Effects of maropitant, acepromazine, and electroacupuncture on vomiting associated with administration of morphine in dogs

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**Objective**—To evaluate effects of maropitant, acepromazine, and electroacupuncture on morphine-related signs of nausea and vomiting in dogs and assess sedative effects of the treatments.

**Design**—Randomized controlled clinical trial.

**Animals**—222 dogs.

**Procedures**—Dogs received 1 of 6 treatments: injection of saline (0.9% NaCl solution), maropitant citrate, or acepromazine maleate or electroacupuncture treatment at 1 acupoint, 5 acupoints, or a sham acupoint. Morphine was administered after 20 minutes of electroacupuncture treatment or 20 minutes after injectable treatment. Vomiting and retching events and signs of nausea and sedation were recorded.

**Results**—Incidence of vomiting and retching was significantly lower in the maropitant (14/37 [37.8%]) group than in the saline solution (28/37 [75.7%]) and sham-acupoint electroacupuncture (32/37 [86.5%]) groups. The number of vomiting and retching events in the maropitant (21), acepromazine (38), 1-acupoint (35), and 5-acupoint (34) groups was significantly lower than in the saline solution (88) and sham-acupoint electroacupuncture (109) groups. Incidence of signs of nausea was significantly lower in the acepromazine group (3/37 [8.1%]) than in the sham-acupoint group (15/37 [40.5%]). Mean nausea scores for the saline solution, maropitant, and sham-acupoint electroacupuncture groups increased significantly after morphine administration, whereas those for the acepromazine, 1-acupoint electroacupuncture, and 5-acupoint electroacupuncture groups did not. Mean sedation scores after morphine administration were significantly higher in dogs that received acepromazine than in dogs that received saline solution, maropitant, and sham-acupoint electroacupuncture treatment.

**Conclusions and Clinical Relevance**—Maropitant treatment was associated with a lower incidence of vomiting and retching, compared with control treatments, and acepromazine and electroacupuncture appeared to prevent an increase in severity of nausea following morphine administration in dogs. (J Am Vet Med Assoc 2014;244:820–829)
profuse vomiting may lead to dehydration, electrolyte depletion, and disturbances in acid-base balance.

Maropitant citrate is a neurokinin-1 receptor antagonist developed specifically to prevent nausea and vomiting in dogs and cats.13 Maropitant prevents acute vomiting associated with a wide range of clinical conditions, such as parvoviral enteritis, gastroenteritis resulting from dietary indiscretion, and pancreatitis as well as acute or delayed vomiting in canine cancer patients undergoing chemotherapy.15,16 Maropitant is effective in preventing nausea and vomiting induced by hydromorphone in dogs.17 To our knowledge, there are no large-scale studies of its effects on morphine-related nausea and vomiting in dogs.

Acepromazine maleate, a phenothiazine tranquilizer, has antidiopaminergic and antihistaminergic properties at low doses in the chemoreceptor trigger zone and anticholinergic effects at higher doses in the emetic center of the brain.18 It has been shown to decrease the incidence of vomiting caused by opioids in dogs.9,10 Acepromazine administered 15 minutes prior to morphine decreased the incidence of vomiting by 50% (2/8 vs 12/16), compared with the incidence in dogs that received acepromazine 15 minutes after opioid administration.9 Acepromazine can cause hypotension because of its vasodilatory properties and therefore may be contraindicated in some patients.19,20 Drugs such as methylxanthines, haloperidol, droperidol, and ondansetron are reported to decrease morphine-related vomiting but are not commonly used in veterinary medicine owing to very limited experience, lack of research or clinical studies, and expense.21–23

Acupuncture, a branch of traditional Chinese veterinary medicine, may have potential use as an antiemetic treatment in veterinary practice.24 Electroacupuncture is a form of acupuncture modality in which a small electric current is passed between pairs of acupuncture needles. In a pilot study,25 electroacupuncture at the pericardium-6 acupoint was shown to decrease the number of vomiting episodes induced by morphine in ferrets by approximately 40% (mean, 5.6 ± 2.2 episodes vs 9.8 ± 0.6 episodes). Electroacupuncture at the pericardium-6 acupoint significantly suppressed retrograde peristaltic contractions and subsequently lowered the number of vasopressin-induced retching and vomiting episodes in dogs by 34.5 ± 7.9% (mean of episodes, 4.9 ± 0.8 vs 1.8 ± 0.2 [retching] and 5.1 ± 0.7 vs 1.6 ± 0.2 [vomiting]).26,27 Acupuncture at acupoints such as pericardium-6, stomach-36, bladder-20, bladder-21, liver-13, or conception vessel-12 has been reported to effectively prevent vomiting in dogs.27–30 Among these acupoints, pericardium-6 is the most frequently studied antiemetic acupoint.31,32 According to traditional Chinese veterinary medicine, pericardium-6 is located on the pericardium meridian, which is used in the treatment of nausea, vomiting, anxiety, seizures, and cardiac arrhythmias.33 Although the physiologic mechanisms by which stimulation of acupoints affects nausea and vomiting remain largely unknown, increasing evidence from clinical trials suggests that stimulation of pericardium-6 is efficacious in preventing nausea and vomiting associated with surgery and chemotherapy in human patients.34–38 To our knowledge, the effect of electroacupuncture has not been extensively studied in dogs for the prevention of nausea and vomiting associated with opioid administration.

The purpose of the study reported here was to assess the effects of maropitant, acepromazine, and electroacupuncture on vomiting, retching, and signs of nausea following morphine administration in dogs. We hypothesized that treatment with maropitant, acepromazine, and electroacupuncture before morphine administration would prevent or decrease the incidence of vomiting and retching and eliminate or decrease the severity of signs of nausea associated with this treatment. We also hypothesized that electroacupuncture would result in a greater degree of sedation, compared with dogs administered a saline (0.9% NaCl) solution, maropitant, or sham-acupoint electroacupuncture treatment.

Materials and Methods

Animals—Dogs ≥6 months of age and of any breed, sex, and body weight that were evaluated through the Merial Shelter Medicine clinical program at the University of Florida College of Veterinary Medicine between July 3, 2011, and August 29, 2012, were considered for inclusion in the study. Only dogs scheduled to receive morphine as part of preanesthetic medication prior to induction of anesthesia for routine procedures (eg, castellation, ovariohysterectomy, or dental cleaning) and classified as ASA status I (healthy with no systemic disease) or status II (mild systemic disease with no functional limitations)39 were recruited for the study. Exclusion criteria included signs of nausea, vomiting, inappetence, or diarrhea noted within the 2 days prior to evaluation. Dogs receiving concurrent medications with known potential for gastrointestinal irritation, such as NSAIDs or glucocorticoids, were excluded because of potential for an additional risk of nausea and vomiting associated with these treatments.40 Dogs that had received any medication classified as an antiemetic, acid reducer, or mucosal coating agent ≤2 days before the procedure were excluded from the study. Dogs with a history of gastrointestinal disorders or those considered difficult to handle were also disqualified from participation. The study was approved by the Institutional Animal Care and Use Committee of the University of Florida. The dogs belonged to animal rescue groups that participated in the Merial Shelter Medicine Program with financial benefit in the form of subsidized routine procedures prior to adoption. Rescue group personnel were informed of the study procedures if a dog met the criteria, and verbal consent of the shelter representative was required for study inclusion.

Study design—Each dog was temporarily housed in a standard clinic cage or run. Food was withheld for 8 hours prior to surgery, but dogs had access to water ad libitum until the time of morphine administration. Dogs that met the inclusion criteria were randomly assigned to 1 of 6 treatment groups by use of a computer program.39 The measurement of heart rate, respiratory rate, body temperature, and body condition scores and the recording of ASA status of each dog were performed by one of the authors (RBK) prior to injectable or electroacupuncture treatment.

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A 9-integer scale system was used for the measurement of body condition score.41 Dogs that were classified as brachycephalic breed or brachycephalic phenotype had this information recorded by the same author. Brachycephalic breeds are characterized as having broad skulls with widened parietal, temporal, and occipital bones; wide-set ocular cavities; and short, blunted maxillae.42 Examples of brachycephalic breeds included Pug, Pekingese, Chihuahua, Cavalier King Charles Spaniel, Shih Tzu, Boxer, English Bulldog, and Boston Terrier.43 Mixed-breed dogs that were phenotypically brachycephalic were also classified as brachycephalic. After evaluation, dogs were assigned to undergo ovariohysterectomy, castration, or dental cleaning. Dogs received injectable treatment (n = 3 groups) or electroacupuncture (3) prior to morphine administration. A sample size of 37 dogs for each treatment group (n = 222 dogs) was calculated with the objective of 80% power (0.80) and a 2-sided type 1 error with a significance level of $\alpha = 0.05$ to detect a clinically meaningful difference of 30% in the incidence of vomiting and retching.

The time of injection or the start of electroacupuncture (ie, start of electrical current delivery) was considered time 0. Morphine was administered 20 minutes later, and dogs were observed for vomiting or retching for 20 minutes after morphine administration. Video recordings were made of each dog for 1 minute before and 1 minute after the experimental treatment and then for 20 minutes after morphine administration. The recordings were later used for assessment of signs of nausea and sedation by a blinded observer. After 20 minutes of observation (40 minutes after treatment), the study ended and dogs were anesthetized for the scheduled surgical procedures.

**Injectable treatments**—Dogs in 3 groups received maropitant citrate5 (1.0 mg/kg, SC), acepromazine maleate5 (0.05 mg/kg [0.022 mg/lb], IM),43 or saline solution (0.1 mL/kg [0.05 mL/lb], SC [placebo]), all at room temperature (approx 24°C). The volume of saline solution was selected to equal the volume of maropitant per kilogram of body weight. All SC injections were made at a single site in the loose skin over the scapular region by one of the authors (RBK). All IM injections were made at a single site into the middle gluteal muscle (midway between the greater trochanter of the femur and the wing of the ilium) by the same author. Dogs were observed for signs of pain or other reactions at the injection site, such as vocalization, skin twitching, scratching or licking, or erythema at the injection site.

**Electroacupuncture treatments**—Dogs in 3 groups underwent electroacupuncture at 1 acupoint (pericardium-6), 5 acupoints (pericardium-6, stomach-36, gallbladder-34, bladder-20, and bladder-21), or a nonacupoint (sham). Sterile acupuncture needles were inserted at acupoints through skin and muscle or fascia. Acupuncture needles 0.5 inches in length and 0.22 mm in diameter (34 gauge) were used in dogs that weighed $<$ 20 kg (44 lb), whereas acupuncture needles 1 inch in length and 0.25 mm in diameter (32 gauge) were used in dogs that weighed $\geq$ 20 kg.6 depending on the location of acupoints and the size of the dog, the needles were inserted to depths of 3 to 10 mm into acupoints and then attached to an electrical stimulator.5 Needles placed at pericardium-6, bladder-20, bladder-21, and the sham acupoint were connected to gallbladder-34 on the ipsilateral side. A low electrical current (6.0 mA for 200 microseconds) was applied for 10 minutes at a frequency of 2 Hz, followed by 10 minutes at 100 Hz. These electroacupuncture frequencies were selected because they have been shown to have antiemetic effects in humans,34,45 and a duration of 20 minutes has commonly been used for acupuncture treatment in animals.35 After 20 minutes, electroacupuncture was terminated and the needles were removed. All dogs were examined for local reactions at the site of needle insertion, such as minor bleeding or swelling. All acupuncture treatments were performed by 1 certified veterinary acupuncturist (RBK) throughout the study.

Acupoint locations were determined in cun (Chinese inches, which are proportional units47 established on the basis of the distance between 2 anatomic landmarks of a body part). In dogs, pericardium-6 is located on the medial aspect of each thoracic limb, 2 cun proximal to the transverse carpal crease of the carpus, in the groove between the flexor carpi radialis and the superficial digital flexor muscles (as a reference, the distance from the center of the elbow to the area just proximal to the carpus is 12 cun). Stomach-36 is located on the cranialateral aspect of each pelvic limb, 3 cun distal to the center of the stifle joint and 0.5 cun lateral to the cranial aspect of the tibial crest, in the belly of the cranial tibialis muscle (as a reference, the distance from the center of the stifle joint to the lateral malleolus is 16 cun).33 Gallbladder-34 is located on the lateral aspect of each pelvic limb at the stifle joint, in a small depression cranial and distal to the head of the fibula.31 Bladder-20 and bladder-21 are located at the dorsolateral aspects of the spinal column, 1.5 cun lateral to the caudal border of the dorsal spinous processes of T12 and T13, respectively (as a reference, the width of the last intercostal space is 1 cun).33 The sham acupoint used in this study was located on the caudomedial aspect of the pelvic limb, 3 cun proximal to the medial malleolus of the tibia, in the thin fleshy tissue on the cranial border of the Achilles tendon (as a reference, at the medial aspect of the forelimb, the distance from the medial epicondyle of the tibia to the medial malleolus is 13 cun). This point was not located on any acupuncture meridian and was $\geq$ 1 cun away from any neighboring acupoints.33

**Administration of morphine and assessments of vomiting and retching**—Morphine sulfate5 (0.5 mg/kg) was administered IM45 in the same manner as described for acepromazine. Morphine was administered on the contralateral side from the acepromazine injection by the same clinician who performed the electroacupuncture or administered the experimentally tested drugs, and this individual performed the 20-minute observation of each dog after morphine administration.

A vomiting event was defined as an episode in which gastrointestinal contents were expelled from the mouth through forceful and sustained contractions of the abdominal muscles. Retching was defined as forceful abdominal contractions occurring without expul-
sion of gastrointestinal contents from the mouth. The number and timing of each discrete vomiting and retching event were recorded. The time to cessation of vomiting and retching was determined by calculating the time from the beginning of the first vomiting and retching event to the end of the last event in each dog. Dogs that vomited only once were excluded from this analysis.

**Nausea and sedation scoring**—Nausea and sedation scores were assessed for each dog before the assigned experimental treatment (time 0), immediately before morphine administration (20 minutes), and at 30, 35, and 40 minutes (10, 15, and 20 minutes after morphine administration, respectively). During data collection, dogs were housed separately and allowed to roam freely in their cages. One clinician (SAR) who was unaware of the allocation of treatments reviewed the videotapes and performed all nausea and sedation scoring.

Signs of nausea were defined as ptyalism, lip licking, swallowing, nervousness, restlessness, and signs of depression. Nausea scores were assigned with whole numbers on a scale of 1 to 4 (1 = no nausea and 4 = worst possible nausea) for each of 3 categories: lip licking or swallowing; salivation; and attitude, mentation, and posture (Appendix 1). This scale was adapted from nausea scales reported in previous studies. The mean nausea score for each dog at each time point was determined on the basis of these 3 values. After measurements, the total nausea score for each group at each time point was used to calculate the mean values for each group.

Sedation was defined as a reduction of activity or excitement. The degree of sedation was quantified with whole numbers on a 5-point scale (1 = no sedation and 5 = maximum possible sedation), which the observer marked on the basis of assessment for 2 categories: the dog’s attitude, mentation, and posture and response to noise (generated by hand clap; Appendix 2). The sedation scoring criteria was a composite simple descriptive score adapted from systems used in previous studies. The mean sedation score for each dog at each time point was determined on the basis of these variables. After measurements, the total score for each group at each time point was used to calculate the mean values for each group.

**Rescue protocol**—To ensure the welfare of study dogs, a rescue antiemetic protocol was devised. Any dog that had ≥ 5 vomiting and retching events during the observation period following administration of morphine would receive maropitant (1.0 mg/kg, SC), and fluid therapy or any additional treatment deemed necessary by the attending clinician would be initiated.

**Statistical analysis**—Normal distribution of the data was assessed by means of a histogram. One-way ANOVA was used to evaluate data that were normally distributed. Body condition score and brachycephalic data were not normally distributed; these data were compared by use of the Kruskal-Wallis nonparametric ANOVA and reported as median (range) values. All other data were reported as mean ± SD. A $\chi^2$ test was used to detect differences among groups for categorical variables (sex, breed, anesthesia status, planned procedure, and brachycephalic or phenotypically brachycephalic breed), whereas Kruskal-Wallis tests were used to detect differences for continuous variables (age, body weight, body temperature, heart rate, respiratory rate, incidence of vomiting and retching, and body condition, nausea, and sedation scores). The number and time to cessation of vomiting and retching events were evaluated by means of Kruskal-Wallis tests, with post hoc testing by means of the Mann-Whitney U test. The level of significance was set at $P < 0.05$ for ANOVA. When the ANOVA indicated a significant difference, a post hoc Bonferroni test was used to correct for the number of comparisons performed in the study. The 6 groups yielded 15 sets of intergroup comparisons; thus, a corrected value of $P < 0.0033$ (0.05/15) was accepted as significant for those comparisons. All statistical analyses were performed with a statistical software program.

**Results**

**Animals**—A total of 222 dogs (114 [51.4%] males and 108 [48.6%] females; mean ± SD age, 2.4 ± 1.9 years; body weight, 13.8 ± 10 kg [30.4 ± 22 lb]; median body condition score, 4.95 [range, 4 to 6]) that met the inclusion criteria were included, and all dogs completed the study. At time 0, mean ± SD rectal temperature was 38.33 ± 0.5°C (101.9 ± 0.9°F), heart rate was 126.7 ± 27.2 beats/min, and respiratory rate was 36.6 ± 14.8 breaths/min. Two hundred (90.1%) and 22 (9.9%) dogs were assigned an ASA status of I and II, respectively. Planned procedures included ovariohysterectomy (108/222 [49.0%]), castration (103 [46.4%]), and dental cleaning (11 [5.0%]). No significant differences were found among groups for any of these signalment or clinical variables or for procedure type. Fifty-three of 222 (23.9%) dogs were classified as brachycephalic or phenotypically brachycephalic breeds; there was no evidence that this factor influenced incidence of vomiting and retching (19/53 vs 62/169; $P = 0.92$). All dogs were included in the analyses of the number, incidence, and time to cessation of vomiting and retching events. Because of technical problems, the video recording of 1 dog in the acromegnoma group was unavailable for nausea and sedation score analysis.

**Clinical observations**—Six dogs, all in the saline solution (placebo) or sham-acupoint electroacupuncture group, had ≥ 5 vomiting events after morphine administration. Four dogs vomited 6 times, and 1 dog vomited 5 times. The remaining dog vomited 9 times and had a trace amount of frank blood evident in the vomitus. All 6 dogs were treated with maropitant (1.0 mg/kg, SC). No further vomiting was noted after the rescue treatment. Two of the 6 dogs subsequently received IV fluid therapy to correct fluid losses prior to anesthetic induction.

Two dogs in the maropitant group had transient signs of pain on injection. Vocalization, skin twitching, and scratching at the injection site were noticed, and the reactions were considered mild or moderate. Erythematosus skin was noted at the injection site in 1 dog a few minutes after maropitant administration. No oth-
er abnormalities were observed at the site of injection, and the signs of pain and erythema resolved over 3 to 5 minutes without treatment. No dogs in the acepromazine or saline solution control groups had signs of pain or other abnormalities at the injection site.

Most dogs that received electroacupuncture treatment in the 1-acupoint (26/37 [70.3%]), 5-acupoint (32 [86.5%]), and sham-acupoint (19 [51.4%]) groups had mild responses, such as flinching or muscle quivering after the insertion of acupuncture needles, but this subsided within 1 minute.

One dog in the saline solution control group and 1 dog in the sham-acupoint electroacupuncture group defecated and strained to defecate for approximately 1 minute after morphine administration. No other abnormal clinical signs were observed during the study, and no dog was withdrawn from the study.

**Incidence of vomiting and retching**—Incidence of vomiting and retching in dogs during the 20-minute observation period following morphine administration in the 6 groups was summarized (Table 1). Results of the initial analysis indicated that dogs in the maropitant group had a significantly lower incidence of vomiting and retching than did dogs in the saline solution (P = 0.001) and the sham-acupoint (P = 0.003) electroacupuncture groups; the incidence was also lower for dogs in the acepromazine group than for those in the saline solution (P = 0.0009) and sham-acupoint electroacupuncture (P = 0.001) groups. The incidence of vomiting and retching did not differ (P = 0.48) between the maropitant and acepromazine groups, and incidence did not differ in the 1-acupoint and 5-acupoint electroacupuncture groups, compared with dogs in the saline solution and sham-acupoint groups (P > 0.05 for all comparisons). There was also no significant (P = 0.24) difference in the incidence of vomiting and retching between the saline solution and sham-acupoint electroacupuncture groups. After applying the Bonferroni correction for pairwise comparisons, the incidence of vomiting and retching was significantly (P < 0.0033) lower in maropitant-treated dogs than in those that received saline solution or sham-acupoint electroacupuncture treatment and was also significantly lower in dogs that received acepromazine than in those that underwent sham-acupoint electroacupuncture.

**Number and time to cessation of vomiting and retching events**—The total number of vomiting and retching events was significantly (P ≤ 0.001) lower in the maropitant, acepromazine, 1-acupoint electroacupuncture, and 5-acupoint electroacupuncture groups, compared with the saline solution or sham-acupoint electroacupuncture groups in the initial analysis, and these differences remained significant (P < 0.0033) after Bonferroni correction (Table 1). The number of vomiting and retching events in the maropitant group did not differ significantly from that of the acepromazine, 1-acupoint electroacupuncture, or 5-acupoint electroacupuncture groups after morphine administration. The number of events also did not differ significantly between the 1-acupoint and 5-acupoint electroacupuncture groups. Mean time to cessation of vomiting and retching for dogs in the maropitant, acepromazine, 1-acupoint electroacupuncture, and 5-acupoint electroacupuncture groups was significantly (P < 0.001 for all comparisons) shorter than that for dogs in the saline solution or sham-acupoint electroacupuncture groups, and these differences remained significant after Bonferroni correction.

**Signs of nausea**—In the initial analysis, incidence of signs of nausea was significantly lower in acepromazine-treated dogs, compared with dogs that received saline solution (P = 0.018), maropitant (P = 0.009), and sham-acupoint electroacupuncture treatment (P = 0.001). The incidence of signs of nausea was also significantly (P = 0.040) lower in the 1-acupoint than in the sham-acupoint electroacupuncture and 5-acupoint electroacupuncture groups, compared with the maropitant (P = 0.028) and sham-acupoint electroacupuncture (P = 0.004) groups, prior to correction for multiple comparisons. There was no significant difference for this variable between the acepromazine and 1-acupoint (P = 0.170) or 5-acupoint (P = 0.662) groups or between the 1-acupoint and 5-acupoint groups (P = 0.350). After Bonferroni correction, acepromazine-treated dogs had a significantly (P = 0.0033) lower incidence of signs of nausea than did dogs that received sham-acupoint treatment (Table 1).

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**Table 1**—Results for evaluation of vomiting and retching and signs of nausea in 222 dogs (37 dogs/group) that underwent various treatments prior to administration of morphine (0.5 mg/kg [0.23 mg/lb], IM).  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline solution</th>
<th>Maropitant</th>
<th>Acepromazine</th>
<th>1-acupoint</th>
<th>5-acupoint</th>
<th>Sham-acupoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting and retching</td>
<td>88</td>
<td>21*</td>
<td>38*</td>
<td>35*</td>
<td>34*</td>
<td>108</td>
</tr>
<tr>
<td>No. of dogs (incidence)</td>
<td>28 (75.7)</td>
<td>14 (37.8)*</td>
<td>17 (45.9)*</td>
<td>24 (64.8)</td>
<td>26 (70.3)</td>
<td>32 (86.5)</td>
</tr>
<tr>
<td>Time to cessation (min)</td>
<td>1.32 ± 1.41</td>
<td>0.06 ± 0.19*</td>
<td>0.48 ± 1.10*</td>
<td>0.20 ± 0.46*</td>
<td>0.15 ± 0.33*</td>
<td>1.87 ± 2.62</td>
</tr>
<tr>
<td>Signs of nausea</td>
<td>11 (29.7)</td>
<td>12 (32.4)</td>
<td>3 (8.1)*</td>
<td>7 (18.9)</td>
<td>4 (10.8)</td>
<td>15 (40.5)</td>
</tr>
</tbody>
</table>

* Dogs were randomly assigned to receive 1 of 6 treatments: maropitant citrate (1.0 mg/kg [0.45 mg/lb], SC), acepromazine maleate (0.05 mg/kg [0.022 mg/lb], IM), saline solution (0.10 mL/kg [0.05 mL/lb], SC), electroacupuncture at 1 acupoint (pericardium-6), electroacupuncture at 5 acupoints (pericardium-6, stomach-36, gallbladder-34, bladder-20, and bladder-21), or electroacupuncture at a sham acupoint. Time to cessation is expressed as mean ± SD. Values for 1 dog in the acepromazine group were excluded from analysis of nausea-related variables because of technical problems.

* Within a variable, value is significantly (P < 0.0033) different from those for the saline solution and sham-acupoint electroacupuncture groups after Bonferroni correction. **Within a variable, value is significantly (P < 0.0033) different from that for the sham-acupoint electroacupuncture group after Bonferroni correction.
The mean nausea scores for the saline solution, maropitant, and sham-acupoint electroacupuncture groups were increased significantly ($P < 0.05$) at 30 and 35 minutes, compared with time 0 (baseline) and 20 minutes (the time of morphine administration) for the same groups, and these remained significant after Bonferroni correction ($P < 0.0033$; Table 2). In contrast, mean nausea scores for the acepromazine, 1-acupoint electroacupuncture, and 5-acupoint electroacupuncture groups did not differ significantly among any of the 5 evaluated time points. Further analysis of nausea scores revealed that overall pooled mean scores for the saline solution, maropitant, and sham-acupoint electroacupuncture groups at all time points after morphine administration were significantly ($P < 0.0033$) higher than those at time 0 and 20 minutes after Bonferroni correction.

**Discussion**

Opioids (eg, morphine, hydromorphone, and oxymorphone) frequently induce nausea and vomiting in dogs when used as analgesics or premedicants. The present study included 222 dogs of ASA status I or II that were scheduled to undergo routine anesthetic procedures, and each received 1 of 6 treatments (injection of saline solution, maropitant, or acepromazine, or electroacupuncture treatment at 1 acupoint, 5 acupoints, or a sham acupoint) starting 20 minutes prior to administration of morphine (0.5 mg/kg, IM). Twenty-eight of 37 (75.7%) dogs that received saline solution and 32 of 37 (86.5%) dogs that underwent sham-acupoint electroacupuncture treatment vomited or retched after morphine administration, a finding consistent with results of previous studies.6,7,34,55 The primary finding of the present study was that treatment with maropitant (1.0 mg/kg, SC) prior to administration of morphine in dogs resulted in a significantly lower incidence of vomiting and retching, compared with that of dogs that received saline solution or sham-acupoint electroacupuncture treatment.

Groups of dogs treated with maropitant, acepromazine (0.05 mg/kg, IM), or 1-acupoint or 5-acupoint electroacupuncture had significantly fewer total vomiting and retching events, and shorter mean time to cessation of vomiting and retching, than did those that received saline solution or underwent sham-acupoint electroacupuncture. Six dogs treated with saline solu-

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**Table 2—Mean ± SD nausea scores for the 6 treatment groups in Table 1.**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Saline solution</th>
<th>Maropitant</th>
<th>Acepromazine</th>
<th>1-acupoint</th>
<th>5-acupoint</th>
<th>Sham-acupoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.0</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>20</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>30</td>
<td>1.4 ± 0.8*</td>
<td>1.5 ± 0.7*</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>1.6 ± 0.9*</td>
</tr>
<tr>
<td>35</td>
<td>1.3 ± 0.5*</td>
<td>1.4 ± 0.7*</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>1.5 ± 0.8*</td>
</tr>
<tr>
<td>40</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.7</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.5</td>
<td>1.1 ± 0.4</td>
<td>1.4 ± 0.2</td>
</tr>
</tbody>
</table>

The time 0 observation was performed immediately prior to administration of the assigned experimental treatment, and the 20-minute observation was performed immediately after morphine administration. Scoring was performed according to a 1 to 4 scale, where 1 = no signs of nausea and 4 = worst possible nausea.

*Within a treatment group, score is significantly ($P < 0.0033$) higher than for time 0 and time 20 after Bonferroni correction; the value for pooled variables (scores for the saline solution, maropitant, and sham-acupoint electroacupuncture groups combined) at these time points is also significantly different from those at time 0 and time 20 after Bonferroni correction.

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**Table 3—Mean ± SD sedation scores for the 6 treatment groups in Table 1.**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Saline solution</th>
<th>Maropitant</th>
<th>Acepromazine</th>
<th>1-acupoint</th>
<th>5-acupoint</th>
<th>Sham-acupoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.2</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.5</td>
<td>1.2 ± 0.4</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>20</td>
<td>1.4 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>2.3 ± 1.1*</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 0.8</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>30</td>
<td>2.5 ± 0.8</td>
<td>2.8 ± 0.9</td>
<td>3.4 ± 0.8*</td>
<td>2.9 ± 0.9</td>
<td>3.0 ± 1.0</td>
<td>2.0 ± 0.8</td>
</tr>
<tr>
<td>35</td>
<td>3.0 ± 0.8</td>
<td>3.2 ± 0.9</td>
<td>3.8 ± 0.9*</td>
<td>3.4 ± 0.8</td>
<td>3.3 ± 0.1</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>40</td>
<td>3.1 ± 0.8</td>
<td>3.2 ± 1.0</td>
<td>3.9 ± 1.0*</td>
<td>3.5 ± 0.9</td>
<td>3.5 ± 1.1</td>
<td>3.1 ± 1.0</td>
</tr>
</tbody>
</table>

Values for 1 dog in the acepromazine group were excluded from analysis of nausea-related variables because of technical problems. Scoring was performed with a 1 to 5 scale, where 1 = no sedation and 5 = maximum possible sedation.

*Within a time point, the score is significantly ($P < 0.0033$) different from those for the saline solution, maropitant, and sham-acupoint electroacupuncture groups after Bonferroni correction.
Maropitant administration (SC) prior to epidural injection of morphine in a dog appeared to prevent vomiting in 1 clinical report. Results of a recent study also indicated that maropitant administered SC 1 hour prior to hydromorphone administration IM prevented vomiting, retching, and signs of nausea in dogs. In the present study, treatment with maropitant SC 20 minutes before morphine administration did not prevent vomiting and retching in all dogs, although it resulted in a significantly lower incidence of vomiting and retching than in dogs that received saline solution or sham-acupoint electroacupuncture treatment. The choice of opioid may have influenced this result because emetic effects appear to be less common in dogs and humans that receive hydromorphone than in those administered morphine. The incidence of vomiting in dogs has been reported as 7 of 16 to 6 of 9 following IM injection of hydromorphone, compared with vomiting in dogs has been reported as 7 of 16 to 6 of 9 following IM injection of morphine. This may be attributable to the higher lipid solubility of hydromorphone, which increases its ability to cross the blood-brain barrier to reach the emetic center in the brainstem and therefore lessen the emetic effects on the chemoreceptor trigger zone, compared with morphine. Another factor may have resulted in failure of maropitant to prevent vomiting and retching in all dogs after morphine administration; the time of maximum plasma concentration for maropitant at a dose 1 mg/kg, SC, is 0.75 hours, so maropitant given 20 minutes prior to morphine administration may not have reached a concentration sufficient to provide an optimal antiemetic effect. We suggest that administration of maropitant via this route 45 to 60 minutes before IM morphine administration may provide better protection against vomiting and retching than was observed in the present study. Nevertheless, the results of our study, along with several other reports, in which maropitant was shown to effectively treat acute vomiting owing to various etiologies in dogs, indicated that it has antiemetic effects in many of these patients.

Although dogs treated with acepromazine 20 minutes before morphine administration had a significantly lower incidence of vomiting and retching than did dogs that received sham-acupoint electroacupuncture treatment, the incidence of these effects did not differ significantly between dogs that received acepromazine and those that received saline solution. In a previous study, dogs administered acepromazine IM 15 minutes before opioid (morphine, hydromorphone, or oxymorphone) injection had a lower incidence of vomiting (7/40 [18%]), compared with dogs that received acepromazine and the opioid concurrently (17/38 [45%]) and those that received the opioid prior to acepromazine (21/38 [55%]). The proportion of acepromazine-treated dogs that vomited or retched in the present study after morphine administration (17/37 [45.9%]) was higher than that of dogs that received the same 0.05 mg/kg dose of acepromazine (2/8) in the study by Valverde et al. These differences may be related to sample size.

Acupuncture has been used to treat a wide variety of gastrointestinal problems, including acute and chronic gastroenteritis, diarrhea, constipation, nausea, vomiting, irritable bowel syndrome, and visceral pain in humans; however, some studies have yielded mixed results regarding the efficacy of this treatment. According to the traditional Chinese medicine system, pericardium-6 is the most important acupuncture point for the treatment of nausea and vomiting in humans and animals. Acupuncture, aquapuncture, or moxibustion at other acupoints, such as bladder-10, bladder-11, bladder-20, bladder-21, stomach-36, gallbladder-34, liver-13, and conception vessel-12, has also been described as having antiemetic effects. However, these points have not been studied to the same extent as pericardium-6. A systematic review concluded that, in humans, pericardium-6 stimulation resulted in less postoperative nausea and vomiting and reduced the need for rescue treatment with antiemetics, compared with sham treatment, although it was less effective than or equally effective as antiemetic medications. In the present study, we investigated the application of electroacupuncture at the pericardium-6 acupoint alone and in a combination of 5 acupoints (pericardium-6, bladder-20, bladder-21, stomach-36, and gallbladder-34) for the prevention morphine-induced emetic effects in dogs. Although the incidence of vomiting and retching in dogs that received these treatments did not differ from that in dogs that received saline solution or sham-acupoint electroacupuncture treatment, the total number of vomiting and retching events in the 1-acupoint and 5-acupoint treatment groups was significantly lower than that in the saline solution and sham-acupoint electroacupuncture groups, consistent with previous studies in dogs and ferrets. The number of vomiting and retching events following morphine administration in dogs of the 1-acupoint (pericardium-6) electroacupuncture group was > 50% less than that for dogs in the saline solution and sham-acupoint electroacupuncture groups. Furthermore, the number of vomiting and retching events did not differ between the 1-acupoint and 5-acupoint treatment groups under the same electrical stimulation settings. It is reasonable to assume that inclusion of the acupoints stomach-36, gallbladder-34, bladder-20, and bladder-21 in electroacupuncture treatment did not have any specific antiemetic effect in these dogs. Further investigation would be necessary to determine whether a combination of acupoints could have antiemetic effects under different circumstances, such as in patients with vomiting caused by chemotherapeutic agents or paroviral enteritis.

Pharmacological studies often include the use of groups that receive a placebo or control treatment. However, controls for procedural interventions, such as surgery and acupuncture, are especially difficult to develop. Various sham techniques for acupuncture and electroacupuncture studies have been developed. These include the use of noninvasive or nonpenetrating needling at the same...
acupoints under investigation to evaluate the effects of needle stimulation of acupoints, the use of nonacupoints without stimulation to investigate the effects of acupoints and of electrical stimulation, and applying the same stimulation used for acupoints at nonacupoints or at different acupoints to investigate acupoint-specific effects. However, in the present study, needle insertion at a nonacupoint for electroacupuncture was used to assess the effects of needling and electrical stimulation not specific to the selected acupoints. The total number of vomiting and retching in dogs that underwent sham-acupoint electroacupuncture did not differ significantly from that of dogs that received saline solution in this study. These data are consistent with the results of previous studies. There has been much debate regarding the use of a penetrating versus nonpenetrating needling technique for sham electroacupuncture treatment. It has been shown that procedures that include needle insertion can elicit neurobiological responses at various levels in the CNS, including the brainstem, thalamus, left cerebellum, and the anterior cingulate cortex. However, our data indicate that needle penetration at the sham acupoint used in this study along with electrical stimulation did not have antiemetic activity. We believe that this sham acupoint, located 3 cm proximal to the medial malleolus of the tibia on the caudomedial aspect of the pelvic limb, could reasonably serve as a sham control in acupuncture trials in dogs and may potentially be useful in other species.

Nausea and retching typically precede vomiting. It is generally assumed that nausea is a prodromal sign of vomiting and may or may not lead to vomiting. Nausea may be induced by several mechanisms, including direct stimulation of the chemoreceptor trigger zone or the emetic center, reduced gastrointestinal motility, or enhanced vestibular sensitivity. Signs of nausea in animals may include signs of depression, salivation, licking of lips, and increased swallowing frequency. Nausea is a highly subjective experience, and its clinical signs can be easily overlooked in veterinary practice. In humans, nausea has been ranked the fourth least desirable adverse effect of anesthesia, despite the availability of effective antiemetics (the 3 least desirable adverse effects, in order, were vomiting, gagging on the tracheal tube, and incisional pain). This suggests that the possible impact of nausea on veterinary patients may warrant more attention than it may have received previously and that better strategies for assessing and preventing nausea in animals are needed.

In the present study, the incidence of signs of nausea following morphine administration was lower in dogs that received acepromazine than in those that had sham-acupoint electroacupuncture treatment, and the severity of these signs did not increase from the baseline value in the acepromazine, 1-acupoint electroacupuncture, or 5-acupoint electroacupuncture groups following morphine administration. However, nausea severity scores were increased 10 and 15 minutes after morphine administration in dogs that received maropitant, saline solution, or sham-acupoint electroacupuncture treatment. Rau et al. found the incidence or severity of signs suggestive of nausea was not significantly lower in dogs that received maropitant treatment as prophylaxis against delayed vomiting associated with doxorubicin treatment, compared with results for dogs that received a placebo. However, results of a more recent study indicated that dogs receiving maropitant had significantly fewer signs of nausea following hydromorphone administration, compared with dogs that received saline solution. One possible explanation of differences among these studies is that severity of emetic effects may vary among different emetogenic agents. Hydromorphone may have a weaker emetic effect in dogs, compared with doxorubicin and morphine, which is more readily controlled with maropitant. The timing of maropitant administration in relation to the administration of the emetogenic agent may also impact the prevention of signs of nausea. In the study by Rau et al., maropitant was given after doxorubicin administration and no prophylactic effect against nausea signs was reported, whereas dogs that received maropitant 1 hour before hydromorphone treatment in the study by Hay Kraus developed no signs of nausea. Additionally, the use of different formulations and dosages of maropitant in the 2 studies may also have influenced these results. An oral formulation of maropitant at a dosage of 2 mg/kg every 24 hours was given in the study by Rau et al. to prevent nausea and vomiting related to doxorubicin treatment; this formulation and dose of maropitant result in a slower onset of antiemetic activity, longer time to reach maximum plasma concentration (1.9 hours), and shorter half-life (4.03 hours), compared with the maropitant treatment used for the prevention of hydromorphone-induced nausea and vomiting in the study by Hay Kraus (1 mg/kg, SC; time to maximum plasma concentration, 0.75 hours; half-life, 7.75 hours). Another possible explanation is that nausea remains difficult to evaluate in dogs. To our knowledge, no review to date has comprehensively assessed available nausea scales for veterinary patients in terms of reliability, validity, and usefulness as clinical assessment tools. The scale used to evaluate signs of nausea in the present study has not been validated for dogs and may lack specificity in the presence of sedation. The lack of severe signs of nausea following morphine administration in dogs that received acepromazine in the present study may have been associated with sedative effects, although sedation did not likely influence these results for dogs that underwent electroacupuncture. Future investigation should include development of objective tools for nausea assessment on the basis of behavior and physiologic measures in a manner similar to that used for acute pain scoring systems for dogs.

References


Appendix 1

Assessment scale used to evaluate signs of nausea\textsuperscript{14,15,50} in 222 dogs that received morphine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip licking and swallowing</td>
<td>None</td>
</tr>
<tr>
<td>Salivation</td>
<td>None</td>
</tr>
<tr>
<td>Attitude, mentation, and posture</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Appendix 2

Assessment scale used to evaluate signs of sedation\textsuperscript{51,52} in 222 dogs that received morphine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitude, mentation, and posture</td>
<td>Alert, playful, or spontaneously inquisitive; with or without tail wagging</td>
</tr>
<tr>
<td>Response to noise</td>
<td>Normal startle reaction (dog turns toward noise or dog cringes)</td>
</tr>
</tbody>
</table>

Noise was generated by a hand clap.