

High-dose buprenorphine results in a greater occurrence of postoperative hyperthermia than morphine in a randomized clinical trial in cats undergoing ovariohysterectomy

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OBJECTIVE

To compare the thermoregulatory and analgesic effects of high-dose buprenorphine versus morphine in cats undergoing ovariohysterectomy.

ANIMALS

94 client-owned cats.

PROCEDURES

Cats were randomized to receive either buprenorphine 0.24 mg/kg or morphine 0.1 mg/kg subcutaneously (SC) during recovery from ovariohysterectomy. Body temperature measurements were obtained before anesthesia, during anesthesia (averaged), at extubation, and 2, 4, and 16 to 20 hours postoperatively. Signs of pain were assessed, and demographic characteristics were compared between groups. The effects of treatment and time on body temperature, point prevalence of hyperthermia (> 39.2 °C), and pain scores were compared with linear or generalized mixed-effect models.

RESULTS

Cats receiving morphine (vs. buprenorphine) were older and heavier (both, $P \leq 0.005$). Other group characteristics did not differ between treatments. Cats receiving buprenorphine (vs. morphine) had higher postoperative temperatures ($P = 0.03$). At 2, 4, and 16 to 20 hours after extubation, the point prevalence of hyperthermia was greater ($P = 0.001$) for cats receiving buprenorphine (55% [26/47], 44% [21/47], and 62% [27/43], respectively) versus morphine (28% [13/46], 13% [6/46], and 47% [21/44], respectively). There were no differences in pain scores between groups or over time. Five cats receiving buprenorphine and 6 receiving morphine required rescue analgesia within the 24-hour period.

CLINICAL RELEVANCE

Administration of buprenorphine (0.24 mg/kg SC), compared with morphine (0.1 mg/kg SC), resulted in higher body temperatures without an apparent advantage with regard to analgesia during the first 20 postoperative hours than morphine. Opioid-induced postoperative hyperthermia could confound the diagnosis of fever from different sources.

The partial mu-receptor agonist buprenorphine is a commonly used opioid during the perioperative period in cats.^{1,2} Its use, as that of several other opioids, has been associated with the development of hyperthermia in this species.³ A highly concentrated formulation of buprenorphine (1.8 mg/mL) is available for use in cats and may provide analgesia for 24 hours after a single injection of 0.24 mg/kg subcutaneously (SC).⁴ This duration is substantially longer than the approximate 6 hours of analgesia obtained with the standard formulation of 0.3 mg/mL, at a dose of 0.02 mg/kg.⁴

In a recent retrospective study in cats,⁵ the use of high-dose buprenorphine resulted in a greater occurrence of postoperative hyperthermia compared with morphine. However, confounding factors, such as the impact of the circadian cycle, could not be assessed. In addition, the analgesic effects of both agents were not investigated. In our study, we investigated the thermoregulatory and analgesic effects of high-dose buprenorphine and morphine in cats undergoing ovariohysterectomy (OVH). We hypothesized that buprenorphine 0.24 mg/kg subcutaneously (SC) would result in higher postoperative rectal

temperatures and lower postoperative pain scores than morphine 0.1 mg/kg SC when administered to cats during recovery from anesthesia and OVH.

Methods

This study was approved by the institution's Veterinary Clinical Studies Committee (protocol No. 031220-03) and follows Animal Research: Reporting of *In Vivo* Experiments guidelines.⁶ Cats undergoing OVH as part of surgical exercises for veterinary students between September and November 2020 were included. Cats were excluded from the study if the American Society of Anesthesiologists physical status was more than 2, if a different surgical procedure was performed in addition to OVH, or if the cats became hyperthermic during anesthesia (prior to the administration of the study agents). Physical status was assigned based on physical examination and bloodwork, including hematocrit, total plasma proteins, blood glucose, and urea concentrations.

All cats were admitted to our institution the day prior to their surgery and were housed individually. Each cat received maropitant (Cerenia; Zoetis) 8 mg total per os (PO), robenacoxib (Onsior; Elanco) 6 mg total PO, and cefovecin sodium (Convenia; Zoetis) 8 mg/kg SC the afternoon prior to the procedure. Food, but not water, was withheld starting the evening prior to anesthesia. Cats were anesthetized and operated between 7 AM and 12 noon, or between 1 and 5 PM.

All cats received dexmedetomidine (Dexdomitor; Zoetis) 20 µg/kg and morphine (West-Ward) 0.1 mg/kg intramuscularly (IM). Approximately 15 minutes later, an intravenous catheter was placed. Ketamine (Ketathesia; Henry Schein Animal Health) 5 mg/kg IM was administered to cats that were insufficiently sedated for catheterization. Anesthesia was induced with propofol (Sagent Pharmaceuticals), administered until intubation was possible, and anesthesia was maintained with isoflurane in oxygen (1 to 2 L/min) using a circular rebreathing system. Cats were placed in dorsal recumbency, and the abdomen was clipped and scrubbed in the induction area, adjacent to the surgical room. No heating devices were used during this period. Cats were then transferred to the surgical table and placed in dorsal recumbency over a circulating warm water blanket (T/PUMP Heat Therapy Pump; Gaymar Industries) and a disposable, impermeable underpad. The warm-water blanket was set at 42 °C. A midline laparotomy was performed. Monitoring included continuous electrocardiogram, pulse oximetry, capnography, esophageal temperature, and oscillometric blood pressure (every 2 minutes). Lactated Ringer solution was administered at 5 mL/kg/h intravenously (IV) to all cats during anesthesia. If the esophageal temperature decreased to less than 36 °C, warm saline bags were placed around the cat's neck and shoulders. All cats breathed spontaneously during the procedure. After surgery was completed, the cats were vaccinated against rabies, and isoflurane was discontinued. Cats were extubated when the swallowing

reflex was observed. In cats that were difficult to restrain manually or appeared aggressive at recovery, dexmedetomidine 1 µg/kg was administered IV. If, on the contrary, a cat appeared overly sedated after extubation, atipamezole (Antisedan; Zoetis) 0.1 mg/kg was administered IM.

Randomization and postoperative data collection

Twelve to 15 cats were operated each week. Cats were randomized to receive either buprenorphine (Simbadol; Zoetis) 0.24 mg/kg SC or morphine 0.1 mg/kg SC, administered once, immediately after extubation. During the first week of the program, an analgesic agent was selected at random by coin toss, and all cats in that week received that agent. The alternate agent was used the following week for all cats. The order was repeated thereafter. All cats received robenacoxib 6 mg PO 4 hours after extubation.

Rectal temperature (digital thermometer; AmerisourceBergen) was measured immediately after extubation and 2, 4, and 16 to 20 hours later. Food and water were available starting 2 hours after extubation. The Glasgow Composite Measure Pain Scale (GCMPS)-Feline⁷ was assessed at 4 and 16 to 20 hours after extubation in all cats. Any cat scoring $\geq 5/20$ received rescue analgesia, consisting of buprenorphine 0.02 mg/kg or morphine 0.1 mg/kg, according to their initial treatment allocation. Cats receiving rescue analgesics were removed from the study from that point onward. All cats were assessed for pain by the same investigator, who was unaware of treatment allocation.

Statistical analysis

Distribution of the residuals was assessed by observation of histograms. Intraoperative temperature was averaged for the duration of the procedure. The age, weight, surgery time (AM or PM), administration of ketamine prior to induction, administration of dexmedetomidine or atipamezole after recovery, and duration of anesthesia were compared between groups with Wilcoxon's tests for continuous variables and Fisher's exact tests for binary ones.

The effects of treatment and time (and their interaction) on temperature (rectal preoperative and postoperative, and esophageal intraoperative) were assessed with a mixed-effects model using cat as the random effect, and treatment, time, and their interaction as fixed effects. All time points were included in the model. The point prevalence of hyperthermia, defined as a temperature > 39.2 °C was calculated at baseline (prior to anesthesia) and at each postoperative time. The effect of treatment, time, and their interaction on the point prevalence of hyperthermia and on the GCMPS-Feline score was assessed with a generalized linear mixed-effects model using a binomial family with a link function "logit."

Statistical analysis was performed with available software.^{8,9} Results are summarized as mean (SD) for parametric data and median (range, minimum to maximum) for nonparametric data. Significance was set at $P < 0.05$.

Table 1—Results for key demographic characteristics, time of procedure, duration of anesthesia, and additional agents administered for 94 cats undergoing ovariohysterectomy and randomly assigned to receive either buprenorphine (0.24 mg/kg; n = 47) or morphine (0.1 mg/kg; n = 47) subcutaneously once immediately after extubation between September and November 2020.

Variables	Buprenorphine group	Morphine group	P value
Age (months) ^a	7 (2–36)	12 (3–96)	0.005
Body weight (kg) ^a	2.4 (1.1–4.9)	2.8 (1.0–4.0)	0.004
Time of procedure (n)			> 0.999
AM	24	24	
PM	23	23	
Duration of anesthesia (min) ^a	170 (115–215)	160 (120–220)	0.360
Ketamine administration (n)	13	13	> 0.999
Dexmedetomidine administration (n)	0	3	0.241
Atipamezole administration (n)	21	28	0.215

Data are reported as number of affected cats unless otherwise indicated.

^aData are reported as median and range.

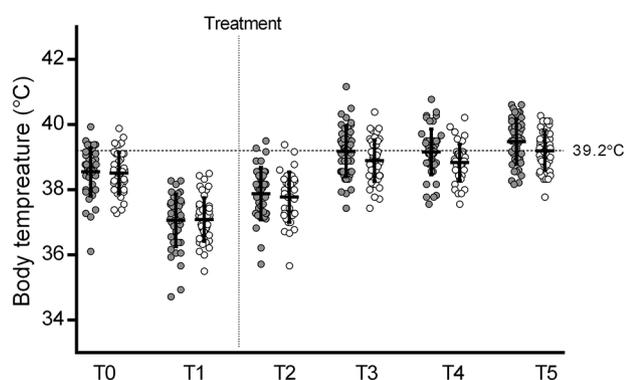


Figure 1—Individual-value plots of rectal temperature prior to anesthesia (T0), mean esophageal temperatures throughout anesthesia (T1), and rectal temperature at extubation (T2) and then at 2 (T3), 4 (T4), and 16 to 20 (T5) hours after extubation for 94 cats undergoing ovariohysterectomy and randomly assigned to receive 1 subcutaneous dose of either buprenorphine (0.24 mg/kg; n = 47; filled circles) or morphine (0.1 mg/kg; n = 47; open circles) immediately after extubation (dotted vertical Treatment line) between September and November 2020. For each plot, the horizontal line between the whiskers represents the mean, the whiskers represent the SD, and each circle represents a result for one cat.

Results

Two cats became hyperthermic during anesthesia and were excluded prior to randomization for opioid treatment. A total of 94 cats were randomized to receive either buprenorphine or morphine upon recovery from anesthesia (47 in each group). Demographic data, time and duration of anesthesia, and administration of ketamine, dexmedetomidine, and atipamezole are summarized (**Table 1**). Cats receiving morphine were older and heavier than those receiving buprenorphine.

Preoperative, intraoperative, and postoperative body temperatures were evaluated (**Figure 1**). Overall, there were significant effects of time ($P < 0.001$) and treatment ($P = 0.033$) on body temperature, with cats receiving buprenorphine having greater values than those receiving morphine. The point prevalence of hyperthermia for cats receiving buprenorphine

and morphine was 55% (26/47) and 28% (13/46) at 2 hours, 44% (21/47) and 13% (6/46) at 4 hours, and 62% (27/43) and 47% (21/44) at 16 to 20 hours after extubation.

There were no differences in the GCMPS-Feline score between treatment groups ($P = 0.244$) or over time ($P = 0.931$). Four hours after recovery, scores were 0 (range, 0 to 7) for cats receiving buprenorphine and 0 (range, 0 to 6) for cats receiving morphine. Four cats receiving buprenorphine and two receiving morphine scored $\geq 5/20$ at this time point and were subsequently removed from the study. At 16 to 20 hours, cats receiving buprenorphine scored 0 (range, 0 to 6) and those receiving morphine scored 0 (range, 0 to 12). One cat in the buprenorphine group and 4 in the morphine group scored $\geq 5/20$ at 16 to 20 hours. All cats were discharged 24 hours after surgery.

Discussion

The main findings from this study are that postoperative temperature and the point prevalence of hyperthermia were greater with this formulation and dose of buprenorphine than with morphine 0.1 mg/kg, and that no differences were found on postoperative pain scores up to 20 hours after recovery from anesthesia.

Hyperthermia secondary to opioid administration in cats has long been described with several agents, including buprenorphine.^{3,10–12} In our study we evaluated buprenorphine at a concentration and dose that offers analgesia for up to 24 hours after a single SC injection.⁴ A recent retrospective study suggested that hyperthermia occurred more often and lasted longer after that formulation of buprenorphine was used compared with a group of cats receiving morphine.⁵ Our prospective study confirms that hyperthermia was found at a greater rate when buprenorphine was used compared with morphine.

Higher rectal temperatures and a greater occurrence of hyperthermia were recorded when buprenorphine was used. Of particular importance, a high incidence of hyperthermia was observed with both agents almost 24 hours after SC administration. Given that some animals were hyperthermic prior to anesthesia and surgery, presumably from the stress

associated with hospitalization and examinations, we surmise that the causes for these elevated temperatures are multifactorial. However, at every time point after administration of opioids, temperature was higher in those cats receiving buprenorphine, suggesting that agent selection played a decisive role in temperature upregulation.

Following an initial increase in temperature observed 2 hours postoperatively, a small decrease was registered for both groups at 4 hours after recovery from anesthesia. However, higher temperatures and a greater point prevalence of hyperthermia were measured again 12 to 16 hours later. Our study does not allow us to investigate the causes for this biphasic change in postoperative temperature. It is possible that stress-induced increases in temperature had more impact the morning after surgery, when residual sedative effects from anesthesia had dissipated.

In our study we defined hyperthermia as a rectal temperature > 39.2 °C, based on previous reports.^{13,14} It is unclear whether this level of hyperthermia, or this duration, could result in any clinically significant consequences to cats; all cats in this study were discharged within 24 hours from recovery of anesthesia. Although this level of hyperthermia may not be considered clinically consequential, it could impede or delay the diagnosis of fever, which may result from postoperative infections.

Postoperative discomfort was evaluated with the GCMPs, which was measured at 4 and 16 to 20 hours after recovery from anesthesia. No differences were found between groups, nor within groups, over time. The expected duration of analgesia provided by this dose of buprenorphine (24 hours) is substantially longer than that expected from morphine—an agent with a half-life of 90 minutes after twice the dose used in this study¹⁵—which led us to hypothesize that lower pain scores would be associated with buprenorphine 16 to 20 hours after administration. It is possible that the analgesic effects provided by robenacoxib were sufficient to mask any differences between both opioid agents. Overall, scores were low and only few cats required rescue analgesia.

There are limitations to this study. As mentioned previously, our data do not allow us to examine the contribution of other factors to hyperthermia, such as stress, vaccination, or the contribution of preoperative morphine administered to all cats. However, given the similar management between groups, we do not expect that those effects would have introduced a bias toward one treatment group. Hyperthermia associated with the vaccine used is reported as a very rare event, and hence, unlikely to have contributed to our results in a substantial manner.¹⁶ There were differences between groups in terms of age and weight. We cannot comment on whether these differences could have introduced a bias in the results. A pain score was only assessed shortly after surgery and the next morning. Unfortunately, we were not able to obtain pain scores during the evening of surgery.

In summary, administration of buprenorphine 0.24 mg/kg SC to cats following OVH resulted in higher temperatures and a greater point prevalence of

hyperthermia (> 39.2 °C) than morphine 0.1 mg/kg SC during the first 20 postoperative hours. We found no advantages to using buprenorphine with regard to postoperative pain scores after OVH in cats compared with morphine.

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