Evaluation of the analgesic effects of epidurally administered morphine, alfentanil, butorphanol, tramadol, and U50488H in horses

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Objective—To evaluate and compare effects of epidurally administered morphine, alfentanil, butorphanol, tramadol, and U50488H on avoidance threshold to noxious electrical stimulation over the dermatomes of the perineal, sacral, lumbar, and thoracic regions in horses.

Animals—5 healthy adult horses.

Procedure—Using a Latin square complete repeated-measures design, horses were randomly assigned to receive 1 of 6 treatments (morphine, alfentanil, butorphanol, tramadol, U50488H, or sterile water) at intervals of at least 7 days. Agents were injected epidurally at the first intercoccygeal epidural space, and electrical stimulation was applied at repeated intervals for 24 hours to the dermatomes of the perineal, sacral, lumbar, and thoracic regions. Avoidance threshold to electrical stimulation was recorded.

Results—Administration of butorphanol, U50488H, and sterile water did not induce change in avoidance threshold. Alfentanil increased avoidance threshold during the first 4 hours, but not significantly. Tramadol and morphine significantly increased threshold and analgesic effects. Complete analgesia (avoidance threshold, > 40 V) in the perineal and sacral areas was achieved 30 minutes after tramadol injection, compared with 6 hours after morphine injection. Duration of complete analgesia was 4 hours and 5 hours after tramadol and morphine injections, respectively.

Conclusions and Clinical Relevance—Epidural administration of tramadol and morphine induces long-lasting analgesia in healthy adult horses. Epidural administration of opioids may provide long-lasting analgesia in horses without excitation of the CNS. (*Am J Vet Res* 2000;61:1579–1586)

Epidural analgesia consists of injection of an analgesic drug into the epidural space and action on the spinal cord after diffusion in the region of the gray matter of the dorsal horn.[1,2] Epidural analgesia is an effective technique to treat acute and chronic pain as well as provide preemptive, intraoperative, and postoperative analgesia. Local anesthetic drugs such as lidocaine and bupivacaine have been used in humans and other animals to induce epidural analgesia and anesthesia.[3] Phencyclidine derivatives such as ketamine, α_2-adrenoceptor agonists such as xylazine and detomidine, and opioid drugs such as morphine, oxymorphone, and butorphanol induce epidural analgesia in veterinary species.[3-8,a] These agents are usually used alone or in combination. Although local anesthetics induce anesthesia by blocking sympathetic, sensory, and motor function of spinal nerves, α_2-adrenoceptor agonists, ketamine, and opioids induce analgesia by highly selective actions on spinal receptors. Meperidine in high doses may induce peripheral nerve block.[2,4]

Tramadol hydrochloride is a centrally acting nonopiate analgesic drug with opioid and nonopioid mechanisms of action that causes activation of central pain inhibitory mechanisms (the opioid and the descending monoaminergic systems).[9] Approximately 30% of the analgesic effect of tramadol can be reversed by administration of naloxone in humans.[10,11] Tramadol differs from typical μ opioid agonists in that it does not cause adverse effects such as respiratory depression, constipation, or sedation.[10] When administered epidurally in humans, tramadol is one-thirtieth as potent as morphine.[12]

Butorphanol is a κ opioid partial agonist and μ antagonist. It is lipid soluble, 2.5 times more potent than morphine when administered by routes that cause systemic distribution in horses, and the opioid most commonly used clinically in this species.[3] U50488H is a highly selective lipid-soluble κ opioid agonist that has been reported to cause analgesia without CNS excitement in horses when administered IV.[13]

Horses are used in sporting and working situations that predispose them to musculoskeletal injuries such as tissue and joint tears and inflammation, which may lead to acute and chronic pain. Postoperative discomfort and pain can be treated and prevented in some instances with regional anesthetic and analgesic techniques.[6,14-16] The most potent pain-relieving substances known are opioid analgesics, but these drugs are not used extensively in horses, because substantial sympathetic stimulation and CNS excitation are observed when opioids are administered IV. Narcotics such as morphine, fentanyl, pentazocine, and butorphanol are potent locomotor stimulants in the horse when administered IV.[17-23] The mechanisms for CNS excitation are unknown but may be related to cerebral catecholamine release (especially norepinephrine and dopamine) and opiate receptor activation.[24] Results of studies in horses indicate that catecholamine inhibition and opiate receptor antagonism with naloxone block these CNS excitatory effects.[22,24] These facts suggest that routes of

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administration that do not result in systemic distribution of these drugs, particularly for morphine-like drugs, should be explored so that horses could benefit from opioid analgesic effects without CNS excitation.

Epidural opioid administration offers a potentially useful alternative to routes of administration that result in systemic distribution in horses. Results of some studies indicate that morphine alone, or the combination of morphine and detomidine, administered epidurally, provides profound analgesia for hind limb pain in horses.[7,25]

The use of α_2-adrenoceptor agonists to induce analgesia and surgical anesthesia is well-known in equine patients.[5,25-28] The pharmacologic, pharmacokinetic, and clinical effects of epidurally administered opioid drugs are not known in horses. Physicochemical properties of opioids may cause different onsets of action among different drugs when administered epidurally. To the authors' knowledge, reports describing differences between lipophilic and hydrophilic opioids, between opioid agonists and partial agonists, and between μ and κ opioid agonists, administered epidurally to horses, have not been published. The purpose of the study reported here was to evaluate the analgesic effect of epidurally administered morphine, alfentanil, butorphanol, tramadol, and U50488H on avoidance threshold to noxious electrical stimulation of dermatomes of perineal, lumbosacral, and thoracic areas in horses.

Materials and Methods

Experimental design—After approval by the University of Minnesota Institutional Animal Care and Use Committee, 5 healthy mature horses (2 geldings and 3 mares) were studied. Mean ± SD body weight was 511 ± 47 kg, and age was 10.8 ± 2.2 years. All horses were tractable and easy to work with; however, they were not specifically conditioned to the experimental procedure. Using an incomplete Latin square crossover complete repeated-measures design (6 agents × 5 horses), horses were randomly assigned to 6 treatment groups (5 analgesic groups and 1 control group that received treatment with sterile water). The agents were administered epidurally with intervals ≥ 7 days between treatments. Investigators involved in collection of data were blinded to the identity of the agent being tested. The null hypothesis was that there would be no difference between effects of epidurally administered analgesics and sterile water on pain threshold to electrical stimulation in horses. The 1-tail alternative hypothesis was that epidurally administered analgesics would increase the pain threshold to electrical stimulation in horses, compared with administration of sterile water (control group). The acceptable level of significance (α) was 5% for rejecting the null hypothesis in favor of the alternative hypothesis. Measurements of response variables took place immediately prior to epidural injection and 5, 10, 20, 30, 40, 50, 60, 90, 120, 150, and 180 minutes after injection and then hourly to 24 hours after administration.

Analgesics and epidural injections—For epidural injections, an 18-gauge 3.0-in sterile epidural needle[b] was placed in the first intercoccygeal space in awake standing horses held in stocks. The space was located by palpation while manipulating the tail in a dorsoventral direction. The skin over the region was clipped, surgically prepared, and covered with a sterile transparent dressing.[c] After location of the first intercoccygeal vertebral space, the skin and subcutaneous tis-

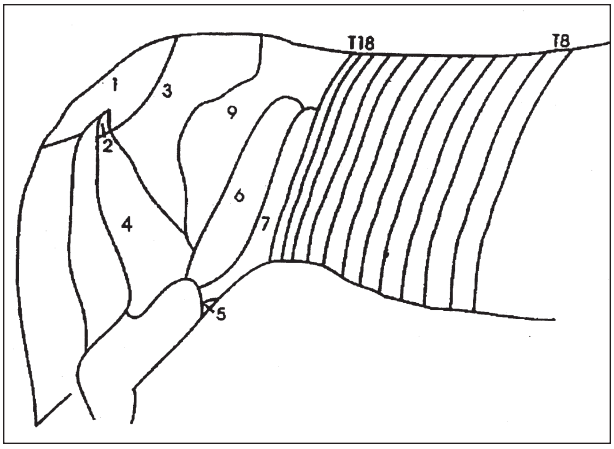

Figure 1—Schematic diagram of the right lateral view of the dermatomes of a horse. T18, T8 = Thoracic dermatomes innervated by thoracic spinal nerves. 7 = Lumbar dermatome innervated by L1. 6 = Lumbar dermatome innervated by L2. 9 = Lumbar dermatome innervated by L1 to L6. 5 = Lumbar dermatome innervated by L3. 3 = Sacral dermatome innervated by S1 to S5. 4 = Sacral dermatome innervated by L6 to S2. 1 = Perineal dermatome innervated by the femoral nerve. 2 = Perineal dermatome innervated by S3 to S4. 8 = Perineal dermatome innervated by L1 to L6.

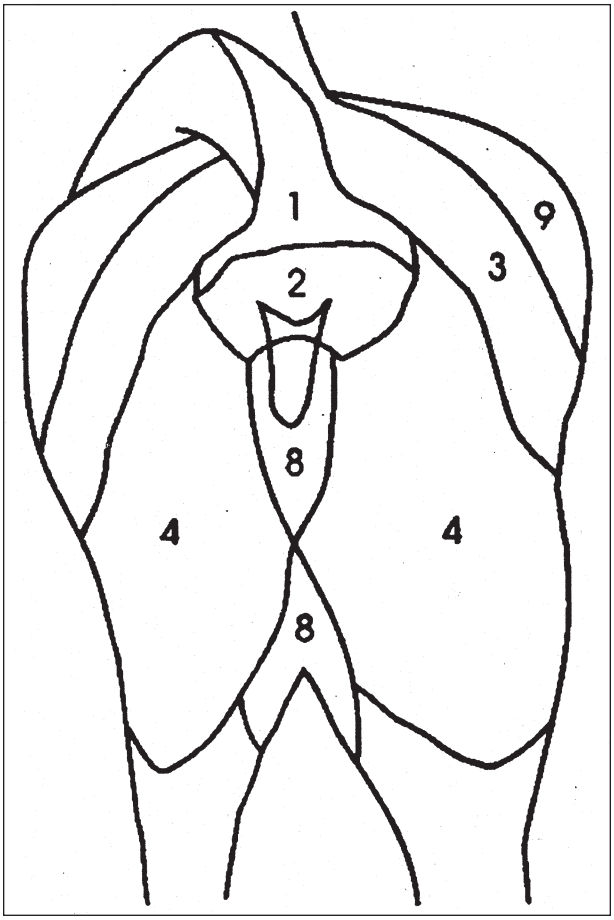

Figure 2—Schematic diagram of the caudal view of the dermatomes of a horse. 1 = Perineal dermatome innervated by the femoral nerve. 2 = Perineal dermatome innervated by S3 to S4. 8 = Perineal dermatome innervated by L1 to L6. 3 = Sacral dermatome innervated by S1 to S5. 4 = Sacral dermatome innervated by L6 to S2. 9 = Lumbar dermatome innervated by L1 to L6.

sue above the space were desensitized by administration of 3 ml of a 2% solution of lidocaine. Before injection, correct placement of the needle in the epidural space was verified by a sterile-water hanging-drop technique and negligible resistance to air injection. To ensure that a venous sinus was not inadvertently penetrated, aspiration was performed before injection of the epidural agents. Morphine[d] (0.1 mg/kg of body weight), alfentanil[e] (0.02 mg/kg), butorphanol[f] (0.08 mg/kg), tramadol[g] (1.0 mg/kg), U-50488H[h] (0.08 mg/kg) or sterile water for injection, in equal volume (20 ml), were injected into the epidural space at a rate of 1 ml/10 s. The U50488H was prepared as a 10-mg/ml solution in sterile water and filtered through a 0.45-µm bacterial filter.[i]

Analgesic evaluation—Avoidance of a painful stimulus and analgesia were assessed by use of a constant current nerve stimulator[j] that induced an electrical stimulation. Two clip electrodes were placed manually, approximately 5 cm apart, over dermatomes of the perineal, sacral, lumbar, and thoracic areas on each horse's right side (**Fig 1 and 2**). Serial stimulation (10 to 80 V direct current, 50 Hz, 10-ms duration) was applied to assess analgesia. Voltage was increased at 10-V increments. Positive pain responses were defined as purposeful avoidance movements of tail, limbs, trunk, head, and neck, attempts to kick, and turning the head toward the site of electrical stimulation at the time the stimulation was applied. Horses' eyes were covered to prevent the horse from viewing the operator at the moment of the electrical stimulus. The voltage at which avoidance movement first occurred was recorded and considered the threshold for avoidance. Threshold levels > 40 V were considered to represent complete analgesia, sufficient for skin incision.

Dermatomes were the superficial cutaneous areas innervated by the thoracic, lumbar, sacral, and coccygeal nerves, as described.[3,29,30] The thoracic dermatomes innervated by the thoracic spinal nerves were numbered correspondingly from T18 cranially to T8. The lumbar dermatome innervated by the ventral branch of L1 was designated No. 7. The region innervated by the ventral branch of L2 was designated No. 6. The region innervated by the dorsal branches of L1 to L6 was designated No. 9. The area innervated by the ventral branch of L3 was designated No. 5. The sacral dermatome innervated by the dorsal branches of S1 to S5 was designated No. 3. The region in the sacral area innervated by the ventral branches of L6 to S2 was designated No. 4. The perineal dermatome innervated by the **femoral nerve** was designated No. 1. Dermatome 2 was designated as the area innervated by the ventral branches of S3 and S4. Dermatome 8 was designated as the area innervated by ventral branches of L2, L3, and dorsal branches of L1 to L6 (Figs 1 and 2). For interpretation of the results, thoracic dermatomes were considered to be T8 to T18, lumbar dermatomes were No. 5, 6, 7, and 9, sacral dermatomes were No. 3 and 4, and perineal dermatomes were No. 1, 2, and 8.

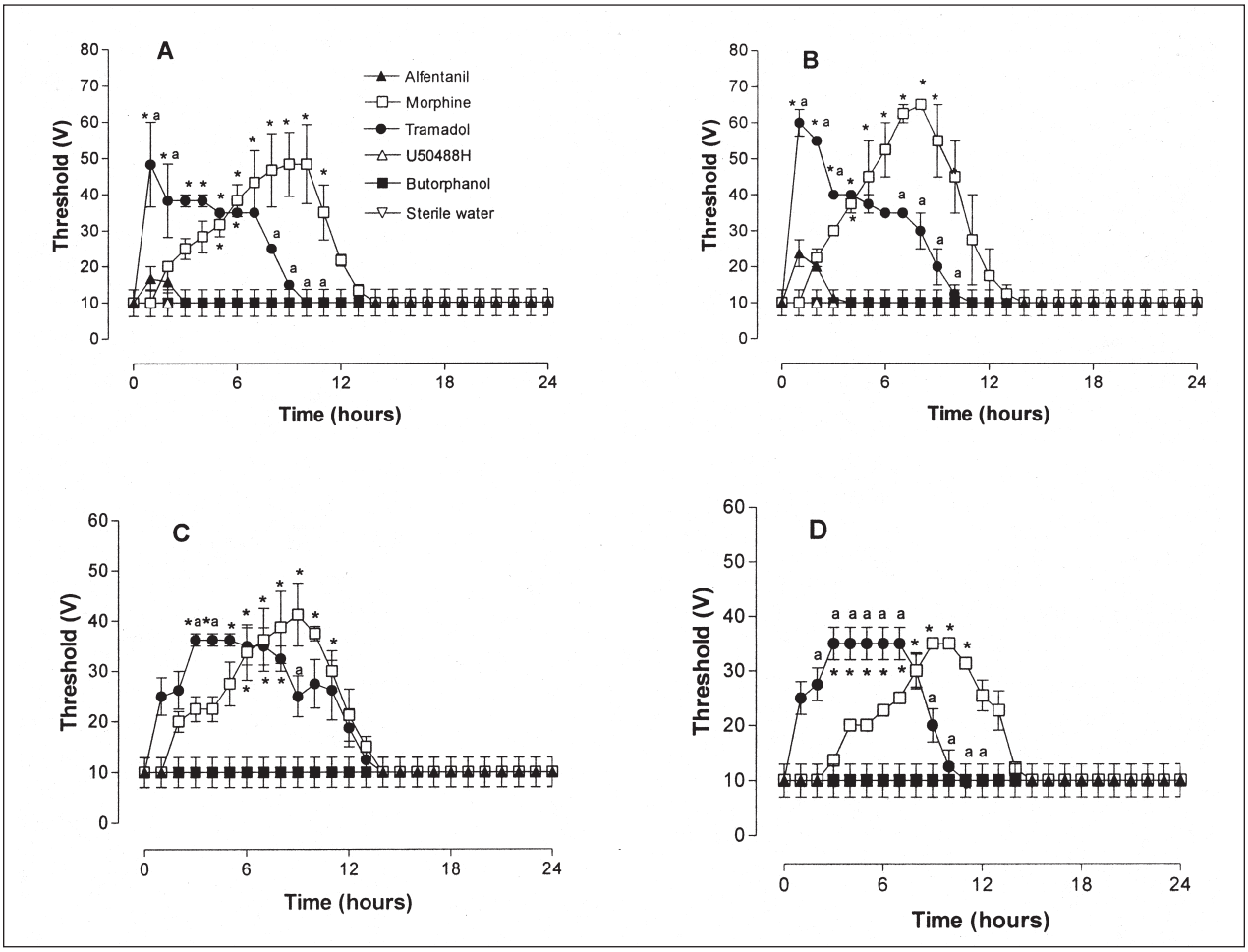

Figure 3—Avoidance threshold to electrical stimulation in dermatomes of perineal (A), sacral (B), lumbar (C), and thoracic (D) regions in 5 horses. Data were collected for 24 hours after epidural injection of morphine (0.1 mg/kg of body weight), alfentanil (0.02 mg/kg), butorphanol (0.08 mg/kg), tramadol (1.0 mg/kg), U50488H (0.08 mg/kg), or sterile water (equivalent volume). *Significant ($P < 0.05$) difference from baseline values and control group. [a]Significant ($P < 0.05$) difference from morphine.

Sample size and statistical analyses—Sample size calculation was performed by consideration of a minimum detectable difference of 30 V, an expected SD of residuals of 7.5 V, and 6 treatment groups. Power was 0.99 with a confidence interval of 95%. To compare qualitative factors (analgesics) for data measured by use of numeric values, 2-way repeated measures ANOVA and the **area under the curve (AUC)** were used. A Bonferroni test was used when differences between means were considered significant at $P < 0.05$. Data were expressed as mean ± SD.

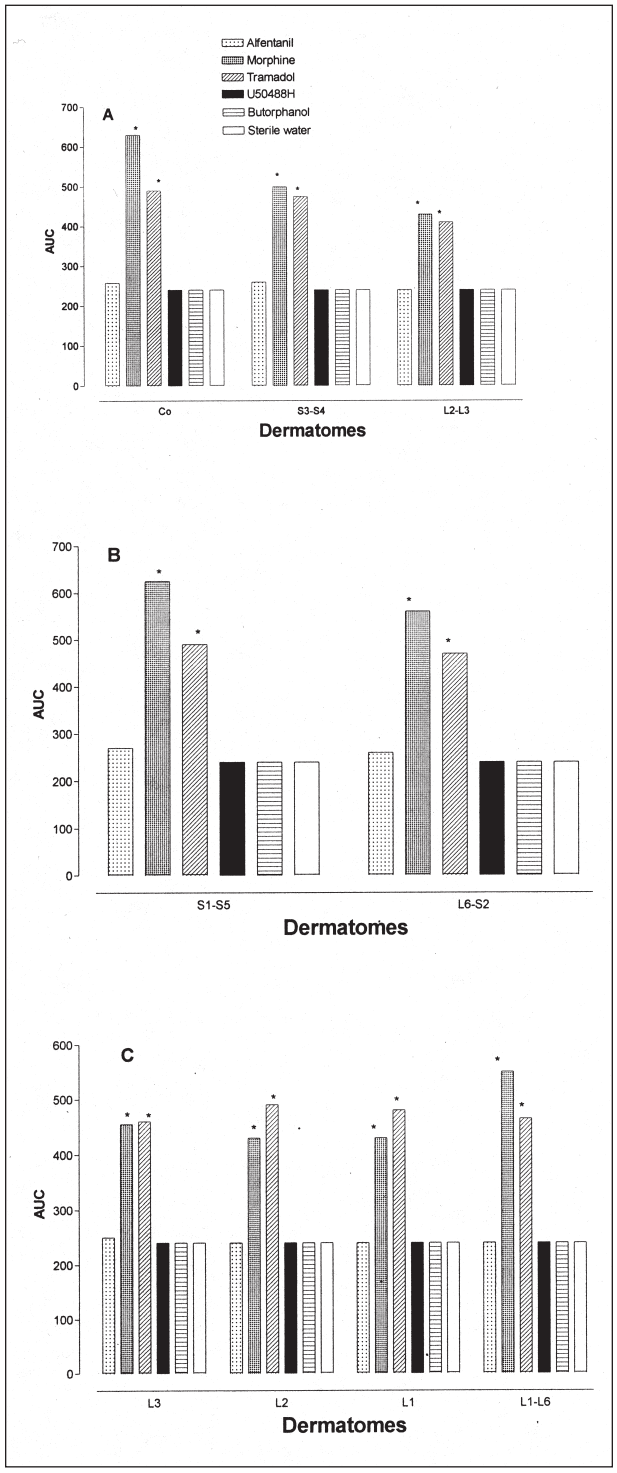

Figure 4—Area under the curve (AUC [V • h]) for avoidance threshold to electrical stimulation on dermatomes of perineal (A), sacral (B), and lumbar (C) regions in 5 horses. Data were collected for 24 hours after epidural injection of morphine, alfentanil, butorphanol, tramadol, U50488H, or sterile water. *Significant ($P < 0.05$) difference from baseline values and control group. Co = Perineal dermatome innervated by the femoral nerve.

Results

All epidural injections were performed without major difficulties. When positive results for the sterile water hanging drop technique were not evident or there was resistance to air injection, the needle was withdrawn and reintroduced. Blood was never withdrawn from the epidural needle. Horses had signs of discomfort such as turning the head toward the site of injection or attempting to move away from the injection during administration of the 20-ml solution.

All horses had signs of conscious response to 10-V stimulation at all dermatomes before the epidural injection. Administration of sterile water, the κ agonist U50488H, and the partial agonist butorphanol did not induce change in the avoidance threshold for electrical stimulation after epidural administration. For these drugs, the threshold was 10 V on all dermatomes during the 24-hour study period (**Fig 3**). For these drugs, AUC was identical to that of the control group (250 V•h; **Fig 4 and 5**).

Administration of alfentanil induced an increase in the avoidance threshold to electrical stimulation from 10 to 20 V after 30 minutes in dermatomes of the perineal region and after 20 minutes in dermatomes of the sacral region, although differences from baseline values were not significant. There were no changes in avoidance threshold for the lumbar and thoracic regions after alfentanil administration (Fig 3). There was no significant change in AUC for alfentanil in any region (Fig 4).

Administration of tramadol induced an avoidance threshold of 48.3 ± 3.7 V for the perineal region and 36.0 ± 3.6V for the sacral region after 20 minutes, which lasted for 6.5 hours. At the lumbar and thoracic regions, thresholds of 36.2 ± 1.25 and 35 ± 3.0 V, respectively, were obtained at 3 hours and lasted for 5 hours. The AUC was significantly greater than that of baseline and the control group in all regions (Fig 4).

Administration of morphine increased the threshold for the perineal region to 31.6 ± 3.3 V at 5 hours, which lasted for 6 hours. In the sacral region, a threshold of 37.5 ± 2.5 V was obtained at 4 hours and lasted for 6 hours. In the lumbar region, a threshold of 33.7 ± 5.5 V was induced at 6 hours and lasted for 5 hours. For the thoracic region, significantly increased avoidance threshold was obtained at 8 hours and lasted for 3 hours (Fig 3). Administration of morphine induced similar increases in AUC, as did tramadol, and these increases were significantly greater than values at baseline, in the control group, and in all other treatment groups in all regions (Fig 4).

The maximum avoidance threshold for tramadol was 60 V and was achieved at 1 hour in sacral region dermatomes. For morphine, maximum avoidance threshold was 65 V and was achieved at 8 hours in dermatomes of the sacral region (Fig 3).

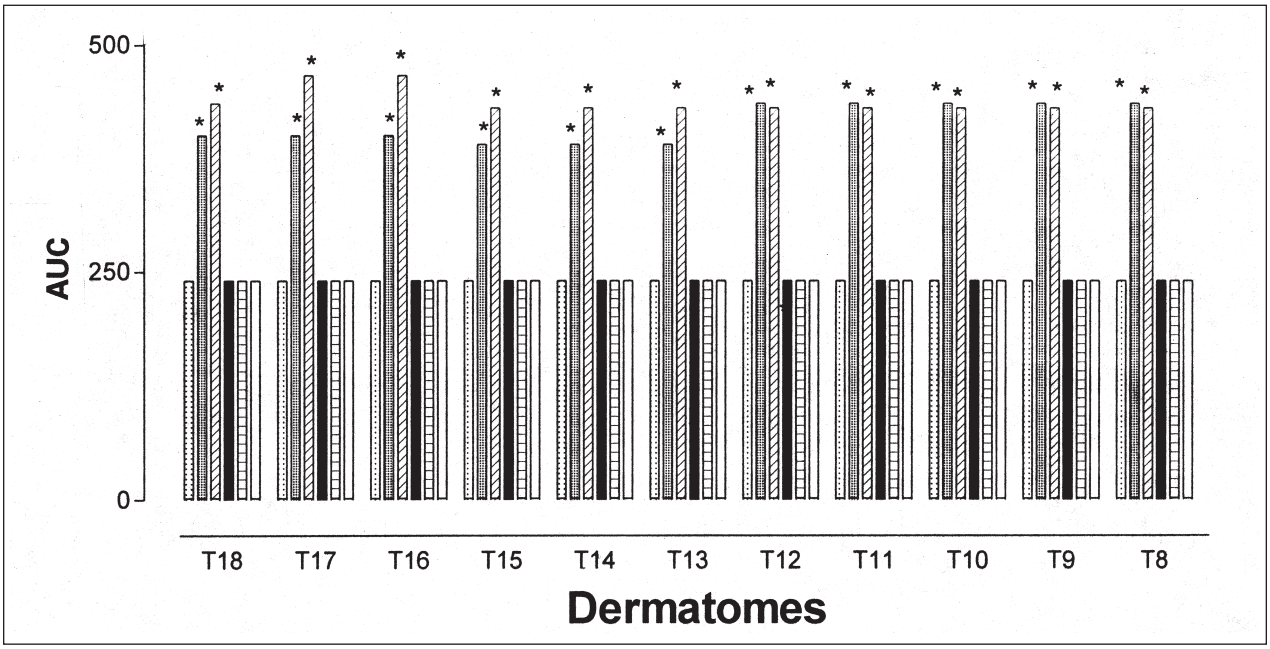

Figure 5—Area under the curve (AUC [V • h]) for avoidance threshold to electrical stimulation of dermatomes of the thoracic region in 5 horses. Data were collected for 24 hours after epidural injection of morphine, alfentanil, butorphanol, tramadol, U50488H, or sterile water. *Significant ($P < 0.05$) difference from baseline values and control group. *See* Figure 4 for key.

Discussion

Horses may develop hind limb ataxia after injection of large volumes of fluid into the caudal epidural space. In one study,[31] 4 horses were administered 20 to 40 ml of new methylene blue dye solution into the first intercoccygeal space; the solution migrated 12 vertebral spaces and caused ataxia in 1 horse and ataxia and sternal recumbency in another horse immediately after injection. In the same study, results indicated that 9.3 ml of the new methylene blue solution administered at the first intercoccygeal space migrated forward 6 vertebral spaces.[31] The typical volume recommended for caudal epidural injection in horses ranges from 10 to 15 ml, irrespective of drug or drug combination used.[3,29,30] Analgesia after cesarean section in humans is prolonged when fentanyl is diluted in 20 ml of physiologic saline (0.9% NaCl) solution, compared with dilution in 10 ml.[32,33] In our study, neither ataxia nor recumbency was observed in horses after injection of 20 ml of solution into the caudal epidural space, although most horses turned their head toward the site of injection or moved forward in the stocks. The 20-ml volume used in this study was dictated by the dose used and the formulation of alfentanil that was commercially available. We concluded that 20 ml of solution injected at the rate of 1 ml/10 s is painful when administered into the caudal epidural space in horses, possibly because of compression of sacral and lumbar spinal nerves. Other factors such as pH of the solution and preservatives may also induce pain. All drugs used in our study were preservative-free aqueous preparations, although differences in pH of the solutions were not determined.

Of the 5 drugs investigated in our study, only morphine and butorphanol have been studied in horses by use of epidural administration. Therefore, to best determine effective doses of alfentanil, tramadol, and U50488H when administered epidurally to horses, we reviewed studies in horses, humans, and other species in which these drugs were administered IV or epidurally. Extrapolation of the doses was done with the knowledge that in most species the equianalgesic epidural dose of opioids is a fraction of the dose administered IV. For instance, in another study,[a] doses of 0.1 mg/kg and 0.05 mg/kg of morphine administered epidurally were effective in providing analgesia in horses. These dose rates represent 1/3 to 1/20 of the doses of morphine recommended for IV administration with xylazine in horses.[34,35]

Results of our study indicated that the selective κ agonist U50488H, at a dose of 0.08 mg/kg administered epidurally, does not induce significant changes from baseline values or from findings in control horses for the threshold to electrical noxious stimulation in horses. This drug is reported to induce potent analgesia without CNS excitation in horses when administered IV at 0.04 mg/kg, 0.08 mg/kg, and 0.16 mg/kg.[13] The dose of U50488H used in our study was 0.08 mg/kg. To the authors' knowledge, the effects of epidural administration of U50488H have not been reported in any species. At the time of the study, a commercially available form of U50488H was not marketed.

Butorphanol is the most common κ opioid agonist used in human and veterinary medicine, however, it possesses a relatively short duration of action and limited analgesic potency to extremely painful stimuli, compared with other drugs.[2,32] There are few reports of the effects of epidural administration of butorphanol. For the relief of pain in humans after cesarean section, lumbar epidural administration of butorphanol in doses of 0.015 mg/kg, 0.03 mg/kg, and 0.06 mg/kg induced 4.82, 5.53, and 8.05 hours of analgesic effect,

respectively.[36] Intravenously administered butorphanol (0.2 mg/kg, 0.4 mg/kg, and 0.8 mg/kg) did not change the **minimum alveolar concentration (MAC)** for halothane in dogs in response to noxious stimulation induced with a tail clamp.[37] When administered IV, 0.05 mg/kg of butorphanol did not decrease the MAC of halothane when electrical stimulation was applied to the fetlock of the forelimb in ponies.[38] Caudal epidural administration of 0.05 mg/kg of butorphanol, diluted to a final volume of 0.15 ml/kg in saline solution, did not change the halothane MAC when electrical stimulation was applied to the hind limbs and forelimbs in horses.[39] Because of the lack of efficacy of 0.05 mg/kg of butorphanol in these 2 studies, which used a well-accepted pain model (reduction of MAC of an inhalant anesthetic), we used a higher dose (0.08 mg/kg) of butorphanol in the study reported here. We hypothesize that the lack of analgesic effect observed with opioid κ agonists in our study could be related to the number and distribution of κ opioid receptors in the spinal cord in horses, to high lipid solubility that caused rapid systemic absorption, and to the dose that was administered.

Alfentanil is considered to be a potent opioid analgesic drug in humans that, when administered IV, decreases the MAC of isoflurane in response to skin incision.[40] In horses, alfentanil administered IV at 94.8, 170.0, and 390.9 ng/ml mean plasma concentrations did not change the MAC of halothane in response to a supramaximal electrical stimulus of the oral mucous membranes, probably because CNS stimulation opposed the analgesic effect of the drug.[41] This could be related to catecholamine release induced by opioids when administered by routes that cause systemic distribution.[22,24] In our study, 0.02 mg/kg of alfentanil induced an increase in the avoidance threshold for noxious electrical stimulation to the dermatomes of the perineal and sacral regions without signs of CNS excitation, which indicated that, compared with administration via other routes, epidural administration of alfentanil is unlikely to induce catecholamine release from the CNS. It is recognized that highly lipid-soluble opioids such as fentanyl and alfentanil are rapidly transferred from the epidural space to the subarachnoid space and to plasma after epidural administration.[2,42] Cephalad movement of lipid-soluble opioids is limited by uptake into the spinal cord after transfer into the subarachnoid space.[32] We believe that the reason that alfentanil induced an increase in the threshold for the noxious stimuli only in the perineal and sacral regions and not in the lumbar and thoracic areas is because it has higher lipid solubility, compared with tramadol and morphine. Epidural administration of highly lipophilic opioids should be performed immediately adjacent to spinal cord binding sites to improve selectivity of spinal analgesia.[42] The dose of epidurally administered alfentanil used in our study was similar to the recommended doses for humans. In humans, 0.02 mg/kg or a total single dose of 0.5 to 1.0 mg of epidurally administered alfentanil has an onset of action of 15 minutes and a duration of analgesic effect of 1 to 3 hours.[43] Epidural injections in humans are usually made at the caudal lumbar or lumbosacral spaces[42], sites that are much closer to the lumbosacral nervous plexus than the intercoccygeal space used in our study of horses. Although the increase in the electrical threshold induced by alfentanil was not significant in our study, the onset for increased electrical threshold and duration of effect was similar to that observed in humans. It is probable that the appropriate dose for epidural administration of alfentanil is approximately 0.02 mg/kg for horses. We suggest that higher doses and other sites of epidural injection should be tested for comparison with intercoccygeal epidural administration of alfentanil in horses before being used clinically.

In our study, tramadol had a faster onset time than morphine in all dermatomes. Pharmacokinetic characteristics of opioids determine their ability to cross the blood-brain barrier.[32] Tramadol and morphine have similar chemical structure, volume of distribution, and protein-binding fraction. Tramadol has higher tissue affinity than morphine.[9,32,44] Therefore, we concluded that the onset time for tramadol was faster than that of morphine because of its higher tissue affinity, which would allow tramadol to cross the dura mater faster than morphine. After crossing the dura mater, lipid-soluble drugs tend to bind to the receptors in the spinal cord, whereas water-soluble drugs tend to remain in the CSF. Tramadol was 30 times less potent than morphine when administered epidurally in humans.[12] The dose of tramadol used in the study reported here (1.0 mg/kg) was similar to that used in humans (1.43 mg/kg).[12] In our study, significant differences between effects of 1.0 mg/kg of tramadol and 0.1 mg/kg of morphine on the AUC were not detected. We concluded that in horses, epidurally administered tramadol is 10 times less potent than morphine. Tramadol induced faster onset time and more intense analgesia over the dermatomes of the perineal and sacral regions, compared with the lumbar and thoracic regions, perhaps because of the opioid receptor binding characteristics of tramadol attributable to its higher tissue affinity. The less intense analgesic effect observed at the lumbar and thoracic areas could be attributable to the ability of tramadol to inhibit amine neuronal uptake at the descending monoaminergic pathways involved in analgesia.

Results of the study reported here indicated that 0.1 mg/kg of morphine administered epidurally induced significant differences in avoidance threshold among dermatomes from the perineal region to the thoracic region. These results may be explained by the migration of morphine forward in the epidural space from the point of injection. In the event of morphine migration to the brain, some degree of CNS excitation would have been observed. Signs of CNS excitation were not observed in the horses in the study reported here.

The analgesic effects of epidurally administered morphine or morphine combined with detomidine in horses have been described.[25,a] When 0.2 mg of morphine/kg was combined with 0.03 mg of detomidine/kg and administered epidurally, profound analgesia was induced in the hind limbs of lame horses.[25] In 1 horse with severe signs of pain in the hind limb, morphine was successfully used to provide long-lasting pain relief.[7] Time of onset for analgesia induced by caudal

epidural administration of morphine in horses was 20 minutes for hind limb pain when a catheter was used; analgesia of thoracic dermatomes was maintained for 8 hours.[7,a] In 1 study[12] of experimental hind limb lameness in horses, the combination of morphine and detomidine administered epidurally induced analgesia within 1 hour. In the study reported here, onset of analgesia ranged from 4 to 8 hours for sacral to thoracic regions, respectively. These results are similar to those described in the literature and can be explained by morphine's pharmacokinetic characteristics (low lipid solubility, 23% in nonionized form, 35% protein binding, and 224-L volume of distribution).[32] Caudal epidural administration of morphine induces analgesia for an extended period; segmental analgesia induced by caudal epidural administration of morphine in horses lasts from 8 to 19 hours.[a] Results of our study indicated that duration of analgesia induced by caudal epidural administration of morphine was variable. Analgesic duration was greater on the dermatomes closest to the epidural injection site and lesser on the thoracic dermatomes. Duration of effect of an epidurally administered opioid is influenced by the number of molecules retained in the CSF and spinal tissue and by the dissociation kinetics of the drug.[45] Among the opioids used in our study, morphine has the greatest dissociation kinetic values, which could explain the long-lasting effect. Over the dermatomes of the lumbar and thoracic region, duration of effect was less than that detected over the perineal and sacral regions and can be explained by the distance from the site of injection and a possible dilutional effect of the CSF. Both factors would contribute to a small number of morphine molecules available to bind to the opioid receptors in the lumbar and thoracic spinal cord.

Caudal epidural administration of tramadol or morphine has potential in management of perineal and lumbosacral pain in horses. Regional differences exist in the intensity and duration of pain relief provided by these drugs; tramadol had a faster onset of action than morphine, but duration of effect was shorter.

[a]Robinson EP, Moncada-Suarez JR, Felice L. Epidural morphine analgesia in horses (abstr). *Vet Surg* 1994;23:78.
[b]Reusable technique needle, Tuohy, thin wall, Becton-Dickinson Co, Rutherford, NJ.
[c]Bioclusiv transparent dressing, Johnson & Johnson, Arlington, Tex.
[d]Infumorph 200, Elkin-Sinn, Cherry Hill, NJ.
[e]Alfenta, Janssen Pharmaceutica Inc, Pistcataway, NJ.
[f]Stadol, Bristol-Myers Squibb Co, Princeton, NJ.
[g]Silador, Sanofi do Brasil SA, Rio de Janeiro, RJ, Brazil.
[h]U50488H, Sigma Chemical Co, St Louis, Mo.
[i]µStar 0.45 µm CA, Costar, Cambridge, Mass.
[j]Physiograph, E & M Instruments Co, Houston, Tex.

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