

# Comparison of oral and subcutaneous administration of buprenorphine and meloxicam for preemptive analgesia in cats undergoing ovariohysterectomy

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**Objective**—To compare the effectiveness of preoperative PO and SC administration of buprenorphine and meloxicam for prevention of postoperative pain-associated behaviors in cats undergoing ovariohysterectomy.

**Design**—Randomized controlled study.

**Animals**—51 female cats (4 to 60 months old; weight range, 1.41 to 4.73 kg [3.1 to 10.4 lb]).

**Procedure**—Cats received 1 of 5 treatments at the time of anesthetic induction: buprenorphine PO (0.01 mg/kg [0.0045 mg/lb]; n = 10), buprenorphine SC (0.01 mg/kg; 10), meloxicam SC (0.3 mg/kg [0.14 mg/lb]; 10), meloxicam PO (0.3 mg/kg; 10), or 0.3 mL of sterile saline (0.9% NaCl) solution SC (control group; 11). Sedation scores and visual analog scale and interactive visual analog scale (IVAS) pain-associated behavior scores were assigned to each cat 2 hours before and at intervals until 20 hours after surgery.

**Results**—Cats receiving meloxicam PO or SC had significantly lower IVAS scores (2.91 and 2.02, respectively), compared with IVAS scores for cats receiving buprenorphine PO (7.55). Pain-associated behavior scores for cats administered buprenorphine or meloxicam PO or SC preoperatively did not differ significantly from control group scores. Rescue analgesia was not required by any of the cats receiving meloxicam, whereas 3 of 10 cats receiving buprenorphine PO, 2 of 10 cats receiving buprenorphine SC, and 1 of 11 cats receiving the control treatment required rescue analgesia.

**Conclusions and Clinical Relevance**—On the basis of pain-associated behavior scores, cats receiving meloxicam PO or SC before ovariohysterectomy appeared to have less pain after surgery than those receiving buprenorphine PO preoperatively. (*J Am Vet Med Assoc* 2005;227:1937–1944)

Elective ovariohysterectomy is one of the most common surgical procedures performed in companion animals in general veterinary practice. It is well recognized that pain-associated behavior patterns are evident in cats after ovariohysterectomy.<sup>1,2</sup> The severity of the

signs of pain and discomfort can vary depending on the degree of soft tissue trauma and the pain threshold of the individual animal. Among animals, age, sex, breed, species, and previous experiences are also associated with variations in response to injury.<sup>3–6</sup> Despite acknowledgement that pain following surgery is experienced by cats undergoing ovariohysterectomy, there is reluctance for veterinary practitioners to intervene. In 1 study,<sup>7</sup> 957 of 958 (99.9%) respondents agreed that cats had signs of pain following routine ovariohysterectomy but only 249 (26%) provided any kind of analgesic intervention. In a survey<sup>8</sup> of Australian veterinarians, data from approximately 486 respondents indicated that the rate of analgesic administration by veterinarians to cats undergoing ovariohysterectomy was only 6%.

Systemic administration of analgesics before surgery may reduce the need for pain intervention postoperatively. Analgesic agents are administered preemptively to decrease anxiety and provide analgesia to the patient prior to a noxious stimulus. These effects are achieved through modulation of peripheral and central sensitization to pain during the operative and postoperative periods.<sup>2,9</sup> Although it is difficult to demonstrate the preemptive analgesic effect of a specific drug, it is well recognized that administration of analgesic drugs prior to the initiation of a painful stimulus provides more effective pain relief than administration of those drugs postoperatively.<sup>9–11</sup> In addition, when effective analgesia is achieved during the operative and postoperative periods, intraoperative requirements for anesthetic agents and the risk of postoperative complications are decreased.<sup>12</sup>

Veterinary practitioners are often reluctant to administer analgesics before surgery because of a lack of familiarity with available drugs, concerns regarding adverse effects, and the need for record keeping of controlled substances.<sup>1,2,13</sup> Treatment options for provision of preemptive analgesia include administration of opioids, neuroaxial blocker agents (local anesthetic agents), and nonsteroidal anti-inflammatory drugs (NSAIDs). When administered preoperatively, these analgesic agents are efficacious in decreasing signs of pain following ovariohysterectomy in a variety of species.<sup>2,12,14–18</sup> However, limited information is available regarding preemptive analgesia in cats; after administration of such intervention, the expected behavioral responses or the interpretation of these behaviors cannot routinely be extrapolated from 1 species to another, even among domestic animals.<sup>14,19,20</sup> The purpose of the study reported here was to compare the effectiveness of preoperative

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PO and SC administration of buprenorphine and meloxicam for prevention of pain-associated behavior in cats after undergoing ovariohysterectomy. We hypothesized that cats administered either buprenorphine or meloxicam preoperatively would have decreased pain-associated behavior scores after ovariohysterectomy, compared with those of a control group.

## Materials and Methods

**Animals**—Fifty-one healthy (American Society of Anesthesiologists' category 1) sexually intact female cats (4 to 60 months old) that weighed 1.41 to 4.73 kg (3.1 to 10.4 lb) were included in the study. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Tennessee, and permission for participation of each cat was obtained from the owner. All cats were considered healthy on the basis of history, physical examination findings, serum glucose and serum total solids concentrations, and PCV. For each cat, food, but not water, was withheld for 12 hours prior to anesthesia.

**Experimental protocol**—Cats were randomly assigned by lottery to receive 1 of the following treatments: buprenorphine<sup>a</sup> PO (0.01 mg/kg [0.0045 mg/lb];  $n = 10$ ), buprenorphine SC (0.01 mg/kg; 10), meloxicam<sup>b</sup> SC (0.3 mg/kg [0.14 mg/lb]; 10), meloxicam PO (0.3 mg/kg; 10), or a control treatment (0.3 mL of saline [0.9% NaCl] solution,<sup>c</sup> SC; 11). Cats receiving analgesic agents PO were also administered sterile saline solution (0.3 mL) SC, and cats receiving analgesic agents SC were also administered water (0.5 mL) PO. Cats in the control group received sterile saline solution SC and water PO. For each cat, a baseline (ie, preoperative) visual analog scale (VAS) pain score,<sup>14</sup> interactive VAS (IVAS) pain score,<sup>14</sup> and sedation<sup>2</sup> score were assigned by a single observer (KMT) 2 hours before sedation and before administration of any of the experimental treatments.

Forty-five minutes before commencement of surgery, cats were sedated with acepromazine maleate<sup>d</sup> (0.05 mg/kg [0.023 mg/lb], IM) and ketamine hydrochloride<sup>e</sup> (5 mg/kg [2.3 mg/lb], IM). Each cat was then given its allotted treatment (1 treatment/cat). Oral administrations of treatments were accomplished via insertion into the buccal pouch with a syringe. Anesthesia was induced with isoflurane (3% to 5%) in oxygen (4 L/min) that was delivered by use of mask; after tracheal intubation, anesthesia was maintained with isoflurane in oxygen for the duration of surgery. A peripheral vein was catheterized with a 22-gauge, 1-inch, over-the-needle, fluorinated ethylene propylene polymer catheter.<sup>f</sup> To provide volume replacement and cardiovascular support, fluids<sup>g</sup> were administered IV at a rate of 20 mL/kg/h (9.1 mL/lb/h) after catheter placement and maintained at that rate throughout the operative period.<sup>21</sup> A total dose of 10 mL/kg (4.5 mL/lb) of fluids was typically administered to each cat. The ventrum of each cat was shaved from the xyphoid process to the pubis, and the skin was aseptically prepared before the cat was transported into the surgical suite. All cats underwent routine ovariohysterectomy through a 2- to 3-cm midline incision by the same experienced surgeon (KMT).

**Measurements**—Intravenous catheters were removed before extubation. Once extubated, each cat was placed in a recovery cage in a cat-only ward for postoperative observation by a trained observer (KMT) who was unaware of the treatment that had been administered. Duration of surgery (time from initial incision to skin closure) and duration of anesthesia (time from induction to extubation) were recorded for each cat. Three hours after recovery from anesthesia (ie, time of extubation), food and water were offered, and an assessment of the cat's appetite was recorded at 4 and 20

hours. At 20 hours after extubation, 0.5 mL of blood was obtained for measurement of PCV and serum glucose and total solids concentrations.

For each cat, VAS, IVAS, and sedation scores were assigned by a single observer (KMT) at extubation (time 0) and 30 minutes and 1, 2, 3, 4, 5, 6, and 20 hours after recovery from anesthesia. For VAS and IVAS scores, the estimated degree of pain was marked on a 100-mm line; 0 mm (score, 0) represented no signs of pain, and 100 mm (score, 100) represented signs of the worst imaginable pain. The VAS scores were based on observations of each cat's resting behavior. A cat that approached the cage door, arched its back for attention, or stretched out in a relaxed position and actively groomed itself was considered to have a VAS pain score of 0; a VAS score of 100 would be assigned if the cat was recumbent and breathing open-mouthed or had lost consciousness after recovery from anesthesia. The IVAS score was recorded after opening the cage door, talking to the cat, petting its head, and palpating its abdomen. A cat that did not object to or avoid abdominal palpation and had no flinching of skin or muscle during palpation was considered to have an IVAS score of 0. A cat that vocalized, appeared agitated, and made attempts to bite the handler during palpation or that had lost consciousness after recovery from anesthesia was assigned an IVAS score of 100. The estimated degree of sedation was marked on a 100-mm line; 0 mm (score, 0) represented an alert cat, and 100 mm (score, 100) represented a nonresponsive cat.

Cats with VAS scores  $\geq 30$  or IVAS scores  $\geq 50$  during postoperative monitoring were administered a rescue analgesic (butorphanol<sup>h</sup> [0.4 mg/kg {0.18 mg/lb}, IM]) as needed. Data collected after butorphanol administration were not included in the statistical analyses. At the completion of the study, all cats were returned to their caregivers.

**Statistical analysis**—The effects of treatment, time, and treatment-by-time interaction on sedation scores and VAS and IVAS pain scores in ovariohysterectomized cats were evaluated by use of a mixed-model ANOVA procedure.<sup>1</sup> Cat was included in the model as a random factor. Time as a repeated measure was evaluated and removed from the model on the basis of the  $-2$  log likelihood statistic, which indicated that there was no improvement in fit of the model to the data. Non-normally distributed sedation, VAS, and IVAS scores were transformed by use of a rank procedure.<sup>1</sup> Significant differences in least square means among the various levels of treatment, time, and treatment-by-time interaction were adjusted by use of the Bonferroni method. The Pearson correlation coefficient was used to evaluate the relationship among sedation scores and VAS and IVAS pain scores. Descriptive data are reported as the least squares mean  $\pm$  SD. A value of  $P \leq 0.05$  was considered significant.

## Results

Fifty-one cats were included in the study, and all remained healthy throughout the study. Mean  $\pm$  SD age of the cats was  $12.9 \pm 10.5$  months (median, 12 months); mean weight was  $2.6 \pm 0.73$  kg ( $5.7 \pm 1.6$  lb; median, 2.6 kg). Mean duration of surgery was  $11.2 \pm 2.9$  minutes (median, 10 minutes), and mean duration of anesthesia was  $40.4 \pm 12.6$  minutes (median, 40.4 minutes). Among the treatment groups, age and weight of cats and durations of surgery and anesthesia were not significantly different. All cats had similar changes in appetite at 4 and 20 hours after extubation, and all cats were eating and drinking at the time of discharge. Compared with preoperative baseline values, PCV and serum glucose and total solids concentrations at 20

hours after surgery were not significantly different. Oral drug administration was uncomplicated in all cats; no treatment-associated drooling, facial pawing, or other behavior abnormalities were observed.

Rescue analgesic was administered at 2, 5, or 6 hours after surgery to 3 cats that received buprenorphine PO; at 3 or 5 hours after surgery to 2 cats that received buprenorphine SC; and at 5 hours after surgery to 1 cat that received the control treatment. These differences were not significant. Results collected from these 6 cats after administration of rescue analgesic were not included in the VAS, IVAS, and sedation score analyses.

Before sedation or administration of any experimental treatments (baseline), all cats had sedation, VAS, and IVAS scores of 0. There were no significant differences in VAS scores among groups at any time. Compared with findings at 5 and 6 hours after surgery, VAS scores in all groups were significantly ( $P = 0.016$  to  $< 0.001$ ) increased at 1 and 2 hours after surgery. Compared with baseline data, cats receiving buprenorphine PO had significant increases in VAS scores at 1 ( $P = 0.002$ ), 2 ( $P = 0.004$ ), and 3 hours ( $P = 0.021$ ) after surgery; cats receiving buprenorphine SC had significant increases in VAS scores at 30 minutes ( $P = 0.009$ ) and 1 ( $P < 0.001$ ), 2 ( $P = 0.008$ ), and 5 hours ( $P = 0.038$ ) after surgery (Figure 1). Compared with baseline data, cats receiving meloxicam PO had significant increases in VAS scores at 30 minutes ( $P = 0.001$ ) and 1 ( $P < 0.001$ ), 2 ( $P = 0.017$ ), and 3 hours ( $P = 0.003$ ) after surgery; cats receiving meloxicam SC had significant increases in VAS scores 30 minutes ( $P = 0.017$ ) after surgery. Compared with baseline data, cats receiving the control treatment had significant increases in VAS scores at 1 ( $P = 0.019$ ), 2 ( $P < 0.001$ ), and 3 hours ( $P < 0.001$ ) after surgery.

The IVAS scores for cats receiving meloxicam PO or SC were significantly ( $P = 0.037$  and  $0.006$ , respectively) lower than scores assigned to cats receiving buprenorphine PO. There were no significant ( $P > 0.3$ )

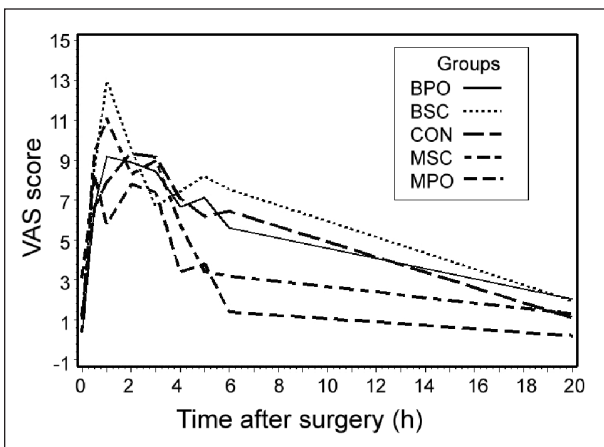


Figure 1—Least square mean visual analog scale (VAS) scores of pain-associated behaviors in 51 cats that underwent ovariohysterectomy after preoperative treatment with buprenorphine (0.01 mg/kg [0.0045 mg/lb]) administered PO (BPO;  $n = 10$ ), buprenorphine (0.01 mg/kg) administered SC (BSC; 10), meloxicam (0.3 mg/kg [0.14 mg/lb]) administered PO (MPO; 10), meloxicam (0.3 mg/kg) administered SC (MSC; 10), or saline (0.9% NaCl) solution (0.3 mL) administered SC (control treatment [CON]; 11).

differences between cats given meloxicam PO or SC and cats receiving buprenorphine SC. Compared with findings in the control group, pain-associated behavior scores in cats administered buprenorphine PO or SC or meloxicam PO or SC preoperatively were not significantly ( $P > 0.3$ ) different. Compared with baseline data, cats receiving buprenorphine PO had significant increases in IVAS scores at 1 ( $P = 0.001$ ), 2 ( $P < 0.001$ ), 3 ( $P = 0.022$ ), and 4 hours ( $P < 0.001$ ) after surgery; cats receiving buprenorphine SC had significant increases in IVAS scores 3 hours ( $P = 0.001$ ) after surgery (Figure 2). Compared with baseline data, cats receiving meloxicam PO or SC and cats receiving the control treatment had no significant differences in IVAS scores at any time after surgery.

In all groups, sedation scores increased significantly from baseline values from 0 to 3 hours (range,  $P = 0.001$  to  $< 0.001$ ) after surgery and returned to baseline values by 4 hours after surgery (Figure 3). There

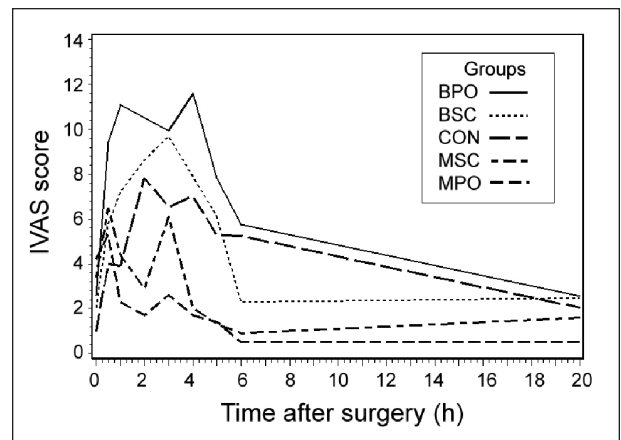


Figure 2—Least square mean interactive VAS (IVAS) scores of pain-associated behaviors in 51 cats that underwent ovariohysterectomy after preoperative treatment with buprenorphine (0.01 mg/kg) administered PO (BPO;  $n = 10$ ), buprenorphine (0.01 mg/kg) administered SC (BSC; 10), meloxicam (0.3 mg/kg) administered PO (MPO; 10), meloxicam (0.3 mg/kg) administered SC (MSC; 10), or saline solution (0.3 mL) administered SC (CON; 11).

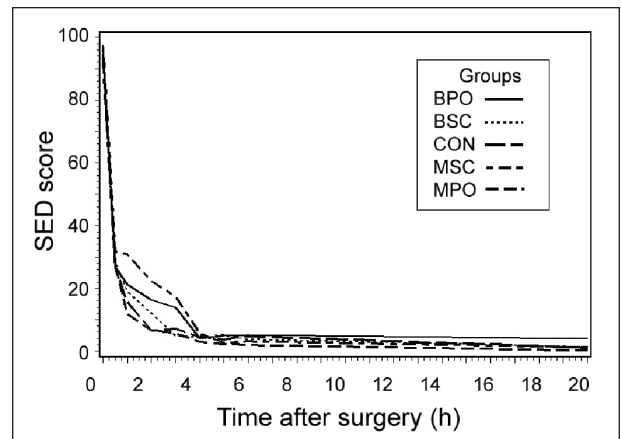


Figure 3—Least square mean sedation (SED) scores in 51 cats that underwent ovariohysterectomy after preoperative treatment with buprenorphine (0.01 mg/kg) administered PO (BPO;  $n = 10$ ), buprenorphine (0.01 mg/kg) administered SC (BSC; 10), meloxicam (0.3 mg/kg) administered PO (MPO; 10), meloxicam (0.3 mg/kg) administered SC (MSC; 10), or saline solution (0.3 mL) administered SC (CON; 11).

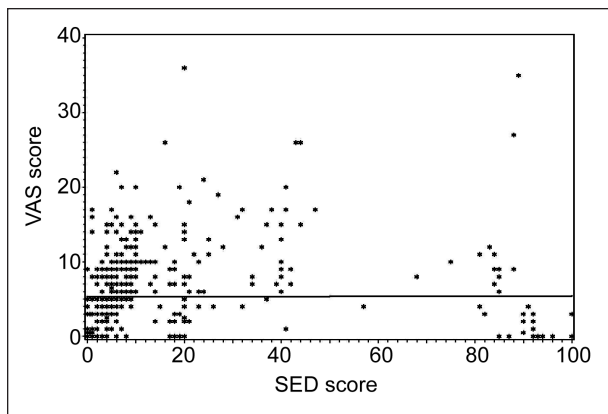


Figure 4—Correlation between SED scores and VAS pain scores obtained 0 to 20 hours after ovariohysterectomy in 51 cats that received preoperative treatment with buprenorphine PO or SC, meloxicam PO or SC, or saline solution SC.

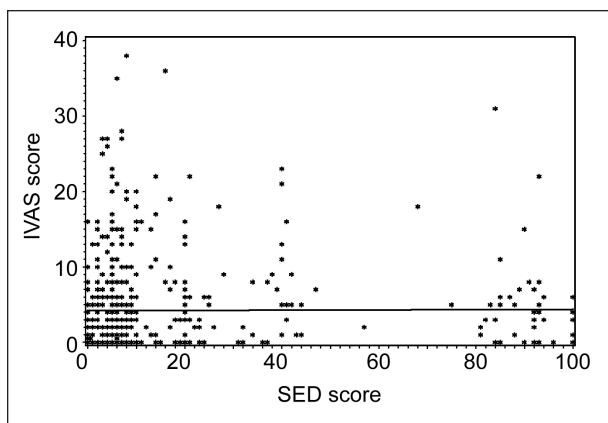


Figure 5—Correlation between SED scores and IVAS pain scores obtained 0 to 20 hours after ovariohysterectomy in 51 cats that received preoperative treatment with buprenorphine PO or SC, meloxicam PO or SC, or saline solution SC.

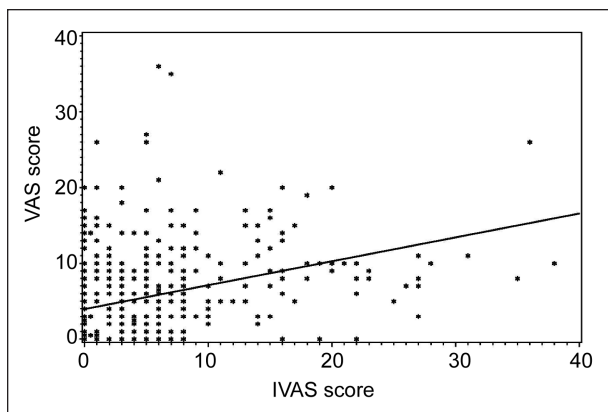


Figure 6—Correlation between VAS pain scores and IVAS pain scores obtained 0 to 20 hours after ovariohysterectomy in 51 cats that received preoperative treatment with buprenorphine PO or SC, meloxicam PO or SC, or saline solution SC.

were no significant differences among groups at any time for sedation. Mean sedation scores in each treatment group peaked at extubation (time 0 score, 94.9); in comparison, mean sedation scores in all groups were significantly decreased (ie, cats were less sedated) at 30

minutes ( $P < 0.001$ ) and 1 ( $P < 0.001$ ) and 2 hours ( $P < 0.001$ ) after surgery.

There was no correlation between sedation scores and VAS or IVAS pain scores in any group at any time point ( $r = 0.007$  and  $0.009$ , respectively; Figures 4 and 5). There was a significant but poor correlation ( $P < 0.001$ ;  $r = 0.35$ ) between VAS and IVAS pain scores for all groups (Figure 6).

## Discussion

In cats undergoing ovariohysterectomy that had been administered buprenorphine PO or SC, meloxicam PO or SC, or a control treatment, there were no significant differences in VAS pain scores among treatment groups at any time after surgery. When palpation of the surgical site was performed and an IVAS score was assigned, cats receiving buprenorphine PO had significantly greater pain scores, compared with scores for cats receiving meloxicam PO or SC. Although the presence of various behavioral cues (posture, temperament, locomotion, vocalization, and appetite) may be helpful in recognizing signs of pain in domestic animals, the quantification of pain remains problematic.<sup>20</sup> In cats, objective measurements of variables such as heart rate, respiration rate, temperature, and plasma cortisol concentrations have not consistently been correlated with signs of pain after surgery, and therefore, assessment of the need for postoperative analgesia is often based on behavioral indicators.<sup>14,21,22</sup> However, behavioral changes associated with pain in cats can be very subtle. Some cats may vocalize or thrash about, but more often, cats with pain will rest quietly in the corner of their cage or hide from observers. Some cats will take a hunched or curled position, reacting only when the pain-affected area is manipulated.<sup>13,23</sup> Because cats may also withdraw in stressful or uncomfortable environments, pain-associated behavior changes in this species are harder to quantify with descriptive scales. Results of previous studies<sup>2,14,15</sup> have indicated that VAS and IVAS scores correlate with signs of pain after surgery in cats, and most evaluators will include interaction with the animal and manipulation of the surgical site (to obtain an IVAS score) in their assessment to increase the sensitivity of the scoring system. In the present study, there was a significant but poor correlation between VAS and IVAS pain scores for all treatment groups; thus, palpation of the surgery site may be more useful than observation alone in assessing cats for pain-related behaviors. It is possible that intraobserver variation resulted in the poor correlation between the VAS and IVAS pain scores in the study reported here. However, there is minimal intraobserver variation when the observer is allowed to become familiar with the scoring system prior to the start of a trial.<sup>17</sup>

In the present study, cats had the most evident pain-associated behaviors 1 to 2 hours after surgery. The mean duration of surgery was 11.2 minutes; this is relatively short, compared with previous studies<sup>2,22,24-26</sup> in which surgery duration ranged from 27 to 60 minutes. Additionally, in most previous studies,<sup>2,15,22,24-26</sup> surgeries were performed by different veterinary students with limited surgical experience; cats in our study probably underwent comparatively less tissue

trauma because of the short surgery time and experience level of the surgeon. Recovery from surgery in the present study would more likely be consistent with those that take place in typical small animal practices.

Compared with findings in the control group, there were no significant differences in pain-associated behavior scores and the number of cats requiring additional doses of analgesic in the groups receiving buprenorphine (PO or SC) or meloxicam (PO or SC) preoperatively. True differences may have remained undetected because of the small number of cats included in the study. Formal power calculations indicated that approximately 115 animals in each group would be required to address this question. Another explanation for lack of significant differences between each of the 4 analgesic treatment groups and the control treatment group is that the selected surgery (ovariohysterectomy) may not have induced sufficient pain to allow detection of small to moderate differences among cats. The pain scales used in our study may not have been sensitive enough to detect subtle differences among treatment groups. Studies<sup>27,28</sup> in humans have revealed that adults can distinguish between 11 and 21 degrees of pain, whereas children using pictorial scales can distinguish only 6 degrees of pain. In cattle and sheep, it has been suggested<sup>29,30</sup> that 3 to 4 degrees of pain may be distinguished. Certain types of pain may have a depressive effect on alertness and activity, leading to inaccuracy in pain assessment when the evaluation is based on behavioral responses.<sup>31,32</sup>

Cats that received meloxicam SC returned to baseline VAS scores rapidly (1 hour) after surgery, whereas cats that received meloxicam PO still had pain-associated behaviors 3 hours after surgery. In cats given either meloxicam PO or SC, incisional palpation did not elicit signs of pain and IVAS scores did not differ significantly from baseline values at any time after surgery. Postoperatively, NSAIDs are considered to be extremely effective as analgesic agents, with the added benefit that they are not controlled substances. Preoperative use of NSAIDs, however, remains controversial because of their potentially harmful adverse effects. Compared with other species, cats are generally more susceptible to the toxic effects of NSAIDs because of a relative deficiency in the transferring enzyme glucuronyl transferase.<sup>33</sup> Because of this alteration in drug metabolism, findings from clinical trials in other species cannot be applied to cats. Nonsteroidal anti-inflammatory drugs are not usually administered prior to surgical procedures because of concerns about their effects on renal perfusion and platelet function. Currently available NSAIDs vary in their inhibition of cyclooxygenase (COX)-1 and COX-2. The NSAIDs that derive most of their beneficial effects (analgesic and anti-inflammatory activities) through selective inhibition of COX-2 may have a wider margin of safety than nonselective NSAIDs and are also less likely to induce renal dysfunction, gastric mucosal erosions, and inhibition of platelet function, which are adverse effects often associated with nonselective NSAIDs.<sup>34-37</sup> Meloxicam is an enolic acid COX-2-selective NSAID with potent anti-inflammatory activity, low renal and gastrointestinal toxicity, and a long half-life.<sup>38,39</sup> After parenteral or oral administration

in cats, the half-life of meloxicam is reported<sup>40</sup> to be 11 to 21 hours. In the present study, provision of rescue analgesia was not required for any cats given meloxicam; this was likely because of the drug's long duration of action. The duration of action of meloxicam administered SC in cats undergoing ovariohysterectomy is at least 20 hours when the drug is administered after induction of anesthesia.<sup>24</sup>

In previous studies in dogs, meloxicam was effective in decreasing local inflammatory response in experimentally induced shoulder joint synovitis,<sup>41</sup> attenuating stifle joint synovitis induced by use of sodium urate crystals,<sup>42</sup> and treating chronic locomotive disorders.<sup>43</sup> Meloxicam administered after ovariohysterectomy in cats is as effective as carprofen, ketoprofen, and tolfenamic acid in controlling pain postoperatively.<sup>24,25</sup> In those studies,<sup>24,25</sup> there were no significant differences in sedation scores among cats treated with meloxicam, carprofen, ketoprofen, or tolfenamic acid after ovariohysterectomy. Risk of meloxicam toxicosis may increase with preexisting renal disease or hypotension secondary to anesthesia or blood loss.<sup>44,45</sup> In our study, we chose to administer meloxicam preoperatively because IV fluid supplementation would be initiated before and continued during the surgical procedure. All cats remained clinically healthy throughout the study and were eating and drinking prior to discharge.

Cats that received buprenorphine PO or SC had significantly greater VAS pain scores 3 and 4 hours after surgery, respectively, compared with preoperative baseline values. Cats that received buprenorphine PO had pain-associated behaviors (assessed via IVAS scores) for as long as 5 hours after surgery. In previous studies<sup>2,17</sup> of cats, buprenorphine appeared to provide more analgesia than pethidine after ovariohysterectomy and was more effective and possibly had a longer duration of action, compared with morphine, after soft tissue and orthopedic procedures. However, ketoprofen (2 mg/kg [0.91 mg/lb], IM) appeared to provide more effective analgesia than buprenorphine (0.006 mg/kg [0.003 mg/lb], IM) when given to cats after ovariohysterectomy.<sup>2</sup> The dose of buprenorphine chosen in that study was at the lower limit of the dosage range (0.006 to 0.01 mg/kg, IV, IM, SC, or PO) for treatment of acute postoperative pain in cats. In a study<sup>46</sup> in which increases in thermal threshold were used as a measure of antinociception, buprenorphine administration (0.01 mg/kg) provided no significant increase in thermal threshold for several hours after administration, compared with a saline solution control treatment; however, once an effect was detected, the drug's antinociceptive duration of action was > 6 hours. When delivered transmucosally, buprenorphine has 100% bioavailability and its pharmacokinetics are similar to those of the drug after IM and IV administration, suggesting that mucosal delivery of buprenorphine should be as effective as IM or IV delivery.<sup>47</sup> Buprenorphine is a partial mu agonist that has limited adverse effects; however, its analgesic effects may have a maximum limit despite increasing doses.<sup>13,48</sup> The drug's onset of action (approx 1 hour) is relatively slow, but duration of action exceeds 8 hours after IM injection.<sup>2,13,48,49</sup> Because of the short duration of surgery in

the present study, initiation of pain may have occurred before the prior peak activity level of buprenorphine was achieved, thereby reducing the preemptive analgesic effects of the drug and potentially resulting in higher postoperative pain scores. Additionally, behavior changes in the cats may have resulted in misinterpretation of pain-related behaviors, although this is unlikely to have been the cause of increased IVAS scores in cats receiving buprenorphine. Although morphine has been reported<sup>50</sup> to cause hyperexcitability in cats, altered behavioral responses have not been reported secondary to administration of buprenorphine.

Low doses of ketamine and acepromazine were used in our study to provide sedation and immobilization prior to induction of anesthesia. In cats, acepromazine (0.05 mg/kg, IV) administered in combination with oxymorphone and butorphanol (dose of each, 0.05 mg/kg, IV) enhanced the antinociceptive effects of the opioids 15 minutes after administration but did not significantly affect threshold responses 30 or more minutes after drug administration.<sup>51</sup> To our knowledge, potentiation of the antinociceptive properties of NSAIDs by acepromazine in cats has not been reported. The effectiveness of ketamine as an analgesic is currently under debate. In humans undergoing limb amputation<sup>52</sup> or tonsillectomy,<sup>53</sup> ketamine given as an IV bolus at induction of anesthesia and continued as a low-dose constant rate infusion did not significantly reduce central sensitization, incidence and severity of postoperative pain, or analgesic requirements after surgery. In dogs undergoing forelimb amputation, constant rate infusion of ketamine (combined with fentanyl infusions) during and after surgery decreased postoperative pain scores that were based on pain-associated behaviors.<sup>54</sup> In cats, ketamine (2 mg/kg) increased the thermal threshold 15 and 30 minutes after IV administration<sup>k</sup>; at 60 minutes after ketamine administration, thermal threshold had returned to the baseline value but was significantly decreased below baseline value between 210 and 390 minutes after administration of the drug, suggesting that ketamine may cause delayed-onset hyperalgesia. Because duration of analgesia provided by a single IV dose of ketamine has been reported<sup>55-57</sup> to be relatively short and the systemic availability decreased after IM injection, we are unsure that preoperative administration of ketamine to the cats of our study provided any notable analgesic effects 1 or more hours after surgery. We therefore do not recommend it as the sole analgesic drug administered preoperatively in cats undergoing ovariohysterectomy.

Results of a recent study<sup>58</sup> in rats have suggested that the effects of perioperative administration of ketamine, when combined with fentanyl or morphine, may be dependent on the specific mu-opioid agonist. Whereas ketamine antagonized the antinociceptive effects of fentanyl, it potentiated the effects of morphine.<sup>58</sup> These findings are consistent with results of other studies<sup>59-61</sup> that have indicated that morphine antinociception is enhanced by antagonists of N-methyl-D-aspartate receptors. Proposed mechanisms by which ketamine exerts its antagonistic effects on certain opioids include competition for blood-brain

barrier transport proteins, competition for the mu receptor, and drug differences in mu receptor-subtype binding.<sup>58,62-64</sup> Whereas morphine is a hydrophilic agent, fentanyl and ketamine are highly lipophilic drugs, and competition for blood-brain barrier transport proteins may occur when drugs with high lipophilicity are used in combination.<sup>58</sup> Buprenorphine is a highly lipophilic partial mu agonist<sup>65</sup> that, when combined with ketamine, may compete for the same blood-brain barrier transport protein, resulting in a decrease in the antinociceptive properties of buprenorphine. In the study reported here, cats receiving buprenorphine may have had an increase in pain-associated behaviors because of the antagonistic effects of ketamine. Given the experience of the surgeon, the degree of tissue trauma, and duration of surgery, the residual analgesic effects of ketamine may well have been enough to diminish behaviors overt enough to be identified as being pain associated. Further research is needed to determine whether ketamine has an antagonistic effect on the antinociceptive properties of buprenorphine and to elucidate the exact underlying mechanisms in cats.

Because the cat's level of consciousness inevitably affects pain assessment,<sup>66</sup> sedation scores were included in the study of this report. There were no significant differences in sedation scores after surgery among treatment groups, and cats remained sedated for < 4 hours after surgery. Results of previous studies<sup>2,17,25</sup> in cats have indicated that meloxicam and buprenorphine administered preoperatively or postoperatively have no significant effect on the degree of sedation after ovariohysterectomy.

In the present study, it was not feasible to include positive and negative control treatments (ie, groups of cats undergoing surgery without preoperative administration of analgesics and receiving analgesics without undergoing surgery). Additionally, if a nonsurgical group had been included, abdominal bandages would have been required on all cats to hide surgical incisions from the observer to avoid identification of treatment groups. This could have affected the observer's ability to palpate the incision site and may have changed the cats' behaviors after surgery.<sup>14</sup>

Our data indicated that cats receiving meloxicam PO or SC preoperatively apparently had significantly fewer signs of pain following ovariohysterectomy, compared with cats receiving buprenorphine PO. One dose of meloxicam (0.3 mg/kg, PO or SC) administered once preoperatively is recommended by these authors to decrease postoperative pain in cats undergoing routine ovariohysterectomy. In each cat undergoing ovariohysterectomy, individual assessment should be performed after surgery and additional interventional analgesic treatment given when warranted.

- a. Buprenex, Norwich Easton, Reckitt & Colman Pharmaceuticals Inc, Richmond, Va.
- b. Metacam, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
- c. Sodium chloride, physiologic saline solution, Phoenix Scientific Inc, St Joseph, Mo.
- d. Acepromazine maleate, Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
- e. Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa.
- f. Jelco, Medex Inc, Carlsbad, Calif.

- g. Lactated Ringer's solution, Baxter Healthcare Corp, Deerfield, Ill.  
 h. Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa.  
 i. Proc Mixed, SAS, version 9.1, SAS Institute Inc, Cary, NC.  
 j. Proc Rank, SAS, version 9.1, SAS Institute Inc, Cary, NC.  
 k. Robertson SA, Lascelles BDX, Taylor PM. Effect of low-dose ketamine on thermal thresholds in cats (abstr), in *Proceedings. Am Coll Vet Anesth* 2003;30:110.

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