Efficacy of long-acting methadone using a combination of oral and injectable formulations in postoperative dogs.

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ABSTRACT

The purpose of the study was to evaluate the perioperative efficacy and tolerability of subcutaneous methadone/fluconazole followed by oral methadone/fluconazole/naltrexone (methadone/fluconazole) compared to intramuscular buprenorphine followed by oral codeine (buprenorphine).

Enrollment included intact dogs (n=239 total; n=119 for methadone/fluconazole, n=120 for buprenorphine) for ovariohysterectomy or castration as part of a surgery class (IACUC approved). Dogs were later placed for adoption. One dog (methadone/fluconazole) was excluded from postoperative assessment due to an additional surgery to control hemorrhage. Methadone/fluconazole (0.5/2.5 mg/kg) was administered SC preoperatively and once postoperatively; oral methadone/fluconazole/naltrexone (0.5/2.5/0.125 mg/kg) q12h started ~24h postoperatively. Buprenorphine was administered preoperatively (0.02 mg/kg IM) and postoperatively (0.01 mg/kg IM); oral codeine administration (1-2 mg/kg q8h) started ~8h postoperatively. All dogs received NSAIDs daily starting ~18h (methadone/fluconazole) or ~8h (buprenorphine) postoperatively. All dogs received acepromazine (premedication), ketamine/midazolam (induction) and isoflurane anesthesia. Third year veterinary students performed anesthesia and surgery with faculty oversight. The Glasgow Composite Pain Scale-Short Form assessed postoperative pain; treatment failures included total pain scores exceeding 6 or need for additional postoperative analgesia/sedation.

Enrollment included 47 castration, 72 ovariohysterectomy (methadone/fluconazole) and 44 castration, 76 ovariohysterectomy (buprenorphine) procedures. Propofol was additionally needed for anesthesia induction in 2/119 methadone/fluconazole and 8/120 buprenorphine dogs. Ephedrine was administered for intraoperative hypotension in 4/119 (methadone/fluconazole) and 8/120 (buprenorphine) dogs. One dog (methadone/fluconazole) received intraoperative atropine. Mean±SD postoperative rectal temperatures were 96.1±2.0 °F (methadone/fluconazole) and 97.0±1.7 °F (buprenorphine). Treatment failures included 1/118 (methadone/fluconazole) and 8/120 (buprenorphine) dogs.

Methadone/fluconazole ± naltrexone was effective and well tolerated in perioperative dogs.

INTRODUCTION

Numerous studies have shown common surgical procedures, such as ovariohysterectomies and castrations, result in postoperative pain in dogs. Controlling postoperative pain can be difficult due to need for frequent drug administration and lack of oral opioid formulations. Although NSAIDs can be administered orally once daily, they alone are only moderately effective in controlling postoperative pain in canine ovariohysterectomies and castrations. We have developed oral and injectable long-acting methadone formulations which provide 24 hours of high efficacy analgesia with just two doses. Inclusion of the pharmacokinetic enhancer fluconazole increases the oral bioavailability and duration of methadone in dogs. The oral formulation also contains the opioid antagonist naltrexone (methadone/fluconazole/naltrexone), in which naltrexone produces no effect in dogs due to its low bioavailability. However if ingested by a human, either intentionally or unintentionally, naltrexone will antagonize methadone due to its greater oral bioavailability and active metabolite in humans. Our goal was to evaluate the safety and efficacy of injectable followed by oral long-acting methadone in postoperative dogs. The hypothesis was long-acting methadone would provide safe and effective postoperative analgesia in dogs.

MATERIALS AND METHODS

Enrollment = 239 healthy dogs from local shelters, to undergo routine soft tissue surgery (ovariohysterectomy or castration).
There were wo treatments, allocated to treatment by week.

Buprenorphine/codeine (buprenorphine): n = 44 male, 76 female (120 total dogs)
- Buprenorphine pre- (0.02 mg/kg SC, ~12:30P) and postoperative (0.01 mg/kg SC ~4:00P)
- Codeine 1-2 mg/kg PO q 8h and NSAID (carprofen or meloxicam) starting night postop

Long-acting methadone (methadone/fluconazole): n=47 male, 72 female (119 total dogs)
- Methadone/fluconazole (0.5/2.5 mg/kg) SC pre- (~9:00A) and postoperative (~4:00P)
- Methadone/fluconazole/naltrexone (0.5/2.5/0.125 mg/kg PO) q12h started ~18h postoperatively. (7:00A the following day) with an NSAID (carprofen or meloxicam)

Anesthesia, surgery and monitoring
- All dogs were also administered acepromazine, ketamine/midazolam, and isoflurane
  - Propofol administered if the student was unable to intubate with ketamine/midazolam
- Student anesthetists performed the anesthesia under faculty supervision
- Anesthetic monitoring included capnography (end tidal CO2; ETCO2): 8 dogs continuous, 7 dogs intermittent per day, HR, RR, doppler blood pressure and isoflurane concentration
- Surgery started at ~1:00P in a student surgery course (Tuesdays & Wednesdays)
- Student surgeons performed standardized surgeries under faculty supervision
- Postoperative monitoring included the Glasgow Composite Pain Scale (GCPS) and sedation assessed as none (0), slight (1), moderate (2), profound (3), or unresponsive (4)
- Serum chemistry profiles determined before and 48 hours after Tuesday surgeries

RESULTS AND DISCUSSION

- Propofol was additionally needed for intubation in 8/120 (buprenorphine) and 2/119 (methadone/fluconazole) dogs. The additional anesthesia may have been due to anesthetic sparing effects of methadone or prolonged effects of ketamine/midazolam as fluconazole decreases elimination of ketamine and midazolam.
- The mean (range) anesthesia times were 150.5 (30-240) minutes (buprenorphine) and 145.7 (70-245) minutes for methadone/fluconazole.
- Ephedrine was administered for intraoperative hypotension in 8/120 (buprenorphine) and 4/119 (methadone/fluconazole) dogs, and could be random variability or due to higher concentrations of isoflurane required for anesthesia.
- Atropine was administered prior to ephedrine intraoperatively to 1 dog (methadone/fluconazole) for hypotension.
- One dog (methadone/fluconazole) received mechanical ventilatory support when the ETCO2 remained at 60 mm Hg with intermittent positive pressure ventilation. Isoflurane was administered at 2.5% when ventilatory support initiated, subsequently 0.5 – 0.75% isoflurane maintained anesthesia suggesting excessive isoflurane administration occurred.
- Postoperative temperatures were 97.0 ± 1.7 °F (buprenorphine) and 96.1 ± 2.0 °F (methadone/fluconazole).
- One dog (methadone/fluconazole) was excluded as it required a second surgery for continued hemorrhage thought to be due to an underlying condition affecting hemostasis.
- The mean ETCO2 value for buprenorphine (42 mm Hg) was lower than methadone/fluconazole (46 mm Hg) which may have been due to greater opioid effects of methadone or failure to account for methadone's anesthetic sparing effect.
- The mean inhaled isoflurane percentage was lower by ~0.5% throughout the anesthetic period for methadone/fluconazole compared to buprenorphine suggesting an anesthetic sparing effect.
- Sedation ≥ profound (unable to rise) @ 9:00 PM day of surgery (first time point assessed, ~4 hours from end of surgery) occurred in 6 /120 (buprenorphine) and 6/118 (methadone/fluconazole) dogs. The prolonged recoveries were likely related to the long anesthesia times typical of student surgeries.
- Treatment failure occurred in 8/120 (buprenorphine) dogs with 5 due to high GCPS>6, 2 administered dexmedetomidine and 1 acepromazine during anesthesia/recovery. Treatment failure occurred in 1/118 (methadone/fluconazole) due to GCPS>6. These data suggest methadone/fluconazole is a highly effective analgesic.
- Overall GCPS scores decreased over time in the postoperative period (Figure 1)
- There were no clinically relevant changes in serum chemistry profiles 48 hours after surgery in either treatment (Table 1).

SUMMARY AND CONCLUSIONS

Long-acting methadone was effective in providing preoperative sedation and lowered the need for additional anesthetic induction agents in soft tissue surgery dogs. Dogs administered long-acting methadone had slightly higher mean ETCO2 and lower mean isoflurane concentrations to maintain anesthesia compared to buprenorphine. Additional intraoperative cardiovascular support was administered less frequently to dogs administered long-acting methadone compared to buprenorphine. Long-acting methadone required less rescue analgesia or intra/postoperative sedation compared to buprenorphine. There were no clinically relevant changes in serum chemistry profiles in either treatment.

Long-acting methadone is a safe and effective analgesic in soft tissue surgery dogs. It provides convenient twice daily administration using parenteral and oral formulations which are expected to increase dosage compliance. Incorporation of a deterrent to human abuse/misuse into the oral formulation may decrease the risk for intentional or unintentional human exposure for the oral formulation.

Figure 1 – Glasgow Composite Pain Scale Scores

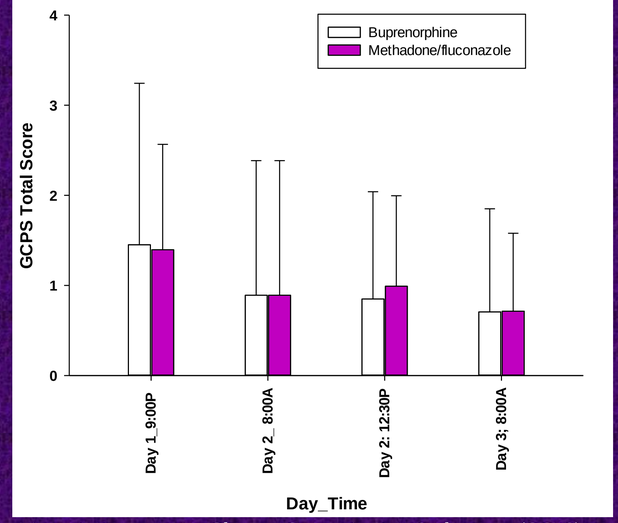

Figure 1. Postoperative Glasgow Composite Pain Scale scores (GCPS). Surgery ended on Day 1 at ~5:00P.

Parameters	Buprenorphine (n=60 dogs)		Methadone/fluconazole (n=58 dogs)	
	Pre	Post	Pre	Post
CREA (mg/dL)	0.72 ± 0.27	0.73 ± 0.25	0.80 ± 0.26	0.80 ± 0.23
BUN (mg/dL)	15.8 ± 5.0	14.7 ± 4.4	15.9 ± 5.1	15.8 ± 6.3
TP (g/dL)	6.4 ± 0.8	6.2 ± 0.7	6.4 ± 0.6	6.3 ± 0.6
ALB (g/dL)	3.0 ± 0.3	2.9 ± 0.3	3.1 ± 0.3	3.0 ± 0.2
ALT (U/L)	43.8 ± 24.7	45.7 ± 24.6	46.6 ± 30.9	46.4 ± 24.2
ALKP (U/L)	94.2 ± 55.6	107.9 ± 57.5	90.5 ± 54.0	138.3 ± 60.3
GGT (U/L)	2.93 ± 1.68	2.03 ± 1.28	2.98 ± 1.67	2.62 ± 1.20
TBIL (mg/dL)	0.16 ± 0.13	0.17 ± 0.15	0.16 ± 0.12	0.13 ± 0.06
CHOL (mg/dL)	189.5 ± 33.7	200.7 ± 35.6	199.4 ± 50.4	210.6 ± 54.7

Table 1. Serum chemistry values pre- and postoperative.

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