IV, and decreased compared to control group at 5, 20, 25 and 60 minutes.

[2]Acepromazina: Acepran ® - Univet - Indústria Veterinária, SP.
[3]Levomepromazina: Neozine ® - Rhodia Farma, São Paulo.
[4]Azaperone: Stresnil ® - Janssen - Rhodia-Mérieux Ltda., Paulínea, São Paulo

The 0.11 mg/kg IV dose did not change SLA, although again, a large individual change can be observed (Figure 1A). As for HP, the 0.11 mg/kg dose had a depressing effect ($P<0.05$) at 5 minutes (Figure 1B). The maximum depressing effect can be observed at 10 minutes, which remained significant up to 90 minutes after the injection. Figure 1B' shows a good dose-response relationship.

The behavioral evaluation after the 0.5 and 0.75 mg/kg IM doses of levomepromazine were administered (Figure 2) shows that these doses did not affect SLA and HP. From the 10 tested mares with doses of 0.75, one showed ataxia and another excessive sweating from 5 minutes time.

With 1.0 mg/kg IM, mean SLA increased ($P<0.05$) from 25 minutes time, and remained up to the end of the experimental period, with significant differences at times 30, 75, 90, 120 and 180 minutes. HP values were quite different and lower than the control group 5 minutes after the injection and remained throughout the trial, with significant differences at times 60, 75, 90, 120, 150, 240 and 300 minutes compared to control group. For both SLA and HP, a good dose-response was observed (Figures 2A' and 2B').

The administration of 0.25 mg/kg of azaperone did not change SLA compared to control group (Figure 3A). The HP decreased ($P<0.05$) for mares treated with this dose between 10 and 270 minutes (Figure 3B). It should be mentioned that the mares remained calm and had eyelid ptosis. Lack of motor coordination was observed in one animal, while two others showed stereotyped movements (ground digging).

The 0.5 mg/kg dose of azaperone did not change SLA during the first 90 minutes after drug administration (Figure 3A). The HP was evident between 10 and 45 minutes, but less intensely than observed with the 0.25 mg/kg IV dose (Figure 3B). The behavioral assessment showed that four out of 10 horses had excessive sweating, while two displayed stereotyped movements.

SLA increased during the first 5 minutes after 1.0 mg/kg IV dose of azaperone, decreasing significantly after that, and it was significantly different compared to control group at 180 minutes. At this dosage, nine out 10 horses had intense sweating, all had muscle tremors, two had lack of coordination and one was intensely agitated to the point of kicking the walls and the door of the stall. The depressing effect of this azaperone dose over HP was significant after 10 minutes, while HP reduction remained significant until the end of evaluation (Figure 3B). In Figure 3B', it becomes evident that this high dosage exceeded the maximum response dose.

Figure 4A shows that the antinociceptive effect of 0.5 mg/kg azaperone dose determined by increasing STRL, occurred 5 minutes after the injection and lasted 30 minutes, decreasing progressively after this, approaching the control group (90 minutes). Likewise, the effect on HWRL lasted between 5 and 60 minutes, and disappeared progressively until 240 minutes, when values became similar to control group. The other drugs had no satisfactory antinociceptive effect at the dosages studied.

Azaperone antinociceptive pattern on STRL was different when compared to control groups, levomepromazine 0.75 mg/kg IM and acepromazine 0.08 mg/kg IV. This effect started 5 min after the injection and lasted up to 60 min ($P<0.05$) (Figure 4A). Similar effect was observed for HWRL, except for 0.75 mg/kg IM levomepromazine dose, which increased between 30 and 45 minutes ($P<0.05$) (Figure 4B).

DISCUSSION

In a recent study, Driessen et al. (2011) concluded that the positive contribution of acepromazine for the homeostasis of arterial blood pressure, as well as quality of induction and return from anesthesia should not be avoided due to the extremely low risk of penile dysfunction in non-castrated males. Castro (1981) determined that with a 0.3 mg/kg IV acepromazine dose, 11 out 20 animals showed mild or pronounced excitation, described as staggering gait, behavior that became evident 5 minutes after the injection and lasted for another 5 minutes. This study tested much lower doses, which could explain the lack of significant increase in SLA at the studied doses. Castro (1981) reports that nine out 20 animals showed gradual sedation, evidenced by apathy, followed by drowsiness and muscle relaxation, 15 minutes after acepromazine injection.

HP evaluation showed significant sedation of all animals at all tested doses, with maximum effect verified 10 minutes after the injection for the doses 0.05 and 0.11 mg/kg IV and significant depressing effect up to 90 minutes after the injection. These results differ from those described by Marroum et al. (1994). These authors reported maximum effect for the 0.15 mg/kg IV dose, 20 minutes after the injection. They also scored eyelid ptosis and movements. These results coincide with the 0.08 mg/kg IV dose tested in this study. Another researcher, Short (1998) reported maximum tranquilizer and sedative effects of acepromazine between 15 and 20 minutes, after dosages that ranged from 0.02 to 0.06 mg/kg IV. In the present study, the maximum effect was observed between 10 and 20 minutes. The absence of significant adverse effects observed here is consistent with the findings of Short (1998).

Marques (1981) tested doses between 0.2 and 0.3 mg/kg IV of acepromazine, higher than in this study, in two groups of 10 horses each, and observed a tranquilizer effect 5 minutes after the injection, which was characterized as drowsiness, listlessness and moderate lack of coordination, similar to those reported here. In another study, Love et al. (2011) reported that after IV administration of 0.05 mg/kg of acepromazine, the animals showed a reduction of the response to thermal stimulus lasting about 30 minutes. In this study it was not possible to prove the antinociceptive effect of acepromazine.

Levomepromazine behaved completely different from acepromazine, as it promoted evident and dose

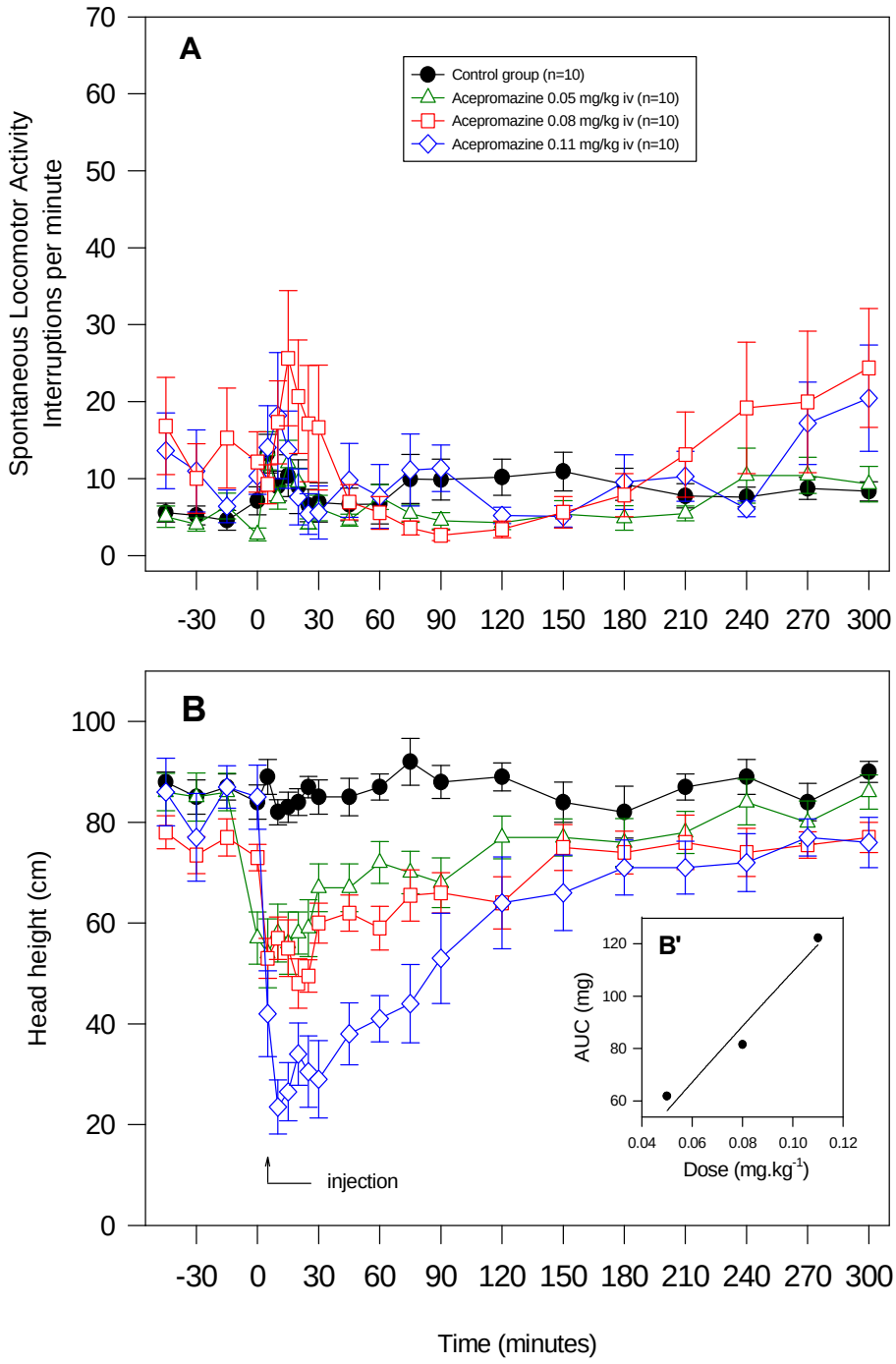

Figure 1 - A. Changes in spontaneous locomotor activity (SLA) of horses after IV administration of acepromazine (0.5; 0.8; 1.1 mg/kg) or saline (control group). **B.** Head ptosis after administration of acepromazine or saline. Vertical bars show mean standard error. **B'.** Dose-response relationship.

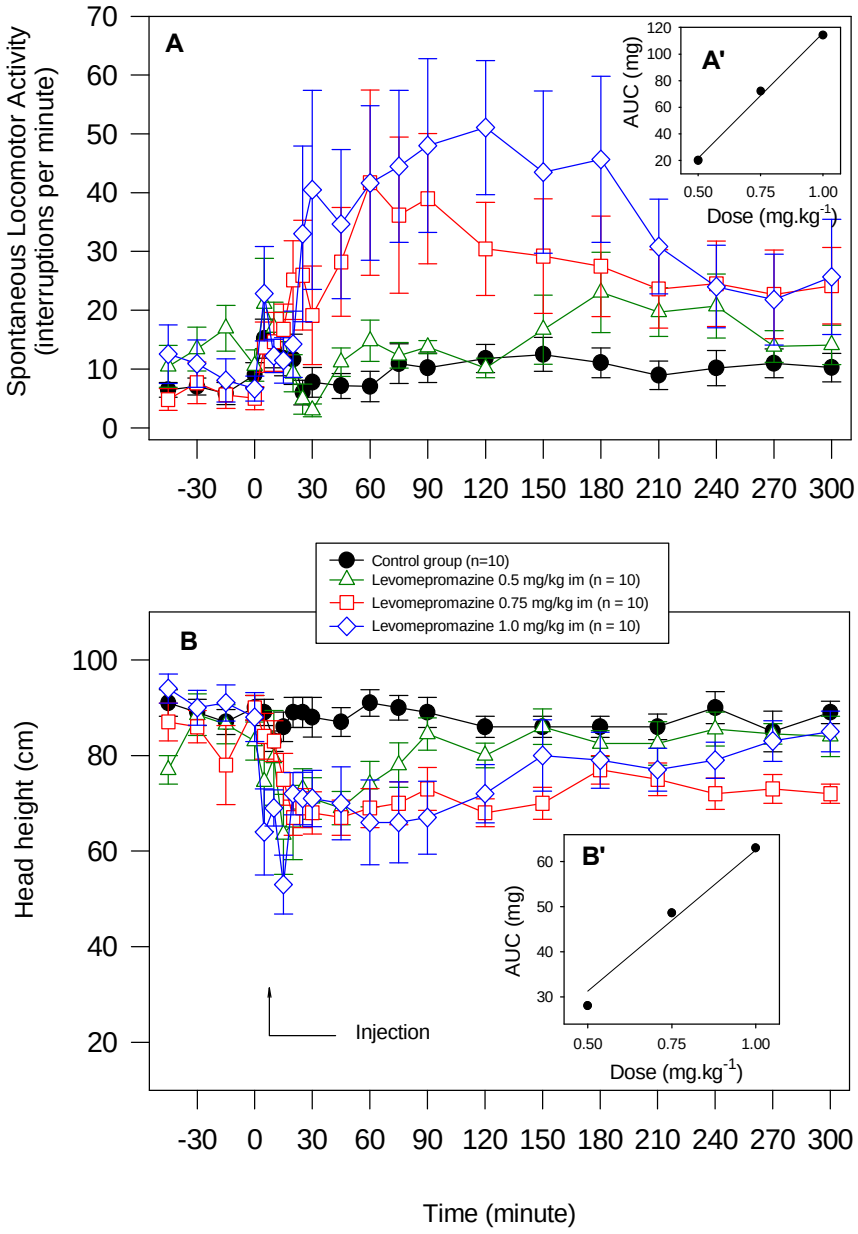

Figure 2 - A. Changes in spontaneous locomotor activity (SLA) of horses after IM administration of levomepromazine (0.5; 0.75; 1.0 mg/kg) or saline (control group). **A'.** Dose-response relationship. **B.** Head ptosis after administration of levomepromazine or saline. Vertical bars show mean standard error. **B'.** Dose-response relationship.

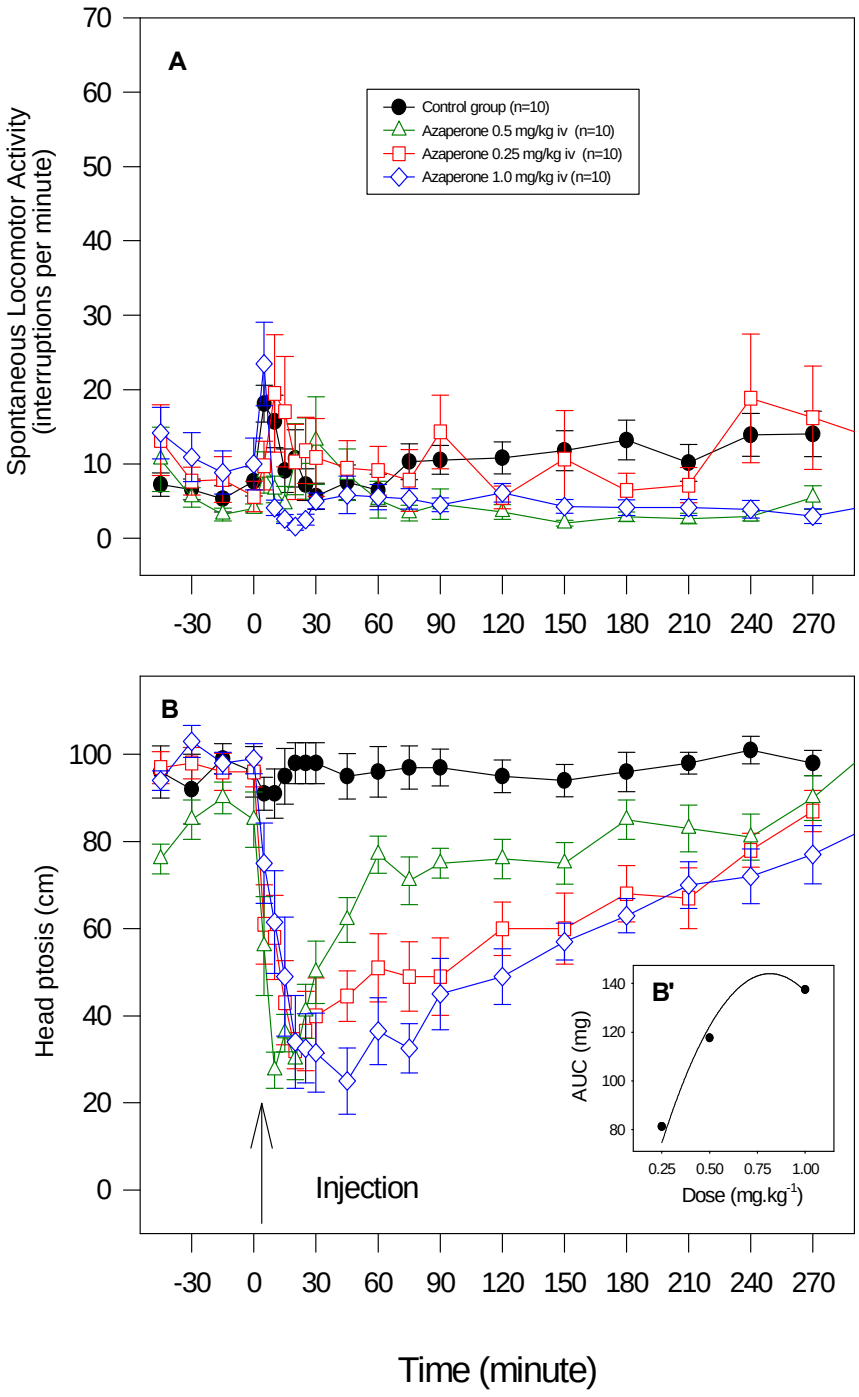

Figure 3 - A. Changes in spontaneous locomotor activity (SLA) of horses after IM administration of azaperone (0.5; 0.25; 1.0 mg/kg) or saline (control group). **B.** Head ptosis after administration of azaperone or saline. Vertical bars show mean standard error. **B'.** Dose-response relationship.

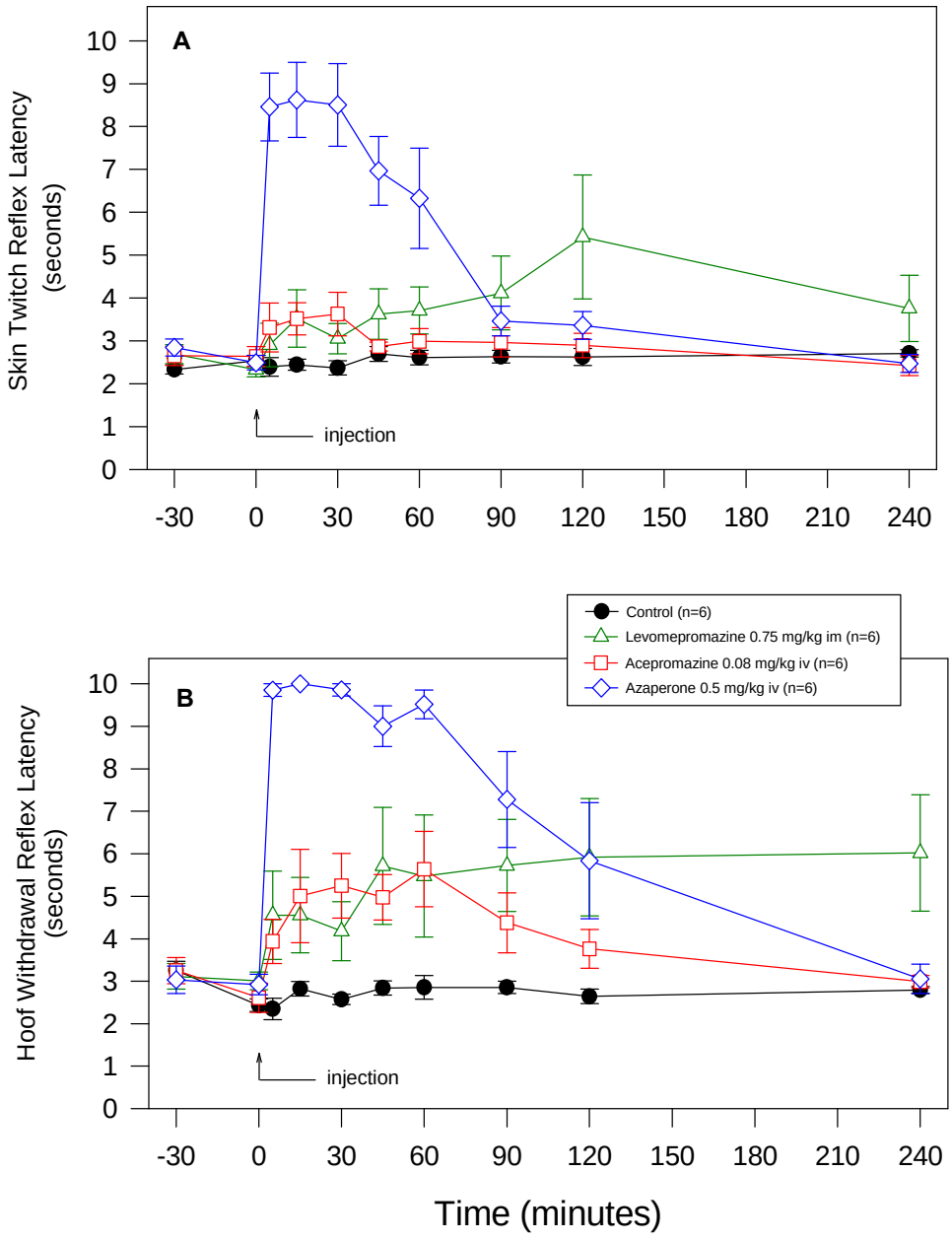

Figure 4 - A. STRL in horses after administration of levomepromazine (0.75 mg/kg IM), acepromazine (0.08 mg/kg IV), azaperone (0.5 mg/kg iv) or saline (control group). **B.** HWRL increased after administration of levomepromazine, acepromazine, azaperone or saline. Vertical bars show mean standard deviation.

dependent increase of SLA but, on the other hand it was not as efficient to induce HP as acepromazine did.

Marques (1986) stated that 4 minutes after the IV administration of 1.0 mg/kg levomepromazine in horses, there was apathy or excitement, mild lack of motor coordination, muscle tremors, eyelid ptosis and sweating. Some of these effects were well evidenced in the individual behavior stalls. The large, individual SLA variation during the first 30 minutes after levomepromazine administration resulted in lack of statistical difference when compared to the control group. Sweating was also quite pronounced. There are no reports in the literature studying the analgesic effects of levomepromazine administered isolated. In this study, it was noted a quite discreet effect of levomepromazine on STRL and HWRL, but with no statistically significant differences.

While studying rats, Mataqueiro et al. (2004) reported a different result. When treated with levomepromazine, the rats presented reduced SLA compared to control group, for a longer time than the group treated with azaperone. From the tested substances, azaperone was the most efficient sedative, but with numerous adverse effects such as sweating and ataxia. Perhaps, this is the main reason this substance is usually not employed with this purpose. All cases were also dose dependent.

In one of the few studies on the azaperone effects in horses, Araújo (1979) reported remarkable excitement of the horses when azaperone was administered intravenously. This excitement was observed in the first five minutes after the 1.0 mg/kg dose was injected, followed by apathy. The author reported no significant difference in the respiratory movements and temperature 40 minutes after the injection, and remained so until the end of the experimental period. The same author also observed sweating, which was also remarkably seen here for all doses and considered the most important side effect. This author also describes ptosis of the head and lips in all animals, approximately 10 minutes after the injection. Our results are consistent with these results, since there was a marked HP that varied for the tested dosages only regarding how long the effect lasted. Araújo (1979) reported that the animals remained sedated for a period of about 20 to 30 minutes. In the experimental design used here, there was a longer lasting effect, even at the 0.5 mg/kg dose. However, the different administration route of the drug should be taken into account. The same author reported that animals tested with azaperone did not respond either to external or cutaneous stimuli, which allowed the administration of other drugs in a group of animals without any reaction. Similarly, in the present study, azaperone caused a significant increase of STRL and HWRL, confirming these results.

Some studies suggest that the basal ganglia may be involved in the processing of pain information. Anatomical findings showed the existence of nociceptive projections of neurons from the substantia nigra to the striatum. Early evidence of the development of basal ganglia of the dopaminergic system in chronic pain in humans was published by Jaaskelainen et al. (2001), whose results suggested a dysfunction of the dopaminergic nigro-striatal of these patients. Thus, new therapeutic possibilities can be developed for the treatment of chronic pain.

According to Emilien et al. (1999) the pre-frontal cortex, defined as the essential cortical projection area of the mediodorsal thalamic nucleus, is implicated in the control of locomotor activity and cognitive processes, such as affection and emotional behavior in human beings According to the authors, the prefrontal cortex is the main area where neuroleptics act. These characteristics are linked to behavior and nociception, which is why levomepromazine and acepromazine were more efficient as sedative compared to antinociceptive agent. Probably the non-significant increase of the HWRL compared to the control group was more closely associated with the regulation of the motor activity than with the pain.

Until now, no data can be found in the literature to explain the antinociceptive effect of azaperone described here, once there are no reports about the action of this drug on the GABAergic system, for instance. Therefore, it is possible to formulate two hypotheses: (1) azaperone acted intensely depressing the motor cortex by antagonizing the dopaminergic system, which instead of abolishing the pain sensation, abolished the incapacity of the tested animals to react muscularly to the painful stimuli; (2) azaperone could have acted intensely on D2 dopaminergic receptors associated with an indirect agonist action on GABAergics. The latter hypothesis is supported by reports of Zhang *et al*. (1997).

CONCLUSIONS

Both acepromazine and azaperone have a significant sedative effect. With regard to nociception, the effect was evident when azaperone was used, but not when phenothiazine tranquilizers were used. This effect, however, could be related to muscle relaxation.

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REFERENCES

ARAUJO, M. L. **Emprego do azaperone em equinos**. Belo Horizonte, Universidade Federal de Minas Gerais, 1979. 40p. Dissertação de Mestrado - Escola de Veterinária da UFMG, 1979.

CASTRO, E. A. **Emprego do cloridrato de ketamina associado à acepromazina e éter gliceril guaiacol para a indução da anestesia geral pelo halotano em equinos.** Belo Horizonte, Universidade Federal de Minas Gerais, 1981. 49p. Dissertação de Mestrado – Escola de Veterinária da UFMG, 1981.

DRIESSEN, B.; ZARUCCO, L.; KALIR, B.; BERTOLOTTI, L. Contemporary use of acepromazine in the anaesthetic management of male horses and ponies: a retrospective study and opinion poll. **Equine Veterinary Journal**, v.43, n.1, p.88-98, 2011.

EISENCHLAS, J. H.; GARRIGUE, N.; JUNIN, M.; DE SIMONE, G. G. Low dose levomepromazine in refractory emesis in advanced cancer patients: an open-label study. **Palliative Medicine**, v.19, p.71-75, 2005.

EMILIEN, G.; MALOTEAOUX, J. M.; GEURTS, M.; HOOGENBERG, K.; CRAGG, S. Dopamine receptors - physiological understanding to therapeutic intervention potential. **Pharmacology & Therapeutics**, v.84, p.133-156, 1999.

GREEN, B.; PETTIT, T.; FAITH, L.; SEATON, K. Focus on levomepromazine. **Current Medical Research and Opinion,** v.20, n.12, p.1877-1881, 2004.

HATTA, K.; TAKAHASHI, T.; NAKAMURA, H.; FUJII, S.; YAMASHIRO, H.; ASUKAI, N., YONEZAWA, Y. Prolonged upper airway instability in the parenteral use of benzodiazepine with levomepromazine. **Journal of Clinical Psychopharmacology**, v.20, n.1, p.99-101, 2000.

JAASKELAINEN, S. K.; RINNE, J. O.; FORSSELL, H.; TENOVUO, O.; KAASINEN, V.; SONNINEN, P.; BERGMAN, J. Role of the dopaminergic system in chronic pain - a fluorodopa-PET study. **PAIN**, v.90, n.3, p.257-260, 2001.

KAMERLING, S. G.; WECKMAN, T. J.; DEQUICK, D. J.; TOBIN, T. A method for studying cutaneous pain perception and analgesia in horses. **Journal of Pharmacological Methods**, v.13, p.267-274, 1985.

KAMERLING, S. G.; CRAVENS, W. M. T.; BAGWELL, C. A. Objective assessment of detomidine-induced analgesia and sedation in the horse. **European Journal of Pharmacology**, v.151, p.1-8, 1988.

LOVE, E. J.; TAYLOR, P. M.; MURRELL, J.; WHAY, H. R. Effects of acepromazine, butorphanol and buprenorphine on thermal and mechanical nociceptive thresholds in horses. **Equine Veterinary Journal.** doi: 10.1111/j.2042-3306.2011.00412.x, 2011

MARQUES, J. A. **Uso do cloridrato de ketamina associado à acepromazina e flunitrazepam na indução da anestesia geral pelo fluotano em equinos.** Belo Horizonte: Universidade Federal de Minas Gerais, 1981. 37p. Dissertação de Mestrado - Escola de Veterinária da UFMG, 1981.

MARQUES, J. A. **Estudo das alterações cardiopulmonares e hematológicas em equinos premedicados com flunitrazepam e levomepromazina e anestesiados pela cetamina**. Botucatu: Universidade Estadual Paulista, 1986. 54p. Tese de Doutorado – Faculdade de Medicina Veterinária e Zootecnia da UNESP, 1986.

MARROUM, P. J.; WEBB, A. I.; AESCHBACHER, G.; CURRY, S. H. Pharmacokinetics and pharmacodynamics of acepromazine in horses. **American Journal of Veterinary Research**, v.55, n.10, p.1428-1433, 1994.

MATAQUEIRO, M. I.; D´ANGELIS, F. H. F.; DE-CAROLI-NETO, A.; ROSSI, C. A.; QUEIROZ-NETO, A**.** Comparative study of the sedative and antinociceptive effects of levomepromazine, azaperone and midazolam in laboratory animals. **Arquivo Brasileiro de Medicina Veterinária e Zootecnia**. v. 56, n.3, p.340-345, 2004.

MUIR, W. W.; HUBBELL, J. A. E. **Manual de anestesia veterinária**. 3.ed. Porto Alegre: Artmed, 2001. 432p.

PAWSON, P.: Sedativos In: **Farmacologia Clínica de Pequenos Animais**. 1.ed. Rio de Janeiro: Elsevier, 2010. p.113-124.

SAMS, R. A.; GERKEN, D. F.; DETRA, R. L.; STANLEY, S. D.; WOOD, W. E.; TOBIN, T. Identification of metabolites of azaperone in horse urine. **American Pharmaceutical Association**. v.85, n.1, p.79-84, 1996.

SANDERSEN, C; MOUITHYS-MICKALAD, A; DE LA REBIE`RE, G; DEBY, G; SERTEYN, D; FRANCK, T. Modulating effects of acepromazine on the reactive oxygen species production by stimulated equine neutrophil. **Veterinary Anaesthesia and Analgesia**, v.38, n.2, p.83–89, 2011.

SHORT, C. E. Fundamentals of pain perception in animals. **Applied Animal Behaviour Science,** v.59, n.1, p.125-133, 1998.

SIVARAMAN, P.; RATTEHALLI, R.; JAYARAM, M. B. Levomepromazine for schizophrenia. **European Psychiatry**, v. 26, supplement 1, p.1507, 2011.

ZHANG, S.; TANG, J. S., YUAN, B. Involvement of frontal orbital cortex in descending inhibition of nociception mediated by periaqueductal gray in rats. **Neurocience Letters,** v.224, n.1, p.142-146, 1997.