Rethinking Perioperative Vomiting In Dogs

Advisory Board

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Reviewed and Supported by:

- IVAPM
- Fear Free

[Image of a veterinarian examining a dog]
Introduction

In April 2019, an expert panel was assembled to discuss the future of perioperative antiemetics, with the intent of developing a set of best practice recommendations and implementation strategies. The goal was to elevate the level of care for patients concerning postoperative vomiting, return to feeding, and recovery quality. Within this discussion, the board also addressed the advantages that this approach holds for the healthcare team, practice, and pet owners. The implementation strategies shared by the board cover both logistical tips as well as communication guidelines for sharing this information with your team and pet owners.

Parallels between Anesthesia and Antiemetics

Before 1960 there were no recognized veterinary anesthesiologists in North America, and anesthesia in veterinary procedures continued to be used sparingly into the 1970s. At one point, it was even thought that “The induction of veterinary anesthesia was delayed by the misperception that the induction of anesthesia in animals was painful—and unnecessary—one needed but to hobble the animal.”1 Parallels exist between the history of analgesia in pets and the current research being done into perioperative emesis, with the future of antiemetics aimed at improving care of surgical patients. Dr. Ralph Harvey speaks enthusiastically about the parallel, stating that both medical advances represent similar rejuvenations of patient care models. Other members of the board in this space echo his thoughts:

“I think of it as how we (veterinarians) thought about pain management 20–30 years ago in that ‘animals don’t feel pain the way people do’...now that sentiment has been dispensed with and pain management is at the forefront of good patient care. I think that we are evolving in the same way with respect to perianesthetic vomiting and nausea.” Dr. Bonnie Kraus

Brief overview of Opioid use

Opioids have been a critical component of preanesthetic protocols:

• Excellent analgesia
• Good level of sedation
• No negative hemodynamic consequences
• Inhalant sparing, reducing the risk of hypotension
• Particularly useful for geriatric and cardiac patients
• Reversible effects
• Wide variety of options within the field for flexible protocols

The board shared the opinion that, even with the current focus on ‘opioid-sparing’ anesthesia protocols, opioids still have an important place in balanced veterinary anesthesia protocols. It was stated that opioids as a class of medicine are fairly benign, except for vomiting as a significant side effect.

The importance of a good recovery

A gradual, successful recovery after surgery has benefits that extend beyond the patient to the pet owner, the clinic team, and the practice itself. These benefits are discussed in more detail in the following section.

But first, what are the characteristics of a successful recovery and what factors influence your likelihood to achieve them?

The members of the advisory board identified 3 key areas that help create goals for what they consider an ideal recovery:

• A gradual, calm transition to wakefulness with no vomiting
• Awake and responsive in the clinic with good homeostasis
• Ambulatory upon discharge and rapid return to feeding

Following that, 3 strategies were discussed that particularly influence these success indicators:

• Appropriate and balanced analgesia
• Sedation to help in the transition to wakefulness after the procedure
• Use of Cerenia (maropitant citrate) perioperatively to hasten the return to normal feeding upon recovery.6
How is Perioperative vomiting affecting your practice?

• Aspiration pneumonia
• Delayed return to feeding
• Practice health
• Clinic team satisfaction
• Quality of life

Aspiration pneumonia

From a medical perspective, perianesthetic vomiting can be an extremely negative side effect because of the rare, but highly fatal, risk of aspiration pneumonia.

Several of the experts who were assembled shared experiences that they’d had with aspiration pneumonia, demonstrating the lasting effects that a serious complication during a routine surgery can have.

“It’s catastrophic when aspiration pneumonia happens. Even if it’s not very common, it’s still worth preventing.” Dr. Tamara Grubb

Dr. Bonnie Kraus was driven to investigate the literature on this complication further and found that vomiting was frequently associated as a complicating factor.

While the incidence of vomiting during surgery varies depending on the anesthetic type, dose, and administration, the advisory board felt strongly that the risk of perianesthetic vomiting was unacceptable and warranted the administration of a preanesthetic antiemetic in every procedure.

“Veterinarians have long pledged ourselves to the relief of suffering. The earlier big target was pain relief, and we achieved that part of the goal with a significant unfortunate trade-off of increased suffering associated with vomiting. Now we have both the knowledge and the tools to counteract and relieve the suffering of vomiting as well.” Dr. Ralph Harvey
Delayed return to feeding

Delayed return to feeding after a surgical procedure can have an array of effects on the patient and pet owner. Below are some of the benefits of returning to feeding that were discussed by the board:

**Medical**
- Return to normal gut function; maintain gastrointestinal (GI) integrity
- Maintenance of a healthy microbiome/reduction in risk of bacterial translocation
- Support for the immune system
- Positive nitrogen balance for restoring blood sugar
- Return to feeding for diabetic and pediatric patients as soon as they are alert enough to eat

**GI Function**

Prolonged periods of fasting in dogs have been shown to alter the species and diversity of bacteria present in the GI microbiota. Dr. Ralph Harvey highlighted the effects of an imbalanced microbiota, particularly relating to its relationship with the immune system. Dr. David Twedt agreed, providing more detail into the factors that are involved:

> “Not eating changes the bacterial flora, you have greater risk for translocation of bacteria, endotoxins, GI integrity. So yeah, that’s the big thing now in GI is this dysbiosis or imbalance of the microbiome...getting animals to eat is very important.” Dr. David Twedt

**Animal Welfare**

- Return to normal feeding is an indicator of lack of pain, fear (maladaptive stress response), anxiety, and nausea

**Pet owner peace of mind and satisfaction**

- Pet owners interpret normal feeding as happiness and quality of life in their pet
- Lack of eating can be interpreted by the owner as “anger” toward them; it fractures the human-animal bond
- The multi-pet household goes back to normal
- Drives the perception of good quality of care and strengthens the bond with the hospital and veterinary team

> “I deal with nausea and inappetence on a daily basis, and we know how inappetence and not eating are tied to quality of life...owners associate feeding their pets with health and love.” Dr. Sue Ettinger

**Pet Owner Experience**

Inappetence may impact the human-animal bond: In the experience of the advisory board veterinarians, pet owners tended to view a dog rejecting food after surgery as a rejection of the pet owners themselves, leading to pet owner guilt.

Dr. Ralph Harvey also asserted that pet owners think that food is love and a delayed return to feeding fractures the bond between pet and owner. It was further suggested by Dr. Tamara Grubb that a pet owner is likely to anthropomorphize his/her pet and draw the conclusion that the pet is in fact mad at the owner over the surgery.

Following this, she paraphrased her pet owner’s typical perspective: “When they eat, I know they’re happy...and everything’s going to be OK.”
Practice health

The experience of the pet owner was discussed hand in hand with the perception of the veterinary clinic, since a positive pet owner experience is good for the health of the practice. The primary insight discussed was the concept of value: A pet owner who is happy with his/her pet’s surgery will see the value of the clinic’s services, which is what drives pet owner willingness to pay:

“This will pay for value. And we want value-added experiences, options & standards of care in our hospitals.” Dr. Ralph Harvey

This was a wide consensus among the board, as members agreed that a pet and owner who share a stronger bond on discharge are happier with the clinic and more likely to be loyal customers in the future.

Practice operation costs can also improve due to the need for fewer team members and less overhead being tied up by surgical complications, extra patient holding time, repeated visits or therapy, phone calls regarding the dog not eating, and challenging pain management.

Clinic team satisfaction

Patients vomiting after surgery or complications during surgery can be profoundly damaging to the well-being and peace of mind of the healthcare team. The clinic team carries this stress and guilt into their personal lives, and it can lead to conflict amongst the team, long-term job dissatisfaction, and employee turnover.

On top of directly dealing with surgical complications and clean-up duties, the healthcare team also values their bond with the owner. Dr. Sue Ettinger related the improvement of team mental health to the reduction of aggravated phone calls and emails from pet owners to her staff.

“Absolutely, it lowers stress for your healthcare team. It lowers the incidence of bites and scratches. And those are, in part, some of the benefits that are seen with Fear Free approaches.” Dr. Ralph Harvey

Quality of life

Ultimately, improvements to surgical routines relate back to the importance of the patient’s quality of life and how it is impacted by perioperative discomfort, anxiety, and pain.

What does it mean to prioritize the patient’s quality of life in a clinic protocol? Consider the perspective of the dog owner. Among pet owners, 63.2%4 considered their pets to be family members. Another 35.8% considered their pets to be pets or companions. The remaining 1% considered their pets to be property, and that feeling is trending upward.

In 2018, that percentage climbed all the way to 85% of dog owners.5 This means that the large majority of dog owners are likely valuing pros and cons of their dog’s surgery in the same way they would evaluate a procedure involving any other family member.

“This is happier pets, happier clients, a happier team.” Dr. Sue Ettinger

The advisory board participants were passionate about changing the perspective about canine vomiting as a minor occurrence, when in fact it contributes to misery and suffering, leading to fear, anxiety, and stress for the dog. Prevention has a positive impact on quality of life for the dog, the healthcare team, and the owner.

Do pet owners consider their pet to be a member of their family?

In a study, of the 12 dogs that returned to feeding by 6 hours into recovery, 4/12 (33.3%) had received placebo treatment and 8/12 (66.7%) had been treated with Cerenia pre-operatively. Seven of 13 placebo-treated dogs (53.8%) had not eaten at least 100 grams of food 20 hours after surgery while only one Cerenia-treated dog (6.7%) still had not eaten a total of 100 grams of food at 20 hours.
# Common perceptions & current insights

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<thead>
<tr>
<th>Perception #1</th>
<th>Perception #2</th>
<th>Perception #3</th>
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<tr>
<td><strong>Vomiting in dog is “normal” and not distressing to the dog</strong></td>
<td><strong>Preanesthetic vomiting in dogs is desirable to ensure the stomach is empty and thus reduce the risk of aspiration</strong></td>
<td><strong>Patients suspected of having a foreign body should not receive Cerenia®</strong></td>
</tr>
<tr>
<td>While dogs seem to easily vomit (and often eat) stomach contents, “nausea” is subjective. Since dogs are a non-verbal species, we need to use that term knowing that they can’t tell us what they are feeling. Dogs that vomit on the way to the veterinary hospital for an operation (motion sickness and/or anxiety), and that vomit at the hospital or after a procedure, are very likely experiencing some degree of discomfort and fear.</td>
<td>Despite perceptions, vomiting is not an effective tactic to empty the stomach.</td>
<td>When an obstruction or foreign body is suspected, use antiemetic therapy conservatively while continuing to test for obstruction.</td>
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> “So I presume that our animals who come to us, who have nausea as a result of motion sickness or as a result of our premeds, are suffering from that same bad feeling for a long period of time.” Dr. Ralph Harvey

> “In the early days of our anesthesia training, we thought if animals vomited preoperatively, their stomach would be empty and that, that might even be a benefit. And yet we saw many patients who would vomit repeatedly showing, demonstrating for us that the vomiting did not necessarily empty their stomach.” Dr. Ralph Harvey

> Dr. David Twedt’s experience with patients’ suffering from GI obstructions found that Cerenia “stops dogs that have obstructions from vomiting, and it has really been shown not to have major effects on increasing or decreasing GI motility.”
How to get patients back on their paws faster

A study performed at Colorado State University with Dr. David Twedt’s research team found that canine patients given a dose of Cerenia® preanesthetically were more likely to eat within 3 hours after extubation than patients dosed with morphine preanesthetically. 64.7% of dogs given Cerenia returned to eating within 3 hours, compared to only 15.3% of patients with morphine.6

The results are in line with recent research on the use of Cerenia, which found that it significantly reduced vomiting in dogs that were premedicated with morphine. This study further reported that the use of Cerenia improved the quality of recovery (as measured by decreased aimless movements, vocalization, and panting) compared to placebo-treated dogs.2

Cerenia has also been adopted by Dr. Harvey and his colleagues from the teaching hospital at University of Tennessee College of Veterinary Medicine. He attributed the school-wide adoption of adding an antiemetic to the anesthetic protocol to a better understanding around the reduction of fear, anxiety and stress in their patients, and getting them to eat sooner post-surgery.

What can we learn from human health studies?

An article published in March 2019 investigated the incidence of postdischarge nausea and vomiting (PDNV) in humans and found that these figures were underreported; the actual number of surgical patients who suffer from PDNV is much higher than they originally thought.7

Similarly, Dr. Ralph Harvey referenced a body of work in human medicine that compared the cost of antiemetic medications with the cost of complications such as an episode of aspiration or delayed recovery, which found that these overhead costs were quite high.8

A consensus guideline printed for human postoperative nausea and vomiting management reports that human patients identify nausea and vomiting as one of the most dreaded postoperative consequences, often ranking it above pain. The guidelines specify the need to move toward the use of evidence-based prophylactic treatment, highlighting the importance of prevention of these symptoms as opposed to reactionary medicine.9

It is possible that dogs experience nausea in the same way that people do: Dr. Harvey tends to presume that animals presenting with vomiting due to motion sickness or perioperative medication experience negative feelings of nausea over a long period of time. However, it is impossible to say for sure because it is a nonmeasurable subjective experience. Therefore, veterinarians and veterinary antiemetics tend to focus on perioperative vomiting compared to the human discussion of preoperative nausea and vomiting (PONV) and PDNV.

“I see that people are really concerned about nausea and vomiting. But I see that they’re equally concerned about their animals...and they’re willing to pay the same amount to relieve that.” Dr. David Twedt
Looking through the eyes of the pet owner

Recall the AVMA statistics concerning pet owners’ relationships with their pets: 85% of dog owners consider them as family members. In the same way that they wouldn’t consider the cost of a family member’s surgery, they often have other prominent values when approaching veterinary care.

Dr. Ralph Harvey describes the power of value-added care, a philosophy of providing care that emphasizes enriching and improving the patient experience, focusing not on the cost that is being charged, but the value that is being provided. It all starts with having the conversation with pet owners and educating them about the services provided.

In a survey of 897 pet owners 84% of them would be concerned if their pet vomited when they got home from surgery, and 59% said that they are willing to spend the necessary time and also pay for antiemetic treatment for their pet: They value the care of their pet more than the time or cost associated with this side effect of anesthesia.” Dr. Bonnie Kraus

Board Recommendations for Best Practice

1. Use of an antiemetic in canine general anesthesia is best practice, even without opioids.
2. Change our thinking about emesis: Centrally driven emesis is normal; peripherally driven is not. It is aversive and destructive.
3. Change our mindset to a preventive/proactive one to avoid discomfort and distress.
4. Focus on return to normal feeding as much as on emesis: the importance of eating on gut function, immune function, and the microbiome.
5. Relieve FAS – fear, anxiety, stress and improve quality of life.

“We first started seeing this with better pain management. When people would say, “Wow! My dog did so much better this time than last time,” it was pain management then and now it’s more antiemetics, but you’re absolutely right, they notice that. It is important.” Dr. Tamara Grubb

“When we were trying to get people to do pain management, they would ask the clients if they were willing to pay for pain management. And I think most veterinarians found that the owners were absolutely willing to pay for it, and I think maybe treatment of peri-anesthetic vomiting & nausea goes the same way...in that you ask owners if they would be willing to pay for anti-emetic treatment...we have found that >90% are concerned about their dog experiencing nausea & vomiting associated with anesthesia and are willing to pay for treatment to avoid this side effect in their pet.” Dr. Bonnie Kraus

“For me, I have gotten to the point where I have added Cerenia® as part of the anesthesia protocol in my oncology practice. While I also use Cerenia commonly in my chemotherapy patients as a preventative and to treat emesis, I have just made it part of my anesthetic protocol in general.” Dr. Sue Ettinger
Happier pets, happier clients, a happier team: path to best practice

Talking about the importance of controlling perioperative vomiting is one thing, but the board recognized that the challenge is in the implementation. They shared some of their own best practices as to how they were able to incorporate this routine into their busy practices:

• Include antiemetic as a default cost, built into the package for most surgeries. Dr. Bonnie Kraus: “We don’t ask clients if they want pain management; we provide pain management, and that’s become the standard of care.”

• Speak with pet owners in a way that communicates the value of your services. This includes educating pet owners about the potential incidence of nausea, as well as educating around the broad effects of delayed return to feeding and how an antiemetic can improve it. Additionally, this means educating your team on how best to collect patient information. Dr. Sue Ettinger: “It’s the nurses who are going in, in many situations, or the students or whoever we’re training, and asking, ‘How’s the appetite?’ That’s not the right question, because the pet owner might say good when they are only getting the pet to eat homecooked food and not their regular food. A better question is: what are they eating? Whether it’s after chemo, anesthesia or the recovery period afterwards, we must help the owner identify a decreased or poor appetite so we can treat it accordingly.”

• When possible, avoid guessing about what educated pet owners want to pay for in the course of their pet’s surgery: The board members use Cerenia® routinely in most surgeries because their pet owners find it to be a positive value-add.

• In the event that a pet owner needs to discuss lower cost options, or for non-income-generating surgeries such as some spays and neuters, consider ways to offer 2 tiers of treatment while still advocating for and educating about the inclusion of a base level of antiemetic dosing in every protocol.

• Involve the whole clinic team in developing new surgical routines. Administering antiemetics means less vomit for the healthcare team to clean up and more happy patients. With whole clinic buy-in, we see whole clinic benefit. The ad board members discussed the importance of everyone taking part, and Dr. Sue Ettinger shared her thoughts on her nursing team: “That’s how programs are successful: You have to have the team. The whole team, it’s not just the doctors; it’s the nurses as well... I think that’s how you make protocol successful.”

• Have a team member arrive at the clinic an hour early to accept surgical patients and administer subcutaneous antiemetic in preparation for surgery. If timing is a concern? Dr. Bonnie Kraus: “We know that the clients have no problem waiting, coming in early, an extra hour... so if they had all their surgery animals dropped off with one technical staff there, and could dose them in the morning.”

• Consider alternative routes of administration if it is not possible to have the antiemetic treatment given an hour before surgery.

“I think it’s just habit that says we can’t do it.” Dr. Tammy Grubb
For the prevention of acute vomiting, dispense whole or half tablets in strengths that most closely result in a 2 mg/kg dose:

- Dogs and for the treatment of vomiting in cats.
- Motion sickness in dogs. CERENIA (maropitant citrate) Injectable Solution is indicated for the prevention and treatment of acute vomiting in dogs.

The chemical structure of maropitant citrate is:

\[
\text{R}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N}^+\text{C}_6\text{H}_4(\text{OH})\text{C}_6\text{H}_4(\text{OH})_2\text{H}
\]

The following adverse reactions were reported during the conduct of a US clinical field trial where CERENIA Tablets were administered once daily for 2 consecutive days. Dogs may have experienced more than one of the observed adverse reactions:

1. The following adverse reactions were reported during the course of a US field study for the prevention of acute vomiting in dogs treated with CERENIA Tablets at a minimum of 2 mg/kg orally once daily for up to 5 consecutive days:

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- Post-Approval Experience (CERENIA Tablets - Revised May 2019)

The following adverse reactions were reported during the course of a US field study for the prevention of acute vomiting in dogs treated with CERENIA Tablets at a minimum of 8 mg/kg orally once daily for up to 5 consecutive days:

- Dogs (24 to 108 months of age)

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Allergic reactions typically resolve with treatment within 48 hours after discontinuing CERENIA administration. Changes in heart rate, atria, conduction, heart failure, tremors, hiccups, lack of consciousness, recumbency, injection site reactions (swelling, inflammation, and edema). Cases of death (including euthanasia) have been reported. Cats: The following adverse reactions were reported during the course of a US field study for the treatment of vomiting in cats treated with 1 mg/kg CERENIA Injectable Solution subcutaneously once daily for up to 2 consecutive days.

Frequency of Adverse Reactions by Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (n=62)</th>
<th>CERENIA (n=133)</th>
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<tbody>
<tr>
<td># dogs % occur</td>
<td># dogs % occur</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.2)</td>
<td>8 (6.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

For the major metabolite, 10.4% of the maropitant dose was recovered in urine and 9.3% in feces. Plasma protein binding of maropitant in cats cleared by an enzyme known as cytochrome P-450 (CYP). The hepatic metabolism of maropitant involves two cytochrome P-450 isoenzymes: CYP2D15 and CYP3A12. However, as doses increase (20–50 mg/kg PO), dose proportionality is re-established.

Vomiting is a complex process coordinated centrally by the emetic center which consists of several brainstem nuclei (area postrema, nucleus tractus solitarius, dorsal motor nucleus of the vagus) that receive and integrate sensory stimuli from central and peripheral sources and motor nuclei that control the movement of the stomach. The vomiting center, or emetic center, is considered the key neurotransmitter involved in emesis. By inhibiting the binding of substance P within the vomiting center, CERENIA Tablets and Injectable Solution may delay or prevent vomiting.

Clinical Pharmacology: Pharmacodynamics

Following oral administration, mean time to reach Cmax was within 2.5 h. The absolute bioavailability of maropitant was low (24%) following oral administration of 2 mg/kg maropitant. After an oral dose, prandial status does not significantly affect the extent of oral bioavailability. Greater than 98% of the administered dose can be expected with an increase in dose (11–16 mg/kg). However, as doses increase (20–50 mg/kg PO), dose proportionality is re-established. Based on in vitro enzyme kinetics, inactivation of a high capacity enzyme (CYP3A12) may contribute to this return to dose linearity. Following administration of oral placebo, the maropitant concentrations reached steady state approximately after 4 and 8 days following 2 and 8 mg/kg, respectively. The oral drug absorption ratios were 2.4 ± 0.8 and 4.81 ± 0.6, respectively, after oral administration of 2 and 8 mg/kg, respectively. The exposure of 10 week old puppies to maropitant was lower than that observed in adult dogs, particularly after doses of 1 or 2 mg/kg.

In a study of veterinary cancer patients, dogs were treated with CERENIA Injectable Solution or placebo 1 hour prior to cisplatin (prevention) and 4 hours after cisplatin (prophylaxis). Following administration of apomorphone (central emetic stimulus), vomiting was observed in 33% (4 of 12) of Beagle dogs treated with CERENIA Tablets and 100% (12 of 12) of Beagle dogs treated with placebo tablets. Following administration of spray of peppermint apomorphine, vomiting was observed in 33% (4 of 12) of Beagle dogs treated with CERENIA Tablets and 10% (1 of 10) of Beagle dogs treated with placebo tablets in a study of 275 canine patients presented to veterinary hospitals with a history of acut vomiting, dogs were initially administered CERENIA Injectable Solution or placebo on Day 0. Following the initial dose, dogs allocated to the CERENIA group were treated using either CERENIA Tablets or injectable placebo solution twice daily at the discretion of the clinician. Dogs allocated to the placebo group were treated using either an injectable placebo solution or placebo tablets once daily at the discretion of the clinician. Of the 199 dogs included in the analysis for effectiveness, 27 of 54 dogs (50%) in the placebo group displayed vomiting at some time during the study and 31 of 145 dogs (21.4%) in the treated group displayed vomiting during the study period.

PK Parameter | SC at 1 mg/kg (n=6) | IV at 1 mg/kg (n=6) | PO at 2 mg/kg (n=8) | PO at 2 mg/kg (n=8) |
<table>
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<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>102.99±46.06</td>
<td>296.62±66.77</td>
<td>81.3±22</td>
<td>561±362</td>
</tr>
<tr>
<td>AUC0-24 (ng*h/mL)</td>
<td>1440±3890</td>
<td>3890±1440</td>
<td>6730±3890</td>
<td>9200±4600</td>
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<tr>
<td>Tmax (hr)</td>
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<td>0.40±0.30</td>
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</tr>
<tr>
<td>PK Parameter</td>
<td>SC at 10 mg/kg (n=6)</td>
<td>IV at 10 mg/kg (n=6)</td>
<td>PO at 2 mg/kg (n=8)</td>
<td>PO at 2 mg/kg (n=8)</td>
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<tr>
<td>Cmax (ng/mL)</td>
<td>1701±5648</td>
<td>3787±8504</td>
<td>81.3±22</td>
<td>561±362</td>
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<tr>
<td>AUC0-24 (ng*h/mL)</td>
<td>6730±3890</td>
<td>9200±4600</td>
<td>6730±3890</td>
<td>9200±4600</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
</tr>
</tbody>
</table>

CERENIA is formulated using sodium sulfobutyloxyethyl-ß-cyclodextrin (SBECD), which exhibits enhanced binding to maropitant at refrigerated temperature may mitigate this response (see Pharmacokinetics (CERENIA Tablets)).

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product use involving these data. The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA CVM.

The absolute bioavailability of maropitant was much higher following SC injection (91% of 1 mg/kg) than after PO administration (24% at 2 mg/kg). Decreased with established normal intussusception due to the presence of hemorrhage and the critical role of the CERENIA Injectable Solution.

Pharmacokinetic Parameters in Beagle Dogs (Mean±SD or Mean and Range)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>SC at 1 mg/kg (n=6)</th>
<th>IV at 1 mg/kg (n=6)</th>
<th>PO at 2 mg/kg (n=8)</th>
<th>PO at 2 mg/kg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>102.99±46.06</td>
<td>296.62±66.77</td>
<td>81.3±22</td>
<td>561±362</td>
</tr>
<tr>
<td>AUC0-24 (ng*h/mL)</td>
<td>1440±3890</td>
<td>3890±1440</td>
<td>6730±3890</td>
<td>9200±4600</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.43±0.33</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
</tr>
</tbody>
</table>

The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product use involving these data.

CERENIA Injectable Solution.

Pharmacokinetic Parameters in Beagle Dogs (Mean±SD or Mean and Range)

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>SC at 10 mg/kg (n=6)</th>
<th>IV at 10 mg/kg (n=6)</th>
<th>PO at 2 mg/kg (n=8)</th>
<th>PO at 2 mg/kg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>1701±5648</td>
<td>3787±8504</td>
<td>81.3±22</td>
<td>561±362</td>
</tr>
<tr>
<td>AUC0-24 (ng*h/mL)</td>
<td>6730±3890</td>
<td>9200±4600</td>
<td>6730±3890</td>
<td>9200±4600</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
<td>0.40±0.30</td>
</tr>
</tbody>
</table>
For Prevention: Total Number of Vomiting Episodes.

Frequency Distribution of Numbers of Vomiting Episodes in the analysis for effectiveness, 27 of 54 dogs (50%) in the placebo group displayed vomiting at some time during the study and 31 of 145 dogs (21.3%) in the maropitant group displayed vomiting at some time during the study. Percent of Cats Vomiting for Each Study Day by Treatment.

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Treatment</th>
<th># of Cats</th>
<th># vomited</th>
<th>% vomited</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Placebo (2) PO</td>
<td>1</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

The effectiveness of Cerenia administered at 1 mg/kg IV was demonstrated by bridging the results of a PK study to clinical data supporting effectiveness of 1 mg/kg administered SC. The IV and SC administration of a single dose of 1 mg/kg maropitant are equivalent, based on the bioavailability of the IV and SC formulations and the same therapeutic window.

**ANIMAL SAFETY**: Laboratory and field studies have demonstrated that Cerenia Tablets are well tolerated in dogs after oral administration.

**Tolerance Studies (Cerenia Tablets)**

Twenty-four Beagle dogs (14 males and 10 females) between 11 and 25 weeks of age were administered Cerenia Tablets orally once daily for 6 days at 0, 1, 3, and 5 mg/kg. Treatment-related increases in feed consumption were variable throughout the 4 week acclimatization period. Two dogs that received 8 mg/kg maropitant orally for 2 days were below the reference range for reticulocyte counts. Decreases in reticulocyte counts were also seen in 4 of 16 placebo treated dogs (SC saline) for 5 days. End of study body weights in the 20 mg/kg group were 8-15% lower than baseline body weights.

**Dogs (Ingestible)**

Fifty-six Beagle dogs (28 males and 28 females) approximately 16 weeks of age were administered Cerenia Injectable Solution subcutaneously once daily for 15 days at 0, 1, 3, and 5 mg/kg. There were no deaths in dogs treated in the 1 or 3 mg/kg groups (18 dogs each). Reticulocyte counts were not available for this dog. Cerenia Injectable Solution should be stored at refrigerated temperature 2-8°C (36-46°F). Use within 90 days of first vial puncture. Stopper may be punctured a maximum of 25 times.

**Burner**: It is recommended that the vial be punctured a maximum of 25 times.

**STORAGE CONDITIONS:**

Cerenia Injectable Solution should be stored at refrigerated temperature 2-8°C (36-46°F). Use within 90 days of first puncture. If the vial is punctured a maximum of 25 times, it should be discarded.

**Hypersensitivity**

There were no deaths in dogs treated in the 1 or 3 mg/kg groups (18 dogs each). Reticulocyte counts were not available for this dog. Cerenia Injectable Solution should be stored at refrigerated temperature 2-8°C (36-46°F). Use within 90 days of first vial puncture. Stopper may be punctured a maximum of 25 times.
In-clinic challenge

Try this in your clinic: Choose a series of canine anesthesia patients and give half of them Cerenia® preoperatively. With the other patients, maintain your regular operative routine.

Then, ask your clinic staff if they can identify which recovering dogs had received Cerenia. Have them look for signs such as return to feeding, panting, and vocalization. Members of the advisory board found that most of the time, clinic staff can identify the happier patients with ease.

“When I talk to veterinarians and they're not completely convinced about adding Cerenia on, I say, why don’t you get 5 dogs and give those Cerenia, 5 others don’t. Don’t tell your techs what animal is getting what and just see if they can tell a difference. And pretty much invariably they can. They see that the animal seems to feel more comfortable, they’re eating sooner, and just their demeanor—they can tell the difference.” Dr. David Twedt

References:

Cerenia (maropitant citrate)

Try Cerenia in your clinic today to see these results for your patients, your clients, and your team.

IMPORTANT SAFETY INFORMATION: Use Cerenia Injectable subcutaneously for acute vomiting in dogs 2 to 4 months of age or either subcutaneously or intravenously in dogs 4 months of age and older. Safe use has not been evaluated in dogs with gastrointestinal obstruction, or those that have ingested toxins. Use with caution in dogs with hepatic dysfunction. Pain and vocalization upon injection is a common side effect. In people, topical exposure may elicit localized allergic skin reactions, and repeated or prolonged exposure may lead to skin sensitization. See full Prescribing Information, attached.