Pharmacologic Control of Acute Vomiting

Initial nonspecific management of vomiting includes NPO (in minor cases a 4-12 hour period of nothing per os may be all that is required), fluid support, and antiemetics. Initial feeding includes small portions of a low fat, single source protein diet starting 6-12 hours after vomiting has ceased. Drugs used to control vomiting will be discussed here.

The most effective antiemetics are those that act at both the vomiting center and the chemoreceptor trigger zone. Vomiting is a protective reflex and when it occurs only occasionally treatment is not generally required. However, patients that continue to vomit should be given antiemetics to help reduce fluid loss, pain and discomfort.

For many years I strongly favored chlorpromazine (Thorazine), a phenothiazine drug, as the first choice for pharmacologic control of vomiting in most cases. The HT-3 receptor antagonists ondansetron (Zofran) and dolasetron (Anzemet) have also been effective antiemetic drugs for a variety of causes of vomiting. Metoclopramide (Reglan) is a reasonably good central antiemetic drug for dogs but not for cats. Maropitant (Cerenia) is a superior broad spectrum antiemetic drug and is now recognized as an excellent first choice for control of vomiting in dogs and cats. In addition to antiemetic effect, maropitant also provides visceral analgesic effect. Maropitant is also the first choice for prevention of motion sickness vomiting in both dogs and cats.

Metoclopramide (Reglan) is a gastric prokinetic drug that also has central antiemetic effect. Metoclopramide increases gastric and proximal small intestinal motility and emptying without causing acid secretion, decreases enterogastric reflux, and provides inhibition of the chemoreceptor trigger zone. The central antiemetic effect is mediated through antagonism of dopaminergic D2 receptors in the chemoreceptor trigger zone of the medulla to inhibit vomiting induced by drugs, toxins, metabolic disease, and acid-base imbalances. Metoclopramide is a less effective central antiemetic drug in cats than in dogs because serotonin receptors, rather than dopaminergic receptors, predominate in the CTZ of cats. For vomiting in cats, I generally usually use metoclopramide only if a prokinetic effect is desired. Chlorpromazine, dolasetron, ondansetron, or maropitant should be used as a first or second choice to control acute frequent vomiting in cats. Parvovirus can cause gastric hypomotility and therefore the promotility effects of metoclopramide may prove beneficial. However, maropitant, dolasetron, or ondansetron are more effective drugs than metoclopramide for managing vomiting caused by parvovirus. Further, maropitant also helps provide visceral analgesia and is the best single drug choice in parvo cases.

The recommended injectable dose of metoclopramide is 0.2 to 0.5 mg/kg IM or SC given TID to QID as needed. Metoclopramide can also be given IV as a constant rate infusion (1 - 2 mg/kg over 24 hours). Metoclopramide should not be used if gastric outlet obstruction or GI perforation is suspected, or in patients with a seizure disorder.
**Metoclopramide - Clinical Applications for Chronic Vomiting**

Several clinical applications for use of metoclopramide in dogs with chronic vomiting have been identified. These include gastric motility disorders, gastroesophageal reflux disease (GERD), primary or adjunctive therapy for antral and pyloric mucosal hypertrophy, and as treatment for nausea and vomiting caused by various other disorders. While cisapride is a superior prokinetic drug, metoclopramide is an effective drug and is often the first choice for prokinetic effect, with cisapride used as a second choice if metoclopramide is not effective. Other drugs that are sometimes used for prokinesis are low dose erythromycin and the H2-receptor blocker ranitidine (Zantac).

Gastric motility disorders have been recognized with increased frequency in veterinary medicine, but are still overlooked. Gastric stasis, characterized by abdominal discomfort, periodic bloating, borborygmus, nausea and vomiting may be associated with a number of clinical states that include inflammatory disorders (e.g., chronic gastritis, IBD), gastric ulcers, gastroesophageal reflux, infiltrative lesions (e.g., neoplasia), and chronic gastric dilatation. Metabolic disturbances that may cause gastric stasis include hypokalemia, hypercalcemia, acidosis, anemia, and hepatic encephalopathy. Short-term continued vomiting that is observed in some cases after apparent recovery from viral enteritis may be due to abnormal gastric motility. Transient (3 to 14 days) gastric hypomotility may also occur after gastric or abdominal surgery. Motility disorders with no organic cause may be best classified as idiopathic. For any of the disorders listed, the primary cause should be treated, and metoclopramide may be a valuable short-term adjunct to therapy in these cases, along with feeding low fat foods in divided amounts. Metoclopramide alternatively may be used as the primary treatment on a long-term basis for idiopathic hypomotility disorders. Metoclopramide has also been useful in treatment of dogs that have chronic vomiting characterized by episodes occurring routinely in the early morning and containing bilious fluid.

In general, patients less than 4.5 kg (10 lb) receive 2.5 mg per dose, 4.5 to 18 kg (11-40 lb) 5 mg per dose, and greater than 18 kg (40 lb) 10 mg per dose. Metoclopramide is given 30 to 45 minutes before meals and again at bedtime. Animals that require chronic medication may need only 1 to 2 doses daily. Because of its short half-life, the drug is not effective when given by intravenous or intramuscular bolus injection for purposes other than when only one treatment would be administered (i.e., to aid in evacuating the stomach if an anesthetic procedure in a non-fasted patient becomes necessary, pre-radiologic contrast study). Subcutaneous administration into fat may be of benefit when oral therapy is contraindicated and an intravenous line is not available.

Metoclopramide is less effective as a promotility drug than cisapride (see later discussion). While many animals with gastric hypomotility respond well to metoclopramide, some have a less than desired response. If a patient with a suspected gastric hypomotility disorder has an inadequate response to metoclopramide, cisapride should be tried next.

**Side Effects**

Some adverse effects may occur if metoclopramide is given in the usual therapeutic doses. Clients should be apprised of these before the medication is prescribed. These effects are uncommon in animals, and somewhat more common in humans.
Motor restlessness and hyperactivity may occur; and when observed, these signs usually begin 20 to 30 minutes after a dose and last 4 to 5 hours. The reaction can range from mild to quite dramatic. Alternatively, drowsiness and depression occasionally occur. Side effects are infrequent in cats, but clients have reported disorientation, frenzied behavior, and hiding tendencies associated with the medication. Hospitalized animals may chew excessively at catheter sites or be more aggressive toward hospital staff. Sometimes these effects are subtle and nursing staff need to be observant. These side effects are reversible (diphenhydramine [Benadryl 2.2 mg/kg IV] or discontinuing the drug) but generally do not subside when lower doses are given. Unless side effects are infrequent, the use of metoclopramide should be discontinued if adverse reactions are seen. Cisapride does NOT cause these same type of adverse reactions. Metoclopramide crosses the blood brain barrier, cisapride does not.

In general, metoclopramide should not be given to epileptic patients. Other contraindications include evidence of significant mechanical obstruction, simultaneous use of anticholinergic agents (antagonism of metoclopramide’s effects), and pheochromocytoma.

**Ondansetron - Clinical Applications for Acute Vomiting**

Ondansetron (Zofran) is a potent antiemetic drug that has proven to be effective in both humans and animals for control of severe vomiting. It has been used in human cancer patients undergoing cisplatin therapy, a drug that frequently causes nausea and severe vomiting, with very good results. Ondansetron acts as a selective antagonist of serotonin S3 receptors (a principal mediator of the emetic reflex). S3 receptors are found primarily in the CTZ, on vagal nerve terminals, and in the gut in enteric neurons. The principal site of action of ondansetron is in the area postrema, but it also has some peripheral gastric prokinetic activity.

In my experience, ondansetron has produced very good results in either controlling or at least significantly decreasing the frequency of vomiting in dogs and cats with frequent or severe vomiting, including in dogs with severe parvovirus enteritis, in pancreatitis patients, and cats with hepatic lipidosis. The recommended dose is 0.5 to 1 mg/kg IV given as a slow push every 6 to 12 hours (based on patient response). Frequently dogs that appear quite distressed due to nausea and vomiting look much more relaxed and comfortable within 15 minutes of receiving ondansetron. There are no reports of any significant side effects such as diarrhea, sedation, or extrapyramidal signs in human and animal trials. While Zofran was quite expensive for many years, it came off patent in 2007 and is now more affordable for use at any small animal hospital. *Currently, however, my top antiemetic drug of choice is maropitant (Cerenia), because it is a highly effective antiemetic drug but also because it provides visceral analgesic effects as well.* Animals with significant liver disease may be best managed with ondansetron or dolasetron, as maropitant should be used with caution in animals with significant hepatic dysfunction (although it is not contraindicated – some clinicians have used maropitant successfully and safely in animals with liver disease).

**Dolasetron**

Dolasetron (Anzemet) is also a 5-HT3 receptor antagonist antiemetic drug, with action similar to ondansetron. It is a slightly less expensive alternative to ondansetron and only needs to be administered once daily. Indications are the same as for ondansetron, namely, for control of frequent vomiting that is poorly responsive to lesser expensive front-line
antiemetic drugs. The dose is 0.5-1 mg/kg IV once daily. Dolasetron is generally well tolerated in animals.

**A NEWER ANTIEMETIC DRUG FOR DOGS**

Most drugs used to control vomiting in animals have been developed for use in humans. There has been a need for a broad-spectrum antiemetic drug for use in animals that is effective in a variety of situations, has a rapid onset of action, is safe and affordable, and is available in both injectable and oral preparations. **Maropitant citrate (Cerenia)** is a newer broad-spectrum antiemetic drug that is indicated for the treatment of acute vomiting in dogs. Maropitant is a neurokinin receptor antagonist that blocks the pharmacologic action of the neuropeptide substance P in the central nervous system. Substance P is found in significant concentrations in the nuclei comprising the emetic center and is considered a key neurotransmitter involved in emesis. By inhibiting the binding of substance P within the emetic center, maropitant provides broad-spectrum effectiveness against both neural and humoral causes of vomiting.

Clinical trials and recent clinical experience, since August 2007 when the drug was released for use in the U.S., have shown maropitant to be very effective for control of a variety of causes of acute vomiting in dogs. It is administered as a once-daily injection (0.45 mg/lb [1 mg/kg] SC for dogs), which is a significant advantage over many other antiemetic drugs, and has a rapid onset of action. Maropitant is also available in tablet form for outpatient use, which makes it a very attractive choice for use in small animal practice. It is the drug of choice for dogs with motion sickness.

**CAUTION:** We generally advise that Cerenia be used at a reduced dose (50%) for animals with significant hepatic dysfunction, OR select an alternative antiemetic for animals with liver disease – e.g., ondansetron or dolasetron.

**The issue of stinging on injection:** Information from clinical experience and studies indicates that there is less likelihood for stinging to occur with maropitant injections when the product is kept refrigerated. The current guidance is that the solution should be kept refrigerated and drawn up and injected right away at refrigerated temp. In practice a sting can still be expected in some patients even when the product is kept refrigerated.

**CATS:** Studies have now been done using maropitant in cats and some clinicians in general practice have been using it since 2008. In May 2012 Cerenia was approved for use in cats and also in puppies as young as 8 weeks of age.

**Recommended dose of maropitant for cats:**

- **Injectable:** 0.5-1 mg/kg SC or IV (give SLOWLY over 60-90 seconds if administering IV)
- **Oral:** (1 to 2 mg/kg). This is the starting dose recommended for prevention of motion sickness in cats as well; i.e., somewhat lower than the canine dose for motion sickness.

**Note:** On January 14, 2016, Zoetis announced a new label claim for IV use of Cerenia. In two separate bioequivalence studies conducted in 2015 by Zoetis in dogs and cats, when delivered intravenously, CERENIA reached concentration and absorption levels as quickly as with subcutaneous injection. Additionally, two separate safety studies in dogs and cats
indicated no related effects on survival or clinical findings, and there were no reports of pain on intravenous injection.

**Consider Using Cerenia More Routinely Administered PRE-Operatively**

Some practices have now instituted the practice of including an injection of Cerenia administered routinely in the pre-operative period. I am a strong proponent. Reasons for doing this include:

- Help prevent post-op vomiting and nausea and decrease chances of aspiration
- Adjunctive visceral analgesia
- Improved patient comfort in the post-op period
- Earlier return to eating, with improved appetite and volume of food consumption

In this setting, Cerenia can be administered anytime in the pre-op period. If morphine or hydromorphone are going to be given as part of the pre-anesthesia sedation and preemptive analgesia plan, and the clinician desires to prevent vomiting secondary to these emetogenic drugs, Cerenia is administered 45 minutes prior to the emetogenic drugs. In one study when Cerenia was administered 45 minutes prior to morphine at 0.5 mg/kg, 0/15 dogs vomited, while 15/16 dogs who received saline instead of Cerenia vomited at least once (and 4 of the dogs vomited 4 times). We have seen excellent post anesthesia recovery periods in dogs that have undergone a variety of procedures, including OVH/neuter as well as prolonged anesthesia for dental procedures, major abdominal procedures, etc. We are also using Cerenia more routinely prior to performing endoscopic procedures.

The uniform response is that most patients recover more smoothly, more quietly and are presumably more comfortable overall. Clients of course are very happy when their pet eats earlier than would be otherwise expected. This has represented a gratifying advance in patient care in many ways - - helping our patients be more comfortable is always good.

**How long can Cerenia be used on a consecutive days schedule?**

The original label guidance stated that Cerenia should not be given for more than 5 consecutive days (injectable or oral at the anti-emesis dose) and for 2 days at the motion sickness prevention dose. However, experience has shown that in some patients Cerenia has been used safely and effectively on a longer term basis (anecdotal reports, e.g., patients with neoplasia or renal disease that were experiencing ongoing nausea, vomiting, and inappetence). Many of these patients have a much better quality of life while on Cerenia, as they have less nausea and vomiting and a much better appetite. There are cats that have been treated with a daily oral dose for months to several years. Use of Cerenia in this fashion is being investigated further.

Further, in 2015 the label was changed, based on studies that evaluated the effect of maropitant when given at various doses for longer periods of time. Cerenia has a high safety profile and a longer duration of use, based on each patient’s individual needs, is now well accepted.
A study was presented at the Veterinary Cancer Society (VCS) meeting in San Diego Oct. 29-November 1, 2010, and then subsequently at the ACVIM Forum in Denver in June 2011: **Pharmacokinetics of maropitant citrate dosed orally to dogs at 2 mg/kg and 8 mg/kg once daily for 14 consecutive days.** Two groups of eight healthy beagle dogs were administered maropitant citrate at 2 or 8 mg/kg orally once daily for 14 days. Concentrations of maropitant and its metabolite were measured in plasma using a LC-MS/MS assay. Pharmacokinetic parameters were estimated using non-compartmental pharmacokinetic techniques and a modeling approach was used to estimate steady-state.

Results: The model estimate for the number of doses required to reach 90% of steady-state was 4.30 for 2 mg/kg and 8.09 for 8 mg/kg. Four dogs experienced a single dose of vomiting.

Conclusions: Dosing maropitant citrate beyond the original label duration of 5 days was well tolerated by healthy dogs. During the 14 days of dosing there was accumulation, however, steady-state was reached after approximately 4 doses for daily 2 mg/kg dosing and 8 doses for daily 8 mg/kg oral dosing.

**Use of Oral Maropitant (Cerenia)**

- Confident there is no GI foreign body (i.e., do not use ongoing antiemetic therapy if there could be a foreign body lodged in the GI tract)
- Prevent vomiting during cyclosporine, azithromycin, or other drug induction period (use for 3-5 days in conjunction with the start of a drug that might cause vomiting)
- Vomiting flare-ups in IBD patients (or other chronic disorders)
- Pancreatitis, parvovirus, etc for a few days after vomiting is fairly well controlled with injectable maropitant. Excellent control of nausea may help improve appetite and earlier food intake
- Prevention of vomiting in chemotherapy patients
- Prevention of motion (“car”) sickness
- Renal disease patients – and perhaps chronic use (these patients may benefit tremendously and we have observed many patients that eat better, do not vomit or exhibit nausea, and feel better overall. Studies are ongoing).

**Cisapride**

Cisapride is a potent GI prokinetic drug and is superior in action to metoclopramide. It is no longer on the market for use in humans, as of 2000, because of an association with fatal arrhythmias. There are no reports of similar complications existing in dogs and cats, however, and cisapride continues to be readily available to veterinarians through compounding pharmacies.

Cisapride has broader promotility effects than metoclopramide (e.g., cisapride has demonstrated excellent efficacy in management of colonic inertia and small intestinal ileus).
In contrast to metoclopramide, which has central effect at the CRTZ in addition to its peripheral effects, cisapride has no known direct antiemetic properties. Another contrast is that metoclopramide's prokinetic effect is most significantly on the stomach. It is NOT a reasonable choice for treatment of small intestinal ileus.

The most relevant uses of cisapride in animal patients include treatment of gastroparesis, especially in patients that experience significant side effects from metoclopramide (e.g., hyperactivity and other dystonic reactions) or where metoclopramide is not sufficiently effective, idiopathic constipation, gastroesophageal reflux disease (if H2-receptor antagonists or proton pump inhibitors and dietary management alone are not effective), and postoperative ileus.

Cisapride is extremely well tolerated by animal patients. I have used cisapride in dogs and cats that have experienced neurologic side effects from metoclopramide. I have observed no adverse reactions to cisapride in any of these patients, even in those whose side effects to metoclopramide included very bizarre behavior changes. The suggested dose of cisapride is similar to what has been recommended for metoclopramide (see earlier discussion).