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RESEARCH PAPER

Effects of intraarticular ropivacaine and morphine on lipopolysaccharide-induced synovitis in horses

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Abstract

Objective To compare the intraarticular (IA) analgesic effects of ropivacaine and morphine in horses with experimentally induced synovitis.

Study design Randomized, blinded cross-over design.

Animals Twelve healthy mixed breed horses between 8–15 years old.

Methods Synovitis was induced in the left radiocarpal joint with an injection of lipopolysaccharide (*Escherichia coli* 055:B5). Six hours later, the horses were treated with an IA injection of 40 mg of ropivacaine (ROPI), 40 mg of morphine (MOR), 20 mg of ropivacaine added to 20 mg of morphine in saline (RM) or 4 mL of saline (SAL), as control. Analgesia was measured subjectively using a numerical rating scale, a simple descriptive scale, pain upon maximal flexion of the carpus and by the range of motion exhibited by the affected joint. Data are reported as mean ± SD and were analyzed using ANOVA. Blood and synovial data were analyzed by split plots in time with units (treatments: SAL, ROPI, MOR and RM) and subunits (times: T0–24), in a completely randomized design with six replicates. Mean comparisons were made by Tukey's test; differences were considered significant at $p < 0.05$.

Results Ropivacaine had a clinical analgesic effect with a relative short duration (~2.5 to 3.5 hours). Morphine had a slower onset of action than ROPI, but a stronger analgesic effect of longer duration. The RM showed an earlier onset of action than MOR and had a strong analgesic effect for the 24-hour post-injection period. All treatments caused a significant decrease in total nucleated cells compared with the control, 24 hours after administration.

Conclusions and clinical relevance Morphine alone or in combination with ropivacaine produced a strong analgesic effect of prolonged duration, which may offer pain relief for acute synovitis for at least 24 hours.

Keywords analgesia, equine, intraarticular, morphine, ropivacaine, synovitis.

Introduction

Joint injuries are common in horses and, in one survey, 33% of lameness originated from articular injuries (Leme et al. 1999). Pathologic conditions that involve the joints of horses cause a decrease in their athletic performance (Todhunter & Lust 1990). Primary synovitis is a lesion that usually develops in the carpal and metacarpo/metatarsophalangeal joint of young horses during the early stages of training (McIlwraith 1987). Synovitis is characterized by joint effusion and decreased range of motion. Pain is generated when thermal, chemical and mechanical stimuli in the joint activate peripheral afferent fibers (Hall et al. 2001). Additionally, the release of proinflammatory mediators (bradykinins, prostaglandins and leukotrienes) decreases the potential for activation of peripheral afferent receptors (Todhunter & Lust 1990).

Pre-emptive, peri-operative, and post-operative/post-injury analgesia for synovitis can be provided in a number of ways. Combinations of different analgesic methods, described as multimodal analgesia, have proven to be highly effective in other species and should be appropriate for horses (Aguiar 2005). Combinations of analgesics that act through different mechanisms produce a synergistic or at least additive effect (Aguiar 2005; Taylor 2005). Evidence shows that opioids, such as morphine, can produce an analgesic effect through peripheral receptors (Stein 1996; Sheehy et al. 2001; Benson 2002) and this analgesic effect is enhanced in the presence of inflammation (Keates et al. 1999). Studies in humans (Stein et al. 1991) and in dogs (Sammarco et al. 1996; Keates et al.1999) indicated that small doses of intraarticular (IA) morphine can promote effective analgesia after arthroscopic surgery.

Local anesthetics are often used in equine practice for both diagnosis and treatment of musculoskeletal injuries of the distal limbs (Monteiro 2005). Local anesthetics act by producing conduction blockade in sensory neurons and retarding the influx of Na^+ ions. They have variable potency, stability, toxicity and capability of penetrating different tissues. Ropivacaine is a long-lasting amino-amide local anesthetic (McClure 1996) that shows similar physical properties to bupivacaine, except that it is a pure S-(−) enantiomer. Ropivacaine promotes vasoconstriction whereas lidocaine, mepivacaine and bupivacaine promote vasodilation (Hall et al. 2001). Rautoma et al. (2000) claim that ropivacaine has dynamic and kinetic functions that are similar to bupivacaine but with less neuronal and cardiac toxicity, furthermore, its decreased lipid solubility, mainly on myelinated motor fibers (alpha), shows that ropivacaine contributes to a faster return of motor function (Williams 1996). To date, there is little or no information available concerning the disposition and pharmacokinetics of ropivacaine and its effects on joint analgesia in horses. The present study evaluated the analgesia provided by ropivacaine and morphine in horses with lipopolysaccharide-induced synovitis.

Materials and methods

Horses used in this experiment were managed according to the rules and regulations of the Institutional Animal Care Use Committee at the University (protocol 1.28/05). Twelve healthy mixed breed horses aged 8–15 years and weighing 316 ± 33 kg (weight range from 280 to 380 kg) were randomly assigned to four equal treatment groups: Saline/control (SAL), ropivacaine (ROPI) (1% ropivacaine chloride, Naropin; Astra Zeneca, MA, USA), morphine (MOR) (1% morphine sulphate; Dimorf, Cristália Ltda, Itapira, SP, Brazil), and ropivacaine with morphine (RM), in a two period cross-over study, with a 30 day-washout period between treatments.

All horses were maintained in stalls and received hay and water *ad libitum* during the experimental protocol. Temperature, heart and respiratory rate measurements, blood and synovial fluid analysis, and an orthopedic examination to rule out pre-existing musculoskeletal injuries were performed in all horses. The left radio-carpal joint was aseptically prepared prior to arthrocentesis. A volume of 1 mL of lipopolysaccharide (0.5 ng/joint) (*Escherichia coli* 055:B5; Sigma Chemical Co., St Louis, MO, USA) was injected into the radio-carpal joint. Six hours later, the horses received an IA injection of either SAL (4 mL of 0.9% saline); ROPI (40 mg of 1% ropivacaine in 0.9% saline), MOR (40 mg of 1% morphine in 0.9% saline) or RM (20 mg of ropivacaine and 20 mg of morphine in 0.9% saline).

Rectal temperature, heart and respiratory rate, mucous membrane color, capillary refill time and gut motility were recorded prior to LPS injection (T-6), 6 hours after LPS injection (T0) and at 30 minutes (T0.5), 1.5 (T1.5), 2.5 (T2.5), 3.5 (T3.5), 6 (T6), 12 (T12), 18 (T18) and 24 hours (T24) after injection of treatments and finally at 48 hours to rule out joint inflammation. The range of motion (normal *versus* reduced), pain upon maximal flexion of the carpus (MFP) (none *versus* present), and degree of lameness using a modified version of the standard American Association of Equine Practitioners (AAEP 1991) grading system, described here as the Numerical Rating Scale (NRS), (0-none, 1-difficult to observe and inconsistent, 2-difficult to observe, but consistent, 3-moderately discernible, 4-obvious lameness with full weight-bearing, 5-not weight-bearing) were determined by two investigators blinded to treatment. The horses were evaluated by one of these investigators before injection (baseline) and at T0-24 hours after drug injection. The NRS and SDS were the only two variables analyzed and compared to T0 (6 hours after LPS injection) while other variables were compared to baseline (T-6). All horses were videotaped trotting and images were stored for later