Antinociceptive effects of epidural administration of hydromorphone in conscious cats

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Objective—To evaluate the antinociceptive effects of epidurally administered hydromorphone in conscious, healthy cats.

Animals—7 healthy adult cats.

Procedures—An epidural catheter was implanted in each cat. Thermal threshold (TT) was measured by increasing the temperature of a probe placed on the thorax and monitoring the cat’s response. Mechanical threshold (MT) was measured by manually inflating a modified blood-pressure bladder affixed to a thoracic limb and monitoring the response. After the baseline TT and MT values were determined, hydromorphone (0.05 mg/kg) or an equal volume of saline (0.9% NaCl) solution was epidurally injected. The TT and MT were again measured at 15, 30, 45, 60, 120, 180, 240, 300, 360, and 480 minutes after injection.

Results—TT and MT did not change significantly from baseline values at any point after saline solution was administered. The MT and TT values were significantly higher than the baseline value at 15 minutes and at 120 and 180 minutes after hydromorphone administration, respectively. The MT and TT values after hydromorphone administration were also significantly different from those obtained at 30 minutes and at 15 minutes and 120 to 300 minutes, respectively, after administration of saline solution. No significant changes in skin temperature were detected after either treatment.

Conclusions and Clinical Relevance—Epidural administration of hydromorphone at a dosage of 0.05 mg/kg yielded thermal and some mechanical antinociceptive effects in cats, and no hyperthermia was detected. Additional studies of the antinociceptive effectiveness and duration of epidurally administered hydromorphone in clinical situations are required. (Am J Vet Res 2009;70:1187–1192)
adipose tissue. Following rapid and sustained systemic uptake from fatty tissue, lipophilic opioids are recirculated to spinal and supraspinal nerve centers, where they exert their systemic analgesic effects. This action results in segmentalized analgesia, and cranial spread of opioid through the spinal cord is less likely. Hydrophilic opioids such as morphine slowly penetrate the meninges, resulting in a slower onset of effect, but the elimination of morphine from CSF is delayed, allowing cranial distribution of morphine in the CSF and long duration of action.

In one study, epidural administration of morphine was evaluated in cats at a dose of 1 mg/kg, and the analgesic effect began at 60 minutes and persisted for at least 12 hours after injection. In another study involving cats, a dose of 0.1 mg of morphine/kg yielded no significant effect on the minimum alveolar concentration of isoflurane, whereas a 31% decrease in the minimum alveolar concentration was detected in a different study in which the same dose was used. The duration and interval to onset of antinociception were not reported for either study. A retrospective study of epidurally administered morphine at a dose of 0.1 to 0.4 mg/kg in cats revealed that analgesia persisted for a mean ± SD interval of 15.6 ± 4 hours, which is a value similar to that of another study. Epidural administration of fentanyl in cats can increase the pain threshold for 20 minutes in hind limbs and appears to have no effect on forelimbs. To the authors’ knowledge, there are no reports of the effects of epidural administration of hydromorphone in cats. The purpose of the study reported here was to investigate the antinociceptive effects of epidurally administered hydromorphone in conscious healthy cats. The lipid solubility of hydromorphone is intermediate between that of morphine and the highly lipid-soluble fentanyl. Therefore, we believed that hydromorphone would have a rapid onset of antinociceptive effects after epidural administration and an intermediate duration of effect relative to other opioids.

Materials and Methods

Animals—Seven healthy adult domestic shorthair research cats (2 sexually intact females and 5 neutered males) were used in the study. The mean ± SD age was 4.5 ± 1.6 years (range, 2.3 to 7.7 years), and the mean body weight was 4.5 ± 1.3 kg (range, 2.3 to 6.4 kg). The cats were housed as a colony in a climate-controlled room. Water was provided ad libitum, and dry and canned commercial cat food was provided twice daily.

Four weeks before the study began, the cats were tested for FIV and FeLV infections, and results were negative for all cats. At that time, the cats were dewormed with pyrantel pamoate and vaccinated against feline panleukopenia virus, feline calicivirus, and feline herpesvirus. Serum biochemical analyses and CBCs were performed, and results were within reference limits for all cats. The cats were socialized and familiar with the study procedure and the testing environment. For the test period, cats were housed in adjacent cages and provided with food and water. The study protocol was approved by the University of Saskatchewan Animal Care Protocol Review Committee, and all cats were cared for in accordance with Canadian Council for Animal Care guidelines.

Epidural catheter implantation—A vascular access port composed of a port and a central venous catheter designed for use in animals was used for epidural drug administration. For catheter implantation, medetomidine (0.01 mg/kg) and hydromorphone (0.1 mg/kg) were administered IM in each cat. Anesthesia was subsequently induced with propofol or isoflurane and maintained with isoflurane in oxygen through a Bain breathing circuit. Cefazolin sodium (22 mg/kg) was administered IV prior to surgery, and a crystalloid fluid was administered IV at a rate of 10 mL/kg/h throughout the procedure. The vascular access port was implanted as described elsewhere, with a slight modification (L6 rather than L7 was used). Briefly, an intramedullary pin was used to make a hole in the dorsal lamina of L6, and the distal end of the catheter was passed caudally to the lumbosacral area. The distal port position of the lumbosacral space was used to approximate the position at which opioids would be epidurally administered in clinical settings. The receiving port of the catheter was passed cranially under the skin to lie between the scapulae. The catheter and access port were sutured in place, and the whole unit was completely covered with skin. The position of the distal end of the catheter in the lumbosacral area of the cat was confirmed by use of fluoroscopy and injection of contrast agent. The dead space of each catheter was measured before implantation and recorded to estimate the amount of fluid to be used to flush the catheter later in the study. Seven days after surgical implantation, to confirm the location of the catheter distal port, 0.2 mL of 2% lidocaine hydrochloride/kg was injected through the catheter to yield reversible bilateral hind limb and tail paralysis. The cats were rested for another 7 days, after which the test sessions began. The catheter with its subcutaneous port remained implanted in the cats for a period of up to 5 months.

Instrumentation for sensory-threshold measurements—The day before testing, the hair of each cat was clipped on either side of the cranialateral aspect of the thorax and around the right thoracic limb between the carpal and elbow joints. Thermal and mechanical thresholds were measured by applying a mild, transient heat or mechanical stimulus to elicit nociception. Each device had a predetermined cutoff point at which the nociceptive stimulus would be shut off automatically to avoid causing any tissue trauma.

For measurement of thermal threshold, a small probe containing a heater element and a temperature sensor (fixed together in thermally conducting epoxy resin) was held against the shaved skin of the lateral aspect of the thorax by use of an elastic band and a pressure bladder. The pressure bladder overlying the probe was inflated manually to 100 mm Hg to ensure even contact between the probe and the skin. Before each test, the skin temperature was measured. When activated, the probe heated at 0.6°C/s with a safety cutoff at 53°C to prevent burns. During each measurement, the stimulus was terminated when the cat responded by jumping, flinching, or turning toward the probe or
when the cutoff was reached. Skin temperature at the termination of the stimulus was recorded and considered the thermal threshold.

For measurement of mechanical threshold, pressure stimulation was applied via a plastic bracelet taped around the forelimb. The bracelet held 3 pressure pins, each tipped with a 2.4-mm-diameter ball bearing, in a 10-mm triangle, advanced against the craniolateral surface of the forelimb by manual inflation of a modified blood pressure bladder. After bracelet application to 1 forelimb, cats were allowed to relax in the cage for at least 10 minutes before any testing. The cuff was then connected to a 3-way stopcock, a 30-mL syringe, and a pressure transducer via noncompliant arterial manometer tubing. The transducer was calibrated by use of a mercury column. After the manometer line was attached to the bladder, 1 threshold test was carried out. The bladder was manually inflated with the 30-mL syringe at approximately 1.5 mL/s until the cat reacted (limb shaking, head turn, or vocalization). At that point, cuff pressure was recorded immediately and the pressure in the cuff was released. A cutoff pressure to prevent skin damage if the cat did not react was provided automatically when the syringe was fully compressed at a pressure of 850 mm Hg.

Experimental design—A crossover study design was used, with a 7-day washout period between treatments. Treatment consisted of epidurally administered saline (0.9% NaCl) solution or hydromorphone (0.05 mg/kg) diluted with saline solution such that the total volume of hydromorphone was 0.2 mL/kg. Cats were randomly allocated (by lottery) to treatment order, and all cats received both treatments. Injections were aseptically performed by use of a Huber needle, through the receiving port of the implanted vascular access port. After treatment administration, saline solution (0.20 to 0.25 mL) was used to flush the dead space in the port and catheter.

Skin temperature and thermal and mechanical thresholds were determined 4 times at 15-minute intervals prior to treatment, and their mean value was taken as the baseline value. The same measurements were obtained at 15, 30, 45, 60, 120, 180, 240, 300, and 480 minutes after treatment. All thermal and mechanical thresholds were determined once at each time point by the same investigator (PVMS), who was unaware of the treatment order. Throughout the testing periods, cats were also monitored for behavior and adverse effects, including nausea, vomiting, mydriasis, and changes in activity and skin temperature.

Statistical analysis—All statistical analyses were performed by use of computer software. Descriptive statistics were computed to confirm that values of each measured variable (skin temperature and thermal and mechanical thresholds) were normally distributed. Variable values for each treatment were analyzed for changes with time by means of a 1-way ANOVA for repeated measures, followed by the Dunnett test. Variable values at each time point were compared between treatments by use of a 2-way ANOVA for repeated measures at each time point were compared between treatments by use of a 2-way ANOVA for repeated measures, followed by the Dunnett test. Variability values for each treatment were analyzed for changes with time by means of a 1-way ANOVA for repeated measures, followed by the Dunnett test.

Results

Skin temperature did not vary significantly with time when cats received epidurally administered saline solution or an equivalent volume of hydromorphone, nor did it differ according to treatment received. When cats received saline solution, there was no significant increase in thermal-threshold values during the 8-hour measurement period. When cats received hydromorphone, thermal-threshold values were significantly (P < 0.01) higher than the baseline value at 120 to 180 minutes after epidural administration. The maximum increase in the thermal-threshold value from the baseline value was 6.5 ± 2.9°C at 180 minutes after hydromorphone administration. Thermal-threshold values were significantly higher at 15 and 120 to 300 minutes after hydromorphone administration, compared with respective values after saline solution administration (Figure 1).

After epidural administration of saline solution, there was no significant increase in mechanical-threshold values from the baseline value with time. The maximum and only significant increase in mechanical threshold was at 15 minutes after epidural administration of hydromorphone, at which time the value was 210 ± 183 mm Hg. The mechanical-threshold value was significantly higher at 30 minutes after hydromorphone administration, compared with the value 30 minutes after saline solution administration (Figure 2).

No behavioral changes or adverse effects were evident after epidural administration of saline solution. After epidural administration of hydromorphone, 1 cat vomited within 5 minutes, and 3 cats had signs of nausea, including lip licking and salivation, within the first 15 minutes. Five of 7 cats had signs of light sedation within 15 minutes after hydromorphone was administered. Euphoria (purring, rubbing, kneading with the forepaws, rolling, and becoming affectionate) was evident in 6 cats, beginning 45 minutes after injection.

Figure 1—Mean ± SD thermal-threshold values before (baseline; BL) and at various points after epidural administration of hydromorphone (0.05 mg/kg, squares) or an equivalent volume of saline (0.9% NaCl) solution (triangles) in 7 healthy cats. *Value for hydromorphone is significantly (P < 0.05) different from the baseline value. †Values at indicated point differ significantly (P < 0.05) between treatments.
The euphoria lasted 2 hours in 3 cats and up to 6 hours in the remainder. Mydriasis was evident in all cats after hydromorphone administration. No adverse respiratory effects were detected at any point after either treatment, nor were any adverse effects (ie, inflammation, burns, or ulceration) evident at the site of the vascular access port.

**Discussion**

In the study reported here, antinociceptive responses to mechanical and thermal stimuli were detected in healthy cats after epidural administration of hydromorphone, although results varied between the 2 types of threshold measurements. When thermal-threshold values associated with epidural hydromorphone administration were compared with those achieved after saline solution administration, an antinociceptive effect of hydromorphone was evident at 15 and 120 to 300 minutes after injection. When the baseline thermal-threshold value was compared with values obtained after hydromorphone administration, an antinociceptive effect was evident at 120 and 180 minutes after injection. These results might have indicated that hydromorphone, with its intermediate lipid solubility, migrated cranially after epidural administration and yielded antinociceptive effects in the thoracic region of cats, unlike the characteristics of highly soluble fentanyl.

In humans, lumbar epidural administration of hydromorphone or morphine also results in cranial migration of the drug, the peak concentration of drug in CSF samples obtained at C7-T1 is evident at 60 minutes after administration. That finding supports the results of another study that suggest lumbar epidural administration of hydromorphone yields excellent analgesia after thoracotomy in humans. Results of our study in cats differed from those of the human studies with respect to the interval to onset of analgesia. Initial onset of antinociceptive effects after epidural hydromorphone administration was rapid in our study but was interrupted by a long interval of nonsignificant differences between hydromorphone and saline solution values obtained during the 8 hours after injection. This period of nonsignificant differences could have been attributable to the low number of cats evaluated (and, hence, low power to detect a difference if there was one), a pharmacokinetic effect, or an inadequate dosage of hydromorphone. Another explanation could be that we detected early systemic analgesia followed by a delayed period of local, spinally mediated analgesia. At 15 and 30 minutes after hydromorphone administration, results indicated an antinociceptive effect at the region of the thorax and forelimb, and this may have reflected an initial systemic effect mediated via central opioid receptors.

The early increase in thermal- and mechanical-threshold values was accompanied by rapid onset of nausea (within 2 to 3 minutes), followed by sedation in most cats, which made it obvious to the individual performing the measurements that the cats had been treated with hydromorphone, despite attempts to keep treatment identity hidden. This rapid onset of cortically mediated adverse effects supported the supposition that hydromorphone is rapidly systemically absorbed. In humans, hydromorphone is detectable in the systemic circulation 1 minute after lumbar epidural administration, and the plasma hydromorphone concentration peaks 4 minutes after injection. However, hydromorphone can also be detected in CSF samples obtained from the cervical region 10 minutes after injection, and the CSF hydromorphone concentration peaks 60 minutes after injection. Given this rapid cranial migration of hydromorphone in humans, it is unclear whether the systemic action detected in our study in cats was truly a result of substantial initial uptake of hydromorphone into systemic circulation with subsequent distribution to the brain or the result of intrathecal cranial spread. A limitation of our study is that plasma and CSF concentrations of hydromorphone were not measured throughout the study period. As such, it cannot be determined whether early onset of antinociceptive effects after epidural hydromorphone administration in cats was through systemic uptake, rapid cranial migration, or a combination of both.

The thermal-threshold results suggested that the initial systemic analgesia detected in the cats in the present study did not persist until local spinal analgesia had taken effect, indicating a slow actual interval to onset of 120 minutes after injection for thoracic spinal analgesia in cats. The exact interval to onset could not be determined from the results because 60 minutes after injection of hydromorphone, thermal and mechanical thresholds were measured only hourly. More frequent measurements might have revealed an earlier onset of antinociceptive effects. In humans and horses, hydromorphone has a shorter latency to effect after epidural administration than the latency detected in our study, but in contrast, the antinociceptive effects achieved in those species are persistent. In the study involving horses, the threshold for avoidance of electrical stimulation significantly increased from the initial value at 20 minutes after epidural injection to a maximum threshold value was obtained in the perineal region 60 minutes after injection. In the thoracic region, as for most dermatomes, the maximal antinociceptive
effect of epidural hydromorphone administration was achieved 70 minutes after injection. In the study reported here, the duration of antinociceptive effects associated with epidural hydromorphone administration (300 minutes when results were compared with those for saline solution and 180 minutes when results were compared with the value obtained before drug administration) was shorter than the duration of analgesia reported for cats to which hydromorphone was administered IM (345 minutes when results were compared with those for saline solution) or IV (450 minutes when results were compared with the value obtained before drug administration) at 0.1 mg/kg. On the other hand, in another study involving cats, a significant increase in thermal threshold after IV administration of hydromorphone at the same dosage (compared with the value obtained before drug administration) persisted for only 200 minutes. In that study, a significant increase in mean thermal threshold was detected between 5 and 80 minutes after IV administration of hydromorphone at 0.05 mg/kg. When results for similar dosages of hydromorphone are compared, duration of antinociceptive effects appears to be superior after epidural versus IM or IV administration of hydromorphone. However, results of the present study also suggested that duration of antinociceptive effects after epidural hydromorphone administration is inferior to that after epidural morphine administration in cats. Testing methods in the present study yielded different results. Use of the thermal-threshold device revealed an antinociceptive effect of epidural hydromorphone administration at 120 and 180 minutes after injection, whereas use of the mechanical-threshold device did not. The failure of the mechanical-threshold device to detect this delayed effect might have been attributable to the different spinal cord segments innervating the 2 test sites. The spinal nerves innervating the thoracic limb (C6 through T1) are more cranially than the intercostal nerves. Different nociceptive pathways may also account for the differences in antinociceptive responses to mechanical and thermal stimuli. A thermal stimulus mainly affects C fibers, whereas the mechanical stimulus used in the present study involves receptors in the skin as well as receptors in muscle and periosteum of the thoracic limb and therefore activates Aδ and C fibers. Results of other studies also suggest that the mechanical-threshold device is not as sensitive as the thermal-threshold device at detecting antinociceptive effects of opioids. It also must be mentioned that we might have detected an antinociceptive effect and possibly a sustained effect of epidural hydromorphone administration had the mechanical-threshold device been placed at a region caudal to the forelimb (eg, hind limb or tail). Although reliable for detection of systemically administered opioids, the thermal-threshold and mechanical-threshold devices would require some modification for additional use in epidural studies.

In our study, no significant increase in skin temperature was evident after epidural hydromorphone administration. There are concerns about the potential for clinically important hyperthermia to develop when hydromorphone is used in cats. Dosage and route of administration appear to influence the development of hyperthermia. Intravenous administration of hydromorphone at dosages of 0.025 and 0.05 mg/kg is not associated with changes in skin temperature, but a significant increase as well as clinical signs of hyperthermia reportedly developed in a cat after IV administration of 0.1 mg of hydromorphone/kg.

In the study reported here, epidural hydromorphone administration yielded thermal and some mechanical antinociceptive effects in cats. Before clinical recommendations for epidural hydromorphone administration in cats can be made, additional studies on the antinociceptive effectiveness of epidurally administered hydromorphone are required, including studies of different dosages of hydromorphone and different sites for placement of the mechanical-threshold device.

References