Analgesic effects of epidural administration of hydromorphone in horses

Cláudio C. Natalini, DVM, PhD, and Renata L. Linardi, DVM, MS

Objective—To evaluate the effects of epidural administration of hydromorphone on avoidance threshold to noxious electrical stimulation of the perineal, sacral, lumbar, and thoracic regions in horses.

Animals—6 healthy adult horses.

Procedure—Horses were assigned to receive hydromorphone (0.04 mg/kg) or a control solution (20 mL of sterile water) administered epidurally into in the first intercoccygeal space. Treatments were administered at time intervals of ≥ 7 days. Electrical stimulation was applied for 6 hours after epidural injection over the dermatomes of the perineal, sacral, lumbar, and thoracic regions, and the avoidance threshold voltage was recorded.

Results—Administration of sterile water did not change the avoidance threshold. Hydromorphone significantly increased the avoidance threshold by 20 minutes after injection, which lasted until 250 minutes after epidural administration in the perineal, sacral, lumbar, and thoracic regions. Profound analgesia (avoidance threshold > 40 V) was achieved only in the perineal region at 60 minutes after epidural administration of hydromorphone. Analgesia for all dermatomes was considered moderate for 250 minutes after epidural injection.

Conclusions and Clinical Relevance—Epidural administration of hydromorphone increases the avoidance threshold to noxious electrical stimulation in the perineal, lumbar, sacral, and thoracic regions in horses for 250 minutes after injection. Hydromorphone epidural administration may prove useful in the management of horses with pain of moderate to mild intensity. (*Am J Vet Res* 2006;67:11–15)

Epidural anesthesia and analgesia have been used in human and veterinary medicine as an effective technique to treat patients with acute and chronic pain as well as provide preemptive, intraoperative, and postoperative analgesia.[1,2] Epidural analgesia is obtained by the injection of analgesic drugs, such as opioids, α_2-adrenergic agonists, and dissociative agents, into the epidural space and their resulting action on the spinal cord after diffusion in the region of the gray matter of the dorsal horn.[2-4] Opioids are the most potent pain-relieving substances, but their use is limited in horses because they tend to stimulate the CNS when administered IV.[5] Opioids reach the subarachnoid space and provide analgesia by acting on various receptors within the dorsal horn of the spinal cord and mesolimbic system, midbrain periaqueductal gray matter, and several thalamic and hypothalamic nuclei, thus interfering with nociceptive neural transmission within the CNS.[4] The mechanisms for CNS excitation in horses are unknown but may be related to cerebral release of catecholamines such as norepinephrine and dopamine and activation of opiate receptors.[6,7]

The advantage of the epidural route of administration is that it can be used to provide analgesia in horses without causing sedation or excitation of the CNS. Some studies[8-10] have revealed that epidural administration of morphine alone or in combination with detomidine provides profound analgesia for horses with signs of pain in their hind limbs.

The pharmacologic and clinical effects of epidurally administered opioids are not completely understood in horses, but there is evidence that analgesia results from a regional effect, although there is systemic absorption that may be responsible for some of the effects.[3] Physicochemical properties of opioids may cause differing onsets of action among drugs when administered epidurally. Hydromorphone is a μ-opioid agonist that is 8 times as potent as morphine and more lipid soluble than morphine.[11] When compared to fentanyl, it is less lipid soluble.[4] Intermediate lipid solubility may improve the ability of an opioid to provide spinal analgesia, resulting in a more rapid onset of action. The biggest advantage of epidural administration of hydromorphone would be a more rapid onset of action, compared with the effects of morphine, and longer-lasting analgesia, compared with that of other analgesics (eg, detomidine and ketamine) used for epidural anesthesia in horses.

Considering that the clinical effects after epidural administration of more lipid-soluble opioids are currently poorly understood, the purpose of the study reported here was to evaluate analgesic effects after epidural administration of hydromorphone as determined by the avoidance threshold to noxious electrical stimulation of dermatomes in the perineal, sacral, lumbar, and thoracic regions of horses.

Materials and Methods

Animals—Six healthy adult horses from a university teaching herd at our facility were used in the study. Horses ranged from 445 to 570 kg (mean ± SD, 466 ± 69 kg). The protocol was approved by the Louisiana State University School of Veterinary Medicine Institutional Animal Care and Use Committee.

Study design—Each horse was maintained on pasture and placed in a stall shortly before each experiment. Horses were sedated for insertion of catheters and measurement instruments. A catheter was inserted in the epidural space at least 24 hours before each experiment. Food was withheld overnight before each experiment, but horses had access to water.

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From the Equine Health Studies Program, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803.
Address correspondence to Dr. Natalini.

Each horse received 2 treatments (hydromorphone and sterile water [control treatment]); horses were assigned to receive the treatments in a random order. The agents were administered epidurally with an interval of at least 7 days between treatments. Response variables were measured immediately before epidural injection and at 10-minute intervals during a period of 360 minutes after injection.

Analgesics and epidural injections—Horses were restrained in a standing position and sedated by administration of xylazine hydrochloride[a] (0.5 to 1 mg/kg, IV). The first coccygeal space (space between the first and second coccygeal vertebrae) was located by palpation of the area with simultaneous manipulation of the tail in a dorsoventral direction. The skin over the region was clipped and surgically scrubbed, and a sterile 17-gauge, 7.5-cm Tuohy needle[b] was aseptically inserted in the epidural space. Successful epidural puncture and placement of the needle in the epidural space was confirmed by use of the hanging-drop technique. Then, a 20-gauge epidural catheter[c] was introduced through the needle and advanced 20 cm in a cranial direction. After the catheter was confirmed to be appropriately placed (ie, no resistance to injection of sterile saline [0.9% NaCl] solution[d] containing heparin as an anticoagulant), the catheter was sutured to the skin, covered with sterile gauze, and maintained in place for the duration of the experiment. No other aftercare was provided.

Hydromorphone[e] (0.04 mg/kg) diluted in sterile saline solution or an equivalent volume of a control solution of sterile water (20 mL) was injected through the catheter at a rate of 1 mL/10 s. After each injection, the catheter was flushed with 5 mL of heparinized saline solution.

Analgesic evaluation—Avoidance to noxious stimulation was assessed by the use of an electrical stimulator.[f] Two adhesive electrodes were placed approximately 5 cm apart over each of 9 dermatomes that include 5 anatomic areas (**Figure 1**). The perineal-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.

Hair was not clipped from the skin over the dermatomes. Serial electrical stimulation (10 to 80 V with increases of 10-V increments; direct current, 50 Hz; duration of 10 milliseconds) was applied to assess analgesia before and at 10-minute intervals for 360 minutes after epidural administration. 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. 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.[10] 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, 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 ± SD. Measured variables were evaluated for an effect of time and treatment (hydromorphone vs sterile water) by use of a 2-way ANOVA. Significance for time points and within treatments over time was determined by use of Bonferroni post hoc methods. Significance was set at values of $P \leq 0.05$. All

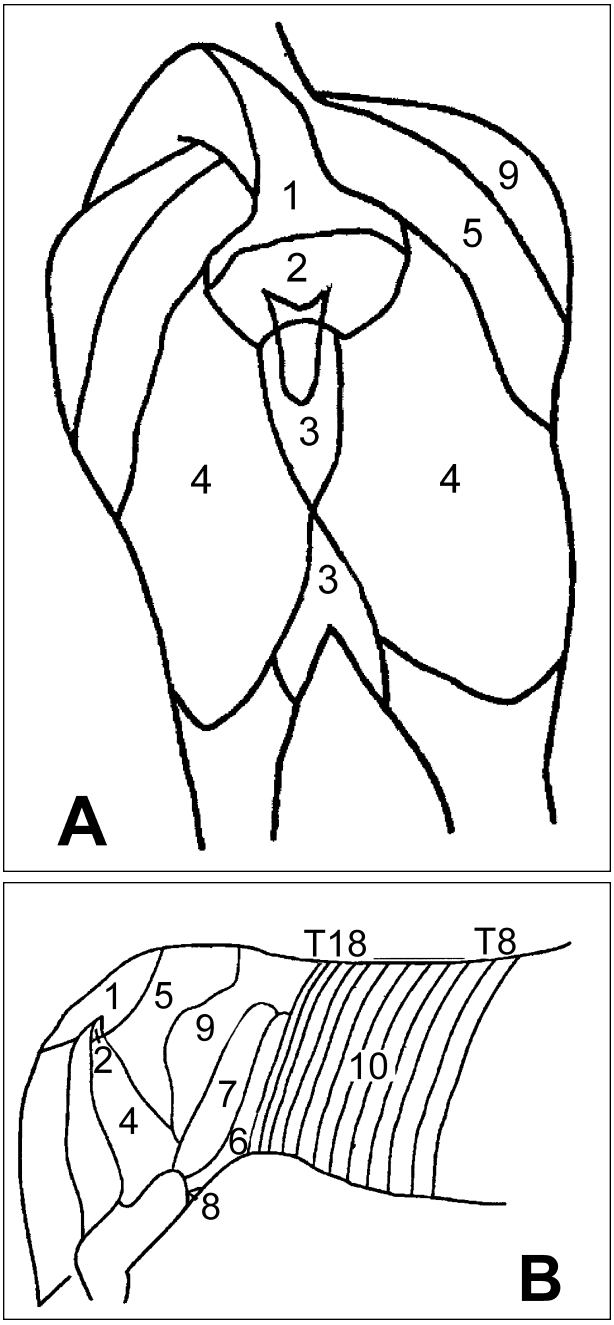

Figure 1—Schematic depiction of the caudal (A) and lateral (B) views of the dermatomes of the perineal (dermatomes 1 to 3), sacral (dermatomes 4 and 5), lumbar (dermatomes 7 to 9), and thoracic (dermatome 10) regions of horses. Innervation for each dermatome is as follows: 1 and 2, coccygeal roots of the pudendal and caudal rectal nerves; 3, ventral branches of lumbar nerves L1 to L3; 4, caudal cutaneous femoral nerve originating from sacral nerves S1 and S2; 5, sacral nerves S1 to S5; 6, lumbar nerve L1; 7, lumbar nerve L2; 8, lumbar nerve L3; 9, lumbar nerves L1 to L6; and 10, thoracic nerves T8 to T18.

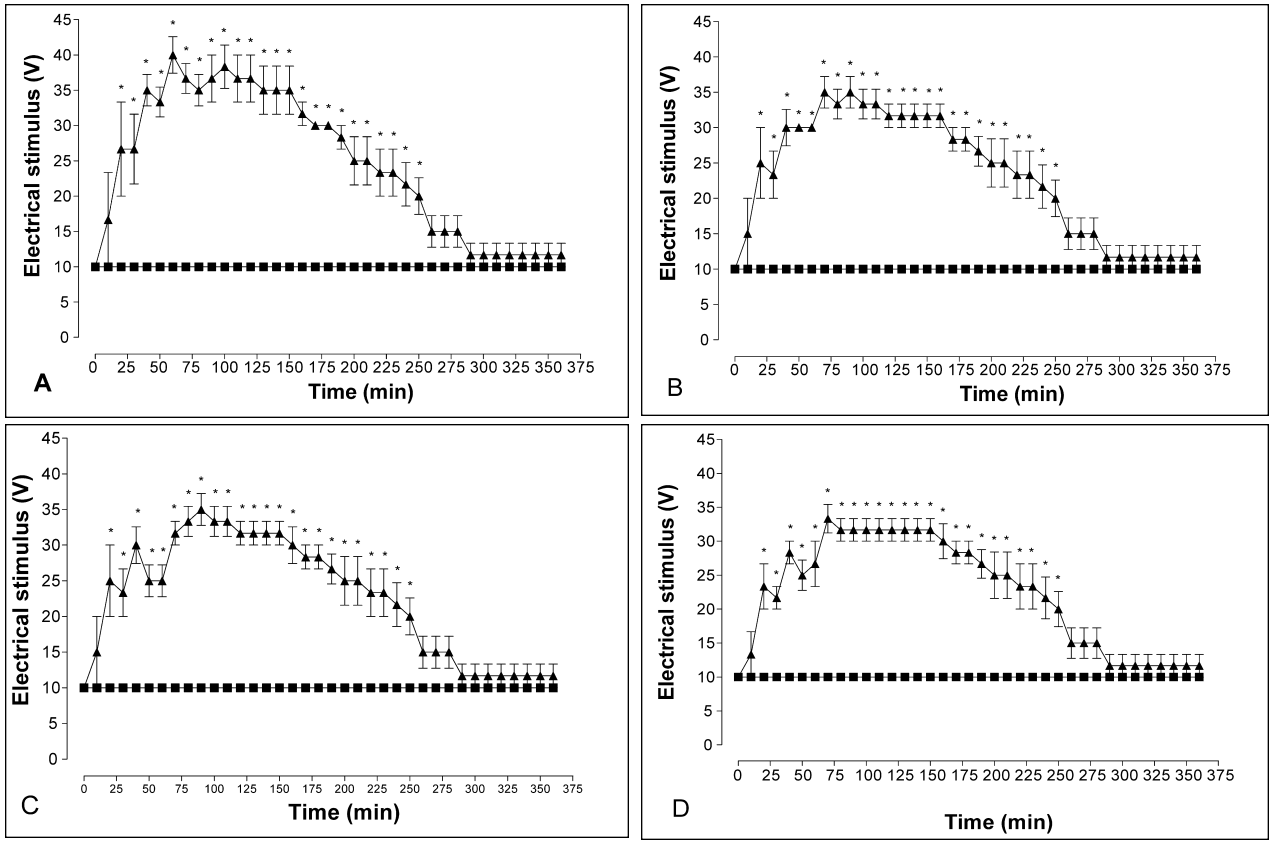

Figure 2—Mean ± SD avoidance threshold for electrical stimulation of the perineal (A), sacral (B), lumbar (C), and throracic (D) regions after epidural administration of hydromorphone (triangles) or sterile water (squares) in horses. *Within a time point, value differs significantly ($P < 0.05$) from the value for the control (sterile water) group.

analyses were performed by use of a commercially available statistical program.[g]

Results

All horses responded to a stimulation of 10 V at all dermatomes before epidural administration of treatments. Similarly, all horses responded to a stimulation of 10 V after epidural administration of the control treatment (sterile water) for all time points of the 6-hour experimental period. Thus, epidural administration of sterile water did not change the avoidance threshold for electrical stimulation.

Epidural administration of hydromorphone caused an increase in the avoidance threshold to electrical stimulation during the period of evaluation for dermatomes of all regions. The avoidance threshold was significantly higher 20 minutes after epidural injection, which lasted for 250 minutes after injection (**Figure 2**). In the perineal region, a maximum avoidance threshold of 40 V, which indicated profound analgesia, was obtained 60 minutes after epidural administration, but it lasted for only 10 minutes. The avoidance threshold was increased, but not significantly from the value determined before epidural injection, for all dermatomes for > 250 minutes.

Although sedation was not systematically evaluated by use of a scoring system, subjective observation by the observer (who was not aware of the treatment or voltage administered to each horse) suggested that neither sterile water nor hydromorphone at the dose used in this study induced appreciable sedation or ataxia. None of the horses had adverse systemic effects after the study was completed.

Epidural catheters were removed after the study was completed, and the horses were observed for a period of 1 week before they were returned to the university teaching herd. None of the horses had adverse reactions during the 1-week period after completion of the study.

Discussion

The volume typically recommended[2,12,13] for epidural injection in horses ranges from 10 to 15 mL, irrespective of the drug or drug combination used. Large volumes of fluid injected into the epidural space may induce hind limb ataxia because of mechanical compression of the nerve endings.[14] We did not observe adverse effects after injection of 20 mL of solution for either the control or hydromorphone treatment.

It also should be mentioned that the use of sterile water for the control treatment could have had a dilution effect on CSF and changed the specific gravity of the fluid. The authors are not aware of any reports describing the possible effects from dilution of CSF with sterile water and how it would impact sensory and motor perception in horses.

In humans, epidural administration of sterile water is related to neurotoxic effects in the spinal cord.[11] In the study reported here, we did not observe

sedation or ataxia after epidural administration of sterile water and hydromorphone. Epidural administration of preservative-free hydromorphone but not sterile saline solution to sheep during a 30-day chronic administration study[1] caused extensive fibroproliferative and sterile granulomatous reactions in the epidural space associated with hind limb ataxia.

Lowering of the head has been described as evidence of sedation in horses after epidural administration of morphine (0.05 and 0.1 mg/kg)[10,15]; however, we did not observe signs of sedation in the study reported here. In 1 study,[16] the concentration of hydromorphone in CSF obtained from the cervical area was undetectable 240 minutes after epidural administration in humans. This could explain the lack of sedation in our horses as a result of a deficiency of cranial migration of a more lipid-soluble opioid, such as hydromorphone, compared with that of the more hydrosoluble morphine. In that study[16] in humans in which effects of epidural administration of hydromorphone and morphine were compared, both drugs induced moderate sedation and there was no significant difference between the effects of the 2 opioids.

Because hydromorphone has intermediate lipid solubility, it does not migrate toward the head, which prevents sedation in humans. This is in contrast to morphine, which causes lowering of the head in horses after epidural administration.[17,18] In addition, hydromorphone does not induce muscle relaxation, compared with effects for the α_2-adrenoceptor.[8] These factors could be the reason that ataxia and sedation were not observed in the study reported here. Another explanation could be that because of its hydrosolubility, morphine would be readily available for systemic absorption from the epidural space via epidural vessels, whereas hydromorphone would be trapped by fat in the epidural space, precluding it from causing sedation via systemic absorption. It is unknown at this time whether hydromorphone in CSF or systemic absorption would induce sedation in horses, but the study reported here proved that epidural administration of hydromorphone (0.04 mg/kg) did not cause sedation in horses.

The site of injection also may play a role in onset of action, intensity of analgesic effect, and duration of analgesia after epidural administration. In a clinical study[19] in humans, it was indicated that epidural administration of hydromorphone provides equivalent analgesia, although with more rapid onset and shorter duration, compared with the effects of morphine. In our study, hydromorphone administered as an epidural had a rapid onset of action that differed from that for morphine but was similar to that for tramadol, as described in another study.[10] This was expected because hydromorphone is more lipid soluble than morphine and will cross the dura mater faster. Hydromorphone tends to bind to receptors in the spinal cord, whereas water-soluble drugs, such as morphine, tend to remain in the CSF, which delays onset of action.[4]

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. Analysis of results of studies[7,20-26] in horses indicates that inhibition of catecholamines and antagonism of opiate receptors with naloxone will block CNS excitation. Lack of CNS excitation in our study could be explained by a slower transfer of the opioid agonists from the epidural space to the CNS, compared with rapid occupation of cerebral opioid receptors after IV administration. Other explanations could be the dilution effect of the CSF on the solution administered and binding of hydromorphone to opioid receptors in the spinal cord.

Hydromorphone reportedly[18,19] provides excellent analgesia following epidural administration in the lumbar region in humans. In addition, it has been suggested[27] in humans that hydromorphone has a shorter latency to effect and reduced incidence of opiate-related adverse effects in the spinal cord, such as nausea, vomiting, and pruritus. In the study reported here, an increase in the noxious electrical threshold was observed 20 minutes after epidural administration of hydromorphone and lasted for 250 minutes in dermatomes of the perineal, sacral, lumbar, and thoracic regions. Morphine induces a slow onset of analgesia that lasts for 4 to 8 hours. Epidural administration of morphine in horses results in moderate analgesia over the dermatomes of the perineal and sacral regions that lasts for 6 hours and over the lumbar and thoracic areas that lasts for 3 hours.[10]

After crossing the dura mater and arachnoid membrane, lipid solubility determines the rapidity with which a drug will bind to receptors in the spinal cord and cause its effects. It is recognized that highly lipid-soluble opioids, such as alfentanil and fentanyl, are rapidly transferred from the epidural space to the subarachnoid space.[4] The rapid onset of action after epidural administration and more intense analgesia observed with hydromorphone in our study can be explained by its intermediate lipid solubility, compared with the lipid solubility for morphine.[19]

The analgesic effect obtained in the study reported here was considered moderate because the avoidance threshold for noxious electrical stimulation increased from 10 V to < 40 V for most of the dermatomes. Only for dermatomes of the perineal region and for approximately 10 minutes did the electrical threshold reach 40 V. The authors in 1 study[10] on epidural administration of opioids in horses considered threshold values of 40 V or more to be profound analgesia sufficient for a 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.

Duration of effect after epidural administration of opioids is influenced by the number of molecules retained in the CSF and spinal tissue and by dissociation kinetics of the drug.[4] Morphine is the μ-opioid agonist that has the greatest dissociation kinetic values, which explains its long-lasting effects. Although hydromorphone is more lipid soluble than morphine, it has the same dissociation kinetic values, which explains its long-lasting effects.

Epidural administration of hydromorphone at the dose and volume used in the study reported here did not appear to cause sedation and ataxia and offers a potentially useful alternative to systemic administration in horses. Analysis of the results indicates that this dose of hydromorphone administered epidurally in horses may induce a rapid onset of moderate analgesia with long-lasting effects. Additional studies on the analgesic effectiveness of epidural administration of hydromorphone in clinical situations are warranted.

a. Xylazine, Fort Dodge Laboratories Inc, Fort Dodge, Iowa.
b. Reusable Tuohy technique needle, thin wall, Becton-Dickinson Co, Rutherford, NJ.
c. Epidural catheter, Arrow International Inc, Reading, Pa.
d. 0.9% sodium chloride, Abbott Laboratories, North Chicago, Ill.
e. Hydromorphone, Elkins-Sinn Inc, Cherry Hill, NJ.
f. Grass S88 stimulator, Astro-Med Inc, West Warwick, RI.
g. Prizm Graph, GraphPad Software, San Diego, Calif.

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