Efficacy of maropitant for treatment and prevention of emesis caused by intravenous infusion of cisplatin in dogs

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Objective—To evaluate the efficacy of maropitant, a novel neurokinin-1 receptor antagonist, to treat and prevent emesis caused by IV infusion of a chemotherapeutic dose of cisplatin (70 mg/m²) in dogs.

Animals—64 healthy 6-month-old Beagles (32 males and 32 females).

Procedures—To evaluate the effect of maropitant on ongoing emesis, 24 dogs were randomized to 2 treatment groups (12 dogs each). Saline (0.9% NaCl) solution or maropitant (1 mg/kg) was administered once by SC injection immediately following the first emetic event after cisplatin infusion. Dogs were assessed for emesis for 6 hours after initiation of cisplatin infusion. To evaluate the use of maropitant for the prevention of emesis, 40 dogs were randomized to 4 treatment groups (10 dogs each). Placebo or maropitant (1, 2, or 3 mg/kg) was administered PO as a tablet. Cisplatin infusion was initiated at 19 hours after treatment, and dogs were assessed for emesis for 6 hours.

Results—No treatment-related adverse events were observed in either study. For the treatment of ongoing emesis, significantly fewer emetic events were observed for maropitant-treated dogs, compared with placebo-treated dogs (mean, 5.2 vs 15.8), and the mean time to cessation of emesis was significantly shorter (0.65 vs 1.65 hours). In the prevention of emesis, maropitant-treated dogs had significantly fewer emetic events (means, 2.7, 1.1, and 0.5 for maropitant at 1, 2, and 3 mg/kg, respectively), compared with placebo-treated dogs (mean, 20.3).

Conclusions and Clinical Relevance—Results suggest that maropitant is safe and effective in the treatment and prevention of cisplatin-induced emesis in dogs. (Am J Vet Res 2007;68:48-56)

For those mammals, including dogs, cats, and humans, that have the response, emesis has evolved primarily as a protective reflex that removes noxious substances from the stomach. Emesis is also found in a wide range of clinical disease processes.1-3 Persistent and severe emesis leads to dehydration and acid-base and electrolyte disturbances and can be life-threatening.4 Treatment of emesis reduces distress and prevents potentially life-threatening complications, while a thorough investigation is undertaken to identify and, where possible, treat the underlying cause. Furthermore in dogs, care needs to be taken to distinguish true emesis from pharyngeal retching or regurgitation, the latter being a physiologically normal mechanism used by adults to feed puppies.

Emesis is thought to be regulated by a series of nuclei located in the brainstem, within the reticular formation of the medulla oblongata and including the NTS, collectively referred to as the emetic center.1-6 The emetic center receives inputs via a number of afferent pathways from the cerebral cortex, vestibular apparatus, and CTZ located in the area postrema7 as well as vagal or sympathetic afferents from peripheral sensory receptors in the stomach, intestinal tract, other abdominal organs (eg, uterus, bladder, and kidneys), and peritoneum1,4,6,8 Within the emetic center, key neurotransmitter receptors include 5-HT3 (serotonin), a2-adrenergic (norepinephrine), and NK1 (sensitive to substance P) receptors.5,9,12 Other neurotransmitter receptors found in those regions of the brain involved with the emetic response include D2 (dopaminergic), H1 and H3 (histaminergic), 5-HT1A (serotoninergic), µ- and δ-opioid (endorphin), and M1 and M2 (cholinergic) receptors.2,12,13 Activation of the emetic center leads, via efferent pathways, to a collection of clinical signs recognizable as nausea and ultimately results in the forcible expulsion of gastric contents.3,13 Key neurotransmitter receptors thought to play an important role in the final part of the efferent pathway to the gastrointestinal musculature include 5-HT4, M2, and dopaminergic receptors.2,12,13 Convergence of the stimulant pathways through the emetic center means that abolition of activity at this level has the potential to prevent emesis, whether generated peripherally or centrally.14 This concept has been confirmed

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>NTS</td>
<td>Nucleus tractus solitarius</td>
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<tr>
<td>CTZ</td>
<td>Chemoreceptor trigger zone</td>
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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
<tr>
<td>NK1</td>
<td>Neurokinin-1</td>
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<tr>
<td>BSA</td>
<td>Body surface area</td>
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<tr>
<td>VAS</td>
<td>Visual analogue score</td>
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<tr>
<td>BBB</td>
<td>Blood-brain-barrier</td>
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in studies\textsuperscript{11,14-17} in which NK1 receptor antagonists binding to NK1 receptors within the NTS provided broad-spectrum antiemetic activity.

In numerous studies mostly investigating the role of NK1 receptor antagonists as antiemetics for humans, cisplatin has been shown to be a reliable emetic in experiments with ferrets,\textsuperscript{7,18-28} dogs,\textsuperscript{18,26,27,29-33} cats,\textsuperscript{26,34} and house-musk shrews (Suncus murinus).\textsuperscript{28,35,36} Cisplatin principally acts on enterochromaffin cells in the gastric mucosa, stimulating vagal and sympathetic afferent nerves via serotonin (5-HT\textsubscript{3}) receptors,\textsuperscript{9,15} but in cats, cisplatin also acts on the CTZ.\textsuperscript{37} Neurokinin-1 receptor antagonists have previously been found to be effective in animals in preventing emesis induced by a range of emetics, including cisplatin, copper sulphate, apomorphine, and syrup of ipecac (ipecacuanha), or following stimulation of the vestibular apparatus in motion sickness.\textsuperscript{11,13,22,38-39} Because these experiments included emetics acting peripherally via the vagal afferent pathway to the NTS, centrally via the CTZ, or by both routes, it is clear that NK1 receptor antagonists have the potential to be clinically efficacious against emesis induced by a wide range of stimuli. Several NK1 receptor antagonists with similar molecular structures have been characterized, such as CP-96,345, CP-99,994, CP-122,721, GR205171, and GR203040.\textsuperscript{10,15,16,19,28,39-42} and some have been developed for use in humans, including aprepitant and ezlopitant.\textsuperscript{43,44}

Maropitant,\textsuperscript{a} (25,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine monohydrate, is a novel NK1 receptor antagonist with potential for use as a general antiemetic in dogs and may be able to inhibit the emesis associated with the use of cisplatin for chemotherapy. This compound is the product of a specific clinical development program of several years’ duration in the search for an improved antiemetic for dogs. The success of NK1 receptor antagonists in humans, particularly for the treatment of emesis associated with chemotherapy\textsuperscript{43,49} suggests that this class of compound might be appropriate for use in dogs.\textsuperscript{50}

In the study reported here, we describe the results of 2 investigations in which maropitant was administered to dogs via either the SC or PO route and compared with placebo. The objective was to determine the efficacy of maropitant in the treatment and prevention of cisplatin-induced emesis in dogs.

\textbf{Materials and Methods}

\textbf{Study approval and design—}This study was conducted following ethical review in accordance with national legislation and animal welfare guidelines for international standards of good clinical practice.\textsuperscript{97} Standard operating procedures relating to maintenance of animal welfare were in place at the site prior to study commencement, and the personnel were specifically trained to ensure the highest standards of animal husbandry.

Split-plot designs were used with 1-way treatment structures and either 2 or 4 treatments. Each treatment contained equal numbers of male and female dogs. Each dog was the experimental unit. Dogs were randomized to treatment within sex to blocks of 4 dogs and to individual pens. Each block contained either 2 (treatment study) or 1 (prevention study) same-sex dogs from each treatment. As a result of practical considerations, dogs in each block received an infusion of cisplatin at the same time, but at different times than dogs in other blocks.

\textbf{Treatments—}Maropitant (as maropitant citrate)\textsuperscript{a} was administered either in the commercial injectable formulation (active moiety, 10 mg/mL; 1 mg/kg, SC) or as prototype commercial tablets (active moiety, 10 mg/tablet; 1, 2, or 3 mg/kg, PO). Exact doses were achieved by shaving tablets as required. Dogs that served as negative controls received either physiologically normal saline (0.9\% NaCl) solution or placebo tablets containing the same excipients as the test article but without the active moiety. Saline solution was administered by SC injection at a volume equivalent to that of the maropitant formulation. All SC injections were made at a single site at the back of the neck.

Cisplatin was administered as an IV infusion to provide a total dose of 70 mg/m\textsuperscript{2} of BSA.\textsuperscript{48} The BSA was calculated by use of the following formula\textsuperscript{49}:

\[ \text{BSA} (\text{m}^2) = (10.1 \times \text{W}^{0.75}) \times 10^{-4} \]

where W is body weight in grams. The appropriate volume of cisplatin\textsuperscript{43} (1.0 mg/mL) was diluted in physiologically normal saline solution to provide a standard volume of 40 mL and administered at 2.0 mL/min with an automatic syringe-driver for approximately 20 minutes. Infusions were administered via an IV catheter placed in a cephalic vein and flushed with 5 mL of saline solution before and after administration of cisplatin to ensure patency and avoid residual cisplatin remaining in the catheter prior to catheter removal. A separate dispensing team administered treatments, and personnel responsible for making clinical assessments were masked to treatment allocation throughout the studies.

\textbf{Animals—}Dogs used in the 2 studies were Beagles,\textsuperscript{c} aged ≥ 6 months and weighing between 6.8 and 11.0 kg on the day of or day before treatment administration. Each dog was uniquely identified and had been routinely immunized against common infectious diseases (canine parvovirus disease, canine distemper, infectious canine hepatitis, leptospirosis, canine infectious tracheobronchitis caused by Bordetella bronchiseptica, and upper respiratory tract disease caused by parainfluenza virus 3) ≥ 1 month prior to the day of treatment, and anthelmintics were administered ≥ 14 days prior to treatment. No other medication was administered within the 2 weeks prior to the studies. On arrival at the site, all dogs were acclimatized to the surroundings for ≥ 7 days. Dogs were individually penned, fed once daily with an appropriate quantity of commercial pelleted diet,\textsuperscript{4} and provided water ad libitum (except during the cisplatin infusion). Room temperature and ventilation were automatically controlled. During the acclimatization period, all dogs were introduced to the observation pens to ensure familiarity with their surroundings. During the study, dogs were moved to the 4 individual observation pens in blocks of 4 same-sex dogs to avoid any behavioral alterations. To ensure that a replacement dog of the same sex was available in the event of a dog being withdrawn from a study, a larger
pool of dogs was acclimatized from which suitable dogs were randomly selected within sex for participation in the studies. Prior to enrollment, a veterinarian examined each dog to ensure that it was in good general health. During the studies, any dog could be withdrawn on welfare grounds at the discretion of the examining veterinarian. At completion, immediately following the final clinical observation in each study, all dogs were euthanatized by lethal injection of sodium pentobarbital and disposed of by incineration.

**Treatment of ongoing emesis study**—Twenty-four dogs were randomly allocated to 2 treatment groups of 12 dogs each. Groups were balanced for sex, and dogs received a single SC injection of either saline solution or maropitant (1 mg/kg). Dogs in each block of 4 (2 dogs/treatment) received IV infusions of cisplatin. Immediately following completion of the infusion, dogs were transferred to the observation pens and observed for emesis with the number of discrete emetic events being counted from 1 hour after initiation of the infusion until 6 hours after infusion. For each dog, treatment was administered (saline solution or maropitant) immediately following the first observed emetic event. Signs of nausea were assessed by use of a VAS and recorded every 20 minutes during the same period. In addition, clinical examinations were made by a veterinarian 30 minutes prior to cisplatin infusion and repeated at 20 minutes and 2, 8, and 24 hours after maropitant treatment.

**Prevention of emesis study**—Forty dogs were randomly allocated to 4 treatment groups of 10 dogs each. Groups were balanced for sex, and dogs received a single administration of tablets containing either placebo or maropitant (at 1, 2, or 3 mg/kg). Treatments were administered at time 0. Dogs were fed approximately 4 hours after treatment, and any food remaining 2 hours later was removed. A veterinarian made clinical examinations 20 minutes before and 20 minutes and 3 hours after maropitant treatment. Dogs in each block of 4 (1 dog/treatment) received IV infusions of cisplatin, commencing at 19 hours after maropitant treatment. Immediately following completion of the infusion, dogs were transferred to observation pens and observed for signs of emesis from 19.5 to 25 hours after maropitant treatment. Visual analogue scores for nausea were recorded for each dog every 15 minutes from 19.5 to 24.75 hours after maropitant treatment. In addition, clinical examinations were made by a veterinarian at 30 minutes prior to cisplatin infusion (18.5 hours after maropitant treatment) and repeated at 25 hours after maropitant treatment.

**Assessment of emetic events and VAS for nausea**—Each of the 4 observation pens was positioned so that all 4 could be observed at the same time. In each study, 1 trained technician counted emetic events and another assessed nausea by a VAS. To maintain consistency, the same technician was responsible for observing and recording either the emetic events or nausea VASs throughout each study. Technicians were masked to treatment allocation throughout each study. An emetic event was defined as emesis or retching as a single occurrence or a sequence of occurrences in close succession. Each discrete emetic event was recorded. Signs interpreted as representing nausea included salivation, increased frequency of or exaggerated swallowing motions, licking of the lips, lethargy and signs of depression, and restlessness. Each score for clinical signs of nausea was made by an observer placing a pen mark on a 100-mm line. A separate sheet of paper was used for each record. The more severe the signs of nausea, the further the mark was placed towards the right hand end of the line. Subsequently, the distance to the right was measured and scored in millimetres (such that the higher the score in mm the more severe the clinical signs of nausea). This method of assessing nausea was developed in-house and validated in preliminary studies.

**Data analysis**—Data were entered into a computerized statistical program for analysis. The number of emetic events recorded after each treatment was analyzed by use of a mixed linear model for repeated measures. Prior to analysis, data were subjected to a square root transformation to better meet assumptions of normality and equal variances. Time to cessation of emesis was calculated for each dog, summarized for each treatment, log transformed, and analyzed by use of a mixed linear model. Nausea VAS were summarized and analyzed with a mixed linear model with repeated measures. A priori contrasts among estimates of least squares means were used to assess treatment differences. The optimum oral dose of maropitant for prevention and treatment of emesis was determined from the prevention study. The optimum dose was assessed by calculating the significance of any difference between the mean number of emetic events that occurred at each dose and the mean for the next higher dose rate. The optimum dose was that which resulted in significantly fewer emetic events than the next lower dose but which did not result in a significantly different number of events, compared with a higher dose. All treatment differences were assessed at the 2-sided 5% level of significance (P ≤ 0.05).

**Results**

**Clinical safety**—No abnormal clinical observations related to the administration of treatment were recorded for any of the dogs in either study. In the treatment of ongoing emesis study, 1 saline solution–treated dog was observed to pass a small quantity of watery feces 7 hours after treatment but was clinically normal at the subsequent observation. At 6 hours after cisplatin infusion in the prevention of emesis study, 3 dogs (2 treated with placebo and 1 treated with maropitant at 1 mg/kg) had a degree of lethargy associated with the cisplatin-induced emesis. Apart from emesis and signs of nausea, no other abnormal clinical observations were reported during the studies and no dog was withdrawn from either study for any reason.

**Treatment of ongoing emesis**—When treatment was administered after the first emetic event following cisplatin infusion, the mean number of emetic events observed in dogs treated with placebo (3.2; range, 3 to 10) was significantly (P < 0.001) lower than for dogs receiving saline solution (15.8; range, 6 to 31; Table 1). Analysis of the least squares mean number

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**Table 1**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Mean Emetic Events</th>
<th>Range</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>15.8</td>
<td>6-31</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>4-18</td>
<td>P ≤ 0.05</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>3-12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5.2</td>
<td>1-9</td>
<td></td>
</tr>
</tbody>
</table>

Note: Differences were assessed at the 2-sided 5% level of significance (P ≤ 0.05).
of emetic events occurring in sequential 30-minute periods, commencing 1 minute after treatment, revealed that no significant \( P = 0.216 \) difference existed between maropitant and saline solution treatments in the first 30-minute period, although maropitant-treated dogs had slightly fewer such events (mean, 4.1 [range, 3.2 to 5.2] vs mean, 5.2 [range, 3.9 to 6.6]; Table 2). However, the mean number of emetic events was significantly reduced by maropitant treatment, compared with saline solution, in each of the following 30-minute periods: 31 to 60 minutes \( (P < 0.001) \); 61 to 90 minutes \( (P < 0.001) \); and 91 to 120 minutes \( (P = 0.012) \). Beyond 2 hours after treatment, the mean number of emetic events for saline solution and maropitant was 0 as a result of cessation of the emetic effect of cisplatin. The least squares mean time (95% confidence interval) to cessation of emesis for dogs treated with maropitant was 39 minutes, (28 to 54 minutes), compared with 96 minutes (69 to 133 minutes) for dogs treated with saline solution \( (P < 0.001) \).

The nausea VAS for saline solution increased and peaked between 1 and 60 minutes after treatment. In contrast, the nausea VAS for maropitant, which was initially slightly higher than for saline solution, declined immediately after treatment (Figure 1). Analysis of nausea VASs by use of a mixed linear model revealed that overall nausea VAS for dogs treated with maropitant was significantly \( (P = 0.013) \) lower than that for dogs treated with saline solution. At each subsequent 20-minute assessment period from 21 to 80 minutes after treatment, nausea VASs for maropitant were significantly lower than for saline solution as follows: 21 to 40 minutes \( (P = 0.021) \); 41 to 60 minutes \( (P < 0.001) \); and 61 to 80 minutes \( (P < 0.001) \).

Prevention of emesis—Following cisplatin infusion, 19 hours after oral administration of treatments, all dogs that had received maropitant had significantly \( (P < 0.001) \) less emetic events than placebo-treated dogs, irrespective of the dose of maropitant administered. All placebo-treated dogs vomited after cisplatin infusion. Of the dogs treated with maropitant, 2 dogs treated with 1 mg/kg, 2 dogs treated with 2 mg/kg, and 4 dogs treated with 3 mg/kg did not vomit after cisplatin infusion. The least squares mean number (95% confidence interval) of emetic events for placebo was 20.3 (15.89 to 25.36) events, compared with 2.7 (1.8 to 3.7) events for maropitant at 1 mg/kg, 1.1 (0.25 to 2.42) events at 2 mg/kg, and 0.5 (0.02 to 1.46) events at 3 mg/kg (Table 3). Analysis by use of a general linear model revealed that the numbers of emetic events ob-

### Table 1
Mean number of emetic events and time to cessation after treatment of ongoing emesis caused by cisplatin infusions in dogs.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose, route</th>
<th>No. of dogs</th>
<th>No. of emetic events</th>
<th>Time to cessation of emesis (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (0.9% NaCl)</td>
<td>1 mL/kg, SC</td>
<td>12</td>
<td>15.8</td>
<td>96 (69–133)</td>
</tr>
<tr>
<td>Maropitant</td>
<td>1 mg/kg, SC</td>
<td>12</td>
<td>5.2*</td>
<td>39* (28–54)</td>
</tr>
</tbody>
</table>

*Significant \((P < 0.05)\) difference between control (saline solution) and maropitant treatment. LSM = Least squares mean. CI = Confidence interval.

### Table 2
The LSM (95% CI) number of emetic events in 30-minute periods after treatment of ongoing emesis caused by cisplatin infusions in 24 dogs.

<table>
<thead>
<tr>
<th>No. of emetic events after treatment</th>
<th>1–30 min</th>
<th>31–60 min</th>
<th>61–90 min</th>
<th>91–120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline solution</td>
<td>5.2 (3.9–6.6)</td>
<td>5.9 (4.5–7.4)</td>
<td>2.7 (1.8–3.7)</td>
<td>0.3 (0.1–0.8)</td>
</tr>
<tr>
<td>Maropitant</td>
<td>4.1 (3.2–5.2)</td>
<td>0.3 (0.1–0.6)*</td>
<td>0.0 (0.0–0.1)*</td>
<td>0.0 (0.0–0.1)*</td>
</tr>
</tbody>
</table>

*See Table 1 for key.

Figure 1—Least squares mean (LSM) nausea VASs in sequential 20-minute periods after treatment with saline (0.9% NaCl) solution (1 mL/kg, SC; open circles) or maropitant (1 mg/kg, SC; closed circles) of ongoing emesis caused by cisplatin infusions in dogs. *Significant \((P < 0.05)\) difference between treatments at indicated time points.
served in dogs that received maropitant at 2 or 3 mg/kg were significantly ($P = 0.016$) fewer than in dogs receiving 1 mg/kg, but no significant difference ($P = 0.325$) was found between dogs receiving maropitant at 2 or 3 mg/kg. Thus, on the basis of selecting the minimum effective dose, the optimum dose of maropitant for reduction of emesis between 19 and 23 hours after cisplatin infusion was determined to be 2 mg/kg. Emesis for placebo-treated dogs commenced 1.43 hours after initiation of cisplatin infusion (20.43 hours after placebo treatment), and the final emetic event for these dogs occurred at 4.4 hours after the start of cisplatin infusion (23.4 hours after placebo treatment).

The nausea VAS peaked between 21 and 22.5 hours after cisplatin infusion for all treatments, which corresponded to the period of maximum emesis; however, during this period, maropitant-treated dogs had significantly lower nausea VASs than placebo-treated dogs (Figure 2). Overall analysis of nausea VASs by use of a mixed model with repeated measures revealed that the least squares mean (95% confidence interval) nausea VAS for dogs treated orally with maropitant (3.7 [1.84 to 5.60] at 1 mg/kg, 1.8 [0.78 to 2.83] at 2 mg/kg, and 1.6 [0.67 to 2.58] at 3 mg/kg) was significantly ($P < 0.001$) lower than that for dogs receiving placebo (12.8 [9.83 to 15.87]), but no significant differences were found in VASs between doses of maropitant (Table 4).

**Discussion**

Maropitant is a novel NK1 receptor antagonist for use in dogs that, by preventing propagation of impulses through the emetic center, has the potential to alleviate emesis arising either centrally or peripherally. In our study, the optimum oral dose to prevent cisplatin-induced emesis was 2 mg/kg. It is assumed that the tablet formulation was homogeneous, such that shaving the tablets to give the correct dose by body weight was accurate. Preliminary dose-response investigations have indicated that the standard dosage regimen, for either treatment or prevention of emesis, should be 1 mg/kg by SC injection or 2 mg/kg as oral tablets, with the dose being given once every 24 hours for up to 5 days as required. This is supported by pharmacokinetic data demonstrating that in dogs, these 2 maropitant dosage regimens provide similar peak plasma concentrations (with means of 92.0 ng/mL delivered by 1 mg/kg, SC, and 81.0 ng/mL from 2 mg/kg, PO). However, as might be expected, the time taken to achieve maximum plasma concentrations is shorter following SC administration (with means of 0.75 hours for 1 mg/kg, SC and 1.9 hours for 2 mg/kg, PO). Hence, for treatment of ongoing emesis, the injectable route offers a
more rapid onset of efficacy. This was confirmed in our study, in that emesis was significantly reduced from 30 minutes after SC administration. Although the parenteral route may be preferred for the treatment of acute emesis, the oral route is probably more appropriate for long-term studies of emesis at home for the prevention of emesis, such as might arise from motion sickness or prior to planned chemotherapy.

In our study, maropitant was highly effective in the treatment of ongoing emesis and the prevention of emesis, even when the emetic was administered for up to 19 hours after treatment with maropitant. Furthermore, no apparent adverse clinical observations were recorded that related to the administration of maropitant. Results of previous studies indicate that cisplatin will reliably induce emesis in dogs for up to 4 hours after administration, and indeed, this was confirmed in the placebo-treated dogs of our emesis prevention study. Results of our study indicate that maropitant provides a clinically useful preventative antiemetic effect for up to 23 hours after administration. If longer periods of emetic control are required to meet the clinical needs of patients, results of other research in dogs indicate that treatment may be repeated daily for up to a total of 5 days with either formulation of maropitant.

The use of cisplatin for experimentally induced emesis mimics that of peripheral initiation of emesis by afferent stimuli from the gastrointestinal and urogenital tracts, such as that resulting from dietary indiscretion, ingestion of toxic substances, presence of infection, obstruction of the gastrointestinal tract, renal disease, or pyometra. However, because cisplatin-induced emesis is controlled via the emetic center, blocking the emetic pathway at the level of the emetic center should not only prevent cisplatin-induced emesis but also block other emetic pathways that are controlled via the emetic center. Such neural pathways include signals from the CTZ (eg, triggered by endotoxins, uremia, apomorphine, and cardiac glycosides), vestibular apparatus (eg, motion sickness), or cerebral cortex (eg, anxiety or anticipation). Together, these examples represent a wide range of the potential causes of emesis in dogs seen in veterinary clinics.

In the evaluation of a compound for use as an antiemetic, it is of prime importance that a reliable form of experimentally induced emesis is selected and that appropriate evaluation techniques are used. In our study, cisplatin was used as the emetic, and subsequently, each discreet emetic event was recorded, and nausea was periodically assessed by a VAS from the associated clinical signs. To minimize inconsistencies in interpretations, the same observer recorded emesis or nausea VAS throughout each study. In experimental studies, it has been common practice to use cisplatin as an emetic in dogs and ferrets since the 1980s. Cisplatin has a strong emetic activity with a consistent and reproducible effect in dogs, lasting for up to approximately 4 hours; most dogs have an early onset of emesis (within 1 to 1.5 hours) after administration with multiple episodes of emesis and peak activity occurring around 2 hours after administration. Other means of experimentally induced emesis have also been investigated. Copper sulphate acts peripherally via activating 5-HT receptors on the gastrointestinal mucosa, activating 5-HT receptors in the vagal and sympathetic afferents to the emetic center in the brainstem and subsequently causing emesis. This has been elucidated by sectioning of the vagus and splanchnic afferent nerves, which abolishes emesis induced by cisplatin in ferrets and dogs, and by 5-HT receptor agonists in cats. Historically, it was believed that cisplatin had a central emetic effect, particularly in cats, acting in the CTZ to stimulate 5-HT receptors because it was thought that ablation of the area postrema abolished the response. Although these early reports fitted a generally held hypothesis that all chemotherapeutically induced emesis was controlled via the CTZ, these data may be misleading in dogs, as the experimental lesions may have been more widespread and incorporated the NT5 because of its anatomic close proximity to the CTZ. Further evidence of the direct connection between the vagal and sympathetic afferents to the emetic center comes from studies on the use of 5-HT receptor antagonists to inhibit cisplatin-induced emesis. One 5-HT receptor antagonist, ondansetron, has been found to provide clinically useful antiemetic efficacy against acute emesis in humans receiving cisplatin chemotherapy. However, it has been shown in dogs that 5-HT receptor antagonists will inhibit cisplatin-induced emesis only if they can penetrate the BBB. Because the emetic center lies within the BBB but the CTZ lies outside the BBB, these data imply that the 5-HT receptor antagonists are binding to serotonin receptors located at the level of the emetic center and not within the CTZ.

Metoclopramide is an antiemetic commonly used in veterinary clinical practice that is active as an antagonist at D2 and 5-HT3 receptors in the CTZ and that has prokinetic activity at D2 receptors located in the gastrointestinal wall. However, while it is effective in the control of emesis induced with apomorphine and has clinical efficacy in the treatment of general emesis, the use of metoclopramide to reduce emesis after administration of cisplatin has, on occasion, been disappointing, even when used in combination with dexamethasone, which is a recognized protocol for the prevention of chemotherapy-induced emesis in human cancer patients. High doses of metoclopramide are thought to be more efficacious, however, these are associated with extrapyramidal signs caused by central D2 activity, and the recommended dose regimen requires the daily dose to be divided and given on 2 or 3 occasions at 8- to 12-hour intervals. In contrast, a number of 5-HT3 receptor antagonists (including ondansetron, ICS205-930, zacopride, DAU 6215, granisetron, and others) have proved to be highly effective in controlling acute cisplatin-induced emesis in all species evaluated, including humans and dogs. The 5-HT3 receptor antagonists, such as ondansetron, that have no D2 activity have the additional advantage, compared with metoclopramide, of having no extrapyramidal effects.
effects following administration.50

Within the brainstem, substance P, a strong ligand for the NK1 receptor, is believed to act as a neurotransmitter and NK1 receptor antagonists have been demonstrated to be effective against cisplatin-induced emesis in humans34 and ferrets.15,19,22,30,31 Experiments in ferrets have shown that NK1 receptors are present in the emetic center.15 Early evidence has suggested the presence of NK1 receptors in the area postrema as well as in the NTS in the emetic center.15,60 However, more recent studies9,10 have indicated that the antiemetic effect of NK1 receptor antagonists in dogs is primarily if not wholly enacted at the level of the NTS. This was shown by experimental destruction of the area postrema, which eliminates apomorphine-induced emesis but fails to abolish the emesis induced by copper sulphate, whereas NK1 receptor antagonists continue to prevent emesis stimulated by copper sulphate in dogs in which the area postrema had been destroyed.10 Furthermore, because the CTZ lies outside the BBB, it is clear that the antiemetic activity of NK1 receptor antagonists is linked directly to their ability to penetrate the BBB and reach the emetic center.16,21

It is important to note, however, that some species differences exist with regard to the pattern of emesis observed after administration of cisplatin. For example, in dogs, cisplatin causes acute emesis but does not demonstrate the delayed or late-onset emesis associated with cisplatin administration in humans. Consequently, ferrets that have delayed or late-onset emesis associated with cisplatin are generally used to investigate this aspect of chemotherapy-induced nausea and emesis in humans.18,20,30 Cisplatin-induced delayed emesis in humans and ferrets is inhibited by NK1 receptor antagonists,45 but 5-HT3 antagonists (eg, ondansetron) that have good activity against acute-onset emesis have relatively little antiemetic efficacy against delayed emesis in humans.35,38 Furthermore, in contrast to acute emesis, sectioning the vagus does not abolish the delayed response, and this may be related to the release of serotonin and substance P into the bloodstream by enterochromaffin cells of the gastrointestinal tract. Whether this also occurs in dogs is presently unclear. In humans, there is increased urinary output of the serotonergic metabolite, 5-hydroxyindoleacetic acid, within 24 hours after cisplatin administration, but plasma concentrations of this metabolite do not increase in dogs.45

Cisplatin is widely used as a chemotherapeutic agent for the treatment of both human and canine cancer patients. Its use as an emetic in laboratory model studies is well established. Hence, its use in these studies is both clinically relevant and scientifically appropriate. The dosage of cisplatin (70 mg/m2) used in these studies is within the dose range commonly recommended by oncologists for canine chemotherapy49,61 and can be expected to reliably induce emesis. Published data have indicated that at doses ≥ 50 mg/m2, cisplatin induces emesis in virtually all human patients.45,60 The results presented here imply that not only should maropitant have good efficacy as a general antiemetic in dogs, but that it also has great potential for the treatment and prevention of chemotherapy-induced nausea and emesis. When administered for chemotherapeutic purposes, it is essential that saline diuresis is performed for over 4 to 6 hours prior to administration of the cisplatin infusion to minimize the risk of nephrotoxicity.98 Diuresis is not performed in the cisplatin-emesis model because the objective is to provide a consistent emetic challenge. The use of healthy, clinically normal young dogs probably accounts for the absence of apparent clinical signs of toxicity associated with cisplatin in the present studies, in contrast to the higher incidence of nephrotoxicity reported when cisplatin is administered therapeutically to canine cancer patients. However, the preplanned study end point avoided the onset of more chronic clinical signs and ensured the maintenance of a high standard of animal welfare.

In conclusion, results of our study suggest that maropitant has a potent antiemetic effect in dogs. The antiemetic effect has a rapid onset following SC injection (30 minutes) and lasts for up to 24 hours after treatment. Furthermore, it also has potential to treat and prevent emesis caused by cisplatin administered at chemotherapeutic dose rates.

References


