Long-acting injectable methadone (methadone-fluconazole) provides safe and effective postoperative analgesia in a randomized clinical trial for dogs undergoing soft tissue surgery

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OBJECTIVE
To assess the pharmacokinetics, clinical efficacy, and adverse effects of injectable methadone with the pharmacokinetic enhancer fluconazole (methadone-fluconazole), compared with the standard formulation of injectable methadone, in dogs after ovariohysterectomy. We hypothesized that 2 doses of methadone-fluconazole would provide 24 hours of postoperative analgesia.

ANIMALS
3 purpose-bred dogs (pharmacokinetic preliminary study) and 42 female dogs from local shelters (clinical trial) were included.

PROCEDURES
Pharmacokinetics were preliminarily determined. Clinical trial client-owned dogs were blocked by body weight into treatment groups: standard methadone group (methadone standard formulation, 0.5 mg/kg, SC, q 4 h; n = 20) or methadone-fluconazole group (0.5 mg/kg methadone with 2.5 mg/kg fluconazole, SC, repeated once at 6 h; n = 22). All dogs also received acepromazine, propofol, and isoflurane. Surgeries were performed by experienced surgeons, and dogs were monitored perioperatively using the Glasgow Composite Measure Pain Scale–Short Form (CMPS-SF) and sedation scales. Evaluators were masked to treatment.

RESULTS
Findings from pharmacokinetic preliminary studies supported that 2 doses of methadone-fluconazole provide 24 hours of drug exposure. The clinical trial had no significant differences in treatment failures or postoperative CMPS-SF scores between treatments. One dog (methadone-fluconazole group) had CMPS-SF > 6 and received rescue analgesia. All dogs had moderate sedation or less by 1 hour (methadone-fluconazole group) or 4 hours (standard methadone group) postoperatively. Sedation was completely resolved in all dogs the day after surgery.

CLINICAL RELEVANCE
Methadone-fluconazole with twice-daily administration was well tolerated and provided effective postoperative analgesia for dogs undergoing ovariohysterectomy. Clinical compliance and postoperative pain control may improve with an effective twice-daily formulation.

Current opioids require frequent (typically every 4 hours) injections to maintain analgesia in postoperative dogs.1–6 This can lead to breakthrough pain if the effect of the dose is lost prior to another dose. This may negatively impact postoperative analgesic control during overnight hours in hospitals without 24-hour staffing. Development of an injectable formulation that provides prolonged analgesia would be clinically useful for postoperative management in dogs.

There are no FDA-approved opioid analgesics with label indications for use in dogs in the United States. Methadone is a μ-opioid receptor agonist that is approved by the FDA for analgesic use in people and that is approved in some countries for injectable use in dogs. In dogs, methadone has a relatively short half-life due to rapid hepatic metabolism presumably by the enzyme cytochrome P450.1,3,7,8 Fluconazole acts as a pharmacokinetic enhancer of
orally administered methadone in dogs by inhibiting this rapid metabolism and resulting in prolonged central opioid effects and clinical analgesia. The pharmacokinetic result of this interaction is increased methadone oral bioavailability (when both drugs are administered orally) and a prolonged half-life of methadone presumably through decreased clearance. To the authors’ knowledge, the effect of fluconazole on parenteral methadone metabolism has not been reported.

The purpose of the study presented here was to assess the pharmacokinetics, clinical efficacy, and adverse effects of injectable methadone with the pharmacokinetic enhancer fluconazole (methadone-fluconazole), compared with the standard formulation of injectable methadone, in dogs after ovariohysterectomy. The hypothesis was that the methadone-fluconazole group would maintain adequate analgesia for 24 hours with 2 doses, compared with the 4 doses of standard formulation methadone, in clinical patients undergoing soft tissue surgery.

Materials and Methods

Animals

The preliminary pharmacokinetic trial and prospective randomized clinical trial were approved by the Institutional Animal Care and Use Committee of Kansas State University. The preliminary pharmacokinetic study was performed in purpose-bred mixed-breed dogs. Three 2-year-old dogs were included: 2 sexually intact males and 1 sexually intact female with a body weight range of 9.4 to 11.9 kg. The clinical trial enrolled female dogs from local animal shelters, which were returned to the shelters for adoption after completing the study. The dogs arrived the day before surgery and were determined to be healthy based on history, physical examination, PCV, total solids, and a negative heartworm test. The targeted enrollment was 40 sexually intact female dogs (20 dogs per treatment group) weighing 3 to 40 kg.

Treatments

Drug compounding was needed for the methadone-fluconazole formulation as no commercial formulations are available. Methadone injection (10 mg/mL), approved by the FDA for human use (Akorn, Inc), was combined with a solution of fluconazole active pharmaceutical ingredient to formulate the methadone-fluconazole solution for injection. This yielded a final concentration of methadone at 5 mg/mL and fluconazole at 25 mg/mL. The FDA-approved fluconazole solution for injection’s concentration was too low (2 mg/mL) to provide a reasonable volume for SC injection. There are no FDA-approved methadone formulations for dogs; hence, the reason the product approved for use in humans was used in an extralabel manner. Extralabel drug use was performed with client consent and complied with provisions of Animal Medicinal Drug Use Clarification Act (AMDUCA) and 21 CFR §530.

The preliminary pharmacokinetic trial was conducted in a sequential block design. All dogs received 3 different methadone formulations separated by at least 72 hours in the following order. The first formulation (standard methadone) was a standard solution of methadone injection (10 mg/mL for human use). The second formulation was a solution consisting of methadone injection diluted to 5 mg/mL with polyethylene glycol (PEG) 400 (45% final concentration) and ethyl alcohol (5% final concentration), referred to as methadone PEG, which is the vehicle for the methadone-fluconazole. The third formulation (methadone-fluconazole) was an identical solution to the second formulation but also contained 25 mg/mL of fluconazole. Fluconazole was obtained as 99.7% pure powder for research and development use with direct comparative assay traceability to United States Pharmacopeia methods using fluconazole injection as the comparator with a full certificate of authenticity (Sigma-Aldrich). The methadone PEG and methadone-fluconazole formulations were filtered through a 0.45-μm filter prior to injection. The methadone PEG and methadone-fluconazole solutions were administered within 24 hours of drug formulation and stored refrigerated (4°C). All formulations were administered SC at a methadone dose of 0.5 mg/kg and repeated once at 6 hours. The fluconazole dose for the methadone-fluconazole formulation was 2.5 mg/kg, SC, based on previous studies with oral fluconazole. Blood samples were obtained prior to the first dose and at 15, 30, and 45 minutes and 1, 2, 4, and 6 hours. After obtaining the 6-hour sample, the second dose was administered. Blood samples were also obtained at 6.25, 6.5, 6.75, 7, 8, 12, 24, and 32 hours after the first dose. Plasma was separated and stored frozen until analysis for methadone and fluconazole by a previously validated liquid chromatography–mass spectrometry method.

Dogs in the clinical trial were enrolled over 5 weeks with 8 to 10 dogs per surgery day. Dogs were blocked daily based on weight and then randomly assigned in a 1-to-1 ratio to treatment groups: the standard methadone group, which received the standard methadone formulation at 0.5 mg/kg, SC, every 4 hours, or the methadone-fluconazole group, which received a formulation of 0.5 mg/kg methadone and 2.5 mg/kg fluconazole SC preoperatively and repeated once at 6 hours postoperatively. Each dog received an initial dose of either standard methadone or methadone-fluconazole SC at 7:30 AM (± 30 minutes) the day of surgery along with acepromazine (VetOne; 0.05 mg/kg, SC) as premedication. The methadone-fluconazole group received 1 additional methadone-fluconazole dose at 2:00 PM (2 doses total). The standard methadone group received further methadone doses at 12:00 PM, 4:00 PM, and 8:00 PM (4 doses total). To maintain masking, saline injections were administered at 2:00 PM to the methadone group, and the methadone-fluconazole group received saline injections at 12:00 PM, 4:00 PM, and 8:00 PM. All doses of methadone and saline were administered by a single researcher (BK), and other investigators were masked to treatment. Treatment with carprofen (Putney; 4.4 mg/kg, PO, q 24 h) was...
initiated 24 hours postoperatively in all dogs and continued for 5 days.

**Surgical procedure**

Standard ovariohysterectomies were performed by experienced faculty surgeons (EEK, DAU, KAB, AJC, BC) between 8:00 AM and 12:10 PM, with anesthesia monitored by registered veterinary nurses (GJ, RJO) and supervised by an experienced board-certified anesthesiologist (DEM) according to previously published methods. Following premedication, IV catheter placement started at 7:30 AM (± 30 minutes). Anesthesia was induced with propofol (IVAOES Animal Health; 4 mg/kg, IV) titrated until intubation was possible. Dogs were intubated, and anesthesia was maintained with isoflurane (Piramal Critical Care) in oxygen. Lactated Ringer’s solution (Dechra Veterinary Products) was administered at a rate of 5 mL/kg/h throughout the surgery.

All dogs were maintained on a warm water recirculating blanket from anesthesia induction until they were returned to their individual runs. Anesthesia monitoring included heart rate, respiratory rate, pulse oximetry (NPB-40; Nellcor Puritan Bennett), and noninvasive systolic blood pressure (Parks Medical Electronics Doppler ultrasound). Interventions were set to occur if the heart rate > 150 beats/min by checking and adjusting anesthetic depth and reasessing cardiac rhythm; heart rate < 50 beats/min by checking and adjusting anesthetic depth; respiratory rate < 4 breaths/min by manual ventilation; pulse oximetry < 95% by confirming pulse oximeter probe placement and adjusting anesthetic depth and manual ventilation; and systolic blood pressure < 80 mm Hg by checking and adjusting anesthetic depth and administration of IV fluid bolus of 10 mL/kg body weight. Atropine and epinephrine were available if needed for cardiovascular support. Dogs remained in recovery and on the warm water recirculating blanket until they were extubated and ambulatory and their rectal temperature was at least 37.2 °C.

**Data collection**

The effects of the methadone were measured by assessing signs of pain, sedation, and rectal temperature. Glasgow Composite Measure Pain Scale—Short Form (CMPS-SF; on a scale of 0 [no sign of pain] to 24 [if mobile] or 20 [if nonmobile] for combined total scores of various signs of pain) and sedation assessment (on a scale of 0 [no sedation] to 4 [unresponsive]) scores were obtained on the day of arrival (day 0) as baseline; postoperatively on the day of surgery (day 1) at 12:00 PM, 1:00 PM, 2:00 PM, 4:00 PM, 6:00 PM, and 8:00 PM; and the day after surgery (day 2) at 8:00 AM, 12:00 PM, and 5:00 PM; and on day 3 at 7:30 AM. All sedation and pain assessments were performed by a single researcher (ZB) masked to treatment. A CMPS-SF total score > 6 (or > 5 if the dog was nonmobile) was used as the cutoff for treatment failure and for which rescue analgesia (morphine, 0.25 mg/kg, SC) was administered. Treatment failure was the pivotal efficacy outcome. The secondary outcome was CMPS-SF total score.

Body temperature, ease of catheter placement, and adverse effects, such as vomiting, were also recorded.

**Statistical analyses**

For the preliminary pharmacokinetic study, statistical comparison of the results for the 24-hour plasma concentration between the treatment groups was performed with 1-way ANOVA (SigmaPlot, version 12.5, Systat Software Inc). The terminal half-life after the second dose for each treatment was calculated by log-linear regression using at least 3 time points on the terminal slope (Phoenix, 64-bit version, Certara Inc). The half-life was compared statistically using a 1-way ANOVA on natural log-transformed data as the raw data were not normally distributed. Differences were considered significant when values of \( P \) were < 0.05 and the post hoc power analysis was at least 0.8.

For the clinical trial, treatment failure was the primary outcome measure and CMPS-SF total score was the secondary variable. The null hypothesis was that standard methadone would be more effective (proportion of treatment failures) than methadone-fluconazole. The alternative hypothesis was that there would be no difference in the efficacy (proportion of treatment failures) between standard methadone and methadone-fluconazole. The a priori sample size was estimated based on the expected proportion of treatment success at least 0.95 for the positive control (standard methadone) as previously reported in dogs undergoing ovariohysterectomies. The expected proportion of efficacy for methadone-fluconazole was set to 0.6 (the previously reported success rate of a placebo in dogs undergoing soft tissue surgery). The desired power of 0.8 and an alpha of 0.05 yielded a sample size of at least 18 animals per treatment. The sample size analysis for the secondary variable, CMPS-SF total score, was based on an expected mean of 2 for standard methadone and 3 for methadone-fluconazole, based on a drug proven effective in soft tissue surgery in dogs, with standard deviations of 1, an alpha = 0.05 and power of 0.8 yielded a sample size of 12 animals per group. Based on these sample size calculations, at least 20 animals per treatment were enrolled. For the clinical trial data, the proportion of treatment failures was compared using the Fisher’s exact test with \( P \) < 0.05 considered significant. The CMPS-SF total scores were compared for differences using the Mann-Whitney rank sum test as the data were not normally distributed, with \( P \) < 0.05 considered significant.

**Results**

The methadone-fluconazole solution for injection remained clear throughout the administration periods with no signs of color change, cloudiness, visible particulates, or sedimentation. The preliminary pharmacokinetic trial yielded pharmacokinetic parameters for the standard methadone, methadone PEG, and methadone-fluconazole treatments (Figure 1).

The plasma methadone concentration range 6 hours after the first dose of methadone-fluconazole (before
the second dose) was 33 to 48 ng/mL, compared with 18 to 28 ng/mL after the standard methadone treatment and 21 to 34 ng/mL after the methadone polyethylene glycol (PEG) treatment. The plasma methadone concentration at 24 hours after the first dose was significantly higher in the methadone-fluconazole treatment (range, 20.3 to 32.5 ng/mL), compared with the standard methadone treatment (range, 3.4 to 7.2 ng/mL; \( P = 0.004 \)) and methadone PEG treatment (range, 3.6 to 10.6 ng/mL; \( P = 0.005 \)). Similarly, the terminal half-life of methadone-fluconazole (range, 7.2 to 8.7 h) was significantly longer than for standard methadone (range, 3.8 to 5.4 h; \( P = 0.049 \)) and methadone PEG (range, 3.5 to 5.6; \( P = 0.036 \)).

The rectal temperature, a marker for central opioid effects in dogs, was below baseline longer after treatment with methadone-fluconazole, compared with standard methadone (Figure 2). The rectal temperatures after treatment with methadone PEG were not reported as the dogs were very excited and hyperthermic (baseline rectal temperatures, 38.9, 39.4, and 40.0 °C [reference range, 37.5 to 39.2 °C]) prior to dosing. Plasma concentrations of fluconazole (methadone-fluconazole) included peak concentrations after the first dose (range, 2.7 to 3.1 µg/mL) at 4 hours and after the second dose (range, 4.7 to 5.0 µg/mL) at 7 to 12 hours (Figure 3).

Forty-three healthy female dogs were initially enrolled for the single-center clinical trial. Twenty dogs were assigned to receive the standard methadone treatment, and 23 dogs were assigned to receive the methadone-fluconazole treatment. Based on dentition (all adult teeth present), all dogs were > 6 months of age. Three dogs were identified as previously spayed. One spayed dog (methadone-fluconazole group) was identified by the presence of a tattoo, discovered after anesthesia induction (during surgical preparation), and was therefore excluded from the study because the dog did not undergo surgery during the study. Two dogs (methadone-fluconazole group) were identified during surgery as previously spayed but were still included in the results because they underwent abdominal exploratory to confirm. Thus, there were 42 dogs.
included 20 in the standard methadone group and 22 in the methadone-fluconazole group. The mean body weights of the dogs were 15.9 kg (range, 3.9 to 30.1 kg) for the standard methadone group and 14.2 kg (range, 3.4 to 44.8 kg) for the methadone-fluconazole group.

All dogs in both groups had adequate sedation from their premedication to allow for intravenous catheter placement. All injections were well tolerated with no signs of overt pain from either formulation, and there was no difficulty in administering the methadone-fluconazole solution (ie, easy syringeability). No pain or abnormalities were observed at the injection sites for the duration of the study.

The mean intravenous induction doses of propofol were 3.5 mg/kg (range, 1.9 to 4.9 mg/kg) for standard methadone and 3.4 mg/kg (range, 2.2 to 4.9 mg/kg) for methadone-fluconazole. The mean durations of anesthesia and surgery were 53 minutes (40 to 69 minutes) and 27 minutes (16 to 53 minutes), respectively, for standard methadone group and 50 minutes (37 to 69 minutes) and 24 minutes (12 to 41 minutes), respectively, for methadone-fluconazole group. No anesthetic adjustments were needed for heart rate or pulse oximetry falling outside of predetermined set points.

**Figure 3**—Mean ± SD fluconazole plasma concentrations for the dogs described in Figure 1 after receiving methadone-fluconazole treatment (2.5 mg/kg of fluconazole and 0.5 mg/kg of methadone, SC) at time 0 and 6 hours later. The black circles represent the mean and whiskers represent the SD. See Figure 1 for rest of the key.

**Figure 4**—Mean ± SD Glasgow Composite Measure Pain Scale-short form (CMPS-SF) total score (on a scale of 0 [no sign of pain] to 24 [if mobile] or 20 [if nonmobile] for combined total scores of various signs of pain) for 42 client-owned dogs randomly assigned to receive doses of methadone (0.5 mg/kg, SC) either as a standard methadone treatment (methadone solution, 10 mg/mL, 0.5 mg/kg, SC, q 4 h; standard methadone group; n = 20; black bars) or as a methadone-fluconazole treatment (methadone concentration of 5 mg/mL in a solution containing fluconazole 25 mg/mL with PEG 400 and ethanol; 0.5 mg/kg methadone and 2.5 mg/kg fluconazole preoperatively and repeated once 6 hours postoperatively; n = 22; gray bars) at each time point with the first prior to surgery as a baseline (day 0) and the remaining time points after ovariohysterectomy surgery (days 1 to 3) in a clinical trial. Acepromazine (0.05 mg/kg, SC) was administered as anesthetic premedication at 7:30 am (± 30 minutes) the day of surgery (day 1), and surgeries were performed between 8:00 am and 12:00 pm. Anesthesia was induced with IV propofol and maintained with inhaled isoflurane. All dogs received carprofen (4.4 mg/kg, PO, q 24 h), starting 24 hours after surgery (day 2). The bars represent the mean total CMPS-SF score, the whiskers represent the SD, and the arrow indicates surgery time. *Results differed significantly (P < 0.05) between treatment groups.
induction as a routine procedure for all dogs. After anesthetic induction, intermittent positive-pressure ventilation was provided throughout anesthesia at 1 to 2 breaths/min, but spontaneous respiratory rates remained above 4 breaths/min. Systolic blood pressure dropped below 80 mm Hg in some patients (4 from the standard methadone group; 6 from the methadone-fluconazole group), all of which were managed with anesthetic depth adjustment and IV fluid bolus. No dogs were administered atropine or epinephrine.

The range of times for completion of anesthesia was between 8:42 AM and 12:10 PM for the standard methadone group and between 8:43 AM and 12:08 PM for the methadone-fluconazole group. One dog was excluded from the first postoperative assessment (12:00 PM) in each treatment (2 total) as they were not sufficiently recovered from anesthesia and surgery; otherwise, the remaining dogs were recovered sufficiently to obtain the 12:00 PM CMPS-SF evaluation. One dog (methadone-fluconazole group) received rescue analgesia because of a peak CMPS-SF score of 9 at 1:00 PM. However, treatment failure based on CMPS-SF > 6 was not significantly different between treatment groups (P > 0.99). There was no significant difference in mean postoperative CMPS-SF between treatment groups. The methadone-fluconazole group showed a significantly higher mean preoperative CMPS-SF score (day 0; Figure 4).

All dogs were able to walk (sedation score ≤ 2) by 1:00 PM (methadone-fluconazole group) and 4:00 PM (standard methadone group) the day of surgery (day 1). Sedation score was 0 or 1 in all dogs by 8:00 AM the day following surgery (day 2). The highest percentage of dogs with sedation score > 1 (slight sedation) occurred in the standard methadone group at 1:00 PM on the day of surgery (Figure 5). Two dogs in the standard methadone group had sedation scores of 4 (unresponsive) within 2 hours postoperatively, 1 at 15 minutes postoperatively, and 1 at 3.5 hours postoperatively (after the second dose of methadone).

Vomiting occurred in dogs postoperatively, including 3 dogs in the standard methadone group and 1 dog in the methadone-fluconazole group. In the standard methadone group, 1 dog vomited once the day of surgery, 1 dog vomited twice the day of surgery, and 1 dog vomited once the day after surgery. In the methadone-fluconazole group, 1 dog vomited twice the day of surgery. None of the vomiting was deemed severe enough to administer antiemetics.

**Discussion**

The purpose of this study was to compare a long-acting formulation of methadone (methadone-fluconazole) to a standard methadone formulation. The preliminary pharmacokinetic studies resulted in significantly higher plasma concentrations at 24 hours for the methadone-fluconazole treatment as well as significantly longer terminal half-lives compared to standard methadone or methadone with PEG. We included the methadone PEG formulation to assess the effects of the fluconazole solubilizing agents and difference in methadone concentration used in the formulations. There were no differences between the standard methadone and methadone PEG treatments suggesting that neither the solvents nor methadone concentration significantly influenced the pharmacokinetic differences. Pain was not observed during SC injection of standard methadone, methadone PEG, or methadone-fluconazole.

The effective methadone plasma concentrations for clinical pain control have not been defined in dogs. Methadone plasma concentrations associated with mechanical and thermal antinociception in dogs during a constant rate intravenous infusion was 17 ng/mL. In dogs, plasma methadone concentration ≥ 21.3 ng/mL has been associated with decreases in rectal temperature, a centrally mediated opioid effect that parallels responses to antinociception. Therefore, plasma methadone concentration of 20 ng/mL was the chosen target methadone plasma concentration for our preliminary pharmacokinetic study. Standard methadone and methadone

![Figure 5](image-url)
PEG failed to maintain 20 ng/mL at 24 hours when administered twice, 6 hours apart. However, methadone-fluconazole maintained 20 ng/mL for all 3 dogs through at least 24 hours with 2 doses 6 hours apart. The plasma concentrations of methadone 6 hours after the first dose of methadone-fluconazole were 33 to 48 ng/mL, suggesting the second dose of methadone-fluconazole may be able to be administered later than 6 hours while still maintaining targeted plasma concentrations. Further studies assessing the pharmacokinetics of methadone-fluconazole are needed in a larger number of animals as well as assessing the effects of prolonging the dosing interval from 6 to up to 12 hours.

For the clinical trial, the methadone-fluconazole group received 2 doses, whereas the methadone standard group received 4 doses. The dosing protocol for the standard methadone solution is based on the approvals for analgesia in dogs in some countries. Only 1 dog received rescue analgesia (methadone-fluconazole group) indicating that both protocols were highly effective. In comparison, studies that used a placebo control group for soft tissue surgery in dogs had a 36 to 42% rate of rescue analgesia and treatment failures in placebo-treated dogs. Although different studies cannot be compared directly, the results of this study indicate methadone-fluconazole is a highly effective analgesic injection when administered twice in a 24-hour period.

The methadone-fluconazole group had a significantly higher preoperative average CMPS-SF total score (day 0), with the highest score being 3 (demeanor 3 = nervous, anxious, fearful). This is likely due to a limitation of the CMPS-SF combined with random chance in group allocation. The dogs were allocated to their group prior to arrival based on body weight to prevent bias. The scale uses behavioral cues to assess pain, which can result in fear, anxiety, or preexisting conditions such as mechanical lameness being scored as part of the pain scale. The higher preoperative pain scores may reflect random placement of more anxious or fearful dogs in the methadone-fluconazole group. It is also important to note that the CMPS-SF was designed more to distinguish between animals requiring intervention for pain, not slight differences in scores.

Treatment failure was identified for 1 dog (CMPS-SF > 6) among the 22 dogs in the methadone-fluconazole group and none of the 20 dogs in the standard methadone group. This was not a significant difference between groups. The treatment failure occurred for a 3.4-kg terrier mix estimated by the shelter to have been 9 years old. This treatment failure could be due to true breakthrough pain in the postoperative period; individual variability of the dog to the anesthesia, analgesia, behavior, personality; or limitations of the CMPS-SF in discerning dysphoria, fear, or anxiety from pain.

Postoperative sedation occurred for each treatment. The greatest postoperative sedation in the methadone-fluconazole group had dogs with grade 3 sedation at the 12:00 AM time point on day 1 (the first measurement after surgery). Sedation in this group nearly resolved at 8:00 AM the morning of day 2 with only grade 1 sedation observed. The standard methadone group had the greatest postoperative sedation of grade 4 sedation at 12:00 AM on day 1. Sedation also nearly resolved in this group by 8:00 AM the morning of day 2 with only grade 1 sedation observed.

Fluconazole was used in this study as a pharmacokinetic enhancer of methadone to produce increased duration of plasma concentration. Fluconazole is proven to be a safe medication in dogs, with the fluconazole dose used in this study (5 mg/kg/d, PO) below the no observable adverse effect level (NOAEL) of the drug (7.5 mg/kg/d for 6 months), and the methadone-fluconazole formulation was only administered for 1 day (ie, 5 mg/kg total dose of fluconazole). The effects of fluconazole on intrinsic or commensal fungal organisms (eg, Malassezia spp) was not assessed in this study. However, with the short duration of administration, the authors hypothesize that effects on microflora would be minor.

Isoflurane, lactated Ringer’s solution and carprofen were used according to their FDA-approved label. Acepromazine was used at a dose lower than the label dose for dogs, which is consistent with current recommendations. There are no FDA-approved opioid analgesics with label indications for use in dogs currently available in the United States, so methadone, with FDA-approved label indication for use in humans, was used in an extralabel manner at a dosage and route consistent with label indications for use veterinary medicine in other countries. The methadone-fluconazole formulation used in the present study was not commercially available and as such was compounded specifically for this study and used in an extralabel manner. It is important to note different compounding methods may alter the pharmacokinetics, desired effects, and adverse effects of a specific formulation. All extralabel drug use complied with AMDUCA and 21 CFR §530.

Overall anesthesia was well tolerated with some expected deviations from normal parameters. The interventions were due to systolic blood pressure falling below 80 mm Hg by indirect Doppler ultrasonic flow detector. The most likely reasons for this are due to the cardiovascular effects of acepromazine, propofol, and isoflurane. The combination of acepromazine, propofol and isoflurane has documented hypertensive effects in dogs (when administered with butorphanol) in a previous study consistent with this study. Therefore, this was not an unexpected finding in this study and routine anesthetic management addressed these adverse effects.

Methadone is a safe and effective analgesic for postoperative soft tissue patients. A previous clinical trial enrolled 43 female dogs to assess standard methadone (0.5 mg/kg, SC, q 4 h; n = 13) or oral administration of methadone-fluconazole-naltrexone (0.5 to 1 mg/kg methadone, 2.5 to 5 mg/kg fluconazole, and 0.125 to 0.25 mg/kg naltrexone, PO, q 12 h; n = 30). Surgical, anesthetic, and postoperative pain assessments and personnel were nearly identical to this study. Treatment success (ie, no

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rescue analgesia) occurred in all 43 of those dogs. Between the 2 studies, methadone provided success in 84 of 85 (98.8%) dogs following soft tissue surgery.

The stability or degradation profile of the methadone-fluconazole solution was not determined. The long-term stability of the solution at room temperature and refrigerated needs to be determined prior to the widespread manufacturing of this or any formulation in addition to sterility testing as with any sterile injectable solution.

These results support the use of methadone-fluconazole as a viable option for providing postoperative analgesia. There was no significant difference in postoperative pain scores or treatment failures compared to a standard methadone treatment. The adverse effects associated with the methadone-fluconazole and methadone standard formulations were typical, with both sedation and vomiting noted. The long-acting methadone-fluconazole formulation would prove beneficial if it is available for widespread use in veterinary medicine due to the more feasible dosing protocol. Additionally, the lower need for opioid handling may be beneficial in decreasing opioid diversion or misuse due to decreased access; however, that would require further assessment.

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Dr. Hyun Joo performed the plasma drug analysis. Dr. Brad Crauer was one of the veterinary surgeons, and Ms. Gina Jensen contributed as a veterinary nurse, anesthetist, and case coordinator.

Kansas State University has a provisional patent and a patent pending on the methadone-fluconazole formulation with Drs. B. KuKanich and K. KuKanich as 2 of the patent holders.

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