Effect of dosing interval on efficacy of maropitant for prevention of hydromorphone-induced vomiting and signs of nausea in dogs

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Abstract
Objective—To evaluate the effect of dosing interval on the efficacy of maropitant for prevention of opioid-induced vomiting and signs of nausea in dogs.

Design—Randomized prospective clinical study.

Animals—50 client-owned dogs that underwent an elective surgical procedure.

Procedures—Dogs were randomly assigned to receive maropitant (1 mg/kg [0.45 mg/lb], SC), then hydromorphone (0.1 mg/kg [0.045 mg/lb], IM) at 0 (simultaneously; group 0; n = 10), 15 (group 15; 10), 30 (group 30; 10), 45 (group 45; 10), or 60 (group 60; 10) minutes later. Dogs were monitored for vomiting and signs of nausea for 30 minutes after hydromorphone administration. A historical control group of similar dogs (n = 9) that were administered hydromorphone (0.1 mg/kg, IM) but not maropitant served as the referent for comparison purposes.

Results—Vomiting was recorded for 6 dogs in group 0 and 2 dogs in group 15. Signs of nausea were recorded for 10 dogs in group 0, 9 dogs in group 15, 8 dogs in group 30, 6 dogs in group 45, and 1 dog in group 60. Compared with dogs in the historical control group, vomiting was significantly decreased and prevented when maropitant was administered 15 and 30 minutes, respectively, before hydromorphone; signs of nausea were significantly decreased only when maropitant was administered 60 minutes before hydromorphone.

Conclusions and Clinical Relevance—Results indicated that vomiting was significantly decreased and then prevented when maropitant was administered to dogs 15 and 30 minutes before hydromorphone. However, signs of nausea were significantly decreased only when the dosing interval was 60 minutes.

Disciplines
Comparative and Laboratory Animal Medicine | Small or Companion Animal Medicine | Veterinary Toxicology and Pharmacology

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Bonnie L. Hay Kraus, DVM

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Conclusions and Clinical Relevance—Results indicated that vomiting was significantly decreased and then prevented when maropitant was administered to dogs 15 and 30 minutes before hydromorphone. However, signs of nausea were significantly decreased only when the dosing interval was 60 minutes. (Am J Vet Med Assoc 2014;245:1015-1020)

Hydromorphone is a synthetic μ-opioid receptor agonist that is commonly used alone or in combination with tranquilizers or sedatives as an anesthetic premedication, as part of an anesthesia induction regimen for high-risk patients, and as an intraoperative and postoperative analgesic. Hydromorphone does not cause histamine-induced vasodilation and hypotension following IV administration, and that property, along with its low cost, has contributed to the widespread use of hydromorphone for pain management in dogs.1-3

In dogs, opioid administration frequently results in unwanted adverse effects, including bradycardia, respiratory depression, behavior changes (eg, sedation, dysphoria, or excitement), urine retention or decreased urine production, and gastrointestinal abnormalities (eg, signs of nausea, vomiting, and defecation).4-6 Signs of nausea and vomiting occur frequently in dogs after administration of morphine, hydromorphone, and oxymorphone. The incidence of vomiting associated with hydromorphone administration ranges from 0% to 100% and is dependent on the dose and route of administration, study conditions, population, duration that food was withheld prior to administration, and concurrent administration of acepromazine.7-10

Vomiting during the perioperative period can result in aspiration of gastric contents, esophagitis and subsequent esophageal stricture, unnecessary tension on sutures, and increases in intracranial and intraocular pressures. Prolonged or prolonged vomiting can cause dehydration, electrolyte and acid-base imbalances, and prolonged hospitalization.11 Thus, the avoidance and prevention of nausea and vomiting during the perioperative period are important objectives in human medicine. Both human patients and anesthesiologists rate nausea and vomiting among the top anesthesia-associated adverse effects to be avoided.11 In fact, many human patients consider nausea and vomiting to be more distressing than postsurgical pain.12,13 In dogs, vomiting and regurgitation, especially when associated with anesthesia and hydromorphone administration, are risk factors for the development of aspiration pneumonia.14-18 Underlying gastrointestinal dysfunction, upper airway abnormalities, and surgical interventions put brachycephalic breeds of dogs at an increased risk of vomiting, regurgitation, aspiration, death during the perianesthetic

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>Cmax</td>
<td>Peak plasma concentration</td>
</tr>
<tr>
<td>NK1</td>
<td>Neurokinin 1</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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</table>

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Maropitant was provided by Zoetis, Florham, NJ. No other external funding was provided for this study.

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period, compared with those risks in the general canine population. 19,20

Prevention of signs of nausea and vomiting during the perioperative period is garnering attention in veterinary medicine. Maropitant is a highly selective NK1 antagonist that was developed and approved for the treatment and prevention of vomiting in dogs. Clinically, it is used to treat vomiting resulting from various causes and to prevent vomiting subsequent to a broad spectrum of emetic stimuli including motion sickness and administration of cisplatin, apomorphine, hydromorphone, morphine, or copper sulfate. 10,21-25

Results of a recent study 16 indicate that maropitant (1.0 mg/kg [0.45 mg/lb], SC) effectively prevents signs of nausea and vomiting in dogs when administered 1 hour prior to hydromorphone (0.1 mg/kg [0.045 mg/lb], IM). In another study, 17 maropitant (1.0 mg/kg, SC) administered to dogs 20 minutes prior to morphine (1.0 mg/kg IM) significantly decreased, but did not eliminate, vomiting and retching and had no effect on the incidence of signs of nausea, compared with those incidences for dogs that were administered saline (0.9% NaCl) solution instead of maropitant prior to morphine. The objective of the study reported here was to evaluate the effect of dosing interval on the efficacy of maropitant for the prevention of hydromorphone-induced vomiting and retching and signs of nausea.

Materials and Methods

Animals—Client-owned dogs ≥ 6 months old that were admitted to the Lloyd Veterinary Medical Center at Iowa State University between January and August 2012 for elective surgery or advanced imaging that required anesthesia were considered for study enrollment. To be included in the study, each dog had to be classified as ASA 20 status I (healthy with no evidence of systemic disease) or status II (mild systemic disease with no functional limitations) on the basis of results of a complete physical examination, CBC, and serum biochemical analysis. The final study population consisted of 30 dogs (18 spayed females, 4 sexually intact females, 22 castrated males, and 6 sexually intact males) that ranged in age from 6 months to 10.9 years and weight from 1.3 to 57.3 kg (2.9 to 126.1 lb) and included a mixture of purebred and mixed-breed dogs. Owner consent was obtained for each dog prior to study enrollment, and all study procedures were approved by the Iowa State University Institutional Animal Care and Use Committee.

Study design—a card-draw technique 26 was used to randomly assign each dog to 1 of 5 treatment groups. All dogs were premedicated with maropitant citrate 6 (1.0 mg/kg, SC) and then hydromorphone (0.1 mg/kg, IM) at 0 (ie, the same time; group 0; n = 10), 15 (group 15; 10), 30 (group 30; 10), 45 (group 45; 10), or 60 (group 60; 10) minutes later.

Food, but not water, was withheld from all dogs beginning at 10:00 AM the night before anesthesia, which resulted in food being withheld from dogs for 8.5 to 15 hours prior to maropitant administration. All SC injections were administered under the loose skin on the dorsal midline between the scapulae, and all IM injections were administered in the lumbar epaxial muscles. A trained observer (BHK) monitored each dog for 30 minutes after hydromorphone administration and recorded emetic events (vomiting and retching) and whether the dog had signs of nausea. This observer was aware of the treatment group assignment for each dog. Vomiting was defined as the expulsion of stomach contents from the mouth. Retching was defined as forceful contraction of abdominal muscles without expulsion of stomach contents from the mouth. Each discrete vomiting or retching event was recorded. Signs of nausea were defined as salivation and increased frequency of or exaggerated swallowing motions and licking of lips; the presence of any of those signs was considered positive for signs of nausea. Dogs that vomited or retched were considered to have signs of nausea regardless of whether the other signs of nausea were observed because it is generally assumed that nausea is a prodromal sign of vomiting or retching.

Historical control group—A group of dogs (n = 9) that were administered saline (0.9% NaCl) solution 1 hour prior to hydromorphone during another study 10 was used as a historical control group to serve as a referent for comparison with treatment groups of the present study. That study 10 was approved by the Iowa State University Institutional Animal Care and Use Committee, and owner consent was obtained for each dog prior to study enrollment. Those dogs were similar to the dogs of the present study in that they were admitted to the Lloyd Veterinary Medical Center for an elective surgery and were classified as ASA status I or status II on the basis of results of a complete physical examination, CBC, and serum biochemical analysis. The group consisted of a mixture of purebred and mixed-breed dogs (6 females and 3 males) with a mean ± SD age of 5.3 ± 2.75 years and weight of 27 ± 16.5 kg (59.4 ± 36.3 lb). All dogs were administered saline solution (0.1 mL/kg, SC) under the loose skin on the dorsal midline between the scapulae 1 hour before hydromorphone (0.1 mg/kg, IM), which was injected in the lumbar epaxial muscles. The trained observer (BHK) that monitored the dogs of the present study also monitored each dog of that study 10 for 30 minutes after hydromorphone administration and recorded emetic events (vomiting and retching) and whether the dog had signs of nausea. The definitions of vomiting, retching, and signs of nausea used in that study 10 were the same as those used in the present study.

Statistical analysis—A 1-way ANOVA was used to compare the mean age and weight among the treatment groups (groups 0, 15, 30, 45, and 60) and the historical control group. A χ² test was used to assess differences in the sex distribution between the respective treatment groups and the historical control group. The outcomes of interest were the incidence of emetic events (vomiting or retching) and signs of nausea. A 2-tailed Fisher exact test was used compare the incidence of each outcome between the respective treatment groups and the historical control group. For all analyses, values of P ≤ 0.05 were considered significant.

Results

The mean age (P = 0.589) and weight (P = 0.322) and sex distribution (P = 0.158) of dogs did not dif-
fer significantly among the treatment groups and the historical control group. The number of dogs that vomited or retched and had signs of nausea within 30 minutes after hydromorphone administration for each treatment group and the historical control group was summarized (Table 1). The incidence of vomiting or retching was significantly \( P = 0.023 \) less for group 15, compared with that for the historical control group. None of the dogs in groups 30, 45, and 60 vomited or retched within 30 minutes after hydromorphone administration, which suggested that administration of maropitant at least 30 minutes prior to hydromorphone prevented vomiting and retching. The respective incidences of signs of nausea for groups 0, 15, 30, and 45 did not differ significantly from that for the historical control group. The incidence of signs of nausea for group 60 was significantly \( P < 0.001 \) less than that for the historical control group, which suggested that administration of maropitant at least 60 minutes prior to hydromorphone reduced the occurrence of signs of nausea.

**Discussion**

Results of the present study indicated that administration of maropitant \((1.0 \text{ mg/kg, SC})\) to dogs 1 hour prior to administration of hydromorphone \((0.1 \text{ mg/kg, IM})\) was effective in preventing vomiting and retching and reducing the incidence of signs of nausea and confirmed the findings of another study. Further, in the present study, administration of maropitant at least as little as 15 minutes prior to hydromorphone administration was effective in reducing the incidence of vomiting and retching. This time frame was substantially shorter than that required for maropitant to reduce \(30 \text{ minutes}\) and cease \(39 \text{ minutes}\) cisplatin-induced emesis in dogs. Maropitant \((1.0 \text{ mg/kg, SC})\) administration to dogs achieves a Cmax of 92 ng/mL at 0.75 hours after injection. On the basis of the results of the present study, it appears that the antiemetic activity of maropitant can be achieved well before the time required for the drug to reach its Cmax, especially when maropitant is administered before the emetic challenge (ie, before opioid administration). However, the pharmacokinetic-pharmacodynamic relationship of the NK1-antagonist activity of maropitant remains relatively unexplored.

Neurokinin 1 antagonists (eg, maropitant) and their active metabolites have highly potent receptor-binding affinity and are thought to penetrate the blood-brain barrier and mediate their biological effect through occupation of NK1 receptors in the brain. Because maropitant is highly protein bound, only a small fraction of the total dose remains unbound to protein after injection and available to cross the blood-brain barrier to elicit pharmacological activity. Results of a study indicate that the antiemetic activity of maropitant in dogs lasts for 19 hours following oral administration of 2.0 mg of maropitant/kg, even when the mean plasma concentration of maropitant or its active metabolites is assumed to be < 40 ng/mL. In the present study, SC administration of maropitant to dogs 15 minutes before hydromorphone resulted in a significant reduction in the incidence of opioid-induced vomiting or retching, which provided further evidence that the in vivo activity of maropitant for prevention of opioid-induced emesis was achieved at plasma or CSF drug concentrations less than the Cmax. Additional research is warranted to determine the ability of maropitant and its active metabolites to penetrate the blood-brain barrier and the concentration of maropitant in the plasma or CSF necessary to induce its antiemetic effects.

Although maropitant administration at least 15 minutes before hydromorphone administration effectively reduced or prevented vomiting or retching in the present study, a significant decrease in the incidence of signs of nausea was apparent only when maropitant was administered 60 minutes prior to hydromorphone. In human patients, nausea is subjectively described as an unpleasant sensation associated with the awareness of the urge to vomit. The mechanisms that cause nausea remain unclear but are thought to be associated with stimuli from high brain centers that disrupt the normal contraction and relaxation patterns of the stomach, which changes gastrointestinal motility and gastric acid secretion and causes reverse peristalsis. Clinical signs associated with nausea in human patients include increased salivation, pallor, tachycardia, hot and cold sensations, and diaphoresis. In dogs, nausea is described as a sensation that precedes vomiting and may or may not lead to vomiting, and the clinical signs of nausea in dogs include depression, salivation, licking of lips, and increased swallowing. Visual analogue scale scores for signs of nausea in dogs treated with apomorphine (ie, a centrally acting emetic) 1 hour after maropitant administration were lower than those for placebo-treated dogs during the first 12 minutes after apomorphine administration. However, when dogs were treated with syrup of ipecac (ie, a peripherally acting emetic), the VAS scores for signs of nausea for dogs that were premedicated with maropitant, compared with those for dogs

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**Table 1—Number of dogs that vomited or retched and had signs of nausea within 30 minutes after hydromorphone (0.1 mg/kg, SC) 1 hour previously (historical control group) or maropitant (1.0 mg/kg, SC) at 0 (ie, same time; group 0), 15 (group 15), 30 (group 30), 45 (group 45), or 60 (group 60) minutes previously.**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of dogs in group</th>
<th>Vomiting or retching</th>
<th>Signs of nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical control</td>
<td>9</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>2*</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
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<td>8</td>
</tr>
<tr>
<td>45</td>
<td>10</td>
<td>0*</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>0*</td>
<td>1*</td>
</tr>
</tbody>
</table>

*Within a column, value differs significantly \( P \leq 0.05 \) from that for the historical control group.
that were premedicated with a placebo, did not differ significantly within the first 33 minutes after syrup of ipecac administration but were significantly lower between 36 and 60 minutes after syrup of ipecac administration. In both instances, maropitant significantly decreased but did not eliminate emesis, compared with a placebo, and it was more effective for reducing the incidence of emesis than it was for reducing the incidence of signs of nausea. Healthy dogs that were administered maropitant immediately after cisplatin had significantly decreased VAS scores for signs of nausea for up to 80 minutes, compared with control dogs that were administered saline solution instead of maropitant. Results of a recent study in which dogs were orally administered maropitant (2.0 to 4.0 mg/kg [0.9 to 1.8 mg/lb]) or a lactose monohydrate placebo 2 hours prior to hydromorphone (0.1 mg/kg, IM) indicate that, although maropitant effectively prevented vomiting, 12 of 20 (60%) maropitant-treated dogs developed signs of nausea. In that study, of the 12 maropitant-treated dogs that developed signs of nausea, 10 had signs that were subjectively classified as moderate or severe, whereas only 2 of 16 placebo-treated dogs that developed signs of nausea had signs that were classified as moderate or severe. Findings of the present study indicated that the injectable formulation of maropitant has a clear advantage over the oral formulation for the prevention of signs of nausea in dogs, although it must be administered at least 1 hour before opioid administration for this effect to be realized.

A limitation of the present study was the failure to obtain VAS scores for signs of nausea for dogs in each of the treatment groups. This data would have allowed the severity of signs of nausea to be correlated with the dosing interval between administration of maropitant and hydromorphone. The obvious advantage of maropitant administration to veterinary patients is the prevention of vomiting during the perioperative period and the associated decrease in patient morbidity and death; however, another advantage of maropitant administration is the reduction in patient discomfort caused by nausea. Human patients widely report that nausea causes discomfort and distress. It should be assumed that nausea may affect veterinary patients similarly, and steps should be taken to prevent or treat signs of nausea in those patients.

Another limitation of the present study is that the observer that recorded emetic events and the presence of signs of nausea was aware of (ie, not blinded to) the treatment group assignment for each dog, and that observer's conscious or unconscious predisposition might have generated bias. In both human and veterinary medicine, many randomized clinical trials are conducted without the outcome assessor being blinded. Blinding of outcome assessors can increase the time, cost, and logistic complexity of clinical trials and does not guarantee that the results will not be biased. However, results of multiple systematic reviews indicate that observer bias tends to occur when nonblinded assessors record measurement of scale, time-to-event, and binary outcomes. For randomized clinical trials with binary outcomes, use of nonblinded assessors biased treatment effect estimates and exaggerated ORs by 36%. However, in that systematic review, the pooled OR for blinded versus nonblinded assessors (ie, observer bias) was 0.55 for randomized trials with subjective outcomes and 0.93 for randomized trials with less subjective outcomes, which suggested that there was very little difference between blinded and nonblinded observers. Bias is more likely to occur in trials with subjective measures than it is in trials with objective outcomes. The outcomes assessed in the present study were considered to be categorical and objective (ie, either the dogs vomited, retched, or had signs of nausea or they did not during the 30 minutes after hydromorphone administration); subjective outcomes such as the measurement of the severity of the signs of nausea were not assessed. Therefore, blinding the observer was not considered necessary and likely would not have substantially affected the results or conclusions of this study; however, the presence of observer bias cannot be ruled out.

The use of a historical control group from a study performed by the same investigator at the same institution as the present study might also be considered a limitation. Use of data from a historical control group has several advantages, including a reduction in the number of patients required for a clinical trial, which decreases the cost and shortens the duration of the trial. When the historical control group consists of subjects that received an ineffective treatment (ie, a placebo), use of data from those subjects may have an ethical advantage because fewer subjects receive the ineffective treatment. Additionally, reduced allocation of subjects to a placebo group might make recruitment easier and increase the feasibility of study completion. For those reasons, the use of historical control data has become increasingly important in human clinical trials and has been used to some extent in veterinary medicine. In a seminal paper, Pocock outlined the conditions for the acceptable use of data from a historical control group, which include the same criteria for subject enrollment, same methods for treatment evaluation, and comparable distribution of subject characteristics. Pocock's final condition is that the study for which use of a historical control group is being considered should be performed by the same organization with most of the same clinical investigators as the study that is providing the data for the historical control group. The present study fulfilled all the requirements for use of a historical control group.

Maropitant administration to dogs and cats has garnered the interest of clinicians because of its analgesic as well as its antiemetic properties. Neurokinin 1 receptors and substance P are involved in pain perception via central and peripheral pathways that include sensory afferent fibers, dorsal root ganglia, the dorsal horn of the spinal cord, ascending spinal cord projections, and higher nerve centers. During a surgical procedure in which traction was applied to the ovarian ligament of female dogs and cats, administration of maropitant to the anesthetized animals caused a significant decrease in the minimum alveolar concentration of sevoflurane, compared with the minimum alveolar concentration of sevoflurane required for animals that did not receive maropitant. The antiemetic, antinausea, and possible adjunct analgesic properties of maropitant make
it an attractive, cost-effective addition to sedatives and opioid analgesics in anesthetic premedication protocols for veterinary patients.

In the present study, administration of maropitant to dogs at least 15 minutes before hydromorphone significantly decreased the incidence of vomiting orretching during the first 30 minutes after hydromorphone administration, compared with that for dogs that did not receive maropitant prior to hydromorphone. However, maropitant had to be administered at least 60 minutes before hydromorphone to significantly decrease signs of nausea. Thus, for dogs in which the avoidance of vomiting and signs of nausea is imperative, maropitant should be administered 1 hour prior to an opioid analgesic. The antiemetic, antinausea, and adjunct analgesic properties of maropitant make it an attractive alternative for inclusion in veterinary preanesthetic protocols.

References

a. Cerenia, Zoetis, Florham Park, NJ.


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**From this month’s AJVR**

**Multivoxel proton magnetic resonance spectroscopy of inflammatory and neoplastic lesions of the canine brain at 3.0 T**

Krystina L. Stadler et al

**Objective**—To describe findings of 3.0-T multivoxel proton magnetic resonance spectroscopy ([1H- MRS]) in dogs with inflammatory and neoplastic intracranial disease and to determine the applicability of 1H-MRS for differentiating between inflammatory and neoplastic lesions and between meningiomas and gliomas.

**Animals**—33 dogs with intracranial disease (19 neoplastic [10 meningioma, 7 glioma, and 2 other] and 14 inflammatory).

**Procedures**—3.0-T multivoxel [1H-MRS was performed on neoplastic or inflammatory intracranial lesions identified with conventional MRI. N-acetylaspartate (NAA), choline, and creatine concentrations were obtained retrospectively, and metabolite ratios were calculated. Values were compared for metabolites separately, between lesion categories (neoplastic or inflammatory), and between neoplastic lesion types (meningioma or glioma) by means of discriminant analysis and 1-way ANOVA.

**Results**—The NAA-to-choline ratio was 82.7% (62/75) accurate for differentiating neoplastic from inflammatory intracranial lesions. Adding the NAA-to-creatine ratio or choline-to-creatine ratio did not affect the accuracy of differentiation. Neoplastic lesions had lower NAA concentrations and higher choline concentrations than did inflammatory lesions, resulting in a lower NAA-to-choline ratio, lower NAA-to-creatine ratio, and higher choline-to-creatine ratio for neoplasia relative to inflammation. No significant metabolite differences between meningiomas and gliomas were detected.

**Conclusions and Clinical Relevance**—1H-MRS was effective for differentiating inflammatory lesions from neoplastic lesions in dogs. Metabolite alterations for 1H-MRS in neoplasia and inflammation were similar to changes described for humans. Use of 1H-MRS provided no additional information for differentiating between meningiomas and gliomas. Proton MRS may be a beneficial adjunct to conventional MRI in patients with high clinical suspicion of inflammatory or neoplastic intracranial lesions. (Am J Vet Res 2014;75:982–989)