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Morphine or Tramadol Administration by Epidural Route in Horses - Clinical Evaluation

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ABSTRACT

***Background*:** Opioids are widely used in veterinary medicine, but their use is restricted in horses due to their potential adverse effects, such as reduced intestinal motility and excitation. Morphine and tramadol are opioids recommended for pain control in horses, and the absorption of these drugs by the epidural route is relatively slow due to low lipid solubility, resulting in longer duration of the analgesic effect and a reduction in undesirable effects. This study aimed to monitor the clinical and behavioral alterations in horses administered morphine or tramadol by the epidural route.

***Materials, Methods & Results*:** Eight horses (2 males and 6 females) with mean weight of 336.3 ± 33.4 kg and age of 5.5 ± 1.3 years were allocated to 3 groups in a cross-over design, in which tramadol (TG) [1 mg/kg], morphine (MG) [0.2 mg/kg], and 0.9% NaCl (CG) were administered in a previously implanted epidural catheter. The clinical parameters heart rate (HR), respiratory rate (*rR*), rectal temperature (RT) were measured before treatment administration (MB), 5 (M5), 10 (M10), 20 (M20), 30 (M30), 40 (M40), 50 (M50), and 60 min (M60) after epidural injection. Intestinal motility scores, latency to defecate, and behavioral alterations were evaluated at MB, M10, M30, M60, 120 (M120), 240 (M240), 480 (M480), and 960 min (M960) after treatment administration. Parametric data were subjected to one-way analysis of variance with the Student-Newman-Keuls retest and non-parametric data to the Friedman or Kruskal-Wallis test followed by the Dunn's test, both with significance set at $P \leq 0.05$. Rectal temperature increased considerably in the CG animals from MB (36.8ºC) to M60 (37.4ºC) and in the MG at M20 and M60 (37.4ºC) in relation to MB (36.9ºC). The values of HR, *rR*, and motility scores on the left side did not vary significantly between groups and moments. However, there was a 40% reduction in right-sided intestinal motility scores (upper and lower quadrants) in the MG. In addition, the total intestinal motility score (sum of the four quadrants), 30 min after treatment administration, remained reduced until M120, compared to MB. Concomitantly, 50% of the MG animals had increased latency to defecate, although this was not significant.

***Discussion*:** The maintenance of heart rate and respiratory rate parameters after administration of morphine [0.2 mg/kg] by the epidural route is related to the absence of sympathetic interference and the route of administration. Similarly, the study found no significant differences in the cardiorespiratory system after epidural administration of tramadol at a dose of 1 mg/kg. Generally, such alterations are associated with high doses, associations with other pharmacological classes, or exacerbated use of the opioid. The increase in body temperature in CG and MG is presumably associated with climatic conditions, as it was believed that opioids did not interfere with this parameter. The drop in right-sided and total intestinal motility scores in MG triggered an increase in latency to defecate, which may be associated with the blockade of opioid receptors in the myenteric nervous system, which promotes a reduction in cholinergic tone. There were no alterations in the motility score and latency to defecate after epidural administration of tramadol, as there were after oral or intravenous administration. The slight alterations and absence of variations in clinical parameters caused by the administration of morphine and tramadol by the epidural route in horses, respectively, reinforce the use of these drugs in pain control, given their analgesic potential, already proven in previous studies.

Keywords: analgesia, pain control, equine, motility, opioids.

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INTRODUCTION

There are several classes of drugs for the treatment of pain in horses, especially non-steroidal anti-inflammatory drugs, alpha2-agonists, local anesthetics, and opioids [15]. The use of opioids in horses has been questioned for a long time, due to the possible adverse effects related to the gastrointestinal system and excitation [23].

Morphine is classified as a pure μ agonist and analgesic and, for a long time, its use was discouraged in the species given the adverse effects observed, such as increased heart rate, arterial and central venous pressures, respiratory depression, hypothermia, and inhibition of intestinal motility [27]. Despite this, morphine is indicated for analgesia in horses, either alone or in combination with sedatives to facilitate surgical procedures [16].

Tramadol is considered an atypical opioid, used to treat mild to moderate pain in horses [7,16,28]. This drug differs from other opioids as it minimally interferes with the cardiorespiratory system, gastrointestinal tract, or sedation, and is therefore applicable to acute, chronic, and continuous pain [8]. The use of tramadol is indicated by the epidural route in equine pain management and there are no reports of the development of colic in horses after administration of the drug by this route [7,17,20]. Considering the physiological alterations that opioids can cause in horses, this study aimed to monitor the clinical and behavioral alterations in horses administered morphine and tramadol by the epidural route.

MATERIALS AND METHODS

Animals

Eight adult horses (2 castrated males and 6 non-pregnant females) were used, with mean weight of 336.3 ± 33.4kg and age of 5.5 ± 1.3 years. The horses were in good body condition and were kept in paddocks where they received hay (*Cynodon* sp.), mineral salt[1] (Supra Sal®) for horses and water *ad libitum*.

Animal preparation

The animals were allocated to 3 experimental groups in a cross-over design: tramadol group (TG), morphine group (MG), or control group (CG), with an interval of at least 15 days between each experimental trial, which was carried out in the morning to avoid circadian variations. The catheter was implanted the previous afternoon after trichotomy of the sacrococcygeal region. The sacrococcygeal space was identified after movement of the tail in a dorsoventral direction, and then infiltrating it with 2% lidocaine hydrochloride[2] [Xylestesin 2%® - 3 mL/animal, single-dose] was infiltrated into the subcutaneous space of the sacrococcygeal vertebrae. Five min after anesthetizing the area, the skin was pierced with a scalpel to place the Tuohy 16G[3] (BD®) spinal needle in the epidural space. After confirming its correct location, which was done by the absence of resistance and the pendant drop test, the epidural catheter 18G4 (Perifix®) was introduced cranially (15 cm) and fixed to the skin. Until the start of the experiment, the animals were kept in paddocks with free access to water and food.

Experimental procedure

The animals were not fasted and were placed in the horse chute under natural climate conditions. The animals were administered of morphine[2] [Dimorf® - 0.2 mg/kg, single-dose] in the MG or tramadol[2] [Tramadon® - 1.0 mg/kg, single-dose], in the TG or 0.9% NaCl5 [Saline Solution, 0.9% Sodium Chloride® - single-dose] in the CG through the previously implanted epidural catheter.

Application was standardized at 2 min and final volume (mL) was adjusted with 0.9% NaCl, according to equation 3.4+ (0.013 x weight of animal in kg) [9]. Next, a 0.9% NaCl solution was administered, calculated according to the catheter size (approximately 1 mL), with the aim of pushing the residual treatment volume out of the catheter. For the 1st 60 min, animals were kept in the horse chute and then returned to their original paddocks.

Evaluated parameters and material collection

The parameters evaluated were: heart rate (HR), in beats per minute (bpm), carried out using a stethoscope; respiratory rate (*rR*), in respiratory movements per minute (mpm), by counting the movement of the rib cage and rectal temperature (RT), measured using a digital thermometer in degrees Celsius. The moments at which these parameters were assessed were before the treatment administration (MB), 5 (M5), 10 (M10), 20 (M20), 30 (M30), 40 (M40), 50 (M50), and 60 min (M60) after the epidural injection.

Intestinal motility was investigated by auscultation of the upper right quadrant (URQ) to assess the ileocecal valve, cecum, and right dorsal colon; the

upper left quadrant (ULQ) to assess the left dorsal colon and small intestine; the lower right quadrant (LRQ) to assess the right ventral colon; and the lower left quadrant (LLQ) to assess the left ventral colon. Each quadrant was given an intestinal motility score according to Singh *et al*. [25] in 1997: 0 (no sounds); 1 (crackling, barely audible, and muffled sounds, with a frequency of one per minute); 2 (crackling, barely audible, and muffled sounds, with a frequency of more than once per minute); 3 (audible borborygmi, with a frequency of once per minute); and 4 (audible borborygmi, with a frequency of two to four per minute). The procedure was performed at MB, M10, M30, M60, 120 (M120), 240 (M240), 480 (M480), and 960 min (M960) after the epidural. Intestinal motility auscultation was assessed by the same evaluator throughout the experiment.

The intestinal motility results were grouped into a right-sided intestinal motility score (sum of the URQ and LRQ scores), a left-sided intestinal motility score (sum of the ULQ and LLQ scores), and a total score (sum of the scores of the 4 quadrants).

The interval between the administration of tramadol or morphine or 0.9% NaCl, by the epidural route, and the animal's 1st defecation was called the latency to defecate and recorded in min in all procedures, for subsequent grouping into intervals. In addition, scores adapted were used to observe possible abdominal discomfort [29]. Observations were made at MB, M10, M30, M60, M120, M240, M480, and M960 after the epidural.

Statistical analysis

Scientific Data Analysis and Graphing Software (Sigma Plot 11.0) was used for statistical analyses. The data were initially subjected to the Shapiro-Wilk normality test. Data relating to variations in HR, rR, and RT were subjected to one-way analysis of variance (ANOVA) with multiple replications. The means between each moment of the groups and the moments within each group were compared using the Student-Newman-Keuls test ($P \leq 0.05$) to detect significant differences.

The sum of the scores for intestinal motility, behavioral alterations, and latency to defecate were subjected to the Friedman test (same group) and the Kruskal-Wallis test (between groups), followed by the Dunn's test to detect significant differences ($P \leq 0.05$).

RESULTS

The values of HR, *rR*, and RT are described in Table 1. HR and *rR* showed no significant difference between the moments and between the groups. In this study, there was a significant increase in temperature in the CG animals from MB (36.8ºC) to M60 (37.4ºC), as was also observed in the MG at M20 and M60 (37.4ºC) in relation to MB (36.9ºC). No alterations in rectal temperature were seen after epidural tramadol injection.

There was no significant difference in the left-sided motility score between the moments or between the groups. The reduction in the sum of the intestinal motility scores of the URQ and LRQ was only observed in MG at M30 when compared to MB (Table 2).

The total intestinal motility score, which comprised the sum of the 4 quadrants, decreased significantly by 40% in the GM at M30, M60, and M120, when compared to the MB, as illustrated in Table 3. Even with the reduction in the intestinal motility score, there were no signs of abdominal discomfort. Discrete behavioral alterations were observed in only 1 animal in the MG, 30 min after treatment administration, but these were transient. No behavioral alterations were observed in the other animals and groups.

There was no significant difference in the latency time to defecate, but it was observed that only 50% of the MG animals defecated within 300 min, whereas 100% and 85.7% of the CG and TG animals, respectively, defecated within the same time period (Table 4).

DISCUSSION

Several reports have used epidural injection of morphine in different species, such as dogs [14], cats [1], and horses [6], at a dose of 0.1 mg/kg to produce analgesia. The dose of 0.2 mg/kg of morphine was adopted based on a previous study in horses, in which intestinal transit and motility were assessed [22].

According to the study of the pharmacological profile of morphine (up to 0.1 mg/kg) after epidural administration single-dose or repeated doses in horses, it did not statistically reduce physiological parameters such as heart rate [18]. Other studies also found no significant alterations in this parameter after a dose of 0.1 mg/kg of morphine by the epidural route in horses and ponies [5-11]. Similarly, this study found no significant differences in similar parameters, even with twice the dose, as did [22], due to the absence of sympathetic interference and because the animals were healthy.

Table 1. Means (± DPM) of heart rate (HR), in beats per minute (bpm); respiratory rate (r_R), in movements per minute (mpm); and rectal temperature (RT) in degrees Celsius (ºC), of horses treated with epidural injection of 0.9% NaCl (CG n = 8) or 0.2 mg/kg of morphine (MG n = 8) or 1.0 mg/kg of tramadol (TG n = 7).

		MB	M5	M10	M20	M30	M40	M50	M60
FC	GC	42 ± 7	40 ± 5	40 ± 5	40 ± 4	44 ± 5	44 ± 7	44 ± 5	42 ± 6
	GM	44 ± 4	46 ± 7	47 ± 9	46 ± 8	51 ± 7	48 ± 11	50 ± 10	51 ± 7
	GT	44 ± 6	44 ± 7	43 ± 7	44 ± 7	44 ± 8	46 ± 6	47 ± 6	47 ± 4
fR	GC	12 ± 2	13 ± 3	12 ± 3	11 ± 3	12 ± 2	12 ± 2	12 ± 2	12 ± 2
	GM	12 ± 2	11 ± 1	11 ± 1	11 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 1
	GT	13 ± 2	14 ± 2	14 ± 2	15 ± 2	14 ± 3	15 ± 3	14 ± 2	14 ± 2
TR	GC	36.8 ± 0.3	37.1 ± 0.5*	37.2 ± 0.5*	37.1 ± 0.4*	37.2 ± 0.5*	37.3 ± 0.4*	37.4 ± 0.5*	37.4 ± 0.4*
	GM	36.9 ± 0.7	37.3 ± 0.4	37.3 ± 0.6	37.4 ± 0.6*	37.3 ± 0.5	37.3 ± 0.6	37.2 ± 0.6	37.4 ± 0.5*
	GT	37.2 ± 0.6	37.4 ± 0.5	37.6 ± 0.5	37.6 ± 0.5	37.5 ± 0.5	37.4 ± 0.5	37.5 ± 0.4	37.5 ± 0.4

*Difference (Student-Newman-Keuls test $P \leq 0.05$) in relation to MB.

Table 2. Median, minimum and maximum of the sum of intestinal motility scores in the upper and lower right quadrants of horses treated with epidural injection of 0.9% NaCl (CG n=8) or 0.2 mg/kg of morphine (GM n=8) or 1.0 mg/kg of tramadol (TG n=7).

	MB	M10	M30	M60	M120	M240	M480	M960
GC	5 (5-6)	5 (4-5)	5 (5-5)	5 (4-5)	5 (4-6)	5 (5-6)	5 (5-6)	6 (4-6)
GM	6 (5-6)	4 (3-4)	3* (2-4)	3 (2-5)	3 (2-4)	6 (4-6)	6 (5-6)	6 (5-6)
GT	6 (5-6)	5 (4-6)	5 (4-5)	6 (4-6)	6 (4-6)	5 (5-6)	6 (6-6)	6 (6-6)

* Difference (Dunn's test $P \leq 0.05$) in relation to MB.

Table 3. Median, minimum and maximum of the sum of intestinal motility scores in the four quadrants of horses treated with epidural injection of 0.9% NaCl (CG n = 8) or 0.2 mg/kg of morphine (MG n = 8) or 1.0 mg/kg of tramadol (TG n = 7).

	MB	M10	M30	M60	M120	M240	M480	M960
GC	11 (10-12)	11 (9-11)	11 (10-11)	10 (10-11)	11 (10-12)	11 (11-12)	11 (10-12)	12 (11-12)
GM	12 (11-12)	9 (8-10)	7* (5-8)	7* (5-9)	7* (5-9)	11 (8-12)	11 (11-12)	12 (11-12)
GT	12 (11-12)	11 (10-12)	10 (10-11_	12 (10-12)	12 (10-12)	11 (11-12)	12 (12-12)	12 (12-12)

*Difference (Dunn's test $P \leq 0.05$) in relation to MB.

Table 4. Distribution of latency to defecate in horses treated with epidural injection of 0.9% NaCl (CG n = 8) or 0.2 mg/kg of morphine (MG n = 8) or 1.0 mg/kg of tramadol (TG n = 7).

Interval*	GC	GM	GT
0 - 150	75%	37.50%	71.40%
150 - 300	25%	12.50%	14.30%
300 - 450	0%	37.50%	14.30%
450 - 600	0%	12.50%	0%

*minutes.

Epidural injection of morphine in horses did not alter *rR*, as in several studies which found no respiratory depression after the administration of 0.1 mg/kg or 0.2 mg/kg of morphine by the epidural route in horses [10,20,22]. Respiratory depression is more commonly associated after parenteral administration of opioids, but in a low incidence, as observed in humans (0.25%) [4].

Few studies have reported significant clinical variations caused by the epidural tramadol injection in horses. By inhibiting the reuptake of monoamines, the adverse effects of tramadol include tachycardia, hypertension, and seizures [13]. However, these effects are related to high doses, excessive use of the drug, or administration with drugs that also inhibit serotonin reuptake [28]. In this study, tramadol at a dose of 1 mg/kg by the epidural route did not alter the respiratory rate, thus remaining within physiological values. When evaluating the effects of epidural opioid analgesics in horses [20], similar results were obtained with administration of tramadol by the same route and dose.

According to the systemic and local evaluation associated with long-term peridural catheterization and administration of morphine-detomidine in horses [26], opioids hold little effect on body temperature. When evaluating the clinical effect after epidural injection of morphine (0.1 mg/kg) in horses [11], a slight rise in body temperature was observed, which coincided with the beginning of the afternoon, as observed in this study. The intravenous administration of tramadol in horses in increasing doses resulted in a decrease in rectal temperature 40 min after the end of the last dose [3], which was not observed in the horses evaluated in this study. In sheep, epidural injection of tramadol (1 mg/kg) also resulted in a decrease in rectal temperature from 75 to 120 min after the drug was administered, which may be due to sympathetic nerve blockade and hypotension [12].

In studies evaluating the analgesic effects after epidural injection of morphine (0.1 mg/kg) or tramadol (1.0 mg/kg), head movement and trunk restlessness were observed [21]. Previous reports using a dose of 0.1 mg/kg of morphine applied by the epidural route did not cause any behavioral alterations [11]. Behavioral alterations, such as abnormal weight distribution and occasional digging movements, were observed in the study in only one animal, 30 min after morphine administration by the epidural route, and were transient.

Epidural opioids have been reported to cause mild gastrointestinal alterations, such as reduced gastrointestinal motility and decreased frequency of defecation, but without the concomitant occurrence of colic [18]. Concomitantly, use of morphine by the epidural route in horses at a dose of 0.2 mg/kg temporarily reduced gastrointestinal motility, but without triggering colic or abdominal discomfort [22].

Furthermore, this study found that the epidural injection of morphine reduced intestinal motility by 40%, and consequently 50% of the animals had increased latency to defecate, although not significantly (Table 4). This can be explained by the fact that there are opioid receptors in the myenteric nervous system, and when they are blocked by morphine, acetylcholine is released and cholinergic tone is reduced [2].

There are reports that tramadol does not interfere with intestinal motility when administered orally or intravenously at a dose of 2.0 mg/kg in horses [19]. However, when evaluating the effects of tramadol (2 m/kg) after intravenous injection in horses, signs of abdominal discomfort were noted [24]. Although the literature lacks information on the effects of epidural tramadol injection in horses, in this study there was no significant difference in the time to defecate with epidural tramadol injection (1.0mg/kg) and no alterations were observed in the motility score by the same route.

CONCLUSION

The use of morphine by the epidural route in horses (0.2 mg/kg) statistically and temporarily reduced gastrointestinal motility, but did not cause significant alterations in clinical and behavioral conditions. Tramadol administered epidurally (1.0 mg/kg) did not alter the parameters evaluated, such as behavioral scores and gastrointestinal motility. The results of this study show that the use of morphine or tramadol by the epidural route in horses is safe and an effective alternative for pain control, given its analgesic potential, which has already been proven in previous studies.

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***Ethical approval*.** The study was approved by the Animal Ethics Committee (CEUA) of the School of Agricultural and Veterinarian Sciences (FCAV) of the Universidade Estadual Paulista "Júlio de Mesquita Filho" - Jaboticabal Campus, number 008401/13.

***Declaration of interest*.** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of paper.

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