Antinociceptive effects of butorphanol, buprenorphine, or both, administered intramuscularly in cats

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Objective—To characterize the antinociceptive action of IM-administered butorphanol, buprenorphine, or a combination of both by use of a thermal threshold method in cats.

Animals—2 male and 4 female domestic cats.

Procedures—In a controlled, masked, randomized, crossover study design, thermal thresholds were measured by use of a thermal threshold–testing device developed for cats. Each cat received 4 treatments 1 week apart, consisting of 2 simultaneous IM injections in a random order (butorphanol-saline [0.9% NaCl] solution, buprenorphine-saline solution, butorphanol-buprenorphine, and saline solution-saline solution). The tester was unaware of the treatment given. Thermal thresholds were measured prior to injection, at intervals up to 12 hours, and at 22 hours after injection.

Results—There was no significant change in threshold over time after saline solution administration. All 3 opioid treatment groups had significant increases in thermal threshold, compared with pretreatment values (butorphanol, from 50 minutes to 8 hours; buprenorphine, from 35 minutes to 5 hours; and butorphanol-buprenorphine, from 50 minutes to 8 hours). Thermal thresholds did not differ significantly among opioid treatments at any time points, and thermal thresholds of only 2 opioid treatments (butorphanol at 50 minutes and butorphanol-buprenorphine at 8 hours) were significantly different from that of saline solution.

Conclusions and Clinical Relevance—All 3 opioid treatments provided similar antinociception, although there was considerable intercat variability in the response to the different opioid treatments. This emphasizes the importance of assessing each patient individually and applying the treatment that works best for that patient. (Am J Vet Res 2007;68:699–703)

The recognition of perioperative pain in cats and the awareness by the veterinary profession of the necessity to treat pain has grown over the past 2 decades. As late as 1989, only 7% of cats undergoing major surgery at a university teaching hospital received postoperative analgesia.1 By 2001, 94% of cats undergoing orthopedic surgery received postincisional analgesics.2 The most common perioperative analgesic used in cats, butorphanol, has historically been perceived to have a relatively short duration of action and to be effective only for mild to moderate pain.3

There is interest in administering butorphanol in combination with buprenorphine to enhance the effect of butorphanol as an analgesic.4 After IM injection, butorphanol has a rapid onset of action but is short acting, whereas buprenorphine has a delayed onset and a longer duration of action.5 It is hypothesized that administering the 2 agents simultaneously will take advantage of the beneficial properties of both: the rapid onset of butorphanol and the longevity of buprenorphine. However, because butorphanol is an OP2 (κ) receptor agonist and OP3 (μ) receptor antagonist6 and buprenorphine is an OP2 receptor antagonist and OP3 receptor agonist,7 it is possible that coadministration could result in an antagonistic effect.

The study reported here was designed to investigate the antinociceptive effects of commonly used doses of butorphanol and buprenorphine administered IM simultaneously to cats and compare results with those achieved by administering each agent individually or a saline (0.9% NaCl) solution control. Our hypothesis was that all 3 opioid treatments would result in significant antinociception, compared with saline solution, and that the simultaneous administration of butorphanol and buprenorphine would result in a pharmacodynamic profile different from the administration of either agent individually.

Materials and Methods

Six domestic shorthair cats (4 spayed females and 2 castrated males) ranging in age from 7 to 9 months and weighing 4.03 ± 0.25 kg (mean ± SEM) were used in this study. Cats were fed ad libitum with a complete dry diet and were housed as a colony in a climate-controlled room with a cycle of 12 hours of light and 12 hours of darkness.
hours of darkness. The cats were socialized to caretakers and familiar with the study procedure and testing environment. The study was approved by the Institutional Animal Care and Use Committee of the University of California.

For each test period, 2 cats were housed individually in adjacent cages and provided with food, water, litter tray, and toys. The day before each test, each cat was weighed and the lateral aspect of its thorax was clipped. The side of the thorax to be clipped was randomly assigned the first week and alternated for each successive week. The antinociceptiometric method used was an increasing thermal stimulus. Thermal threshold was measured by use of a system developed specifically for use in cats. Briefly, a small probe containing a heating element and adjacent temperature sensor was held against the cat’s clipped thorax by a circumferential elasticated band. An air bladder between the elasticated band and probe was manually inflated to 100 mm Hg to ensure consistent contact between the probe and skin. The probe was placed on the cat at least 15 minutes prior to the first test. Before each reading, the probe was connected to the control panel by a flexible ribbon cable that allowed the cats to move freely during measurements. Skin temperature was measured, the heater was activated, and the cat was observed for a reaction. The rate of temperature rise was 0.6°C/s, with a safety cutoff of 55°C to prevent thermal burns. The stimulus was terminated when any of the following responses were observed: turning to bite the probe, jumping away from the probe, jumping up from a recumbent position, or when the cutoff was reached, whichever occurred first. Skin temperature at the termination of the stimulus was recorded and considered the thermal threshold. All thermal thresholds were determined by the same investigator (JAJ) who was unaware of treatment group assignments.

Three baseline threshold measurements were recorded at 15-minute intervals before administration of a treatment. After 10 minutes had elapsed from the last baseline measurement, each cat received each of 4 treatments in a randomized order with 1 week between treatments. Each treatment consisted of 2 epaxial IM injections in the following combinations: butorphanol (0.2 mg/kg) and saline solution (0.1 mL/kg), buprenorphine (0.02 mg/kg) and saline solution (0.1 mL/kg), butorphanol (0.2 mg/kg) and buprenorphine (0.02 mg/kg), and saline solution (0.1 mL/kg) and saline solution (0.1 mL/kg). Buprenorphine and butorphanol were diluted with saline solution so that the volume administered was 0.1 mL/kg. Thermal thresholds were measured at 5, 20, 35, 50, and 65 minutes and at 2, 3, 4, 5, 6, 8, 12, and 22 hours after treatment. Prior to the experiments, and at the end of each week, the probes were calibrated against a thermometer and the results were adjusted on the basis of the derived regression.

**Statistical analysis**—Thermal threshold and skin temperature data were analyzed by means of a split plot ANOVA with a repeat factor of time according to the model

\[ Y = \mu + \alpha + \beta + \alpha\beta + C + \pi + \text{Error}_t + \tau + \tau\alpha + \tau\beta + \tau\alpha\beta + \text{Error}_c, \]

where Y denotes the response variable (threshold, skin temperature); \( \mu \) denotes the overall mean; \( \alpha \) denotes the fixed effect of butorphanol; \( \beta \) denotes the fixed effect of buprenorphine; \( C \) denotes the random effect of cat; \( \pi \) denotes the fixed effect of period (treatment order); \( \tau \) is the error term for the effects of time and its interactions. The Bonferroni t test for multiple comparisons was used where appropriate to determine differences between groups at each time and at which time points each treatment group differed from time 0 (before treatment). Significance was set at \( P < 0.05 \).

**Results**

There was no significant effect of treatment order on skin temperature or thermal threshold. There was an effect of time on skin temperature only in the saline solution group. At 2 hours, skin temperature was significantly lower than pretreatment and different from the other 3 groups at the same time period. No other significant differences in skin temperature were recorded (Figure 1).

There was no significant change in thermal threshold over time in the saline solution group. Thermal threshold was significantly increased from the pretreatment value in the 3 other groups as follows: butorphanol from 50 minutes to 8 hours; buprenorphine from

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**Figure 1**—Mean ± SD skin temperature in 6 cats before (Pre) and after IM administration (time 0) of saline (0.9% NaCl) solution, butorphanol, buprenorphine, or a combination of butorphanol and buprenorphine. *Within a treatment, value is significantly (P < 0.05) different from value before administration.
35 minutes to 5 hours; and butorphanol-buprenorphine from 50 minutes to 8 hours. Only 2 treatments yielded significantly different results from that of saline solution at any time: butorphanol at 50 minutes and butorphanol-buprenorphine at 8 hours. None of the opioid treatments were different from each other at any time. Although all cats had some response to all 3 opioid treatments (Figure 2), there was a large intercat variation in the magnitude and duration of response (Figure 3).

Discussion

Results of previous studies\(^5\,9\,10\) indicate that butorphanol has a last onset but short duration of action, making it unsuitable as a perioperative analgesic without repeated administration. Lascelles and Robertson\(^5\) reported that cats receiving butorphanol IV had a significant increase in thermal threshold by 15 minutes after treatment and that the effect lasted for 180 minutes.\(^5\) In another study, cats that received butorphanol IM had an increase in threshold at 5 minutes, but this effect was not apparent at any later time points.\(^3\) The results of the study reported here conflict with previous data, in that increase in threshold was not detected until 50 minutes after injection, but the effect lasted 8 hours. In comparison to Lascelles and Robertson’s study,\(^5\) the onset of effect may have been longer in the present study because of the smaller dose and IM versus IV administration. The pharmacokinetics of butorphanol after IM injection in cats have not been determined, but butorphanol is rapidly absorbed after injection in other species.\(^11-13\) Two pharmacodynamic studies\(^5\,10\) revealed butorphanol to have significant antinociception within 15 minutes of IM injection, supporting the assumption that butorphanol is rapidly absorbed in cats and rapidly binds to the receptor. It is uncertain why there was a 45-minute difference in the onset of butorphanol’s effect in the present study versus the study by Robertson et al.\(^5\) but it is important to mention that the cats in that study had a unique response not only to butorphanol, but to buprenorphine and morphine as well. This suggests that distinct populations of cats, as well as individuals, respond differently to various classes of opioids.

The variation in response to butorphanol among populations and individual cats also extends to duration of action.\(^5\,9\,10\) The dose of butorphanol administered does not appear to influence the duration of action.\(^10\) Individual variability in response to butorphanol was detected in a visceral nociception study that used the same dose as the present study, where duration of effect varied from 0 to at least 360 minutes in individual cats.\(^14\) In other species, the duration of action of butorphanol is variable and is affected by the type of stimulus against which it is evaluated. Dogs tested with a visceral pain model had a maximum duration of analgesia of 53 minutes.\(^15\) In 2 studies that used a somatic pain model, horses had antinociception for 30 minutes\(^16\) and 60 minutes.\(^17\) In visceral pain models, horses had a duration of antinociception from 57 minutes to 4 hours.\(^16-18\) In a thermal threshold model, sheep had a significant increase in threshold up to 130 minutes.\(^19\)

It was hypothesized that the addition of buprenorphine, which in previous studies\(^5,20\) had a slow onset
but a prolonged duration of action, would extend the duration of analgesia provided by butorphanol alone. Buprenorphine slowly enters the CNS and binds with high affinity to the OP3 receptor, causing a delayed onset and prolonged duration of action. In sheep tested with a thermal threshold model, thresholds were not significantly increased until 45 minutes after IV injection but they remained increased for 210 minutes. After IV injection, threshold response in cats was significantly higher at 30 minutes, peaked at 90 minutes, and was effective to 6 hours. A previous study that used IM injection in cats did not reveal a significant effect until 240 minutes, but efficacy extended to 12 hours. The present study revealed different pharmacodynamics, with an onset of 35 minutes and duration of 5 hours. The delayed onset is consistent with other studies, but the reason for the difference in duration of action is uncertain. Dose response trials of buprenorphine in cats have not been conducted, so it is uncertain whether variations in dose could cause differences in the duration of effect. This seems unlikely because the dose in the present study was twice that of the previously cited study in which effects lasted at least 12 hours. As with butorphanol, population and individual variability most likely contributed to the difference in response to buprenorphine that was detected.

In previous studies, there was substantial intercat variability in response to treatments. In a previous study, when 0.4 mg of butorphanol/kg was administered IV, the effect in 1 cat was pronounced and prolonged, whereas in another, the response was not significantly different from the pretreatment value. Similar findings were detected in the present study. After receiving butorphanol, 1 cat had a significant increase in thermal threshold lasting from 50 minutes until 8 hours, whereas another cat had minimal response to the same treatment.

The effects of the combination of the 2 opioids also varied among cats. For example, when buprenorphine and butorphanol were given simultaneously to 1 cat, maximum threshold (55°C) was attained at 8 time points. In contrast, in another cat, maximum threshold was never reached with the same treatment. This large variation in individual response to the treatments resulted in a large SD when individual results were grouped by treatment. Although all opioid treatments caused increased thermal threshold, compared with pretreatment results, the variance in individual response precluded the ability to reject the null hypothesis that the opioid treatments would be no different from saline solution. To prevent serious burns, the thermal threshold device in this study was set to cutoff at 55°C. It is possible, if the device reached cutoff at a particular time point, that the cat may have tolerated a higher thermal threshold, which would have generated more robust results. The sample size (n = 6) for this study was based on previous experiments that used the same design and had significant results. Robertson et al. were able to detect a difference in thermal threshold between saline solution and buprenorphine by the use of 6 cats, but only at 3 time points. The dose used in the present study (0.02 mg/kg) was twice that used in the previously cited study; it was anticipated that the stronger dose would make for more robust results while still being within the dose range commonly used in a clinical setting. Lascelles and Robertson were able to detect a difference in thermal threshold between saline solution and butorphanol by use of 6 cats, but the dose of butorphanol was twice that used in the present study. The decision to use a smaller dose was based on this same study, which revealed no dose-response relationship for butorphanol by use of the thermal nociceptive model. A retrospective power analysis determined that approximately 3 times the number of cats used in this study would have been needed to detect the observed difference, with 80% power. The overall variation in response between the different opioid treatments appeared to be small, suggesting that an even larger study group or a different method of nociception would be necessary to differentiate the 3 treatments.

Individual variability in the antinociceptive effects of opioids has been detected in many species, and the variability appears to be multifactorial, with sex, genotype, type of noxious stimulus, receptor (OP3 vs OP2), and relative efficacy of the agent all affecting individual response. As an example, 1 study compared the antinociception of 4 opioids in 12 strains of rats and found sex differences in all strains, with the opioids being more potent in males than females. However, the magnitude of the difference varied between the strains and by the relative efficacy of the opioid. The differences in response among strains has led to the investigation of genetics as a key factor in determining individual antinociception. It is likely that genetics affect both the pharmacokinetics and pharmacodynamics of opioids through alterations in uptake, biotransformation, transport, elimination, and receptor interaction. It is probable that all of these factors contributed to the differences detected in antinociception in the cats in the present study. Genetic variability has been hypothesized to be the reason an individual cat’s sensitivity to inhaled anesthetics is maintained across different agents. More studies that use larger test populations of genetically similar cats would be necessary to determine whether the differences in response to opioids seen in other species also apply to cats.

The time effect on skin temperature was only present in the saline solution group at 2 hours. At this time, the skin temperature was lower than other time periods for the same treatment and was lower than it was during the 3 opioid treatments at the same time point. At 2 hours, 1 cat had a skin temperature that was 1.2°C lower than the mean of the remainder of its readings and 1.4°C lower than its next lowest reading. This may have been caused by insufficient contact of the probe with the cat’s skin, which caused the reading to be artificially low.

Although butorphanol has historically been characterized as a short-acting analgesic, some of the cats in this study had the most intense and long-acting antinociception from administration of butorphanol. The results of this study support the assumption that butorphanol has a rapid onset; changes in thermal threshold were evident as early as 5 minutes but did not become significant until 50 minutes. The delayed onset of action of buprenorphine in this study was consistent with previous studies but the duration of action
was slightly shorter. It would appear that each cat has a unique response to opioids that act at the OP2 and OP3 receptors, possibly on the basis of genetic variability. Until we can objectively predict a patient’s unique response to different opioids, it is important to assess each individual carefully for evidence of pain and apply the treatment that works best for that patient.

References