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Maropitant prevented vomiting but not gastroesophageal reflux in anesthetized dogs premedicated with acepromazine-hydromorphone

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Abstract

Objective—To evaluate the efficacy of maropitant for prevention of vomiting and gastroesophageal reflux (GER) in dogs following acepromazine-hydromorphone premedication and inhalation anesthesia.

Study design—Randomized, blinded, prospective clinical study.

Animals—Twenty-six dogs admitted for elective soft tissue or orthopedic procedures that were 3.1 ± 3.1 years of age and weighed 20.5 ± 11.4 kg.

Methods—Dogs were randomly assigned to one of two groups: Group M received maropitant (1.0 mg kg^{-1}) and Group S received 0.9% saline (0.1 ml kg^{-1}) intravenously 45–60 minutes before premedication with hydromorphone (0.1 mg kg^{-1}) and acepromazine (0.03 mg kg^{-1}) intramuscularly. An observer blinded to treatment documented any retching or vomiting for 20 minutes before induction with propofol ($2\text{--}6 \text{ mg kg}^{-1}$) and inhalation anesthesia. A pH probe inserted into the distal esophagus was used to detect GER.

Results—None of the dogs in Group M retched or vomited (0/13), 6/13 (46%) in Group S were observed to retch or vomit, and the difference between groups was significant ($p = 0.015$). There were no differences between groups in the number of dogs with GER (Group M: 4/13, Group S: 6/13 dogs) or the number of reflux events. Esophageal pH at the end of anesthesia was significantly lower in both M and S groups in dogs with GER *versus* dogs without GER ($p = 0.004$ and 0.011 , respectively). Only dogs with GER in Group S had significantly lower pH at the end compared to the beginning of anesthesia ($p = 0.004$).

Conclusions and clinical relevance—Intravenous maropitant prevented retching and vomiting associated with acepromazine-hydromorphone premedication. Maropitant did not prevent the occurrence of GER. Fewer dogs in Group M developed GER but further study with a larger number of dogs is necessary to determine if there is a significant difference.

Keywords

acepromazine; gastroesophageal reflux; hydromorphone; maropitant; vomiting

Introduction

Esophagitis, esophageal stricture and aspiration pneumonia are potential consequences of general anesthesia resulting from perianesthetic vomiting, regurgitation and gastroesophageal reflux (GER). GER can be clinically-silent and only detected as fluid reaches the oronasal cavity. GER was reported in 16.3% to 55.0% of anesthetized dogs (Wilson et al. 2007), where premedication choice influenced GER. For example, intramuscular (IM) meperidine tended to reduce GER in dogs *versus* IM morphine, whereas concurrent acepromazine administration tended to increase GER (Wilson et al. 2007). Additionally, increasing morphine from 0 to 1.10 mg/kg IM increased GER occurrence from 27% to 60% of dogs (Wilson et al. 2005).

The dorsal vagal motor nucleus, referred to as the vomiting center, receives many central (chemoreceptor trigger zone [CRTZ] or area postrema) and peripheral (vagal and sympathetic visceral afferents) afferent inputs involving many neurotransmitter systems (Diemunsch and Grélot 2000). Opioid receptor activation in the CRTZ was a proposed mechanism in one study in which approximately 45% of dogs vomited after hydromorphone administration IM (Valverde et al. 2004).

Substance P, the most potent neurokinin-1 (NK-1) receptor agonist, also is involved in emesis at the area postrema and dorsal vagal nucleus (Diemunsch and Grélot 2000). Maropitant citrate is a highly-specific NK-1 receptor antagonist that reduces centrally- and peripherally-mediated vomiting in dogs including hydromorphone-induced vomiting (Sedlacek et al. 2008; Kraus 2012). However, no studies have determined the efficacy of maropitant in reducing vomiting when acepromazine and hydromorphone are co-administered. NK-1 antagonists may also improve human functional bowel diseases such as GER and dyspepsia via smooth muscle relaxation, intestinal motility and secretory effects (Sanger 2004). Their precise roles have not been elucidated and to the author's knowledge there are no published studies assessing GER following maropitant administration and inhalation anesthesia in dogs.

The study hypothesis was that maropitant, administered 45–60 minutes before anesthesia induction, would decrease the occurrence of vomiting and GER in dogs following acepromazine-hydromorphone premedication and general anesthesia.

Materials and methods

This study was approved by the Institutional Animal Care and Use Committee and conducted over one year (2010–2011). Dogs admitted for elective soft tissue or orthopedic procedures were considered and owners' written permissions were obtained. The study included 26 dogs classified as an American Society of Anesthesiologists Physical Status I or II based on absence of physical examination abnormalities, no functional limitations and packed cell volume, total protein and blood urea nitrogen (Azostix, Siemens Health Care Diagnostics, Inc., NY, USA) measurements. Dogs were excluded if owners reported a history of vomiting. There were 18 females and 8 males, aged 3.1 ± 3.1 years (range, 6

months to 10 years) and weighing 20.5 ± 11.4 kg (range, 3.6–49.8 kg). The subjects were a mixture of purebreds (18 dogs) and mixed breeds (8 dogs).

Study protocol

Food, not water, was withheld for at least 12 hours before anesthesia. Dogs were randomly divided into two groups by blindly choosing numbers from a box. Group M was given maropitant (1.0 mg kg^{-1} ; Cerenia, Pfizer Animal Health, NY, USA) and group S saline (0.1 mL kg^{-1} ; Hospira, IL, USA), ensuring equivalent injectate volumes. Both treatments were injected intravenously (IV) through a 23 gauge, 1.9 cm butterfly needle over 5–7 minutes (Safety-Lok Blood Collection Set, BD Vacutainer, NJ, USA). After 45–60 minutes, dogs were premedicated with acepromazine (0.03 mg kg^{-1} ; Boehringer Ingelheim, MO, USA) and hydromorphone (0.1 mg kg^{-1} ; Hospira) IM.

An observer trained to recognize retching or vomiting and blinded to treatment recorded events for 20 minutes following premedication. Vomiting was defined as active oral expulsion of stomach contents; retching was defined as active abdominal muscle contraction without stomach content expulsion.

A cephalic vein catheter (20 gauge, 32 mm, Monoject Veterinary I.V. Catheter, Tyco Healthcare Group, MA, USA) was placed and propofol ($2\text{--}6 \text{ mg kg}^{-1}$; Hospira) administered for endotracheal intubation. Anesthesia was maintained with isoflurane (1.0–2.5% vaporizer setting; nineteen dogs) or sevoflurane (1.0–3.5% vaporizer setting; seven dogs) in oxygen through a circle rebreathing system. A balanced crystalloid solution (Veterinary Plasma-Lyte A, Abbott Laboratories, IL, USA) was infused IV throughout anesthesia ($5\text{--}10 \text{ mL kg}^{-1} \text{ hour}^{-1}$).

Hemoglobin oxygen saturation, heart rate (HR), respiratory rate, oscillometric non-invasive blood pressures (Cardell Veterinary Monitor Model 9401; Midmark, FL, USA) and body temperatures were recorded every 5 minutes. The blood pressure cuff, approximately 40% of limb circumference, was placed around the midantibrachium. End-tidal carbon dioxide concentrations were measured in some patients. No monitoring devices other than the pH probe were inserted into the esophagus.

Esophageal pH measurement

Following induction of anesthesia, a flexible, esophageal pH probe (SureTec pH Disposable pH Catheter, Sierra Scientific Instruments, CA, USA) was inserted into the esophagus. The probe was calibrated at pH 4 and 7 within 1 hour before use and was removed before tracheal extubation. To ensure standardized probe placement, the distance between the mandibular incisor tooth and cranial margin of the 10th rib was measured externally. The probe tip was advanced this distance through the oropharynx into the esophagus, with the assumption that the tip was just oral to the gastroesophageal junction (Wilson et al. 2006, 2007). The probe was taped to the endotracheal tube and just behind the maxillary canines and was connected to a recorder (AccuTrac pH Recorder, Sierra Scientific Instruments) for continual data collection. Data were uploaded at study completion and analyses were performed with specific software (AccuView pH, Sierra Scientific Instruments). GER was defined as 30 second decrease in esophageal pH to < 4 (gastric acid reflux) or an increase

to > 7.5 (bile reflux) (Wilson et al. 2006, 2007). Initial pH values were measured immediately after probe placement when values remained steady for approximately 3 minutes. Ending pH values were taken just before discontinuation of inhalation anesthesia.

Statistical analyses

Patient age, body mass, total anesthetic time, reflux events per case (when present), minimum pH during GER, initial and ending pH (analyzed separately in dogs with and without GER), and initial HR and mean arterial pressures (MAP) were compared between Groups S and M using a one-way ANOVA; a Student-Neuman Keuls test was used for post-hoc analyses (SigmaPlot, Version 12.0, Systat Software Inc., CA, USA). The Fisher exact test was used to test for differences between groups for categorical variables (incidence of retching or vomiting and GER; SigmaPlot, Version 12.0, Systat Software Inc.). All data are reported as mean \pm SD. A p -value < 0.05 was considered significant.

Results

Females were overrepresented in both study groups (Table 1). There were no statistically significant differences between Group S and M in patient age ($p = 0.65$), body weight ($p = 0.63$), or total anesthesia time ($p = 0.41$). The number of intra-abdominal surgeries were similarly distributed across both groups (Group M: 6/13, Group S: 7/13 dogs). No significant differences were found in initial HR (M: 87 ± 16 , S: 82 ± 19 beats per minute⁻¹; $p = 0.54$) and MAP (M: 75 ± 16 , S: 72 ± 21 mmHg; $p = 0.70$) between groups.

No dogs in Group M retched or vomited after premedication whereas retching or vomiting was observed in six out of thirteen dogs (46%) in Group S ($p = 0.015$; Table 1). In Group S, two out of the six dogs retched and four vomited. Although fewer dogs had GER in Group M (4/13, 31%) than S (6/13, 46%), this was not statistically different ($p = 0.68$). Only one dog in Group S had both vomiting and GER. There was also no significant difference in number of reflux events per dog between Groups M and S ($p = 0.36$). Only acidic reflux (pH < 4) events occurred. Minimum pH during GER episodes did not differ between Group M and S ($p = 0.72$; Table 1). When initial and ending pH was analyzed separately in dogs with and without GER, there were no significant differences in initial pH values between Group M and S or between dogs with and without GER (all $p > 0.05$). However, ending esophageal pH was significantly lower in both groups in dogs with GER when compared to dogs without GER ($p = 0.004$ and $p = 0.011$, respectively; Table 1). Ending pH in Group S with GER was significantly decreased from initial pH values in the same group (6.5 ± 0.6 versus 4.1 ± 1.5 ; $p = 0.004$). Initial and ending pH did not differ in Group M with GER (5.7 ± 0.9 versus 4.3 ± 1.7 ; $p = 0.196$).

Discussion

In this study of dogs scheduled for elective procedures, maropitant administered IV 45–60 minutes before premedication with acepromazine-hydromorphone prevented retching and vomiting. These results are similar to a previous investigation of hydromorphone alone (Kraus 2012). The prevalence of GER during anesthesia was not significantly lower in Group M versus Group S. In Group S, esophageal pH at the end of anesthesia (4.1 ± 1.5)

was significantly decreased from initial pH (6.5 ± 0.6) in dogs with GER. Although pH decreased by the end of anesthesia in Group M, it was not significantly different from initial pH values in dogs with GER. However, due to the small sample size (4 dogs), the non-significant lower initial pH in Group M requires further investigation.

Opioid administration frequently results in vomiting via effects within the CRTZ which is outside the blood-brain barrier (Blancquaert et al. 1986). Acepromazine administered to dogs 15 minutes before hydromorphone significantly decreased the prevalence of vomiting from 45% to 18% when the drugs were injected concurrently (Valverde et al. 2004). In the current study, the prevalence of retching and vomiting after concurrent acepromazine-hydromorphone administration was similar (46%), and these effects were prevented by prior maropitant administration. These results support maropitant use as a pharmacologic adjunct when retching and vomiting are considered undesirable effects in a patient that is to be premedicated with acepromazine-hydromorphone.

Although IV maropitant administration was extralabel, this route minimized absorption and distribution variability associated with subcutaneous injection. Since IV maropitant decreases blood pressure for up to 10 minutes in anesthetized dogs (Boscan et al. 2011), this study allowed 45–60 minutes before premedication to avoid confounding results. Despite a reduction in vomiting, maropitant did not reduce GER occurrence or alter initial esophageal pH. In addition, the minimum pH during reflux did not differ significantly between groups. GER was recorded in 31% and 46% of dogs in Groups M and S, respectively, similar to previous reports (Wilson et al. 2007). Ending esophageal pH was significantly lower in dogs with GER in both M and S groups when compared to dogs without GER. Furthermore, ending pH was significantly decreased from initial pH values in dogs with GER in Group S whereas initial and ending pH did not differ in dogs with GER in Group M. Although this suggests that maropitant may have affected pH by procedure end, the numerical differences were small and may not be clinically significant. Since the number of animals that experienced GER was very small, further studies are needed to verify these results. An association between GER and preanesthetic vomiting in dogs was not established in this investigation, consistent with previous reports (Wilson et al. 2005, 2006).

Measuring esophageal pH for detecting GER is a relatively non-invasive and clinically-applicable procedure. If the sensor tip touches the esophageal mucosa, a false negative reading may be obtained as pH would decrease to a lesser extent. In addition, GER of neutral pH may have occurred but would not have been identified.

Although a varied population of dogs was used, the goal was to perform a clinically-applicable study using a consistent anesthetic protocol. A previous study documented no significant effect between isoflurane and sevoflurane on GER occurrence in dogs (Wilson et al. 2006). Studying a larger population will increase the number of dogs exhibiting GER and further elucidate the effects of maropitant on GER.

In summary, this clinical study suggests that maropitant is a useful agent to reduce vomiting associated with acepromazine-hydromorphone administration in dogs. However, 30% of dogs receiving maropitant and 46% of control dogs still experienced GER.

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Table 1

Effects of maropitant (M; 1 mg kg⁻¹) versus 0.9% saline (S; 0.1 ml kg⁻¹) administered IV 45–60 minutes before premedication with hydromorphone and acepromazine followed by propofol and inhalation anesthesia on the occurrence of vomiting and retching, gastroesophageal reflux (GER), and esophageal pH in dogs. Values are reported as mean ± SD. *n* = 13 per group except where noted.

	<u>Maropitant (M)</u>	<u>Saline (S)</u>
<i>I. Population Data</i>		
Gender		
Males (intact/neutered)	5 (1/4)	3 (1/2)
Females (intact/spayed)	8 (6/2)	10 (7/3)
Age (years)	2.8 ± 3.0	3.4 ± 3.3
Body Weight (kg)	21.5 ± 12.5	19.4 ± 10.7
<i>II. Study Data</i>		
Total anesthesia time (minutes)	162 ± 41	146 ± 52
Incidence of vomiting/retching	0/13 dogs	6/13 dogs*
Incidence of GER	4/13 dogs	6/13 dogs
Number of reflux events/case	4 ± 5 (<i>n</i> = 4)	2 ± 1 (<i>n</i> = 6)
Minimum pH during each GER	2.1 ± 0.8	2.2 ± 1.0
Initial esophageal pH		
No GER	6.6 ± 0.8 (<i>n</i> = 9)	6.1 ± 1.5 (<i>n</i> = 7)
GER	5.7 ± 0.9 (<i>n</i> = 4)	6.5 ± 0.6 (<i>n</i> = 6)
Ending esophageal pH		
No GER	6.5 ± 0.6 (<i>n</i> = 9)	6.0 ± 0.8 (<i>n</i> = 7)
GER	4.3 ± 1.7 [†] (<i>n</i> = 4)	4.1 ± 1.5 [‡] (<i>n</i> = 6)

* *p* = 0.015 versus Group M.

[†] Group M: *p* = 0.004, Group S: *p* = 0.011 versus dogs without GER in same respective group.

[‡] *p* = 0.004 versus initial pH in Group S with GER.