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Behavioral and Antinociceptive Effects of Alfentanil, Butorphanol, and Flunixin in Horses

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ABSTRACT

To determine the behavioral and antinociceptive effects of narcotic and non-narcotic analgesics administered by intravenous injection in horses, 10 thoroughbred mares weighing between 450 and 550 kg and ranging in age from 8 to 13 years old were analyzed. The effects of alfentanil, butorphanol, flunixin, and saline solution on the general activity of the horses were investigated by measuring spontaneous locomotor activity (SLA) and head height (HH) in two behavior stalls. The antinociceptive effects of alfentanil (0.02 mg kg^{-1}), butorphanol (0.1 mg kg^{-1}), flunixin meglumine (0.5 mg kg^{-1}), and saline were determined by measuring skin twitch reflex latency (STRL) after thermal cutaneous nociceptive stimulation. A paired Student *t*-test was used to compare SLA and HH between the groups of horses receiving different doses of the same drug at various time points. The Tukey test was used to compare the antinociceptive effect of the treatments. Differences were considered significant when *P* value was $<.05$. Horses treated with opioid analgesics demonstrated excitation, as shown by a significant increase in SLA at all doses tested and by neighing and demonstrating attentive attitudes with movement of the ears, stereotypical walking, and ataxia in most of the animals. HH was elevated only in animals treated with alfentanil. Antinociception was observed at 5 and 30 minutes after administration of alfentanil and butorphanol, respectively. Increased SLA was observed at 30 and 90 minutes after administration of alfentanil and butorphanol, respectively. We observed no effect on antinociception in horses given flunixin. In conclusion, this study suggests that alfentanil has a faster onset and a shorter duration than butorphanol; however, both drugs are able to stimulate the central nervous system.

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1. Introduction

Alleviation of pain in animals is necessary for clinical and surgical procedures [1]. The drugs that are most often used in animal pain management are opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Opioids produce

a dose-dependent analgesic effect and represent the most effective analgesic drug class for treating perioperative pain. Opioids are also typically effective for the treatment of visceral pain [2].

The pharmacodynamic effects of opioids are related to the type of opioid receptor that is stimulated [3]. The mu receptors are distributed throughout the spinal cord, brainstem, midbrain, cortex, and peripheral neurons and are involved in antinociceptive activities, including dose-dependent inhibition of responses to thermal cutaneous stimuli [4]. However, side effects, which include respiratory depression, miosis, reduction of gastrointestinal motility,

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muscle spasms, euphoria, sedation, physical dependence [4], and increased locomotor activity, may follow the use of mu receptor-stimulating opioids such as alfentanil in horses [5]. The kappa opioid receptors are localized in the brain, spinal cord, and peripheral nervous system. The kappa opioid agonists such as butorphanol can suppress the response to visceral chemical stimuli without interfering with somatic nociception [6] while causing little to no effect on locomotor stimulation [7,8].

NSAIDs inhibit the synthesis of prostaglandins, which prevents the initiation of the inflammatory cascade. NSAIDs are used to treat pain associated with chronic musculoskeletal disorders, and the anti-inflammatory properties of NSAIDs in treating visceral pain have been well documented in horses [8]. In addition to their peripheral mechanisms of action, the effect of NSAIDs on the central nervous system, which includes spinal cord antinociception, has been well established [9].

Several studies have pointed out that the antinociceptive effects of NSAIDs on clinical pain involve both peripheral and central nervous system sensitization [10,11]. In a review analyzing the opioidergic effects of NSAIDs on the central nervous system (CNS), the authors concluded that the analgesic effect of these drugs depends on their association with endogenous opioids [12]. Another study [13] in a rat model using carrageenan-induced inflammation of the hind paw, naloxone reversed or prevented the antinociceptive activity of flunixin, suggesting that the antinociception produced by flunixin was mediated by endogenous opioids.

A recent study showed that administration of NSAIDs (dipyrone, diclofenac, ketorolac, and lornoxicam) into the nucleus raphe magnus (NRM) produced antinociception, as shown by increases in the reflex time of rats subjected to tail-flick and hot-plate assays [14]. Naloxone administration into the NRM decreased the antinociceptive effect of the NSAIDs.

Flunixin is an NSAID derived from a carboxylic acid, and the antihyperalgesic mechanism of flunixin is based on the inhibition of cyclooxygenase. Flunixin has analgesic, antipyretic, and anti-inflammatory properties and is one of the drugs most commonly used for the treatment of visceral pain in horses [8].

Musculoskeletal and visceral pain occur commonly in horses, and in determining the ideal pharmacological strategy, the cause, development, and intensity of the process as well as the adverse effects resulting from analgesic therapy should be considered. Therefore, the aim of this study was to investigate and compare the effects of alfentanil, butorphanol, and flunixin on spontaneous locomotor activity and nociception in horses.

2. Materials and Methods

2.1. Animals

Ten thoroughbred mares were used for each group in this study. The horses belonged to the experimental herd of the Faculty of Agricultural and Veterinary Sciences of Jaboticabal, UNESP. The average age of the horses was 9.6 ± 2.8 years old, and the average weight was 500 ± 70 kg. The experimental protocol was approved by the Institutional

Commission of Animal Ethics of FCAV/UNESP (CEBEA-001641).

2.2. Experimental Design

For the investigation of locomotor activity, behavior, and head height (HH), 2 horses (one in each behavior stall) were analyzed each day. The order of drugs and doses administered was randomized. For the investigation of nociception, 4 horses per day received one of the drugs under investigation. The minimum time interval between treatments was 10 days.

2.3. Drugs and Doses

Alfentanil (Rapifen; Jansen-Cilag Farmacêutica Ltda., São José dos Campos, São Paulo, Brazil) was administered at doses of 0.01, 0.02, and 0.03 mg kg⁻¹. Butorphanol (Torbugesic; Fort Dodge Saúde Animal Ltda., Campinas, São Paulo, Brazil) was tested at doses of 0.05, 0.1, and 0.15 mg kg⁻¹. Flunixin meglumine (Banamine; MSD Saúde Animal Ltda., Cotia, São Paulo, Brazil) was administered at doses of 0.25, 0.5, and 1.0 mg kg⁻¹. Saline (NaCl) 0.9% (Solução Fisiológica; Glicolabor Indústria Farmacêutica de Ribeirão Preto, São Paulo, Brazil) served as a control.

Drugs were administered by jugular venipuncture after antisepsis with iodinated alcohol.

2.4. Evaluation of General Activity and Behavior

2.4.1. Technique

General activity was evaluated by measuring spontaneous locomotor activity (SLA) and HH in individual behavioral stalls. The stalls were equipped with four photoelectric sensors (Banner Engineering, Minneapolis, MN) installed 45 cm from the floor and spaced equally around the stall [15-17]. Each interruption of the infrared light beam produced a pulse, which was recorded in counts per minute in a data storage unit (model CR10; Campbell Scientific, Inc., Logan, UT) connected to a computer. Interruptions of the light beams corresponding to each photocell were converted to counts per minute and recorded as the total number of interruptions of the four beams per 5 minutes. The peak SLA refers to the greatest number of interruptions that occurred during a 5-minute time interval. HH was determined by measuring the distance from the ground to the lower lip of the animals with the aid of rulers painted on the walls of the stall. The behavior of excitability was determined qualitatively by the assessment of eye openness, neighing, and an attentive attitude with movement of the ears, stereotypy (walking in circles in a rhythmic manner), and ataxia, which were not quantified but were observed constantly.

The equipment was controlled, animals were observed, and HH was measured in an observation room situated between the two stalls. This room was fitted with a window composed of special glass, which prevented the animals from becoming aware that they were under observation.

2.4.2. Experimental Procedure

The animals were confined to the stalls for 12 hours before the start of the experimental procedures to allow

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