Efficacy of orally administered maropitant citrate in preventing vomiting associated with hydromorphone administration in dogs

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Objective—To evaluate the effectiveness of orally administered maropitant citrate in preventing vomiting after hydromorphone hydrochloride administration in dogs.

Design—Randomized, blinded, prospective clinical study.

Animals—40 dogs with American Society of Anesthesiologists status of I or II, >6 months of age, and weighing between 24 and 58.2 kg (52.8 and 128.04 lb).

Procedures—Dogs were randomly selected to receive maropitant (2.0 to 4.0 mg/kg [0.9 to 1.8 mg/lb]) or placebo (lactose monohydrate) orally 2 hours prior to receiving hydromorphone (0.1 mg/kg [0.045 mg/lb], IM). A blinded observer recorded the occurrence of vomiting or signs of nausea (eg, salivation or lip-licking) during a 30-minute period after hydromorphone administration. Two-tailed Fisher exact tests were used to compare the incidences of vomiting and signs of nausea with or without vomiting between treatment groups.

Results—Of the 20 dogs receiving maropitant, none vomited but 12 (60%) developed signs of nausea. Of the 20 dogs receiving placebo, 5 (25%) vomited and 11 (55%) developed signs of nausea; overall, 16 of 20 (80%) dogs in the placebo treatment group vomited or developed signs of nausea. Compared with the effects of placebo, maropitant significantly decreased the incidence of vomiting but not signs of nausea in dogs administered hydromorphone.

Conclusions and Clinical Relevance—Among the 40 study dogs, the incidence of vomiting associated with hydromorphone administration was 25%. Oral administration of maropitant prevented vomiting but not signs of nausea associated with hydromorphone administration in dogs. (J Am Vet Med Assoc 2014;244:1164–1169)
broad spectrum of emetic stimuli, including cisplatin, apomorphine, copper sulfate, and motion sickness. Results of a previous study in dogs indicate that maropitant citrate (1.0 mg/kg [0.45 mg/lb], SC) injected 1 hour prior to premedication with hydromorphone (0.1 mg/kg [0.045 mg/lb], IM) was effective in preventing vomiting and signs of nausea. However, SC injection of maropitant has been associated with pain, especially when the drug has been stored according to label instructions at room temperature (approx 20° to 25°C). Intravenous administration of maropitant constitutes extralabel usage and has been associated with hypotension in dogs and cats. Maropitant tablets administered at a minimum dosage of 2.0 mg/kg (0.9 mg/lb) orally once a day are labeled for the prevention of acute vomiting in dogs; such oral administration would provide a nonpainful treatment option (compared with SC administration of the drug) and avoid development of cardiovascular adverse effects. Therefore, the goal of the study reported here was to evaluate the effectiveness of administration of the oral formulation of maropitant in preventing vomiting associated with hydromorphone hydrochloride administration in dogs.

Materials and Methods

Study population—The study was approved by the Iowa State University Institutional Animal Care and Use Committee. The owners of dogs brought to the Lloyd Veterinary Medical Center at Iowa State University College of Veterinary Medicine were asked to participate in this study if their dogs were healthy, weighed between 24 and 60 kg (52.8 and 132.0 lb), were being admitted for elective anesthesia and surgery, and would be receiving hydromorphone as an anesthetic premedication drug. Staff and students of Iowa State University College of Veterinary Medicine were contacted via college-wide electronic mail to enroll their own dogs if they were healthy and weighed between 24 and 60 kg in exchange for a CBC and routine serum biochemical analysis. All owners provided informed consent for participation. The study included 40 dogs > 6 months of age that were classified as American Society of Anesthesiologists status I (healthy with no systemic disease) or status II (nonincapacitating systemic disease), as determined from the results of complete physical examination, CBC, and routine serum biochemical analysis.

Among the 40 dogs, there were 22 female dogs (19 spayed and 3 sexually intact) and 18 male dogs (17 castrated and 1 sexually intact); the dogs were 11 months to 9.3 years of age and weighed 24 to 58.2 kg (52.8 to 128.04 lb). The dogs were mixed-breed and purebred dogs. Twenty-two dogs were owned by clients, and 18 dogs were owned by staff or students of the Iowa State University College of Veterinary Medicine.

Experimental treatment—The Iowa State University College of Veterinary Medicine Lloyd Veterinary Medical Center pharmacy compounded colored gelatin capsules to allow the study to be performed in a blinded manner; only pharmacy staff had the key to what was contained in each capsule. Dogs were randomly assigned by simple randomization with a card draw technique to receive 1 or 2 orange capsules containing 60 mg of maropitant citrate (n = 20) once or 1 or 2 white capsules containing 400 mg of lactose monohydrate (placebo; 20) once. In accordance with the maropitant package insert dosing instructions, dogs received 1 or 2 maropitant or placebo capsules on the basis of weight. Dogs that weighed 24 to 30 kg (52.8 to 66 lb) received 1 capsule, and dogs 30.1 to 60 kg (66.22 to 132 lb) received 2 capsules. For dogs in the maropitant treatment group, this corresponded to a drug dose of 2.0 to 2.5 mg/kg (0.9 to 1.14 mg/lb) for dogs that weigh 24 to 30 kg and a drug dose of 2.0 to 4.0 mg/kg (0.9 to 1.82 mg/lb) for dogs that weighed 30.1 to 60 kg.

Oral dosing instructions for maropitant indicate that it should be administered with a small amount of food; therefore, the maropitant capsules were administered with 1 tablespoon of canned dog food. Dogs that refused the capsule (or capsules) and food were administered the capsule (or capsules) by hand without food. Twenty dogs received treatment with maropitant; 10 of those dogs received the capsule (or capsules) with food, and 10 had the capsule (or capsules) administered by hand without food. Twenty dogs received placebo; 10 received the capsule (or capsules) with food, and 10 had the capsule (or capsules) administered by hand without food. Dogs were administered maropitant or placebo 2 hours prior to receiving hydromorphone (0.1 mg/kg, IM) in the lumbar epaxial muscles.

Data collection—A trained observer (BLHK) blinded to treatment group documented the presence or absence of emetic events, total number of discrete emetic events, presence or absence of signs of nausea, and severity of signs of nausea for each dog during a 30-minute period following administration of hydromorphone. Vomiting was defined by expulsion of stomach contents from the mouth. Signs interpreted as nausea included salivation, increased frequency of or exaggerated swallowing motions, and licking of lips. Signs of nausea were subjectively graded as none, mild, moderate, or severe; the maximal severity of signs of nausea noted during the 30-minute period was recorded for each dog.

Statistical analysis—The primary variable used in the analysis of efficacy was whether a dog had ≥ 1 vomiting episodes. A 2-tailed Fisher exact test was performed to compare the incidence of vomiting between the maropitant and placebo treatment groups. The Fisher exact test was repeated with the inclusion of signs of nausea in addition to vomiting. Significance was assessed at a value of P ≤ 0.05. A t test was used to detect incidental differences between the groups that may have occurred on the basis of age and weight. A Mann-Whitney U test was used to compare the overall severity of signs of nausea between the maropitant and placebo treatment groups; for this analysis, severity grades were assigned numerical values as follows: no signs of nausea, 0; mild signs of nausea, 1; moderate signs of nausea, 2; and severe signs of nausea, 3. A Fisher exact test was run to compare the incidence of vomiting and nausea between male and female dogs in the placebo treatment group.

Results

For the 20 dogs that were administered maropitant, the mean ± SD age was 4.4 ± 2.4 years and mean weight
was 35 ± 9.3 kg (77 ± 20.46 lb); there were 7 males and 13 females in this group. For the 20 dogs that were administered the placebo, the mean age was 5.0 ± 2.7 years and mean weight was 34.9 ± 7.2 kg (76.8 ± 15.84 lb); there were 11 males and 9 females in this group. There was no significant difference in age (P = 0.429), weight (P = 0.978), or sex distribution (P = 0.34) between the maropitant- and placebo-treated dogs.

Among the dogs that received maropitant, there was no significant difference in the number of dogs that did or did not vomit (P = 1.0) or that did or did not develop signs of nausea (P = 0.65) between dogs that received the treatment with food or without food. Likewise, among dogs that received placebo, there was no significant difference in the number of dogs that did or did not vomit (P = 1.0) or that did or did not develop signs of nausea (P = 0.58).

Table 1) between dogs that received the treatment with food or without food. Thus, for the maropitant or placebo treatment group, the data from the fed and hand-dosed dogs were pooled to increase the power of the study.

In the placebo treatment group, there was no difference between males and females with regard to the incidence of vomiting (P = 0.319) or number of dogs with signs of nausea (P = 1.0). Among the 20 placebo-treated dogs, 5 (4 males and 1 female; 25%) vomited and 16 (9 males and 7 females; 80%) developed signs of nausea. Of the 5 dogs that vomited in the placebo treatment group, 2 vomited only once and 3 vomited > 1 time. In the maropitant treatment group, none of the 20 dogs vomited; however, 12 (60%) developed signs of nausea. Of the 5 dogs that vomited in the placebo treatment group, 2 vomited only once and 3 vomited > 1 time. In the maropitant treatment group, none of the 20 dogs vomited; however, 12 (60%) developed signs of nausea. Orally administered maropitant significantly decreased the incidence of vomiting (P = 0.047) but not the incidence of signs of nausea (P = 0.301), compared with the effects of placebo, in the study dogs.

In the maropitant treatment group, 8 of 20 dogs did not develop signs of nausea. Among the 12 maropitant-treated dogs that developed signs of nausea, severity was subjectively graded as mild for 2, moderate for 4, and severe for 6. Overall, signs of nausea were moderate to severe in 10 of the 12 dogs. In the placebo treatment group, 4 of the 20 dogs did not develop signs of nausea. Among the 16 placebo-treated dogs that developed signs of nausea, severity was graded as mild for 14 and moderate for 2; none of the dogs had signs of nausea graded as severe. Overall, signs of nausea were mild in 14 of the 16 dogs. However, there was no significant (P = 0.363) difference in the overall subjective grading of severity of signs of nausea between the maropitant and placebo treatment groups.

**Discussion**

The results of the present study indicated that the oral formulation of maropitant citrate, administered at a dose (minimum, 2.0 mg/kg, PO) specified for the prevention of acute vomiting in the label instructions, was effective in preventing vomiting in dogs receiving hydromorphone hydrochloride (0.1 mg/kg, IM). This finding correlated well with results of a recent study in the injectable formulation given at a dose of 1.0 mg/kg, SC, 1 hour prior to administration of hydromorphone in dogs. Subcutaneous injection of maropitant may be associated with pain, which is a particular problem when the injectable solution is stored at room temperature. The drug solution is formulated with sulfobutylether-cyclodextrin, with which maropitant forms a molecular complex that provides higher drug solubility and improved injection-site tolerance; at warmer temperatures, there is greater complex dissociation. It is suggested that the injectable form of maropitant should be refrigerated until administration to minimize injection reactions. Recent studies that investigated the minimal alveolar concentration–sparing effects of maropitant indicate that extralabel IV administration of maropitant may cause hypotension in both dogs and cats. Oral administration of the drug avoids injection-associated pain, the need for refrigeration of the drug solution, issues with extralabel usage, and cardiovas-
cular adverse effects. Tablets can be administered to dogs by their owners at home, which may also provide a more convenient route and timing of treatment for the prevention of emesis prior to planned elective anesthesia and surgery that will involve administration of hydromorphone or other opioid drugs known to elicit vomiting.

In the present study, orally administered maropitant was more effective in preventing vomiting after hydromorphone administration in dogs than it was in previous experiments\(^3\) that used syrup of ipecac (peripherally acting emetogen) and apomorphine (centrally acting emetogen). In those experiments,\(^2\) orally administered maropitant administered to dogs at a minimum dose of 2.0 mg/kg 1 hour prior to administration of a known emetogen significantly reduced but did not eliminate the incidence of vomiting. Pharmacokinetic data\(^5\) indicate that the plasma concentration of maropitant is maximal at 1.9 hours after oral administration of a 2.0 mg/kg dose. Therefore, the effectiveness of maropitant in the prevention of vomiting induced by a known emetogen may be increased if an interval of 2 hours is allowed to elapse between the 2 treatments.

Despite the effectiveness of maropitant in preventing vomiting in the present study, there was no significant difference in the incidence of signs of nausea between maropitant- and placebo-treated dogs. In a study evaluating treatment of motion sickness in dogs by Benchouai et al.,\(^3\) maropitant (8.0 mg/kg [3.64 mg/lb], PO) administered 1 hour prior to a car ride did not have an effect on the incidence of signs of nausea. Hypersalivation and retching were reported as the most common adverse effects (9/17 dogs) in field studies\(^2\,\^3\) of the safety and efficacy of maropitant administration (8.0 mg/kg, PO) 1 hour prior to transportation for the prevention of motion sickness. Similar findings were reported when dogs were administered apomorphine 1 hour after administration of maropitant (2.0 mg/kg, PO), in which visual analog scores for signs of nausea for maropitant-treated dogs were not significantly different from those for placebo-treated dogs except at the 3- and 6-minute time points.\(^3\) However, hypersalivation was not reported as an adverse reaction in field studies\(^5\,\^3\) of the prevention of acute vomiting in dogs treated with maropitant tablets at a minimum dosage of 2.0 mg/kg, PO, once daily for up to 5 consecutive days. Dogs in the present study were not specifically observed for signs of nausea during the interval between administration of the maropitant or placebo capsule (or capsules) and administration of hydromorphone. A limitation of this study was the inability to discern between signs of nausea caused by maropitant and signs of nausea caused by hydromorphone. A distinct advantage of injection of injectable maropitant. This is contrary to findings in humans, where being female imparts a 2- to 4-fold increase in risk, the strongest patient-related risk factor, for perioperative nausea and vomiting.\(^9\) Prepubescent girls lack this increased likelihood of perioperative nausea and vomiting, which may imply that the risk is related to hormonal factors. All of the female dogs in the placebo treatment group in the present study were spayed, which may have eliminated any hormonal influences on sex differences in the incidence of nausea and vomiting.

The incidence of vomiting associated with hydromorphone administration in dogs was 25% in the study of this report. The reported incidence of vomiting associated with hydromorphone administration ranged widely (0% to 100%) depending on the study conditions (withholding of food), study population, dose and route of administration, and concurrent use of acepromazine.\(^2\,\^3\,\^4\) Smith et al.\(^2\) reported that no dogs vomited or developed signs of nausea when treated IM with either hydromorphone (0.22 mg/kg [0.1 mg/lb]) alone or hydromorphone with acepromazine (0.05 mg/kg [0.023 mg/lb]). The dogs in that study\(^2\) were research dogs, and food was not withheld prior to drug administration. Valverde et al.\(^6\) reported that 5 of 10 dogs vomited when hydromorphone (0.1 mg/kg) and acepromazine (0.05 mg/kg) were administered IM at the same time and that administration of acepromazine 15 minutes prior to hydromorphone decreased the incidence of vomiting to 5 of 21 dogs, presumably because of the blockade of dopamine receptors in the chemoreceptor trigger zone.\(^6\) The dogs in that study\(^6\) were client-owned dogs undergoing elective surgery, and although the fact was not reported, the assumption is that food was withheld prior to planned clinical anesthesia. In the pharmacokinetic study involving healthy research Beagles by KuKanich et al.,\(^7\) the incidence of vomiting varied with the dose and route of administration of hydromorphone. At a dose of 0.1 mg/kg, IV, hydromorphone induced vomiting in 3 of 9 dogs, whereas 6 of 8 dogs given the same dose SC vomited.\(^7\) Following IV administration of given 0.5 mg of hydromorphone/kg (0.23 mg of hydromorphone/lb) to 9 dogs, none vomited; however, following SC administration of the same dose, 8 of 8 dogs vomited.\(^7\) It is postulated that at lower doses or through slower absorption, opioids reach the chemoreceptor trigger zone but not the vomiting center and therefore result in emesis, whereas at higher doses or via IV administration, opioids reach the vomiting center and block the effects on the chemoreceptor trigger zone.\(^8\) In a study by Hofmeister et al.,\(^9\) only 5 of 23
(22%) dogs that received hydromorphone alone or with acepromazine vomited. The dogs in that study were random-source female dogs that were anesthetized at a surgical exercises laboratory for third-year veterinary students, and food was not withheld from the dogs prior to drug administration. In another study, 6 of 9 client-owned dogs from which food had been withheld vomited after administration of hydromorphone (0.1 mg/kg, IM). The influence of dose and route of administration of opioid drugs on the incidence of vomiting is well established; however, the influence of withholding food or the source of the study dogs on the incidence of vomiting has not been as well established. According to Smith et al and Hofmeister et al, it appears that lack of food withholding decreases the incidence of vomiting associated with hydromorphone. In the present study, there was no significant difference in the incidence of vomiting regardless of whether the dogs received the study treatment with or without a small amount of food. However, for each experiment, food had been withheld from the dog from 10:00 pm the previous evening as per client instructions for dogs undergoing anesthesia. The small amount of food included with the maropitant or placebo treatment may not have been sufficient to influence the incidence of vomiting.

The source of the study dogs may be another important factor influencing the incidence of vomiting associated with hydromorphone. The incidence of vomiting in acclimated research dogs following treatment with hydromorphone alone or in combination with acepromazine has been reported as 0% and 22%. The present study involved 40 dogs, 22 (55%) of which were client owned and 18 (45%) of which were staff or student owned. Many of the staff- and student-owned dogs visited the Iowa State University College of Veterinary Medicine Lloyd Veterinary Medical Center on a regular basis and therefore may have been acclimated to the environment and less anxious than the client-owned dogs. In human patients, a higher anxiety level is significantly associated with a more frequent incidence of perioperative vomiting and nausea. Fear, anxiety, memory, anticipation, and pain are known to be higher center inputs to the vomiting center and can elicit vomiting. These inputs to the nucleus tractus solitarius from the cerebral cortex, triggered by fear and anxiety, along with visual afferents stimulate the emetic center directly. The influence of fear and anxiety on the incidence of perioperative nausea and vomiting in dogs has not been studied, to the author's knowledge.

Prevention of perioperative vomiting in dogs, especially those at higher risk for aspiration pneumonia (eg, brachycephalic dogs; dogs with neurologic dysfunction, head trauma, or suspected increased intracranial pressure; and dogs undergoing intracranial surgery), may have a clear advantage in avoidance of patient morbidity and death. In this respect, both the injectable formulation of maropitant administered at 1.0 mg/kg, SC, 1 hour prior to opioid premedication and the oral formulation administered at a minimum dose of 2.0 mg/kg, PO, 2 hours prior to opioid premedication are equally effective in the prevention of vomiting. However, an additional consideration in veterinary patients may be the prevention of signs of nausea. Humans undergoing anesthesia report high levels of discomfort and dissatisfaction associated with perioperative nausea and vomiting. Both anesthesiologists and patients rate nausea and vomiting among the anesthesia outcomes to be most avoided, and it is considered by many patients to be more distressing than postsurgical pain. In fact, human patients are willing to spend up to $100 out of pocket for an effective antiemetic. The cost of injectable maropitant is approximately $0.20/kg ($0.09/lb), which would be $4.00 for a 20-kg (44-lb) dog. As veterinarians, we cannot know with certainty that perioperative nausea and vomiting cause discomfort or distress for our patients, as it does for humans. Morton et al suggested the use of critical anthropomorphism to evaluate animal suffering, and indicated that where doubt exists in the interpretation of animal suffering, the benefit of the doubt should lie with the animal. That is, if a human is likely to experience discomfort or distress under particular conditions, then it should be assumed, unless there is clear evidence to the contrary, that an animal of another species may be similarly affected.

Results of the present study have indicated that the incidence of vomiting associated with hydromorphone administration in a mixed group of 40 client- and staff- or student-owned dogs from which food had been withheld was only 25%. Oral administration of maropitant at a minimum dose of 2.0 mg/kg prevented vomiting but not development of signs of nausea when given 2 hours prior to hydromorphone administration in dogs.

References