Analgesic, hemodynamic, and respiratory effects induced by caudal epidural administration of meperidine hydrochloride in mares

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Objective—To determine the analgesic, hemodynamic, and respiratory effects induced by caudal epidural administration of meperidine hydrochloride in mares.

Animals—7 healthy mares.

Procedure—Each mare received meperidine (5%; 0.8 mg/kg of body weight) or saline (0.9% NaCl) solution via caudal epidural injection on 2 occasions. At least 2 weeks elapsed between treatments. Degree of analgesia in response to noxious electrical, thermal, and skin and muscle prick stimuli was determined before and for 5 hours after treatment. In addition, cardiovascular and respiratory variables were measured and degree of sedation (head position) and ataxia (pelvic limb position) evaluated.

Results—Caudal epidural administration of meperidine induced bilateral analgesia extending from the coccygeal to S1 dermatomes in standing mares; degree of sedation and ataxia was minimal. Mean (± SD) onset of analgesia was 12 ± 4 minutes after meperidine administration, and duration of analgesia ranged from 240 minutes to the entire 300-minute testing period. Heart and respiratory rates, rectal temperature, arterial blood pressures, Hct, Pa_{O_2}, Pa_{CO_2}, pHa, total solids and bicarbonate concentrations, and base excess were not significantly different from baseline values after caudal epidural administration of either meperidine or saline solution.

Conclusions and Clinical Relevance—Caudal epidural administration of meperidine induced prolonged perineal analgesia in healthy mares. Degree of sedation and ataxia was minimal, and adverse cardiorespiratory effects were not detected. Meperidine may be a useful agent for induction of caudal epidural analgesia in mares undergoing prolonged diagnostic, obstetric, or surgical procedures in the anal and perineal regions. (*Am J Vet Res* 2001;62:1001–1007)

Caudal epidural analgesia (CEA) is routinely used for pain relief and control of rectal tenesmus associated with a variety of diagnostic, obstetric, and surgical procedures performed in the anal and perineal regions of standing horses.[1] Commonly used drugs for CEA include the local anesthetics lidocaine,[2-5,a] carbocaine,[6] and ropivacaine,[7,a] the α_2-adrenoceptor agonists xylazine[8-12] and detomidine,[12-14] combinations of lidocaine and xylazine[5] or lidocaine and ropivacaine,[a] and ketamine.[15] Morphine[16,b] and a combination of morphine and detomidine[17] also have been used to induce CEA with some advantages over local anesthetics, as they induce prolonged analgesia and minimal ataxia. All except the opioids may induce ataxia, postural instability, or recumbency in horses.

Meperidine is a synthetic phenylpiperidine-derivative opioid and exerts the strongest local anesthetic effect among the clinically used opioids. It has been used successfully to induce local and regional analgesia and postoperative analgesia in humans.[18-27] To our knowledge, no studies have described the effects of epidurally administered meperidine on perineal analgesia in mares. For this reason, the purpose of the study reported here was to evaluate perineal analgesia, sedation, ataxia, and hemodynamic and respiratory effects induced by caudal epidural administration of meperidine hydrochloride in mares.

Materials and Methods

Mares—Seven healthy mares (4 Thoroughbreds, 3 Standardbreds), ranging from 10 to 20 years in age (mean ± SD, 14 ± 4.1 years) and 510 to 610 kg in body weight (560 ± 45 kg), were used in this study. At least 8 weeks prior to the study, the left carotid artery of each horse was surgically elevated to a subcutaneous position. The study protocol and experimental design were approved by The Ohio State University Laboratory Animal Care and Use Committee.

Preparation of mares—For each experiment, mares stood in restraining stocks in a quiet climate-controlled room from 9:00 AM to 5:00 PM. Prior to each experiment, hair over the left carotid artery, right jugular furrow, and sacrococcygeal area was clipped, and the skin was prepared for aseptic placement of intravascular catheters and an epidural needle. Catheters and the epidural needle were placed after infiltration of skin and subcutaneous tissues with 2% lidocaine.[c] An 18-gauge 30-cm catheter[d] was inserted into the exteriorized left carotid artery for measurement of systemic **arterial blood pressures (ABP)** and for collection of arterial blood samples. Proper positioning of the arterial catheter was confirmed at the time of insertion and prior to blood pressure determinations by observing characteristic pressure waveforms on an oscilloscope. Arterial pressure waveforms were obtained, using a calibrated strain-gauge transducer.[e] The point of the shoulder was considered the zero pressure point. Mean carotid blood pressure was obtained by electronic inte-

Received Jul 18, 2000.
Accepted Oct 23, 2000.
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Supported in part by Equine Research Funds of The Ohio State University College of Veterinary Medicine.
Presented in part at the 25th meeting of the American College of Veterinary Anesthesiologists, San Francisco, Calif, Oct 12-13, 2000.
The authors thank Dr. Jean Powers for assistance with statistical analyses, and Jenifer Gadawski, Steven Schumacher, and Chad Andrews for technical assistance.

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gration of the signal obtained from the blood pressure transducer. Surface ECG leads were placed for continual monitoring of a base-apex ECG, and a thermometer probe[f] was placed approximately 20 cm into the rectum for determination of deep rectal temperature. A 30-cm length of 240-polyethylene tubing was inserted into the right external jugular vein as a precaution in case IV administration of tranquilizers and anesthetics was required in mares that became excited or recumbent, respectively, after epidural administration of meperidine.

Epidural needle placement—An 18-gauge 8.75-cm spinal needle[g] was placed into the epidural space along the median plane at the first coccygeal (Co1-Co2) interspace. The tip of the needle was directed at a 10 to 30° angle perpendicular to the spinal cord. The needle was slowly advanced, with the bevel pointing craniad, until the interarcuate ligament was perceived. The stylet was removed, and a 3-ml syringe was attached. The interarcuate ligament was pierced, using a loss of resistance technique for identifying the epidural space.[1] The needle was advanced to its full length (8.75 cm) or until the needle tip contacted the floor of the vertebral canal, from which it was withdrawn 0.25 cm. Radiography verified the vertebral location of the needle in situ. The distance from the skin to the free lumen of the epidural space was measured by measuring the distance between the needle hub and skin puncture site and subtracting the distance from the length of the free end of the needle. In addition, correct needle placement was verified by ensuring that the measured distance of the free end of the epidural needle remain unchanged between radiography and injection and by detecting minimal resistance to injection of 5 ml of air, meperidine, or saline (0.9% NaCl) solution.

Experimental protocol—After placement of catheters and the epidural needle, rectal thermometer probe, and ECG leads, each mare was allowed to stand undisturbed for at least 60 minutes prior to treatment. Meperidine hydrochloride[h] (5%, 0.8 mg/kg of body weight) or a similar volume of sterile saline solution[i] was administered via the epidural needle at a rate of approximately 1 ml/6 sec to each mare on 2 occasions, using each regimen in random sequence. At least 2 weeks elapsed between experiments. Test and control solutions were prepared on the morning of each experiment by an investigator other than the one performing measurements and placed in syringes that were labeled only with the mare's identification number.

Baseline (time 0) measurements were obtained just prior to epidural injection of meperidine or saline solution. Hemodynamic and respiratory measurements and analgesia, sedation, and ataxia scores were obtained before (time 0) and 5, 10, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, and 300 minutes after epidural injection. Response to noise and sudden movements, severity of sweating, and frequency of urination were also recorded at these times. **Heart rate (HR)** and rhythm were determined from the ECG. **Respiratory rate (RR)** was determined by counting thoracic and abdominal excursions for 1 minute. Arterial blood samples (2 ml) were collected anaerobically from the carotid artery catheter into heparinized plastic syringes. The syringes were capped and placed in an iced water bath, and samples were analyzed within 20 minutes of collection for determination of Pa_{O_2}, Pa_{CO_2}, and pHa by use of a microprocessor blood gas analyzer.[j] All blood gas values were corrected for rectal temperature, which was measured just prior to blood collection. Hematocrit and concentration of **total solids (TS)** were measured from arterial blood samples by use of a microhematocrit method[k] and refractometer,[l] respectively. Standard bicarbonate concentration and **base excess (BE)** were calculated. Electrocardiograms and systolic, diastolic, and mean ABP were observed on the oscilloscope and recorded simultaneously by a photographic recorder[m] at a rate of 25 mm/s at each sample collection time.

To minimize the effect of stimulation on sedation and cardiopulmonary data,[11,14] the order in which data were collected was as follows: evaluation of behavior (ie, degree of sedation and ataxia and response to noise and sudden movements), measurement of HR and RR, measurement of hemodynamic variables, collection of carotid artery blood samples, and evaluation of analgesia. For evaluation of analgesia, electrical stimuli were applied first, followed by thermal stimuli and, finally, needle-prick stimuli. To avoid observer-dependent subjective differences, behavioral responses and analgesia were evaluated by the same person (RTS).

Catheters and the epidural needle were removed after completion of each experiment, and mares were walked back to their stalls. All mares were examined for neurologic deficits and wound infections at needle and catheter puncture sites 24 hours after catheterization and epidural needle placement.

Assessment of analgesia—Analgesia was defined as an increase in response threshold, compared with baseline values, to application of noxious electrical and thermal (heat) stimuli at the perineal dermatome and needle-prick stimuli at the region extending from the coccygeal to S1 dermatomes. Stimulation was applied until an **avoidance response (AR)** was observed; AR included a skin-twitch reflex, any abrupt movement of the tail, limbs, or torso, or movement of the head toward the stimulus coincident with application of the stimulus.

To ensure that the site of electrical stimulation was consistent throughout each experiment, two 20-gauge 2.5-cm-long needles were pierced through a skin fold on either side of the vulva, approximately 5 cm apart. An alligator clip electrode was attached to each needle shaft and a peripheral nerve stimulator.[n] At least 3 square-wave monophasic pulses were generated at a rate of 1 pulse/10 s and pulse width of 200 microseconds. A numbered control knob was used to adjust the amplitude of the output current, beginning with the lowest current and increasing the current by approximately 5 mA until an AR was observed. The digital display indicated the current delivered in milliamperes, and the avoidance threshold was taken as the current at which an AR was observed. Time to onset and duration of perineal analgesia were recorded as the first time after treatment that avoidance threshold was > 40 mA and the total time that avoidance threshold remained > 40 mA, respectively.[7] If an AR was not detected at the maximum output of the peripheral nerve stimulator, the avoidance threshold was assumed to equal the maximum output (ie, 80 mA).

A specially designed instrument[o] with a heat device was used to determine response to thermal (heat) stimulation. This instrument consisted of a linear ramped-intensity incandescent bulb housed in a metal cylinder.[28] The heat device was handheld at a right angle over the center of a temperature probe[p] that was placed on the skin of the perineum from which hair had been clipped. A run button was manually pressed until a **skin-twitch reflex (STR)** and AR were noticed. **Latency of radiant heat-evoked STR (STRL)** and perineal skin temperature after heat application were displayed on the heat-lamp analgesia meter and precision thermometer,[q] respectively, and recorded. A stimulus of < 48 C for < 20 seconds was used. This stimulus resulted in no visible epidermal damage.

To assess the extent of diffusion of meperidine within the epidural space at each data collection period, superficial skin pricks (ie, pinching the surface of the skin with a 22-gauge 2.5-cm-long needle), deep skin pricks (ie, inserting the needle tip through the skin), and deep muscle pricks (ie,

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Table 1—Analgesic effects induced by caudal epidural administration of meperidine hydrochloride (5%, 0.8 mg/kg of body weight) to healthy mares

Breed (age)	Weight (kg)	Skin-to-needle tip distance (cm)	Location of needle tip*	Time to onset of analgesia (min) †	Duration of analgesia (min)‡	Distribution of analgesia§
Th (14 y)	610	8.50	S5–Co1	15	300	S2–coccygeal
Th (11 y)	605	8.75	S5	10	240	S3–coccygeal
Th (14 y)	525	8.75	S5	15	270	S3–coccygeal
Th (10 y)	615	8.50	S5–Co1	15	300	S1–coccygeal
Sb (20 y)	510	8.75	S5	5	300	S1–coccygeal
Sb (10 y)	540	8.75	S5	10	300	S2–coccygeal
Sb (19 y)	540	8.50	S5–Co1	15	300	S1–coccygeal

*Vertebral level. †Measured from time of administration of meperidine to loss of avoidance response to application of electrical stimuli (> 40 mA) to the perineal area. ‡Measured from time of administration of meperidine to return of avoidance response to application of electrical stimuli (> 40 mA) to perineal area. §Range of bilaterally desensitized dermatomes 60 minutes after administration of meperidine.
Th = Thoroughbred. Sb = Standardbred.

inserting the needle to its full length through the skin and underlying tissues, with bleeding at the puncture site) were applied to adjacent dermatomes starting at the coccyx and moving forward to the sacral region and distal to the pelvic limbs until an AR was observed. Degree of sensory perception to needle-prick stimulation at each dermatome was scored on a scale of 0 to 3,[11,12] where 0 indicated an AR was detected after superficial skin prick, 1 indicated no AR was detected after superficial skin prick, 2 indicated no AR was detected after deep skin prick, and 3 indicated no AR was detected after deep muscle prick. The most rostral skin area from which no AR was elicited to deep muscle prick 60 minutes after administration of meperidine was indicated with adhesive tape, photographed, and recorded.

Assessment of sedation and ataxia—Degree of sedation was assessed by observing head position and droopiness of eyelids.[12] Sedation was scored on a scale of 0 to 2, where 0 indicated no change in position of head or eyelids from baseline, 1 indicated the muzzle was lowered to the elbow and the eyelids were slightly droopy, and 2 indicated the muzzle was lowered to the carpus and the eyelids were droopy.

Degree of ataxia was assessed by observing pelvic limb position and scored as 0 or 1. An ataxia score of 0 indicated no change in limb position from baseline, whereas 1 indicated that the mare was supporting its weight on 3 legs or swaying slightly. Responses to noise and sudden movements of personnel were also recorded.

Statistical analyses—Scores of behavioral responses (sedation, ataxia), analgesia, and cardiovascular and respiratory variables were expressed as the mean ± SD for each treatment group. Mean values were compared between and within groups over time by use of a 2-way ANOVA with repeated measures and a Dunnett *t*-test.[r] Categorical data were analyzed by use of a Fisher exact test. Values of $P < 0.05$ were considered significant.

Results

Analgesic effects of meperidine—The distance from the skin at the first coccygeal intervertebral space to the needle point within the epidural space varied between 8.5 and 8.75 cm (mean ± SD, 8.6 ± 0.1 cm). Epidural injection of meperidine at vertebral levels extending from the sacrococcygeal intervertebral space to S5 resulted in various degrees of bilateral analgesia, with dermatomal spread of analgesia ranging from all coccygeal spinal cord segments to S1 (**Table 1**). Results of analgesic tests revealed that dermatomes supplied by the caudal, caudal rectal, perineal, and pudendal nerves were desensitized in all mares. In addition, analgesia was induced in dermatomes supplied by the caudal cutaneous femoral nerves in 2 mares. Blockade of motor

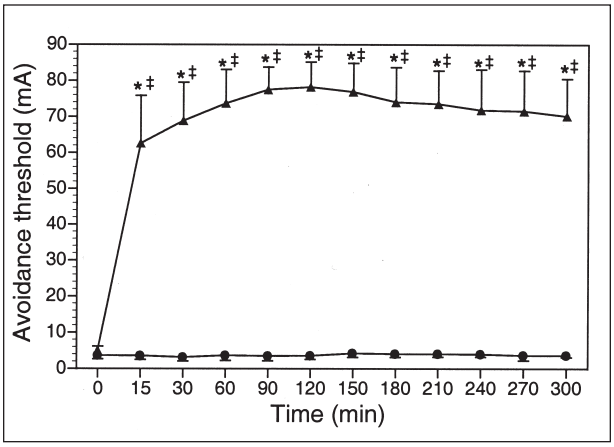

Figure 1—Mean (± SD) avoidance threshold in 7 mares before (time 0) and after caudal epidural administration of meperidine hydrochloride (5%; 0.8 mg/kg of body weight; closed triangles) or saline (0.9% NaCl) solution (controls; closed circles). Electrical stimuli of increasing intensity were applied to the perineal area; the avoidance threshold was defined as the current at which an avoidance response was detected. *Significantly ($P < 0.001$) different from baseline (time 0) value. ‡Significantly ($P < 0.001$) different from control value.

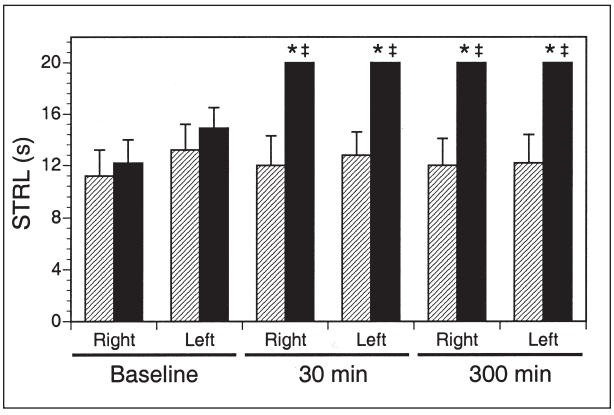

Figure 2—Mean (± SD) latency of radiant heat-evoked skin-twitch reflexes (STRL) in 7 mares before (baseline) and 30 and 300 minutes after caudal epidural administration of meperidine (black bars) or saline solution (striped bars). A thermal stimulus of < 48 C was applied bilaterally to the perineal area; STRL was defined as the stimulation time required to induce an avoidance response. *See* Figure 1 for key.

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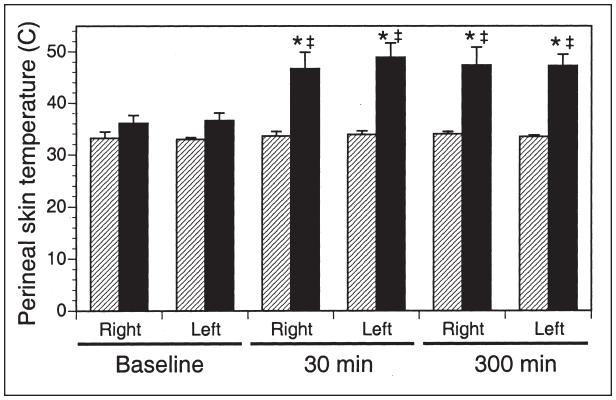

Figure 3—Mean (± SD) perineal skin temperature in 7 mares before (baseline) and 30 and 300 minutes after caudal epidural administration of meperidine (black bars) or saline solution (striped bars). A thermal stimulus of < 48 C was applied bilaterally to the perineal area until STRL was determined (< 20 seconds). *See* Figure 1 for key.

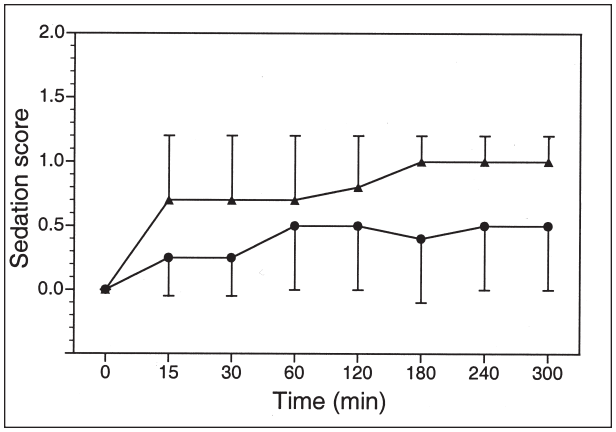

Figure 4—Mean (± SD) sedation score in 7 mares before and after caudal epidural administration of meperidine (closed triangles) or saline solution (closed circles). Scores indicate position of head and eyelids; a score of 0 indicates no change from baseline position, 1 indicates the muzzle was lowered to the level of the elbow and eyelids were slightly droopy, and 2 indicates the muzzle was lowered to the level of the carpus and eyelids were droopy. Significant differences within or between groups were not detected.

fibers resulted in flaccidity of the tail and buckling of 1 pelvic limb in 1 mare. Blockade of parasympathetic fibers of the pelvic nerves resulted in relaxation of genitalia and dilatation of the rectum in all mares.

Onset of perineal analgesia (ie, avoidance threshold > 40 mA) ranged from 5 to 15 minutes (mean ± SD, 12.1 ± 3.9 minutes) after meperidine administration, whereas maximum analgesia (avoidance threshold, 74 ± 12 mA) was achieved between 60 and 180 minutes (121 ± 35 minutes; **Fig 1**). Duration of perineal anesthesia in horses given meperidine epidurally ranged from 240 to at least 300 minutes (287 ± 24 minutes). Epidural injection of saline solution did not significantly alter avoidance threshold to electrical stimulation, compared with baseline values.

Thirty and 300 minutes after epidural administration of meperidine, mean STRL and perineal skin temperature in response to thermal stimulation were significantly ($P < 0.001$) increased, compared with baseline and control-group values **(Fig 2 and 3)**. Mean

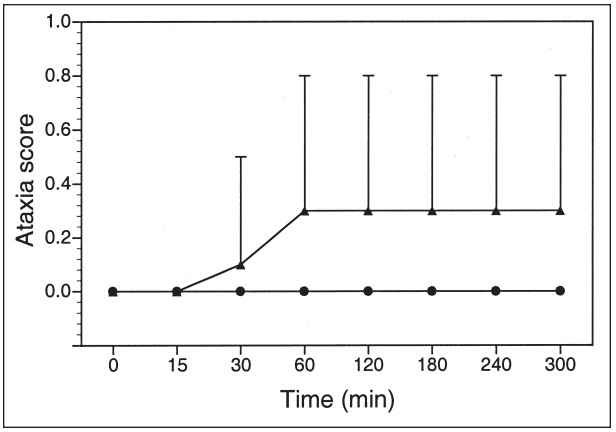

Figure 5—Mean (± SD) ataxia score in 7 mares before and after caudal epidural administration of meperidine (closed triangles) or saline solution (closed circles). Scores indicate pelvic limb position; a score of 0 indicates no change from baseline position, whereas 1 indicates that the mare was supporting its weight on 3 legs or swaying slightly. Significant differences within or between groups were not detected.

maximum analgesia score in response to muscle needle-prick stimulation of the sacrococcygeal dermatomes was 2.3 ± 0.5. The maximum score was achieved 60 minutes after meperidine administration and did not significantly decrease for the remainder of the 300-minute test period. Administration of saline solution had no significant effect on STRL, perineal skin temperature, or analgesia score.

Effects of meperidine on sedation and ataxia— Meperidine treatment resulted in a moderate degree of sweating at perineal dermatomes. All mares given meperidine were mildly sedated, as evidenced by lowering of the head and drooping of the upper eyelids. The mean maximum sedation score of 0.9 ± 0.2 was detected 180 minutes after meperidine injection. Sedation scores remained high for the remainder of the 300-minute testing period; however, they did not differ significantly from baseline scores **(Fig 4)**. The mean maximum ataxia score of 0.3 ± 0.6 was achieved 60 minutes after injection. Ataxia scores also remained high for the remainder of the observation period; however, they were not significantly different from the baseline scores **(Fig 5)**. Significant differences in sedation and ataxia scores were not detected between treated and control groups.

All mares were calm and remained standing during each experiment. No mare urinated during the 300-minute observation period, but 6 mares urinated soon after they were returned to their stalls. No mare developed neurologic deficits or wound infections at needle or catheter puncture sites 24 hours after epidural needle placement and catheterization.

Cardiopulmonary effects of meperidine—Mean Hct, HR, RR, rectal temperature, ABP, pHa, Pa_{O_2}, Pa_{CO_2}, BE, and concentrations of bicarbonate and TS did not change significantly from baseline values following epidural administration of either meperidine or saline solution, nor were significant differences in these variables detected at any time between groups. Baseline values were as follows: Hct, 35.0 ± 5.0%; HR,

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34.6 ± 3.4 beats/min; RR, 19.7 ± 5.5 breaths/min; rectal temperature, 37.8 ± 0.1 C; systolic ABP, 158.4 ± 4.2 mm Hg; diastolic ABP, 109.0 ± 4.1 mm Hg; mean ABP, 128.7 ± 6.1 mm Hg; pHa, 7.429 ± 0.006; Pa_{O_2}, 107.9 ± 11.5 mm Hg; Pa_{CO_2}, 40.1 ± 1.4 mm Hg; BE, 2.2 ± 1.2 mEq/L; bicarbonate concentration, 26.3 ± 1.2 mEq/L; and TS concentration, 6.3 ± 0.4 g/dl.

Discussion

Epidural administration of meperidine as a bolus dose (8 ml of a 5% solution/500 kg of body weight) consistently fulfilled our criteria for inducing long-lasting (5 hours) perineal analgesia in mares. Determination of analgesia in mares is inherently difficult because of the wide range of pain tolerance or perception of pain between mares. In addition, opioid drugs exert their effects via multiple receptor sites that are differentially affected depending on the source of nociception or pain. However, by use of electrical, thermal, and needle-prick stimuli, we were able to detect complete analgesia at the perineal dermatomes in all mares. We also found a wide range of caudal desensitized zones in mares in response to deep muscle needle pricks. Response to deep muscle needle pricks identified the cranial limits of meperidine in the epidural space and concomitant analgesia of spinal segments extending bilaterally from the coccyx to S1 in 3 mares, the coccyx to S2 in 2 mares, and the coccyx to S3 in 2 mares. Presumably, the presence of a nerve sheath and absorption of meperidine by surrounding tissues considerably altered drug availability to the target nerves. Factors that were not standardized but that may have influenced the area affected by epidurally administered meperidine were the exact position of the needle tip, capacity of the epidural space, degree of neural uptake and vascular or lymphatic absorption of meperidine, and elimination of meperidine.[1] Ideally, the amount of meperidine injected is determined by considering the total dose (volume × concentration) of meperidine, the site and conformation of the mare, the depth of needle insertion into the vertebral canal (ie, the actual distance of the needle bevel to the spinal cord), and the extent of regional analgesia required.[1] In our study, the tip of the epidural needle was placed at the fifth sacral vertebra in 4 mares and at the sacrococcygeal intervertebral space in 3 mares to allow deposition of a small volume of 5% meperidine adjacent to the coccygeal nerves and last 3 pairs of sacral nerves.

We have developed and established the proper use of the radiant heat analgesia meter in horses. A slow (1 to 20 seconds) ramping of thermal intensity was used to induce subtle increases in pain and make the pain threshold more obvious. Although we did not microscopically examine skin sections, tissue damage attributable to excessive thermal stimulation was not grossly obvious when exposure time to 65% of the 56 W lamp was limited to < 20 seconds. We found a close relationship between response to electrical and deep muscle needle-prick stimulation at the perineum in meperidine-treated horses, such that an avoidance threshold of 40 mA seemed to be the typical current above which mares did not respond to deep muscle needle-prick stimulation. Therefore, 40 mA was used as the avoidance threshold for determining onset and duration of analgesia.

Response to electrical stimulation was a more sensitive indicator of analgesia than response to needle-prick stimulation and was more likely indicative of onset of analgesia, peak analgesic effect, and regression of analgesia. The time range required to reach maximum perineal analgesia in mares (15 to 40 minutes) was similar to the time range required to reach maximum pain relief after peridural administration of meperidine in humans (15 to 30 minutes).[29,30] Similarly, duration of perineal analgesia in mares (5 hours) after caudal epidural administration of meperidine was comparable to the mean duration of analgesia (3 to 6 hours) in humans after peridural administration of a 50- to 100-mg bolus dose of meperidine.[25,29,31,32]

We also observed a close relationship between responses to electrical and thermal stimulation of the perineal skin of mares after meperidine administration, such that the maximum thermal stimulation (48 C) did not elicit an AR in horses in which the avoidance threshold was > 60 mA. Electrical stimulation at a current of 60 mA in humans has been assessed as equivalent to the intensity of stimulation caused by surgical incision.[33]

Although our data do not permit an unequivocal definition of the mechanism of analgesia induced by meperidine, it is probable that meperidine induced regional analgesia primarily via its local anesthetic effects. The local anesthetic effects of epidurally administered meperidine (eg, perineal analgesia and decreased tail muscle and anal sphincter tone) closely resembled the effects induced in mares by caudal epidural administration of lidocaine, carbocaine, or ropivacaine.[2-7,a] In the present study, 1 mare with caudal analgesia extending from the coccygeal to S1 dermatomes had proprioception deficits in the pelvic limbs and leaned against the restraining stocks, indicating a possible local anesthetic action of meperidine on the motor neurons of the pelvic limbs. Further investigation is required to determine the minimum effective analgesic concentration of meperidine in CSF and plasma of horses and whether meperidine, at low concentrations, may reduce excitability at cranial lumbar (L1-L6) spinal nerves without induction of conduction block in horses.

The site of action and the mechanism by which epidurally administered meperidine induces selective and motor nerve block in humans and laboratory animals are speculative. Because opioid receptors have been found in sensory axons,[34] it is possible that conduction block in nerves may be, at least in part, the result of either specific opioid receptor-mediated mechanisms or nonspecific membrane conduction blocking effects.[35,36] Alternatively, meperidine is structurally similar to local anesthetics and is capable of inducing regional anesthesia separate from its opioid-receptor agonistic effects.[37] In vitro, the local anesthetic effects of meperidine on mammalian peripheral nerves and nerve conduction typically cannot be reversed by naloxone,[38] suggesting that the local action is more likely mediated by a nonopioid receptor-dependent mechanism. In 1 study,[39] the local anesthet-

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ic effects of clinically relevant concentrations of meperidine (705 µM) blocked the in vitro conduction in 61.5% of 39 myelinated and unmyelinated axons of rats and significantly reduced conduction block velocity in the remaining unblocked axons. These effects were not reversible by naloxone. Most recently, the blocking effects of meperidine on different ion channels of peripheral nerve fibers of *Xenopus laevis* has been investigated.[40] Externally applied meperidine reversibly blocked all ion channels evaluated in a concentration-dependent manner.

In our study, mares that received meperidine were mildly sedated, as evidenced by lowering of the muzzle and drooping of the eyelids, probably as a result of the systemic absorption of meperidine. The sedative effects of epidurally administered meperidine resembled those of epidurally administered morphine[b] but were less pronounced than the effects of epidurally administered xylazine[8-12] or detomidine.[12-14] Excitement, such as that induced after IV administration of meperidine, was not detected in any mare.

Because of its longer duration of local anesthetic action, meperidine may be superior to mepivacaine,[6] ropivacaine,[7] or ketamine[15] for inducing CEA during prolonged perineal surgery in standing mares. It also may be superior to xylazine[5,8-12] and detomidine,[13,14] because onset of perineal analgesia is more rapid (5 to 15 minutes vs 15 to 30 minutes) with less sedation and ataxia and fewer cardiovascular and respiratory depressive effects. Epidurally administered meperidine may also be superior to epidurally administered morphine[b] in horses, not only because onset of analgesia is faster (5 to 15 minutes vs 4 to 6 hours), but also because morphine can induce adverse effects such as hypotension and skin wheals.[b] The commercially available meperidine solution (50 mg meperidine/ml) we used contained preservative (0.1% metacresol). However, we did not detect neurologic deficits in any mare 24 hours after epidural administration. To our knowledge, there is also no evidence that peridural administration of meperidine in humans results in neurologic damage.[30,33]

Further research is necessary to determine whether caudal epidural administration of meperidine results in conditions suitable for performing prolonged surgical, obstetrical, and diagnostic procedures in the perineal region of standing mares. In humans, meperidine has been used successfully for controlled pain management and sedation during the perioperative period.[18] Intravenous,[20] epidural, or spinal (intrathecal) administration of meperidine has resulted in high-quality pain relief after thoracotomy,[21] labor and delivery,[22] and Cesarean section.[23,24] In addition, epidural administration of meperidine in humans has been shown to consistently provide better analgesia with smaller dose requirements, lower plasma concentrations, and fewer adverse effects such as nausea, vomiting, pruritus, drowsiness, and respiratory depression, compared with IV or IM administration.[20,25,26]

[a]Luna SPL, Bueno SK, Cruz ML, et al. Extradural anaesthesia using lidocaine, ropivacaine, hyperbaric lidocaine and a combination of lidocaine and ropivacaine in mares (abstr). *Vet Anaesth Analg* 2000;27:57.

[b]Robinson EP, Moncada-Suarez JR, Felice L. Epidural morphine analgesia in horses (abstr). *Vet Surg* 1994;23:78.

[c]Lidocaine 2% injectable, Phönix Scientific Inc, St Joseph, Mo.

[d]Vialon polymer resin radiopaque intracath, Deseret Medical Inc, Sandy, Utah.

[e]Gould Statham Instruments Inc, Hato Ray, Puerto Rico.

[f]YSI 400 probe tele-thermometer, Scientific Division, Yellow Springs Instrument Co Inc, Yellow Springs, Ohio.

[g]Monoject, Sherwood Medical, St Louis, Mo.

[h]Demerol 5%, Abbott Laboratories, North Chicago, Ill.

[i]Biostatic sodium chloride for injection, USP 0.9%, Elkins-Sinn Inc, Cherry Hill, NJ.

[j]ABL 500-K pH and blood gas analyzer, Radiometer-Copenhagen, Copenhagen, Denmark.

[k]Criticaps, micro-hematocrit capillary tube reader, Monoject Scientific, St Louis, Mo.

[l]10436 Veterinary refractometer, Cambridge Instruments, Buffalo, NY.

[m]Simultrace recorder model VR-12, Electronics for Medicine, Pleasantville, NY.

[n]Digi Stim III, Neuro Technology Inc, Houston, Tex.

[o]Specific product, Columbus Instruments International Corp, Columbus, Ohio.

[p]408, Banjo surface probe, Scientific Division, Yellow Springs Instrument Co Inc, Yellow Springs, Ohio.

[q]YSI Precision 4000, Scientific Division, Yellow Springs Instrument Co Inc, Yellow Springs, Ohio.

[r]Systat for Windows, version 5.2, Systat Inc, Evanston, Ill.

References

1. Skarda RT. Local and regional analgesic techniques: B. horses. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. *Lumb and Jones' veterinary anesthesia.* 3rd ed. Baltimore: The Williams & Wilkins Co,1996;448–478.

2. Slusher SH. Caudal epidural anesthesia in horses. *Vet Med Small Anim Clin* 1981;76:1373–1775.

3. Schelling CG, Klein LV. Comparison of carbonated lidocaine and lidocaine hydrochloride for caudal epidural anesthesia in horses. *Am J Vet Res* 1985;46:1775–1377.

4. Fikes LW, Lin HC, Thurmon JC. A preliminary comparison of lidocaine and xylazine as epidural analgesics in ponies. *Vet Surg* 1989;18:85–86.

5. Grubb TL, Riebold TW, Huber MJ. Comparison of lidocaine, xylazine, and xylazine/lidocaine for caudal epidural analgesia in horses. *J Am Vet Med Assoc* 1992;201:1187–1190.

6. Skarda RT, Muir WW. Continuous caudal epidural and subarachnoid anesthesia in mares: a comparative study. *Am J Vet Res* 1983;44:2290–2298.

7. Skarda RT, Muir WW. Analgesic, hemodynamic and respiratory effects of caudal epidurally administered ropivacaine hydrochloride in mares. *Vet Anaesth Analg* 2001;28:61–74.

8. LeBlanc PH, Caron JP, Patterson JS, et al. Epidural injection of xylazine for perineal analgesia in horses. *J Am Vet Med Assoc* 1988; 193:1405–1408.

9. LeBlanc PH, Caron JP. Clinical use of epidural xylazine in the horse. *Equine Vet J* 1990;22:180–181.

10. LeBlanc PH, Eberhart SW. Cardiopulmonary effects of epidurally administered xylazine in the horse. *Equine Vet J* 1990; 22:389–391.

11. Skarda RT, Muir WW. Analgesic, hemodynamic, and respiratory effects of caudal epidurally administered xylazine hydrochloride solution in mares. *Am J Vet Res* 1996;57:193–200.

12. Skarda RT, Muir WW. Comparison of antinociceptive, cardiovascular, and respiratory effects, head ptosis, and position of pelvic limbs in mares after caudal epidural administration of xylazine and detomidine hydrochloride solution. *Am J Vet Res* 1996;57: 1338–1345.

13. Skarda RT, Muir WW. Physiologic responses after caudal epidural administration of detomidine in horses and xylazine in cattle. In: Short CE, von Poznak A, eds. *Animal pain*. New York: Churchill Livingstone Inc, 1992;292–302.

14. Skarda RT, Muir WW. Caudal analgesia induced by epidural or subarachnoid administration of detomidine hydrochloride solution in mares. *Am J Vet Res* 1994;55:670–680.

15. Gómez de Segura IA, Rossi R-de, Santos M, et al. Epidural

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injection of ketamine for perineal analgesia in the horse. *Vet Surg* 1998;27:384–391.

16. Valverde A, Little CB, Dyson DH, et al. Use of epidural morphine to relieve pain in a horse. *Can Vet J* 1990;31:211–212.

17. Sysel AM, Pleasant RS, Jacobson JD, et al. Efficacy of an epidural combination of morphine and detomidine in alleviating experimentally induced hindlimb lameness in horses. *Vet Surg* 1996;25:511–518.

18. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984;61:276–310.

19. Sandu L, Mungin CO, Ionescu C, et al. Clinical and experimental data concerning conduction anesthesia and analgesia with pethidine. *Chirurgie* 1983;32:75–79.

20. Paech MJ, Moore JS, Evans SF. Meperidine for patient-controlled analgesia after cesarean section. Intravenous versus epidural administration. *Anesthesiology* 1994;80:1268–1276.

21. Etches RC, Gammer TL, Cornish R. Patient-controlled epidural analgesia after thoracotomy: a comparison of meperidine with and without bupivacaine. *Anesth Analg* 1996;83:81–86.

22. Rosaeg OP, Lindsay MP. Epidural opioid analgesia after Cesarean section: a comparison of patient-controlled analgesia with meperidine and single bolus injection of morphine. *Can J Anaesth* 1994;41:1063–1068.

23. NganKee WD, Lam KK, Chen PP, et al. Epidural meperidine after cesarean section: a dose-response study. *Anesthesiology* 1996;85: 289–294.

24. Perriss BW, Latham BV, Wilson IH. Analgesia following extradural and IM pethidine in post-Cesarean section patients. *Br J Anaesth* 1990;64:355–357.

25. Brownridge P, Frewin DB. A comparative study of techniques of postoperative analgesia following Caesarean section and lower abdominal surgery. *Anaesth Intensive Care* 1985;13:123–130.

26. Jarnell RW, Polis T, Reid GN, et al. Patient-controlled analgesia with epidural meperidine after elective Cesarean section. *Reg Anesth* 1992;17:329–333.

27. Kaza R, Lawlor M, Allen W, et al. Epidural meperidine provides surgical anesthesia for critically ill patients undergoing major surgery (lett). *Anesth Analg* 1993;77:1084.

28. Barnhart MD, Hubbell JAE, Muir WW, et al. Pharmacokinetics, pharmacodynamics, and analgesic effects of morphine after rectal, intramuscular, and intravenous administration in dogs. *Am J Vet Res* 2000;61:24–28.

29. Glynn CJ, Mather LE, Cousins MJ, et al. Peridural meperidine in humans: analgesic response, pharmacokinetics, and transmission into CSF. *Anesthesiology* 1981;55:520–526.

30. Sjöström S, Harvig P, Persson P, et al. Pharmacokinetics of epidural morphine and meperidine in humans. *Anesthesiology* 1987;67:877–888.

31. Stapleton JV, Austin KL, Mather LE, et al. A pharmacokinetic approach to postoperative pain: continuous infusion of pethidine. *Anaesth Intensive Care* 1979;7:25–32.

32. Cousins MJ, Mather LE, Glynn CJ, et al. Selective spinal analgesia. *Lancet* 1979;1:1141–1142.

33. Zbinden AM, Maggiorini M, Peter-Felix S, et al. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia: I. motor reactions. *Anesthesiology* 1994;80:253–260.

34. Fields HL, Emson PC, Leigh BK, et al. Multiple opioid receptor sites on primary afferent fibers. *Nature* 1980;284:351–353.

35. Hunter EG, Frank GB. An opiate receptor on frog sciatic nerve axons. *Can J Physiol* 1979;57:1171–1174.

36. Frank GB. Two mechanisms for the meperidine block of action potential production in frog's skeletal muscle; non-specific and opioid drug receptor mediated blockades. *J Physiol (Lond)* 1975;252:585–601.

37. Hassen HG, Akerman B, Pilcher CWT, et al. Antinociceptive effects of localized administration of opioids compared with lidocaine. *Reg Anesth* 1989;14:138–144.

38. Power I, Brown DT, Wildsmith JAW. The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. *Reg Anesth* 1991;16:204–208.

39. Jaffe RA, Rowe MA. A comparison of the local anesthetic effects of meperidine, fentanyl, and sufentanil on dorsal root axons. *Anesth Analg* 1996;83:776–781.

40. Bräu ME, Koch ED, Vogel W, et al. Tonic blocking action of meperidine on Na^+ and K^+ channels in amphibian peripheral nerves. *Anesthesiology* 2000;92:147–155.

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