Comparison of perioperative analgesic efficacy between methadone and butorphanol in cats

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Objective—To compare the perioperative analgesic effect between methadone and butorphanol in cats.

Design—Randomized controlled clinical trial.

Animals—22 healthy female domestic cats.

Procedures—Cats admitted for ovariohysterectomy were allocated to a butorphanol group (n = 10) or methadone group (12) and premedicated with butorphanol (0.4 mg/kg [0.18 mg/lb], SC) or methadone (0.6 mg/kg [0.27 mg/lb], SC), respectively, in combination with acepromazine (0.02 mg/kg [0.01 mg/lb], SC). Anesthesia was induced with propofol (IV) and maintained with isoflurane in oxygen. A multidimensional composite scale was used to conduct pain assessments prior to premedication and 5, 20, 60, 120, 180, 240, 300, and 360 minutes after extubation or until rescue analgesia was given. Groups were compared to evaluate isoflurane requirement, propofol requirement, pain scores, and requirement for rescue analgesia.

Results—Propofol and isoflurane requirements and preoperative pain scores were not different between groups. During recovery, dysphoria prevented pain evaluation at 5 minutes. Pain scores at 20 minutes were significantly lower in the methadone group, and 6 of 10 cats in the butorphanol group received rescue analgesia, making subsequent pain score comparisons inapplicable. After 6 hours, only 3 of 12 cats in the methadone group had received rescue analgesia.

Conclusions and Clinical Relevance—In the present study, methadone appeared to be a better postoperative analgesic than butorphanol and provided effective analgesia for 6 hours following ovariohysterectomy in most cats. (*J Am Vet Med Assoc* 2013;243:844–850)

Methadone is a widely used pure μ-opioid receptor agonist in human and veterinary medicine. It is assumed to be adequate for severe pain because its pharmacological properties are similar to morphine and its antinociceptive potency is 10 to 50 times that of morphine.[1]

Methadone is also an antagonist at the *N*-methyl-D-aspartate receptors, inhibits the reuptake of serotonin and noradrenaline, and promotes the blockade of nicotinic cholinergic receptors.[2–4] These are additional mechanisms thought to play a role in methadone-mediated analgesia.[4] Methadone does not undergo hepatic glucuronidation in cats and may therefore have an advantage over other opioids (such as morphine) because it is less likely to accumulate.[5]

Several studies have been performed evaluating the use of methadone in cats. The effects of perioperative IM administration of racemic methadone, levomethadone, and dextromoramide have been compared in cats through indicators of postoperative pain.[6] The authors concluded that methadone administered at 0.6 mg/kg (0.27 mg/lb) provided effective analgesia in cats following ovariectomy, without behavioral, respiratory, or cardiovascular adverse effects. The effects of SC administration of methadone (0.2 mg/kg [0.09 mg/lb]), morphine (0.2 mg/kg), buprenorphine (0.02 mg/kg [0.009 mg/lb]), or saline (0.9% NaCl) solution on thermal and pressure thresholds in cats have been compared.[7] The authors concluded that methadone appeared to be a promising alternative to morphine. The plasma concentrations and behavioral, antinociceptive, and physiologic effects of methadone administered IV (0.3 mg/kg [0.14 mg/lb]) and via oral transmucosal routes (0.6 mg/kg) in cats were compared, and the authors concluded that methadone administered via either route may be useful for perioperative pain management.[8] A study[9] comparing the use of methadone (0.5 mg/kg [0.23 mg/lb], IM), butorphanol (0.4 mg/kg [0.18 mg/lb], IM), and buprenorphine (0.02 mg/kg, IM) failed to detect

Abbreviations

P_{ETCO_2}	End-tidal partial pressure of carbon dioxide
EtISO	End-tidal isoflurane concentration
HR	Heart rate
MAC	Minimal alveolar concentration
MAP	Mean arterial blood pressure
MNT	Mechanical nociceptive threshold
RR	Respiratory rate
Spo_2	Oxygen saturation as determined by means of pulse oximetry
VAS	Visual analogue scale

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any difference in the postoperative analgesic effects of the 3 drugs when administered with acepromazine for neutering. That study assessed pain with a VAS as well as an MNT with a pressure rate onset device.

Butorphanol is a μ-opioid (OP2) receptor agonist and μ-opioid (OP3) receptor antagonist.[10] Butorphanol induces analgesia through its μ-opioid receptor agonist activity; however, its analgesic properties have been questioned.[11] Butorphanol is believed to provide adequate visceral but poor somatic analgesia.[12] Notwithstanding variation in response among populations and individual cats, butorphanol has a fast onset but short duration of antinociception (reported to be [mean ± SD] 2.7 ± 2.2 hours after IM administration) in several studies,[12–15] requiring repeated administration to be effective. Butorphanol is also reported to be unsuitable as the sole pain-relieving drug for the treatment of moderate to severe pain following surgery.[16]

The purpose of the study reported here was to evaluate the analgesic effect of methadone, compared with butorphanol, in cats by use of a partially validated multidimensional composite pain scale. The null hypothesis was that butorphanol and methadone provide the same degree of analgesia in the postoperative period following ovariohysterectomy.

Materials and Methods

Animals and experimental design—The study was designed as a randomized controlled clinical trial and was approved by the animal ethics committee of the institution where the study was performed. During an approximately 5-month period, domesticated female cats ranging in age from 4 months to 4 years that were referred to the University Veterinary Hospital for elective ovariohysterectomy were included in the trial after agreement and signed consent were obtained from the owners and after the cats were determined to be healthy by means of physical examination and basic blood analysis including measurement of PCV, serum total protein concentration, BUN concentration, and blood glucose concentration. The cats were then randomly allocated to a butorphanol (n = 10) or methadone (12) group. The randomization was performed by use of a commercially available software package.[a]

The cats were premedicated by means of SC administration between the scapulae with acepromazine[b] (0.02 mg/kg) in combination with butorphanol[c] (0.4 mg/kg) or methadone[d] (0.6 mg/kg). Twenty minutes later, a 22-G, 25-mm over-the-needle catheter was placed in one of the cephalic veins. Anesthesia induction was started 30 minutes after premedication with a constant rate infusion of propofol[e] (1.5 mg/kg/min [0.68 mg/lb/min], IV) administered to effect with a calibrated syringe pump[f] until orotracheal intubation was achieved. The endotracheal tube was then connected to a pediatric rebreathing system,[g] and isoflurane[h] in oxygen (1 to 2 L/min) was administered to effect to maintain anesthesia. All cats maintained spontaneous ventilation. A balanced crystalloid solution[i] was administered IV at a rate of 10 mL/kg/h (4.5 mL/lb/h) during anesthesia. A calibrated multiparametric anesthesia monitor[j] displayed continuous ECG, EtISO, HR, RR, P_{ETCO_2}, and Spo_2 data. Mean arterial blood pressure was obtained with a noninvasive oscillometric blood pressure device.[k] The cuff used for the blood pressure measurements was placed proximal to the right metacarpal region, and its width was approximately 40% of the limb circumference.

Bradycardia and hypotension were defined as an HR of < 90 beats/min and an MAP of < 60 mm Hg, respectively. Bradycardia was treated with glycopyrrolate[l] (0.005 mg/kg [0.002 mg/lb], IV) as required. Hypotension was treated with IV fluid therapy (10 mL/kg for 10 minutes, repeated if required) and dopamine[m] infusion at 7 μg/kg/min (3.2 μg/lb/min), IV.

The same community practice surgeon performed all of the ovariohysterectomy surgeries following the surgical standards of the institution (midline approach). Anesthesia time was defined as the time from the start of anesthetic induction to the time of extubation, and surgery time was defined as the time from the primary skin incision to the placement of the last skin suture. The postoperative temperatures reported were obtained rectally just before extubation. Pain assessments were performed before administration of anesthetic premedication (baseline) and after surgery at 5, 20, 60, 120, 180, 240, 300, and 360 minutes after extubation or until rescue analgesia was administered. If at any time point the evaluation score exceeded 9 of 28, the patient was determined to be in moderate to severe pain and was given rescue analgesia (methadone, 0.2 mg/kg, IV). All cats received meloxicam[n] (0.2 mg/kg, SC), following the last pain score evaluation or if rescue analgesia was dispensed.

The anesthetist and the pain evaluator were unaware of the treatment that the cats received. All cats were intubated and monitored by the same anesthetist and were assessed by the same pain evaluator.

Evaluation of the anesthetic-sparing effect at induction of anesthesia with methadone versus butorphanol—The anesthetic-sparing effect of methadone versus butorphanol was indirectly assessed 30 minutes after premedication. The propofol constant rate infusion was administered at a rate of 1.5 mg/kg/min, IV, and was discontinued once intubation without coughing was achieved. The amount of propofol used was recorded for each cat, and the mean propofol induction dose required to induce anesthesia was calculated for the 2 groups. The opioid used for the group requiring less propofol was considered to have a more anesthetic-sparing effect at induction.

Evaluation of the isoflurane-sparing effect of methadone versus butorphanol—Similarly, the isoflurane-sparing effect of methadone versus butorphanol was assessed by comparing the amount of isoflurane required to maintain general anesthesia between the 2 groups. Every 5 minutes, the depth of anesthesia was checked by noting the clinical signs, including degree of relaxation of the temporomandibular articulation, position of the eyes, and absence of a palpebral reflex. The EtISO was increased by 0.2% increments in cats that reacted to surgical stimuli. If a cat was perceived as being at a level of anesthesia that was too deep (relaxed temporomandibular articulation, eyes centrally positioned, and absence of palpebral reflexes), the EtISO was decreased by 0.1% increments. The mean EtISO

required to maintain anesthesia was calculated for the 2 groups. All cats were monitored with the same calibrated monitor.

Pre- and postoperative pain assessments—All pain assessments were performed by the same board-certified veterinary anesthesiologist, who was unaware of treatments, according to a published pain scoring system.[17] From the pain assessment results, 4 scores were defined. The preoperative score was the baseline pain evaluation score determined before premedication and was analyzed to detect any baseline difference between the 2 groups and to detect any abnormal behavior that may have interfered with the scoring system. The rescue analgesia score was 0 if no rescue analgesia was administered during the postoperative 360-minute period and 1 if rescue analgesia was administered. The last evaluation score was assigned on the basis of the time point at which the last pain score evaluation was performed and thus reflected the time at which rescue analgesia was given if required. If the last pain score evaluation was performed after 5, 20, 60, 120, 180, 240, 300, or 360 minutes, the cat was given a last evaluation score of 7, 6, 5, 4, 3, 2, 1, or 0, respectively. The time point evaluation score was the postoperative pain evaluation score at each time point (5, 20, 60, 120, 180, 240, 300, and 360 minutes).

All blood pressures recorded before premedication and at each pain score evaluation time point were measured with a veterinary-specific handheld oscillometric blood pressure measurement device.[o] The cuff used for the blood pressure measurements was placed proximal to the right metacarpal region, and its width was approximately 40% of the limb circumference. The arterial systolic blood pressure values of these measurements were used in the scoring system.

Physiologic variables monitored during general anesthesia—During anesthesia, cats were assessed every 5 minutes for HR, RR, P_{ETCO_2}, Spo_2, and MAP. Heart rate and RR were derived from the Spo_2 reading and P_{ETCO_2} reading, respectively.

Pain reaction at injection of the premedication and injection site reaction at last pain evaluation—Cats were minimally restrained during the anesthetic premedication injection. The anesthetist held the skin between the 2 scapulae, inserted the needle SC, waited several seconds, and then injected the drugs. The cats were subjectively evaluated for signs of pain (abrupt movements and vocalization) at the time of injection. A score of 0 was given if no signs of pain were detected, and a score of 1 was given for signs of pain.

Cats were examined by the same anesthetist for injection site reaction after the last pain score evaluation. This was done by palpation of the skin between the 2 scapulae at the injection site to detect any sign of inflammation (eg, edema, heat, or pain). This variable was given a score of 0 if no inflammatory reaction was detected and a score of 1 if there were signs of inflammation.

Statistical analysis—Data analysis was performed by use of a commercially available software package.[p] Comparisons of weight, isoflurane requirement (mean EtISO), HR, RR, $Etco_2$, MAP, anesthesia time, and surgery time were analyzed with a 2-tailed *t* test. The Shapiro-Wilk test was used to test for normality of residuals. Age, propofol requirement (mean propofol induction dose), preoperative score, last evaluation score, and time point evaluation scores were analyzed by means of a 2-tailed Mann-Whitney exact test. To account for multiple comparisons, a Bonferroni adjustment was used on the intraoperative physiologic variables (HR, RR, P_{ETCO_2}, and MAP). The rescue analgesia score was analyzed with the Fisher exact test. Values of $P < 0.05$ were deemed significant.

Results

Cats, anesthesia time, and surgery time—Of the 22 female cats that were included in this study, 12 were allocated to the methadone group and 10 to the butorphanol group. Mean ± SD weight of the cats was 2.8 ± 0.5 kg (6.2 ± 1.1 lb; range, 2.1 to 3.8 kg [4.6 to 8.4 lb]) and 2.9 ± 0.3 kg (6.4 ± 0.7 lb; range, 2.7 to 3.4 kg [5.9 to 7.5 lb]) for the methadone and butorphanol groups, respectively ($P = 0.61$). Median age was 9 months (range, 4 to 37 months) and 11.5 months (range, 5 to 33 months) for the methadone and butorphanol groups, respectively ($P = 0.42$). Nineteen cats were domestic shorthairs, 2 were Ragdolls, and 1 was a British Shorthair. No cats were removed from the study after enrollment, and no cats died or were euthanized during the study. Mean ± SD anesthesia times were 51 ± 8.3 minutes and 54 ± 10.13 minutes for the methadone and butorphanol groups, respectively ($P = 0.40$). Mean ± SD surgery times were 21 ± 3.6 minutes and 22 ± 5.6 minutes for the methadone and butorphanol groups, respectively ($P = 0.56$). Mean postoperative rectal temperature (for all cats) was 36.1 ± 0.6°C (97.0 ± 1.1°F).

Evaluation of the anesthetic-sparing effect at induction of methadone versus butorphanol—The median dose of propofol needed to induce general anesthesia via a slow constant rate infusion IV was 8.95 mg/kg (4.1 mg/lb; range, 6.8 to 16.7 mg/kg [3.1 to 7.6 mg/lb]) and 7.8 mg/kg (3.5 mg/lb; range, 6.6 to 14.6 mg/kg [3.0 to 6.6 mg/lb]) for the methadone and butorphanol groups, respectively ($P = 0.39$). Although subjectively observed, excitation was seen during induction of anesthesia in most cats in the 2 groups.

Evaluation of the isoflurane-sparing effect of methadone versus butorphanol—The mean ± SD concentration of isoflurane needed to maintain general anesthesia was 0.9 ± 0.2% and 1.0 ± 0.3% for the butorphanol and methadone groups, respectively ($P = 0.22$). The 95% confidence interval for the difference (methadone minus butorphanol) was –0.08% to 0.35%.

Pre- and postoperative pain assessments—Median preoperative scores were not significantly different between the methadone and butorphanol groups (**Table 1**). At the first postoperative pain assessment (5 minutes), most cats (19/22) were dysphoric and still exhaling a large amount of isoflurane, making their evaluation impossible to complete. At 20 minutes, pain assessment scores from all cats were obtained. Median 20-minute scores were significantly ($P < 0.001$) higher for the butorphanol group than the methadone group.

Table 1—Median (range) pain evaluation scores obtained before and after ovariohysterectomy for cats premedicated with acepromazine and butorphanol or methadone.

	Before surgery		5 minutes		20 minutes		60 minutes		120 minutes		180 minutes		240 minutes		300 minutes		360 minutes	
Group	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score	n	Score
Butorphanol	10	0 (0–0)	0	NS	10	10 (5–18)	4	7.5 (2–11)	2	2 (0–4)	2	3 (2–4)	2	6.5 (4–9)	1	3	1	3
Methadone	12	0 (0–1)	3	6 (1–6)	12	4 (0–8)	12	5.5 (0–8)	12	5 (0–8)	12	4.5 (1–11)	11	4 (0–6)	11	5 (0–9)	8	2.5 (1–7)

Maximum possible pain score was 28. Scores were assigned before surgery and after extubation following surgery for 360 minutes or until rescue analgesia was given (when pain score was ≥ 9).

Subsequent time point pain assessment scores were not statistically analyzed because most cats in the butorphanol group had received rescue analgesia and were not evaluated further.

Three of 12 cats in the methadone group and 9 of 10 cats in the butorphanol group required rescue analgesia ($P = 0.01$). In the butorphanol group, 6, 2, 1, and 1 cats received pain evaluation scores indicating moderate to severe pain at 20, 60, 240, and 360 minutes, respectively. In the methadone group, 2 cats received pain evaluation scores indicating moderate to severe pain at 180 or 300 minutes and 1 cat that become more aggressive was not evaluated at 360 minutes. Individual pain evaluation scores of all 8 cats in the methadone group that were evaluated at 360 minutes were lower at that time point, compared with their 20-minute pain scores. Median values of the last evaluation scores were 0 (range, 0 to 3) and 6 (range, 0 to 6) for the methadone and butorphanol groups, respectively ($P = 0.01$).

Physiologic variables monitored during anesthesia—No significant differences between treatment groups were detected at any time point during anesthesia for HR, RR, P_{ETCO_2}, or MAP. Mean ± SD HR, RR, P_{ETCO_2}, and MAP were, respectively, 139 ± 36 beats/min, 21 ± 9 breaths/min, 30 ± 8 mm Hg, and 78 ± 28 mm Hg for the methadone group and 134 ± 31 beats/min, 17 ± 7 breaths/min, 28 ± 9 mm Hg, and 80 ± 28 mm Hg for the butorphanol group. Oxygen saturation of hemoglobin remained > 95% in all cats.

To treat hypotension, 9 of 12 cats and 9 of 10 cats required a transient increase in IV fluid administration rate (10 mL/kg for 10 minutes) in the methadone and butorphanol groups, respectively. One cat from the methadone group also received a dopamine infusion for a short period (< 15 minutes) at 7 µg/kg/min, IV, before the start of surgery. Five cats from the butorphanol group and 1 cat from the methadone group required a single dose of glycopyrrolate (0.005 mg/kg, IV) during that same period.

Pain reaction at injection site—None of the cats in either group had signs of pain during injection of the premedication. In addition, at the time of the last evaluation, no cats had signs of subcutaneous or cutaneous reactions at the site of the injection.

Discussion

The present study was designed to assess the analgesic efficacy of methadone for regulatory purposes to obtain registration for administration of methadone for perioperative analgesia in cats in Australia. The dose used for butorphanol was the registered dose, and the dose used for methadone was determined in a pilot study. Premedication drugs were administered SC because this route is often preferred by general practitioners to facilitate placement of an IV catheter. Subcutaneous injections are considered by most practitioners to be less painful than IM injections; however, drug absorption is less reliable.[7] Because ovariohysterectomy is known to be a painful procedure requiring analgesia, a negative control group was not included in the study design for ethical reasons.[18]

All cats involved in this study were client owned and representative of the domestic population. Most were young domestic shorthairs; however, 3 purebred cats were also included. There were no outstanding differences in temperament. Although sedation level was not objectively assessed, the level of sedation following premedication in both groups was low. This was in agreement with findings by Bortolami et al,[9] who used similar doses. In the present study; however, it was possible to place IV catheters in all cats without any further administration of sedative drugs. Agitation, dysphoria, or vomiting was not observed in either group.

A minimum oxygen flow rate of 1 L/min was used to decrease the time constant (capacity of the breathing system divided by fresh gas flow rate) of the rebreathing system. This allowed for a quicker response (in changes of the inhalant anesthetic concentration) of the system to vaporizer setting changes.

There was no significant difference between the 2 groups with respect to the dose of propofol required to induce anesthesia. In both groups, the mean dose required was greater than the manufacturer's recommended dose of 6 mg/kg (2.7 mg/lb, IV) and was close to the reported dose required for tracheal intubation of unsedated cats.[19] The high doses of propofol required in the present study could have resulted from lack of sedation from the premedications. In addition, the slow injection rate (1.5 mg/kg/min) likely contributed to the higher-than-expected doses of induction agent. The syringe pump was a limiting factor because it was not capable of a higher rate of injection. The speed of administration of the induction agent is an important factor in promptly achieving an optimal blood concentration to induce smooth anesthesia without any complications.[20,21] Ultimately, agitation caused by induction will result in a larger total amount of induction agent required to achieve anesthesia.[22] Consequently, the mean dose of propofol required to achieve induction of

anesthesia in this study must be considered in context; its purpose was only to enable comparison between the 2 groups and not to achieve recommended doses.

The MAC for isoflurane has been reported to be 1.62% in cats.[23] Although the present study did not evaluate MAC, the amount of isoflurane required to maintain anesthesia in both groups (1.0 ± 0.3% and 0.9 ± 0.2% for the methadone and butorphanol groups, respectively) was less than the MAC. The low isoflurane requirement was most likely attributable to the sedative effects of acepromazine and the antinociceptive effects of methadone and butorphanol.[2–4,13,15,24] In cats, the degree of MAC reduction that occurs with the perioperative use of opioids is a balance between the antinociceptive qualities of opioids, which promote MAC reduction, and the excitatory characteristics of opioids, which oppose MAC reduction and sedation. The limited MAC reduction seen in cats, compared with dogs, which frequently have sedation following opioid premedication, is suggested to be attributable to opioid-induced stimulation of the sympathetic nervous system.[25–29]

The present study used a partially validated multidimensional composite scale for assessing postoperative pain in cats undergoing ovariohysterectomy.[17] To the authors' knowledge, no other partially validated pain assessment scale has been described for use in cats. The expression of pain is considered to be multidimensional, and tools that evaluate multiple domains of pain are more accurate than those that only measure 1 domain, namely intensity (eg, a VAS, numeric rating scale, or simple descriptive scale).[30,31] The composite scale evaluates 4 domains: psychomotor change, protection of wound area, physiologic variables, and vocal expression of pain. Each domain comprises certain factors, such as posture, reaction to palpation, and systolic arterial blood pressure. The total score is based on the sum of the 4 domains and may range from 0 (no signs of pain) to 28 (maximum signs of pain). Scores < 9, from 9 to 20, and > 20 are considered indicative of mild, moderate, and severe pain, respectively.[17]

There are at least 2 limitations of the pain scale that was used in this study: all factors and domains of the scale are weighted equally, and the intensity of pain is assumed to be reflected in the total pain score. Thus, it is only possible to evaluate whether a cat has more or less pain, but it is not possible to quantify the specific amount of pain.[17] The fact that this pain scale was able to detect a significant difference in pain scores between the methadone and butorphanol groups could be an indication of good sensitivity of the scoring system.

The need for rescue analgesia may also be used to evaluate the efficacy of analgesic drugs.[17,32] The triggering pain score of 9 (of 28) for rescue analgesia was selected as a score that indicates moderate pain.[17] Although most cats (9/12) in the methadone group did not require rescue analgesia, 3 cats did. This highlights the importance of assessing pain on a case-by-case basis and modifying analgesia to suit the individual patients' requirements, rather than assuming that a certain procedure will or will not require analgesia. Considerable individual response to opioids has been reported in cats.[13,15] Because butorphanol has a shorter duration of antinociceptive action than methadone, it is not surprising that the butorphanol group had a significantly earlier requirement for rescue analgesia than did the methadone group.[6,13,15,33]

Most cats regained consciousness quickly after administration of isoflurane ended and were still exhaling isoflurane at the time of the first postoperative pain evaluation (5 minutes). The dysphoria detected at this time could have affected the scoring system and also did not allow for complete scoring evaluation because blood pressure could not be determined. Scores obtained for this period were not analyzed further. The butorphanol group had significantly higher scores at 20 minutes, compared with the methadone group. In addition, 6 of 10 cats from the butorphanol group had pain scores necessitating rescue analgesia. Because cats that received rescue analgesia were not evaluated further, comparison of pain scores between the 2 groups at subsequent time points was not possible.

Of the 8 cats in the methadone group fully evaluated at 360 minutes, 6 had lower pain scores than at their 20-minute evaluation. This could be attributable to the greater accuracy of this pain scale to detect pain during the early postoperative period, as suggested by Brondani et al.[17] Cats may also adapt to pain over time, resulting in a reduction in the signs of pain.[17]

In the present study, cats premedicated with butorphanol prior to ovariohysterectomy had greater postoperative pain scores than did cats premedicated with methadone, possibly because butorphanol has a shorter duration of action than methadone or because methadone, a μ-opioid receptor agonist, provides better analgesia for moderate to severe pain than butorphanol, which is a μ-opioid receptor antagonist and κ-opioid receptor agonist.[11,16,34] The present results conflict with those of a previous study[9] in which methadone provided comparable analgesia to butorphanol in cats after neutering (ovariohysterectomy or castration). In that study,[9] a VAS and an MNT testing device[q] were used. The use of the VAS calls those results into question because such methods of pain evaluation are unreliable in assessing acute or perioperative pain in a hospital setting.[31,35] In addition, the study failed to detect analgesic effects of methadone by use of the MNT because the postoperative pressure threshold was not greater than the preoperative one.[9] For the same reason, the hyperalgesic effect of surgery was masked. Their results could be attributable to poor sensitivity of the MNT in cats undergoing ovariohysterectomy and the antihyperalgesic effects of methadone.

Physiologic data collected during anesthesia in the present study indicated that neither opioid had severe deleterious effects on vital functions and both could be used safely for premedication prior to general anesthesia. Periods of hypotension or bradycardia were detected prior to surgical incision in both groups; however, these changes were transient and resolved during surgery. The most likely explanation for the hypotension is the moderate effect on the cardiovascular system (peripheral vasodilation, myocardial depression, or both) caused by perioperative administration of sedative and anesthetic drugs such as acepromazine, propofol, and isoflurane. Although the use of glycopyrrolate or dopa-

mine would have interfered with the collection of MAP and HR, their use is standard procedure at the authors' institution to treat minor changes in the cardiovascular system. The cats, being part of a clinical trial, were supposed to receive the routine standard of care. Respiratory rate, Et_{CO_2}, and Sp_{O_2} were adequate for cats undergoing anesthesia and surgery, and there were no substantial periods in which respiratory functions were depressed sufficiently to endanger the patient.

None of the cats in either group had pain reactions from injection of the premedication or inflammation or pain at the site of the injection when evaluated after surgery. Although efforts were made to properly evaluate these 2 factors, evaluation remained subjective. It is difficult to differentiate pain caused by needle insertion from pain caused by injection of the product. The investigator used a small-gauge needle and delayed the injection of the premedication by several seconds following insertion of the needle in an attempt to differentiate these 2 sources of pain. It should also be noted that localization and inspection of the skin at the precise site of injection were difficult because the site was not clipped.

It is important to remember that in the United States, although butorphanol is approved for use in cats, use of methadone is considered extralabel in veterinary patients.[36] The Animal Medicinal Drug Use Clarification Act of 1994 made extralabel drug use an FDA-regulated veterinary medical activity, allowing veterinarians to prescribe approved animal and human drugs for extralabel use when the health of an animal is threatened or when suffering or death may result from failure to treat animals.[37] There are restrictions to extralabel drug use, and guidelines need to be followed by the prescribing veterinarian: patients need to be assessed, no similar approved drug for the condition and the species can be available on the market, patient identity must be recorded, and an extended withdrawal period must be applied when relevant.[37] An exception exists for non–food-producing animals, and approved human drugs may be considered for extralabel use even when an approved animal drug for that species and condition exists.[37]

Within the conditions of the present study, methadone administered as a premedication at 0.6 mg/kg, SC, provided effective postoperative analgesia for at least 6 hours following ovariohysterectomy surgery in most cats. Methadone appeared superior to butorphanol in inducing an adequate period of effective postoperative analgesia.

a. Microsoft Excel for Mac 2011, version 14.1.0, Microsoft Corp, Redmond, Wash.
b. A.C.P. 2, Acepromazine maleate 2 mg/mL, Delvet Pty Ltd, Sven Hills, NSW, Australia.
c. Butormidor injection, butorphanol tartrate 10 mg/mL, Ausrichter Pty Ltd, Camperdown, NSW, Australia.
d. Ilium methadone injection, methadone hydrochloride, 10 mg/mL, Troy Laboratories Australia Pty Ltd, Glendenning, NSW, Australia.
e. Provine 1%, propofol emulsion injection, 10 mg/mL, Claris Lifesciences Ltd, Burwood, NSW, Australia.
f. Graseby 3300 PCA Pump, SIMS Graseby Ltd, Walfort, Hertfordshire, England.
g. Small Animal Anesthesia Machine V701001, SurgiVet, Smiths Medical PM Inc, Waukesha, Wis.
h. Isorrane, Isoflurane USP, 100%, Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia.
i. Hartmann's Solution for Injection, Fresenius Kabi Pty Ltd, Pymble, NSW, Australia.
j. PM-900 Express Masimo SET, Shenzhen Mindray Bio-Medical Electronic Co Ltd, Nanshan, China.
k. Cardell Veterinary Vital Signs Monitor 9402, CAS Medical Systems Inc, Branford, Conn.
l. Glycosate vet injection, glycopyrrolate 0.28 mg/mL, Nature Vet Pty Ltd, Glenorie, NSW, Australia.
m. DBL Sterile Dopamine concentrate 40 mg/mL, Hospira Australia Pty Ltd, Melbourne, VIC, Australia.
n. Metacam, meloxicam 5 mg/mL, Boehringer Ingelheim Pty Ltd, North Ryde, NSW, Australia.
o. petMAP graphic, Ramsey Medical Inc, Tampa, Fla.
p. SPSS Statistics, version 20, IBM Corp, Armonk, NY.
q. ProD, Topcat Metrology Ltd, Ely, Cambridgeshire, England.

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