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Effects of Maropitant Citrate or Acepromazine on the Incidence of Adverse Events Associated with Hydromorphone Premedication in Dogs

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Background: Vomiting is a common complication associated with the use of hydromorphine for pre-emptive analgesia in dogs. The ideal anti-emetic protocol for prevention of this complication has not been established.

Hypothesis: Maropitant administered concurrently or before hydromorphone would reduce the incidence of vomiting, signs of nausea, ptyalism, and increased panting compared to administration of acepromazine or a 0.9% saline control.

Animals: Sixty mixed-breed female dogs scheduled for ovariohysterectomy.

Methods: Randomized, blinded, placebo-controlled experimental study. Dogs were assigned to 4 experimental groups with 15 dogs per group. All groups received 0.2 mg/kg of hydromorphone IM. Group "Control" received 0.1 mL/kg saline SC 30–45 minutes before hydromorphone, group "Marop1" received 1 mg/kg maropitant SC 30–45 minutes before hydromorphone, group "Ace" received 0.02 mg/kg IM acepromazine 30–45 minutes before hydromorphone, and group "Marop2" received 1 mg/kg SC maropitant concurrently with hydromorphone. A trained and blinded observer documented adverse events from the time hydromorphone was administered until the time dogs were induced for surgery.

Results: Marop1 had significantly less vomiting (0%) compared to Control (87%; $P < .01$) and Ace (53%; $P < .01$). Marop2 had significantly less vomiting (27%) compared to Control ($P < .01$). Marop1 had significantly greater incidence of ptyalism (73%) compared to Ace ($P < .01$; 20%). Ace showed significantly less panting (33%) compared to Marop2 (93%; $P < .01$).

Conclusions and Clinical Importance: In healthy dogs, maropitant citrate administered before hydromorphone significantly decreases the incidence of vomiting in dogs but does not improve signs of nausea, ptyalism, or increased panting.

Key words: Antiemetic; Canine; Cerenia; Hydromorphone; Vomiting.

Pre-emptive analgesia is the practice of administering an analgesic modality before a nociceptive event.[1] In veterinary medicine mu-agonist opioids are commonly combined with tranquilizers to provide chemical restraint, relieve anxiety, and provide pre-emptive analgesia. Although mu-agonist opioids deliver dose-dependent analgesia and sedation, they also have well-documented adverse effects such as bradycardia, respiratory depression, changes in thermoregulation, allergic reactions, dysphoria, salivation, nausea, and vomiting.[2] Morphine and hydromorphone are readily available on the market, relatively inexpensive, and highly adaptable to most clinical applications. Both have similar efficacy and adverse effect profiles. Methadone, oxymorphone, and fentanyl, on the other hand, have varying degrees of potency and efficacy, but produce fewer adverse effects in dogs.[2] Oxymorphone is similar to hydromorphone, but causes less vomiting and is more expensive. Fentanyl is a potent pure mu-agonist opioid used routinely in dogs. Although emesis is not a common problem seen with fentanyl, the drug requires a constant rate infusion in order to maintain effective plasma concentrations, and is also more costly.

Abbreviations:

Ace	Acepromazine administered 30–45 minutes before hydromorphone
CRTZ	Chemoreceptor trigger zone
Marop1	Maropitant administered 30–45 minutes before hydromorphone
Marop2	Maropitant administered at the same time as hydromorphone

Opioid-induced vomiting in dogs is a common encountered problem and is dependent on several factors, including the lipophilic nature and receptor profile of the opioid, and the dose and route of administration.[3] Vomiting is seen in 45–100% of dogs receiving hydromorphone.[4] Decreased incidence of preoperative vomiting in dogs has been associated with opioids that are more lipid-soluble, administered with phenothiazines such as acepromazine, or with both.[4–6] For the majority of surgical procedures, preoperative emesis does not impose serious risks. There are specific instances, however, when vomiting before surgery could increase morbidity.[7–9] Examples include esophageal dysfunction, high gastrointestinal obstructions, gastric volvulus, esophageal herniation, severe gastric/esophageal ulcerations, highly irritating gastric contents, increased risk of aspiration pneumonia, increased intracranial and intraocular pressures, neuromuscular diseases, and high cervical disc lesions. Maropitant citrate[a] is a central and peripheral acting

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antiemetic, and is approved for the prevention of emesis in dogs. Acepromazine[b] is a phenothiazine tranquilizer that has antiemetic and antihistamintergic effects via antagonistic properties on the dopamine receptors in the chemoreceptor trigger zone (CRTZ).[10]

The purpose of this paper was to compare maropitant and acepromazine on the incidence of vomiting, signs of nausea, ptyalism, and increased panting in dogs premedicated with hydromorphone. Our hypothesis was that maropitant, when given concurrently with or before hydromorphone in healthy dogs, would provide better antiemetic effects, and induce less signs of nausea, ptyalism, and panting activity, compared to saline or acepromazine.

Materials and Methods

Study Population

This study was approved by the Mississippi State University Institutional Animal Care and Use Committee. Mixed-breed intact female dogs of unknown age presented to the Mississippi State University College of Veterinary Medicine from area shelters were included in the study. The dogs were used as part of a veterinary surgery class for elective ovariohysterectomies. A sample size calculation was performed in order to determine the number of dogs needed to utilize 4 experimental groups. Assumptions for the sample size calculations included an alpha level of 0.05, a power of 0.80, and anticipated proportions of dogs vomiting of 0.1 for maropitant given before hydromorphone and 0.5 for hydromorphone.[11] Further assuming a one-sided test, the calculated sample size was 15 dogs per group. Proportions were justified based on a study examining the antiemetic effects of acepromazine associated with opioid administration in dogs.[4] Sixty dogs, weighing 1.5–32.5 kg (mean ± SD = 16.6 ± 8.5 kg) and classified as ASA status 1 based on complete physical exams, hematocrit, total protein, and heartworm test, were enrolled in the study.

Study Protocol

Using a commercial software program,[c] dogs were randomized and assigned to one of 4 experimental groups. Group "Control" received 0.1 mL/kg of 0.9% saline SC 30–45 minutes before the administration of 0.2 mg/kg of hydromorphone[d] intramuscularly. Group "Marop1" received 1 mg/kg maropitant SC 30–45 minutes before 0.2 mg/kg of hydromorphone intramuscularly. Group "Ace" received 0.02 mg/kg of acepromazine intramuscularly 30–45 minutes before 0.2 mg/kg of hydromorphone intramuscularly. Group "Marop2" received 1 mg/kg maropitant SC at the same time 0.2 mg/kg of hydromorphone was administered intramuscularly. Food was withheld from all dogs 12 hours before premedication; however, water was always available. A trained observer (SH) blinded to the treatment groups documented emetic events, signs of nausea, ptyalism, and increased panting from the time the hydromorphone was administered until the time dogs were induced for surgery. Vomiting was defined as abdominal contractions followed shortly by expulsion of stomach contents from the mouth. Signs of nausea were characterized by excessive licking of the lips, excessive swallowing, and a hunched posture. Increased panting was defined as a noticeable increase in panting behavior in dogs during the period of premedication, before versus after hydromorphone administration.

The data were analyzed by Fisher's Exact Test[e] to determine if there were associations between the treatment group and the occurrence of adverse effects. Each side effect (emesis, signs of nausea, salivation, and panting) was assessed individually. If a significant association was found between the proportion of dogs exhibiting and not exhibiting the side effect among the four treatment groups, pairwise comparisons were made between treatment groups. A significance level of 0.05 was used for comparisons among all groups, whereas Bonferroni's correction was used to adjust for the effect of multiple pairwise comparisons ($P < .0083$).

Results

All 60 dogs completed the study. Raw data showing the incidence of emesis, signs of nausea, ptyalism, and panting are provided in Table 1. There was a significant difference in the incidence of emesis between groups ($P < .01$). Maropitant administered concurrently with hydromorphone significantly decreased ($P < .01$) the incidence of vomiting (27%) compared to 0.9% saline (87%). Maropitant administered 30–45 minutes before hydromorphone also significantly decreased ($P < .01$) the incidence of vomiting (0%) compared to 0.9% saline, and to acepromazine (53%). There was not a significant difference in signs of nausea between groups ($P = .16$). There was a significant difference in ptyalism between groups ($P = .03$), with maropitant given 30–45 minutes before hydromorphone being associated with a significantly greater ($P < .01$) chance of ptyalism (73%) compared to acepromazine (20%). There was a significant difference in panting between groups ($P < .01$). Acepromazine was associated with significantly less ($P < .01$) incidences of increased panting (23%) compared to maropitant given concurrently with hydromorphone (93%).

Table 1. Incidence of emesis, signs of nausea, ptyalism, and increased panting in each experimental group (n = 15 dogs per group). "Control" indicates saline administered before hydromorphone; "Marop1" indicates maropitant administered before hydromorphone; "Ace" indicates acepromazine administered before hydromorphone; "Marop2" indicates maropitant administered concurrently with hydromorphone.

	No. of Dogs; Emesis	No. of Dogs; Nausea	No. of Dogs; Ptyalism	No. of Dogs; Increased Panting
Control	13/15 (87%)[a]	9/15 (60%)[a]	7/15 (47%)[a,b]	11/15 (73%)[a,b]
Marop1	0/15 (0%)[b]	3/15 (20%)[a]	11/15 (73%)[a]	11/15 (73%)[a,b]
Ace	8/15 (53%)[a,c]	7/15 (47%)[a]	3/15 (20%)[b]	5/15 (33%)[a]
Marop2	4/15 (27%)[b,c]	6/15 (40%)[a]	7/15 (47%)[a,b]	14/15 (93%)[b]

Values within a column that share the same superscript are not significantly different ($P > .01$, Bonferroni's correction for multiple comparisons).

Discussion

Based on our study involving hydromorphone use in healthy dogs, administering maropitant 30 to 45 minutes before an opioid significantly decreases the incidence of vomiting compared to saline or acepromazine, while maropitant given concurrently with an opioid significantly decreases the incidence of vomiting compared to saline but not compared to acepromazine. Maropitant is also associated with an increased incidence of ptyalism, whereas acepromazine is associated with a decreased incidence of increased panting.

Mu-agonist opioids produce nausea and emetogenic effects in dogs via the interaction of the delta receptor in the CRTZ.[10] Several factors, such as drug dose, route of administration, and degree of lipophilicity, dictate the emetogenic effects of mu-agonist opioids.[5] Morphine, for example, induces vomiting in up to 100% of dogs when administered IV at low doses.[6] Administration of higher doses of morphine by other routes dramatically decreases the incidence of vomiting.[5] Hydromorphone is about 5 times more potent than morphine, but produces less signs of nausea, emesis, and GI adverse effects.[10] In a recent study 66% of dogs that received intramuscular hydromorphone, with a saline control, vomited.[6] In our study, hydromorphone and saline resulted in an 87% incidence of vomiting (13/15). When maropitant is delivered 1 hour before intramuscular hydromorphone vomiting is prevented in all dogs, a finding that is comparable to the results of our study. Acepromazine administered 15 minutes before hydromorphone will prevent vomiting in 24% of dogs,[4] and in our study acepromazine prevented vomiting in 53% (8/15) of the experimental group.

The pharmacokinetics of maropitant administered SC in dogs have been well documented. The peak mean plasma concentration from a 1 mg/kg dose of maropitant in dogs occurs 45 minutes after subcutaneous administration.[12] In our study, maropitant eliminated vomiting in all dogs when given 30–45 minutes before hydromorphone, but appeared to be less effective (vomiting observed in 27% of dogs) when administered concurrently with hydromorphone. Based on our results, maropitant has antiemetic effects which occur shortly after subcutaneous administration, but are which are most effective when given at least 30 minutes before hydromorphone.

Excessive panting is an adverse effect of morphine and is believed to be related to an initial rise in body temperature.[3] In the dog, hydromorphone is believed to have similar effects on the thermoregulation center as morphine, thus similarly leading to excessive panting. Both hydromorphone and oxymorphone administered as preanesthetics agents initiate excessive panting in experimental dogs.[3] When these drugs are combined with acepromazine, the incidence of panting significantly decreases.[2] In our study, hydromorphone appeared to induce increased panting in most dogs, and this effect seemed to be alleviated by acepromazine but not by maropitant. Phenothiazines cause central nervous system depression and skeletal muscle relaxation, and it is possible that these effects antagonized the hydromorphone-induced panting seen in our dogs.

There are several limitations to this study. We did not include sick or diseased dogs in our study, and the results of our study therefore are not being directly applicable to dogs with conditions that predispose to emesis. Additionally, reporting of adverse effects such as nausea and increased panting was based primarily on the subjective assessment of an anesthesia clinician, since objective scoring systems for such adverse effects have not been established. In order to reduce the impact of the subjectivity of assessment, all clinical signs were evaluated by a single experienced clinician who was blinded to treatment groups. Omitting ptyalism as a sign of nausea, although justifiable on the basis that maropitant alone can cause ptyalism, may have led us to underestimate the incidence of nausea. According to the Freedom of Information Summary regarding the veterinary-approved formulation of maropitant, published in 2007, nausea in dogs is defined as increased salivation, lip licking, frequent and/or exaggerated swallowing motions, lethargy, restlessness, or panting.[13] Finally, although we calculated a sample size that would enable us to elucidate the effects of our various drug protocols on the incidence of vomiting, it is still possible our study was underpowered with regard to achieving significance for other clinical signs such as nausea.

In conclusion, based on our study in healthy dogs, maropitant citrate administered 30–45 minutes SC before hydromorphone markedly diminished the incidence of opioid-induced vomiting compared to concurrent saline or acepromazine. When maropitant was administered concurrently with hydromorphone, the incidence of vomiting was also reduced significantly when compared to a control group, but not when compared to acepromazine. We also detected an association between the administration of maropitant and an increase occurrence of ptyalism, and between the administration of acepromazine and a decreased occurrence of panting. Further studies are needed to better determine the ideal timing of maropitant in association with opioid administration, to determine the effects of maropitant when used with a mu-agonist opioid in sick or debilitated dogs, and to determine whether a combination of maropitant and acepromazine together might better reduce the incidence of both vomiting and panting in dogs receiving opioids.

Footnotes

[a] Cerenia, Zoetis, Florham Park, NJ
[b] Aceproject, Butler-Schein, Dublin, OH
[c] Microsoft Office Excel 2010, Microsoft Corp, Redmond, WA
[d] Dilaudid, West-Ward Pharmaceuticals, Eatontown, NJ
[e] PROC FREQ in SAS for Windows 9.2, SAS Institute Inc, Cary, NC

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