Hydromorphone, a synthetic µ-opioid receptor agonist, is commonly used in veterinary medicine as a premedication, anesthetic induction agent, and analgesic agent. It is relatively inexpensive, compared with other full µ-opioid receptor agonists, and produces minimal histamine-mediated vasodilation and hypotension, compared with morphine.1–5 All full µ-opioid receptor agonists can result in adverse effects in dogs, including bradycardia, respiratory depression, urine retention or decreased urine production, and gastrointestinal signs (eg, vomiting, ptyalism, nausea, and defecation). However, hydromorphone in particular causes a higher incidence of vomiting, ranging from 25% to 87%, compared with its more expensive counterparts, oxymorphone and methadone, and methadone has been reported to have a theoretical antiemetic effect.4–9

Vomiting carries numerous risks, including esophagitis, esophageal stricture, increased intracranial and intraocular pressures, and aspiration pneumonia, and the risk of aspiration pneumonia is especially increased in sedated patients, such as those who have recently been premedicated.10,11 Perioperative vomiting also increases the likelihood of postoperative pulmonary complications, which contribute to higher morbidity and mortality rates.12 Postoperative aspiration pneumonia is not an uncommon phenomenon in veterinary patients, with reported incidences ranging from 0.2% to 25%, depending on the study and the procedures performed.10–14 One study14 that examined risk factors for postanesthetic aspiration pneumonia found that administration of hydromorphone increased the risk that this condition would develop.
Nausea, in addition to causing discomfort, can prolong the surgical recovery period by increasing the time to postoperative feeding. It can also lead to hypersalivation, which can increase the risk of aspiration pneumonia. Research has shown that pet owners are willing to pay more, arrive earlier, and wait longer to prevent their pets from vomiting and feeling nauseated.15

An ideal premedication protocol would be one that provides adequate pain control and sedation while decreasing the frequency of vomiting and nausea. Two different antiemetics—maropitant and ondansetron—are commonly used in dogs. Maropitant is a neurokinin-1 receptor antagonist approved to prevent and treat vomiting in dogs. Ondansetron, a 5-HT3 receptor antagonist, is approved for use in humans to prevent postoperative nausea and vomiting, and nausea and vomiting associated with chemotherapy. It is used in an extralabel manner in dogs to treat vomiting and nausea. Maropitant is available in a number of tablet sizes, allowing for easy administration in dogs of various sizes, whereas ondansetron tablet sizes are more limited, making it cumbersome and potentially impractical to administer to larger dogs. However, maropitant is more expensive and only available from veterinary pharmacies, whereas ondansetron is less expensive and more widely available. Given how frequently these medications are used, it would be helpful for practitioners to know whether one is more effective than the other at preventing vomiting and nausea.

Previous studies4,5,16 have shown that SC and PO administration of maropitant significantly decreased the incidence of vomiting in dogs when given 15 to 60 minutes and 2 hours, respectively, before hydromorphone. Similarly, IV administration of maropitant also decreased the incidence of vomiting when administered 45 to 60 minutes prior to administration of hydromorphone and acepromazine.17 Maropitant prevented signs of nausea in dogs when given SC 60 minutes before hydromorphone, but did not when administered PO 2 hours prior to hydromorphone.5,16 Injectable maropitant was superior to ondansetron for decreasing tranexamic-acid-induced and apomorphine-induced vomiting and nausea in dogs, but the 2 drugs were comparable in decreasing vomiting in dogs with parvovirus and dogs given syrup of ipecac, and ondansetron was superior to maropitant in decreasing cisplatin-induced vomiting and nausea.18–22 To date, no studies directly comparing the effect of oral administration of maropitant and ondansetron in dogs subsequently premedicated with hydromorphone have been conducted. Because many dogs require injectable premedication to facilitate IV catheter placement, giving an additional injection prior to premedication is not practical. Oral formulations may also be more cost effective and could be administered at home by clients or in the hospital by untrained personnel.

The objective of the study reported here was to compare effectiveness of maropitant and ondansetron in preventing preoperative vomiting and nausea in healthy dogs premedicated with a combination of hydromorphone, acepromazine, and glycopyrrolate. We hypothesized that both maropitant and ondansetron would suppress hydromorphone-induced vomiting and nausea.

Materials and Methods

The study protocol was approved by the University of Pennsylvania’s Institutional Animal Care and Use Committee Office of Animal Welfare (ARIES Protocol No. 804132). Written, informed consent was obtained from the owners of all dogs prior to medication administration.

Control dogs

Thirty-one sexually intact female dogs owned by a rescue organization and examined at the Ryan Veterinary Hospital prior to undergoing routine ovariohysterectomy as part of a student surgery laboratory from September 2019 through January 2020 were enrolled in the study as control dogs. All control dogs were deemed to be healthy on the basis of a physical examination performed by a veterinarian. Dogs were hospitalized and fasted overnight in preparation for anesthesia. The following morning, dogs were premedicated with hydromorphone (0.1 mg/kg, IM), acepromazine (0.02 mg/kg, IM), and glycopyrrolate (0.01 mg/kg, IM). Dogs were then monitored for 15 minutes or until sedate enough for IV catheter placement by a single observer (JEB) for any episodes of vomiting. They were also monitored by the same observer for nausea (yes vs no), who assigned a nausea severity score with a visual analog scale (VAS) for 6 signs deemed reflective of nausea (ie, hypersalivation, lip licking, hard swallowing, restlessness, hunched posture, and retching).23,24 For the VAS, the observer placed a mark on a line representing a continuum of severity, with the position of the mark indicative of severity (ie, 0.5 = 50%).

Case dogs

Forty-seven sexually intact female dogs owned by a rescue organization and examined at the Ryan Veterinary Hospital prior to undergoing routine ovariohysterectomy as part of a student surgery laboratory from September 2020 through January 2021 were enrolled in the study as case dogs. All case dogs were deemed to be healthy on the basis of a physical examination. Dogs were hospitalized and fasted overnight in preparation for anesthesia. Block randomization was used to randomly assign dogs to receive maropitant (Cerenia, Zoetis; 2 mg/kg, PO) or ondansetron (Aurobinda Pharma USA; 0.5 mg/kg, PO) during sequential weeks. Tablets were cut into quarters or halves to achieve the appropriate dose, and doses were rounded up when the exact dose could not
be achieved. Tablets were administered in a teaspoon of commercial canned dog food (Purina ProPlan; Nestle) or a pill wrap (Pill Pocket; Mars Petcare) 2 to 2.5 hours prior to premedication with the same drugs as used in the control group. Dogs were monitored for the same time and variables as control dogs by observers (third-year veterinary students) blinded to the treatment administered.

**Sample size calculations**

A 2-sample test of proportions was used to determine the number of dogs required to detect a significant difference between proportions of dogs vomiting with and without antiemetic treatment. The calculation was based on preliminary findings for 31 dogs treated with hydromorphone (0.1 mg/kg, IM), acepromazine (0.02 mg/kg, IM), and glycopyrrolate (0.01 mg/kg, IM) that did not receive an antiemetic treatment. Nineteen of these 31 (61%) dogs vomited, and we assumed that a clinically significant reduction in the percentage of vomiting dogs would be a decrease from 61% without antiemetic treatment to 20% with antiemetic treatment. Additional assumptions included a power of 0.8 and type I error rate of 0.05. The calculation resulted in a required sample size of 22 dogs in each treatment group.

**Statistical analysis**

Results are reported as median and range or count and percentage. Nonparametric statistical analyses were performed because most continuous variables were not normally distributed, as determined visually and by skewness and kurtosis tests for normality. The Fisher exact test was used to compare categorical variables (eg, vomiting and nausea [yes vs no]) between treatment groups, and the 2-sample Wilcoxon rank sum (Mann-Whitney) test was used to compare continuous variables (eg, nausea severity scores) between treatment groups. A Bonferroni correction was applied to account for multiple comparisons, and Bonferroni-corrected \( P \) values are reported. For categorical variables, \( P \) values were multiplied by 6, and for continuous variables, \( P \) values were multiplied by 24. A Bonferroni-corrected \( P \) value < 0.05 was considered significant for all tests. All statistical evaluations were performed with standard statistical software (Stata 14.0 for Mac; StataCorp).

**Results**

Eighty-eight dogs were enrolled in the study: 31 in the control group, 29 in the maropitant group, and 28 in the ondansetron group. Estimated ages for dogs in all 3 groups ranged from 5 months to 6 years; body weight ranged from 2.87 to 28.6 kg. A variety of breeds were represented (Table 1). Median dose of maropitant was 2.1 mg/kg (range, 2.0 to 2.8 mg/kg), and median dose of ondansetron was 0.6 mg/kg (range, 0.5 to 0.7 mg/kg).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Maropitant</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>19.9 (3–28.6)</td>
<td>18.3 (3.5–25.5)</td>
<td>14.5 (2.87–27)</td>
</tr>
<tr>
<td>Breed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Pit Bull</td>
<td>20</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Terrier cross</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Labrador</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Retriever cross</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shepherd cross</td>
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<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Toy breed cross*</td>
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<td>6</td>
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<tr>
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<td>0</td>
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<td>2</td>
</tr>
<tr>
<td>Hound, pointer, or spaniel cross</td>
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<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Other cross</td>
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<td>0</td>
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</tr>
</tbody>
</table>

\*Included Miniature Pinscher, terrier, Chihuahua, Miniature Poodle, Dachshund, and Pomeranian crosses.

A significantly lower percentage of dogs vomited after receiving maropitant (3/29 [10%]), compared with control dogs (19/31 [61%]; \( P = 0.005 \)) and dogs that received ondansetron (15/28 [54%]; \( P = 0.006 \)). There was no significant (\( P > 0.999 \)) difference in the percentage of dogs that vomited between the control dogs and the dogs that received ondansetron. A significantly lower percentage of dogs appeared nauseated after receiving maropitant (3/29 [10%]), compared with control dogs (27/31 [87%]; \( P = 0.005 \)) and dogs that received ondansetron (14/28 [50%]; \( P = 0.006 \)), and a significantly lower percentage of dogs that received ondansetron appeared nauseated, compared with control dogs (\( P = 0.024 \)).

Severity scores (scored on a scale from 0 to 1) for hypersalivation (median, 0.215; range, 0 to 0.726), lip licking (median, 0.489; range, 0 to 0.933), hard swallowing (median, 0.474; range, 0 to 0.866), and hunched posture (median, 0.230; range, 0 to 0.866) in the control dogs were significantly higher than severity scores for hypersalivation (median, 0; range, 0 to 0.5; \( P = 0.002 \)), lip licking (median, 0.133; range, 0 to 1; \( P = 0.002 \)), hard swallowing (median, 0; range, 0 to 0.254; \( P = 0.002 \)), and hunched posture (median, 0; range, 0 to 0.438; \( P = 0.002 \)) in the dogs that received maropitant. Scores for hypersalivation, lip licking, and hard swallowing in control dogs were also significantly higher than scores for hypersalivation (median, 0; range, 0 to 0.896; \( P = 0.002 \)), lip licking (median, 0.05; range, 0 to 0.938; \( P = 0.031 \)), and hard swallowing (median, 0.008; range, 0 to 0.785; \( P = 0.002 \)) in the dogs that received ondansetron. Retching was significantly (\( P = 0.005 \)) more severe in dogs that received ondansetron (median, 0.008; range, 0 to 0.892) than in dogs that received maropitant.
Discussion

In the present study, vomiting was observed in 61% (19/31) of the dogs that received hydromorphone without antiemetic medication, and nausea was observed in 87% (27/31). These values are similar to percentages previously reported in the veterinary literature, with vomiting reportedly occurring in 25% to 87% of dogs and nausea occurring in 22% to 60%, but higher than percentages reported for humans, with opioids causing vomiting in 15% to 25% of human patients and nausea in about 40%.16,24-25

In humans, both ondansetron and aprepitant, an antiemetic in the same class as maropitant that is labeled for use in humans, controlled nausea and vomiting in human patients who experienced or were at risk for opioid-induced vomiting or nausea.26-27 In the present study, the oral formulation of maropitant administered 2 hours prior to hydromorphone significantly decreased the incidence of vomiting and nausea in healthy dogs, compared with control dogs. In contrast, the oral formulation of ondansetron decreased the incidence of nausea but not vomiting, compared with incidences in control dogs. Maropitant also significantly decreased the incidence of both vomiting and nausea in dogs, compared with ondansetron. In this study, dogs that received maropitant displayed less severe signs of nausea (specifically, hypersalivation, lip licking, hard swallowing, and hunched posture), as measured with a VAS, compared with control dogs. Several signs of nausea (hypersalivation, lip licking, and hard swallowing) were also less severe in dogs that received ondansetron than in control dogs. Finally, retching was less severe in dogs that received maropitant than in dogs that received ondansetron.

Many of the dogs enrolled in the present study were stressed or anxious, which was not surprising given their circumstances. Many also began to pant profusely after hydromorphone administration, which can be mistaken for restlessness and could therefore explain why the severity of restlessness did not differ significantly among the 3 treatment groups. Additionally, a hunched posture and retching can occur concurrently with or be mistaken for vomiting; therefore, the authors believe that hypersalivation, lip licking, and hard swallowing may be the best indicators of nausea. Overall, our findings suggest that maropitant may have been more effective than ondansetron at decreasing the incidence, but not the severity, of nausea.

Although a previous study16 also found that oral administration of maropitant at the same dose and same time frame used in the present study prevented hydromorphone-induced vomiting, there was no difference in the incidence of nausea between the maropitant and placebo groups in that study. That study found both a lower incidence of nausea in the placebo group and a higher incidence of nausea in the maropitant group than we found in the present study, which could be related to variations in population between the 2 studies. For example, the previous study16 included both male and female dogs undergoing elective procedures, whereas the present study consisted of sexually intact female dogs undergoing elective ovariohysterectomy. The previous study16 also used a different grading scheme for nausea. Specifically, dogs with any signs of nausea (ie, salivation, increased frequency of or exaggerated swallowing motions, and lip licking) were identified, and nausea was then graded as mild, moderate, or severe. In contrast, dogs in the present study were identified as having or not having nausea, and a VAS was used to assess severity of 6 signs of nausea in each dog. Interestingly, another study6 found that dogs that received maropitant SC prior to premedication with hydromorphone had a higher incidence of ptyalism than did dogs that received saline solution, and the previous study36 found a high incidence of dogs with moderate to severe nausea based on ptyalism. Because no validated scale exists for the assessment of nausea in veterinary patients, direct comparisons among studies are difficult, and further investigation is warranted.

In addition to reducing the incidence of vomiting and incidence and severity of nausea, maropitant has been shown to have many other beneficial effects, including reducing the minimum alveolar concentration during anesthesia, improving quality of recovery, and faster return to feeding postoperatively.28-30 Making it an attractive perioperative medication. Ondansetron, conversely, has not been shown to have these additional positive effects. In the present study, ondansetron did reduce the incidence and severity of nausea, but not the incidence of vomiting, compared with incidence and severity in control dogs. Decreasing the incidence of vomiting typically decreases morbidity rates, especially in populations at risk for aspiration pneumonia or intracranial hypertension. However, in certain circumstances, some clinicians find vomiting preoperatively to be beneficial. For example, in dogs that have not been fasted, vomiting preoperatively, before dogs are excessively sedate, would be preferred to vomiting intraoperatively or postoperatively, when dogs are less able to protect their airways. Additionally, a control dog in the present study was observed to vomit a large portion of a leash or harness, preventing what could have become a foreign body obstruction.

The ability to provide antiemetics orally rather than by injection minimizes discomfort and is typically more cost effective. Oral administration could be performed by untrained veterinary staff at the time of hospital admission or potentially at home by the owners the morning of a procedure. Maropitant tablets may even allow for administration the night prior to a procedure, in that 1 study31 found that the antiemetic activity of maropitant following oral administration in dogs lasted for 19 hours. However, further studies are required to determine the effectiveness of maropitant in mitigating vomiting and nausea at various preprocedural time intervals.
The present study had several limitations. For example, although the study was adequately powered, a larger sample size would have been useful to provide more robust statistical analysis and avoid type II errors. All dogs were sexually intact females, preventing any assessment of variations in drug effect on the basis of sex or neuter status. Although sex and neuter status have not been observed in dogs to the authors' knowledge, in humans, there is a 2- to 4-fold increase in perioperative vomiting and nausea in postpubescent females. Because all of the dogs in our study were sexually intact females, our findings could potentially represent overestimations of the incidences of vomiting and nausea in healthy dogs overall, which could lead to overestimation of the effectiveness of these medications in male dogs and spayed female dogs.

Another limitation of the present study was that the single observer (JEB) for the control group was unblinded, and this portion of the study was performed the year before the treatment group portion to determine the usefulness of proceeding with the study. Although this theoretically could have impacted the nausea severity scores, through an unconscious predisposition to assess nausea as severe, it was deemed unlikely to affect the categorical variables of vomiting and nausea. However, observer bias cannot be precluded, especially for severity of nausea. Observers for both treatment groups were blinded, making comparisons more uniform; however, because of laboratory restrictions related to the COVID-19 pandemic, these observers were veterinary students rather than a single trained observer, which could have led to interobserver variability in nausea severity scoring. Although the VAS has not been validated for use in dogs, it has been validated for measuring severity of nausea in humans and is used commonly in dogs and cats.

The present study aimed to compare the effectiveness of maropitant and ondansetron in preventing hydromorphone-induced emesis, but all dogs were also premedicated with glycopyrrolate and acepromazine. Both of these medications have mild antiemetic properties and could, therefore, have potentially interfered with the incidence or severity of vomiting or nausea observed. However, the incidences of vomiting and nausea in control dogs were similar to those previously reported for dogs premedicated with hydromorphone alone. Additionally, both control and study dogs received the same medications, so inclusion of glycopyrrolate and acepromazine was unlikely to have impacted the results.

Because tablets with discrete drug contents were used in the present study, dogs received slightly varied doses, which could have resulted in slight differences in antiemetic effects. However, this would be the case in clinical practice as well, and all doses were rounded up when necessary. The authors' institution frequently uses doses of 0.5 mg/kg for both oral and injectable formulations of ondansetron, so this was the dose chosen for the present study. However, ondansetron is not labeled for use in dogs, and dosing recommendations range widely (0.1 to 1 mg/kg). Ondansetron administered by injection at a dose of 0.5 mg/kg has been shown to be as effective as maropitant in suppressing low-dose, cisplatin-induced vomiting and to be more effective at suppressing nausea. However, ondansetron has very low oral bioavailability in dogs (< 10%), compared with humans (60% to 70%) and cats (32%). Therefore, it is possible that a higher dose may yield greater antiemetic or antinausea effects.

Maropitant was administered at the label dose in the present study, 2 hours prior to administration of hydromorphone, because time to maximum plasma concentration following oral administration has been reported to be 1.9 hours and half-life has been reported to be 4 hours. Ondansetron, conversely, reaches maximum plasma concentrations about 1 hour after oral administration, with a half-life of 1.3 hours. Therefore, administration of ondansetron 1 hour prior to hydromorphone administration, rather than 2 hours, might have yielded greater antiemetic or antinausea effects. In an attempt to standardize treatment times, both drugs were given 2 hours prior to premedication.

Maropitant and ondansetron are commonly used antiemetic and antinausea medications. The present study found that oral administration of maropitant was effective in decreasing the incidence of hydromorphone-induced vomiting and nausea and the severity of nausea, whereas oral administration of ondansetron was effective in decreasing the incidence and severity of hydromorphone-induced nausea but not vomiting. In the present study, maropitant was also more effective than ondansetron in reducing the incidence of vomiting and nausea, potentially making it a superior choice for inclusion in preanesthetic protocols. However, studies of additional doses and timing regimens for ondansetron administration may be warranted. Comparison of these drugs with other antiemetics, such as metoclopramide; phenothiazines, and low-dose corticosteroids, may also prove informative.

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References


