Pharmacologic Control of Vomiting

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Initial nonspecific management of vomiting includes NPO (in minor cases a 6-12 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 highly 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. Studies and clinical experience have now also shown maropitant to be an effective and safe antiemetic drug for cats. While it is labeled only for dogs, clinical experience has shown it is safe to use the drug in cats as well. Maropitant is also the first choice for prevention of motion sickness vomiting in both dogs and cats.

Phenothiazine antiemetics (chlorpromazine, prochlorperazine) have a broad spectrum effect and are effective in controlling vomiting due to a variety of causes. Chlorpromazine acts on the emetic center, chemoreceptor trigger zone, and on peripheral receptors. It is also thought to function as a calcium channel antagonist. This effect decreases cyclic AMP concentrations in intestinal epithelial cells which leads to decreased intestinal epithelial cell secretion. Further, chlorpromazine has minimal anticholinergic effects. The recommended dose is 0.1 to 0.25 mg/lb IM or SC SID - TID as needed to control vomiting. At this dose there is a minimal sedative effect. Any sedation resulting from use of chlorpromazine, unless pronounced, is not considered a deleterious side effect, and in fact this is often considered a beneficial effect through decreasing the discomfort and distress that can be associated with nausea. Chlorpromazine is an excellent choice for control of nausea. Patient comfort should always be a priority.

A potential side effect of phenothiazine drugs is hypotension, which can result from an alpha-adrenergic blocking action, causing arteriolar vasodilation. This is of minimal concern in well-hydrated patients, and in dehydrated patients it is readily controlled with intravenous fluid support. For patients with vomiting due to renal or liver disease that are already depressed, the dosage of chlorpromazine is often reduced to 0.1-0.15 mb/lb SID-BID. This lower dose is often effective for controlling vomiting and is not likely to cause significantly more sedation.

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 only use metoclopramide if a promotility 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 likely to be more effective than metoclopramide.

The recommended injectable dose of metoclopramide is 0.1 to 0.25 mg/lb IM or SC given TID to QID as needed. Metoclopramide can also be given IV as a constant rate infusion (0.5 - 1.0 mg/lb over 24 hours). Metoclopramide should not be used if gastric outlet obstruction or GI perforation is suspected, or in patients with a seizure disorder. Whereas in the past chlorpromazine and metoclopramide were occasionally used together in dogs in which neither drug was effective in significantly reducing the frequency of vomiting when used alone; currently, ondansetron, dolasetron, or maropitant are preferred as single agent therapy for control of acute, severe emesis. It is possible that the combination of chlorpromazine and metoclopramide may potentiate side effects that may result from use of either drug individually. Animals that are treated with a combination of chlorpromazine and metoclopramide are observed carefully for nervous-type behavior or significant depression. My preference at this time, if both chlorpromazine and metoclopramide are ineffective when given individually, or if there is severe vomiting that does not respond to whichever of these drugs is used first, is to institute dolasetron (Anzemet) or ondansetron (Zofran) therapy (see later discussion).

**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 hypertrphy, 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 10 pounds receive 2.5 mg per dose, 11-40 pounds 5 mg per dose, and greater than 40 pounds 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 house staff need to be observant. Humans describe metoclopramide side effects as quite bothersome and some individuals have said they “felt like they were going to jump out of their skin.” These side effects are reversible (diphenhydramine [Benadryl 1 mg/lb 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, Glaxo Pharmaceuticals) is a potent antiemetic drug that has proven to be very 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 dramatic 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 dramatic 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 0.25 to 0.5 mg/lb 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 affordable for use at any small animal hospital. Its use should be considered in any patient with intractable vomiting (maropitant and dolasetron are the other top choices for this situation). Animals with significant liver disease are best managed with ondansetron or dolasetron, as maropitant must be used with caution in animals with significant hepatic dysfunction.

It is best to treat animals with frequent severe vomiting aggressively in order to significantly decrease the frequency of vomiting and to enhance patient comfort. Oftentimes early use of more aggressive therapy in controlling severe vomiting, in conjunction with other therapy, will hasten an earlier positive response and a shorter hospital stay, with a lower hospital bill than if the patient is allowed to linger too long while it receives less than effective therapy.

**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 0.25-0.5 mg/lb IV once daily. Dolasetron is generally well tolerated in animals. In humans, it has been associated with dose-related ECG interval prolongation (PR, QT, and QRS widening. Headache and dizziness also sometimes occur in humans.

It is strongly recommended that all animal hospitals maintain either Anzemet or Zofran in stock, along with other antiemetic drugs, for most effective control of vomiting from a variety of causes.

**A NEW 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: Use at a reduced dose 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 over the last year 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.

CATS: Studies have now been done using maropitant in cats and some clinicians in general practice have been using it since 2008.

Safety, pharmacokinetics and use of the novel NK-1 receptor antagonist maropitant (cerenia) for the prevention of emesis and motion sickness in cats.

“The present study characterizes the safety, pharmacokinetics, and antiemetic effects of the selective NK-1 receptor antagonist maropitant in the cat. Safety of maropitant was determined following 15 days of subcutaneous (SC) administration at 0.5-5 mg/kg. Maropitant was well tolerated in cats at doses that exceeded the efficacious antiemetic dose range of the drug by at least a factor of 10 and adverse clinical signs or pathological safety findings were not noted at any dose. The pharmacokinetics of maropitant in cats were determined following single dose oral (PO), intravenous (IV) and SC administration. Maropitant had a terminal half-life of 13-17 h and a bioavailability of 50 and 117% when administered PO and SC, respectively. Efficacy was determined against emesis induced either by xylazine or by motion. A dosage of 1 mg/kg maropitant administered IV, SC, or PO prevented emesis elicited by xylazine. The compound had good oral antiemetic activity and a long (24 h) duration of action. Maropitant (1 mg/kg) was highly effective in preventing motion-induced emesis in cats. These studies indicate that the NK-1 receptor antagonist maropitant is well tolerated, safe and has excellent antiemetic properties in cats.”

Recommended dose of maropitant for cats:
Injectable: 0.25-0.5 mg/lb (0.5-1 mg kg) SC or IV (give SLOWLY if administering IV)
Oral: 0.5 mg/lb (1 mg/kg). This is the dose recommended for prevention of motion sickness in cats as well; i.e., somewhat lower than the canine dose for motion sickness.

Cisapride
Cisapride is a potent GI prokinetic drug. 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). Cisapride is unique among prokinetic agents in that it does not have antidopaminergic properties. Whereas metoclopramide antagonizes the inhibitory effects of dopamine and can cross the blood-brain barrier, cisapride has no effect on the central nervous system. Cisapride is a benzamide derivative that promotes GI motility by increasing the physiologic release of acetylcholine from post ganglionic nerve endings of the myenteric plexus, leading to improved motor activity of the esophagus, stomach, small bowel, and large bowel. 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 onset of pharmacologic action of cisapride is approximately 30 to 60 minutes after oral administration.

Cisapride increases lower esophageal pressure and lower esophageal peristalsis compared to placebo and/or metoclopramide. It significantly accelerates gastric emptying of liquids and solids. Small intestinal and colonic motor activity are also significantly enhanced. It enhances antropyloroduodenal coordination, and increases propagation distance of duodenal contractions. Cisapride had been approved for treating gastroesophageal reflux disease in humans, but it also had been shown to be effective in treating a variety of other conditions (e.g., gastroparesis, bile reflux gastritis, nonulcer dyspepsia, intestinal manifestations of systemic disorders, postoperative ileus, constipation, irritable bowel syndrome, and in diagnostic studies [radiographic studies, aid in duodenal intubation of motility and suction catheters]).

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 (0.1 - 0.25 mg/lb orally SID-TID depending on the clinical situation). In general, animals weighing 10 pounds or less receive 2.5 mg per dose, 11-14 pounds 5 mg per dose, and those over 40 pounds 10 mg per dose. The dose can be gradually increased if necessary. As is recommended for metoclopramide, cisapride should be administered no closer than 30 minutes before feeding.
References
