Current data addressing the use of NK-1 receptor antagonists to manage nociception or pain are controversial. Human clinical trials have failed, and results of animal studies are ambiguous. However, a more consistent response has been observed when testing NK-1 receptor antagonists in experimental studies of visceral pain. Neurokinin 1 receptor antagonists decrease the behavioral response during noxious stimulation of the bladder in mice and guinea pigs. In rabbits, NK-1 receptor antagonists decrease the response to colorectal stimulation. An analgesic response has been observed as well in mice and guinea pigs with colonic hypersensitivity. Response to the formalin or capsaicin tests, which are considered a continuous combination of somatic and visceral noxious stimuli, is attenuated with the use of NK-1 receptor antagonist drugs. Thus, the published information raises the question of whether NK-1 receptor antagonists can be effective to treat specific types of noxious stimuli, such as visceral pain.

A good example of the specificity of treatment for pain is the effect of common analgesic drugs such as gabapentin and opioids. Gabapentin prevents and decreases neuropathic pain, but is not effective for acute pain. Opioid drugs commonly used for analgesia can cause paradoxical hyperalgesia in some people. Thus, the current recommendation is to provide treatment for pain according to individual needs, pain source, pain mechanisms, and drug properties.

Neurokinin 1 receptor and its agonist substance P have been reported in pain pathways at the level of the CNS and peripheral nervous system. Nerve terminals including sensory afferents contain both NK-1 receptors and substance P. The dorsal root ganglia and spinal cord dorsal horn contain large amounts of NK-1 receptors and substance P vesicles. Spinal cord–ascending projections to the brainstem and brain areas contain multiple neuropeptides, including substance P. Finally, higher brain structures important in pain perception contain NK-1 receptors. In the nervous system, Mantyh et al reported the presence of NK-1 receptors in visceral tissues such as the bladder, esophagus, and colon.

The purpose of the study reported here was to evaluate the anesthetic-sparing effect of an NK-1 receptor antagonist (maropitant) newly approved for its antiemetic properties in dogs. The hypothesis was that NK-1 receptors may play a role during visceral pain neurotransmission.
Materials and Methods

The study was performed in accordance with the Guide for the Care and Use of Laboratory Animals. The study was approved by Colorado State University Animal Care and Use Committee and by The Morris Animal Foundation.

Eight 1-year-old female hound dogs with a mean ± SD weight of 25.1 ± 4.2 kg were used. The dogs were anesthetized via a mask with 3% sevoflurane in oxygen at 5 L/min. When general anesthesia was achieved, oro-tracheal intubation was performed and anesthesia was administered via the endotracheal tube with sevoflurane at a vaporizer setting of 2% and O₂ flow at 2 L/min. End-tidal sevoflurane, O₂, and CO₂ concentrations were continuously monitored. The end-tidal agent analyzer was calibrated at the beginning of every anesthetic event by use of 3 known sevoflurane concentrations (1.5%, 2.5%, and 3.5%). Inspired O₂ was maintained at > 90%, and expired CO₂ was maintained at 30% to 40% by use of intermittent positive pressure ventilation. Cephalic venous and dorsopedal artery catheters were placed for fluid administration and direct arterial blood pressure monitoring, respectively. The dogs were positioned in dorsal recumbency.

Animals were monitored by use of ECG, direct blood pressure measurement, and esophageal temperature measurement. Respiratory rate and inspired O₂, end-tidal CO₂, and end-tidal sevoflurane concentrations were monitored with the end-tidal agent analyzer as described. The dogs received an isotonic crystalloid solution (5 mL/kg/h, IV), and esophageal temperature was maintained between 37.5° and 39°C. At the end of each study, laparoscopic ovariectomy was performed and dogs were allowed to recover from anesthesia. For postoperative pain management, the dogs received ketoprofen (1 mg/kg, SC) and hydromorphone (0.1 mg/kg, SC) at the time of recovery from anesthesia. At the end of the study, the dogs received a single dose of cepalexin (22 mg/kg, IV) to prevent infection. All dogs recovered without complications and returned to normal behavior (eg, eating, drinking, walking, and playing) the same day.

Laparoscopic surgery—A standard laparoscopic surgery for ovariectomy was performed via access to the abdominal cavity with three 5-mm canulaus along the ventral midline (linea alba). The abdomen was insufflated with CO₂ to reach an intra-abdominal pressure of 6 to 10 mm Hg. The right ovary was identified and fas- ted with 2-0 suture by passing the suture through the abdominal wall. The abdomen was deflated, and the abdomen was closed with a subcutaneous continuous suture with 3-0 Vicryl (Ethicon) and was held in place with surgical tape.

MAC determination—The sevoflurane vaporizer was set at 2% for 30 minutes, and 1 sham ovary stimulation was performed. Following 30 minutes of anesthesia with a steady-state end-tidal sevoflurane concentration, the ovary was stimulated by use of a calibrated force displacement transducer with a pressure range of 0.05 to 2 kg/mm and maximum load of 10 kg. The force used was 6.61 N, and the MAC was determined in triplicate. The response was considered positive when the dog made a purposeful movement or negative when no purposeful movement was observed during 1 minute of ovary stimulation. The sevoflurane end-tidal concentration was increased if the response was positive or decreased if the response was negative by 10% for the next stimulus. Fifteen minutes were allowed between stimuli for anesthetic concentration equilibration. The MAC was determined before administration of maropitant and after 2 doses of maropitant. The MAC values were corrected by use of the calibration values and adjusted to sea level by use of barometric pressure.

Maropitant administration—Following determination of the sevoflurane control MAC, the dogs received a loading dose of maropitant (1 mg/kg, IV, over 10 minutes). At the end of the loading dose, a continuous rate infusion of maropitant (30 μg/kg/h, IV) was started to maintain a plasma concentration of approximately 90 ng/mL during the MAC-determination period. The ovary stimulations to determine MAC were started 10 minutes after the continuous infusion was started. The dose and plasma concentrations recommended for maropitant to have antiemetic properties in veterinary medicine are 1 mg/kg and 90 ng/mL, respectively. Although it constituted extralabel administration, we administered the maropitant IV followed by a continuous rate infusion to minimize variability of absorption and distribution.

Following the MAC determination for the dose of 1 mg/kg, a higher dose was used to determine MAC again. For this, the loading dose used was 5 mg/kg, IV, over 10 minutes, followed by 150 μg/kg/h, IV. The ovary stimulations to determine MAC were started 10 minutes after the continuous rate infusion was started. Three MAC determinations were again determined.

Blood samples were obtained from the arterial catheter to measure plasma maropitant concentrations. Two samples were obtained for each infusion rate: 1 sample when the dogs had a positive MAC response and 1 sample when the dogs had a negative MAC response. Because of financial constraints, plasma maropitant concentrations were measured in only 4 dogs. Maropitant in plasma was quantified by preparing maropitant and trazodone standard solutions in a mixture of acetonitrile and water (50:50). Maropitant was extracted from plasma by adding 100 μL of 0.1N sodium hydroxide and 1,000 μL of methyl tert-butyl ether to 100 μL of sample plasma, vortexing for 10 minutes, and centrifuging at 18,000 × g for 10 minutes. Then, 750 μL of the organic (top) phase was vaporized by use of a concentrator system under low heat for 1 hour and subsequently resuspended in 500 μL of a mixture (50:50) of 10 mM ammonium formate (pH, 3.0) and 0.1% formic acid in acetonitrile. An aliquot of 10 μL was injected into the high-performance liquid chromatography and mass spectrometer system for analysis.

Statistical analysis—Values are reported as mean ± SD. A box-and-whisker plot graph was used to compare the effect of maropitant on MAC determinations. The plasma maropitant concentrations were compared. Statistical analysis was performed with a 2-tailed paired
Physiologic variables were summarized (Table 1). Stimulation of the right ovary and ovarian ligament with 6.61 N elicited a control sevoflurane MAC of 2.12 ± 0.4%. Administration of a low dose of maropitant (1 mg/kg followed by 30 µg/kg/h, IV) decreased the sevoflurane MAC to 1.61 ± 0.4% (P = 0.01), which represented a 24% decrease in the anesthetic requirements, compared with the control treatment.

The high dose of maropitant (5 mg/kg followed by 150 µg/kg/h, IV) decreased the sevoflurane MAC to 1.48 ± 0.4%, which was significantly (P = 0.01) different from control but not from the low-dose group. The high maropitant dose has an anesthetic-sparing effect of 30%, compared with the control treatment.

The dogs recovered without complications. None of the dogs required further postoperative analgesia, and normal behavior such as eating, drinking, walking, and playing returned within 2 to 4 hours after recovery from anesthesia. All dogs were adopted out to homes in the local community.

The low dose of maropitant maintained a plasma concentration of 112 ± 52 ng/mL, which was not significantly different from the targeted concentration of 90 ng/mL. The high dose of maropitant as expected maintained the plasma concentration approximately 5 to 6 times that of the low dose (676 ± 181 ng/mL). Times when the samples were obtained ranged between 30 and 80 minutes after the start of the respective continuous rate infusion dose. Each infusion was maintained for <120 minutes to allow the MAC determinations.

Administration of maropitant IV at both doses induced short-lasting hypotension, decreasing the blood pressure 10 to 20 mm Hg. Blood pressure returned to values similar to baseline values between 5 and 10 minutes after maropitant administration. No significant changes in blood pressure were observed during continuous maropitant administration. No respiratory, cardiovascular, temperature, PCV, or total protein concentration differences were observed during MAC determinations (Table 1).

### Discussion

The present study revealed for the first time that an NK-1 receptor antagonist could be used to decrease anesthetic requirements during noxious visceral stimulation. The NK-1 receptor antagonist decreased the response to noxious stimulation from the ovary. The difference between somatic and visceral analgesia has been addressed. Furthermore, the role of NK-1 receptor antagonists on visceral nociception has been reported.

The principal for MAC determination is the mean anesthetic concentration required to cause immobility in 50% of the subjects exposed to a supramaximal painful or noxious stimulus. Thus, the best method to assess analgesia is not considered anesthesia MAC, but rather the anesthetic requirement to prevent the response to a painful or noxious challenge. However, all potent and common analgesics used decrease the anesthetic MAC requirements in dogs and humans. Thus, MAC determination can be used to test the response to different drugs during a painful or noxious stimulus. If a particular drug reduces the MAC, further studies are required to determine the true analgesic effect of the drug in awake subjects. The advantages of MAC determination during pain assessment are that it provides a controlled environment and decreases variability; subjects are anesthetized, preventing the emotional response to pain; and it is a well-accepted method with clinical applicability.

The number of analgesics proven to manage visceral nociception in veterinary medicine is limited. Current analgesic drugs such as opioids and NSAIDs can have detrimental properties. Opioids can cause constipation, urinary retention, sedation, and dysphoria, whereas NSAIDs can trigger gastrointestinal tract ulcers or renal damage. The new NK-1 receptor antagonist maropitant was developed for its antiemetic properties in dogs. So far, since February 2007, maropitant has been used clinically in dogs with no major adverse effects reported, to our knowledge. Thus, this NK-1 receptor antagonist has the potential to become a visceral analgesic drug with few collateral effects.

The use of noxious stimulation of the ovary to induce visceral pain has been validated, and the technique appears to be consistent and repeatable. Neither desensitization nor hyperalgesia has been observed. In addition, the technique is comparable with skin incision, tail or toe clamp, and electrical stimulation used in standard MAC studies performed in dogs.

Maropitant significantly decreased the MAC for sevoflurane during noxious stimulation of the ovary in dogs, which suggests a potential role for NK-1 receptor antagonists to manage ovarian pain. Further studies on the use of NK-1 receptor antagonist drugs for visceral pain are needed.

### Table 1—Physiologic variables (mean ± SD) measured during sevoflurane MAC determination before (ie, baseline) and after maropitant administration in 8 female dogs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR (breath/min)</th>
<th>PtcO₂ (mm Hg)</th>
<th>HR (beats/min)</th>
<th>SAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>DAP (mm Hg)</th>
<th>Temp (°C)</th>
<th>PCV (%)</th>
<th>TP (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11 ± 4</td>
<td>31 ± 3</td>
<td>111 ± 17</td>
<td>127 ± 16</td>
<td>90 ± 16</td>
<td>71 ± 17</td>
<td>38.2 ± 0.7</td>
<td>42 ± 3</td>
<td>5.1 ± 0.2</td>
</tr>
<tr>
<td>Maropitant (1 mg/kg; 30 µg/kg/h)</td>
<td>9 ± 4</td>
<td>29 ± 3</td>
<td>99 ± 14</td>
<td>119 ± 13</td>
<td>60 ± 12</td>
<td>60 ± 13</td>
<td>35.0 ± 0.2</td>
<td>35 ± 1.7</td>
<td>5 ± 0.2</td>
</tr>
<tr>
<td>Maropitant (5 mg/kg; 150 µg/kg/h)</td>
<td>8 ± 2</td>
<td>30 ± 2</td>
<td>81 ± 10</td>
<td>125 ± 15</td>
<td>62 ± 12</td>
<td>62 ± 13</td>
<td>38.6 ± 0.1</td>
<td>39 ± 3</td>
<td>4.9 ± 0.2</td>
</tr>
</tbody>
</table>

DAP = Diastolic arterial pressure, PtcO₂ = Partial pressure of end-tidal CO₂, HR = Heart rate, MAP = Mean arterial pressure, RR = Respiratory rate, SAP = Systolic arterial pressure, Temp = Esophageal temperature, TP = Total protein concentration.

References:

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References