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Original Research

Antinociceptive and Behavioral Effects of Methadone Alone or in Combination with Detomidine in Conscious Horses

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ABSTRACT

The antinociceptive and behavioral effects of methadone (MET) alone or combined with detomidine (DET) were studied in horses. Intravenous treatments were randomly administered in a two-phase crossover study. In phase 1, six horses were treated with saline (control) or 0.2 or 0.5 mg/kg methadone ($MET_{0.2}$; $MET_{0.5}$, respectively). In phase 2, six horses were treated with 0.01 mg/kg DET alone or with DET combined with 0.2 mg/kg MET ($DET/MET_{0.2}$). Thermal nociceptive threshold (TNT) and electrical nociceptive thresholds (ENT) were recorded by using a heat projection lamp and electrodes placed in the coronary band of the thoracic limbs, respectively. Spontaneous locomotor activity (SLA) was studied by movement sensors in the stall (phase 1). Chin-to-floor distance was assessed in phase 2. In phase 1, the TNT increased significantly for 30 minute after $MET_{0.5}$ but not after saline or $MET_{0.2}$. Hyperesthesia and ataxia were observed in 2 of 6 and 6 of 6 horses after $MET_{0.2}$ and $MET_{0.5}$, respectively. SLA increased significantly for 120 minutes after MET in a dose-dependent way, but not after placebo. In phase 2, DET and $DET/MET_{0.2}$ significantly increased the TNT and ENT above baseline for 15 and 30 minutes, respectively; thresholds were significantly higher with $DET/MET_{0.2}$ than with DET at the same times. Chin-to-floor distance decreased significantly from baseline for 30 minutes, and no excitatory behavior was observed in both treatments. Although the higher dose of MET induced short-acting antinociception, the associated adverse effects may contraindicate its clinical use. The lower dose of MET potentiated DET-induced antinociception without adverse effects, which might be useful under clinical circumstances.

1. Introduction

Opioids are one of the most effective substances known to both prevent and relieve pain. However, the clinical use of opioids in horses may be limited because of adverse effects such as excitement, increased spontaneous locomotor activity (SLA), and decreased intestinal motility [1-3].

Methadone (MET) is a unique analgesic with affinity for various nonopioid receptors and the mu opioid receptor, which provides analgesia and some adverse effects [4]. When doses above 0.5 mg/kg are used, increased SLA and poor motor coordination were observed in horses [1].

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Although the use of lower doses of MET (up to 0.2 mg/kg) may lessen the severity of the adverse behavioral effects [1], the somatic and visceral antinociception are far from ideal in ponies [5].

Lower doses of IV MET (0.1 mg/kg) have been combined with alpha-2 agonists to enhance the analgesic and sedative effects induced by the latter drug [3,6,7]. Levomethadone (0.1 mg/kg), an optical enantiomer of MET, enhanced and prolonged the somatic antinociception induced by detomidine (DET; 0.01 mg/kg) [8]. However, these effects have not been determined with the racemic compound.

This study evaluated the antinociceptive and behavioral effects of MET in conscious horses. It was hypothesized that MET induces dose-dependent antinociception but also adverse effects, such as increases in SLA and motor uncoordination. During the second phase of the study, the sedative and antinociceptive effects of MET in combination with DET were investigated. The hypothesis was that MET would potentiate the alpha-2 agonist-induced antinociceptive effects and mitigate the adverse effects.

2. Materials and Methods

After approval by the institutional animal care committee (protocol 175 of 2008 and 176 of 2008 CEEA), we enrolled 12 healthy adult horses in a two-phase study (6 horses per phase). Health status was based upon physical and laboratory investigations (blood cell count and serum biochemistry). In phase 1, 6 mares (382 ± 18 kg) were used, and in phase 2, 2 geldings and 4 mares (415 ± 20 kg) were used. Experiments were performed in the early morning, starting between 7:00 and 8:00 AM.

2.1. Determination of Nociceptive Thresholds

Thermal nociceptive threshold (TNT) was determined by a hand held 500-W incandescent heat projection lamp, previously described in studies in horses [9]. A nociceptive stimulus was generated by the lamp focused on the shaved skin of the coronary band in the thoracic limb, painted with water soluble black ink. Distance between the lens and the skin was adjusted to 20 cm. The TNT was defined as the time elapsed between focusing the light beam and hoof withdrawal, for a maximum of 10 seconds to avoid tissue damage. The latency response was measured by a precision timer adapted to the equipment and switched on and off simultaneously with the heat lamp. A sham stimulus was provided by a secondary nonfocused lamp to avoid a conditioned response.

Electrical nociceptive threshold (ENT) was determined by applying progressively increasing voltage to the coronary band of the skin of the front limb. Two adhesive skin electrodes were fixed on the dorsal aspect of the shaved coronary band and attached to an electrical stimulator (Grass S-48; Astro-Med) adjusted to deliver alternate current square waves (50 Hz and 10 ms). The voltage was set at 1 V, with progressive increments of 1 V every 5 seconds. The stimulation was interrupted once an avoidance response (hoof withdrawal) was observed or once 40 V was reached. The ENT was considered the voltage associated with hoof withdrawal. For each time point, TNT and ENT were recorded as the mean value of three repetitions performed for each stimulus.

2.2. Evaluation of Spontaneous Locomotor Activity

The SLA was investigated according methods described previously [10]. Horses were left with minimal disturbance in a stall (16×16 m^2) fitted with four pairs of orthogonally oriented infrared beam photoelectric sensors (LAT-2; Banner Engineering). Total number interruptions of the infrared beams, caused by movement of the horses, were displayed every 5 minutes and stored on a computer for subsequent analysis (CR 200 data logger; Campbell Scientific). Baseline SLA was recorded as the arithmetic mean of the 10-minute period preceding drug injection. Postdrug SLA was averaged from the time elapsed after drug injection (time 0 minute). Behavioral changes were recorded, but not quantified, through a small glass-mirrored window, with the observer positioned outside the stall.

2.3. Study Design and Protocol—Phase 1

Six horses were randomly treated with a minimum of 1-week washout interval with 10 mL of 0.9% NaCl solution (control), 0.2 or 0.5 mg/kg MET ($MET_{0.2}$ or $MET_{0.5}$, respectively; Mytedom; Cristália) administered IV by a jugular vein catheter (Angiocath; Becton-Dickinson) over a 1-minute period. Evaluation of TNT and ENT were performed on different days in a quiet environment with horses restrained by a halter.

For thermal treatment evaluation, measurements with the $MET_{0.2}$ and $MET_{0.5}$ doses were performed at baseline (time 0 minute) and at 15, 30, 60, 90, 120, and 180 minutes after opioid administration; electrical stimulation measurements were made only with the $MET_{0.2}$ dose. Measurements were performed for 60 minutes after physiological saline administration in the control treatment.

Evaluation of SLA and behavior were performed on a separate occasion in the same horses receiving the same treatments after an interval of at least 1 month. The day before the experiment, each horse was placed in the behavioral stall. Environmental disturbances were kept to a minimum. Measurements were made at baseline (0 minutes) and at 5, 15, 30, 60, 90, 120, 180, 240, and 300 minutes in all treatment groups.

2.4. Study Design and Protocol—Phase 2

Using a randomized double-blind design, we treated 6 horses with DET alone (0.01 mg/kg, IV; Dormiun V; Agener União) or with a combination of MET and DET, 0.2 mg/kg ($DET/MET_{0.2}$) in the same syringe. The solution was brought to a final volume of 20 mL with physiological saline and administered during a 1-minute period, allowing a minimum of 1-week washout intervals between experiments.

Sedation was evaluated by measuring the chin-to-floor distance, using a scale fitted to the restraint stock. This was followed by assessing the interest for the environment by offering high quality alfalfa hay and by the TNT and ENT evaluations.