# Assessment of the administration of maropitant and loperamide to dogs with cancer for the prevention and reduction of adverse effects associated with the administration of paclitaxel

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**OBJECTIVE**
To evaluate the efficacy of maropitant and loperamide for the prevention and reduction of adverse gastrointestinal effects associated with administration of paclitaxel to dogs with cancer.

**ANIMALS**
168 dogs with cancer.

**PROCEDURES**
The study comprised 2 phases. For phase 1, dogs in the intervention group were administered maropitant and loperamide followed by paclitaxel. Outcomes were compared with those for a control group that received only maropitant and paclitaxel. For phase 2, all dogs of phase 1 that did not receive maropitant and loperamide and that had adverse gastrointestinal effects were enrolled; they received maropitant and loperamide and another dose of paclitaxel.

**RESULTS**
In phase 1, significantly fewer dogs in the intervention group had adverse effects. For dogs that had adverse effects, the intervention group had a lower severity of lack of appetite and lethargy. Also, adverse effects for dogs in the intervention group were of significantly shorter duration than for the control group. In phase 2, significant reductions in adverse effects were observed after administration of maropitant and loperamide. In those dogs that still had adverse effects after administration of maropitant and loperamide, there was a significant reduction in severity of signs of nausea and lethargy.

**CONCLUSIONS AND CLINICAL RELEVANCE**
A combination of maropitant and loperamide was found to be safe for use and effective for reducing or preventing signs of paclitaxel-induced gastrointestinal effects in dogs. (*Am J Vet Res* 2019;80:601–606)

Cancer and cancer treatments can result in adverse consequences. To minimize impairment of quality of life and maximize effectiveness of treatments, it is imperative to consider accepted standard medical protocols in conjunction with assessment of an individual patient's concurrent medical issues as well as the implications of multimodal treatments and polypharmacy.[1]

Paclitaxel is a taxane-class antimicrotubule antineoplastic agent that suppresses spindle microtubule dynamics. Paclitaxel is an effective chemotherapeutic agent in dogs and cats. Additionally, paclitaxel enhances the cytotoxic effects of ionizing radiation and may induce cell death in malignant tumors (eg, mammary gland carcinomas, squamous cell carcinomas, or mastocytomas)[2–5] by triggering apoptosis. Paclitaxel has a narrow margin of safety. Dogs treated with paclitaxel are likely to have adverse effects, and serious adverse effects commonly occur.[6] The most commonly encountered adverse effects of paclitaxel, namely neutropenia and gastrointestinal tract disturbances, generally are a result of collateral damage to rapidly dividing cells. Bone marrow stem cells and gastrointestinal crypt of Lieberkuhn cells are rapidly dividing cells; thus, they are susceptible to the antiproliferative effects of paclitaxel.[7]

Paclitaxel can lead to damage to the intestinal mucosa when the production of cells in the crypts is interrupted.[7,8] The final result is ulceration of the intestines and diarrhea in addition to signs of nausea.[8] Dogs have to be monitored for vomiting, diarrhea, and dehydration during the 2- to 5-day period after chemotherapy administration.[6] Signs can range from mild inappetence and slightly soft feces to severe intractable vomiting and profuse hemorrhagic diarrhea. Dogs with mild clinical signs can often be managed at home with dietary modifications and oral medications. Dogs that vomit even after consumption of only water become dehydrated or lethargic. Dogs

with severe hemorrhagic diarrhea should be hospitalized[4,7,9,10] and treated appropriately.

Paclitaxel is an agent with poor water solubility.[11] Various factors, including solvents, emulsions, micelles, liposomes, microspheres, nanoparticles, cyclodextrins, pastes, and implants, have been used to improve the solubility of paclitaxel and eliminate undesired adverse effects.[11,12]

Maropitant inhibits the vomiting reflex by blocking NK-1 receptors in the medullary vomiting center.[13] Maropitant is effective in the prevention and treatment of acute vomiting and also delays treatment-induced signs of nausea and vomiting in dogs receiving chemotherapy.[4,14–16] Maropitant should be avoided when an animal has gastrointestinal obstruction or perforation. Because maropitant is bound to plasma proteins, it may compete with other highly bound drugs (eg, loperamide).[13]

Loperamide is an opioid-receptor agonist used for the management of nonspecific acute and chronic diarrhea that alters gastrointestinal tract motility by stimulating circular smooth muscle contraction and, therefore, intestinal segmentation.[13] Loperamide also stimulates absorption and inhibits secretion of fluid and electrolytes.[13] Loperamide should be avoided in animals with gastrointestinal tract obstruction.[13]

The objective of the study reported here was to assess the efficacy of a combination of maropitant and loperamide for the prevention and reduction of adverse effects of the gastrointestinal tract associated with the administration of paclitaxel to dogs with cancer. We hypothesized that administration of the combination of maropitant and loperamide would reduce paclitaxel-induced adverse gastrointestinal effects in tumor-bearing dogs.

# Materials and Methods

## Animals

Dogs with cancer admitted to 2 veterinary hospitals[a,b] between June 2015 and May 2017 with the intention that they would receive a cycle of paclitaxel consisting of 4 treatments at 3-week intervals were candidates for the study. Inclusion criteria were a histologically confirmed malignancy for which there was a reasonable expectation of responsiveness to paclitaxel (eg, mammary gland carcinoma and squamous cell carcinoma) and no prior treatment with paclitaxel. Exclusion criteria included the use of drugs with antiemetic or antidiarrheal properties within 7 days of the first paclitaxel treatment, dogs with neoplasia of the gastrointestinal tract, dogs with clinical signs of gastrointestinal tract abnormalities before the first paclitaxel treatment, dogs concurrently receiving medications with the potential for gastrointestinal toxicosis, and dogs concurrently receiving medications for the treatment or prevention of a gastrointestinal tract disorder.

Owners signed a consent form confirming that their dog met the inclusion criteria and that they agreed to comply with the protocol established for the study. Owners were not told whether their dog's treatment included maropitant and loperamide, and the cost of treatment was the same for all dogs in the study, regardless of treatment group. The study was conducted in accordance with ethical guidelines of animal welfare.[17]

## Procedures

The study was conducted in 2 phases. Dogs received a cycle of paclitaxel, which consisted of 4 administrations of the drug at 3-week intervals. Pretreatment evaluation of dogs included a complete physical examination, CBC (including a platelet count), serum biochemical analysis, and urinalysis.

For phase 1, maropitant[c] (2 mg/kg, PO, q 24 h for 4 days beginning 12 hours before paclitaxel administration) and paclitaxel[d] (150 mg/m$^2$, IV, injected over 15 to 30 minutes) were administered to dogs meeting the inclusion criteria. These dogs subsequently received 3 additional treatments with maropitant and paclitaxel at 3-week intervals (control group; n = 92). Another group of dogs were then enrolled in the study. For this group, dogs that met the inclusion criteria received maropitant and loperamide[e] (0.08 mg/kg, PO, q 8 h for 4 days beginning 12 hours before paclitaxel administration) and paclitaxel, which was followed by 3 additional treatments with maropitant and paclitaxel at 3-week intervals (intervention group; 72).

For phase 2, dogs in the control group of phase 1 that had adverse gastrointestinal effects (n = 87) were administered maropitant and loperamide before they received the first dose of paclitaxel during the second cycle of chemotherapy. These dogs subsequently received 3 additional treatments with maropitant and paclitaxel at 3-week intervals. There was an interval of 3 weeks between the end of phase 1 and the start of phase 2.

## Assessment of adverse effects

For phase 1, adverse effects were assessed after only the first paclitaxel administration. For phase 2, adverse effects were also assessed after the administration of maropitant and loperamide and the ensuing dose of paclitaxel.

Each dog was observed for gastrointestinal events for 5 days beginning at the time of paclitaxel administration. All dogs were observed in the hospital for 24 hours after paclitaxel treatment for signs of abnormal health. During that time, a complete physical examination was performed on each dog. Dogs were then discharged to the owners, who were instructed to contact the investigators if any adverse effects were detected after hospital discharge. In addition, all clients were called daily for 5 days after their dogs were discharged from the hospital.

Dogs were monitored for adverse effects, including vomiting, diarrhea, signs of nausea, lack of appetite, and lethargy. Adverse events were evaluated by a veterinarian by use of a scale that corresponded with criteria developed by the Veterinary Cooperative

**Table 1**—Signalment of the dogs in phase 1 of a study to assess the efficacy of maropitant and loperamide for the prevention or reduction of adverse effects of the gastrointestinal tract associated with the administration of paclitaxel.

| Variable | Control | Intervention | Total | *P* value* |
|---|---|---|---|---|
| Sex | | | | 0.280 |
| Male | 37 (40.2) | 37 (48.7) | **74 (44.0)** | |
| Female | 55 (59.8) | 39 (51.3) | **94 (56.0)** | |
| Neuter status | | | | 0.332 |
| Sexually intact | 37 (40.2) | 34 (44.7) | **71 (42.3)** | |
| Castrated or spayed | 55 (59.8) | 42 (55.3) | **97 (57.7)** | |
| Breed | | | | 0.449 |
| Purebred | 75 (81.5) | 58 (76.3) | **133 (79.2)** | |
| Crossbred | 17 (18.5) | 18 (23.7) | **35 (20.8)** | |

Values reported are number (percentage). The control group consisted of dogs that concurrently received maropitant and paclitaxel, and the intervention group consisted of dogs that concurrently received maropitant and loperamide in addition to paclitaxel.

*Values represent results of a Wilcoxon rank sum test and were considered significant at $P < 0.05$.

Oncology Group.[18] Adverse events were graded on a scale that ranged from 0 (none) to 4 (life-threatening event). Information was recorded as the number of adverse events, duration of adverse events, and time of the adverse events (ie, interval from paclitaxel administration until onset of event) for the 5-day period.

## Statistical analysis

The study was conducted in accordance with a nonrandomized, nonblinded, historically controlled design. Efforts were made to ensure the intervention and control groups were comparable with regard to signalment; however, there may have been differences over time or minor variations in the clinical environment. Therefore, in lieu of parametric tests, distribution-free nonparametric tests were chosen for all statistical comparisons.[19]

For phase 1, Fisher exact tests were used to rule out differences in signalment between the intervention and control groups and to determine significant differences in the overall incidence of each adverse effect. Wilcoxon rank sum tests were used to rule out differences in body weight between the intervention and control groups. Mantel-Haenszel linear trend tests were used to compare the groups on the basis of the severity of adverse effects, time to onset of effects, and duration of effects for those dogs that had adverse effects.

For phase 2, the McNemar test of symmetry was used to compare the overall incidence of each adverse effect for paclitaxel with and without the administration of maropitant and loperamide. Wilcoxon signed rank tests were used to compare the severity of adverse effects within dogs that had adverse effects to paclitaxel with and without the administration of maropitant and loperamide. All statistical analyses were performed with statistical software.[f] Significance was set at $P < 0.05$.

# Results

## Animals

A total of 168 dogs were enrolled in the study for phase 1. There were 92 dogs in the control group (maropitant and paclitaxel) and 76 dogs in the intervention group (maropitant and loperamide and paclitaxel; **Table 1**). No significant differences were detected between dogs in the intervention and control groups for signalment factors, including sex ($P = 0.280$), neuter status ($P = 0.332$), and breed (purebred vs crossbred; $P = 0.449$). Mean ± SD body weight of the 168 dogs was 15.7 ± 10.5 kg; body weight did not differ significantly ($P = 0.113$; Wilcoxon rank sum test) between the control (16. 9 ± 10.8 kg) and intervention (14.4 ± 10.0 kg) groups. Of the 92 control dogs in phase 1, 87 (94.6%) had adverse effects and were subsequently enrolled in phase 2 of the study.

**Table 2**—Overall incidence of adverse effects for the dogs during phase 1.

| Adverse effect | Control (n = 92) | Intervention (n = 76) | *P* value* |
|---|---|---|---|
| Vomiting | 55 (59.8) | 5 (6.6) | < 0.001 |
| Diarrhea | 60 (65.2) | 7 (9.2) | < 0.001 |
| Signs of nausea | 80 (87.0) | 13 (17.1) | < 0.001 |
| Lack of appetite | 85 (92.4) | 16 (21.1) | < 0.001 |
| Lethargy | 85 (92.4) | 13 (17.1) | < 0.001 |

There were 87 dogs in the control group and 16 dogs in the intervention group that had at least 1 adverse effect; many dogs had > 1 adverse effect.

*Values represent results of a Fisher exact test and were considered significant at $P < 0.05$.

***See*** Table 1 for remainder of key.

## Phase 1

Overall, fewer dogs had adverse effects when maropitant and loperamide were administered in conjunction with paclitaxel for cancer treatment **(Table 2)**. Specifically, the intervention group had significantly ($P < 0.001$) lower incidences of vomiting, diarrhea, signs of nausea, lack of appetite, and lethargy, compared with results for the control group.

Within the dogs that had adverse effects, the grades of severity for the intervention group were significantly lower for both lack of appetite ($P = 0.002$) and lethargy ($P = 0.037$) than were the grades for these effects for the control group (Table 2). No

**Table 3**—Grade of severity of the adverse effects for dogs during phase 1.

| Adverse effect | Grade | Control | Intervention | *P* value* |
|---|---|---|---|---|
| Vomiting | | | | 0.157 |
| | 1 | 0 (0) | 0 (0) | |
| | 2 | 3 (5.5) | 0 (0) | |
| | 3 | 28 (50.9) | 5 (100) | |
| | 4 | 24 (43.6) | 0 (0) | |
| Diarrhea | | | | 0.483 |
| | 1 | 0 (0) | 0 (0) | |
| | 2 | 1 (1.7) | 0 (0) | |
| | 3 | 32 (53.3) | 5 (71.4) | |
| | 4 | 27 (45.0) | 2 (28.6) | |
| Signs of nausea | | | | 0.099 |
| | 1 | 4 (5.0) | 0 (0) | |
| | 2 | 20 (25.0) | 8 (61.5) | |
| | 3 | 40 (50.0) | 4 (30.8) | |
| | 4 | 16 (20.0) | 1 (7.7) | |
| Lack of appetite | | | | 0.002 |
| | 1 | 0 (0) | 2 (12.5) | |
| | 2 | 11 (12.9) | 2 (12.5) | |
| | 3 | 46 (54.1) | 12 (75.0) | |
| | 4 | 28 (32.9) | 0 (0) | |
| Lethargy | | | | 0.037 |
| | 1 | 6 (7.1) | 4 (30.8) | |
| | 2 | 27 (31.8) | 4 (30.8) | |
| | 3 | 41 (48.2) | 4 (30.8) | |
| | 4 | 11 (12.9) | 1 (7.7) | |

Grade of severity was assigned by use of a scale that ranged from 0 (none) to 4 (life-threatening event) and corresponded with criteria developed by the Veterinary Cooperative Oncology Group.[18]

*Values represent results of a Mantel-Haenszel linear trend test and were considered significant at $P < 0.05$.

***See*** Tables 1 and 2 for remainder of key.

significant differences were found between groups for the grades for vomiting ($P = 0.157$), diarrhea ($P = 0.483$), or signs of nausea ($P = 0.099$; **Table 3**).

For the 16 dogs of the intervention group that had adverse effects, the onset was only 1 day after paclitaxel administration. In contrast for the control group, the onset ranged from 1 to 3 days after paclitaxel administration, with the onset of adverse effects within 1 day in 50 of 87 (57.5%) control dogs that had adverse effects. For the dogs that had adverse effects, the clinical signs developed significantly ($P = 0.003$) more acutely after paclitaxel administration in the intervention group than in the control group. In the dogs of the intervention group that had adverse effects, the effects were of a significantly ($P = 0.040$) shorter duration (1.87 days), compared with the duration for the control group (2.28 days; **Table 4**).

**Table 4**—Time of onset and duration of adverse effects for dogs in phase 1.

| Variable | Control | Intervention | *P* value* |
|---|---|---|---|
| Onset (d) | | | 0.003 |
| 1 | 50 (57.5) | 16 (100) | |
| 2 | 31 (35.6) | 0 (0) | |
| 3 | 6 (6.9) | 0 (0) | |
| Duration (d) | | | 0.040 |
| 1 | 12 (13.8) | 6 (37.5) | |
| 2 | 40 (46.0) | 6 (37.5) | |
| 3 | 29 (33.3) | 4 (25.0) | |
| 4 | 5 (5.7) | 0 (0) | |
| 5 | 1 (1.1) | 0 (0) | |

Onset represents the number of days from paclitaxel administration until first detection of adverse effects.

*Values represent results of a Mantel-Haenszel linear trend test and were considered significant at $P < 0.05$.

***See*** Tables 1 and 2 for remainder of key.

## Phase 2

A total of 87 (94.6%) control dogs in phase 1 had adverse effects and were enrolled in phase 2. There was a significant ($P < 0.001$; McNemar test) reduction in grade of severity for all 5 adverse effects after paclitaxel administration for dogs that were concurrently receiving maropitant and loperamide, compared with when dogs received only maropitant and paclitaxel **(Table 5)**. Lethargy was eliminated in 61 of 85 (71.8%) dogs, and vomiting was eliminated in 51 of 55 (92.7%) dogs during the first 5 days after paclitaxel administration.

For those dogs that still had adverse effects after paclitaxel and concurrent administration of maropitant and loperamide, there was a significant reduction in the mean ± SD grade of severity for nausea (from 2.94 ± 0.7 to 2.23 ± 0.4; n = 17; $P = 0.008$) and lethargy (from 2.71 ± 0.9 to 2.25 ± 0.5; 24; $P = 0.047$). There was not a significant ($P = 0.806$) reduction in grade of severity for lack of appetite (mean grade, 3.1) with and without maropitant and loperamide administration. Reduction in grade of severity was not as-

**Table 5**—Incidence of adverse effects for 87 dogs during phase 2.

| Adverse effect | After paclitaxel and maropitant | After paclitaxel and maropitant and loperamide | Reduction |
|---|---|---|---|
| Vomiting | 55 (63.2) | 4 (7.3) | 51 (92.7) |
| Diarrhea | 60 (69.0) | 5 (8.3) | 55 (91.7) |
| Signs of nausea | 80 (92.0) | 17 (21.3) | 63 (78.8) |
| Lack of appetite | 85 (97.7) | 23 (27.1) | 62 (72.9) |
| Lethargy | 85 (97.7) | 24 (28.2) | 61 (71.8) |

***See*** Tables 1 and 2 for key.

sessed for vomiting or diarrhea because there were too few dogs (4 and 5, respectively) that continued to have these adverse effects.

## Discussion

Chemotherapy-induced nausea, vomiting, and diarrhea are common adverse effects of cancer treatment, especially after paclitaxel administration.[6] In the study reported here, a combination of maropitant and loperamide was evaluated for its ability to prevent paclitaxel-induced gastroenteritis in tumor-bearing dogs. The study was conducted solely to investigate whether maropitant and loperamide would decrease or prevent the adverse gastrointestinal effects of paclitaxel; it was not designed to assess the efficacy of chemotherapy because most of the dogs enrolled already had a very poor to guarded prognosis on the basis of the dimensions of the initial neoplasm or presence of metastases. The anticipated short life expectancies of these dogs also meant that it was not feasible to recruit patients for a third cycle of chemotherapy. Therefore, dogs were enrolled in phase 1 for the first cycle of treatment given the fact the authors had seen severe adverse effects attributable to paclitaxel in previous patients or in phase 2 because the dogs had adverse gastrointestinal effects during the initial cycle of treatment.

The P-glycoprotein is a protein of the cell membrane that pumps drugs out of cells. Loperamide and paclitaxel are P-glycoprotein substrates. Paclitaxel reportedly is pumped from cells by P-glycoprotein in humans, but there currently are no data as to whether paclitaxel is pumped from cells by P-glycoprotein in dogs.[20] Because coadministration of drugs is a common practice in veterinary medicine, pharmacokinetic and toxicological implications may develop when 2 P-glycoprotein substrates are used in the treatment of domestic animals. Mutation of a multiple-drug resistance gene in dogs that likely results in ivermectin sensitivity in several breeds (eg, Collies, Australian Shepherds, Shetland Sheepdogs, Old English Sheepdogs, German Shepherd Dogs, English Shepherds, herding-breed crosses, Silken Windhounds, and Long-haired Whippets) allows loperamide to penetrate the CNS and cause profound sedation.[13] However, there was no evidence of clinically relevant effects with concurrent use of paclitaxel and loperamide in the present study.

Administration of chemotherapeutics results in various degrees of damage to normal cells from the cytotoxic agents. Therefore, clinicians should know how to manage common adverse effects associated with chemotherapy when administering a drug such as paclitaxel. Most commonly, adverse gastrointestinal effects usually are evident 2 to 5 days after chemotherapeutic administration. In the study reported here, the onset of adverse effects was 1 to 3 days after paclitaxel administration for all dogs. More intensive or more frequent monitoring could have resulted in earlier detection of adverse effects.

Paclitaxel has a narrow margin of safety. All treated dogs are likely to have adverse effects, and serious adverse effects commonly occur. Neutropenia and gastrointestinal mucosal toxicosis develop in most treated patients. Clinical signs of gastrointestinal tract abnormalities can range from mild loss of appetite and slightly soft feces to severe vomiting or large amounts of watery or hemorrhagic diarrhea.[4,7,9,10,21,22] Maropitant can decrease the incidence and severity of diarrhea after cytotoxic treatments[10]; therefore, it was not possible to determine the proportion of the antidiarrheal effect of maropitant and loperamide that was attributable to maropitant or to loperamide.

Results of the study reported here supported the contention that maropitant and loperamide can be effective in preventing or delaying the onset of adverse effects (eg, vomiting, diarrhea, signs of nausea, lack of appetite, and lethargy) associated with administration of paclitaxel. Within the dogs that had any adverse effects, those treated with maropitant and loperamide had significantly less severe lack of appetite and lethargy and a significantly shorter duration of adverse effects, compared with results for the control group. No differences were found in the grade of severity of vomiting, diarrhea, or signs of nausea. However, the lack of significant differences may have been attributable, in part, to the fact that so few dogs in the intervention group had any adverse effects.

Human oncology patients have nausea, vomiting, and diarrhea resulting from chemotherapy, and these effects are more difficult to control during subsequent cycles of chemotherapy when they are not adequately controlled after the initial treatment.[23] In the present study, significant reductions in all adverse effects were detected during phase 2 after adminis-

tration of paclitaxel and concurrent administration of maropitant and loperamide in dogs that had adverse gastrointestinal effects after the first treatment with maropitant and paclitaxel.

The prophylactic use of maropitant and loperamide can improve the quality of life and eliminate the need for reduction in the dose of chemotherapeutics in some dogs. Effects on the gastrointestinal tract generally were transient, and dogs recovered in sufficient time to allow continuation of treatment. Prophylactic treatment is the current standard of care in veterinary patients receiving cytotoxic chemotherapeutics such as paclitaxel.[3,10,21,24]

Limitations of the study reported here included participation of the owners to subjectively monitor signs of gastrointestinal toxicosis and to return their dogs to the hospitals when adverse effects were detected. Because the study was not conducted as a randomized design, observer bias cannot be ruled out, and it essentially was conducted as an unmasked study. Additionally, because the dogs were not randomly assigned to treatments in a systematic manner, the impact of other factors may have differed between the first 92 dogs (control group) and the subsequent 76 dogs (intervention group).

In the present study, 168 dogs received paclitaxel with maropitant or paclitaxel with maropitant and loperamide. The combination of maropitant and loperamide was found to be safe for use in tumor-bearing dogs, with no clinically relevant toxic effects that required veterinary intervention. The combination of maropitant and loperamide was highly effective in reducing or preventing paclitaxel-induced adverse gastrointestinal effects in tumor-bearing dogs.

## Footnotes

a. Animal Blue Care, Mijas, Spain.
b. Vetersalud Veterinary Hospital Dr. Moya, Torremolinos, Spain.
c. Cerenia, Zoetis UK Limited, Tadworth, England.
d. Paccal Vet-CA1, Oasmia Pharmaceutical AB, Uppsala, Sweden.
e. Imodium, Johnson & Johnson Medical Ltd, Wokingham, England.
f. IBM SPSS Statistics, version 24.0, Armonk, NY.

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