Analgesic effects of subarachnoidally administered hyperbaric opioids in horses

Cláudio C. Natalini, DVM, PhD; Alexandre da S. Polydoro, DVM, MS; Renata L. Linardi, DVM, MS

Objective—To evaluate the effects of subarachnoidally administered hyperbaric morphine, buprenorphine, and methadone on avoidance threshold to noxious electrical stimulation of the perineal, sacral, lumbar, and thoracic regions in horses.

Animals—6 healthy adult horses.

Procedures—Horses were assigned to receive subarachnoid administration of hyperbaric morphine (0.01 mg/kg), buprenorphine (0.001 mg/kg), methadone (0.01 mg/kg) or 10% dextrose solution in equal volumes (5 mL). Electrical stimulation was applied every 10 minutes for 60 minutes and every 30 minutes for 120 minutes after subarachnoid injection over the dermatomes of the perineal, sacral, lumbar, and thoracic regions, and the avoidance threshold voltage was recorded. Heart and respiratory rate, blood gas tensions, serum electrolyte concentrations, and sedative effects were also evaluated.

Results—Administration of 10% dextrose solution did not change the avoidance threshold. Morphine and methadone significantly increased the avoidance threshold by 10 minutes after injection, which lasted until 120 minutes after subarachnoid administration in the perineal, sacral, lumbar, and thoracic regions. Profound analgesia (avoidance threshold > 40 V) was achieved in all regions. Buprenorphine also significantly increased the avoidance threshold by 10 minutes (36 V) after injection, which lasted 60 minutes and was considered moderate. Heart rate, blood pressure, respiratory rate, and blood gas tensions stayed within reference range. No ataxia, signs of sedation, or CNS excitement were observed.

Conclusions and Clinical Relevance—Subarachnoid administration of hyperbaric morphine or methadone produces intense analgesia for 120 minutes over the dermatomes of the perineal, sacral, lumbar, and thoracic areas without cardiorespiratory depression, ataxia, or CNS excitement in horses. (Am J Vet Res 2006;67:941–948)

Neuraxial administration of local anesthetic results in sympathetic block, sensory analgesia, and motor block. Subarachnoid administration of an anesthetic requires a small mass or volume of drug, compared with epidural administration of an anesthetic, which necessitates the use of a larger mass or volume of local anesthetics that may lead to pharmacologically active blood concentrations and adverse effects and complications. To produce a more segmental effect, hyperbaric local anesthetic solutions are used. Classically, these solutions are denser (hyperbaric), compared with CSF. Density is defined as the weight in grams of 1 mL of solution. Density is a major determinant for distribution, duration, and degree of the effect achieved following subarachnoid administration of local anesthetics.

Subarachnoid injection and catheterization techniques have been extensively described for horses, and no major complications were reported. Compared with epidural administration, subarachnoid injection can be more complicated, as locating landmarks and accessing the lumbosacral subarachnoid space are more time consuming and difficult than the intercoccyeal epidural space. Providing effective analgesia in horses remains challenging. Nonsteroidal anti-inflammatory drugs can be associated with potentially deleterious gastrointestinal tract and renal effects.

Intravenous administration of opioid analgesics has been associated with ileus and behavioral changes in horses. Using μ-opioid receptor agonist through subarachnoid administration to treat horses in pain may bring important advantages.

Subarachnoid administration of opioids has proven to be effective in producing profound and long-lasting analgesia in humans. Morphine is the standard against which all others are compared. Methadone is similar to morphine in potency but highly lipid soluble. Buprenorphine is a partial opioid μ-receptor agonist producing long-lasting analgesia. Sympathetic stimulation and CNS excitation are observed with IV administration of opioids in horses.

Potency and duration effect of opioids following intrathecal or epidural administration is related to their lipid solubility in humans and horses. Many factors have been hypothesized to influence the spread of local anesthetics and opioids within the CSF, including anatomic characteristics of the patient, physical properties of CSF, injection technique, and the dose and properties of the drug.

To our knowledge, no studies have described the effects of subarachnoidally administered hyperbaric opioids on dermatome analgesia in horses. We hypothesized that subarachnoidly administered morphine, methadone, and buprenorphine would provide profound analgesia with minimal sedation or effects on cardiopulmonary function, behavior, and motor function in horses. The purpose of the study reported here was to evaluate and compare the analgesic effect of subarachnoidly administered hyperbaric morphine, buprenorphine, and methadone on pain threshold to electrical stimulation and on behavior, cardiovascular, and respiratory response variables in horses.

Received September 29, 2005.
Accepted December 2, 2005.
From the Equine Health Studies Program, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803 (Natalini, Linardi); and Universidade Federal de Santa Maria, Programa de Pós-graduação em Medicina Veterinária, Santa Maria, RS, Brazil (Polydoro).
Address correspondence to Dr. Natalini.
Materials and Methods

Animals—Six healthy adult horses (2 geldings and 4 mares) from the university teaching herd were used in the study. Horses had a mean $\pm$ SD age of 10.8 $\pm$ 2.2 years and ranged in body weight from 445 to 570 kg (466 $\pm$ 69 kg). The Louisiana State University School of Veterinary Medicine Institutional Animal Care and Use Committee approved the protocol.

Study design—A crossover (6 horses X 4 treatments) design was used. Horses were maintained on pastures and placed in a stall shortly before each experiment. Each horse was sedated with xylazine (1 mg/kg, IV) for insertion of catheters 48 hours before the actual study. For subarachnoid injections, a 19-gauge sterile catheter was placed in the lumbosacral space. Food was withheld overnight before each experiment, but horses had access to water.

Subarachnoid catheterization—The correct region for the subarachnoid catheter placement was determined by palpating the caudal borders of the tuber coxae, the cranial borders of the tuber sacrale, and the midline depression between the sixth lumbar and the second sacral vertebrae. After sedation, all horses had the lumbosacral vertebral interspace clipped and the skin surgically prepared and covered with a sterile transparent dressing. The skin, subcutaneous tissue, and muscle at the lumbosacral region and the supraspinous and interspinous ligaments were locally anesthetized with 2% lidocaine solution. A 17-gauge, 17.78-cm-long epidural needle with stylet was inserted perpendicularly along the median plane of the lumbosacral intervertebral space, until the lumbosacral subarachnoid space was reached. To confirm successful needle placement in the subarachnoid space, the needle stylet was removed, and a clear CSF sample was withdrawn into a syringe. After appropriate placement, the bevel of the needle was directed cephalad, and 20 cm of a sterile 19-gauge, 91.4-cm-long polyurethane spring-wire reinforced epidural catheter was advanced cranially through the needle into the subarachnoid space. The epidural needle was removed, and the catheter was left in place, sutured to the skin, and covered with sterile transparent dressing and gauze sponges. Iodine ointment was applied every 3 days at the site of insertion after checking for signs of skin infection or secretions around the insertion site. Catheters were flushed daily with 10 U/mL of heparinized saline (0.9% NaCI) solution. Catheters were left in place for 28 days. All horses received randomly all 4 treatments, administered subarachnoidally, with ≥ 5 days between each treatment. The investigator (RLL) involved in collection of data and making behavioral observations was blinded as to the identity of the agent being tested. Measurements of response variable took place immediately prior to subarachnoid injection and then at 10, 20, 30, 40, 50, 60, 90, 120, 150, and 180 minutes after subarachnoid injection.

After catheter placement, CSF samples were collected and tested for specific gravity with a refractometer. Specific gravity for equine CSF was determined to be 1.006. Solutions with specific gravity $>1.006$ were considered hyperbaric in relation to equine CSF.

Methadone was chosen because of its similarities with morphine in lipid solubility. Buprenorphine was chosen because of its long duration of action. Doses were approximately one tenth of the doses administered IV in horses. Hyperbaric morphine (0.01 mg/kg), buprenorphine (0.001 mg/kg), and methadone (0.01 mg/kg) in equal volume (5 mL) were obtained by diluting the opioids with 10% dextrose solution for subarachnoid administration. Control group horses received 5 mL of 10% dextrose solution without opioids. The specific gravity of the solutions was 1.043 for 10% dextrose solution, 1.042 for morphine, 1.038 for methadone, and 1.034 for buprenorphine.

Heart rate and blood pressure (systolic, diastolic, and mean) were recorded as well as respiratory rate. By measuring the distance from the muzzle to the floor in centimeters, the amount of sedation was assessed. A lowering of the head over time was considered a sign of sedation. If extreme sedation or recumbency occurred, affected horses would be placed under general anesthesia and mechanically ventilated, have the opioid reversed with naloxone administration, and be transported to the equine intensive care unit. Data were collected before each series of electrical stimulation. Arterial blood gas tensions were also determined prior to and at 90 and 180 minutes after subarachnoid injection to evaluate possible respiratory depressant effects of the opioids.

Dermatomal stimulation was assessed by the use of an electrical stimulator. Two adhesive electrodes were placed approximately 5 cm apart over each of 9 dermatomes that include 5 anatomic areas.25 The perineal and inguinal area included dermatomes 1 and 2, which are innervated by the coccygeal roots of the pudendal and caudal rectal nerves, and dermatome 3, which is innervated by the ventral branches of lumbar nerves L1 to L3. The sacral area included dermatome 4, which is innervated by the caudal cutaneous femoral nerve originating from sacral nerves S1 and S2, and dermatome 5, which is innervated by sacral nerves S1 to S5. The lumbar area included dermatomes 6 (innervated by lumbar nerve L1), 7 (innervated by lumbar nerve L2), 8 (innervated by lumbar nerve L3), and 9 (innervated by lumbar nerves L1 to L6). The thoracic area included dermatome 10, which is innervated by thoracic nerves T8 to T18.

The skin over these dermatomes was not clipped. Serial electrical stimulation (10 to 80 V with increases of 10-V increments; direct current, 50 Hz; duration of 10 milliseconds) from perineal to thoracic dermatomes was applied to assess analgesia before and at 10-minute intervals for 180 minutes after subarachnoid administration. Dermatomes were stimulated 1 at a time. Electrical stimulation was applied at a rate of 10 V/s until a positive response was obtained but not to exceed a maximum of 60 seconds for total time for each dermatome. Positive responses were defined as purposeful avoidance movements of the tail, limbs, trunk, head, or neck; attempts to kick; and turning the head toward the site of electrical stimulation at the time the stimulation was applied. Twitching of the skin was not considered an avoidance response. The voltage at which avoidance was first detected was recorded and considered the threshold for avoidance. A threshold value $>40$ V was considered profound analgesia, in accordance with another report.26 The observer (RLL) was not aware of the treatment administered to each horse or the voltage applied to the dermatomes.

Statistical analysis—Calculation of the sample size was conducted by considering a minimum difference of 20 V between groups as the smallest difference considered significant, at a value of $\alpha = 0.05$ and a power of 0.80 ($n = 6$). Continuous data (threshold voltage) were summarized and graphed as the mean $\pm$ SD. Measured variables were evaluated for an effect of time and treatment (hyperbaric vs 10% dextrose solution) by use of a 2-way ANOVA. Significance for time points and within treatments over time was determined by use of Bonferroni posttest methods. Significance was set at values of $P > 0.05$. All analyses were performed by use of a commercially available software program.

Results

No significant differences were found for cardiovascular and respiratory variables. Heart rate, blood
pressure, respiratory rate, and blood gas tensions stayed within reference range limits. No ataxia, signs of sedation, or CNS excitement were observed. Signs of transient discomfort, as revealed by skin twitching and turning the head toward the injection site, were observed during the injection time and disappeared at the end of the injection. All horses were discharged from the study without clinical signs of complications.

Avoidance threshold for noxious electrical stimulation increased from baseline for buprenorphine, morphine, and methadone. Analgesia was considered profound after 10 minutes at perineal, sacral, lumbar, and thoracic dermatomes and lasted approximately 120 minutes for morphine and methadone.

At 10 minutes, threshold avoidance to electrical stimulation in the perineal region increased from 10 V to 29 ± 11 V, 43 ± 10 V, and 35 ± 10 V for morphine, methadone, and buprenorphine, respectively. At the sacral region, threshold voltage increased from 10 V to 36 ± 12 V, 35 ± 4 V, and 25 ± 7 V for morphine, methadone, and buprenorphine, respectively. At the lumbar region, electrical threshold increased from 10 V to 28 ± 8 V, 40 ± 6 V, and 25 ± 5 V for morphine, methadone, and buprenorphine, respectively. At the thoracic region, avoidance threshold increased from 10 V to 39 ± 12 V, 35 ± 9 V, and 33 ± 7 V for morphine, methadone, and buprenorphine, respectively.

Increase in avoidance threshold was detected from 10 to approximately 180 minutes in all dermatomes for all opioids, being more pronounced up to 90 minutes for methadone and 120 minutes for morphine. With buprenorphine, avoidance threshold was increased from 10 to approximately 30 V for about 40 minutes (Figure 1). Maximum avoidance threshold in the perineal dermatome was obtained at 50 minutes (47 ± 10 V) minutes, 10 minutes (43 ± 10 V), and 40 minutes (31 ± 7 V) with morphine, methadone, and buprenorphine, respectively. In the sacral dermatome, maximum avoidance electrical threshold was observed at 40 minutes (47 ± 13 V), 90 minutes (47 ± 4 V), and 30 minutes (31 ± 5 V) with morphine, methadone, and buprenorphine, respectively. The lumbar dermatome had peak threshold at 50 minutes (40 ± 11 V), 10 minutes (40 ± 6 V), and 20 minutes (32 ± 7 V) with morphine, methadone, and buprenorphine, respectively. In the thoracic dermatome, peak threshold was obtained at 40 minutes (52 ± 5 V), 90 minutes (43 ± 14 V), and 10 minutes (33 ± 8 V) with morphine, methadone, and buprenorphine, respectively.

Horses started to have a stronger response when the threshold decreased to < 40 V in any dermatome for morphine and methadone and responded more aggressively when buprenorphine was used. Most consistently, horses looked toward the site of electrical

---

Figure 1—Mean ± SD avoidance threshold for electrical stimulation of the perineal (A), sacral (B), lumbar (C), and thoracic (D) regions after subarachnoid administration of hyperbaric buprenorphine (triangles), hyperbaric morphine (squares), hyperbaric methadone (inverted triangles), or 10% dextrose solution (circles) in horses. *Within a time point, value differs significantly (P < 0.05) from the value for the control (10% dextrose solution) group.
stimulation when avoidance threshold was < 40 V; made movements of the tail, limbs, trunk, head, or neck when the avoidance threshold was < 30 V; and kicked when it was < 20 V. No response was observed when the electrical threshold was > 40 V. The control group treated with 10% dextrose solution only did not have any changes in the avoidance threshold, and all horses responded to 10-V electrical stimulation with strong movements and kicking.

Discussion

The subarachnoid administration of hyperbaric morphine, buprenorphine, and methadone was effective in producing short-lasting analgesia from the perineal to thoracic regions without motor impairment or CNS excitation. At 10 minutes, threshold avoidance to electrical stimulation in the perineal region increased from 10 V to 29 ± 11 V for morphine, 43 ± 10 V for methadone, and 35 ± 10 V for buprenorphine. Increased avoidance threshold for noxious electrical stimulation was significantly different after 10 minutes of subarachnoid injection for all 3 opioids but not for 10% dextrose solution. Hyperbaric methadone produced a significantly faster onset of action, compared with morphine and buprenorphine. This may be the result of the high lipid solubility of methadone and the high density of the solution used, as the drug could contact the spinal cord receptors faster than when an isobaric solution is used. The short duration of analgesic effects obtained in our study limits the use of this technique when a single injection is administered, but when an epidural catheter is placed, long-term profound analgesia can be produced with multiple administrations over time.

The use of subarachnoidally administered local anesthetics has been described for horses. Several potential complications and adverse effects have been described including significant increase in heart rate and subcutaneous temperature, decreases in respiratory rate and rectal temperature, and complete loss of motor control of pelvic limbs. In our study, no abnormalities or adverse effects were observed.

Previous studies in horses have been limited to epidural administration of opioids. Central nervous system excitation is described following IV administration of opioids in horses. Narcotics, such as morphine, fentanyl, pentazocine, and butorphanol, are potent locomotor stimulants in horses when administered IV. Mechanisms for CNS excitation are unknown but may be related to cerebral release of norepinephrine and dopamine. Results of studies in horses indicate that inhibition of catecholamines and antagonism of opiate receptors with naloxone will block CNS excitation. Lack of CNS excitation in the horses of our study could be explained by a segmental effect of the hyperbaric solutions without cephalad migration to supraspinal regions of the CNS, whereas rapid occupation of cerebral opioid receptor occurs after IV administration of opioids.

The volume typically recommended for epidural administration of opioids ranges from 10 to 15 mL, irrespective of the drug or drug combination used. Larger volumes of fluids injected into the epidural space may induce hind limb ataxia because of mechanical compression of the nerve endings. Discomfort during the subarachnoid injection was observed in our study even though only 5 mL of total volume was injected. We believe that the discomfort experienced in our study was the result of the hyperbaric nature of solutions in relation to the equine CSF. Baricity of an agent of intrathecal administration is defined as a relative density of the agent to that of the CSF at a specified temperature. A solution that is denser than the CSF could produce discomfort when in contact with the spinal cord because of its baricity. A heavier solution would reach the spinal cord rapidly and mechanically produce discomfort.

In humans, epidural administration of sterile water is related to neurotoxic effects on the spinal cord. To our knowledge, no reports exist in the literature regarding the potential neurotoxic effects of 10% dextrose solution. We did not examine the spinal cord of our horses after the study was completed as this was not a terminal study and all horses were kept alive and returned to the teaching herd. Up to 48 hours after subarachnoid administration, no signs of ataxia or motor impairment were observed.

Another aspect concerning the safety of subarachnoid administration of opioids is their compatibility with CSF and neural tissue. Solutions of opioids for potential use in subarachnoid injections such as morphine, methadone, and buprenorphine in saline (0.9% NaCl) solution have a pH in the range of 4.52 to 6.85. When mixed with human CSF, each lowered the pH of CSF by ≤ 0.3.

Animal studies of potential damage to the spinal cord with epidural catheters and repeated injection of opioids have not revealed substantial histologic changes when nonpreservative free opioids were used. The most compatible solutions are the preservative-free solutions. In our study, we did not use preservative-free opioids, but no acute neurotoxic signs were observed in our study.

Lowering of the head has been described as evidence of sedation in horses after epidural administration of morphine, methadone, and buprenorphine. In our study, we did not observe signs of sedation in our study. Solutions used in our study were hyperbaric in relation to the equine CSF; so this could explain the lack of sedation in our horses as a result of no or minimal cephalad migration. Methadone and buprenorphine are more lipid soluble than morphine. When isobaric solutions of methadone and buprenorphine are subarachnoidally administered to humans, cranial migration is not likely to occur because of fat tissue absorption. Subarachnoid injection of isobaric morphine does produce sedation in humans as a result of cranial migration.

In a study on epidural administration of opioids in horses, threshold values of ≥ 40 V were considered to correspond to profound analgesia that would allow skin incision. The stimulation rate (10 V/s) in our study was considered appropriate because the horses had sufficient time to recover from the serial stimulation. A total stimulation time of 1 to 3 minutes was necessary for each series of stimulation, but
remain in the CSF, which delays onset of action. We cord, whereas water-soluble drugs such as morphine lipid-soluble opioids bind to receptors on the spinal cord, whereas water-soluble drugs such as morphine remain in the CSF, which delays onset of action. We hypothesized that the higher density of the hyperbaric opioid solutions we used produced a fast onset of action of lipid-soluble drugs and morphine because it prevented these drugs from being highly diluted in the CSF. Data from a study done in sheep indicate that isobaric lipophilic opioids such as methadone exert their effects predominantly on tissues near the site of injection, different from isobaric hydrophilic agents such as morphine because of a dilutional effect in CSF. Another explanation could be that the hyperbaric drugs did bind to spinal cord opioid receptors faster as a result of a gravity effect because a hyperbaric solution will flow downward. As the horses were in standing position, after the injection above the spinal cord, a downward flow would bring these drugs into contact with the spinal cord faster. A faster onset of action for morphine was obtained in our study, compared with epidural injection of morphine. Hyperbaric morphine probably bound to the spinal cord receptors immediately after injection, producing faster onset of action, compared with epidural administration in horses. A cranial and caudal migration of the hyperbaric solutions of morphine, buprenorphine, and methadone can be inferred because an increase in avoidance threshold for electrical noxious stimulation was observed cranially and caudally from the site of injection.

If hyperbaric solutions settle by gravity, a more segmental analgesic effect would be expected. This was not confirmed in our study once the intense analgesic effects were observed in all dermatomes after 5 minutes. We hypothesize that the hyperbaric solution migrated along the spinal cord receptors cranially and caudally.

Buprenorphine is classified as a partial agonist at the µ-opioid receptor that has moderate intrinsic activity, high affinity for µ-opioid receptors, and slow dissociation. Chemical characteristics of buprenorphine can explain the mild analgesic effects obtained with hyperbaric buprenorphine in our study. The analgesic effect obtained with buprenorphine in our study was considered moderate because the avoidance threshold for noxious electrical stimulation increased from 10 V to < 40 V for all dermatomes. Morphine and methadone significantly increased the avoidance threshold for electrical noxious stimulation after 5 minutes of subarachnoid injection. Excellent analgesia was obtained with both drugs with a short onset of action, compared with caudal epidural administration of morphine that produces an onset of action from 4 to 8 hours. prolonged onset of action with epidural isobaric morphine can be explained by the pharmacokinetic characteristics of morphine (low lipid solubility, 23% in the nonionized form, protein binding of 35%, and 224L volume of distribution). In a study that compared intrathecal administration of morphine and methadone in humans who underwent total knee or hip replacement, both drugs provided excellent analgesia, but morphine produced a longer duration than that of methadone. Caudal epidural administration of morphine produced analgesia in horses that lasted from 8 to 19 hours. In the same study, analgesia was greater on the dermatomes closest to the epidural injection site and lesser on the lumbar and thoracic dermatomes. The authors of that study suggested that the distance from the site of injection and a possible dilutional effect of the CSF could explain the differences as a result of a smaller number of morphine molecules available to bind to the opioid receptors in the lumbar and thoracic spinal cord.

Duration of effect following subarachnoid administration of an opioid is influenced by the number of molecules retained in the CSF and spinal tissue and by the dissociation kinetics of the drug. In our study, morphine produced significantly longer-lasting analgesic effect than methadone and buprenorphine over the dermatomes of the thoracic region. Morphine has greater dissociation kinetic values than methadone and buprenorphine, which could explain the longer-lasting effect. However, we cannot explain why the same effect was not observed over the dermatomes of the perineal, sacral, or lumbar regions. It is unknown whether the 10% dextrose solution used to prepare the hyperbaric solutions would change the dissociation kinetic values for morphine, methadone, and buprenorphine and how this would affect duration and intensity of analgesic effect.

We conclude that the subarachnoid injection of hyperbaric morphine or methadone produces intense analgesia for 120 minutes over the dermatomes of the perineal, sacral, lumbar, and thoracic areas without cardiorespiratory depression, ataxia, or CNS excitement in horses. Subarachnoid administration of hyperbaric morphine or methadone may prove useful for pain management of severe intensity in horses.

References
4. Skarda RT, Muir WW. Segmental epidural and subarachnoid...