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Important Update:

In order to remain compliant with the most current regulatory guidelines, we have updated the labeling on our SR formulations from Buprenorphine and Meloxicam SR to Buprenorphine and Meloxicam in Polymer. **As of April 1, 2024, SR preparations mentioned in the attached study are now labeled as in Polymer**, with no changes to the formulation of the medication(s).

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Comparison of Side Effects between Buprenorphine and Meloxicam Used Postoperatively in Dutch Belted Rabbits (*Oryctolagus cuniculus*)

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One of the challenges facing veterinarians and investigators who use rabbits (*Oryctolagus cuniculus*) as a surgical model in biomedical research is choosing an appropriate and efficacious postoperative analgesic without systemic complications and side effects. The objective of this study was to evaluate the gastrointestinal side effects associated with the postoperative use of buprenorphine in Dutch Belted rabbits. We also evaluated the analgesic meloxicam as an alternative to opioid administration during the postoperative period. Rabbits were assigned to 1 of 3 treatment groups during the postoperative period after routine ovariohysterectomy: buprenorphine (n = 10), meloxicam (n = 10), and incisional infiltration with bupivicaine (no treatment control; n = 10). Feed intake, fecal production, weight loss, urine output, and other physiologic parameters were monitored and behavior and pain assessments were performed for 7 d after surgery and compared with baseline values collected before surgery. All rabbits showed decreased pellet consumption, fecal production, and weight on day 1 after surgery. This effect was severe in some rabbits that received bupivicaine; therefore treatment of this entire group with metoclopramide, fluids, and hay was instituted to reverse gut stasis. No significant difference in feed consumption and fecal production was present between the buprenorphine- and meloxicam-treated groups. On the basis of these results, meloxicam appears to be a suitable alternative or adjunct to buprenorphine for alleviating postoperative pain with minimal risk of anorexia and gastrointestinal ileus.

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal antiinflammatory drug.

Because of its small size and amiable temperament, the Dutch Belted Rabbit (*Oryctolagus cuniculus*) is gaining popularity as a companion animal and a model for biomedical research. A common circumstance when working with rabbits is the clear lack of reliable data regarding appropriate and effective postoperative analgesia. As a result, practicing veterinarians and researchers are forced to rely on analgesic protocols extrapolated from other small mammals. Due to a variety of physiologic, anatomic, and behavioral differences among rabbits, this practice is suboptimal. Further, the response in rabbits to treatments commonly used in private practice and laboratory animal medicine can be difficult to evaluate.

A common analgesic for use in rabbits postoperatively is buprenorphine. Buprenorphine is a partial agonist with very high affinity for the mu opioid receptor but with only partial activity.[3] Despite its partial activity, buprenorphine has been shown to be effective at controlling postoperative pain; side effects are primarily gastrointestinal and include nausea, anorexia, and disruption of gut peristalsis (ileus) in a variety of mammalian species.[11] Studies have shown that morphine, a related narcotic, has both centrally mediated and gut-specific inhibition of small intestinal transit and motility.[1,7] In mice treated with multiple doses of buprenorphine, decreased food consumption and weight loss occurred during the postoperative period.[8] In rats, multiple doses of buprenorphine given beyond postoperative day 1 resulted in sustained weight loss despite increased food consumption.[9] In addition rats receiving high doses of buprenorphine (0.5 mg/kg SC) exhibited signs of pica and developed gastric distension.[5] Although these gastrointestinal side effects can be mild and easily reversed in other mammalian species, similar gastrointestinal signs in rabbits potentially could progress to overt gut stasis. Therefore, it is important to seek analgesic alternatives to prolonged buprenorphine (and opioid) use in rabbits.

A substitute for buprenorphine is a long-acting nonsteroidal antiinflammatory drug (NSAID) preferential for cyclooxygenase (COX) 2, such as meloxicam, which has analgesic, antiinflammatory, and antipyretic properties.[10] Meloxicam blocks COX2-related prostaglandins that are considered to be nonphysiologic and incite various responses associated with inflammation, such as vasodilation, change in capillary permeability, and potentiation of other chemical mediators of inflammation and chemotaxis.[10] Because of its preferential inhibition of COX2-related prostaglandins, meloxicam has fewer gastrointestinal side effects than do other less specific NSAIDs. Further, a drug that inhibits COX2 at a lower concentration than that necessary to inhibit COX1 is safer and more desirable.[2] The benefits associated with the use of meloxicam in the perioperative period are well-documented. A 2003 study in which dogs given 0.1 mg/kg meloxicam or a placebo showed no significant differences in development of gastric erosions between meloxicam and control groups.[11] Meloxicam has also been shown to be

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especially effective in controlling postoperative visceral pain. In 1 study, meloxicam given during routine ovariohysterectomy of cats provided adequate analgesia.[17] Finally, although the elimination half-life of meloxicam is species-specific, the drug generally is considered to be long-acting, averaging 24 h in dogs.[14] The prolonged half-life of meloxicam leads to fewer administrations and potentially fewer stressful human–rabbit interactions.

The objective of the present study is to assess whether the known side effects of buprenorphine occur in Dutch Belted rabbits (*Oryctolagus cuniculus*), through careful monitoring and data collection of eating and voiding behaviors, physical well being, and physiologic body functions. We evaluated the NSAID meloxicam as an equal or better alternative to opioid use during the postoperative period. We expect that meloxicam administration, when used as a postoperative analgesic for ovariohysterectomy, would result in clinically normal surgical recovery without unwanted gastrointestinal side effects, such as anorexia or gut stasis.

Materials and Methods

Animals. This study was approved by the Johns Hopkins University Institutional Animal Care and Use Committee and is in compliance with the Animal Welfare Act[20] and the *Guide for the Care and Use of Laboratory Animals*.[13]

Thirty female Dutch Belted rabbits (*Oryctolagus cuniculus*) weighing approximately 2.0 to 3.0 kg were obtained from Myrtle's Rabbitry (Thompsons Station, TN). Twenty-nine rabbits were used in this study; 1 rabbit died during surgery as a result of anesthetic complications. All rabbits were specific-pathogen-free for *Bordetella bronchiseptica*, *Salmonella* spp., *Coccidia* spp., cilia-associated respiratory bacillus, *Encephalitozoon cuniculi*, *Pasteurella multicoda*, and *Treponema cuniculi.* On arrival, the rabbits were housed individually in stainless steel cages [62 cm (length) × 42 cm (height) × 64 cm (depth); Hazleton Systems, Aberdeen, MD) with perforated floors suspended above a collecting tray. The rabbits were allowed 5 to 7 d to acclimate to environmental conditions (room temperature, 21.6 to 23.3 °C; relative humidity, 30% to 34%), light cycle (12:12-h photoperiod), and commercial rabbit diet (High-Fiber Rabbit Diet 2031, Harlan, Frederick, MD), supplemented with timothy hay (Johns Hopkins Farm, Baltimore, MD). All rabbits had free access to water via automatic watering.

Baseline parameters. Once the rabbits were acclimated, the supplemental hay was removed, and all rabbits were fed exactly 250 g of the commercial rabbit diet daily. The average New Zealand White consumes 120 to 180 g of commercial pelleted diet per day.[4] An additional 70 g was added to account for variation in the breed and individual rabbit feeding patterns. Baseline parameters were collected 24 h after rabbits were fed the measured feed and included behavior and pain assessment, food intake and fecal production (measured in grams), urine output (subjective), body weight (measured in kilograms), physical examination with abdominal palpation and auscultation, complete blood count and clinical chemistry, and rectal culture (Figure 1). Baseline parameters were recorded as day 0 of the study.

Behavior and pain were measured and scored by quiet observation of individual rabbits from a distance. The guidelines used for behavioral change and pain assessment included attitude, posture, grooming, and activity level on a scale of 1 to 5 (Figure 1). The baseline physical examination parameters included temperature, heart rate, respiratory rate, mucous membrane color and moisture, and abdominal palpation and auscultation. Food intake was measured by weighing the food remaining after 24 h of consumption and subtracting that number from the initial 250 g of commercial food. Subsequently the feeders were once again filled with 250 g of commercial diet. Fecal production was determined by collecting and weighing the fecal pellets from the collecting trays after a 24-h period. A subjective assessment of urine output was made based on the presence (or absence) of urine in the collecting trays. Body weight was measured by using a baby scale (Tanita Best Weigh, Tanita Corporation, Tokyo, Japan). Blood was collected from the ear or saphenous vein. Blood parameters monitored on days 0 (baseline), 2, and 5 postoperatively included white blood cell count, hematocrit, glucose, blood urea nitrogen, creatinine, sodium, and potassium. Samples for rectal culture were collected with rectal swabs.

Surgical procedure. In preparation for routine ovariohysterectomy, each rabbit was anesthetized with 25 mg/kg ketamine (Ketaset, Fort Dodge Laboratories, Fort Dodge, IA) combined with 0.3 mg/kg diazepam (Diazepam, Hospira, Lake Forest, IL) intramuscularly. Once sedated, the rabbits were prepared aseptically for surgery and transported to the surgical suite. Isoflurane (Isoflo, Abbott Animal Health, Abbott Park, Illinois) at 2% to 4% and mixed with oxygen (2 L/min) was provided by face mask to maintain anesthesia. During surgery, the following parameters were monitored: body temperature, respiratory rate, heart rate and oxygenation (pulse oximetry), cardiac rhythm (electrocardiography), end-tidal CO_2 (capnography), and blood pressure (noninvasive). The rabbits were kept warm with forced-air blankets (model 505, Bair Hugger, Arizant Healthcare, Eden Prairie, MN). The rabbits were allowed to recover in a warmed environment until their body temperatures returned to normal and they were in sternal recumbency. Once the rabbits were fully awake they were returned to their cages and fed 250 g of the commercial rabbit diet. All rabbits were monitored for signs of discomfort and pain, including restlessness, anorexia, and guarding of the incision site.

Each rabbit underwent routine ovariohyterectomy through a 5- to 6-cm ventral midline laparotomy incision. The abdominal incision and skin was closed in 2 layers with 2-0 Vicryl (Ethicon, Somerville, NJ). During the recovery phase, 200 mL of subcutaneous fluid (lactated Ringers) was administered to each rabbit. The rabbits were assigned randomly to 3 treatment groups. The 3 postoperative analgesic treatments were: buprenorphine (Buprenex, Renckitt Benckiser Pharmaceuticals, Richmond, VA), 0.03 mg/kg IM every 12 h for 48 h (n = 10); meloxicam (Metacam, Boehringer Ingelheim Vetmedia, St Joseph, MO), 0.2 mg/kg SC every 24 h for 48 h (n = 10); and postoperative 0.5% bupivicaine (Hospira, Lake Forest, IL), 0.5 mL infused locally at the incision (n = 9). These dosages were based on published recommendations.[14] Any rabbit that exhibited either complete lack of appetite or scant to absent fecal production was supplemented with 0.5 mg/kg metoclopramide (once daily for 2 d) and 1 handful of timothy hay.

The rabbits were monitored for 7 d postoperatively by the same observer who collected the baseline parameters. The observer was not blinded to treatment groups due to extensive involvement in postoperative treatment administration. The parameters measured included: behavior and pain assessment based on cage-side observation, measured food intake and fecal output, presence of urine, physical examination with abdominal palpation and auscultation, and character of the incision (Figure 1). On days 2 and 5, the postoperative assessment also included a complete blood count and clinical chemistry, body weight measurement, rectal temperature, and rectal cultures by rectal swab (BBL Port-A-Cul, Becton, Dickson and Company, Sparks,

Daily observations					
	Appetite	Normal	Abnormal		
	Posture	Normal	Abnormal		
	Grooming	Normal	Abnormal		
Activity score	1 Immobile	2 Lethargic	3 Active	4 Very active	5 Hyperactive
Vital signs					
	Temperature	Low	WNL	Elevated	
	Heart rate	Low	WNL	Elevated	
	Respiratory rate	Low	WNL	Elevated	
	Mucous membranes	Pale	WNL	Injected	
Physical examination					
	Abdominal palpation	WNL	Abnormal		
	Abdominal auscultation	WNL	Abnormal		
Incision site (postoperative)	Redness	Swelling	Inflamed	Healed	
Food intake	Weight (g):				
Fecal output	Weight (g):				
Urine	Yes	No			
Hydration status	Normal	Abnormal			
CBC and chemistries	Day 0	Day 2	Day 5		
Fecal culture	Day 0	Day 2	Day 5		
Body weight (g)	Day 0	Day 2	Day 5		

Figure 1. Chart for recording findings regarding parameters assessed daily preoperatively and postoperatively.CBC, complete blood count; WNL, within normal limits.

MD). Cultures were submitted after performing rectal swabs in rabbits before and after surgery. Rectal swabs were shipped to Charles River Diagnostics (Wilmington, MA) for aerobic and anaerobic culture.

Data analysis. Median food intake, fecal output, weight, rectal temperature, and blood parameters were analyzed by using the Kruskal–Wallis test (nonparametric independent group comparisons using the H test statistic) for comparison over time and across treatment groups. Differences were considered statistically significant at a P level of less than 0.05. Because the observer was not blinded to treatment groups (due to inherent study constraints), rabbit behavior and activity data was not included in statistical analysis and interpretation.

Results

Immediately after surgery, 4 rabbits in the bupivicaine-treated group began to show signs of gut stasis. The rabbits were withdrawn from the study after day 2 for having little to no fecal production. The entire group was treated with metoclopramide (Reglan, Baxter Healthcare Corporation, Deerfield, IL) at 0.3 mg/kg SC once daily for 2 d, 50 mL of fluids (Lactated Ringers) SC once a daily for 2 d, and 1 handful of timothy hay daily for 2 d.

Food intake and fecal and urine output. All 29 rabbits showed an initial decrease in appetite on day 1 postoperatively (Figure 2). Pellet consumption from baseline through day 7 did not differ among treatment groups (Table 1). The meloxicam-treated group had a faster return to baseline food consumption by day 5 (meloxicam-treated rabbits consumed 97% of baseline

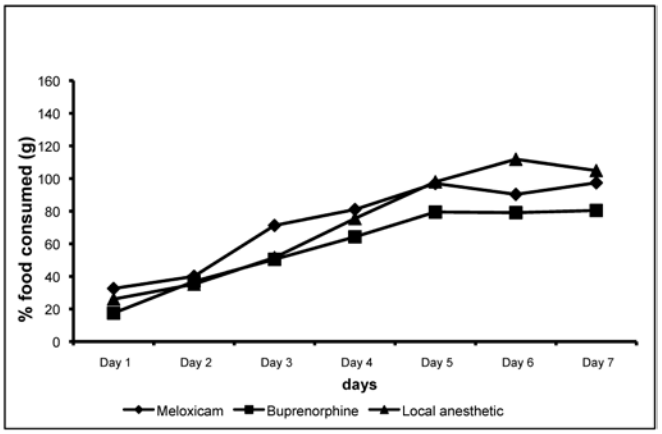

Figure 2. Median food consumption (as a percentage of baseline). Pellet consumption did not differ from baseline through day 7 among treatment groups.

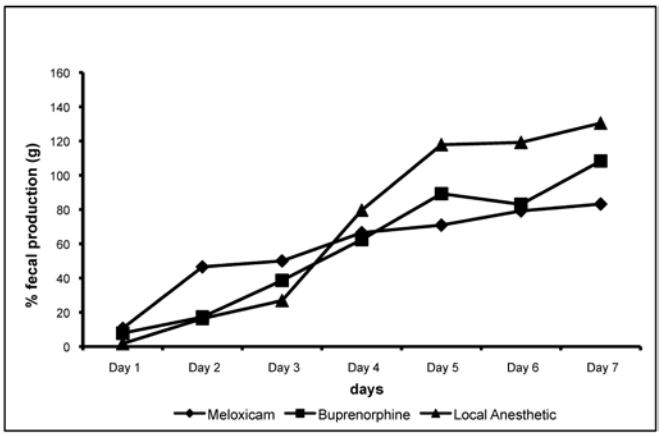

Figure 3. Median fecal production (as percentage of baseline). Fecal production on day 1 after surgery was greater ($P = 0.0256$) in the meloxicam-treated group than the bupivicaine-treated group. Fecal production did not differ across treatment groups between days 2 through 7.

Table 1. *P* values after comparison of the 3 treatment groups over the 7-d period

Day	Food consumption	Fecal production
1	0.1096	0.0246[a]
2	0.4095	0.0871
3	0.1314	0.1857
4	0.4462	0.0588
5	0.5661	0.0112[b]
6	0.2331	0.3930
7	0.3118	0.0912

P values revealed no significant differences in food consumption over the 7 d period. Data from the bupivicaine-treated group on days 3 through 7 were not included in the analyses because these rabbits were treated medically to prevent gut stasis.

[a]Fecal production in the meloxicam-treated group was greater than of the bupivicaine-treated group on day 1 after surgery.

[b]Fecal production was increased in bupivicaine-treated group compared with buprenorphine-treated rabbits on day 5 after surgery.

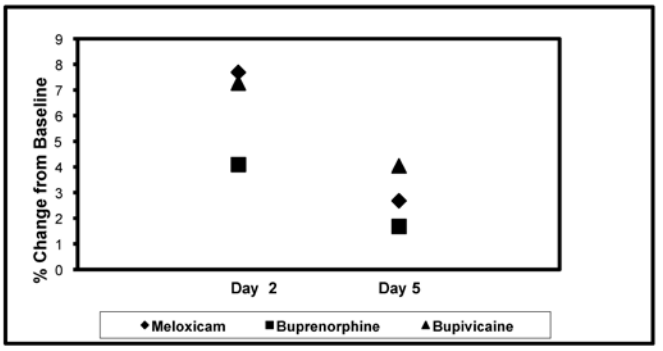

Figure 4. Median weight (as percentage of baseline). Weight loss on day 2 was approximately 3% greater ($P = 0.0352$) in buprenorphine-treated rabbits than bupivicaine-treated rabbits.

levels compared with consumption of 79% of baseline levels by buprenorphine-treated rabbits; Figure 2). Food consumption values for the bupivicaine-treated rabbits were not considered in the analyses after day 2 because these rabbits were medically treated to prevent gut stasis. All 29 rabbits had a greater than 90% decrease in fecal production on postoperative day 1 compared with their median baseline output (Figure 3). The feces in the collecting trays were small, scant, and dry. Statistical analysis revealed a significant ($P = 0.0256$) increase in fecal production in the meloxicam-treated compared with the bupivicaine-treated groups on postoperative day 1 (Table 1). No statistical differences in fecal production were noted across treatment groups between days 2 through 7. The meloxicam and buprenorphine groups slowly approached baseline values for food intake and fecal production through day 7 of the study. The data analysis for the bupivicaine-treated group was not interpreted after day 2 because of the medical rescue effort. However, as a whole, this group responded to the therapy with increases in food intake and fecal production.

All 29 rabbits on the study continued to produce urine and remained well-hydrated as determined by skin tenting, mucous membrane moisture, and bloodwork parameters.

Body weight. All 29 rabbits showed an immediate drop in body weight (approximately 0.2 g each) postoperatively (Figure 4). This decrease in weight can be assumed to have coincided with temporary reduction in appetite. On day 2, weight loss differed between the bupivicaine- and buprenorphine-treated rabbits, with an approximately 3% greater weight decrease in buprenorphine-treated rabbits compared with bupivicaine-treated rabbits (Figure 4). However this difference in weight was no longer significant on day 5 ($P = 0.5922$). Incidentally, all rabbits showed a slow return to baseline body weight by day 5 postoperatively.

Body temperature. Body temperature was monitored as part of the basic physical examination and as a secondary measure to suggest possible infection postoperatively, which could affect the pain score. Body temperature did not differ significantly among treatment groups throughout the study. As expected, body temperature decreased while the rabbits were anesthetized, but all were normothermic before return to their home cages. Body temperature remained normal for all rabbits for the duration of the study (Table 2).

Bloodwork. Complete blood counts and clinical chemistries were obtained as part of the normal minimal data base performed prior to surgery. We were particularly interested in evaluating white blood cell count as a measure of infection or chronic stress and hematocrit, serum electrolytes, and renal parameters to assess hydration status. All rabbits demonstrated mild leukopenia on baseline day 0. On day 5, postoperatively all rabbits were within the normal range for white cell count. The hematocrit for all rabbits remained within normal range

Table 2. Temperature, hematology, and chemistry values (mean ± 1 SD) on days 0, 2 and 5 of the study

	Treatment groups									
	Meloxicam			Buprenorphine			Bupivicaine			Reference range
Parameter	Day 0	Day 2	Day 5	Day 0	Day 2	Day 5	Day 0	Day 2	Day 5	
Temperature (ºC)	38.5 ± 0.6	38.6 ± 0.7	38.8 ± 0.6	39.2 ± 0.3	39.2 ± 0.2	39.3 ± 0.2	39.2 ± 0.5	38.6 ± 0.4	38.9 ± 0.3	38.5–39.5
White blood cells (10^3/μL)	4.4 ± 1.0	4.5 ± 2.1	6.3 ± 1.5	2.9 ± 1.9	6.5 ± 1.0	5.3 ± 1.7	5.3 ± 1.7	6.8 ± 1.4	6.9 ± 1	5.2–12.5
Hematocrit (%)	40 ± 2.54	40 ± 4.2	35 ± 6.7	39 ± 9.4	39 ± 6.5	37 ± 4.4	41 ± 3.6	38 ± 5.7	39 ± 4.3	33–50
Glucose (g/dL)	145 ± 36	102 ± 52	117 ± 16	140 ± 49	96 ± 23	115 ± 32	108 ± 29	114 ± 21	85 ± 13	75–155
Blood urea nitrogen (mg/dL)	20 ± 3	18 ± 3	18 ± 3	19 ± 5	20 ± 6	16 ± 3	16 ± 3	16 ± 2	16 ± 2	13–29
Creatinine (mg/dL)	1.1 ± 0.1	1.0 ± 0.2	0.9 ± 0.1	1.5 ± 0.3	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.8 ± 0.1	0.5–2.5
Sodium (mEq/L)	140 ± 8	148 ± 10	142 ± 2	142 ± 2	142 ± 2	143 ± 2	143 ± 2	145 ± 3	143 ± 2	131–155
Potassium (mEq/L)	3.9 ± 0.7	6.3 ± 2	4.1 ± 0.5	3.5 ± 0.5	5.3 ± 0.6	4.5 ± 0.4	3.7 ± 0.8	3.8 ± 0.6	4.8 ± 0.4	3.6–6.9

for the duration of the study. Biochemical parameters (glucose, creatinine, sodium, calcium, and potassium) remained within normal ranges for all rabbits (Table 2).

Physical examination and abdominal palpation and auscultation. Physical examination parameters of rabbits in the buprenorphine- and meloxicam-treated groups remained similar to baseline values throughout the experiment. However, 4 rabbits in the bupivicaine-treated group had reduction in gut sounds (borborygmi) on days 1 and 2 postoperatively. Borborygmus returned to normal by day 4 postoperatively after initiation of treatment with metoclopramide, fluids, and hay.

Rectal cultures. Rectal swabs were collected to assess normal microbial flora and to verify that there was no gastrointestinal dysbiosis that would account for any gastrointestinal signs. Bacterial culture results varied slightly among the 29 rabbits but overall did not vary for each rabbit with respect to type of bacteria and quantity isolated. Aerobic bacteria commonly isolated in all rabbits included *Corynebacterium* spp., group D *Enterococcus*, *Bacillus* spp., *Proteus mirabilis*, *Escherichia coli*, and *Staphylococcus* spp. Anaerobic bacteria isolated included *Bacteroides* and *Lactobacillus* spp. Especially with regard to anaerobic bacteria, these results illustrate that observed variations in feeding and voiding behaviors did not result in disruption of gastrointestinal flora.

Discussion

Gastrointestinal stasis (ileus) in rabbits can become a medical emergency if not detected promptly. Ileus frequently occurs as a response to environmental stress, diet change, pain, and disease.[4] If detected early in the disease process and if the inciting cause is removed, rapid medical intervention can reverse the condition. The addition of hay to a commercial rabbit diet, administration of subcutaneous or intravenous fluids, administration of metoclopramide, and use of analgesics can improve the animal's condition and prognosis. As seen with the bupivicaine-treated group, gut stasis as exhibited by scant to no fecal production likely was a direct result of postoperative pain and the stress of surgery. Although bupivicaine is considered a long-acting local anesthetic (3 to 8 h of analgesic effect), its duration is insufficient for major surgical procedures.[12] In this study, bupivicaine was infused at the incision site at time of surgical closure, so once the analgesic effect of the bupivicaine block dissipated, the rabbits likely were exposed to pain and discomfort. Four rabbits in this group had decreased food intake, absence of feces, and reduced audible gut sounds. The ileus in these rabbits was rapidly reversed with medical and dietary intervention with administration of metoclopramide, crystalloid fluids, and timothy hay. In the clinical setting, infusion of bupivicaine at the incision site is an effective adjunct to achieving balanced, systemic analgesia. The use of bupivicaine infusion at the incision site is not recommended as the sole means of analgesia for postoperative pain in rabbits.

Part of the study objective was to investigate whether the known side effects of buprenorphine (that is, anorexia and gut stasis) would occur in Dutch Belted rabbits. Although none of the rabbits treated postoperatively with buprenorphine developed overt gut stasis (ileus), their median daily food intakes and fecal outputs indicated an initial decrease in appetite and slight reduction in gastrointestinal motility. However, these rabbits were able to recover appetite and fecal output without medical intervention and remained otherwise healthy throughout the study. This result raises the issue of published reports that state that buprenorphine has a 12-h duration of action.[14] However other studies have shown that the analgesia produced by buprenorphine in rabbits persists for only 8 to 10 h.[21] Because the rabbits in the present study received buprenorphine every 12 h, continuous therapeutic levels may not have been achieved, leaving a 2- to 4-h interval of insufficient analgesia between doses. In addition, buprenorphine is more effective at preventing visceral pain rather than alleviating pain when administered before onset of painful stimuli.[16] For buprenorphine to be most effective in the surgical setting, it should be administered before surgery and every 8 to 10 h thereafter for a total of 48 to 72 h. More research is needed to evaluate whether buprenorphine administered at higher dosages or more frequently for longer durations (for example, every 6 to 10 h for 72 h or longer) would indeed cause overt gastrointestinal side effects in rabbits.

In light of prior anecdotal reports of gastrointestinal side effects with the use of buprenorphine in rabbits and its shorter duration of action, meloxicam appears to be an acceptable alternative for alleviation of postsurgical visceral pain. Meloxicam is an NSAID with very few side effects.[10] The rabbits in the present study received meloxicam every 24 h. This dosing interval for meloxicam may be advantageous over that for buprenorphine, reducing the incidence of stressful human–rabbit encounters and improving compliance with technicians and investigators with its less-frequent administration. In the clinical setting, meloxicam is available also as an oral formulation, eliminating the need to give rabbits intramuscular injections. A study has shown that meloxicam can be safely given to rabbits orally at a dose of 0.3 mg/kg or 1.5 mg/kg for 5 consecutive days with no ill effects.[19] The rabbits in the present study received a

recommended[14] meloxicam dose of 0.2 mg/kg. As our results have demonstrated, the meloxicam-treated rabbits responded in a similar fashion to the buprenorphine-treated rabbits. As mentioned previously in regard to buprenorphine, additional studies should also be conducted for meloxicam to determine whether clinical side effects exist at higher-than-recommended dosages.

Rabbits are prey animals, and masking illness and pain is conducive to their survival. Postural and behavioral changes in response to pain and illness are all subjective indicators and can be quite vague and difficult to interpret. Rabbits may exhibit only subtle postural changes in response to postoperative pain.[15] One of the more common indicators of illness in the rabbit is loss of appetite and weight.[18] Therefore, a reduction in eating and voiding behaviors without any other clinical signs could suggest clinical illness and should be measured frequently during the postoperative period. All of the rabbits in this study had decreased eating and voiding on day 1 postoperatively, most likely due to the stress of surgery, general anesthesia, and postoperative pain. In addition, 4 of the 10 bupivicaine-treated rabbits developed gut stasis as demonstrated by scant to no fecal production; as a result of timely medical intervention, they exhibited a more rapid return toward their baseline food consumption and fecal production than did the other groups. In contrast, meloxicam- and buprenorphine-treated rabbits did not develop overt signs of gut stasis and displayed a slower and more steady return toward baseline values and perhaps would also have benefited from dietary supplementation with hay and fluids.

The original aim of the study was to investigate the possible gastrointestinal side effects of buprenorphine in the New Zealand White rabbit because this is the breed in which we anecdotally noted possible opioid side effects. We instead chose Dutch Belted rabbits because of their smaller size, amiable personalities, and adoptability. Dutch Belted rabbits rarely exceed an average of 5 lbs in weight and are good pets. The New Zealand White rabbits are sometimes prone to aggression and can reach 15 lbs in body weight. Future studies should investigate whether any physiologic differences between New Zealand White and Dutch Belted rabbits make 1 breed more susceptible to gastrointestinal side effects due to the use of opioid derivatives.

On the basis of our study, meloxicam is an appropriate alternative to buprenorphine use for soft-tissue surgery, and either analgesic appears to be appropriate for use with ovariohysterectomy or similar abdominal procedure. In future studies, we plan to evaluate not only the effects of more frequent buprenorphine administration but also the outcomes of combined usage of buprenorphine and meloxicam postoperatively to adhere to the concept of multimodal, balanced analgesia. In addition, this combination will accommodate lower and possibly less frequent buprenorphine dosing. We also may need to investigate supplementation of rabbits undergoing abdominal surgery with hay and preemptive treatment with fluids and metoclopramide. As seen with the bupivicaine treatment group, the rabbits had a favorable return to baseline food consumption and fecal production once treatment was instituted.

The rabbit is a valuable animal model in laboratory research and a species especially susceptible to postoperative complications resulting from stress, pain, antibiotics, and analgesic side effects. This study has shown that meloxicam and buprenorphine were comparable in analgesia after routine ovariohysterectomy. Our results indicate numerous options when choosing an appropriate postoperative analgesic. Buprenorphine and meloxicam at the dosages used in this study caused minimal gastrointestinal side effects, and are recommended for use in rabbits, particularly the Dutch Belted breed. Other dosages and duration of administration of either analgesic could reveal diverse results. Future studies are needed to determine the optimal dose in the domestic rabbit. However, if complications do occur, several available treatment methodologies are efficacious and can be used both preemptively and therapeutically for all forms of surgery and other invasive experimental procedures.

Acknowledgments

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