Effects of buprenorphine on nociception and spontaneous locomotor activity in horses

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Objective—To investigate spontaneous locomotor activity (SLA) and antinociceptive effects of buprenorphine in horses.

Animals—6 healthy adult horses.

Procedures—Horses received each of 3 treatments (10 mL of saline [0.9% NaCl] solution, 5 μg of buprenorphine/kg, or 10 μg of buprenorphine/kg). Treatments were administered IV. Order of treatments was randomized, and there was a 10-day interval between subsequent treatments. Spontaneous locomotor activity was investigated in a behavioral box by use of infrared photoelectric sensors connected to a computer, which detected movement of each horse. Antinociceptive effect was investigated by hoof-withdrawal reflex latency (HWRL) and skin-twitching reflex latency (STRL) after painful stimulation with a heat lamp.

Results—Moderate excitement was observed in all horses from 5 to 10 minutes after the administration of both dosages of buprenorphine. The SLA increased significantly for 6 and 14 hours after IV administration of 5 and 10 μg of buprenorphine/kg, respectively. Values for HWRL increased significantly only at 30 minutes after injection of 5 μg of buprenorphine/kg, whereas STRL and HWRL each increased significantly from 1 to 6 hours (except at 2 and 4 hours) and 11 hours, respectively, after injection of 10 μg of buprenorphine/kg.

Conclusions and Clinical Relevance—IV injection of buprenorphine caused a dose-dependent increase in SLA, but only the dose of 10 μg/kg induced analgesia on the basis of results for the experimental method used. (*Am J Vet Res* 2007;68:246–250).

The complexity of pain perception and response to pain requires a multimodal analgesia treatment, which typically relies on a combination of nonsteroidal anti-inflammatory drugs, local anesthetics, N-methyl-D-aspartic acid antagonists, α_2-adrenoceptor agonists, and opioids.[1] Opioids are one of the most efficient analgesics. They activate 1 or more subclasses of specific opioid receptors in accordance with the affinity or intrinsic activity of each drug.[2] However, the use of opioids is limited in horses because they may cause excitement and increased locomotor activity. These undesirable effects are especially evident after administration of a pure opioid agonist.[3-6]

Buprenorphine is a highly lipophilic semisynthetic partial OP3 (μ) opioid receptor agonist. It may also be defined as an agonist-antagonist opioid because it is a κ receptor antagonist in several species.[7] Buprenorphine has a unique pharmacokinetic pattern, with a high affinity for receptor binding and prolonged effects. It may be an alternative to use of classic opioid receptor agonists for the treatment of horses with acute and chronic pain because it apparently causes less intense adverse effects, especially with regard to the CNS.[8] The high analgesic potency of buprenorphine (25 to 50 times as high as the analgesic potency for morphine), prolonged effects, and low cost have contributed to the widespread use of buprenorphine in laboratory and small domestic animals.[9-11]

Abbreviations

SLA	Spontaneous locomotor activity
HWRL	Hoof-withdrawal reflex latency
STRL	Skin-twitching reflex latency

To our knowledge, only 3 studies[12-14] have reported the effects of buprenorphine in horses. In one study[12] in which investigators assessed the cardiopulmonary changes induced by buprenorphine in healthy horses and horses with chronic obstructive pulmonary disease, excitement and sympathetic cardiovascular stimulation were observed, with no changes in blood gas variables. In another study,[13] the combination of buprenorphine and detomidine did not induce hormonal, metabolic, or physiologic changes, including heart and respiratory rates, pH, Pa_{O_2}, and Pa_{CO_2}. In our preliminary study[14] in the same horses used in the study reported here, we verified that cardiopulmonary and digestive tract alterations were induced by buprenorphine, which revealed excitement and hemodynamic stimulation, minimal

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changes in arterial blood gas tensions, and a decrease in gastrointestinal motility.

The objective of the study reported here was to investigate whether SLA was possibly related to stimulation of the CNS that resulted from the administration of buprenorphine. We also evaluated the timing and intensity of antinociceptive effects induced by various doses of buprenorphine in horses.

Materials and Methods

Animals—Twelve healthy adult horses were used in 2 experiments. Six healthy adult horses (3 males and 3 females; mean ± SD body weight, 360 ± 24 kg) were used to evaluate SLA, and 6 other healthy adult horses (3 males and 3 females; body weight, 396 ± 30 kg) were used to evaluate antinociceptive effects of buprenorphine. Health status was assessed on the basis of results of clinical examination, a CBC, and blood gas analysis. The study was approved by an institutional animal care committee (protocol No. 107/2004).

Experimental design—Each horse received 3 treatments (10 mL of saline [0.9% NaCl] solution, 5 µg of buprenorphine[a]/kg, and 10 µg of buprenorphine[a]/kg). Treatments were administered IV. Order of treatments was randomized, and there was a 10-day interval between subsequent treatments. The day before an experiment, each horse was placed in a behavioral stall (16 × 16 m^2) for habituation to the environment. During the first day in the behavioral stall, each horse was fed 2 kg of a pelleted commercial food[b] and allowed ad libitum access to hay and water. Each horse was fed the pelleted feed and provided fresh hay the following morning (day of the experiment); horses were allowed to eat for 1 hour, and all remaining food was then removed from the stall.

Evaluation of SLA—Horses were not restrained when in the behavioral stall, and disturbances were kept to a minimum. The SLA was investigated in accordance with the method described in another study.[15] The SLA was recorded by pulses generated from 8 juxtaposed photoelectric sensors[c] that emitted an infrared beam. The photoelectric sensors were spaced equally around the stall at a height of 45 cm. A pulse was generated each time the beam was interrupted by the horse. The number of pulses per minute was counted; information was stored in a data recorder[d] connected to a microcomputer for subsequent analysis.

The SLA was recorded for 30 minutes to establish baseline values. Saline solution, 5 µg of buprenorphine/kg, or 10 µg of buprenorphine/kg was then injected. Treatments were administered IV into a jugular vein during a period of 5 seconds. Completion of the injection was designated as time 0. The SLA was recorded at 5, 10, 15, 30, 60, 90, and 120 minutes and thereafter at 2-hour intervals for 16 hours after administration of the treatment. At those same time points, behavior was observed through a small window with the observer positioned outside the stall. Signs of excitement (restlessness, head nodding, digging, shifting of limbs, vocalizing, trotting, and galloping) were recorded but not quantified.

Antinociception evaluation—Conditions were the same with regard to habituation and feeding for horses as those described for the preceding experiment. Disturbances were kept to a minimum, and horses were restrained by use of a halter only during antinociception evaluation.

Response to nociception was evaluated with a heat projection lamp by use of methods adapted from other studies.[16,17] Painful stimuli were applied at 2 sites by rapid exposure to the heat lamp. Application at the first site (lateral surface of the proximal phalanx of the thoracic limb) was used to measure HWRL, which was defined as the amount of time elapsed between focusing the light beam and limb withdrawal. Application at the second site (dorsal point of the shoulders of the horse) was used to measure STRL, which was defined as the amount of time between focusing the light beam and detection of skin twitching.

Hair was shaved from the regions of stimulation, and black water-based ink was painted on the skin before application of the focused light. Use of the ink was intended to provide uniform light reflection and heat absorption. Each latency reflex was obtained by use of a precision timer[e] with accuracy measured to 0.01 seconds. The timer was adapted to the equipment and turned on and off simultaneously with the heat lamp. Five repetitions were performed. The highest and lowest values were removed, and the mean of the remaining 3 values was used for data analysis. The painful stimulus was applied for a maximum of 10 seconds to ensure that the tissues were not injured. A secondary nonfocused lamp was substituted frequently to ensure that the horses did not develop a conditioned response to light perception

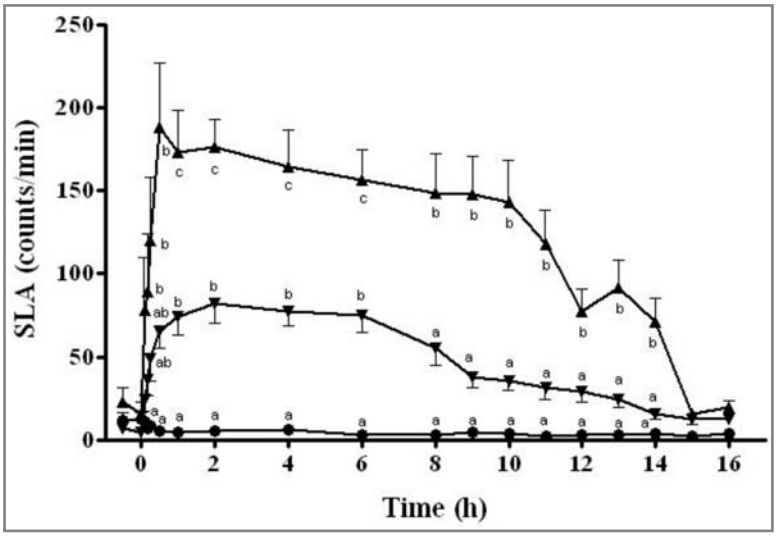

Figure 1—Mean ± SEM values for SLA measured by interruption of light beams emitted from photoelectric sensors after IV administration of saline (0.9% NaCl) solution (circles), 5 µg of buprenorphine/kg (inverted triangles), or 10 µg of buprenorphine/kg (triangles) to 6 horses. There was a 10-day interval between subsequent treatments. Completion of injections was designated as time 0. [a,b,c]Within a time point, values with different letters differ significantly ($P < 0.05$; Tukey test).

rather than to the pain perception caused by the heat of the focused light beam.

Both HWRL and STRL were measured by the same observer (ABC) to establish baseline values. Thirty minutes later, each horse was administered 1 of the 3 treatments (saline solution, 5 µg of buprenorphine/kg, or 10 µg of buprenorphine/kg) as an IV injection. Order of treatments was randomized, and injections were administered into a jugular vein during a period of 5 seconds (time of completion of each injection was designated as time 0). Then, HWRL and STRL were again measured at 0, 5, 15, 30, 60, and 90 minutes and 2, 3, 4, 5, 6, 7, 8, and 11 hours after treatment.

Statistical analysis—Statistical analysis was performed in accordance with the method described elsewhere[18] by use of commercial software.[f] Results were expressed as mean ± SEM. Differences among groups at each time point were compared by use of an ANOVA followed by the Tukey test. Differences were considered significant at values of $P < 0.05$.

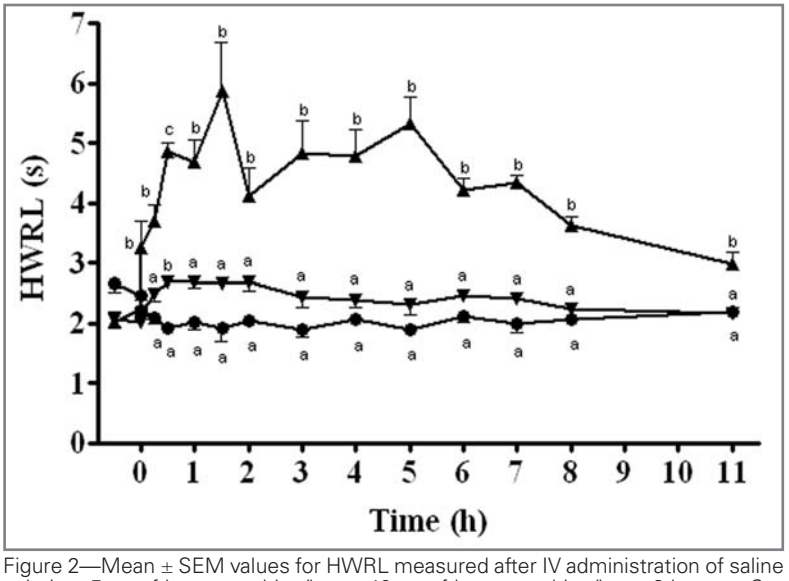

Figure 2—Mean ± SEM values for HWRL measured after IV administration of saline solution, 5 µg of buprenorphine/kg, or 10 µg of buprenorphine/kg to 6 horses. *See* Figure 1 for key.

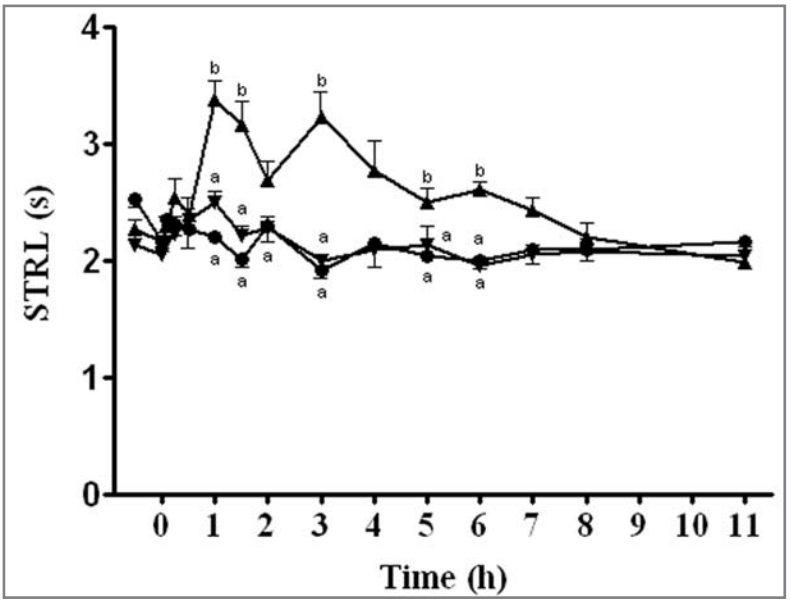

Figure 3—Mean ± SEM values for STRL measured after IV administration of saline solution, 5 µg of buprenorphine/kg, or 10 µg of buprenorphine/kg to 6 horses. *See* Figure 1 for key.

Results

Evaluation of SLA—Excitement was observed in all horses from 5 to 10 minutes after administration of both doses of buprenorphine. Characteristic findings of excitement were restlessness, continuous head nodding, digging, shifting of limbs, vocalizing, trotting, and even galloping.

The SLA was uniform in all horses by 30 minutes after the adaptation period. The light beam was interrupted approximately 10 times/min in all groups of horses before any treatments were administered (**Figure 1**).

The SLA was significantly higher from 1 to 6 hours after administration of 5 µg of buprenorphine/kg and from 15 minutes to 14 hours after administration of 10 µg of buprenorphine/kg, compared with results after administration of saline solution (Figure 1). The SLA was higher from 30 minutes to 14 hours after administration of 10 µg of buprenorphine/kg, compared with the SLA after administration of 5 µg of buprenorphine/kg.

Antinociception evaluation—The HWRL was approximately 2 seconds in horses after administration of saline solution. The HWRL was significantly longer at 30 minutes after administration of 5 µg of buprenorphine/kg, compared with the HWRL after administration of saline solution (**Figure 2**). The HWRL was significantly longer at all time points after administration of 5 µg of buprenorphine/kg, compared with results after administration of 5 µg of buprenorphine/kg or saline solution.

We did not detect a significant difference in STRL when horses were administered 5 µg of buprenorphine/kg or saline solution (**Figure 3**). The STRL was significantly longer between 1 and 6 hours after administration of 10 µg of buprenorphine/kg (except at 2 and 4 hours after administration), compared with the STRL after administration of 5 µg of buprenorphine/kg or saline solution.

Discussion

The IV administration of buprenorphine to horses resulted in a short latency period for increases in SLA as well as for antinociception. In cats, pressure and thermal thresholds increased only at 30 and 45 minutes, respectively, after SC administration of buprenorphine.[19] The fact that the cats of that study were administered bu-

prenorphine by the SC route of administration, whereas the horses of the study reported here were administered buprenorphine by the IV route of administration, could explain the reason we detected a shorter time until onset for the horses of our study.

Various routes of administration in cats can achieve similar plasma buprenorphine concentrations but yield differing maximum increases in thermal threshold above baseline values. Thermal threshold was approximately 12°C above baseline after IV injection of 20 µg of buprenorphine/kg, 10°C after mucosal administration of 20 µg of buprenorphine/kg, and 4°C after IM administration of 10 µg of buprenorphine/kg,[20,21] which revealed that the route of administration of buprenorphine is important for enabling it to reach the effector site. Routes that result in slow uptake may not achieve sufficient concentration gradients to drive the drug into the biophase.

The short time of onset for buprenorphine in horses may be related to the lipophilic characteristics of the molecule, which enable it to quickly bind to opioid receptors in the CNS. In the study reported here, SLA increased more rapidly and for a longer time after administration of 10 µg of buprenorphine/kg. This may have been associated with the high affinity and intrinsic activity of buprenorphine at opioid receptors, which caused prolonged and dose-dependent effects.

Other opioids, such as fentanyl and apomorphine, also increase SLA in horses. Although both of those opioids are pure agonists, their mechanism of action on SLA apparently differs.[3,4] Authors of those studies believe it is likely that fentanyl, but not apomorphine, acts directly on OP3 (µ) receptors because the effects are antagonized by naloxone. Apomorphine increases dopamine release in rats, even in those with lesions in the dopaminergic tract, which indicates that there is no need for a central pathway for the mechanism of action. This effect is comparable to the effect for anfetamine.

The increase in SLA after the administration of buprenorphine in horses may result from activation of dopaminergic pathways. Dopamine, a noradrenaline precursor, is the main catecholamine in the extrapyramidal system of mammals.[7] The striatus body, which is the part of the extrapyramidal motor system related to movement, has a high concentration of dopamine.[22] Catalepsia, stereotyped movements, and increased concentrations of homovalinic acid in the proencephalus have been reported[8] in rodents administered buprenorphine; however, differences among species with regard to how buprenorphine exerts its effects should be considered, and additional studies will be necessary to provide evidence that supports the hypothesis that buprenorphine activates dopaminergic pathways in horses in the same manner that it does in rodents.

Opioid-induced excitement is widely described in healthy people. This excitement can even lead to convulsions.[23] The dose of an opioid necessary to induce excitement is lower in cats, horses, and humans than it is in dogs and monkeys.[24] Opioid-induced excitement has also been observed in healthy horses, even with the use of partial opioid receptor agonists or agonist-antagonist opioids.[3,4,12,25,26] The risk of adverse effects after administration of a dose of morphine in horses is inversely proportional to the intensity of pain.[27] It appears, however, that excitement is minimized or may not be observed in horses that have clinical signs associated with pain and are treated by administration of opioids. This was confirmed in a retrospective study[28] of the postoperative use of morphine in horses in which investigators concluded that the use of morphine was not associated with a greater incidence of adverse effects and may be indicated for use in horses to control or alleviate pain.

In the study reported here, we detected a dose-dependent increase in SLA but analgesia was not observed with the lower dose of 5 µg of buprenorphine/kg. We anticipated that there would be a similar antinociceptive response between the STRL and HWRL; however, analgesia was more prolonged for the HWRL, compared with that for the STRL, after administration of 10 µg of buprenorphine/kg. The possible effect of SLA on the HWRL may explain differences observed in antinociception induced by buprenorphine. A possible error in nociceptive evaluation of the HWRL by use of a thermal stimulus at the phalanx was that an increase in SLA may decrease HWRL; however, in the study reported here, the opposite result was achieved.

To reduce the effects of SLA on HWRL, we used an alternative method adapted by one of the authors (AQ-N) from methods described in other studies.[17,29] For this method, the heat was projected to the dorsal point of the shoulders until cutaneous twitching was observed. According to authors of those other studies,[17,29] the STRL would be more appropriate than the HWRL for investigating the effects of sedatives and opioids because sedatives could delay the HWRL as a result of lethargy and opioids could decrease the HWRL as a result of an increase in SLA.

In the study reported here, the small antinociception observed with the STRL nociceptive test was probably biased by the increased muscular tone and twitching typically observed with the use of opioids in horses, which has been described in ponies treated with morphine or butorphanol[25] and horses treated with alfentanyl.[28] These findings suggest that even if the increase in SLA interfered with the HWRL, this method would appear to be better than the STRL for evaluating antinociception induced by administration of opioids to horses.

For the HWRL, the higher dose of buprenorphine in horses yielded similar antinociception, compared with other reports[30-33] on the use of buprenorphine in other species. In pigs, a decrease in the response to thermal stimulation lasted for 7 hours after administration of 10 µg of buprenorphine/kg and a dose of 5 µg/kg was virtually ineffective.[30] In sheep, administration of 6 µg of buprenorphine/kg induced analgesia for 3 hours (as measured by use of thermal stimulation), although there was no analgesic response evident for mechanical stimulation.[31] Values for a visual analogue scale were reduced for 7 hours after administration of 10 µg of buprenorphine/kg to cats undergoing elective surgeries; in addition, the threshold to thermal stimulation was increased for 12 hours.[11,32] In dogs undergoing arthrothomy, administration of 10 µg of buprenorphine/kg induced analgesia for 7 hours.[33]

Doses of < 10 µg of buprenorphine/kg are virtu-

ally ineffective in some species.[30,31,34] The same result was observed for HWRL in horses in the study reported here. In our study, administration of 10 µg of buprenorphine/kg induced long-lasting analgesia for 11 hours, which is consistent with data reported[10,11,30,32,33] for other species.

Administration of buprenorphine induced a dose-dependent increase in SLA, which should be considered a potential problem in healthy horses. Administration of a dose of 10 µg of buprenorphine/kg resulted in antinociception ranging up to 6 (STRL) or 11 hours (HWRL) after administration in horses. Administration of a dose of 5 µg of buprenorphine/kg did not yield this same antinociception by use of our experimental model.

a. Temgesic, Schering-Plough, Rio de Janeiro, Brazil.
b. Tec Horse 12, Purina, São Paulo, Brazil.
c. LAT-2, Banner Engineering Corp, Minneapolis, Minn.
d. CR200 datalogger, Campbell Scientific Inc, Logan, Utah.
e. FLEX Series 7990, Veeder-Root, Simsbury, Conn.
f. GraphPad Prism, GraphPad Software Inc, San Diego, Calif.

References

1. McMurphy RM. Providing analgesia. In: Moore JN, White NA. *Current techniques in equine surgery and lameness*. 2nd ed. Philadelphia: WB Saunders Co, 1998;2–5.
2. Yaksh TL. Pharmacology and mechanisms of opioid analgesic activity. *Acta Anaesth Scand* 1997;41:94–111.
3. Tobin T, Combie J, Shults T, et al. The pharmacology of narcotic analgesics in the horse III. Characteristics of the locomotor effects of fentanyl and apomorphine. *J Equine Med Surg* 1979;3:284–288.
4. Tobin T, Combie J, Shults T. Pharmacology review: actions of central stimulant drugs in the horse II. *J Equine Med Surg* 1979;3:102–109.
5. Pascoe PJ, Black WD, Claxton JM, et al. The pharmacokinetics and locomotor activity of alfentanil in the horse. *J Vet Pharmacol Ther* 1991;14:317–325.
6. Mama KR, Pascoe PJ, Steffey EP. Evaluation of the interaction of mu and kappa opioid agonists on locomotor behavior in the horse. *Can J Vet Res* 1993;57:106–109.
7. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Gilman AG, Limbird LE, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 9th ed. New York: McMillan Publishing, 1996;521–555.
8. Cowan A, Doxey JC, Harry EJ. The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Br J Pharmacol* 1977;60:547–554.
9. Flecknell PA. Anaesthesia of common laboratory species. In: Flecknell PA, ed. *Laboratory animal anaesthesia*. London: Academic Press Inc, 1996;159–223.
10. Gades NM, Danneman PJ, Wixson SK, et al. The magnitude and duration of the analgesic effect of morphine, butorphanol, and buprenorphine in rats and mice. *Contemp Top Lab Anim Sci* 2000;39:8–13.
11. Robertson SA, Taylor PM, Lascelles BDX, et al. Changes in thermal threshold response in eight cats after administration of buprenorphine, butorphanol and morphine. *Vet Rec* 2003;153:462–465.
12. Szoke MO, Blais D, Cuvelliez SG, et al. Effects of buprenorphine on cardiovascular and pulmonary function in clinically normal horses and horses with chronic obstructive pulmonary disease. *Am J Vet Res* 1998;59:1287–1291.
13. van Dijk P, Lankveld DP, Rijkenhuizen AB, et al. Hormonal, metabolic and physiological effects of laparoscopic surgery using a detomidine-buprenorphine combination in standing horses. *Vet Anaesth Analg* 2003;30:72–80.
14. Carregaro AB, Neto FJ, Beier SL, et al. Cardiopulmonary effects of buprenorphine in horses. *Am J Vet Res* 2006;67:1675–1680.
15. Kamerling SG, Cravens WMT, Bagwell CA. Objective assessment of detomidine-induced analgesia and sedation in the horse. *Eur J Pharmacol* 1988;151:1–8.
16. Kamerling SG, Dequick DJ, Weckman TJ, et al. Dose-related effects of fentanil on autonomic and behavioral responses in performance horse. *Gen Pharmacol* 1985;16:253–258.
17. Kamerling SG, Weckman TJ, Dequick DJ, et al. A method for studying cutaneous pain perception and analgesia in horses. *J Pharmacol Method* 1985;13:267–274.
18. Callegari-Jacques SM. Análise de variância. In: Callegari-Jacques SM, ed. *Bioestatística—princípios e aplicações*. Porto Alegre, Brazil: Editora Artmed, 2003;153–164.
19. Steagall PV, Carnicelli P, Taylor PM, et al. Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *J Vet Pharmacol Ther* 2006;29:531–537.
20. Robertson SA, Taylor PM, Sear JW. Systemic uptake of buprenorphine by cats after oral mucosal administration. *Vet Rec* 2003;152:675–678.
21. Robertson SA, Taylor PM, Sear JW, et al. PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration. *J Vet Pharmacol Ther* 2005;28:453–460.
22. Hornykiewicz O. Dopamine in the basal ganglia. *Br Med Bull* 1973;29:172–178.
23. Wolff BB, Kantor TG, Jarvick ME. Response of experimental pain to analgesic drugs I. Morphine, aspirin and placebo. *Clin Pharmacol Ther* 1966;7:224–238.
24. Muir WW, Skarda RT, Sheehan WC. Cardiopulmonary effects of narcotic agonists and a partial agonist in horses. *Am J Vet Res* 1978;39:1632–1635.
25. Kalpravidh M, Lumb WV, Wright M, et al. Effects of butorphanol, flunixim, levorphanol, morphine, and xylazine in ponies. *Am J Vet Res* 1984;45:217–223.
26. Muir WW, Robertson JT. Visceral analgesia: effects of xylazine, butorphanol, meperidine, and pentazocine in horses. *Am J Vet Res* 1985;46:2081–2084.
27. Muir WW. Drugs used to produce standing chemical restraint in horses. *Vet Clin North Am Equine Pract* 1981;3:17–44.
28. Mircica E, Clutton RE, Kyles KW, et al. Problems associated with perioperative morphine in horses: a retrospective case analysis. *Vet Anaesth Analg* 2003;30:147–155.
29. Queiroz-Neto A, Zamur G, Gonçalves SC, et al. Characterization of the antinociceptive and sedative effect of amitraz in horses. *J Vet Pharmacol Ther* 1998;21:400–405.
30. Rodriguez NA, Cooper DM, Risdahl JM. Antinociceptive activity of and clinical experience with buprenorphine in swine. *Contemp Top Lab Anim Sci* 2001;40:17–20.
31. Nolan A, Livingston A, Waterman AE. Investigation of the antinociceptive activity of buprenorphine in sheep. *Br J Pharmacol* 1987;92:527–533.
32. Stanway GW, Taylor PM, Brodbelt DC. A preliminary investigation comparing pre-operative morphine and buprenorphine for postoperative analgesia and sedation in cats. *Vet Anaesth Analg* 2002;29:29–35.
33. Brodbelt DC, Taylor PM, Stanway GW. A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs. *J Vet Pharmacol Ther* 1997;20:284–289.
34. Slingsby LS, Waterman-Pearson. Comparison of pethidine, buprenorphine and ketoprofen for postoperative analgesia after ovariohysterectomy in the cat. *Vet Rec* 1998;143:185–189.