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RESEARCH PAPER

A comparison of four methods of analgesia in cats following ovariohysterectomy

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Abstract

Objective To evaluate the effectiveness of preoperative administration of oral carprofen, subcutaneous ketoprofen, and local nerve block with bupivacaine in preventing postoperative pain-associated behavior in cats after ovariohysterectomy.

Animals Fifty-two female intact cats.

Materials and methods Cats received butorphanol (0.44 mg kg^{-1} IM), carprofen (2.2 mg kg^{-1} PO), ketoprofen (2.2 mg kg^{-1} SQ), or bupivacaine infiltration block (1.1 mg kg^{-1} SQ) before surgery. Cortisol and drug concentrations and visual analog scale (VAS) and interactive visual analog scale (IVAS) pain-associated behavior scores were measured 2 hours before and 0, 1, 2, 4, 8, 12, and 24 hours after ovariohysterectomy.

Results Cats receiving butorphanol had significantly increased IVAS scores 2 hours after surgery compared with baseline measurements. Cats receiving carprofen, ketoprofen, and bupivacaine had significant increases from baseline in VAS and IVAS scores 1 and 2 hours after surgery. VAS and IVAS scores for cats receiving bupivacaine were significantly greater 1 and 2 hours after surgery than for cats that received butorphanol. Cats receiving carprofen had significant increases in cortisol 1 hour after surgery and significant decreases 24 hours after surgery compared with baseline measurements.

Conclusions and clinical relevance Preoperative carprofen and ketoprofen have effects on pain-associated behavior similar to butorphanol in cats undergoing ovariohysterectomy. Cats receiving bupivacaine blocks may require additional analgesics immediately after surgery.

Keywords analgesia, bupivacaine, butorphanol, carprofen, cats, ketoprofen.

Introduction

Most veterinarians agree that ovariohysterectomy causes postoperative pain in cats (Lascelles et al. 1999). Practitioners are often reluctant to administer perioperative analgesics, however, because of lack of familiarity with available drugs, concerns about side effects, or frustration with the need for record keeping of controlled substances (Lascelles et al. 1999; Wright 2002). The ideal analgesic would be inexpensive, easy to administer, readily available, long-lasting, and effective. It should have few side effects; and would require no special licensing or storage. Besides opioids and alpha-2 adrenoreceptor agonists, options for controlling perioperative pain in cats include oral and injectable nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketoprofen (Ketofen; Fort Dodge Animal Health, Fort Dodge, IA, USA) and carprofen (Rimadyl; Pfizer Animal Health, Exton, PA, USA), and local anesthetics, such as bupivacaine (Bupivacaine HCl; Abbott Labs, North Chicago, IL, USA)

(Hellyer & Gaynor 1998; Lamont 2002). The use of these drugs is attractive because they meet many of the above criteria.

Administration of systemic or local analgesics before surgery may reduce an animal's need for postoperative pain intervention. Stimulation of peripheral nociceptors with surgical trauma can induce peripheral hypersensitivity and upregulation of central neuronal activity, resulting in a prolonged and intensified pain response with further stimulation of the site (Lascelles et al. 1998; Lamont 2002). Once neural pathways are sensitized, the physiologic and behavioral responses to pain may persist, even when the nerves themselves are blocked or transected (Lascelles et al. 1998). Pre-emptive analgesic administration prevents this central sensitization, thus effectively limiting pain perception. Reports of the effectiveness of pre-emptive analgesia in cats are limited (Lascelles et al. 1997; Cambridge et al. 2000; Slingsby & Waterman-Pearson 2002).

The purpose of this study was to evaluate the effectiveness of preoperative administration of oral carprofen, subcutaneous ketoprofen, and regional infiltration block with bupivacaine in preventing pain in cats after ovariohysterectomy. We hypothesized that each of these drugs would reduce pain-associated behavior scores comparable to that of cats treated preoperatively with butorphanol.

Materials and methods

Fifty-two healthy (ASA1) female cats weighing >2.2 kg were included in the study, with 13 cats in each group. The study protocol was approved by the Institutional Animal Care and Use Committee, and permission was obtained from the cats' caregivers before participation. Age of most cats was unknown, although all were suspected to be at least 6 months of age; two cats were at least 5 years old. Health status of the cats was evaluated by physical examination and measurement of preoperative packed cell volume (PCV) and total protein (TP) in all cats and additionally by evaluation of complete blood counts and biochemistry panels in the two older cats. Cats were randomly assigned to receive one of the following analgesics: carprofen (2.2 mg kg^{-1} PO) 2 hours before sedation; ketoprofen (2.2 mg kg^{-1} SQ) after sedation; butorphanol tartrate [Torbugesic; Fort Dodge Animal Health (0.44 mg kg^{-1} IM)] after sedation; or 0.5% bupivacaine infiltration block of the surgical site (1.1 mg kg^{-1} SQ) after anesthesia.

Two milliliters of blood was obtained for measurement of baseline plasma cortisol and drug concentrations 2–3 hours before sedation and before administration of any drugs.

Baseline (preoperative) visual analog scale (VAS) and interactive visual analog scale (IVAS) scores were recorded immediately before venipuncture. Forty-five minutes before surgery, cats were sedated with acepromazine [acepromazine maleate; Boehringer Ingelheim Vetmedica, Inc., St Joseph, MO, USA (0.022 mg kg^{-1} IM)] and ketamine hydrochloride [Ketaset; Fort Dodge Animal Health (4.4 mg kg^{-1} IM)]. Anesthesia was induced with isoflurane in oxygen, delivered by mask, and maintained after tracheal intubation with isoflurane in oxygen. A jugular vein was catheterized with a 20–22 SWG, through the needle, 13 cm Teflon catheter to permit postoperative blood sampling. As described by Smith et al. (1996), lactated Ringers solution (16.5 mL kg^{-1} $hour^{-1}$ for 2 hours) was administered via the jugular catheter, beginning after catheter placement, to provide volume replacement and cardiovascular support. For cats in the bupivicaine group, bupivicaine was administered subcutaneously over a 2.5-cm distance along the midline midway between the umbilicus and pubis. All cats underwent routine midline ovariohysterectomy through a 2-cm incision by the same surgeon (KMT).

Cats were placed in recovery cages in a feline ward for postoperative observation by a trained observer who was unaware of the preoperative treatment protocol. Visual analog scale and IVAS scores were recorded and then blood samples obtained at 0 (extubation), 1, 2, 4, 8, 12, and 24 hours after surgery. Additionally, the observer made note of cats that subjectively had poor recoveries (i.e. violent, thrashing motions or biting handlers) the first 15 minutes after extubation. For VAS and IVAS scores, the observer marked the estimated degree of pain on a 100-mm line, with 0 being no pain, and 100 mm being the worst imaginable pain. Visual analog scale scores were based on observations of the cat's resting behavior. Cats that approached the cage door, arched their backs for attention, or stretched out in a relaxed position and actively groomed were considered to have VAS pain scores of 0; VAS scores of 100 would be given if cats were recumbent and open-mouth breathing or lost consciousness after anesthetic recovery. The IVAS score was recorded after opening the cage door, talking to the cat, petting

its head, and palpating its abdomen. Cats that did not object to or avoid abdominal palpation and had no flinching of skin or muscle with palpations were considered to have IVAS scores of 0. Agitated vocalization and biting during palpation or unconsciousness after anesthetic recovery were to be given IVAS scores of 100.

The jugular catheter was then aspirated and 1 mL of blood was removed temporarily. An additional 2 mL blood sample was aspirated and placed in a heparinized tube, and the initial 1 mL of blood was re-infused. The catheter was then flushed with 1 mL of heparinized saline. The blood sample was centrifuged, the plasma extracted and stored at −20 °C until blood samples from all cats were available for measurement of cortisol and plasma drug concentrations. Plasma cortisol concentrations were measured by radioimmunoassay, and concentrations of the drugs were measured with high performance liquid chromatography using modifications of methods previously published (Furst et al. 1988; Willey et al. 1994; DeGraves et al. 1996; Tahraoui et al. 1996).

Cats with VAS scores greater than 30 mm or IVAS scores of 50 mm or greater during postoperative monitoring received rescue analgesia (butorphanol, 0.4 mg kg^{-1} IM) as needed. Data collected after rescue analgesic administration were not included in the statistical analysis. At the completion of the study, jugular catheters were removed and the cats were returned to their caregivers.

The effects of treatment, time, and treatment by time interaction on cortisol level and VAS and IVAS pain scores in ovariohysterectomized cats were evaluated using a mixed model analysis of variance procedure (Proc Mixed, SAS version 9.0; SAS Institute Inc., Cary, NC, USA). Cat was included in the model as a random factor. Time as a repeated measure was evaluated and removed from the model based on the −2 log-likelihood statistic, which indicated that there was no improvement in fit of the model to the data. Values for cortisol were transformed using the log base 10 in order to approximate a normal distribution. VAS and IVAS analog scores were transformed using the rank procedure due to zeroes in the data (Proc Rank, SAS version 8.0; SAS Institute Inc.). Significant differences in least square means among the various levels of treatment, time, and treatment by time were adjusted using the method of Bonferroni. Descriptive data are reported as the mean ± 1 standard deviation, with significance set at $p \leq 0.05$.

Results

Of the 52 cats included in the study, two cats (one from the butorphanol group and one from the carprofen group) were excluded after surgery because of anemia secondary to accidental overdose of IV fluids (up to 66 mL kg^{-1} total dose over a 2-hour period). A third cat was given ketoprofen instead of bupivacaine. Therefore, 14 cats received ketoprofen; the remaining groups each contained 12 cats. Mean surgery time was 12.1 ± 3.9 minutes (median, 10 minutes) and mean anesthesia time was 30.0 ± 19.2 minutes. Ten cats had poor recoveries, including six cats that received ketoprofen, three cats that received bupivacaine, and one cat that received carprofen. Rescue analgesia was administered 2 hours after surgery in one cat that received a bupivacaine infusion block and 1 hour after surgery in one cat that received ketoprofen. One cat from the ketoprofen group died 7 hours after surgery; results from this cat were not included in the VAS, IVAS, or cortisol data analyses.

All cats had VAS and IVAS scores of 0 before surgery (baseline) and at extubation (time 0). Cats which received butorphanol had no significant changes in VAS scores compared with baseline but had significant increases in IVAS scores 2 hours after surgery (Figs 1 & 2; $p = 0.0231$). Cats receiving carprofen, ketoprofen, and bupivacaine had significant increases from baseline in VAS and IVAS scores 1 and 2 hours after surgery (Figs 1 & 2; $p \leq 0.0122$). In all cats, VAS and IVAS scores were not significantly different from baseline 4–24 hours after surgery.

There were no significant differences in VAS and IVAS scores at any time when comparing cats that received butorphanol, carprofen, or ketoprofen (Figs 1 & 2). Visual analog scale and IVAS scores for cats receiving bupivacaine were significantly greater 1 hour after surgery compared with cats that received butorphanol ($p = 0.002$ and $p = 0.029$, respectively).

Cortisol and peak postoperative plasma drug concentrations were available for nine cats that received butorphanol, eight cats that received carprofen, 10 cats that received ketoprofen, and 10 cats that received bupivacaine. Results were not available for 10 cats because of difficulties with sample procurement (i.e., jugular catheter failure)

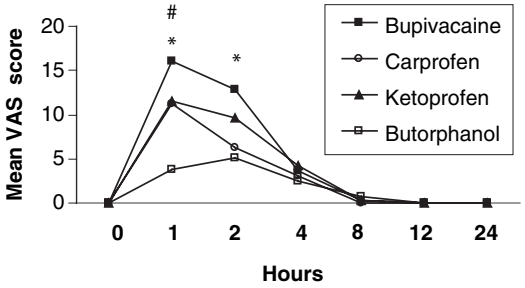

Figure 1 Mean visual analog scale (VAS) scores 0–24 hours after ovariohysterectomy. *Significant increases from baseline in VAS scores were seen 1 and 2 hours after surgery in cats receiving ketoprofen, carprofen, and bupivacaine. #Cats receiving bupivacaine had significantly greater VAS scores 1 hour after surgery than cats that received butorphanol.

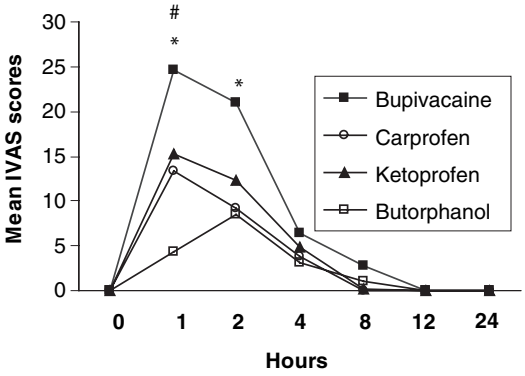

Figure 2 Mean interactive visual analog scale (IVAS) scores 0–24 hours after ovariohysterectomy. *Significant increases from baseline in IVAS scores were seen 1 hour after surgery in cats receiving ketoprofen, carprofen, and bupivacaine and in all cats 2 hours after surgery. #Cats receiving bupivacaine had significantly greater IVAS scores 1 hour after surgery than cats that received butorphanol.

or plasma analysis. Significant differences in plasma cortisol concentrations were only seen in cats receiving carprofen (Fig. 3). Plasma cortisol concentrations of cats receiving carprofen were significantly higher 1 hour after surgery compared with concentrations measured before surgery and 2, 8, 12, and 24 hours after surgery ($p \leq 0.029$). Cortisol concentrations 24 hours after surgery were significantly lower than concentrations measured before surgery and at 0, 1, and 4 hours after surgery ($p \leq 0.0033$). At 24 hours after surgery, cortisol concentrations of cats receiving carprofen were significantly lower than those of cats receiving butorphanol ($p = 0.039$). Cortisol concentrations at other time periods were not significantly different among or between groups.

Peak postoperative plasma concentrations of cats receiving butorphanol occurred at 0 hours for seven cats and 1 hour for two cats. Butorphanol was detectable in the plasma of all nine cats 8 hours after surgery (Fig. 4). Peak plasma concentrations of cats receiving bupivacaine occurred at 0 hours for four cats, 1 hour for three cats, and 4 hours for one cat. Two cats had no detectable drug at any time period. Seven of nine cats had detectable bupivacaine concentrations 8 hours after surgery (Fig. 5). Because plasma concentrations of butorphanol and bupivacaine were extremely low at 8 hours, plasma samples taken 12 or more hours after surgery from these cats were not analyzed. Of the cats receiving carprofen, peak postoperative plasma concentrations occurred at 0 hours for one cat, 1 hour for three cats, 4 hours for one cat, 8 hours for two cats, and 24 hours for one cat. Carprofen was still measurable in the plasma in seven of seven cats 24 hours after surgery (Fig. 6). Peak postoperative plasma concentration occurred at 0 hours for all cats that received ketoprofen. No drug was detectable in 1/10 cats at 4 hours and in 3/9 cats at 8 hours (Fig. 7). Four of ten cats had detectable concentrations of ketoprofen in plasma 24 hours after surgery.

Complications were seen in a 4-kg, 8-year-old Maine coon cat that received ketoprofen before surgery. Preoperative complete blood count (CBC) and biochemical profile were normal, except for increased total protein (9.2 g dL^{-1}; reference range, 5.6–7.1 g dL^{-1}) and decreased albumin (2.6 g dL^{-1}; reference range, 2.7–6.5 g dL^{-1}). Four hours after surgery, the cat became lethargic, tachypneic, and pale. Biochemistry profile and PCV/TP were repeated; abnormalities included hypoproteinemia (5.3 g dL^{-1}; reference range, 5.6–7.1 g dL^{-1}), hypoalbuminemia (1.5 g dL^{-1}; reference range 2.7–6.5 g dL^{-1}), hypochloridemia (3.0 mEq L^{-1}; reference range, 3.3–5.3 mEq L^{-1}), hypocalcemia (7.7 mg dL^{-1}; reference range, 8.2–11.5 mg dL^{-1}), hypocholesterolemia (57 mg dL^{-1}; reference range, 73–265 mg dL^{-1}), and hyperglycemia (304 mg dL^{-1}; reference range, 63–140 mg dL^{-1}). Postoperative liver enzymes, blood urea nitrogen, and creatinine concentrations were within normal limits. Overhydration was suspected because of hypoproteinemia and pallor (PCV 27%;

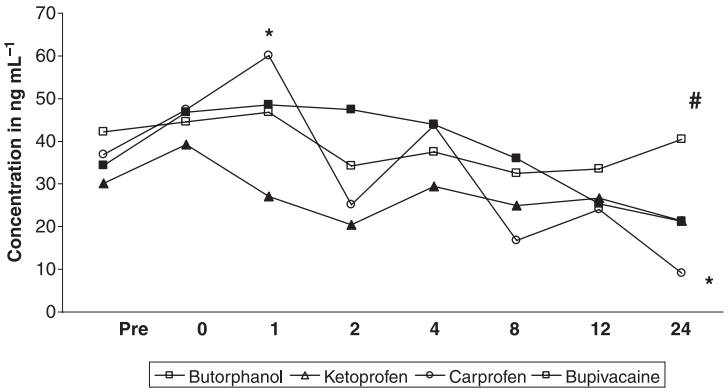

Figure 3 Mean cortisol concentrations before (pre) and 0–24 hours after ovariohysterectomy. *Cats that received carprofen had significant increases in cortisol 1 hour after surgery and significant decrease in cortisol 24 hours after surgery compared with preoperative concentrations. #Cats that received butorphanol had significantly higher cortisol concentrations 24 hours after surgery than cats that received carprofen.

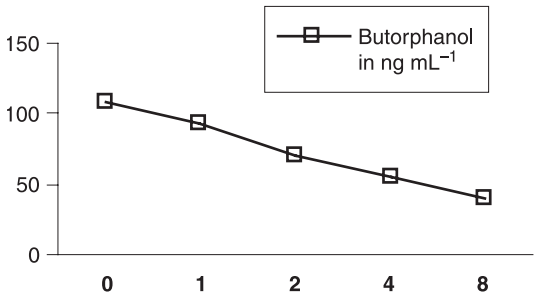

Figure 4 Mean plasma concentrations of butorphanol 0–8 hours after ovariohysterectomy.

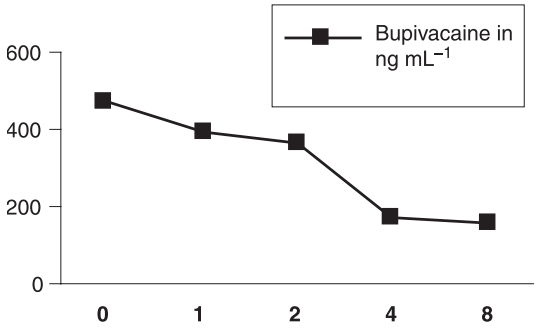

Figure 5 Mean plasma concentrations of bupivacaine 0–8 hours after ovariohysterectomy.

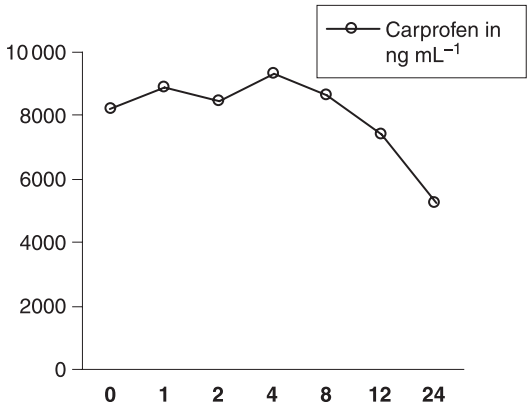

Figure 6 Mean plasma concentrations of carprofen 0–24 hours after ovariohysterectomy.

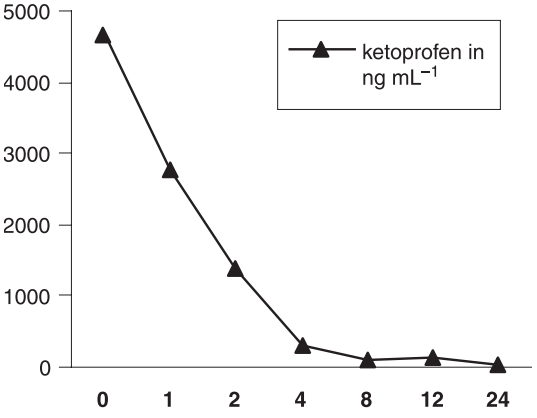

Figure 7 Mean plasma concentrations of ketoprofen 0–24 hours after ovariohysterectomy.

reference range 24–45%), and the cat was placed in an oxygen cage with 40% oxygen. Furosemide (4 mg kg^{-1} IV) and cefazolin (22 mg kg^{-1} IV) were also administered. Respiratory arrest developed

1 hour later, the trachea was intubated and the cat was placed on a ventilator on 100% oxygen but subsequently went into cardiac arrest and was not resuscitated. Post-mortem findings included pulmonary edema, unilateral chronic interstitial nephritis with estimated loss of 50% of renal tissue, and acute suppurative portal hepatitis and cholangitis consistent with ascending biliary infection or portal seeding. None of the post-mortem findings were consistent with acute drug toxicity.

Discussion

In this study, significant increases from baseline in VAS and IVAS scores were seen within 1 or 2 hours after surgery. However, scores four or more hours after surgery were not significantly different from baseline for any group. The average surgery time in this study (12 minutes) was relatively short compared with previous studies, in which surgery duration ranged from 27 to 60 minutes (Slingsby & Waterman-Pearson 1998, 2000; Smith et al. 1999; Ansah et al. 2002). Additionally, ovariohysterectomy was performed by final year veterinary students in most previous studies (Lascelles et al. 1995; Slingsby & Waterman-Pearson 1998, 2000; Smith et al. 1999; Ansah et al. 2002). Cats in our study probably suffered less tissue trauma because of the short surgery time and experience of the surgeon, and postoperative recoveries would more likely be consistent with those seen in the average small animal practice.

Because objective parameters such as heart rate, respiration rate, temperature, and cortisol concentrations have not consistently been correlated with postoperative pain in cats, need for postoperative analgesia is often based on behavioral indicators (Smith et al. 1996, 1999; Cambridge et al. 2000). Behavioral changes associated with pain in cats, however, can be very subtle. Some cats may vocalize or thrash about, but more often cats that are in pain will rest quietly in the corner of the cage or hide from observers. Some cats will take a hunched or curled position, reacting only when the affected area is manipulated (Hellyer & Gaynor 1998; Wright 2002). Because cats may also withdraw in stressful or uncomfortable environments, pain-associated behavior changes in this species are harder to quantify with descriptive scales. Visual analog scale and IVAS scores have been shown to correlate with postoperative pain in cats, and most evaluators will include interaction with the animal and manipulation of the surgical site (IVAS) to increase the sensitivity of the scoring system (Lascelles et al. 1995; Slingsby & Waterman-Pearson 1998; Cambridge et al. 2000). In our study, cats were to be assigned IVAS scores of 100 mm if they lost consciousness after anesthetic recovery. Because of this definition, IVAS scores were 0 immediately after extubation because the cats showed no reaction to abdominal palpation, presumably as they were still under the effects of the anesthetic agents.

Low dosages of ketamine and acepromazine were used in our study to provide sedation and immobilization prior to surgery. In cats, acepromazine (0.05 mg kg^{-1} IV) administered simultaneously with a combination of oxymorphone and butorphanol (0.05 mg kg^{-1} IV each) increased the magnitude of antinociceptive effects of the opioids 15 minutes after administration, but did not provide significantly greater threshold responses 30 or more minutes after administration of the drugs (Briggs et al. 1998). Potentiation of antinociceptive properties of NSAIDs and infiltration blocks by acepromazine in the cat have not been reported. The effectiveness of ketamine as an analgesic is currently under debate. In humans undergoing limb amputation (Hayes et al. 2004) or tonsillectomy (Van Elstraete et al. 2004), ketamine given as an IV bolus at induction and continued as a low-dose constant rate infusion did not significantly reduce acute central sensitization, incidence and severity of postoperative pain, or analgesic requirements after surgery. In another study, ketamine constant rate infusion increased mechanical pain threshold and reduced windup-like pain in humans that received morphine prior to experimentally induced burns (Schulte et al. 2004). Constant rate infusion of ketamine in dogs during and after surgery, when combined with fentanyl infusions, reduced postoperative pain behavior-associated scores in dogs undergoing forelimb amputation (Wagner et al. 2002). In cats, intravenous ketamine (2 mg kg^{-1}) increased thermal threshold 15 and 30 minutes after administration (Robertson et al. 2003). Thermal threshold returned to baseline at 60 minutes but was significantly decreased below baseline between 210 and 390 minutes after administration, suggesting that ketamine might cause a delayed-onset hyperalgesia. Because duration of analgesia provided by a single dose of ketamine has been reported to be relatively short and systemic availability is less when it is given by the intra-

muscular route than after intravenous administration (Heavner & Bloedow 1979; Hanna et al. 1988; Sawyer et al. 1993), we are unsure that preoperative ketamine provided any significant analgesic effects for the cats one or more hours after surgery in our study.

As described by Smith et al. (1996), lactated Ringer's solution (33 mL kg^{-1}) was administered during anesthesia and recovery to provide volume replacement and cardiovascular support. It is not known whether this dose of crystalloid fluid had any dilutional effect on plasma drug and cortisol concentrations. In two cats, fluid rates were miscalculated, resulting in significant hemodilution. These cats were removed from the study.

Cats that received butorphanol had no significant change in VAS scores, but did have increased IVAS scores 2 hours after surgery. It is possible that the combination of acepromazine/ketamine HCl premedication with preoperative IM butorphanol provided sedation that masked visual behavior changes 2 hours after surgery, as pain-associated behavior was notable only after palpation of the incision site. Butorphanol has agonist activity at the κ receptors, which are responsible for analgesia and sedation, and at the σ receptors, which are responsible for autonomic stimulation and dysphoria (Hosgood 1990). Sedative effects of butorphanol alone are variable, but are increased when combined with other drugs (Tranquilli et al. 1988; Hosgood 1990).

Visual and interactive pain scores were significantly increased 1 and 2 hours after surgery compared with baseline in cats that received ketoprofen, carprofen, and bupivacaine, although VAS and IVAS scores of cats that received ketoprofen and carprofen were not significantly different from those of cats that received butorphanol. Bupivacaine injected perineurally can provide pain relief for 2–6 hours (Lemke & Dawson 2000; Lamont 2002). In this study, bupivacaine may have provided less analgesia compared with butorphanol because of its lack of systemic effects. Additionally, bupivacaine's onset of action is 20–30 minutes (Lemke & Dawson 2000); thus, surgical stimulation of nociceptors may have occurred prior to onset of drug effects. Despite significant increases in bupivacaine VAS and IVAS scores, rescue analgesics were only required in one cat in our study. Use of bupivacaine infiltration at the incision site before surgery did not significantly lower postoperative pain scores in dogs undergoing laparotomy, but did decrease the frequency of postoperative analgesic administration (Savvas et al. 2003).

In cats that received carprofen, cortisol concentrations were significantly increased 1 hour after surgery. Cats in our study may have experienced an early increase in cortisol because of slow absorption or delayed onset of action of oral carprofen. Stress, anorexia, and pain may reduce gastric emptying time, intestinal motility, and portal blood flow, reducing or slowing drug absorption (Jamali & Kunz-Dober 1999; Whittem et al. 2000). In our study, plasma concentrations peaked at a mean time of 5.9 hours after surgery (approximately 8.9 hours after oral administration). Although onset of action of carprofen after oral administration has not been reported in cats, delayed onset of action has been noted after subcutaneous administration in this species (Lascelles et al. 1995; Taylor et al. 1996). Cats that received carprofen in our study experienced a prolonged effect, as demonstrated by significant reduction in 24 hour plasma cortisol concentrations compared with those measured before surgery. Elimination half-life of carprofen is 9 hours when administered orally and 19–20 hours when given IV or subcutaneously (Taylor et al. 1996; Parton et al. 2000). Because the pharmacokinetic–pharmacodynamic relationship of NSAIDs is complex, peak plasma concentration may not be a reliable guide for dosing strategies (Lascelles et al. 1998). Additionally, long duration of action and huge variability in elimination rates in cats make multiple dosing of carprofen difficult (Parton et al. 2000).

Pain scores from cats receiving ketoprofen were not significantly different from those receiving carprofen or butorphanol, although cats in the ketoprofen group tended to have rough recoveries compared with other cats. In previous studies, ketoprofen provided analgesia similar to that of carprofen, meloxicam, tolfenamic acid, and buprenorphine, and better than pethidine, when administered after ovariohysterectomy in cats (Slingsby & Waterman-Pearson 1998, 2000). Ketoprofen is not usually administered before surgery because of concerns about its effects on renal perfusion and platelet function. Ketoprofen inhibits both cyclooxygenase (COX) and lipoxygenase and has a direct inhibitory effect on bradykinin (Isaacs 1996). Inhibition of renal prostaglandin synthesis through COX 1 inhibition may result in decreased renal blood flow and glomerular filtration rate (Isaacs 1996). Ketoprofen has good gastrointestinal and

renal safety in well-hydrated patients that have stable cardiovascular function (Maddison 2002). In our study we chose to use ketoprofen preoperatively, as fluid supplementation would be initiated before, and continued after, the surgical procedure. Risk of toxicity may increase with pre-existing renal disease or hypotension secondary to anesthesia or blood loss (Isaacs 1996; Maddison 2002).

One cat that received ketoprofen died 7 hours after surgery, and renal dysfunction may have played a role in its demise. Chronic renal disease in that cat was not evident on preoperative blood chemistry, although the cat had hyperglobulinemia consistent with neoplasia or chronic inflammation (Dimski 1997). Loss of more than 75% of renal function is required before changes in blood urea nitrogen and creatinine are seen in cats with primary renal disease (Dibartola 2000). Signs of NSAID toxicity such as gastrointestinal erosions or inflammation and renal papillary necrosis (Isaacs 1996; Pages et al. 1996), were not noted on postmortem examination. However, these changes may not have occurred rapidly enough to have been observed at the time of this cat's death. It is interesting to note that the cat's liver enzymes and renal blood parameters were normal after surgery, despite the pathology present in those organs. As ketoprofen is highly protein bound (Lees et al. 2003), hypoalbuminemia in this cat may have resulted in a relative overdose of the drug, potentially contributing to the cat's death.

Because this was a clinical study with client-owned animals, we chose not to have positive and negative controls (animals undergoing surgery without additional analgesics, and animals receiving analgesics without surgery). Additionally, if a nonsurgical group had been included, abdominal bandages would have been required on all cats to hide surgical incisions from the blinded observer. This could have affected the observer's ability to palpate the incision site and may have changed the cats' postoperative behaviors.

In conclusion, preoperative oral carprofen and subcutaneous ketoprofen produced similar alterations in pain-associated behavior when compared with preoperative intramuscular butorphanol in cats undergoing ovariohysterectomy. Because of variable and possibly prolonged gastrointestinal absorption of carprofen, administration of the drug more than 2 hours before surgery may be necessary. Cats receiving bupivacaine blocks may require additional analgesics for the first 4 hours after surgery. While preoperative ketoprofen caused no apparent adverse effects in young, healthy, well-hydrated cats, it should be used before surgery with caution because of potential adverse effects.

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