Frequency of vomiting during the postoperative period in hydromorphone-treated dogs undergoing orthopedic surgery

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Objective—To determine the frequency of postoperative vomiting in dogs undergoing routine orthopedic surgery that were treated with hydromorphone and whether that frequency would vary on the basis of administration route.

Design—Noncontrolled clinical trial.

Animals—58 client-owned dogs with cranial cruciate ligament deficiency.

Procedures—Before surgery, all dogs received hydromorphone (0.1 mg/kg [0.045 mg/lb], IM or IV) and 41 dogs also received acepromazine. Anesthesia was induced with diazepam and propofol and maintained with isoflurane in oxygen. Dogs subsequently underwent surgical stabilization of the stifle joint. After surgery, dogs were randomly assigned to receive hydromorphone (0.1 mg/kg) via one of the following routes: IM, IV quickly (for 1 to 2 seconds), or IV slowly (for approx 1 minute). Dogs were monitored for vomiting.

Results—A median of 4 doses of hydromorphone/dog was administered after surgery. One dog was observed to regurgitate once prior to postoperative IM administration of hydromorphone; no dogs vomited at any point during the study period, regardless of the method of hydromorphone administration.

Conclusions and Clinical Relevance—The method of hydromorphone administration had no apparent effect on the likelihood of dogs vomiting. Because no dogs vomited, a particular administration method cannot be recommended. However, findings suggested that hydromorphone can be administered to dogs following orthopedic surgery without a clinically important risk of vomiting or regurgitation. (*J Am Vet Med Assoc* 2012;241:344–347)

Opioid administration has been associated with many adverse effects in dogs, including vomiting.[1–4] Vomiting can lead to other adverse sequelae, such as gastric content aspiration, esophagitis and resultant stricture, tension on suture lines, venous blood pressure increase, subcutaneous bleeding, and prolonged hospitalization.[5] Indeed, hydromorphone administration during the postanesthetic period in dogs with intervertebral disk disease is a risk factor for pneumonia.[6]

Hydromorphone is a synthetic opioid μ-receptor agonist with 5 times the potency of morphine and is the most commonly used preemptive and postoperative analgesic in the authors' hospital.[3,7] The hospital's typical protocol is for dogs undergoing orthopedic surgery to receive 0.1 mg/kg (0.05 mg/lb) of hydromorphone IV or IM as a premedication to provide intraoperative analgesia. After surgery, hydromorphone is administered IV every 4 hours for 8 to 24 hours to continue that analgesia, after which time orally and transdermally administered analgesics are used. Vomiting is occasionally observed in these dogs when hydromorphone is administered before surgery and, less commonly, when it is administered after surgery.

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Abbreviation

CRTZ	Chemoreceptor trigger zone

Emetic and antiemetic effects of opioids have been recognized in dogs, cats, ferrets, and humans.[8–10] The emetic effects are a result of stimulation of the μ-opioid receptors in the CRTZ of the brain. On the other hand, the antiemetic effects are from stimulating μ-opioid receptors in the vomiting center of the brain.[8–10] Studies[1–3] have been conducted to characterize the frequency of vomiting associated with opioids administered at various doses and routes, with or without phenothiazines, in healthy, sedated dogs. Studies[1,2,4,11] have also been performed to assess the frequency of vomiting in dogs after IM opioid administration. To the authors' knowledge, the incidence of postoperative vomiting in dogs treated with hydromorphone has not yet been evaluated.

The purpose of the study reported here was to determine the frequency of vomiting during the postoperative period in dogs that underwent orthopedic surgery and received hydromorphone for analgesia. A second objective was to identify the route of hydromorphone administration (IM or IV) associated with a lower incidence of vomiting. We hypothesized that because drug absorption is generally slower with IM administration than with IV administration, the CRTZ might be stimulated before the vomiting center of the brain, resulting in a higher likelihood of vomiting in dogs treated IV versus IM.

Materials and Methods

Dogs—From October 2007 to February 2008, client-owned dogs with a ruptured cranial cruciate ligament were prospectively enrolled in the study after owner consent was obtained. To be included, dogs needed to have a ruptured cranial cruciate ligament as diagnosed by detection of a cranial drawer sign and be scheduled to undergo surgery to restabilize the stifle joint. Dogs were also required to be otherwise clinically healthy as assessed through their medical history, physical examination, and preanesthetic serum biochemical analysis. In dogs > 6 years of age, an unremarkable CBC was also required, but some dogs < 6 years of age had a CBC performed by the referring veterinarian. Exclusion criteria were a history of systemic diseases known to affect opioid sensitivity or cause gastrointestinal signs, drug sensitivity, and clinicopathologic abnormalities.

Study design—Dogs were randomly assigned to 3 treatment groups for postoperative opioid analgesia by drawing treatment group assignments from a hat. Sample size for each treatment group was calculated with the objective of 80% power to detect a clinically meaningful difference in vomiting incidence of 25%.

Surgery—In preparation for surgery, all dog owners were instructed to stop feeding their dog after midnight the night before surgery, resulting in a minimum 12- to 18-hour period of food withholding. Preanesthetic drugs were given as needed to facilitate catheter placement and successful anesthetic induction. Drugs used included acepromazine (0.02 to 0.12 mg/kg [0.009 to 0.055 mg/lb] in 41 dogs), butorphanol (0.2 mg/kg [0.09 mg/lb] in 1 dog), and hydromorphone (0.05 to 0.1 mg/kg [0.023 to 0.045 mg/lb] in all dogs). The dose of hydromorphone was repeated at anesthetic induction when a delay > 4 hours existed between IV catheter placement and anesthetic induction.

Doses and drug selection for preanesthetic use were determined on an individual basis. The route of hydromorphone administration prior to surgery was unaffected by study group assignment. When sedation was needed to allow catheter placement, drugs were administered IM. When the catheter was placed easily, drugs were administered IV prior to anesthetic induction.

Anesthesia was induced in all dogs with diazepam (0.25 mg/kg [0.11 mg/lb], IV) and propofol (2 to 6 mg/kg [0.9 to 2.7 mg/lb], IV, titrated to effect). Dogs were endotracheally intubated, and anesthesia was maintained with 2% to 3% isoflurane in oxygen in a semiclosed circuit anesthetic system. Fluids (lactated Ringer's solution) were administered IV throughout the procedure at a rate of 10 to 20 mL/kg/h (4.5 to 9.1 mL/lb/h).

Restabilization of the stifle joint was achieved by means of tibial plateau leveling osteotomy or lateral fabellar suture stabilization. The surgical procedure performed was determined by surgeon and owner preference. Lateral fabellar suture stabilization was performed with dogs positioned in lateral recumbency. Tibial plateau leveling osteotomy was performed with dogs positioned in dorsal recumbency, with the pelvis rotated to allow proper limb positioning (with the tibia of the affected limb parallel to the table). All surgeries were performed by the same board-certified surgeon (MPP). At endotracheal extubation, transdermal fentanyl patches (1.56 to 2.94 μg/kg/h [0.71 to 1.34 μg/lb/h]) were applied to the skin clipped of hair on the affected limb in all but 1 dog.

Postsurgical hydromorphone administration—Beginning approximately 4 hours after the preoperative dose of hydromorphone was administered, dogs in the IM group received 0.1 mg of hydromorphone/kg, IM, every 4 hours. Dogs in the second group (slow IV group) received 0.1 mg of hydromorphone/kg, IV, for approximately 1 minute every 4 hours. Dogs in the third group (fast IV group) received 0.1 mg of hydromorphone/kg, IV, for 1 to 2 seconds every 4 hours. The total number of hydromorphone doses each dog received was not standardized. Rather, doses received was dependent on the time of surgery, dosing interval, and when dogs were transitioned to orally administered analgesics.

Hydromorphone administration was not timed; instead, the technicians providing postoperative care were relied on to follow the study protocol. When a dog appeared to be overly sedated, the interval between doses could be extended to 6 hours with the approval of the attending clinician. Likewise, when the clinician noticed signs of pain in the dog, the dosing interval could be shortened.

Physical status assessments—Sedation and pain scores were not assigned. Instead, various parameters were used to assess the degree of sedation or pain, including blood pressure, pulse rate, respiratory rate, vocalization, reaction to palpation of the affected limb, and degree of consciousness or interaction with veterinary attendants. Hydromorphone treatment was transitioned to orally administered analgesics (tramadol and NSAIDs, as indicated) the morning after surgery. Data were recorded for the total number of times hydromorphone was given after surgery. Veterinary attendants were specifically instructed to monitor each dog for vomiting, which was defined as active expulsion of gastric contents from the mouth. Vomition was distinguished from regurgitation in that regurgitation was defined as a passive expulsion of gastric contents from the mouth.

Postoperative treatments and monitoring—All dogs were treated after surgery with fluids (lactated Ringer's solution, 2 to 3 mL/kg/h [0.9 to 1.4 mL/lb/h], IV). Antimicrobials were also administered after surgery, including cefazolin (22 mg/kg [10 mg/lb], slowly IV, q 8 h), with 1 to 3 doses of cefazolin administered/dog during the study period. Three dogs were treated with ampicillin sodium–sulbactam sodium (22 mg/kg, IV, q 8 h) at the preference of the attending clinician for the reason that these were small dogs in which cephalexin could not be administered without having to compound the dose. These 3 dogs were treated with amoxicillin trihydrate–clavulanate potassium after discontinuation of IV antimicrobial administration.

Dogs were monitored postoperatively by the investigators during the daytime and by the staff veterinarians and nurses during the night. All dogs were specifically monitored for vomiting and regurgitation from the point of endotracheal extubation until discharge

from the hospital on the day after surgery. The nursing staff and one of the doctors (LCS) were not blinded to the treatment groups to which dogs had been assigned. All hospital treatment records, used by the nursing staff and retained for the patient's medical record, included information on drugs used and methods of administration. This information was disclosed to the nursing staff and veterinarians. Separate data sheets upon which nursing staff recorded all drugs administered (but not the route of administration) and any incidents of vomiting or regurgitation (including timing) were hung on dogs' cages with the treatment record. This allowed review of data without knowledge of the treatment groups to which dogs belonged.

Statistical analysis—Because of the antiemetic effects of acepromazine, dogs that received the drug during the postoperative period were excluded from the data analysis when they were given acepromazine during the postoperative period. One-way ANOVA was performed to evaluate the differences in age and body weight among the 3 treatment groups to ensure the groups were similar with respect to these variables. The Shapiro-Wilk test for normality was used to ensure the data were normally distributed. Age and body weight are reported as mean ± SD.

Data on the number of doses administered in each group were nonnormally distributed. Consequently, the Kruskal-Wallis test was used to determine differences among the groups for this variable. The median dose count for each treatment group is reported. A value of $P < 0.05$ was considered significant. All statistical analyses were performed with commercially available software programs.[12,a]

Results

Animals—Sixty-two dogs were considered for inclusion in the study; 3 dogs were enrolled twice during the study period. No dogs were rejected from the study for health problems; all dogs underwent surgical stabilization of the stifle joint. Two dogs were receiving thyroxine for hypothyroidism at the time of surgery. One dog was being treated with a zinc supplement for dermatologic disease, and another was receiving ophthalmic cyclosporine for keratoconjunctivitis sicca.

Four dogs received acepromazine during the postoperative period, and 3 of these dogs were withdrawn from the study. One of the 3 excluded dogs had bilateral stifle joint disease and underwent surgery on the contralateral stifle joint 4 months after study withdrawal; this dog was consequently reinstated as a study participant and was counted as 1 of 3 dogs with bilateral repairs in the study period. In the fourth dog, acepromazine was administered between the third and fourth doses of hydromorphone; the dose of hydromorphone administered after the acepromazine was not included in dose counts for the study. A fourth dog was withdrawn from the study for incorrect administration of hydromorphone.

The remaining 58 dogs (28 spayed females, 29 castrated males, and 1 sexually intact male dog), representing 23 breeds, were included in the study. These dogs were distributed among treatment groups as follows: IM, 20; slow IV, 20; and fast IV, 21 (2 dogs were in 2 groups at different times). No difference was detected among treatment groups with respect to age (mean ± SD overall age, 5.6 ± 2.9 years; $P = 0.88$) or body weight (35.8 ± 12.9 kg [78.8 ± 28.4 lb]; $P = 0.50$).

Surgery—Tibial plateau leveling osteotomy was performed 47 times: 15 times in the IM group, 18 times in the slow IV group, and 14 times in the fast IV group. Lateral fabellar suture stabilization was performed 14 times; in 1 dog, medial patellar luxation was corrected concurrently. Two dogs underwent bilateral, staged, tibial plateau leveling osteomy for stifle joint stabilization.

Treatments received—Thirty-nine dogs were treated with an NSAID before surgery; all dogs were treated with an NSAID after surgery. Nonsteroidal anti-inflammatory drugs were not administered until the morning after surgery, typically within 4 hours after the last dose of hydromorphone was administered. One dog was treated with butorphanol and acepromazine 8.5 hours prior to surgery. In this situation, butorphanol was used instead of hydromorphone to facilitate catheter placement. Hydromorphone was subsequently administered IV in this dog 30 minutes prior to anesthetic induction to provide intraoperative analgesia. One aggressive dog was given acepromazine (0.78 mg/kg [0.35 mg/lb], PO) prior to hospital admission.

In the IM group, 13 dogs received acepromazine at a dose of 0.02 to 0.12 mg/kg, IM. In the slow IV group, 13 dogs were given acepromazine at a dose of 0.03 to 0.06 mg/kg (0.014 to 0.027 mg/lb), IM. In the fast IV group, 16 dogs received acepromazine at a dose of 0.03 to 0.09 mg/kg (0.014 to 0.041 mg/lb), IM, and 1 dog received the drug at a dose 0.036 mg/kg (0.016 mg/lb), IV.

During anesthesia, 6 dogs were given an injection of glycopyrrolate, and 1 dog received atropine for bradycardia (heart rate, < 50 beats/min). After surgery, all but 1 dog received a fentanyl patch. For that 1 dog, the owner requested that fentanyl not be used because of a previous adverse experience with the drug in this dog. Four dogs received acepromazine after surgery. All dogs except the 3 small dogs treated with antimicrobial alternatives to cephalexin continued treatment with cephalexin after hospital discharge.

Hydromorphone administration—Each treatment group had a median of 4 doses administered/dog during the study period. There was no significant ($P = 0.76$) difference between the number of doses administered among the groups. One dog in the IM group regurgitated once prior to postoperative hydromorphone administration, and no dogs were observed to vomit in any group. No dogs required adjustments in the postsurgical hydromorphone dosing interval because of signs of sedation or pain.

Discussion

Vomiting in dogs undergoing surgery can occur from stimulation of the CRTZ, gastritis from treatment with NSAIDs, rapid IV administration of cefazolin, underlying gastrointestinal disease, or hypotension and associated poor perfusion to the gastrointestinal tract, resulting in gastritis.[7,13] No dogs vomited (active expulsion of gas-

tric contents) in the present study after hydromorphone administration, regardless of the administration method. Although 1 dog was observed to regurgitate (passive expulsion of gastric contents), this happened before postoperative hydromorphone administration.

A preferred method of hydromorphone administration was not identified because of the lack of vomiting and low incidence of regurgitation. On the basis of these findings, hydromorphone administered IV or IM after surgery is unlikely to result in vomiting in dogs undergoing elective orthopedic surgery. It is unknown whether the same would be true for dogs undergoing soft tissue or emergency surgery.

The frequency of vomiting in the present study is less than that reported for other studies.[1,3] The dogs in our study differed from other study dogs in that they had clinical disease and hydromorphone administration after surgery was the subject of interest. Many factors may explain the lack of postoperative vomiting observed, which was the outcome of interest, in our study. For one, opioids have antiemetic effects,[8–10] and all dogs received at least 1 dose of hydromorphone before surgery, which could have imparted antiemetic effects when subsequent doses were administered after surgery. The CRTZ is located on the floor of the fourth ventricle of the brain, which has fenestrated capillaries, making the CRTZ functionally outside of the blood-brain barrier and causing it to be affected by opioids before the drugs reach the μ-opioid receptors in the vomiting center. The vomiting center is located within the nucleus tractus solitarius in the brainstem, which is protected by the blood-brain barrier. Different opioids cross the blood-brain barrier at different rates. Factors that contribute to the rate of vomiting center stimulation are the degree of lipophilia, dose, and concentration of the drug. Lipophilic opioids, such as fentanyl, or high doses of less lipophilic drugs, such as morphine, stimulate the vomiting center and result in antiemetic effects.[8,9]

A second factor that might explain the lack of vomiting is that acepromazine has antiemetic effects[1] and was given to 41 dogs of the present study. The duration of the drug's antiemetic effects has not been evaluated, to the authors' knowledge. Anticholinergics, which have antiemetic effects in humans, were given to 7 dogs in another study,[7] resulting in gastrointestinal stasis that could have been a sequel to their vagolytic activity. Although fentanyl has antiemetic properties,[6,8,9] application of transdermal fentanyl patches in the dogs after surgery in the present study likely did not influence the results because a therapeutic blood fentanyl concentration is usually not reached until 12 or more hours in dogs and most observations were made during the first 12 hours after surgery.

Postoperative pain is a risk factor for postoperative nausea and vomiting in humans[5]; however, whether pain has a similar effect in dogs has not been assessed. Vomiting is less likely when opioids are given to dogs with signs of pain than when they are given to dogs without such signs.[7] Although no effort was made to quantify the degree of pain in the present study, one may presume that dogs with disease of the stifle joint have a moderate to severe degree of discomfort. This presence of pain might explain the lack of vomiting observed, compared with what might be observed in dogs undergoing a less extensive or invasive surgery such as laparoscopy, which is associated with postoperative nausea and vomiting in a high proportion of human patients (35%).[5]

Limitations of the present study include the lack of continuous observation of dogs after surgery. Although the study was conducted in a clinical setting with 24-hour staffing, dogs were observed a minimum of once per hour. It is possible that dogs could have vomited without the vomitus being noticed or recorded in the medical records. Because food was withheld from midnight of the evening before surgery until the time of surgery, any vomiting that did occur might have been minimally productive, resulting in only foam or bile. Also, dogs could have had silent regurgitation or esophageal reflux, which was not monitored. Such phenomena were not intended to be evaluated as part of the study, but both can result from opioid administration in dogs.[2]

In ideal circumstances, the treatment protocols used in the present study would have been standardized in terms of preoperative sedation and NSAID use. However, because most NSAIDs have similar potential to cause gastroenteritis,[13] the choice of NSAID was likely unimportant. Butorphanol also has antiemetic effects and was given preoperatively to 1 dog. This was > 8 hours before surgery and likely did not impart any antiemetic effects during the postoperative period because of the amount of time that passed.[14]

a. JMP, version 7, SAS Institute Inc, Cary, NC.

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