

Effects of preoperative administration of ketoprofen on anesthetic requirements and signs of postoperative pain in dogs undergoing elective ovariohysterectomy

Kip A. Lemke, DVM, MS, DACVA; Caroline L. Runyon, DVM, MS; Barbara S. Horney, DVM, PhD, DACVP

Objective—To determine the effects of preoperative administration of ketoprofen on anesthetic requirements and signs of postoperative pain in dogs undergoing elective ovariohysterectomy.

Design—Randomized, controlled clinical trial.

Animals—22 clinically normal client-owned dogs.

Procedure—60 minutes before induction of anesthesia, 11 dogs were given ketoprofen (2 mg/kg [0.9 mg/lb], IM), and the other 11 were given saline (0.9% NaCl) solution. Dogs were premedicated with glycopyrrolate, acepromazine, and butorphanol and anesthetized with thiopental; anesthesia was maintained with isoflurane. Ovariohysterectomy was performed by an experienced surgeon, and butorphanol was given 15 minutes before completion of the procedure. Objective behavioral scores and numerical pain scores at rest and with movement were recorded every 2 hours for 12 hours after surgery and then every 4 hours for an additional 12 hours.

Results—Preoperative administration of ketoprofen did not reduce the dose of thiopental required to induce anesthesia or the end-tidal concentration of isoflurane required to maintain anesthesia. Activity levels and median objective behavioral scores were significantly higher 4 and 6 hours after surgery in dogs given ketoprofen than in dogs given saline solution. However, mean numerical pain scores in dogs given ketoprofen were not significantly different from scores for dogs given saline solution at any time.

Conclusions and Clinical Relevance—Results suggest that preoperative administration of ketoprofen does not reduce anesthetic requirements in dogs undergoing elective ovariohysterectomy but may reduce signs of pain after surgery. Results also suggest that the objective behavioral score may be a more sensitive measure of acute postoperative pain than traditional numerical pain scores. (*J Am Vet Med Assoc* 2002;221:1268–1275)

Preoperative administration of nonsteroidal anti-inflammatory analgesic (NSAIA) drugs to dogs

From the Departments of Companion Animals (Lemke, Runyon) and Pathology and Microbiology (Horney), Atlantic Veterinary College, University of Prince Edward Island, Charlottetown, PE, Canada, CIA 4P3.

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Address correspondence to Dr. Lemke.

undergoing surgery is controversial.¹⁻⁴ On the one hand, preoperative use of NSAIA drugs may reduce the amount of anesthetic required to induce and maintain anesthesia and improve postoperative analgesia. On the other hand, preoperative use of these drugs may increase the incidence of hemorrhage and impair renal function during the perioperative period. Further, preoperative administration of NSAIA drugs may be no more effective, in terms of postoperative analgesia, than postoperative administration.

Ketoprofen is an NSAIA drug used to manage acute postoperative pain in dogs. It has a marked central analgesic effect, relative to its peripheral anti-inflammatory effect,⁵ and greater clinical efficacy, compared with most other NSAIA drugs, in humans with moderate to severe pain following surgical removal of an impacted third molar.^{5,6} Ketoprofen is a potent, non-specific inhibitor of cyclooxygenase (COX) and may also inhibit lipoxygenase and decrease synthesis of leukotrienes and prostaglandins.^{7,8} It reversibly inhibits the activity of the constitutive COX isoenzyme (COX-1) and the COX isoenzyme induced by inflammation (COX-2) and has a COX-1:COX-2 selectivity ratio of 0.232 in vitro in canine cells.⁹

Analgesic drugs like ketoprofen that can be given parenterally have a rapid onset of action and are more suitable for perioperative use than are NSAIA drugs that cannot be given parenterally and have a slower onset of action.¹⁰ In people, ketoprofen is highly protein bound (98%) and has a rapid onset of action (1 hour) and a short half-life (1.5 hours) after parenteral administration.¹¹ Further, it rapidly penetrates the blood-brain barrier after IM administration, with detectable concentrations in CSF in 15 minutes, and CSF concentrations equilibrate with plasma concentrations within 2 hours.¹² In dogs, analgesia develops within 30 to 60 minutes and persists for 12 to 24 hours after IM administration of ketoprofen.³

Concurrent administration of highly protein-bound NSAIA drugs and thiopental prolongs sleep time in laboratory animals and people and may reduce the dose of thiopental required to induce anesthesia.^{13,14} Further, NSAIA drugs with a substantial central analgesic effect may reduce inhalant anesthetic requirements during surgery. In women, for instance, preoperative administration of ketorolac appears to reduce isoflurane requirements during vaginal hysterectomy.¹⁵ Conversely, administration of carprofen does not appear to reduce the minimum alveolar concentration (MAC) of halothane or isoflurane in dogs.^{16,17}

Preoperative and postoperative administration of

ketoprofen reduces postoperative pain in dogs undergoing orthopedic or abdominal surgery. Pibarot et al¹⁸ reported that in dogs given ketoprofen (2 mg/kg [0.9 mg/lb], IM) immediately after orthopedic surgery, pain scores were reduced from 4 through 12 hours after surgery, compared with scores for dogs given a single dose of butorphanol (0.2 mg/kg [0.09 mg/lb], IM) or oxymorphone (0.05 mg/kg [0.02 mg/lb], IM) immediately after surgery. Grisneaux et al¹⁹ reported that administration of ketoprofen (2 mg/kg, SC) 30 minutes before induction of anesthesia reduced pain scores and opioid requirements during the first 12 hours after orthopedic surgery. Similarly, Mathews et al²⁰ reported that administration of ketoprofen (2 mg/kg, IV) immediately after induction of anesthesia reduced opioid requirements for the first 20 hours after abdominal surgery, compared with requirements for dogs given a single dose of butorphanol (0.2 mg/kg, IV) immediately after surgery. In that study, a laparotomy, cystotomy, or splenectomy was performed by a student surgeon, and surgery times ranged from 2.5 to 5.0 hours.

In a clinical setting, preoperative administration of ketoprofen may or may not reduce anesthetic requirements and signs of postoperative pain in dogs. To our knowledge, the effect of preoperative administration of ketoprofen on the amount of thiopental required to induce anesthesia or the amount of isoflurane required to maintain anesthesia has not been reported. In addition, although ketoprofen appears to be an effective analgesic after orthopedic surgery and after abdominal surgery performed by student surgeons, the effect of preoperative administration of ketoprofen on signs of postoperative pain in dogs undergoing routine abdominal surgery performed by an experienced surgeon in a clinical setting has not been determined. The purpose of the study reported here was to determine the effects of preoperative administration of ketoprofen on anesthetic requirements and signs of postoperative pain in dogs undergoing elective ovariohysterectomy.

Materials and Methods

Animals—Twenty-two clinically normal client-owned dogs were included in the study. Owners were informed of the potential risks and benefits of the study and provided written consent to enroll their animals in the study. Female dogs between 6 months and 3 years old that weighed between 15 and 35 kg (33 and 77 lb) and that were determined to be healthy on the basis of results of a preoperative examination and clinicopathologic analyses were included in the study. Dogs that were in estrus or pregnant were excluded from the study. The study protocol was reviewed and approved by the Animal Care Committee at the University of Prince Edward Island.

Experimental design—The study was conducted as a prospective, randomized, controlled clinical trial. Dogs enrolled in the study were admitted to the hospital the day before surgery. That afternoon, blood samples were collected for determination of serum cortisol and glucose concentrations. The following morning, dogs were assigned at random to the ketoprofen treatment or control group. Approximately 60 minutes before induction of anesthesia, 11 dogs (mean \pm SD body weight, 22 \pm 6 kg [48 \pm 13 lb]; age, 10 \pm 4 months) were given saline (0.9% NaCl) solution and the other 11 (body weight, 21 \pm 4 kg [46 \pm 9 lb]; age, 13 \pm 9 months) were given ketoprofen^a (2 mg/kg, IM). Approximately 30

minutes before induction of anesthesia, glycopyrrolate (0.01 mg/kg [0.005 mg/lb]), acepromazine (0.05 mg/kg), and butorphanol (0.2 mg/kg) were given IM. Ten minutes before induction of anesthesia, a 20-gauge polytef catheter was placed aseptically into a cephalic vein. Anesthesia was induced with thiopental (5 to 10 mg/kg [2.3 to 4.5 mg/lb], IV) and maintained with isoflurane (1 to 3%) in oxygen (1 to 3 L/min). A fourth of the calculated thiopental dose (10 mg/kg) was given as a bolus, and the remainder was given slowly to effect. Loss of the palpebral reflex, ventromedial rotation of the eyes, relaxation of jaw tone, and loss of the swallowing reflex were used as endpoints for titration of the thiopental dose. After induction of anesthesia and placement of a cuffed endotracheal tube, a 16-gauge polytef catheter was inserted aseptically into a jugular vein to facilitate collection of blood samples during the postoperative period. Ovariohysterectomy was performed by an experienced surgeon (CLR), and butorphanol (0.1 mg/kg [0.05 mg/lb], IV) was given 15 minutes before completion of the procedure. Lactated Ringer's solution was given during surgery at a rate of 10 mL·kg⁻¹·h⁻¹ (4.5 mL·lb⁻¹·h⁻¹). All surgeries were performed on the morning after admission, and total time under anesthesia (ie, time from induction of anesthesia with thiopental to termination of isoflurane administration) was 92 \pm 33 minutes (mean \pm SD) for control dogs and 78 \pm 29 minutes for dogs given ketoprofen. Heart rate, respiratory rate, mean arterial pressure (MAP), esophageal temperature, end-tidal partial pressure of carbon dioxide (PETCO₂), and end-tidal isoflurane concentration were recorded 5 minutes before the skin incision was made and then every 5 minutes for an additional 30 minutes. Loss of the palpebral reflex, ventromedial rotation of the eyes, moderate muscle relaxation, and maintenance of an acceptable PETCO₂ (< 60 mm Hg) and MAP (> 60 mm Hg) were used as end-points for titration of the end-tidal isoflurane concentration. After surgery, objective behavioral (OB) scores (Appendix) were recorded every 2 hours for 12 hours and then every 4 hours for an additional 12 hours. After OB scores were recorded, heart rate, respiratory rate, MAP, and rectal temperature were recorded. Numerical pain (NP) scores at rest and with movement were recorded by a single observer at the same intervals by examining time-lapse videotapes. For assignment of NP scores at rest, the observer viewed a 5-minute videotape of each dog obtained immediately before each sampling interval. For assignment of NP scores with movement, the observer viewed a 5-minute videotape of each dog obtained immediately after each sampling interval. For both NP scores, the observer assigned a score ranging from 0 (no signs of pain) to 100 (signs of the worst pain possible for a dog undergoing ovariohysterectomy). Blood samples for determination of serum cortisol and glucose concentrations were collected immediately after surgery and every 4 hours for an additional 24 hours. The surgeon (CLR) and the veterinary technicians assisting in the study were given the option to withdraw dogs from the study and give supplemental opioids if they believed animals were experiencing moderate to severe pain. All personnel involved in the trial were unaware of which group individual animals had been assigned to.

Instrumentation—During surgery, heart rate and MAP were measured with an oscillometric blood pressure monitor^b; a cuff with a width 40 to 60% of the circumference of the limb was placed just above the carpus. Temperature was measured with an esophageal stethoscope equipped with an electronic sensor.^c A calibrated infrared airway gas monitor^d was used to measure respiratory rate, PETCO₂, and end-tidal isoflurane concentration. Airway gas samples were drawn continuously from an adapter placed between the endotracheal tube and the rebreathing circuit. After surgery, heart rate and MAP were measured in triplicate with the same

oscillometric blood pressure monitor, and mean values were recorded. Respiratory rate was measured by visual observation (1-minute interval), and rectal temperature was measured with a digital thermometer.^c

Clinicopathologic testing—Blood samples were collected into tubes without anticoagulant, and serum was separated from the samples within 30 minutes. Serum cortisol concentration was measured with a commercially available radioimmunoassay.^f Serum glucose concentration was measured with a commercial method^g on an automated analyzer.^h

Statistical analyses—Anesthetic, physiologic, biochemical, and NP score data were analyzed with parametric statistical methods.^{21,22} Dose of thiopental was compared between groups with a 2-sample *t*-test. The other parametric data were analyzed with ANOVA for repeated measures. Two-way ANOVA for repeated measures was used to compare differences between treatments over time. If a significant treatment-time interaction was found, Tukey multiple comparison tests were used to compare treatments at each time period. One-way ANOVA was used to compare differences within treatments over time. If a significant time effect was found, Dunnett multiple comparison tests were used to compare, for each treatment group, values obtained at each recording period with baseline values (ie, values obtained before the initial skin incision, immediately after surgery, or the afternoon before surgery, depending on the variable). For all parametric analyses, a value of $P < 0.05$ was considered significant; data are reported as mean \pm SD.

Objective behavioral score data were analyzed with nonparametric statistical methods.^{21,22} Mann-Whitney rank sum tests were used to compare differences between treatments at each time period. One-way ANOVA was used to compare differences within treatments over time. If a significant ($P < 0.05$) time effect was found, Dunnett multiple comparison tests were used to compare, for each treatment group, values obtained at each recording period with baseline values (ie, values obtained immediately after surgery). For all nonparametric analyses, a value of $P < 0.05$ was considered significant; data are reported as median and interquartile (25th to 75th percentile) range.

Results

Preoperative administration of ketoprofen did not reduce the dose of thiopental required to induce anesthesia or the concentration of isoflurane required to maintain anesthesia. Doses of thiopental (mean \pm SD) required to induce anesthesia in dogs given saline solution and ketoprofen were 6.8 ± 1.6 mg/kg (3.4 ± 0.8 mg/lb) and 6.5 ± 2.0 mg/kg (3.3 ± 1.0 mg/lb), respectively. The end-tidal concentration of isoflurane required to maintain anesthesia was not significantly different between groups at any time during the surgical procedure (Table 1).

Preoperative administration of ketoprofen did not alter heart rate or respiratory rate during surgery, in that mean heart and respiratory rates in dogs given ketoprofen did not differ significantly from values for dogs given saline solution at any time (Table 1). However, significant changes in heart rate over time were detected among dogs given saline solution, with mean values 10 to 30 minutes after the initial skin incision significantly lower than mean heart rate 5 minutes prior to incision. A significant time effect for heart rate was also observed for dogs given ketoprofen, but mean values were not significantly greater or less than the baseline value. A significant time effect for respiratory rate was not observed in either group.

Preoperative administration of ketoprofen did not alter MAP, esophageal temperature, or PETCO₂ during surgery (Table 1), as values for dogs given ketoprofen were not significantly different from values for dogs given saline solution at any time. However, significant changes in MAP and esophageal temperature over time were detected for both treatment groups. In both groups, MAP was significantly increased, compared with baseline values, 5 to 20 minutes after the initial skin incision was made. Similarly, in both groups, esophageal temperature was significantly decreased, compared with baseline values, 5 to 30 minutes after

Table 1—Physiologic variables during surgery in healthy dogs (n = 11/group) undergoing an ovariohysterectomy; dogs were given ketoprofen (2 mg/kg [0.9 mg/lb], IM) or saline (0.9% NaCl) solution 60 minutes before induction of anesthesia

Variable	Time after skin incision (min)							
	-5	0	5	10	15	20	25	30
HR (beats/min)								
Saline solution	119 \pm 13	117 \pm 11	116 \pm 12	109 \pm 11 ^a	111 \pm 11 ^a	108 \pm 11 ^a	105 \pm 7 ^a	104 \pm 9 ^a
Ketoprofen	109 \pm 19	119 \pm 16	109 \pm 20	106 \pm 12	107 \pm 11	103 \pm 11	104 \pm 11	106 \pm 14
RR (breaths/min)								
Saline solution	10 \pm 5	11 \pm 6	14 \pm 11	10 \pm 3	11 \pm 5	9 \pm 5	9 \pm 5	10 \pm 4
Ketoprofen	11 \pm 5	12 \pm 6	12 \pm 4	11 \pm 6	10 \pm 6	10 \pm 5	11 \pm 5	10 \pm 5
MAP (mm Hg)								
Saline solution	60 \pm 9	57 \pm 9	81 \pm 23 ^a	100 \pm 29 ^a	93 \pm 31 ^a	87 \pm 26 ^a	82 \pm 21 ^a	75 \pm 19
Ketoprofen	58 \pm 13	69 \pm 18	96 \pm 23 ^a	101 \pm 22 ^a	92 \pm 17 ^a	79 \pm 15 ^a	75 \pm 16	73 \pm 17
Esophageal temperature (°C)								
Saline solution	37.5 \pm 0.6	37.4 \pm 0.7	37.3 \pm 0.7 ^a	37.1 \pm 0.7 ^a	37.1 \pm 0.8 ^a	37.0 \pm 0.7 ^a	36.9 \pm 0.8 ^a	36.8 \pm 0.8 ^a
Ketoprofen	37.9 \pm 0.8	37.8 \pm 0.8 ^a	37.6 \pm 0.9 ^a	37.5 \pm 0.9 ^a	37.5 \pm 0.9 ^a	37.4 \pm 0.9 ^a	37.3 \pm 0.9 ^a	37.3 \pm 0.9 ^a
PETCO ₂ (mm Hg)								
Saline solution	52 \pm 11	52 \pm 8	47 \pm 9 ^a	53 \pm 8	49 \pm 8	51 \pm 8	52 \pm 8	52 \pm 8
Ketoprofen	52 \pm 7	51 \pm 8	48 \pm 7	51 \pm 7	52 \pm 6	54 \pm 8	51 \pm 6	52 \pm 5
End-tidal isoflurane (%)								
Saline solution	1.5 \pm 0.2	1.4 \pm 0.2	1.5 \pm 0.2	1.5 \pm 0.2	1.5 \pm 0.2	1.5 \pm 0.2	1.4 \pm 0.2	1.4 \pm 0.3
Ketoprofen	1.5 \pm 0.3	1.5 \pm 0.3	1.6 \pm 0.2	1.6 \pm 0.2	1.5 \pm 0.2	1.5 \pm 0.2	1.4 \pm 0.2	1.3 \pm 0.2

Values are reported as mean \pm SD.
^aSignificantly ($P < 0.05$) different from baseline value (ie, value obtained 5 minutes before skin incision).
 HR = Heart rate. RR = Respiratory rate. MAP = Mean arterial pressure. PETCO₂ = End-tidal partial pressure of carbon dioxide.

the initial skin incision was made. Like respiratory rate, PETCO₂ did not change appreciably after the initial skin incision was made. A significant time effect for PETCO₂ was observed for dogs given saline solution but not for dogs given ketoprofen.

Preoperative administration of ketoprofen did not alter heart rate or respiratory rate after surgery, in that values for dogs given ketoprofen were not significantly different from values for dogs given saline solution at any time (Table 2). However, significant changes in heart rate over time were detected for both treatment groups. In dogs given saline solution, mean heart rate was significantly less than the baseline value (heart rate immediately after surgery) from 8 to 24 hours after surgery. Similarly, in dogs given ketoprofen, mean heart rate was significantly less than the baseline value from 12 to 24 hours after surgery. A significant time effect for respiratory rate was not observed for either group.

Preoperative administration of ketoprofen did not alter MAP or rectal temperature after surgery, in that values for dogs given ketoprofen were not significantly different from values for dogs given saline solution at any time (Table 2). However, significant changes over time were detected for both groups. For both groups,

mean MAP was significantly increased, compared with baseline values, from 2 to 24 hours after surgery. Similarly, in both groups, mean rectal temperature was significantly increased, compared with baseline values, from 2 to 24 hours after surgery.

Preoperative administration of ketoprofen had a significant effect on OB scores but not on NP scores (Table 3). Additionally, significant changes over time were detected for both groups. Median OB scores 4 and 6 hours after surgery were significantly higher for dogs given ketoprofen than for dogs given saline solution. Median OB scores were significantly increased, compared with baseline values, from 8 to 24 hours after surgery in dogs given saline solution and from 4 to 24 hours after surgery in dogs given ketoprofen. Mean NP scores at rest and with movement in dogs given ketoprofen were not significantly different from scores in dogs given saline solution at any time. Mean NP scores at rest were significantly increased, compared with baseline values 2 hours after surgery in dogs given saline solution and 2 and 4 hours after surgery in dogs given ketoprofen. Mean NP scores with movement were significantly increased, compared with baseline values, from 2 to 10 hours after surgery in dogs given

Table 2—Physiologic variables after surgery in healthy dogs (n = 11/group) undergoing an ovariohysterectomy; dogs were given ketoprofen or saline solution 60 minutes before induction of anesthesia

Variable	Time after surgery (h)									
	0	2	4	6	8	10	12	16	20	24
HR (beats/min)										
Saline solution	126 ± 27	112 ± 20	104 ± 24 ^a	108 ± 12	106 ± 20 ^a	98 ± 19 ^a	101 ± 20 ^a	88 ± 14 ^a	90 ± 13 ^a	89 ± 21 ^a
Ketoprofen	112 ± 29	106 ± 34	97 ± 15	95 ± 17	97 ± 20	100 ± 20	88 ± 21 ^a	92 ± 22 ^a	90 ± 16 ^a	89 ± 19 ^a
RR (breaths/min)										
Saline solution	17 ± 10	31 ± 26	21 ± 11	27 ± 19	26 ± 10	24 ± 11	29 ± 11	25 ± 10	28 ± 17	38 ± 29
Ketoprofen	14 ± 7	25 ± 23	34 ± 27	20 ± 6	31 ± 26	33 ± 18	38 ± 26	41 ± 24	35 ± 21	39 ± 30
MAP (mm Hg)										
Saline solution	74 ± 18	102 ± 17 ^a	105 ± 19 ^a	106 ± 22 ^a	106 ± 19 ^a	116 ± 23 ^a	111 ± 19 ^a	104 ± 18 ^a	109 ± 27 ^a	108 ± 20 ^a
Ketoprofen	75 ± 12	107 ± 13 ^a	108 ± 12 ^a	107 ± 17 ^a	114 ± 15 ^a	111 ± 17 ^a	109 ± 20 ^a	111 ± 16 ^a	102 ± 13 ^a	103 ± 13 ^a
Rectal temperature (°C)										
Saline solution	36.9 ± 0.8	38.2 ± 1.1 ^a	38.4 ± 0.6 ^a	38.6 ± 0.5 ^a	38.6 ± 0.4 ^a	38.6 ± 0.5 ^a	38.7 ± 0.5 ^a	38.7 ± 0.4 ^a	38.6 ± 0.4 ^a	38.7 ± 0.3 ^a
Ketoprofen	37.3 ± 0.8	38.1 ± 0.6 ^a	38.3 ± 0.5 ^a	38.5 ± 0.4 ^a	38.6 ± 0.5 ^a	38.8 ± 0.4 ^a	38.8 ± 0.5 ^a	38.8 ± 0.3 ^a	38.8 ± 0.2 ^a	38.7 ± 0.3 ^a

^aSignificantly (*P* < 0.05) different from baseline value (ie, value obtained immediately after surgery).
See Table 1 for remainder of key.

Table 3—Pain scores assigned after surgery in healthy dogs (n = 11/group) undergoing an ovariohysterectomy; dogs were given ketoprofen or saline solution 60 minutes before induction of anesthesia

Score	Time after surgery (h)									
	0	2	4	6	8	10	12	16	20	24
Objective behavioral score										
Saline solution	0 (0.0–0.0)	1 (0.0–1.8)	0 (0.0–1.0)	1 (0.3–1.8)	2 ^a (1.0–3.8)	1 ^a (1.0–2.5)	1 ^a (1.0–3.0)	1 (0.0–2.8)	1 ^a (0.3–3.0)	3 ^a (1.3–3.8)
Ketoprofen	0 (0.0–0.0)	1 (0.0–2.0)	2 ^{a,b} (2.0–3.8)	3 ^{a,b} (1.3–4.0)	3 ^a (2.0–4.0)	2 ^a (2.0–2.0)	2 ^a (1.0–3.8)	1 (0.0–2.8)	2 (0.3–3.8)	3 ^a (2.0–5.0)
Numerical pain score at rest										
Saline solution	0 ± 0	13 ± 17 ^a	7 ± 14	6 ± 11	7 ± 12	5 ± 11	5 ± 10	5 ± 6	0 ± 0	1 ± 3
Ketoprofen	0 ± 0	17 ± 2 ^a	15 ± 20 ^a	11 ± 10	3 ± 6	1 ± 2	4 ± 8	3 ± 8	2 ± 3	1 ± 2
Numerical pain score with movement										
Saline solution	0 ± 0	21 ± 28 ^a	13 ± 16 ^a	10 ± 14	14 ± 13 ^a	14 ± 13 ^a	12 ± 11	9 ± 10	6 ± 8	4 ± 7
Ketoprofen	0 ± 0	24 ± 20 ^a	27 ± 19 ^a	16 ± 13 ^a	11 ± 16	8 ± 12	9 ± 9	6 ± 10	5 ± 6	1 ± 2

Objective behavioral scores are reported as median and interquartile (25th to 75th percentile) range. Numerical pain scores are reported as mean ± SD.
See appendix for criteria for assignment of objective behavioral scores. Numerical scores were assigned by a single observer who examined 5-minute videotapes of each dog obtained immediately before (score at rest) and after (score with movement) each sampling interval and assigned a score ranging from 0 (no signs of pain) to 100 (signs of the worst pain possible for a dog undergoing ovariohysterectomy).
^aSignificantly (*P* < 0.05) different from value obtained immediately after surgery. ^bSignificantly (*P* < 0.05) different from value obtained after administration of saline solution.

Table 4—Serum cortisol and glucose concentrations before and after surgery in healthy dogs (n = 11/group) undergoing an ovariohysterectomy; dogs were given ketoprofen or saline solution 60 minutes before induction of anesthesia

Variable	Time after surgery (h)							
	-18	0	4	8	12	16	20	24
Cortisol (nmol/L)								
Saline solution	107 ± 105	303 ± 42 ^a	122 ± 66	106 ± 49	106 ± 59	92 ± 95	83 ± 43	108 ± 70
Ketoprofen	68 ± 35	271 ± 116 ^a	88 ± 72	93 ± 58	111 ± 104	111 ± 83	88 ± 48	80 ± 37
Glucose (mmol/L)								
Saline solution	6.1 ± 0.7	6.3 ± 0.6	5.9 ± 0.7	5.4 ± 0.6 ^a	5.7 ± 0.5	5.8 ± 0.5	5.8 ± 0.5	6.3 ± 0.8
Ketoprofen	5.8 ± 0.6	6.2 ± 0.6	5.6 ± 0.5	5.2 ± 0.9 ^a	5.4 ± 0.6	5.8 ± 0.8	5.6 ± 0.6	5.5 ± 0.9

Values are reported as mean ± SD.
^aSignificantly ($P < 0.05$) different from preoperative value.

saline solution and from 2 to 6 hours after surgery in dogs given ketoprofen. None of the dogs were deemed painful enough to be withdrawn from the study.

Preoperative administration of ketoprofen did not alter serum cortisol or serum glucose concentrations after surgery, in that significant differences between groups were not detected at any time (Table 4). However, significant changes over time were detected for both groups. In both groups, mean serum cortisol concentration was significantly increased immediately after surgery, compared with concentration the day before surgery. Similarly, in both groups, mean serum glucose concentration was significantly decreased 8 hours after surgery, compared with concentration the day before surgery.

Discussion

The first important result of the study reported here was that under the conditions of this study, preoperative administration of ketoprofen did not reduce anesthetic requirements in dogs undergoing elective ovariohysterectomy. The dose of thiopental required to induce anesthesia in dogs given saline solution was nearly identical to that required in dogs given ketoprofen. This result was somewhat surprising, considering that both thiopental and ketoprofen are highly protein-bound drugs and that prior administration of ketoprofen should increase the amount of active, unbound thiopental. Perhaps the drugs bind at different sites, or perhaps small changes in protein binding do not have an appreciable effect on the total amount of active, unbound thiopental, given its large volume of distribution relative to ketoprofen. Similarly, the concentration of isoflurane required to maintain anesthesia was comparable after administration of saline solution or ketoprofen for the duration of the surgical procedure. This result is consistent with previous studies^{16,17} that demonstrated that administration of carprofen did not decrease MAC in dogs anesthetized with halothane or isoflurane. Apparently, ketoprofen's central analgesic action has no effect on the concentration of isoflurane required to maintain anesthesia during elective abdominal surgery.

Perhaps the most important aspect of the study reported here is the use of an OB score designed to detect changes in patient activity levels. Similar behavioral and composite (ie, scales that include both behavioral and physiologic variables) pain scores have been used in previous studies,^{18,23-27} but none limited behaviors to objective, clearly defined criteria. Most compos-

ite pain scoring criteria have been used to measure acute postoperative pain in dogs and are modeled after the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), a behavioral pain scale developed for use in children.²⁸ The CHEOPS was originally designed to measure acute postoperative pain in children in the recovery room. Because behavioral and physiologic variables tend to habituate with time, behavioral scales like the CHEOPS and the composite scales used in veterinary medicine are probably not valid for measuring pain several hours after surgery.²⁹ In addition, behavioral and physiologic variables are often directly altered by prior or concurrent administration of anesthetic and analgesic drugs and may not correlate well with numerical and visual analog pain scores.³⁰⁻³⁴ In the study reported here, we chose to use a behavioral scale that included objective criteria and provided an index of activity level. We also chose to schedule surgical procedures for the same time each day (morning), so that normal diurnal patterns of behavior would not be obscured by procedures performed later in the day. In dogs given ketoprofen, increases in behavioral scores were observed 4 and 6 hours after surgery. Other studies suggest that adequate relief of postoperative pain is associated with a more rapid return to normal behavior and activity levels.^{31,35} Therefore, the increase in activity level observed at these times may be attributable to an analgesic effect that was not detected by analysis of NP scores recorded at rest and with movement.

The other important result of the study reported here was that preoperative administration of ketoprofen did not reduce NP scores in dogs undergoing elective ovariohysterectomy. Single-evaluator NP scales appear to be the most simple, reliable, and valid methods of evaluating acute postoperative pain in dogs.^{35,36} In our study, pain scores were recorded at rest and with movement and were scaled for signs of pain typically associated with ovariohysterectomy to increase sensitivity. However, NP scores at rest and with movement were relatively low throughout the 24-hour period after surgery for dogs in both groups. For instance, for both groups, mean NP scores at rest were significantly increased, compared with baseline values, 2 hours after surgery, but mean score was only 17 for dogs that received ketoprofen and 13 for dogs that received saline solution. Mean NP scores with movement were significantly increased only 2 and 4 hours after surgery and did not exceed a score of 27. By comparison, Mathews et al²⁰ reported that 11 of 12 dogs undergoing abdominal surgery performed by student surgeons and

given butorphanol (0.2 mg/kg, IM) had pain scores ≥ 3 on a 10-point descriptive scale within 10 hours after recovery from anesthesia. The authors thus concluded that preoperative administration of ketoprofen reduced opioid requirements in these dogs. In the present study, abdominal surgery was performed by an experienced surgeon, the procedures were shorter and less traumatic, and lower pain scores would be expected. However, the difference between the 2 methods of assessment is striking and suggests that traditional NP scales lack the sensitivity required to detect low-level, acute postoperative pain in animals.

Given the inherent difficulty associated with objective measurement of pain in animals, clinical researchers should strive to control variability within experimental treatments. In the study reported here, several steps were taken to minimize variation associated with differences among subjects. First, female dogs that were comparable in age, weight, and stage of the reproductive cycle were selected for the study. Second, dogs were admitted on the day before surgery, and procedures were performed the following morning. This was done to limit, as well as to standardize, stress associated with hospitalization and to minimize variations in behavior associated with normal diurnal variability. Third, a single surgical procedure was selected, and each procedure was performed by the same experienced surgeon. Fourth, the anesthetic protocol was standardized, and the anesthesiologist was given the option to withdraw animals from the study if the protocol was deemed inappropriate. Fifth, the analgesic protocol was standardized, and the anesthesiologist, surgeon, and technicians were given the option to withdraw animals from the study if the protocol did not provide adequate pain relief. These methods demonstrate that rigorous control of experimental protocols can be achieved in a clinical setting while maintaining appropriate standards of patient care. In the future, clinical researchers should standardize experimental protocols to a greater degree than has been done in the past. Failure to standardize protocols and reduce experimental error decreases the power of the experimental design and the ability to detect significant analgesic effects.

There are 3 limitations to the results of the study reported here. First, the sample size was small, although it was consistent with sample sizes of similar studies^{20,27} reported in the literature and current recommendations.³⁵ Given the small differences in NP scores at rest and with movement, it is unlikely that increasing the sample size would have revealed a significant difference in scores between groups. Second, the issue of preoperative versus postoperative administration of ketoprofen was not addressed by this study. This type of study, which has been completed for carprofen,³⁷ requires 3 treatment groups (control, preoperative analgesic administration, and postoperative analgesic administration) and at least twice as many animals in each treatment group (ie, 20 to 30 animals/group). Third, this study did not address the effects of preoperative administration of ketoprofen on platelet and renal function. In healthy dogs, preoperative administration of ketoprofen decreases platelet aggregation but

does not alter bleeding time during the perioperative period³⁸ and does not appear to alter renal function.³⁹

Given that ketoprofen did not reduce anesthetic requirements under the conditions of the study reported here, it was not surprising that there were no differences between groups in regard to the physiologic variables recorded during and after surgery. Heart rate, respiratory rate, MAP, and PETCO₂ were stable throughout the surgical procedure and did not differ between groups, suggesting that depth of anesthesia was comparable for the 2 groups. Endogenous prostaglandins do play a central role in the regulation of blood pressure, and NSAIA drugs administered preoperatively could interact with anesthetic drugs given preoperatively and intraoperatively to alter arterial pressure during surgery. For instance, an increase in blood pressure and concurrent decrease in cardiac output can occur after administration of NSAIA drugs.⁴⁰ In the study reported here, preoperative administration of ketoprofen did not appear to alter heart rate or blood pressure intraoperatively, but these changes could have been attenuated by the anesthetic drugs (acepromazine, isoflurane) used in our study.

Serum cortisol and glucose concentrations were measured after surgery in the present study to assess the neuroendocrine and metabolic responses to hospitalization, anesthesia, and surgical trauma. Serum cortisol concentrations in the study reported here are consistent with those reported in other similar studies.^{30,41} Findings in the present study suggest that preoperative administration of ketoprofen did not alter the neuroendocrine and metabolic responses that occur after abdominal surgery.

In summary, results of the study reported here suggest that preoperative administration of ketoprofen does not reduce anesthetic requirements or pain scores after surgery in dogs undergoing an ovariohysterectomy. However, increases in OB scores 4 and 6 hours after surgery suggest that preoperative administration of ketoprofen may reduce pain after surgery and that OB scores may be a more sensitive measure of acute postoperative pain than traditional NP scores. Ketoprofen can be given before surgery to selected patients undergoing elective surgery, provided they have been screened for potential bleeding problems and renal disease and have not been given other drugs that inhibit platelet function (eg, cephalosporin antibiotics). Because of these potentially adverse effects and because preoperative administration of ketoprofen has not been shown to be more effective than postoperative administration, ketoprofen should not be given before surgery on a routine basis. At the Atlantic Veterinary College, dogs undergoing elective ovariohysterectomy are given opioids before and immediately after surgery and are monitored closely for the next 24 hours. If analgesia appears to be inadequate, NSAIA drugs (eg, ketoprofen or meloxicam) are given parenterally for the first 24 hours and then orally until the patient is discharged. In some cases, NSAIA drugs are dispensed to the owner and given orally for an additional 2 to 3 days.

^aAnafen, Merial, Victoriaville, QC, Canada.

^bModel 6000, Sensor Devices, Waukesha, Wis.

^cVSM1, Physiocontrol, Redmond, Wash.

^dPB254 airway gas monitor, Datex, Helsinki, Finland.

^eDigital thermometer, Becton-Dickinson, Mississauga, ON, Canada.

^fCoat-A-Count, Diagnostic Products Corp, Los Angeles, Calif.

^gGlucose GOD-PAP, Roche Diagnostics, Montreal, QC, Canada.

^hHitachi 911, Boehringer, Indianapolis, Ind.

Appendix

Criteria for assigning objective behavioral pain scores in dogs

Variable	Score	Criteria
Posture	0	Recumbent
	1	Sitting
	2	Standing
Mentation	0	Asleep
	1	Calm
	2	Alert
Vocalization	0	None
	1	Intermittent
	2	Constant
Movement	0	None
	1	Intermittent
	2	Constant

The objective behavioral pain score was derived by totalling scores for each of the 4 variables. Potential scores ranged from 0 (low activity level) to 8 (high activity level).

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New Veterinary Biological Products

Product name	Species and indications for use	Route of administration	Remarks
Mycobacterium Tuberculosis Gamma Interferon Test Kit for non-human primates (Biocor Animal Health Inc, Omaha, Neb, US Vet Lic No. 462)	An in vitro diagnostic test kit for detection of tuberculosis in nonhuman primates.	N/A test kit	USDA licensed 8/2/02
Avian Pneumovirus Vaccine, modified live virus (Biomune Co, Lenexa, Kan, US Vet Lic No. 368)	As an aid in the prevention of respiratory disease caused by avian pneumovirus in turkeys at least one week of age or older.	This vaccine is for drinking water or intraocular vaccination.	USDA licensed 8/21/02