Epidural opioids are commonly used to provide analgesia in dogs and cats. The presumed benefits include good quality of analgesia, long duration, and low dose requirement, with a low associated risk for adverse effects. Duration of action of epidural drugs is largely dependent on their lipid solubility. Morphine has been most widely used because of its favorable physico-chemical characteristics (including low lipid solubility), wide availability, and low cost. In humans, dogs, and cats, epidural administration of morphine has been associated with urinary retention.

Clinically, epidural administration of buprenorphine has been proposed as an alternative to epidural administration of morphine in patients in which urinary retention would be of concern. In humans, the analgesic potency of epidurally administered buprenorphine and morphine were compared and had a potency ratio of 8:1. Although results of a retrospective clinical study suggested that epidurally administered morphine provides analgesia in cats, to our knowledge, no controlled study on the analgesic effects of epidurally administered morphine or buprenorphine in cats that used a validated pain model has been reported. The purpose of the study reported here was to compare the antinociceptive effects, by use of a thermal threshold model, of epidural administration of morphine, buprenorphine, and saline (0.9% NaCl) solution in cats and to determine the duration of these effects. We hypothesized that morphine and buprenorphine, compared with saline solution, would significantly and similarly increase the thermal threshold.

**Materials and Methods**

**Animals**—Six healthy adult female spayed domestic shorthair cats (mean ± SD weight, 4.2 ± 1.0 kg) were used in the study. Each cat was studied 3 times, with a minimum of 2 weeks allowed between successive experiments. Food was withheld for 12 hours prior to an experiment. The study was approved by the Institutional Animal Care and Use Committee at the University of California, Davis.

**Epidural drug administration**—Cats were anesthetized with isoflurane in oxygen delivered in an acrylic chamber. Cats' tracheas were then intubated with a cuffed endotracheal tube, and anesthesia was maintained with isoflurane in oxygen.

**Objective**—To determine the antinociceptive effects of epidural administration of morphine or buprenorphine in cats by use of a thermal threshold model.

**Animals**—6 healthy adult cats.

**Procedures**—Baseline thermal threshold was determined in duplicate. Cats were anesthetized with isoflurane in oxygen. Morphine (100 µg/kg diluted with saline [0.9% NaCl] solution to a total volume of 0.3 mL/kg), buprenorphine (12.5 µg/kg diluted with saline solution to a total volume of 0.3 mL/kg), or saline solution (0.3 mL/kg) was administered into the epidural space according to a Latin square design. Thermal threshold was determined at various times up to 24 hours after epidural injection.

**Results**—Epidural administration of saline solution did not affect thermal threshold. Thermal threshold was significantly higher after epidural administration of morphine and buprenorphine, compared with the effect of saline solution, from 1 to 16 hours and 1 to 10 hours, respectively. Maximum (cutout) temperature was reached without the cat reacting in 0, 7, and 11 occasions in the saline solution, morphine, and buprenorphine groups, respectively.

**Conclusions and Clinical Relevance**—Epidural administration of morphine and buprenorphine induced thermal antinociception in cats. At the doses used in this study, the effect of morphine lasted longer and was more intense than that of buprenorphine.
maintained with isoflurane in oxygen via a Bain circuit with a fresh-gas flow rate of 2 L/min. Cats were placed in sternal recumbency. After clipping and aseptic preparation of the lumbosacral area, cats were positioned on a computed tomography table. A 22-gauge, 3.75-cm diamond-point spinal needle was inserted into the epidural space at the level of the lumbosacral junction. Epidural needle placement was confirmed by the absence of CSF (free flowing and after aspiration) and by the loss-of-resistance technique, by use of a glass syringe and 1 mL of air. Correct placement was further confirmed by use of computed tomography, which revealed air (used for the loss-of-resistance technique) in the epidural space. After confirmation that the tip of the needle was in the epidural space, morphine (100 µg/kg diluted with saline solution to a total volume of 0.3 mL/kg), buprenorphine (12.5 µg/kg diluted with saline solution to a total volume of 0.3 mL/kg), or saline solution (0.3 mL/kg) was administered over 30 seconds, according to a Latin square design. Cats were then allowed to recover from anesthesia. Total anesthesia time (from first exposure to isoflurane to extubation) was < 25 minutes, and recovery time (from discontinuation of isoflurane administration, immediately after epidural injection, to extubation) was < 10 minutes. Cats appeared to have fully recovered from anesthesia (able to stand and walk without ataxia) within 60 minutes after discontinuation of isoflurane administration.

**Thermal threshold determination**—Cats were placed in individual cages (80 × 80 × 65 cm) that had a transparent acrylic door and mirrors on each sidewall. Cats were acclimatized to the cage and thermal threshold probe placement for 2 weeks prior to the study. A probe containing a heater element and an adjacent temperature sensor, both embedded in epoxy, was securely taped to the ventral aspect of the base of the tail, which had been clipped the day prior to the experiment. A pressure cuff was placed around the probe and inflated to 100 mm Hg to ensure good contact between the probe and skin. Before each measurement, the probe was connected to a control unit by a flexible cable; cats were allowed to move freely in the cage during testing. Skin temperature was measured and the heater was activated until a reaction (eg, jumping, turning the head toward the probe, strongly flicking the tail, or licking or biting the probe area or cable) was observed or cutout temperature was reached, whichever occurred first. The rate of temperature rise was 0.6°C/s, and a cutout temperature was set at 55°C. If a reaction was observed, the temperature was recorded and considered the thermal threshold and the heater was turned off. Thermal thresholds were always determined by the same investigator (BHP), who was unaware of treatment assignments. Before anesthesia (and therefore before epidural drug administration), baseline skin temperature and thermal threshold were determined in duplicate at 20-minute intervals after allowing at least 30 minutes for equilibration between probe and skin temperatures. Starting 1 hour after epidural administration (ie, at least 30 minutes after extubation), skin temperature and thermal threshold were determined every 20 minutes for 3 hours. Skin temperature and thermal threshold were then measured at 5, 6, 8, 10, 12, 16, and 24 hours after epidural drug administration. A single thermal threshold determination was performed at each time point.

Thermal probes were calibrated weekly during the study. For calibration, the probe was securely attached to the top of a 9.0 × 9.0 × 0.5-cm aluminum plate. An air bubble was placed in a previously drilled horizontal hole so that the tip was directly below the probe and was connected to a digital thermometer, the accuracy of which had been checked against a certified thermometer. The aluminum block was placed on a standard laboratory hotplate that was heated to approximately 85°C and then allowed to cool to 30°C. The readings from the probe and thermocouple were recorded at each 5.0°C decrease in hotplate temperature between 70°C and 30°C. The probe response was linear within that range (R² ≥ 0.998). A calibration curve was constructed by use of linear regression, and observed temperatures were mathematically corrected according to the most recent curve for that probe.

**Statistical analysis**—Power analysis based on the results of a thermal threshold study previously conducted in our laboratory suggested that 6 cats/group would provide a power of 0.95, assuming a 20% difference in thermal threshold between saline solution and treatments and an alpha level of 0.05.

Normal distribution of skin temperature and thermal threshold was verified by use of the Wilk-Shapiro test. Treatment and time effects on skin temperature and thermal threshold were analyzed by use of repeated-measures ANOVA. The Tukey test for comparison of multiple means was used where appropriate to determine differences between time points within each treatment and between treatments at each time point. A χ² test was used to compare the proportions of measurements for which cutout temperature was reached in the morphine and buprenorphine groups. Significance was set at a value of P < 0.05. Data are presented as mean ± SD.

**Results**

An effect of time and treatment on skin temperature was found (Figure 1). Skin temperature was significantly higher in the morphine group than in the saline solution group at several time points. Compared with its respective baseline value, skin temperature was significantly lower 60 minutes after epidural administration of morphine. No other significant change from baseline was detected.

No difference in thermal threshold was found between treatment groups at baseline. Thermal threshold was significantly affected by treatment and time (Figures 2 and 3). Epidural saline solution administration did not result in changes in thermal threshold. In the morphine group, thermal threshold was significantly higher than baseline for the duration of the study. In that group, thermal threshold at 24 hours (1,440 minutes) was significantly lower than from 60 minutes to 12 hours (720 minutes). Thermal threshold was significantly higher in the morphine group than in the saline solution group from 60 minutes to 16 hours (960 minutes).
UTES). In the buprenorphine group, thermal threshold was significantly higher than baseline and the 24-hour (1,440 minutes) value from 80 minutes to 5 hours (300 minutes). Thermal threshold was significantly higher in the buprenorphine group than in the saline solution group from 60 minutes to 10 hours (600 minutes), except at 2 hours (120 minutes) and 6 hours (360 minutes). Thermal threshold was significantly higher in the morphine group than in the buprenorphine group at 3 hours, 3 hours and 20 minutes, 4 hours, and 8 hours (180, 200, 240, and 480 minutes, respectively) after epidural administration. Thermal threshold reached maximal (cut-out) temperature without the cat reacting on 0, 74, and 11 occasions in the saline solution, morphine, and buprenorphine groups, respectively. Cutout temperature was reached significantly more often in the morphine group than in the buprenorphine group.

**Discussion**

Results of this study indicated that epidural administration of 100 µg of morphine/kg or 12.5 µg of buprenorphine/kg induces thermal antinociception in cats. This is in agreement with results of a clinical study suggesting that epidurally administered morphine is efficacious at reducing postoperative pain in dogs and cats.5 Moreover, numerous studies7,9–21 in humans reveal that epidurally administered morphine and buprenorphine induce intense analgesia in various painful conditions.

There were 2 main limitations to the present study. First, a single dose of each opioid was used. Although results of a study7 in humans suggest that the doses selected are equipotent, this has not been confirmed in cats. It is therefore possible that the differences in thermal threshold detected between the 2 opioid groups were related to inadequate dose selection. Second, the study was likely not adequately powered to detect differences between the 2 opioids. Indeed, prospective power analysis was used to ensure sufficient power to detect differences of clinically relevant magnitude between opioid treatments and control treatment; however, power was likely insufficient to detect the smaller differences between the 2 opioid groups.

Thermal threshold was used as the nociceptive stimulus in the study reported here because it has been developed and validated in cats and is sensitive to the effects of opioids.22–24 A disadvantage of this model is that thermal pain is not common in clinical patients. To maximize the likelihood of detecting an effect of the opioids,
we positioned the thermal probe and heater element on the base of the tail rather than on the lateral aspect of the thorax as in previous studies. The extent of the cranial spread of epidurally administered morphine and buprenorphine has, to our knowledge, not been determined in cats, and a lack of effect if the probe had been positioned on the thorax would have raised the question of whether epidurally administered opioids actually do not induce analgesia or whether they just do not diffuse far enough cranially to induce analgesia at that location. The present study was not designed to determine the extent of the analgesic effect. Lack of change in thermal threshold over time has been determined when the probe is positioned on the thorax but not on the base of the tail. However, the lack of change in threshold over time in the saline solution group confirmed that the measurement was stable with the probe positioned on the base of the tail.

Epidural administration of morphine and buprenorphine induced thermal antinociception in the present study. However, the effect of morphine was more consistent, more intense, and longer lasting. Although the study was not designed to determine differences in intensity of analgesia, the cutout temperature was tolerated much more often in cats treated with epidurally administered morphine than with buprenorphine. Moreover, a significant difference in thermal threshold was found between epidurally administered morphine and buprenorphine at several times, including some at which thermal threshold in buprenorphine-treated cats was significantly higher than in saline solution–treated cats (ie, before the effect of buprenorphine ceased). This was in contradiction with a clinical study in dogs in which epidural administration of morphine and buprenorphine were found to induce similar analgesia. The difference between our findings and that clinical study was likely a reflection of the lack of sensitivity of pain assessment in the clinical setting.

The duration of the effect of epidurally administered morphine appeared to be 16 to 24 hours because thermal threshold after morphine administration was still higher than baseline threshold at 24 hours, but the difference with the saline solution group was not significant at that time. In contrast, thermal thresholds in the buprenorphine group were not higher than their baseline after 5 hours, and differences with the saline solution group were only evident for 10 hours. In addition, thermal thresholds in the buprenorphine group were not significantly different from those in the saline solution group at a few times before 10 hours, illustrating both the lower intensity and lower consistency of the effect, compared with effects in the morphine group.

Onset of the effect appeared to be less than 60 minutes for both opioids. By 60 minutes, thermal threshold was indeed higher in both opioid groups than in the saline solution group. Exact onset time could not be determined from the results of the present study because the first thermal threshold determination was conducted 60 minutes after epidural drug administration.

Although the effect was significant in the morphine group only, skin temperature was lower at 60 minutes than at baseline in all groups. This was likely related to the anesthesia required for epidural injection. Body temperature was not measured during anesthesia but likely decreased. A decrease in core temperature is expected to result in cutaneous vasoconstriction, which in turn would decrease skin temperature. Skin temperature was significantly higher in the morphine group than in the saline solution group at several time points. Although, to our knowledge, this effect has not been reported and its exact cause cannot be determined from our study, it is possible that the epidural administration of opioids affects body temperature or cutaneous blood flow and temperature. It has been reported that morphine (3 mg/kg) given intraperitoneally increases body temperature in young cats.

Isoflurane anesthesia was used to allow epidural needle placement. It is unlikely that anesthesia affected the results of the present study because 60 minutes was allowed between epidural injection (the time at which isoflurane administration was discontinued) and the first thermal threshold determination, isoflurane is rapidly eliminated and minimal tissue concentrations are expected 1 hour after its administration has been discontinued, and inhalant anesthetics do not induce analgesia at subanesthetic doses. In contrast, cold blue, which would have decreased thermal threshold and would have reduced the likelihood of detecting differences between treated and control groups (at the earlier times).

In a previous study, epidural administration of morphine or buprenorphine, at the same doses as in the study reported here, did not decrease the MAC of isoflurane in cats. Interestingly, 3 of the 6 cats used in the present study were also used in the previous study. The fact that analgesia was present in these cats suggests that although MAC determination relies on noxious stimulation, a lack of effect on MAC should not be interpreted as suggestive of lack of analgesic effect.

Epidural administration of morphine and buprenorphine induced thermal antinociception in cats. At the doses used in this study, the effect of morphine appeared longer lasting and more intense than that of buprenorphine.

References


a. Sherwood Medical, St Louis, Mo.
 b. Duramorph, Baxter, Deerfield, Ill.
d. RS Components, Corby, Northamptonshire, England.