Comparison of the efficacy and adverse effects of sustained-release buprenorphine hydrochloride following subcutaneous administration and buprenorphine hydrochloride following oral transmucosal administration in cats undergoing ovariohysterectomy

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Important Update:

In order to remain compliant with the most current regulatory guidelines, we have updated the labeling on our SR formulations from Buprenorphine and Meloxicam SR to Buprenorphine and Meloxicam ER. **As of July 1, 2022, SR preparations mentioned in the attached study are now labeled as ER,** with no changes to the formulation of the medication(s).

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Objective—To compare the efficacy and adverse effects of sustained-release (SR) buprenorphine following SC administration and buprenorphine following oral transmucosal (OTM) administration in cats undergoing ovariohysterectomy.

Animals—21 young healthy female cats.

Procedures—As part of anesthetic premedication (0 hours), 10 cats received buprenorphine (0.02 mg/kg) via OTM administration with additional doses at 12, 24, 36, 48, and 60 hours and 11 cats received an equivalent total dose as a single SC injection of SR buprenorphine (0.12 mg/kg). The SR product contained buprenorphine hydrochloride in a proprietary SR matrix. All other anesthetic drugs and a single postoperative dose of meloxicam were administered similarly to all cats. Behavioral and physiologic variables were recorded, and signs of pain were assessed by use of 2 pain assessment scales and von Frey filament testing in each cat prior to premedication administration (baseline), during recovery from anesthesia (RFA), and at 12, 24, 36, 48, 60, and 72 hours.

Results—Heart rate increased and temperature (determined via microchip transponder thermometry) decreased from baseline values during RFA in both groups. Compared with baseline values, pain scores were increased during RFA and at the 12- and 24-hour time points in both groups; von Frey scores were higher during RFA. Behavioral and physiologic variables did not differ significantly between groups at any time point.

Conclusions and Clinical Relevance—In cats undergoing ovariohysterectomy, SC administration of a preoperative dose of SR buprenorphine appeared to have comparable efficacy and adverse effect profile as that of twice-daily OTM administration of buprenorphine before and after surgery. (*Am J Vet Res* 2011;72:461–466)

Buprenorphine is an opioid drug that is classified as a partial μ opioid receptor agonist. It is commonly used in cats because of its proven analgesic efficacy (duration of effect ranging from 6 to 12 hours) via multiple administration routes, lack of adverse effects, and good bioavailability when administered via the OTM route.[1–4] Although the OTM route of administration has improved the ease of treatment, compared with drug delivery via the oral or injectable route, some cats still resist OTM administration. Hence, there is an interest in developing a formulation of buprenorphine that pro-

Abbreviations

CSUPCS	Colorado State University pain and comfort scale
HR	Heart rate
OTM	Oral transmucosal
RFA	Recovery from anesthesia
RR	Respiratory rate
SAP	Systolic arterial blood pressure
SR	Sustained release
VAS	Visual analogue scale

Received November 10, 2009.
Accepted February 11, 2010.
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Supported by Wildlife Pharmaceuticals.
The authors thank Pamela Vogel and Chelsea Sonius for technical support, Jim ZumBrunnen for statistical analysis, Dr. Peter Hellyer for provision of the pain and comfort assessment scale, and Dr. Michael Lappin for provision of the cats used in the study.
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vides a longer duration of analgesia following administration of a single dose. With this goal in mind, a formulation of buprenorphine that provides analgesia for a period of 72 hours following SC injection of a single dose has recently been developed.[a] Such an SR preparation has potential use for postoperative pain control and may also benefit patients that have chronic pain. The purpose of the study reported here was to compare the efficacy and adverse effects of a new SR buprenorphine formulation following SC administration with those of buprenorphine following OTM administration in cats undergoing ovariohysterectomy.

Materials and Methods

Cats—Twenty-one female domestic shorthair cats (mean age, 5.5 months; mean ± SD weight, 2.5 ± 0.54 kg) from the Center for Companion Animal Studies at Colorado State University that were scheduled for routine ovariohysterectomy were included in the study. Cats were considered healthy on the basis of results of physical examination, CBC, and serum biochemical analyses. The study protocol was approved by the Institutional Animal Care and Use Committee.

Study groups—Of the 21 cats, 10 were randomly assigned to receive OTM administration of buprenorphine. As part of the anesthetic premedication, each cat in this group received buprenorphine hydrochloride[b] (0.02 mg/kg) via OTM administration (ie, incremental administration of drug in a cheek pouch [between buccal surface and teeth]) with additional doses administered at 12, 24, 36, 48, and 60 hours. Eleven cats were randomly assigned to receive SC administration of the SR formulation of buprenorphine hydrochloride. As part of the anesthetic premedication, each cat in this group was administered a single SC injection of SR buprenorphine[c] (0.12 mg/kg). This dose was equivalent to the total amount of buprenorphine (ie, six 0.02 mg/kg doses) received by cats in the OTM treatment group. The time of premedication was designated as 0 hours.

SR product—The SR formulation contained buprenorphine hydrochloride in a proprietary SR matrix. The SR matrix consisted of a mixture of DL-lactide-cocaprolactone polymers with *N*-methyl-2-pyrrolidone as a solvent. The molecular weight of the polymers was determined via gel permeation chromatography. The buprenorphine was produced as a pure active pharmaceutical ingredient by an FDA-approved source.[d] The concentration of buprenorphine was determined via UV absorption spectroscopy. The SR formulation was specifically formulated[e] for the research cats used in this study and administered by orders of a licensed veterinarian. No claim of FDA approval of this product has been made.

Anesthesia—With the exception of the buprenorphine treatments, all other aspects of the anesthetic protocol were standardized for cats in both groups. Procedures included administration of additional premedication (acepromazine maleate[f] [0.02 mg/kg], SC, and atropine[g] [0.03 mg/kg], SC), induction of anesthesia (to effect) with ketamine hydrochloride[h] (5 mg/kg, IV) and diazepam[i] (0.3 mg/kg, IV), maintenance of anesthesia with isoflurane[j] in oxygen delivered via a nonrebreathing circuit, and administration of a single dose of meloxicam[k] (0.1 mg/kg, SC) shortly after extubation during RFA.

Evaluations—Monitoring of cats during anesthesia was performed by student anesthetists in a manner consistent with hospital practices and included recording of HR, RR, and SAP at 5-minute intervals. Blood pressure was measured by use of a Doppler ultrasonographic flow detector[l] and a cuff placed on a forelimb (cuff width was approx 40% of the limb circumference). Isoflurane vaporizer settings for each 15-minute interval were averaged, and volume of fluid administered was calculated on the basis of the fluid administration rate and volume of fluid left in the fluid bag. Additionally, student anesthetists noted the quality of sedation (categorized subjectively as profound, good, or poor) for catheter placement. Quality of induction of anesthesia and RFA (categorized subjectively as good, fair, or poor), duration of anesthesia (interval from initiation to cessation of isoflurane administration) and surgery (interval from the first incision to completion of skin closure), and any complications that developed in the time from intubation to extubation (eg, hypotension) were also recorded by the student anesthetists.

Physiologic and behavioral evaluations of each cat were performed by 2 blinded evaluators (DLC and JKR) the night before the scheduled surgery date (baseline; approx 12 hours prior to premedication), between 15 and 45 minutes after extubation during RFA (1 evaluator [DLC]), and 12, 24, 36, 48, and 72 hours after the time of premedication. All of these evaluations were done in the cat's normal group housing unit. For cats in the OTM treatment group, these evaluations were performed just prior to administration of the next dose of buprenorphine, with the exception of the RFA time point. Body temperature was measured via microchip transponder thermometry,[5,m] HR was measured via pulse palpation or auscultation, and RR was measured via observation or palpation of thoracic wall movement.

Pain assessments were also completed by the same 2 blinded evaluators (DLC and JKR) approximately 12 hours prior to administration of premedication (baseline), between 15 and 45 minutes after extubation during RFA (1 evaluator [DLC]), and at 12, 24, 36, 48, and 72 hours and included both objective and subjective evaluations. von Frey (also referred to as Semmes-Weinstein[n]) filaments were used to objectively measure response to peri-incisional application. Up to 20 fibers (size range, 1.65 to 6.65; force equivalence, 0.008 to 300 g) were applied incrementally. Fibers were applied perpendicular to 4 peri-incisional points just until the fiber bent, and the cat's reaction, or lack thereof, was noted. At each time point, the size of the filament to which the cat first responded was recorded.

The subjective pain scales that were used included a VAS (a 10-cm line along which a mark is made by an evaluator to represent perceived level of pain [from 0 cm = no pain to 10 cm = worst pain possible]) and the CSUPCS[o] (a scoring system that uses both visual and interactive patient assessment to evaluate body posture, body tension, behavior and mental state, and response to palpation) to generate

a numeric value from 0 to 4. Each cat's activity before and during manipulation was also subjectively scored by 1 of the 2 evaluators (DLC) on a scale of 1 (sleeping) to 5 (overly active).

The buprenorphine injection site in each cat in the SR treatment group was monitored twice daily for any swelling, alopecia, erythema, crusting, discharge, or pain on palpation throughout the study period and daily thereafter for a period of 2 weeks.

Rescue analgesia—Provision of rescue analgesia (buprenorphine or meloxicam administration in addition to what was scheduled per the study protocol) was an option for any cat at any time during the study period. If following evaluations by the blinded observer cats were assigned borderline scores (ie, a CSUPCS score ranging from 2 to 2.5 or a VAS score ranging from 3.0 to 4.0 cm), the overseeing clinician (JMQ) who was familiar with the normal behaviors of these cats further evaluated the cats to determine whether additional analgesics were necessary. This was done with knowledge of blinded observer scores and included an independent clinical assessment of the cats and evaluation of the response to scheduled analgesic administration (eg, postoperative administration of meloxicam or scheduled buprenorphine administration in the OTM treatment group) when appropriate. Cats with a CSUPCS score > 2.5 or VAS score > 4.0 cm were to immediately receive additional administration of buprenorphine or meloxicam. The response to analgesic administration was evaluated within an hour after drug administration.

Statistical analysis—Physiologic, behavioral, and selected anesthetic data were summarized as mean and SD and analyzed by use of a 2-factor repeated-measures ANOVA to evaluate treatment effects between and within groups. Post hoc comparisons between groups at fixed time points and within a group over time were determined by use of *t* tests to compare least squares means. Data collected at 1 time point were compared by use of *t* tests. Analyses were performed by use of computer software.[p] A value of $P < 0.05$ was considered significant.

Results

During anesthesia, values for HR, RR, and SAP were within reference ranges; no significant differences in those variables were detected between treatment groups. Qualities of sedation, induction of anesthesia, and RFA and incidence of perioperative complications did not differ between groups. For the SR and OTM treatment groups, the mean ± SD durations of anesthesia were 111 ± 20 minutes and 114 ± 25 minutes, respectively, and mean durations of surgery were 59 ± 11 minutes and 72 ± 17 minutes, respectively. Isoflurane administration did not vary between groups; the overall mean ± SD vaporizer settings in the SR and OTM treatment groups were 1.2 ± 0.39% and 1.3 ± 0.44%, respectively. The only variable that differed between treatment groups during the anesthetic period was the volume of fluids administered IV; the volumes were 9.4 ± 2.8 mL/kg/h and 15.5 ± 2.8 mL/kg/h in the SR and OTM treatment groups, respectively.

Cat behavior in the 2 treatment groups from the time of premedication through the 72-hour observation period (as assessed by student anesthetists and blinded observers) was similar; the distribution of sedation and euphoria was recorded with similar frequencies in cats in both groups. Behavioral data before and during manipulation averaged over all time points were 3.3 ± 0.9 for cats in the SR treatment group and 3.1 ± 1 for cats in the OTM treatment group. These values were not significantly different between groups. Dysphoria was not detected in any cat in the present study.

Similarly, physiologic variables and pain scores before premedication, during RFA, or 12, 24, 36, 48, and 72 hours after premedication revealed no significant differences between treatment groups. However, several variables changed significantly from baseline values (obtained the day before surgery, approx 12 hours prior to premedication administration) over time in both treatment groups. Body temperature decreased from baseline values of 38.7 ± 0.4°C and 38.8 ± 0.4°C to 38.2 ± 0.7°C and 38.2 ± 0.9°C during RFA in the SR and OTM treatment groups, respectively (**Table 1**). Additionally, diurnal variations in body temperature were detected in both groups of cats, but these were

Table 1—Mean ± SD values of HR, RR, and body temperature (measured via microchip transponder thermometry) assessed at various time points before and after ovariohysterectomy in 10 cats that received buprenorphine hydrochloride (0.02 mg/kg) via OTM administration as part of anesthetic premedication and at 12, 24, 36, 48, and 60 hours and in 11 cats that received the equivalent total dose as a single SC injection of an SR formulation of buprenorphine hydrochloride (0.12 mg/kg) as part of anesthetic premedication.

	HR (beats/min)		RR (breaths/min)		Body temperature (°C)	
Time point	OTM	SR	OTM	SR	OTM	SR
Baseline	144 ± 22	139 ± 15	53 ± 19	59 ± 13	38.8 ± 0.4	38.7 ± 0.4
RFA	212 ± 41*	202 ± 36*	48 ± 10	51 ± 10	38.2 ± 0.9*	38.2 ± 0.7*
12 h	160 ± 38	157 ± 28	45 ± 9	49 ± 17	38.5 ± 0.5	38.3 ± 0.7
24 h	153 ± 22	151 ± 23	56 ± 14	52 ± 16	38.7 ± 0.5	38.6 ± 0.4
36 h	157 ± 29	151 ± 31	56 ±13	49 ± 15	38.6 ± 0.3	38.4 ± 0.6
48 h	158 ± 29	150 ± 16	64 ± 22	56 ± 10	38.8 ± 0.3	38.8 ± 0.4
60 h	171 ± 39	166 ± 26	58 ± 17	53 ± 12	38.5 ± 0.7	38.5 ± 0.4
72 h	151 ± 17	163 ± 23	53 ± 16	52 ± 12	38.7 ± 0.5	38.6 ± 0.4

Assessments were made approximately 12 hours prior to premedication (baseline), between 15 and 45 minutes after extubation during RFA, and at 12, 24, 36, 48, 60, and 72 hours. *Within a group, value was significantly ($P < 0.05$) different from the baseline value for this variable.

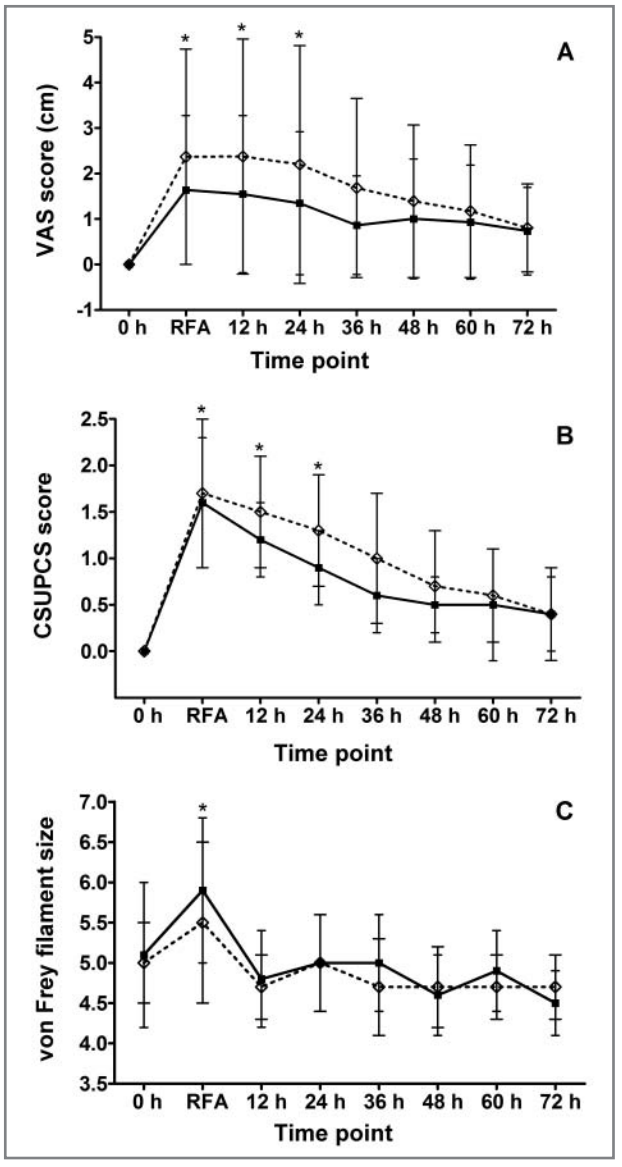

Figure 1—Mean ± SD VAS (A) and CSUPCS (B) scores and von Frey filament response (filament size; C) assessed at various time points before and after ovariohysterectomy in 10 cats that received buprenorphine hydrochloride (0.02 mg/kg) via OTM administration (diamonds) as part of anesthetic premedication and at 12, 24, 36, 48, and 60 hours and in 11 cats that received the equivalent total dose as a single SC injection of an SR formulation of buprenorphine hydrochloride (0.12 mg/kg) as part of anesthetic premedication. Assessments were made approximately 12 hours before premedication (baseline), between 15 and 45 minutes after extubation during RFA, and at 12, 24, 36, 48, 60, and 72 hours. *Within each group at this time point, value was significantly ($P <$ 0.05) different from the baseline (0-hour) value.

not significant. In the SR and OTM treatment groups, the mean HR baseline values were 139 ± 14 beats/min and 144 ± 22 beats/min, respectively; during RFA, these values increased to 202 ± 36 beats/min and 212 ± 41 beats/min, respectively.

In both groups, the VAS and CSUPCS scores were significantly increased during RFA and at the 12- and 24-hour time points, compared with baseline scores. Despite the lack of significant differences in overall scores between groups at these time points, cats in the OTM treatment group had VAS or CSUPCS scores that were subjectively higher than the scores for cats in the SR treatment group, and for some cats in both groups (with a greater number in the OTM group), scores reached values that necessitated additional evaluation and consideration of rescue analgesia. After additional evaluation by the overseeing clinician, planned analgesic administration (eg, meloxicam administration during RFA) and subsequent ongoing assessment, no cats were determined to require additional analgesic administration. With regard to von Frey filament testing in the SR and OTM treatment groups, mean filament size increased significantly from baseline values of 5.10 ± 0.94 and 4.96 ± 0.46, respectively, to 5.92 ± 0.94 to 5.54 ± 0.97, respectively, during RFA (**Figure 1**).

One cat in the SR treatment group had an injection site reaction (a small scab that appeared at the site 1 week after administration of the SR formulation of buprenorphine). The reaction resolved completely without intervention within 7 days.

Discussion

In cats undergoing ovariohysterectomy, SC administration of a single dose of the SR buprenorphine preparation used in the present study appeared to have at least comparable efficacy with and a similar adverse effect profile to findings for twice-daily OTM administration of buprenorphine. The SR formulation consisted of buprenorphine hydrochloride in an SR delivery matrix of DL-lactide-co-caprolactone, which is a water-insoluble polymer that precipitates in body fluids and forms a depot for SR of a drug.[6] A similar formulation with the chemotherapeutic agent cisplatin has steady drug release and minimal tissue reactions.[7] In the present study, the SR formulation of buprenorphine was easy to administer and appeared to be efficacious during the 3-day postoperative study period, compared with buprenorphine administered via the OTM route.

Ovariohysterectomy was selected as the procedure for the study because it is considered to be a standard source of moderate soft tissue pain and is one of the most common surgical procedures performed in small animal patients.[8,9] In our study, which involved veterinary student–performed surgeries, the typical noxious stimulus of the procedure was potentially exceeded; as such, we believe the results of our study should translate well to general practice.

As with any investigation involving evaluation of pain, it was a challenge to develop means of accurate and objective measurement of pain in the cats in the present study. Pain assessment is often a subjective assessment made by an evaluator, which is further complicated by the diversity of demeanors among the population of cats being studied. In an attempt to mitigate these potential confounders, all cats in the present study were evaluated in their group-housing unit (an environment in which they were comfortable) by the same 2 blinded evaluators, and assessments included physiologic measurements, von Frey filament testing, and application of 2 pain evaluation scales. With the use of 2 subjective pain evaluation scales and an objective pain assessment tool, we hoped to balance any bias inherent in each scale. The objective pain assessment

involved peri-incisional application of increasing levels of force by use of von Frey filaments. von Frey filament testing has been used effectively in the evaluation of the analgesic efficacy of opioids in animals.[10] However, results of the present study indicated that the fiber size needed to generate a response (indicating decreased sensitivity to peri-incisional force) increased significantly from baseline during RFA, a finding that contradicted the subjective pain score results at that time point. This discrepancy and decreased reaction to the von Frey filament application in the immediate postoperative period may be attributable to lingering sedative effects of anesthetic drugs. Alternatively, because von Frey filaments were developed to detect upregulation of pain pathways or windup pain, they may not be as sensitive for detection of acute pain and it might have been of more value to use a mechanical threshold device, as described previously by Slingsby et al.[11] It is interesting that HR values during RFA were increased from baseline, which again may reflect lingering anesthetic drug effects or pain. We suspected that the increase in HR was likely related to pain because of the concurrent increase in pain scores during RFA, and concluded that the peri-incisional application of von Frey filaments did not accurately reflect acute pain in the study cats.

A VAS is commonly used for assessment of pain in veterinary patients, and this tool has been validated in humans for use in patients with abdominal pain.[4,9,12] The CSUPCS scale provides a comprehensive tool that accounts for many indicators of pain (posture, behavior, and response to palpation). Although its use has not yet been validated, changes in the CSUPCS scores generally paralleled changes detected with the VAS in this study. In addition, the changes in scores derived from the VAS and the CSUPCS scale in our study were proportional to both objective and subjective assessments following buprenorphine administration in cats in other studies.[2–4]

Although there were no significant differences in measured physiologic variables or pain evaluation scores between the 2 treatment groups, pain scores in the OTM treatment group were subjectively (albeit not significantly) higher than those in the SR treatment group during RFA and throughout much of the observed postoperative period. No cats received rescue analgesics, but individual cats in both groups (a greater number in the OTM treatment group) had scores that warranted additional evaluation during RFA, and some cats in the OTM treatment group had borderline CSUPCS or VAS scores at the 12- and 24-hour time points. In both instances, cats responded favorably to the planned administration of analgesic medications (eg, scheduled dose of meloxicam or buprenorphine). It is possible that with more frequent evaluation during the latter part of each drug-dosing interval in the OTM treatment group, we might have considered that more cats were uncomfortable and significant differences in pain scores (VAS, CSUPCS, or von Frey filament assessment) between the 2 groups may have become evident. No cats in the SR treatment group were deemed to need additional analgesics at the 12- and 24-hour time points.

The use of meloxicam, an NSAID, is a potential confounder in evaluating the true analgesic efficacy of either buprenorphine product in the present study. The decision to administer meloxicam was made in keeping with the standard of care for pain control within our teaching hospital, especially because the ovariohysterectomies were performed by senior veterinary students and the authors anticipated that more tissue trauma and associated pain would occur than that typically generated during surgeries performed by experienced veterinary practitioners. We hypothesized that the influence of meloxicam would be similar in both treatment groups and would not significantly influence the comparison of analgesic efficacy between treatment groups. Given our primary goal to compare analgesic efficacies of 2 buprenorphine products and our wish not to completely mask their effectiveness, we elected to use a lower dose than that typically recommended for postoperative use in cats. At the recommended dose (0.3 mg/kg) as stated on the package insert, SC administered meloxicam is absorbed rapidly, and although it has some early beneficial effects, there is an interval of approximately 5 hours before it reaches peak analgesic efficacy.[8] In the present study, it is likely that meloxicam did not influence pain evaluation scores during the immediate postoperative period, as is evident from the increase in pain scores from baseline in both groups. The reported duration of analgesic effect following administration of the recommended 0.3 mg/kg dose in cats with experimentally induced inflammation is approximately 24 hours.[8] Although it did appear that meloxicam provided analgesia during the early postoperative period in the present study and that meloxicam possibly influenced pain evaluations at the 12-hour time point despite the low dose administered, the drug was considered unlikely to have had a major effect at the 24-hour time point, at which pain evaluation scores remained increased from baseline in both treatment groups. Also, had the meloxicam been masking a lack of efficacy of the SR formulation of buprenorphine, one might have expected pain scores to increase as the effects of the meloxicam diminished; this was not observed, and pain scores in both treatment groups decreased over the remainder of the study period.

In the present study, there was a difference in the volume of IV fluids administered to cats in each group during the anesthetic period. We believe this finding to have little importance because the incidence of hypotension was the same between the 2 treatment groups, and the mean fluid volume for the SR treatment group was greatly influenced by a large fluid volume administered to 1 cat. One injection site reaction developed in a cat that received the SR formulation of buprenorphine. This cat developed a small scab over the site of the injection. If this SR formulation of buprenorphine becomes more widely used, and especially if its use is considered for chronic pain management in cats (in which repeated administration is necessary), the frequency and character of injection site reactions will need to be monitored. Other than this single adverse event, results of the present study suggested that the SR buprenorphine product had a tolerable adverse effect profile and was at least as efficacious as buprenorphine administered via the OTM route in cats undergoing ovariohysterectomy. This leads us to conclude

that administration of a SR buprenorphine product may be a viable option for analgesia in cats.

a. Wildlife Pharmaceuticals, Fort Collins, Colo.
b. Buprenorphine 0.3 mg/mL, Hospira, Lake Forest, Ill.
c. Buprenorphine hydrochloride (proprietary) sustained release 2 mg/mL, Wildlife Pharmaceuticals, Fort Collins, Colo.
d. Johnson Matthey, Biomedical Materials, West Deptford, NJ.
e. Wildlife Pharmaceuticals, Fort Collins, Colo.
f. Acepromazine maleate, Vedco, St Joseph, Mo.
g. Atropine, Vedco, St Joseph, Mo.
h. VetaKet, Lloyd laboratories, Shenandoah, Iowa.
i. Diazepam, Hospira, Lake Forest, Ill.
j. Isoflurane, Altane, Minrad, Bethlehem, Pa.
k. Metacam, Boehringer Ingelheim, St Joseph, Mo.
l. Parks Medical Electronics, Aloha, Ore.
m. IPTT-300 transponder, Bio Medic Data Systems Inc, Seaford, Del.
n. North Coast Medical Inc, Morgan Hill, Calif.
o. CSUPCS available from the authors on request or from the IVAPM website.
p. SAS/STAT, version 9.2, SAS Institute Inc, Cary, NC.

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