Analgesic efficacy of preoperative administration of meloxicam or butorphanol in onychectomized cats

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Objective—To determine analgesic efficacy and adverse effects of preemptive administration of meloxicam or butorphanol in cats undergoing onychectomy or onychectomy and neutering.

Design—Randomized controlled study.

Animals—64 female and 74 male cats that were 4 to 192 months old and weighed 1.09 to 7.05 kg (2.4 to 15.5 lb).

Procedure—Cats received meloxicam (0.3 mg/kg [0.14 mg/lb], SC) or butorphanol (0.4 mg/kg [0.18 mg/lb], SC) 15 minutes after premedication and prior to anesthesia. A single blinded observer measured physiologic variables, assigned analgesia and lameness scores, and withdrew blood samples for each cat at baseline and throughout the 24 hours after surgery. Rescue analgesia (butorphanol, 0.4 mg/kg, IV or SC) or administration of acepromazine (0.025 to 0.05 mg/kg [0.011 to 0.023 mg/lb], IV) was allowed.

Results—Meloxicam-treated cats were less lame and had lower pain scores. Cortisol concentration was higher at extubation and lower at 1, 5, and 12 hours in the meloxicam-treated cats. Fewer meloxicam-treated cats required rescue analgesia at 3, 5, 12, and 24 hours after extubation. General impression scores were excellent or good in 75% of meloxicam-treated cats and 44% of butorphanol-treated cats. There was no treatment effect on buccal bleeding time; PCV and BUN concentration decreased in both groups, and glucose concentration decreased in meloxicam-treated cats.

Conclusions and Clinical Relevance—Preoperative administration of meloxicam improved analgesia for 24 hours without clinically relevant adverse effects in cats that underwent onychectomy or onychectomy and neutering and provided safe, extended analgesia, compared with butorphanol. (*J Am Vet Med Assoc* 2005;226:913–919)

Conservative estimates indicate that approximately 14.4 million cats (24% of owned cats) in the United States undergo onychectomy.[1] Short-term and long-term complications of onychectomy are ill-defined, as are the adverse consequences of failure to perform this surgery in some cats.[1] However, the potential development of acute postoperative pain after onychectomy is a generally accepted consequence.[1,2] Heightened awareness and concern for animal pain have resulted in several recent studies[3-7,a] that examined the treatment of acute postoperative pain from onychectomy.

Butorphanol is a mixed agonist-antagonist opioid approved for use as an analgesic in cats. Butorphanol (0.4 mg/kg [0.18 mg/lb]) provides analgesia and improves the outcome in cats undergoing onychectomy, compared with placebo,[3] and provides analgesia similar to that of fentanyl patches.[4,6] However, butorphanol is a scheduled drug and requires repeated administration.

Meloxicam is an enolic acid **nonsteroidal anti-inflammatory drug (NSAID)** with potent anti-inflammatory activity in animal models, low gastrointestinal and renal toxicity, and a long half-life.[8] In cats, the half-life is reported to be 11 to 21 hours after parenteral and oral administration.[9] Additionally, meloxicam has antiarthritic, analgesic, and antipyretic activity[10] and is believed to be cartilage-sparing.[8,11] Its use in cats was recently approved. Antinociception is exerted peripherally and centrally by NSAIDs.[12] The therapeutic anti-inflammatory actions of NSAIDs are attributable to inhibition of inducible **cyclooxygenase (COX)**-2, whereas the undesirable adverse effects such as gastrointestinal tract irritation and nephrotoxicosis are attributable primarily to inhibition of the constituitive enzyme COX-1.[8] Review[13] of recent studies indicates that COX-2 may have some constitutive functions associated with bone metabolism and renal, ovarian, uterine, nerve, and brain function as well as a gastrointestinal protective role. It is therefore important to determine the safety profile of an NSAID in a given target species, particularly if the relative COX-1 and -2 effects are unknown for that species. The assessment of relative COX-1 or -2 effects is complicated by the in vitro model chosen to characterize the efficacy and toxicity.[14] In dogs, meloxicam inhibits COX-2 twelve times as effectively as COX-1.[14] To our knowledge, the relative preferential inhibitory effects on COX-2 versus -1 are unknown in cats. However, meloxicam is well tolerated and an effective analgesic when administered for 5 days (0.3 mg/kg [0.14 mg/lb], SC or PO, followed by 0.1 mg/kg [0.05 mg/lb], PO, for 4 days) in cats with acute or chronic locomotor disease.[15,b] The optimal single dose of meloxicam in a pyretic endotoxin model was 0.3 mg/kg, IV.[9]

Postoperative administration of meloxicam (0.2 mg/kg [0.09 mg/lb], SC) has been used successfully for analgesia in cats undergoing ovariohysterectomy.[16] Preoperative use of NSAIDs has been limited because of the potential loss of protection of renal blood flow during hypovolemia and anesthetic-induced hypotension by limiting COX-1 and its normally protective

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prostaglandin products.[16] An additional concern about preoperative use of NSAIDs is inhibition of platelet function by inhibition of COX.[17] Meloxicam has minimal antithromboxane activity in dogs[18] so it should not interfere with hemostasis in clinically normal patients.

Preoperative NSAID administration prevents amplification of nociception that accompanies tissue trauma and inflammation.[17] The NSAIDs are not true prostaglandin antagonists, but prevent the release of new endogenous prostaglandins, so that circulating prostaglandins continue to exert their hyperalgesic effect.[17] In cats, meloxicam (0.3 mg/kg, SC) administered after induction but before ovariohysterectomy has favorable effects.[19]

The purpose of the study reported here was to compare analgesia and adverse effects of preoperative administration of meloxicam with those of butorphanol in cats that underwent onychectomy or onychectomy plus surgical neutering.

Materials and Methods

Cats—With permission of the Hospital Review Committee for Clinical Studies and informed consent by the owners, 64 female and 74 male cats between 4 and 192 months of age that weighed 1.09 to 7.05 kg (2.4 to 15.5 lb) were used (**Table 1**). Cats that received onychectomy (n = 78) or onychectomy-neutering (60) received either meloxicam (72) or butorphanol (66) at 1 of 4 clinics in a randomized controlled study. Allocation of cats to 1 of 2 treatment groups was done according to order of evaluation at each clinic. The investigator or designee (but not the observer) supervised the evaluation and recruitment of cats and was the test article administrator. Randomization was balanced to maintain allocation of the 2 treatments within each successive 4 cats.

Cats were excluded if they had a history of blood dyscrasia or hepatic, renal, or cardiac disease. Cats receiving an NSAID or a corticosteroid within 14 days or glycosaminoglycans within 30 days were excluded. Physical examinations and screening of blood analyses (PCV, hemoglobin, glucose, sodium, potassium, chloride, BUN, and creatinine) were completed before surgery (baseline) and 24 hours after surgery. Blood samples were drawn by direct venipuncture.

Surgery—Surgical technique was left to the discretion of the veterinarians at each location. At 1 clinic, all cats were treated surgically by different senior veterinary students under the supervision of a veterinary surgeon. Onychectomies were performed with a disarticulation technique with a scalpel or guillotine technique. The front feet were bandaged for 18 to 24 hours after surgery. Cats were premedicated with acepromazine (0.05 mg/kg [0.02 mg/lb], IM) and glycopyrrolate (0.011 mg/kg [0.005 mg/lb], IM), and anesthesia was induced with propofol (4 to 6 mg/kg [1.8 to 2.7 mg/lb], IV) and maintained on isoflurane and oxygen. At 1 clinic, cats received a balanced isotonic solution IV (22 mL/kg [10 mL/lb] the first hour, followed by 11 mL/kg [5 mL/lb] the remaining time). Cats received either meloxicam[c] (0.3 mg/kg, SC) or butorphanol[d] (0.4 mg/kg, SC) 15 minutes after premedication. Signs of pain of injection were scored from 1 to 4.[e] The injection site was evaluated for swelling and redness at 24 hours after surgery.

Table 1—Variables (mean ± SD) associated with 138 cats in a study of analgesic efficacy of preoperative administration of meloxicam (n = 72) or butorphanol (66) before onychectomy or onychectomy and surgical neutering.

Variable	Meloxicam	Butorphanol
Age (mon)	24.8 ± 32.1	20.2 ± 21.7
Weight (kg [lb])	3.5 ± 1.5 (7.7 ± 3.3)	3.4 ± 1.4 (7.5 ± 3.1)
No. of cats		
Onychectomy	41	37
Onychectomy-ovariohysterectomy	14	16
Onychectomy-castration	17	13

Laboratory analyses—Blood samples for glucose[f] and cortisol[g] determinations were taken at baseline; extubation; and 1, 3, 5, and 12 hours after extubation. Blood biochemical tests for screening analyses were conducted with an automated analyzer[f] with blood samples obtained directly from the syringe, according to the manufacturer's guidelines. Blood samples were collected and placed in EDTA tubes for evaluation of cortisol concentration and platelet count. If the screening test cartridge failed, blood collected and placed in an EDTA tube was used to repeat the tests with an additional cartridge, which falsely increases potassium concentration. Plasma was separated from the rest of the blood for determination of cortisol concentration. A small sample (0.5 mL) was left in the EDTA tube for platelet count[g] at baseline and extubation. Samples for cortisol determination and platelet counts were shipped on dry ice to a different laboratory.[g] Buccal bleeding time[h] and platelet count were performed at induction and extubation.

Clinical evaluation—A single blinded observer at each clinic measured variables for each cat. Heart rate (beats per minute), heart rate score (1 = heart rate ≤ 10% of preoperative value, 2 = heart rate 11% to 30% of preoperative value, 3 = heart rate 31% to 50% of preoperative value, and 4 = heart rate > 50% of preoperative value), respiratory rate (breaths per minute), and respiratory pattern (1 = normal, 2 = mild abdominal assistance, and 3 = marked abdominal assistance) were recorded at baseline and at 0.5, 1, 3, 5, 8, 12, and 24 hours. Temperament score[e] was recorded at baseline and at 5, 8, 12, and 24 hours after extubation. Temperament was scored beginning at 5 hours after extubation when the effects of anesthesia had dissipated. Tenderness of the forepaw (measured with a palpometer[i]; the paw was squeezed, and the number at which time the cat either vocalized or pulled away was recorded), pain score,[e] **visual analog scale** (**VAS**; observer marks a representative point on a 10-cm line representing no pain at the left edge and worst pain possible on the right edge; the distance in centimeters from the left edge is measured and recorded), cumulative pain score, and gait-lameness score were recorded at baseline; extubation; and (except gait-lameness score[e] and tenderness[i]) 0.5, 1, 3, 5, 8, 12, and 24 hours after extubation. Recovery score[e] was assigned at extubation. Rescue analgesia (butorphanol [0.4 mg/kg], IV, IM) was administered if the recovery score was 5, pain score was 3 or 4, or cumulative pain score was > 8. If recovery score was 5 after rescue administration of butorphanol, acepromazine (0.025 to 0.05 mg/kg [0.011 to 0.023 mg/lb], IV) was administered. Time to rescue analgesia from extubation and number of cats that required rescue analgesia were recorded. Appetite[e] was evaluated at 5, 12, and 24 hours after extubation as ate versus did not eat; urination and defecation were recorded. A general impression score[e] was assigned at the 24-hour time point.

Statistical analyses—In a previous study,[3] no differences were found when cats were stratified by procedure (eg, onychectomy, onychectomy-neuter, and onychectomy-ovariohysterectomy), so we did not stratify our study. In this positive control study, repeated-measures ANOVA[j] or ANOVA[j] were used for all variables except general impression score and number of injections; χ^{2}[j] analysis was performed for number of injections and general impression score. A mixed-model ANOVA for repeated measures was used with time and treatment as fixed effects and site as a random effect. Site was not significant and was dropped from the model. If baseline values were significantly different for any variable, percentage change from baseline was evaluated with a mixed-model ANOVA for

repeated measures. For all comparisons, $P < 0.05$ was considered significant. Data were expressed as mean ± SD.

Results

The cats that received meloxicam and butorphanol were similar in age and weight; equal numbers of cats received each surgery (Table 1). Pain score on injection was significantly ($P < 0.001$) greater for butorphanol-treated cats (2.1 ± 1.3) than for meloxicam-treated cats (1.3 ± 0.7). Few physiologic differences were detected between the 2 treatment groups (**Table 2**). Heart rate and heart rate score were lower in meloxicam-treated cats at 12 ($P < 0.001$) and 5 ($P = 0.029$) hours after extubation, respectively. Respiratory rate was higher in meloxicam-treated cats at 24 hours after extubation ($P = 0.015$), and respiratory rate score was lower in meloxicam-treated cats at 1 ($P = 0.042$) and 5 ($P = 0.049$) hours after extubation.

From 1 to 24 hours, meloxicam-treated cats had lower gait-lameness scores (range, $P = 0.005$ to $P < 0.001$), pain scores (range, $P = 0.025$ to $P < 0.001$), VAS (range, $P = 0.05$ to $P < 0.001$), and cumulative pain scores ($P = 0.03$ to $P < 0.001$) than butorphanol-treated cats (**Table 3**). Temperament for cats in each treatment group was not different at any time point. Recovery scores were not different between meloxicam-treated cats (2.7 ± 1.1) and butorphanol-treated cats (2.9 ± 0.9). Cortisol concentration was higher at baseline ($P = 0.009$) and at 1 ($P = 0.009$), 5 ($P = 0.011$), and 12 ($P = 0.004$) hours after extubation in the butorphanol-treated cats; cortisol concentration was lower in the butorphanol-treated cats at extubation ($P = 0.003$). Because baseline concentrations of cortisol were different, percentage change in cortisol from baseline to other sampling times was examined. The percentage change in serum cortisol from baseline minus other sampling times was significantly ($P = 0.003$) higher only at baseline minus time 0 (extubation). At 5- ($P = 0.044$) and 8-hour ($P = 0.012$) time points, meloxicam-treated cats had a higher pain threshold than butorphanol-treated cats, as measured by evaluation of tenderness. More meloxicam-treated cats (75%) had excellent and good general impression scores than butorphanol-treated cats (44%; $P < 0.001$). A lower percentage of meloxicam- than butorphanol-treated cats required rescue analgesia at the 3-, 5-, 12-, and 24-hour time points (range, $P = 0.049$ to $P < 0.001$; **Table 4**); butorphanol-

Table 2—Cardiopulmonary variables (mean ± SD) in cats that received preoperative administration of butorphanol or meloxicam for onychectomy or onychectomy and surgical neutering.

Variable	Treatment	Baseline	Extubation	0.5 h	1 h	3 h	5 h	8 h	12 h	24 h
Heart rate (beats/ min)	Butorphanol	185 ± 29	186 ± 33	207 ± 29	207 ± 29	197 ± 29	197 ± 31	188 ± 28	193 ± 28	188 ± 26
	Meloxicam	186 ± 30	197 ± 31	200 ± 28	200 ± 28	200± 30	189 ± 29	182 ± 27	180 ± 33*	179 ± 27
Heart rate score	Butorphanol	1.0 ± 0	1.4 ± 0.8	1.8 ± 0.9	1.7 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.6
	Meloxicam	1.0 ± 0	1.4 ± 0.7	1.6 ± 0.9	1.6 ± 0.7	1.6 ± 0.8	1.3 ± 0.6*	1.3 ± 0.6	1.2 ± 0.5	1.2 ± 0.5
Respiratory rate (breaths/min)	Butorphanol	57 ± 21	37 ± 14	43 ± 16	44 ± 16	42 ± 15	43 ± 13	45 ± 17	43 ± 13	41 ± 14
	Meloxicam	60 ± 21	37 ± 17	44 ± 16	46 ± 15	46 ± 17	45 ± 17	46 ± 18	46 ± 20	48 ± 19*
Respiratory rate score	Butorphanol	1.1 ± 0.2	1.7 ± 0.7	1.4 ± 0.5	1.3 ± 0.5	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
	Meloxicam	1.0 ± 0.1	1.8 ± 0.7	1.3 ± 0.5	1.2 ± 0.4*	1.1 ± 0.3	1.1 ± 0.2*	1.1 ± 0.3	1.1 ± 0.3	1 ± 0

*Significant ($P < 0.05$) difference between treatment groups.

Table 3—Subjective and objective measurements (mean ± SD) of pain in cats that received preoperative administration of butorphanol or meloxicam for onychectomy or onychectomy and surgical neutering.

Variable	Treatment	Baseline	Extubation	0.5 h	1 h	3 h	5 h	8 h	12 h	24 h
Sedation score	Butorphanol	1.2 ± 0.5	2.0 ± 1.0	1.5 ± 0.8	1.3 ± 0.6	1.3 ± 0.6	1.2 ± 0.5	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
	Meloxicam	1.7 ± 0.4	1.9 ± 0.9	1.4 ± 0.6	1.7 ± 0.4	1.1 ± 0.3*	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.2
Pain score	Butorphanol	1.0 ± 0	2.7 ± 1.4	2.7 ± 0.9	2.5 ± 0.8	2.6 ± 0.9	2.5 ± 0.8	2.2 ± 0.7	2.2 ± 0.8	1.7 ± 0.7
	Meloxicam	1.0 ± 0	2.7 ± 1.1	2.4 ± 0.9	2.2 ± 0.7*	2.1 ± 0.6*	1.9 ± 0.6*	1.7 ± 0.6*	1.7 ± 0.6*	1.5 ± 0.5*
VAS	Butorphanol	0 ± 0	3.4 ± 2.6	2.8 ± 1.6	2.8 ± 1.6	2.6 ± 1.8	2.4 ± 01.6	2.0 ± 1.6	1.9 ± 1.7	1.3 ± 1.4
	Meloxicam	0 ± 0	3.1 ± 2.3	2.6 ± 1.5	2.2 ± 1.3*	1.8 ± 1.1*	1.5 ± 1.1*	1.3 ± 1.1*	1.2 ± 1.0*	0.8 ± 0.9*
CPS	Butorphanol	4.3 ± 0.5	7.6 ± 3.0	7.3 ± 2.2	6.8 ± 1.6	6.7 ± 1.8	6.5 ± 1.6	5.8 ± 1.2	5.9 ± 1.4	5.3 ± 1.0
	Meloxicam	4.2 ± 0.4	7.7 ± 2.5	6.7 ± 2.0	6.1 ± 1.4*	5.8 ± 1.1*	5.3 ± 1.0*	5.2 ± 1.1*	5.1 ± 1.0*	4.7 ± 0.8*
Gait-lameness	Butorphanol	1.0 ± 0	NA	3.7 ± 0.9	3.5 ± 0.9	3.3 ± 0.9	3.0 ± 1.0	3.0 ± 0.9	2.9 ± 1.0	2.0 ± 0.9
	Meloxicam	1.0 ± 0	NA	3.4 ± 1.0	2.9 ± 0.8*	2.5 ± 0.7*	2.3 ± 0.8*	2.2 ± 0.8*	2.0 ± 0.8*	1.7 ± 0.7*
Palpometer	Butorphanol	3.2 ± 2.5	NA	2.2 ± 2.1	2.4 ± 2.0	2.9 ± 2.0	2.4 ± 2.3	1.8 ± 1.9	2.2 ± 2.3	2.3 ± 2.6
	Meloxicam	3.2 ± 2.5	NA	2.8 ± 2.4	2.7 ± 2.5	3.2 ± 2.3	3.2 ± 2.4*	2.8 ± 2.3*	2.9 ± 2.2	2.5 ± 2.5
Cortisol (µg/dL)	Butorphanol	6.7 ± 4.7	3.9 ± 3.6	NA	7.5 ± 4.0	6.0 ± 3.5	6.0 ± 3.1	NA	6.0 ± 3.3	NA
	Meloxicam	5.1 ± 3.9*	5.7 ± 3.6*	NA	5.4 ± 3.3*	5.0 ± 3.4	4.4 ± 3.1*	NA	4.2 ± 3.0*	NA
Glucose (mg/dL)	Butorphanol	96 ± 21	108 ± 30	NA	117 ± 41	111 ± 28	108 ± 18	NA	107 ± 17	97 ± 18
	Meloxicam	96 ± 20	108 ± 19	NA	110 ± 27	109 ± 25	106 ± 19	NA	100 ± 18	92 ± 15

VAS = Visual analog score. CPS = Cumulative pain score. NA = Not available.
See Table 2 for remainder of key.

Table 4—Number (%) of cats that required rescue analgesia (butorphanol) at various times after onychectomy.

Treatment	Extubation	0.5 h	1 h	3 h	5 h	8 h	12 h	24 h	Total No. of injections
Butorphanol	34 (52)	15 (23)	10 (15)	22 (33)	15 (23)	5 (8)	10 (15)	4 (6)	115
Meloxicam	39 (54)	15 (21)	4 (6)	3 (4*)	2 (3*)	1 (1)	1 (1*)	0 (0*)	65
No. of cats	73	30	14	25	17	6	11	4	180

See Table 2 for key.

treated cats required 1.7 ± 1.6 butorphanol injections versus 0.9 ± 0.9 injections in meloxicam-treated cats ($P < 0.001$). The number of butorphanol administrations at each time period was determined (**Table 5**). Time to first intervention was not significantly different between butorphanol- (48 ± 120 minutes) and meloxicam-treated cats (17 ± 31 minutes).

There was no difference in pre- and postoperative buccal bleeding times between treatments. The butorphanol-treated preoperative buccal bleeding time (65 ± 30 seconds) and postoperative time (76 ± 34 seconds) were not different from the meloxicam-treated preoperative (68 ± 28 seconds) and postoperative times (78 ± 34 seconds), but the meloxicam preoperative versus postoperative time was significantly longer ($P = 0.046$). The differences between the pre- versus postsurgery BUN concentrations in the butorphanol- and meloxicam-treated groups were significantly different ($P < 0.001$ and $P = 0.021$, respectively); the postsurgery BUN concentrations in the butorphanol- and meloxicam-treated groups were also significantly different ($P < 0.05$; **Table 6**). The differences between the pre- and postsurgery PCVs were significant for the butorphanol- and meloxicam-treated cats ($P = 0.021$ and $P < 0.001$, respectively), but there was no difference between treatment groups. Although there were no differences between treatment groups for serial glucose concentrations (Table 3), at 24 hours the mean blood glucose concentration in the meloxicam group was significantly ($P < 0.001$) lower than that at baseline and lower than that in the butorphanol group ($P < 0.001$; Table 6). No redness or swelling at the injection site was noted in either treatment group at 24 hours after surgery. There was no treatment effect for appetite.

Discussion

Evaluating analgesics in cats is difficult because of the problems associated with assessing the degree of pain. Physiologic variables to evaluate pain have been examined[3–6,20-22] with variable results, although systolic blood pressure has shown promise.[21] Changes in physiologic variables have also been included in cumulative pain scores[5-7,23] in an attempt to increase their usefulness in evaluating pain and analgesics. Categoric descriptive analgesia or pain scores have been used alone[3,4,a] and included in cumulative pain scores. Simple descriptive scores that evaluate interaction with an observer, including responses to wound palpation, have also been used.[2] A VAS and an interactive VAS performed by trained observers have been validated in cats.[2] The requirement for intervention or rescue analgesics when a cat meets defined pain criteria has also been used to evaluate analgesia.[3,4,16,19,a] For onychectomy, lameness scoring has been successfully included in the evaluation.[3,4,a] Other aspects of postoperative behavior such as recovery scores,[3,4] behavioral or temperament scores,[3,4,a] isolated behaviors,[24] appetite,[2,4,5] and overall acceptability of postoperative recovery[16] have been included in an attempt to make pain evaluation based on behavior more sensitive. Objective data evaluating lameness, such as a forcemat[4] or quantitating nociceptive threshold with a palpation device,[16] complement subjective measurements of pain.

Other attempts to gather objective data regarding pain and analgesics have included evaluation of stress-related hormones and metabolites. Although often impractical for clinical decisions about pain management, stress-related hormones and metabolites have proven variably helpful during research. Plasma cate-

Table 5—Number (%) of cats that required 0 to 6 administrations of rescue analgesia (butorphanol) after surgery.

	Butorphanol		Meloxicam			
No. of butorphanol administrations	**No. of cats (%)**	**Subtotal No. of injections**	**No. of cats (%)**	**Subtotal No. of injections**	**Total No. of cats**	**Total No. of injections**
0	19 (29)	0	24 (33)	0	43	0
1	13 (20)	13	36 (50)	36	49	49
2	16 (24)	32	8 (11)	16	24	48
3	9 (14)	27	3 (4)	9	12	36
4	4 (6)	16	1 (1)	4	5	20
5	3 (5)	15	0 (0)	0	3	15
6	2 (3)	12	0 (0)	0	2	12
Total No. of cats	**66**		**72**		**138**	
Total No. of injections		**115**		**65**		**180**

Table 6—Serum biochemical values (mean ± SD) at baseline and 24 hours after surgery in cats that received preoperative administration of butorphanol or meloxicam for onychectomy or onychectomy and surgical neutering.

	Baseline		24 h	
Variable	**Butorphanol**	**Meloxicam**	**Butorphanol**	**Meloxicam**
Glucose (mg/dL)	95 ± 21	97 ± 21	97 ± 18*	92 ± 15*†
BUN (mg/dL)	23 ± 4	24 ± 5	18 ± 24†	21 ± 9†
Creatinine (mg/dL)	1.15 ± 0.29	1.18 ± 0.29	1.06 ± 0.29	1.05 ± 0.30
Sodium (mmol/L)	149 ± 4	149 ± 4	149 ± 6	149 ± 5
Potassium (mmol/L)	4.3 ± 1.7	4.3 ± 1.5	3.8 ± 0.8	4.0 ± 1.0
Chloride (mmol/L)	122 ± 3	122 ± 3	122 ± 5	123 ± 4
Platelets (X 10^3/mL)	244.5 ± 127.2	277.9 ±172.4	218.5 ± 123.6	249.0 ± 128.5
PCV (%)	34.5 ± 5.6	34.3 ± 6.1	31.5 ± 6.1†	29.6 ± 6.3†
Hemoglobin (g/dL)	11.9 ± 2.0	11.7 ± 2.1	10.7 ± 2.0	10.1 ± 2.2

†Significant ($P < 0.05$) difference from baseline value.
See Table 2 for remainder of key.

cholamines have been examined after onychectomy[21,25] with inconsistent results. Individual variation, timing of collection, methods of collection, and methods analysis may affect catecholamine values. Evaluation of plasma catecholamines as indicators of stress is complicated by their short half-life. Epinephrine and norepinephrine are secreted within the first second of sympathetic nerve stimulation, reaching maximum concentrations within a minute of stimulation.[26] The hormones are rapidly destroyed by local tissue enzymes and cellular uptake.[26] The duration of action of these catecholamines is usually no more than 1 to 3 minutes after sympathetic nerve stimulation.[26] Plasma norepinephrine has been used extensively to test overall sympathetic nervous system activity, but it may be a faulty guide.[27] The source of plasma norepinephrine is primarily from sympathetic nerves, whereas only a small amount is from the adrenal medulla.[26] There is local inactivation (neuronal uptake) of norepinephrine, so only a small fraction of norepinephrine spills over into venous drainage.

Cortisol is both indicative of pain[20,21] and unrelated to pain.[2] Stress of handling[28] may contribute to variability of cortisol concentrations in clinical studies, and placement of bandages without surgery increases plasma cortisol concentration in cats.[2] Anesthesia causes a transient increase in cortisol concentration that is not sustained.[21] Glucose also has been used to evaluate stress in cats undergoing anesthesia and surgery.[20-22,29] Surgery typically increases glucose concentrations.[20-22] For our study, we included variables that had previously proven valuable in assessing pain in cats, particularly cats undergoing onychectomy with or without surgical neutering.

The surgical time was not standardized. Although there were no significant site effects, different plasma concentrations of both butorphanol and meloxicam may have influenced some of the variables at some time points. Because the therapeutic plasma concentrations of meloxicam and butorphanol are not known and there were no published pharmacokinetic data in cats at the time this study was conducted, commonly used doses of each drug were administered in a clinically relevant time sequence. In our experience, the time to peak plasma meloxicam concentrations after SC administration in cats is 1.5 hours. Our data indicate that administration of meloxicam earlier might provide improved analgesia at extubation and through 1 hour after extubation.

In this study, preoperative administration of meloxicam did not significantly affect temperament, recovery score, or appetite, compared with the effects of butorphanol, but there were differences within treatments over time for some of the variables. For example, appetite increased in both treatment groups.

As stated earlier, physiologic variables may be indicative of pain but may also reflect other sympathetic stimulation or direct effects of administered drugs. In our study, the heart rate at the 12-hour time point and heart rate score at 5 hours in the meloxicam-treated group were significantly lower than that in the butorphanol-treated group. The clinical importance of the differences at 5 and 12 hours after extubation was difficult to evaluate, but such differences may have been attributable to increased comfort in the meloxicam group. The butorphanol-treated group was expected to have lower heart rates during the first few hours after administration because of vagal stimulation, but this did not appear to be true. Any decrease in heart rate caused by butorphanol should be transient because of the short duration of action of butorphanol (5.8 hours for visceral analgesia).[30] Similarly, the clinical importance of differences in respiratory rate and respiratory scores is difficult to interpret. In the meloxicam-treated cats, the respiratory rate was higher at 24 hours, but the effort was lower at 1 and 5 hours than in the butorphanol-treated cats. These results suggest that physiologic variables should not be used alone to estimate pain.

Each method of estimating pain, either subjectively (ie, pain score, VAS, cumulative pain score, and gait-lameness score) or objectively (ie, palpometer), indicated that meloxicam provided superior analgesia to butorphanol. At 1 hour and continuing for 24 hours after extubation, mean scores for all subjective assessments suggested that the meloxicam-treated cats were more comfortable. The palpometer score was significantly lower for the meloxicam-treated cats at 5 and 8 hours. The cats were less agitated in the meloxicam-treated group at 3 hours.

Cats that received butorphanol had significantly higher cortisol concentrations at baseline, but by extubation, meloxicam-treated cats had higher cortisol concentrations. At 1, 5, and 12 hours after extubation, butorphanol-treated cats had higher cortisol concentrations. Cortisol concentration was higher than the reference range (0.5 to 3.5 μg/dL)[31] in all cats at all times. Cortisol concentration decreased at extubation in cats in the butorphanol-treated group and increased over 24 hours, which was similar to the cortisol response to onychectomy in cats that received preoperative administration of butorphanol or transdermal fentanyl in a previous study.[6] The increased cortisol concentration at extubation in the meloxicam-treated cats may have been related to the lower plasma concentrations of meloxicam. As time progressed, the cortisol concentrations in the meloxicam-treated cats decreased, as would be expected with the longer onset and duration of action of meloxicam, whereas the plasma cortisol concentrations in the butorphanol-treated cats increased, as would be expected with quick onset and short duration of action of butorphanol.

Comparing our cortisol results to other investigations is complicated by the fact that the results of postoperative administration of analgesics on cortisol concentration are different from those of preemptive analgesia. Cortisol concentrations are increased in purpose-bred cats undergoing ovariohysterectomy by a veterinarian whether receiving postoperative analgesics or not, but less so when low and high doses of butorphanol were administered.[21] The cortisol concentrations in client-owned cats undergoing ovariohysterectomy with a similar anesthesia protocol but operated on by veterinary students are higher at the end of anesthesia and at extubation[22] than the concentrations in cats undergoing ovariohysterectomy in the previous

study.[21] The administration of high and low butorphanol doses to client-owned cats decreases cortisol concentration.[22] However, when client-owned cats operated on by veterinary students are administered butorphanol, the cortisol concentrations are not decreased to the same extent as purpose-bred cats that do not receive analgesics and are ovariohysterectomized by a veterinarian.[21] Reasons for the differences in the 2 populations of cats are speculative but may be related to surgical time, tissue trauma, and time to therapeutic plasma drug concentrations. When ketoprofen, oxymorphone, or buprenorphine is administered at extubation to cats undergoing onychectomy, all postoperative cortisol concentrations are higher than the preoperative cortisol concentration.[5] The largest difference in corrected cortisol concentration (eg, subtracting preanesthesia cortisol) is seen at 4 hours,[5] with buprenorphine having a smaller difference than the other 3 treatments. In contrast, the cortisol concentration in meloxicam-treated cats was higher at extubation and lower over 24 hours. The clinical importance of cortisol concentrations in this study was difficult to interpret because of the difference in baseline cortisol concentration between the 2 groups.

When examined over time, the serial glucose concentrations were not different between meloxicam and butorphanol treatment groups. However, in the meloxicam treatment group, postoperative glucose concentration was significantly lower than the preoperative concentration. Although the difference in glucose concentration in the meloxicam treatment group was small, meloxicam may have contributed to a reduction in stress. Ovariohysterectomy in cats results in increased glucose concentration.[29] The effect of analgesia on glucose concentration in cats is variable depending on the analgesic agent (eg, butorphanol[21,22] or fentanyl[20]) and whether the analgesic agent is administered preemptively[22] or postoperatively.[21,22] It may be that the large increases in glucose concentration seen in previous studies were not detected in our study because preemptive analgesia was provided for all patients and rescue analgesia was provided when criteria for intervention were met.

The difference in glucose and cortisol concentrations in cats treated preemptively or postoperatively is consistent with the suggestion that to be most effective, nociception should be inhibited prior to the initiation of the painful stimulus.[32-34] Noxious afferent signals during surgery contribute to central sensitizations and increased postoperative pain.[35] The administration of an analgesic prior to nociception provides preemptive analgesia; analgesia administered before the noxious stimulus outlasts the duration of action of the analgesic in the body.[36] Therefore, analgesia should be provided before surgery. As indicated earlier, NSAIDs are not true competitive antagonists[17] and any prostaglandins already present will be expressed,[17] so the preemptive use of NSAIDs would be most beneficial.

In addition to the efficacy of analgesics, the safety of the chosen analgesic must also be considered. Opioids such as butorphanol,[3,4,6] fentanyl,[4,20] buprenorphine,[5] and oxymorphone[5] have been studied with regard to pain from onychectomy. Ketoprofen, an NSAID, has also been evaluated for onychectomy-induced pain.[5] Each drug has advantages and disadvantages. All opioids have the potential to cause bradycardia and hypoventilation, although more so with pure μ-agonists. Although not common, the opioids have the potential to cause dysphoria in cats. In our study, the butorphanol-treated cats were more agitated 3 hours after extubation. Butorphanol is a schedule IV drug and requires documentation for the practicing veterinarian. The short duration of action of butorphanol requires repeated administration to be effective for the 2 to 3 days that are required to improve outcome in onychectomized cats.

Meloxicam appeared to have a good safety profile in the cats in our study. Preoperative administration of meloxicam did not result in significant differences in platelet count or concentrations of creatinine, sodium, potassium, chloride, PCV, BUN, or hemoglobin, compared with butorphanol. The BUN and PCV decreased similarly in both treatment groups and was not clinically important. No difference in buccal bleeding time was detected between treatments, but there was a significant difference between the pre- and postoperative buccal bleeding times of the meloxicam-treated cats (68 to 78 seconds). Such a small change is not clinically important and is much < 2 minutes. These findings are consistent with the suggestion that meloxicam will not prolong hemostasis in clinically normal animals.[9]

Study cats in the meloxicam and butorphanol treatment groups that received rescue analgesia were not excluded from the study. The influence of rescue cannot be separated from our results but were anticipated to affect each treatment group equally. If only rescue without other variables is considered, there were no differences in rescue between treatment groups at extubation and 0.5, 1, and 8 hours, but significantly fewer cats in the meloxicam treatment group received intervention at 3, 5, 12, and 24 hours. Also, if the actual number of interventions is considered, butorphanol-treated cats required more injections (1.7 ± 1.6) than the meloxicam-treated cats (0.9 ± 0.9).

Meloxicam administered once improves analgesia for 24 hours after surgery without causing clinically relevant adverse effects in cats undergoing onychectomy or onychectomy-neutering, as determined subjectively and objectively. The timing of injection of meloxicam as well as other preemptive analgesics in relation to surgery should be considered with regard to the time required for attaining therapeutic plasma concentrations. Therapeutic plasma concentrations (actual amount of drug needed to provide analgesia) will differ for individual cats and have not been established. The time to reach therapeutic plasma concentrations for an individual is also likely to be different than the mean time to reach maximal plasma concentration of 1.5 hours. In consideration of these factors, it may be appropriate for the practitioner to adjust the timing of presurgical administration to allow for surgical time and to monitor the cat closely shortly after surgery to ensure adequate pain management has been achieved. Until more specific recommendations based on evidence-based medicine can be made, administration of meloxicam 1.5 hours before recovery is a suggested guideline. Although the cats in our study were evaluat-

ed for only 24 hours, results of a previous study[3] indicate that analgesia should be provided for at least 2 days. Further study is indicated to examine analgesic use for the second and third day postoperatively.

a. Dodam JR, Boedeker B, Gross M, et al. Phospholipid-encapsulated bupivacaine and analgesia after onychectomy in cats (abstr). *Vet Anaesth Analg* 2002;29:101.
b. Justus C, Philipp H. Multi-centre study on clinical efficacy and tolerance of meloxicam (Metacam) in cats with acute locomotor disorders (abstr), in *Proceedings*. Meet Br Small Anim Vet Assoc 1994;175.
c. Metacam, Boehringer Ingelheim Vetmedica Inc, Elwood, Kan.
d. Torbugesic-SA/Torbugesic, Fort Dodge Laboratories, Overland Park, Kan.
e. Available from author upon request.
f. i-STAT, Heska, Fort Collins, Colo.
g. Antech Diagnostic Laboratory, Southhaven, Miss.
h. Simplate P, Animal Blood Bank, Vacaville, Calif.
i. D_2Palpometer, University of Victoria Innovation and Development Corp, Victoria, BC, Canada.
j. SAS Release 8.01, SAS Institute Inc, Raleigh, NC.

References

1. Patronek GJ. Assessment of claims of short- and long-term complications associated with onychectomy in cats. *J Am Vet Med Assoc* 2001;219:932–937.
2. Cambridge AJ, Tobias KM, Newberry RC, et al. Subjective and objective measurements of postoperative pain in cats. *J Am Vet Med Assoc* 2000;217:685–690.
3. Carroll GL, Howe LB, Slater MR, et al. Evaluation of analgesia provided by postoperative administration of butorphanol to cats undergoing onychectomy. *J Am Vet Med Assoc* 1998;213:246–250.
4. Franks JN, Boothe HW, Taylor LA, et al. Evaluation of transdermal fentanyl patches for analgesia in cats undergoing onychectomy. *J Am Vet Med Assoc* 2000;217:1013–1020.
5. Dobbins S, Brown NO, Shofer FS. Comparison of the effects of buprenorphine, oxymorphone hydrochloride, and ketoprofen for postoperative analgesia after onychectomy or onychectomy and sterilization in cats. *J Am Anim Hosp Assoc* 2002;38:507–514.
6. Gellasch KL, Kruse-Elliott KT, Osmond CS, et al. Comparison of transdermal administration of fentanyl versus intramuscular administration of butorphanol for analgesia after onychectomy in cats. *J Am Vet Med Assoc* 2002;220:1020–1024.
7. Winkler KP, Greenfield CL, Benson GJ. The effect of wound irrigation with bupivacaine on postoperative analgesia of the feline onychectomy patient. *J Am Anim Hosp Assoc* 1997;33:346–352.
8. Engelhardt G, Bogel R, Schnitzer CHR, et al. Meloxicam: influence on arachidonic acid metabolism. Part 1. In vitro findings. *Biochem Pharm* 1995;51:21–28.
9. Justus C, Quirke JF. Dose-response relationship for the antipyretic effect of meloxicam in an endotoxin model in cats. *Vet Res Commun* 1995;19:321–330.
10. McKellar QA, May SA, Lees P. Pharmacology and therapeutics of non-steroidal anti-inflammatory drugs in the dog and cat: 2 individual agents. *J Small Anim Pract* 1991;32:225–235.
11. Rainsford KD, Skerry TM, Chindemi P, et al. Effects of the NSAIDs meloxicam and indomethacin on cartilage proteoglycan synthesis and joint responses to calcium pyrophosphate crystals in dogs. *Vet Res Commun* 1999;23:101–113.
12. Mathews K. Nonsteroidal anti-inflammatory analgesics; indications and contraindications for pain management in dogs and cats. *Vet Clin North Am Small Anim Pract* 2000;30:783–801.
13. DuBois RN, Abramson SB, Crofford L. Cyclooxygenase in biology and disease. *FASEB J* 1998;12:1063–1073.
14. Kay-Mugford P, Benn SJ, LaMarre J, et al. In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. *Am J Vet Res* 2000;61:802–810.
15. Lascelles BDX, Henderson AJ, Hackett IJ. Evaluation of the clinical efficacy of meloxicam in cats with painful locomotor disorders. *J Small Anim Pract* 2001;42:587–593.
16. Slingsby LS, Waterman-Pearson AE. Postoperative analgesia in the cat after ovariohysterectomy by use of carprofen, ketoprofen, meloxicam or tolenamic acid. *J Small Anim Pract* 2000;41:447–450.
17. Lee VC, Rowlingson JC. Pre-emptive analgesia: update on nonsteroidal anti-inflammatory drugs in anesthesia. *Adv Anesth* 1995;12:69–110.
18. Poulson Nautrup B, Justus C. Effects of some veterinary NSAIDs on ex vivo thromboxane production and in vivo urine output in the dog, in *Proceedings*. Symp Recent Adv Non-steroidal Anti-inflammatory Ther Small Anim, 1999;25–28.
19. Slingsby LS, Waterman-Pearson AE. Comparison between meloxicam and carprofen for postoperative analgesia after feline ovariohysterectomy. *J Small Anim Pract* 2002;43:286–289.
20. Glerum LE, Egger CM, Allen SW, et al. Analgesic effect of the transdermal fentanyl patch during and after feline ovariohysterectomy. *Vet Surg* 2001;30:351–358.
21. Smith JD, Allen SW, Quandt JE, et al. Indicators of postoperative pain in cats and correlation with clinical criteria. *Am J Vet Res* 1996;57:1674–1678.
22. Smith JD, Allen SW, Quandt JE. Changes in cortisol concentration in response to stress and postoperative pain in client-owned cats and correlation with objective clinical variables. *Am J Vet Res* 1999;60:432–436.
23. Ansah OB, Vainio O, Hellsten C, et al. Postoperative pain control in cats: clinical trials with medetomidine and butorphanol. *Vet Surg* 2002;31:99–103.
24. Cloutier S, Newberry RC, Cambridge AJ, et al. Behavioral signs of pain in cats, in *Proceedings*. 2002 Am Vet Soc Anim Behav Annu Symp Anim Behav Res 2002;51–54.
25. Benson GJ, Wheaton LG, Thurmon JC, et al. Postoperative catecholamine response to onychectomy in isoflurane-anesthetized cats, effect of analgesics. *Vet Surg* 1991;20:222–225.
26. Guyton AC. Introduction to endocrinology. In: *Textbook of medical physiology*. 8th ed. Philadelphia: WB Saunders Co, 1991;810–818.
27. Esler M, Jennings G, Korner P, et al. Measurement of total and organ-specific norepinephrine kinetics in humans. *Am J Physiol* 1984;247:E21–E28.
28. Willemese T, Vroom MW, Mol JA, et al. Changes in plasma cortisol, corticotrophin, and α-melanocyte-stimulating hormone concentrations in cats before and after physical restraint and intradermal testing. *Am J Vet Res* 1993;54:69–72.
29. Hardie EM, Rawlings CA, George JW. Plasma-glucose concentrations in dogs and cats before and after surgery: comparison of healthy animals and animals with sepsis. *Am J Vet Res* 1985;46:1700–1704.
30. Sawyer DC, Rech RH. Analgesia and behavioral effects of butorphanol, nalbuphine, and pentazocine in the cat. *J Am Anim Hosp Assoc* 1987;23:438–446.
31. Turnwald GH, Willard MD. Endocrine, metabolic and lipid disorders. In: Willard MD, Tvedten H, Turnwald GH, eds. *Small animal clinical diagnosis by laboratory methods*. Philadelphia: WB Saunders Co, 1989;155–188.
32. Hansen BD. Analgesic therapy. *Compend Contin Educ Pract Vet* 1994;16:868–875.
33. Katz J, Kavanagh BP, Sandler AN, et al. Preemptive analgesia. *Anesthesiology* 1992;77:439–446.
34. Tverskoy M, Cozacov Y, Ayache M, et al. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesth Analg* 1990;70:29–35.
35. Kavanagh BP, Katz J, Sandler AN. Pain control after thoracic surgery. *Anesthesiology* 1994;81:737–759.
36. Tverskoy M, Oz Y, Isakson A, et al. Premptive effect of fentanyl and ketamine on postoperative wound hyperalgesia. *Anesth Analg* 1994;78:205–209.