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Effect of Methadone Combined With Acepromazine or Detomidine on Sedation and Dissociative Anesthesia in Healthy Horses

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ABSTRACT

The aim of this study was to compare the effects of methadone combined with detomidine or acepromazine on the quality of sedation and its influence over dissociative anesthesia in healthy horses. In a crossover design, seven horses were administered with 0.1 mg/kg methadone and 0.02 mg/kg detomidine intravenously (group MD) or 0.1 mg/kg methadone and 0.05 mg/kg acepromazine intravenously (group MA). Subsequently, anesthesia was induced with a combination of 2.2 mg/kg ketamine and 0.1 mg/kg midazolam intravenously. Descriptive scales and footages were used to evaluate the quality of sedation, induction, anesthesia maintenance, and recovery. Physiological parameters, arterial blood gas, and electrolytes were assessed from baseline to the recovery of anesthesia. The MA group showed lower arterial blood pressure and higher heart rate compared with the group MD. A slight decrease in arterial blood oxygen levels was observed after recumbency, more prominently in the MA group. There was no difference in the quality or time of induction or maintenance or recovery of anesthesia between groups. The results suggest that both premedication protocols produce good sedation and quality of anesthesia. Methadone combined with detomidine produced a good cardiopulmonary stability compared with methadone combined with acepromazine and might be safer to be used as premedication for dissociative anesthesia compared with methadone combined with acepromazine in healthy horses.

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1. Introduction

Alpha-2-adrenergic agonists and phenothiazines have been commonly used as sedatives, analgesics, and preanesthetic agents in equine anesthetic management. When administered alone, however, alpha-2-adrenergic agonists are frequently associated with reduction in heart rate (HR) and lower cardiac output and increased systemic and pulmonary vascular resistance [1–4]. Likewise, phenothiazine alone may reduce the cardiac output and peripheral vasodilatation, leading to hypotension [5,6]. Despite the drawbacks, alpha-2-adrenergic agonists promote better sedation than phenothiazines in conscious horses [7–10].

The combination of opioids and alpha-2 adrenergic agonists or phenothiazines enhances analgesia and sedation while reducing the side effects commonly associated with opioid usage, such as central nervous system excitation and decrease in the gastrointestinal tract motility [8–13,22]. Among the opioids often used in premedication, methadone has been increasingly preferred owing to its relative clinical safety and its sedative [14], antinociceptive [10,12], and behavioral effects [12] in conscious horses.

Although methadone alone does not increase antinociceptive thresholds in horses [12,13], the combination of methadone and detomidine has yielded positive results, suggesting its usefulness in the anesthetic management of horses undergoing surgical procedures [10]. Moreover, methadone combined with detomidine produces deep sedation and better antinociceptive effects than methadone combined with acepromazine [10]. The effects of these combinations have been compared in conscious horses, but their influence on dissociative anesthesia remains unclear.

Animal welfare/ethical statement: The study was approved by the Institutional Animal Care Committee of the University of São Paulo under protocol number 2500070416.

Conflict of interest statement: All authors declare that this manuscript represents an original and unpublished material. Authors also declare that this scientific study was conducted following the ethical research guidelines and there is no conflict of interest that would prejudice its impartiality.

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The purpose of this study was to assess the influence of either type of premedication on the quality of sedation and dissociative anesthesia and to determine their impacts on the physiological parameters in healthy horses. Owing to the characteristics of the drugs, detomidine was expected to produce better sedation and a better quality and longer lasting anesthesia than acepromazine when combined with methadone.

2. Material and Methods

The study population consisted of seven mixed-breed adult horses of either sex, weighing 371 ± 20.1 kg (mean ± standard deviation). The health status was assessed using physical examination and hematological and biochemical profile. Each horse underwent both premedication protocols once with a 30-day minimum washout period, and the first treatment was assigned randomly. This study was conducted after the approval of the Institutional Animal Care Committee (2500070416).

All horses were fasted for food for 12 hours before every procedure, with free access to water. Each animal was administered with an intravenous (IV) combination of 0.1 mg/kg methadone (Mytedon 1%, Cristalia, Itapira, Brazil) and 0.02 mg/kg detomidine (Dormiun V 1%, Agener Uniao, Embu-Guaçu, Brazil) (MD group) or 0.05 mg/kg acepromazine (Acepran 0.2%, Vetnil, Louveira, Brazil) (MA group). The quality of sedation was rated 25 minutes after premedication (−5 minutes) based on the agreement of two observers blinded to the treatment, adapted from Taylor et al (2013) [15], and was graded as follows: 0, no sedation and no ataxia; 1, mild sedation, slight drop of the head, and mild ataxia; 2, moderate sedation, drop of the head, and moderate ataxia; 3, marked sedation and ataxia to recumbency.

After 30 minutes, the horses were administered with a combination of 2.2 mg/kg ketamine (Quetamina 10%, Vetnil, Louveira, Brazil) and 0.1 mg/kg midazolam (Dormire 0.5%, Cristalia, Itapira, Brazil), IV (0 minutes) for anesthesia induction. The quality of induction was rated from 0 to 4 based on the scoring system for induction characteristics by Kerr, McDonell, and Young (1996) [16]. Briefly, it can be summarized as follows: 0, smooth induction; 1, smooth induction with no risk to the horse or handlers but some unpredictable movements; 2, achieved recumbency but with rigidity and unpredictable movements, risking injury to the horse or handler; 3, considerable movement or excitation during induction, attempts to stand, risk to the horse or staff; 4, failure to achieve recumbency by the horse. Footages were obtained using a tripod-mounted camera (Canon Universal Camera Tripod 1.80 m, Sao Paulo, Brazil), for the posterior assessment by an experienced observer blind to the treatments.

Physiological parameters were obtained at baseline (−30 minutes), immediately before induction (−5 minutes), and 5, 10, 15, and 90 minutes after induction. While horses were standing (−30, −5, and 90 minutes), HR, respiratory frequency (*f*r), rectal temperature (RT; °C), and gut sounds were assessed with cardiac auscultation using a stethoscope, observation of costal movement, a digital thermometer (Rigid Digital Thermometer MC-245, Omron, Sao Paulo, Brazil), and abdominal auscultation of the four quadrants for 1 minute, resulting in score values from 0 to 16 [17]. Systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), and mean arterial blood pressure (MAP) were measured by means of an oscillometric monitor (Bionet BM5; Bionet Co Ltd, Seoul, South Korea), with the cuff's width being half the diameter of the tail and placed over the coccygeal artery. Blood pressure values were corrected to the level of the heart base by a correction factor of 0.77 mmHg/cm, estimated between the base of the tail and the point of the shoulder [5].

From 5 to 15 minutes after recumbency, HR was obtained using ECG (lead II), with the electrodes in a base−apex arrangement; gut sounds were assessed only from the right quadrants; and blood pressure was measured by means of an oscillometric monitor, without the correction factor. Arterial blood gas analysis was performed at baseline, −5 minutes, and 10 and 90 minutes after induction. A sample of arterial blood (1 mL) was collected from the transverse facial artery in a previously heparinized syringe, after a 0.5-mL lidocaine (Xylestesin 2%, Cristalia, Itapira, Brazil) local block. The sample was analyzed immediately using a portable blood gas and electrolyte analyzer (i-STAT, Abbott Point of Care Inc, Princeton, NY). The *f*r and RT were assessed as described previously.

A rope-assisted recovery was used in a padded recovery stall. The quality of recovery was assessed using the footages and a scoring system (Fig. 1), which was modified from the system by Valverde et al (2013) [18] and included the sum of scores of 10 events during the recovery to obtain a total score. This total score was matched to an overall descriptive score (Fig. 2), ranking the recovery on a scale from 1 to 6, with the lowest number indicating the best recovery. The influence of the two premedication treatments on the duration of dissociative anesthesia was assessed through the time period required for induction, from the ketamine/midazolam injection until the achievement of lateral recumbency; the duration of anesthetic maintenance, from lateral recumbency until the first movement; and the recovery period, from the first attempt to stand until standing without support was achieved.

The Shapiro−Wilk test was used to evaluate the normality. Parametric data were compared to the baseline data using the analysis of variance (ANOVA), followed by Bonferroni post-test and paired *t*-test, between groups. Nonparametric data were compared to the baseline of each group using ANOVA, followed by Friedman's post-test and Wilcoxon test, between groups. Parametric data are expressed as mean ± standard deviation, whereas nonparametric data are expressed as median [interquartile range]. Differences were considered significant at *P*-values < .05.

3. Results

In both the treatment groups, all horses showed deep sedation at −5, scoring 2 [1,2] in the MA group and 3 [2,3] in the MD group, and no obvious arousal or increased locomotor activity occurred.

Recovery quality scoring system

A) Overall attitude	**F) Move to stand**
1. Calm	1. Methodical
2. Calm/determined	2. An organized scramble
3. Confused, dizzy	3. Used walls for support
4. Frantic	4. Ricocheting off walls
B) Activity during recumbency	**G) Strength**
1. Quiet, occasional stretching or head movement	1. Near full
2. Tense	2. Mildly rubbery
3. Struggling	3. Dog-sitting before standing
C) No. attempts to sternal	4. Repeated attempts due to weakness
(No. = score)	**H) No. attempts to stand**
D) Move to sternal	(No. = score)
1. Smooth, methodical	**I) Balance and coordination:**
2. Fighting mat, but controlled	1. Solid
3. Crashing, flopping over	2. Moderate 'dancing'
E) Sternal phase	3. Reflex saves
1. An organized pause	4. Careening
2. Nonexistant	5. Falls back down
3. Multiple	**J) Knuckling**
4. Multiple, with struggle	1. None
	2. Hind limbs only
	3. All four limbs

Fig. 1. Scoring system for quality of recovery.
Modified from Valverde et al (2013) [18].

Descriptive recovery score
1: Smooth, calm and easy recovery in one attempt, no ataxia or mild ataxia of <5 mins' duration
A (1), B (1), C (1), D (1), E (1-2), F (1), G (1), H (1) I (1) J (1) = 10–11
2: Calm recovery with some difficulty or weakness, 1–3 attempts, mild ataxia of >5 but <10 mins' duration
A (1), B (1), C (1-2), D (1), E (1-2), F (1-2), G (1-2), H (1-3) I (2) J (1-2) = 11-18
3: As 2 but ataxia of >10 mins' duration
A (2), B (1), C (1-2), D (1), E (1-2), F (1-3), G (2-3), H (1-3) I (2) J (1-2) = 13-21
4: Incoordinated recovery with notable difficulty and weakness, >3 attempts, marked ataxia, stumbling, ataxia duration of >10 but <20 mins' duration
A (3), B (2-3), C (2-3), D (1-2), E (2-3), F (3-4), G (3-4), H (3-5) I (3) J (2-3) = 24-32
5: Difficult recovery with disorderly efforts and unable to stand in the first 5 attempts. Marked ataxia that can last for up to 20 mins or more
A (4), B (2-3), C (3-x), D (2-3), E (2-3), F (3-4), G (4), H (5-x) I (3-5) J (2-3) = 30-40
6: Accident

Fig. 2. Descriptive recovery score.
Modified from Valverde et al (2013) [18].

Although there was no statistical difference between the groups, horses in the MD group displayed lower head height and palpebral and labial ptosis and lower response to environmental stimuli. The only physiological change after premedication (−5 minutes) was a decrease in *fr* in the MA group.

No difference was found in the quality of induction, with scores of 1 [0; 1] and 1 [0; 3] in the MA and MD groups, respectively, although the MA group had a shorter induction (31 seconds [12; 25]) than the MD group (40 seconds [32; 43]) ($P = .04$). There was no difference in the quality or the time of anesthesia, with a maintenance of 19 minutes [27; 33] for the MA group and 26 minutes [25; 34] for the MD group. During anesthesia, horses belonging to the MD group maintained HR baseline values, whereas those in the MA group showed a significant increase and maintained values nearing 60–70 bpm from 5 to 15 minutes ($P < .01$). The MD group had an increase in the arterial blood pressure, with higher SAP, MAP, and DAP after 5 minutes, returning to baseline levels afterward ($P < .03$). Conversely, the MA group had a decrease in SAP from 5 to 10 minutes ($P = .01$), and lower SAP, MAP, and DAP than the MD group from 5 to 15 minutes ($P < .01$), with the MAP consistently bordering low on 70 mmHg. Reduction in gut sounds was observed after 10 minutes equally in both groups.

Blood gas changes were not observed in standing horses. Respiratory depression occurred in the MA group, as *fr* decreased in relation to the baseline right after premedication, maintaining lower values than in the MD group throughout the procedure. Rectal temperature significantly decreased after 15 minutes in the MA group (Table 1). Although values for pH and $PaCO_2$ remained unchanged, a decrease in arterial blood oxygen levels (SaO_2) occurred in both groups 10 minutes after induction, being more evident in the MA group (Table 2). There was an increase in HCO_3^- in the MD group from 10 to 90 minutes, but there was no change in either group in other electrolytes, such as Na^+ and K^+.

The recovery quality was similar in both groups, with the scores of 2 [2; 2] and 2 [1; 4] for the MA and MD groups, respectively. Likewise, similar recovery times were recorded for both groups, being 15 minutes [9; 29] for the MA group and 17 minutes [12; 26] for the MD group.

4. Discussion

Methadone combined with detomidine causes more marked signs of sedation compared with methadone combined with acepromazine, although the sedation scores did not differ between

Table 1
Mean ± standard deviation or median [interquartile range] of physiological parameters of healthy horses premedicated with methadone (0.1 mg/kg) and acepromazine (0.05 mg/kg) (MA) or detomidine (0.02 mg/kg) (MD).

Parameter	Group	Time (Minutes)					
		−30	−5	5	10	15	90
HR (bpm)	MA	40 [38; 40]	44 [34; 46]	72 [51; 83][b]	64 [54; 79][b]	71 [50; 77][a,b]	38 [32; 42]
	MD	40 [37; 47]	30 [27; 34]	37 [33; 38]	32[31; 37]	32 [29; 37]	40 [34; 44]
SAP (mmHg)	MA	118 [112; 118]	95 [90; 110]	94 [87; 95][a,b]	93 [91; 94][a,b]	94 [93; 96][b]	103 [102; 120]
	MD	126 [120; 135]	124 [112; 160]	165 [142; 176][a]	156 [139; 163]	146 [127; 152]	115 [112; 120]
MAP (mmHg)	MA	86 [80; 89]	71 [66; 85]	69 [67; 74][b]	72 [71; 74][b]	77 [74; 77][b]	78 [70; 105]
	MD	86 [83; 101]	91 [84; 119]	125 [114; 137][a]	120 [108; 124]	103 [94; 116]	97 [93; 104]
DAP (mmHg)	MA	70 [66; 87]	56 [55; 71]	61 [60; 63][b]	62 [61; 62][b]	66 [62; 66][b]	71 [61; 95]
	MD	81 [75; 87]	81 [71; 103]	116 [107; 124][a]	92 [85; 106]	93 [86; 99]	78 [77; 95]
fr (mpm)	MA	22 ± 6	14 ± 2[a]	17 ± 5	14 ± 4	14 ± 4[b]	17 ± 4
	MD	24 ± 8	18 ± 5	21 ± 8	21 ± 8	22 ± 4	19 ± 5
RT (°C)	MA	37.9 ± 0.3	37.6 ± 0.3	37.7 ± 0.4	37.8 ± 0.4	37.5 ± 0.6[a]	37.5 ± 0.7
	MD	37.7 ± 0.5	38.1 ± 0.8	38.0 ± 0.5	37.9 ± 0.6	37.9 ± 0.6	37.5 ± 0.7
Gut sounds	MA	10 [8; 10.5]	5 [4.5; 7]	—	2 [2; 2.75][a]	—	5 [4.5; 5.5]
	MD	10 [7; 1.5]	4 [4; 5]	—	2 [2; 2][a]	—	4 [4; 4]

Abbreviations: bpm, beats per minute; DAP, diastolic arterial pressure; *fr*, respiratory frequency; HR, heart rate; MAP, mean arterial pressure; RT, rectal temperature; SAP, systolic arterial pressure.
Gut sounds score from 0 to 16 (Carregaro et al., 2014) [17].
Measurements taken immediately before premedication (−30 minutes, baseline), 25 minutes after premedication (−5 minutes), every 5 minutes after induction with ketamine (2.2 mg/kg) and midazolam (0.1 mg/kg), and at the end of recovery (90 minutes).
[a] Indicates difference to baseline (−30 minutes).
[b] Indicates difference in a moment between groups.

Table 2
Mean ± standard deviation of blood gas and electrolytes of healthy horses premedicated with methadone (0.1 mg/kg) and acepromazine (0.05 mg/kg) (MA) or detomidine (0.02 mg/kg) (MD).

Parameter	Group	Time (Minutes)			
		−30	−5	10	90
pH	MA	7.42 ± 0.02	7.41 ± 0.01	7.42 ± 0.03	7.42 ± 0.01
	MD	7.43 ± 0.02	7.41 ± 0.03	7.43 ± 0.04	7.47 ± 0.02[b]
$PaCO_2$ (mmHg)	MA	33.1 ± 7.1	38.6 ± 9.5	35.2 ± 3.3	32.9 ± 6.1
	MD	31.8 ± 4.2	33.3 ± 4.4	38.0 ± 2.5	38.9 ± 4.6
PaO_2 (mmHg)	MA	84 ± 7.3	82 ± 18.3	53 ± 12.8[a]	75 ± 8.9
	MD	90 ± 13.2	92 ± 12.9	63 ± 7.2[a]	77 ± 7.8
HCO_3^- (mmol/L)	MA	21.2 ± 3.8	22.2 ± 3.5	22.9 ± 2.2	21.9 ± 4.1[b]
	MD	21.3 ± 2.4	21.4 ± 3.9	25.1 ± 1.8[a]	28.1 ± 3.0[a]
SaO_2 (%)	MA	95.8 ± 1.0	94.6 ± 1.5	85.1 ± 7.0[a,b]	95.7 ± 1.6
	MD	96.7 ± 1.6	96.6 ± 1.5	90.5 ± 3.8[a]	95.7 ± 1.6

Abbreviations: HCO_3^-, bicarbonate; pH, hydrogen potential; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; SaO_2, arterial oxygen saturation.
[a] Indicates difference to baseline.
[b] Indicates difference between groups.

groups. These results are consistent with previous studies in which alpha-2-adrenergic agonists promoted better sedation compared with phenothiazine, attesting the synergistic effects of these drugs [8,10]. The expected arousal or increased locomotor activity due to the opioid administration [12,19] did not occur probably because of the combination with sedatives [3,10]. Although the induction time recorded in the MA group was shorter than in the MD group, we believe that this difference is clinically irrelevant.

Methadone combined with acepromazine appears to have had a stronger impact on the cardiorespiratory parameters, immediately after premedication and throughout the procedure. Acepromazine promotes peripheral vasodilation, followed by reduction in the systemic arterial blood pressure [5]. Accordingly, the MA group had a significantly lower MAP between 5 and 15 minutes, with an increase in HR up to 72 [51; 83] bpm, which may have been a physiological response to hypotension [20,21]. In contrast, the MD group had an increase in blood pressure after 5 minutes, with mild hypertension (MAP > 90 mmHg) after premedication. It is likely that this mild hypertension was related to the administration of detomidine, which causes peripheral arterial vasoconstriction, leading to short-term hypertension [1–3].

It has been shown that the combination of detomidine/opioid can slightly prevent the negative effects of detomidine on HR [3,8,22]. In addition, when detomidine alone is administered, it produces a slight to no change in *fr* but decreases HR, resulting in impaired pulmonary gas exchange, especially due to a ventilation–perfusion mismatch [22]. It has been suggested that such conditions can improve with the administration of an opioid, such as butorphanol, which depresses *fr*, creating a better match with the persistent low blood flow, leading to blood oxygen values closer to the baseline [22]. In the present study, *fr* was slightly depressed in the MD group, with no change in HR, which are conditions similar to those observed in the aforementioned studies. Thus, the presence of methadone might have prevented the negative cardiovascular and blood gas effects that would otherwise have occurred with detomidine alone, hence contributing to a slightly more stable anesthesia in the MD group.

The ventilation–perfusion mismatch contributes to a decrease in the blood oxygen levels in recumbent animals, as the pulmonary blood perfusion in standing horses is superior to that in horses anesthetized in lateral recumbency [23] while $PaCO_2$ can remain unchanged, as also described by Hubbell and Muir (2015) [24]. Accordingly, while there was no change after premedication, both the groups showed a decrease in PaO_2 and SaO_2 10 minutes after induction, probably because the animals were already recumbent at the time. A decrease in PaO_2 is also expected because of the depressant effects of alpha-2-adrenergic agonists and phenothiazines, which can be enhanced by opioids [3,8,25,26]. To improve PaO_2 and SaO_2, 100% O_2 flow can be supplied during recumbency [24,27].

HCO_3^- significantly increased in the MD group from 10 to 90 minutes, consistent with the previous studies [2,3,28], but kept within the physiological reference values for the species. A significant decrease in gut sounds ensued equally in both the groups after the administration of the premedication. These findings had already been expected, as the protocols included opioids, tranquilizers, and alfa-2-adrenergic agonists, known for producing such effects [5,9,29–31]. Despite a decrease in RT in the MA group after 15 minutes, values were considered physiologically acceptable.

Although there was no difference in the quality or length of recovery between the groups, horses belonging to the MA group had more homogeneous recovery scores. The duration of the drugs has been as described as 45–60 minutes for IV detomidine and 4–6 hours for IV acepromazine [30]. Consequently, all animals belonging to the MA group would still be well under the effect of the premedication while detomidine would be nearing its offset. As individual metabolism may slightly influence the duration of a drug, this moment could have resulted in a less heterogeneous recovery for the MD group.

A limitation of this study was the absence of acepromazine and detomidine control groups because of which the influence of the methadone combination on the cardiorespiratory parameters and quality of anesthesia could only be inferred from previous studies. Moreover, the small number and heterogeneity of the animals used in this study may account for the fact that some variables, such as sedation levels or induction time, showed slight discrepancy with observations from the research group.

5. Conclusions

Both combinations were a safe sedative protocol and produced similar effects over the quality and duration of dissociative anesthesia, although methadone combined with detomidine promoted better cardiovascular stability and higher blood oxygen levels compared with methadone combined with acepromazine.

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