A Rational Approach to Anti-Emetic Drug Selection & Cerenia Update

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APPROACH TO VOMITING

Vomiting is a complex reflex act that can result from a number of conditions. Depending on the underlying cause of vomiting, antiemetic drugs may be indicated. Understanding the vomiting reflex and mechanism of action of various drugs will allow the clinician to select the appropriate drug. Vomiting must be distinguished from regurgitation and gastroesophageal reflux. The best way to determine this is to imitate the two acts for the client, emphasizing the repetitive abdominal contractions seen in the vomiting patient. The timing of the event with respect to eating, the volume of material brought up, or contents (unless it contains bile, suggesting true vomiting) do not reliably distinguish vomiting from regurgitation. Vomiting is a reflex act that includes abdominal contractions and prodromal signs, including behavioral changes, salivation, and repeated swallowing attempts. It must be emphasized that these signs are variable. Complications of vomiting include aspiration pneumonia, malnutrition, electrolyte imbalances, acid-base disturbances, and dehydration. In most cases it is helpful to establish a definitive diagnosis, but this is not always necessary or possible.

VOMITING REFLEX

The vomiting reflex begins with afferent receptors located in visceral organs (including gastrointestinal tract, pancreas, heart, liver, genitourinary tract, and peritoneum) and pharynx. Afferent impulses travel through the vagus and sympathetic nerves to the central pattern generator (previously known as the vomiting center) located in the medulla. Vomiting can also be initiated by stimulation of the chemoreceptor trigger zone (CRTZ), also located in the medulla. The CRTZ is sensitive to blood-borne substances. The vomiting reflex can also be initiated by input from the cerebral cortex (rare in animals vs. humans) and from the vestibular apparatus (i.e. motion sickness). Thus, vomiting can be initiated through a “humoral” pathway, caused by blood-borne substances stimulating the CRTZ, or a “neural” pathway, caused by stimulation of the vomiting center from vagosympathetic, CRTZ, vestibular, or cerebral neurons. Examples of vomiting caused by activation of the humoral pathway include chemotherapy drugs, digitalis, uremic toxins, and apomorphine. Examples of vomiting caused by activation of the neural pathway include gastroenteritis, pancreatitis, peritonitis, motion sickness, and emotions (cerebral input). It has also been suggested that vomiting can be initiated by both of these pathways simultaneously. Once receptor activation occurs to stimulate the
vomiting reflex, the efferent limb of the reflex begins with prodromal signs of salivation and excessive swallowing.
Several neurotransmitters and their respective receptors stimulate the CRTZ. Below is a list of the neurotransmitters and their respective receptors:

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor</th>
</tr>
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<tbody>
<tr>
<td>Substance P</td>
<td>NK-1</td>
</tr>
<tr>
<td>Dopamine</td>
<td>D_2-Dopaminergic</td>
</tr>
<tr>
<td>5-Hydroxytryptamine</td>
<td>5-HT_3-Serotonergic</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>M_1-Cholinergic</td>
</tr>
<tr>
<td>Histamine</td>
<td>H_1- and H_2-Histaminergic</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α_2-Adrenergic</td>
</tr>
<tr>
<td><strong>met-, leu-enkephalin</strong></td>
<td><strong>ENK</strong>_µ-Enkephalinergic</td>
</tr>
</tbody>
</table>

In the dog, dopamine and histamine are significant neurotransmitters in the CRTZ, whereas these are much less important in the cat. Therefore metoclopramide (a D_2-dopaminergic antagonist) is less effective in the cat for control of vomiting, and apomorphine (a D_2-dopaminergic agonist) is less emetogenic in the cat. On the other hand, α_2-adrenergic and 5-HT_3-serotonergic receptors are more important in the CRTZ in the cat versus the dog. Therefore xylazine (an α_2-adrenergic agonist) is emetogenic in the cat versus the dog, and ondansetron (a 5-HT_3-serotonergic antagonist) helps prevent vomiting mediated through the CRTZ in the cat (whereas this agent works peripherally in the dog).

In the central pattern generator (emetic center), NK-1 and α_2-adrenergic receptors are the most clinically important. Therefore, NK-1 antagonists (such as maropitant) and pure α_2-receptor antagonists (such as yohimbine) and mixed α_1- and α_2-receptor antagonists (such as prochlorperazine) are effective antiemetics. It is likely that much of the antiemetic effects of phenothiazine drugs act through inhibiting α-receptors (and other receptors) in the CRTZ.

The most important peripheral receptor mediating vomiting in the dog are the NK-1 and the 5-HT_3-serotonergic receptors. Activation of these receptors can occur through inflammation of the gut, luminal distention (the more proximal in the intestine, the more potent), toxins, chemotherapy agents, etc. Antagonists of NK-1 receptors (such as maropitant) and the 5-HT_3-serotonergic receptors (such as ondansetron) help abolish vomiting by these mechanisms. Motility modification through peripheral receptor effects can also control vomiting. Antagonism of D_2-dopaminergic receptors with metoclopramide will increase gastric emptying and proximal intestinal motility in the dog and cat. Activation of 5-HT_3-serotonergic receptors with cisapride will increase propulsive gastrointestinal motility from the lower esophageal sphincter to the colon. Activation of motilin receptors will also improve gastric emptying during the fasting state. This can be accomplished with low dose erythromycin (0.5 to 1.0 mg/kg PO or IV tid).
CONTROL OF VOMITING

**α₂-Adrenergic Antagonists**

- Prochlorperazine (Compazine®) 0.5 mg/kg tid, SQ, IM, Rectal Suppository
- Chlorpromazine (Thorazine®) 0.2-0.4 mg/kg tid SQ, IM
- Yohimbin (Yobine®) 0.25-0.5 mg/kg bid SQ, IM

**D₂-Dopaminergic Antagonists**

- Metoclopramide (Reglan®) 0.2-1 mg/kg qid PO, SQ, IM; CRI @ 2-4 mg/kg/day
- Domperidone (Motilium®) 0.1-0.3 mg/kg bid IM, IV
- Prochlorperazine (Compazine®) 0.5 mg/kg tid, SQ, IM, Rectal Suppository
- Chlorpromazine (Thorazine®) 0.2-0.4 mg/kg tid SQ, IM

**H₁-Histaminergic Antagonists**

- Diphenhydramine (Benadryl®) 2-4 mg/kg tid PO, IM
- Dimenhydrinate (Dramamine®) 4-8 mg/kg tid PO
- Prochlorperazine (Compazine®) 0.5 mg/kg tid, SQ, IM, Rectal Suppository
- Chlorpromazine (Thorazine®) 0.2-0.4 mg/kg tid SQ, IM

**M₁-Muscarinic Cholinergic Antagonists**

- Scopolamine (Hyoscine®) 0.03 mg/kg qid SQ, IM
- Prochlorperazine (Compazine®) 0.5 mg/kg tid, SQ, IM, Rectal Suppository
- Chlorpromazine (Thorazine®) 0.2-0.4 mg/kg tid SQ, IM

**5-HT₃-Serotonergic Antagonists**

- Ondansetron (Zofran®) 0.5-1 mg/kg bid PO, or 30 min prior to chemotherapy, or 0.1-0.5 mg/kg bid IV
- Dolasetron (Anzemet®) 0.5-1 mg/kg bid PO, or 30 min prior to chemotherapy, or 0.1-0.5 mg/kg bid IV
- Granisetron (Kytril®) No dose available
- Metoclopramide (Reglan®) 0.2-1 mg/kg qid PO, SQ, IM; CRI @ 2-4 mg/kg/day

**5-HT₄-Serotonergic Agonists**

- Cisapride (Propulsid®) 0.5-1 mg/kg tid PO, or 1-1.5 mg/kg bid PO
- Tegaserod (Zellnorm®) 0.25-0.5 mg/kg bid-tid PO

**Motilin Agonists**
**Erythromycin**

0.5-1 mg/kg tid PO, IV

**NK-1 Antagonists**

Maropitant (Cerenia®)

Dogs: 1 mg/kg SQ sid, 2 mg/kg PO sid, or 8 mg/kg PO sid for motion sickness
Cats: 1 mg/kg PO and SQ sid

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**Maropitant (Cerenia™): A New Class of Antiemetics**

**Introduction:**

Maropitant (Cerenia™) is a recently approved antiemetic for use in the dog. It is a neurokinin-1 (NK-1) receptor antagonist. Its corresponding neurotransmitter is substance P. Maropitant is absorbed through the intestinal tract via the surface membrane pump P-glycoprotein (PgP), and undergoes principally hepatic metabolism through the cytochrome P450 system. Following hepatic metabolism, oral bioavailability is 24% in the dog (closer to 50% in the cat).

**Efficacy Studies:**

Several studies were conducted for registration purposes (FDA/EMEA) and were therefore randomized, controlled, blinded, conducted to GCP and considered statistically significant at P<0.05. The objective of one study in normal dogs was to evaluate the efficacy of injectable maropitant in the prevention of emesis induced by apomorphine or syrup of ipecac compared to other anti-emetics (metoclopramide, chlorpromazine, and ondansetron). Apomorphine induces vomiting primarily through stimulation of receptors in the chemoreceptor trigger zone (CRTZ), whereas ipecac acts on peripheral receptors in the stomach. In this study, only maropitant demonstrated efficacy against both emetic agents. Both metoclopramide and chlorpromazine only prevented vomiting from apomorphine (thus only acting centrally in the CRTZ), and ondansetron only prevented vomiting from ipecac (thus only acting peripherally). This suggests a broader spectrum effect of maropitant compared with the other antiemetics studied.

In a U.S. field study, maropitant was compared with placebo in dogs with acute vomiting from a variety of causes. The study findings demonstrated that maropitant administered SQ at 1 mg/kg or orally at 2 mg/kg was highly effective in reducing emesis in dogs presenting to veterinary hospitals with a recent history of vomiting. In addition, oral administration of maropitant at 2 mg/kg as a follow-up to an injectable dose was shown to be effective against ongoing vomiting.

In a European field study, maropitant was compared with metoclopramide in dogs with acute vomiting from a variety of causes. This study showed that maropitant efficacy was significantly superior to metoclopramide when vomiting was evaluated by either videotape or by direct observation.
Another study evaluated the efficacy and safety of the injectable formulation of maropitant for both prevention and treatment of cisplatin-induced vomiting in canine cancer patients undergoing cisplatin chemotherapy at 11 US veterinary practices. In this study, saline or maropitant was administered 1-hour prior to cisplatin and either was administered as soon as possible after an emetic event was observed. The results showed that 83% (34/41) of the dogs pretreated with saline vomited, whereas only 5% (2/39) of the dogs pretreated with maropitant vomited following cisplatin. This demonstrated superiority of maropitant for the prevention of vomiting. Once vomiting occurred (in either group), 56% (22/39) of the saline treated group had ongoing vomiting and needed to be “rescued”, whereas only 5% (2/39) of the maropitant treated group were withdrawn for ongoing vomiting and needed to be “rescued”. This demonstrated superiority of maropitant for the treatment of vomiting.

Maropitant was also evaluated for the prevention and safety in puppies or older dogs with a history of motion sickness in three separate studies. In these studies, maropitant or placebo was administered to dogs 1-10 hours prior to a car ride. Only 7-16% of dogs vomited after maropitant administration, compared with 52-68% of dogs that received a placebo, thus demonstrating significant protection from motion sickness-induced emesis.

In summary, maropitant has been demonstrated to have a broad spectrum of efficacy in prevention studies with oral tablets and injectable solution against both central and peripheral emetogens. This includes challenge by apomorphine (central), ipecac (peripheral), and cisplatin (central and peripheral). In addition, maropitant has been shown to have efficacy for treatment of vomiting with the injectable solution only (since it is difficult to administer oral tablets to vomiting dogs). Finally, maropitant provides significant protection from motion sickness-induced emesis.

Studies in cats have shown that maropitant is well tolerated in cats at anti-emetic doses (15 days at up to 5 mg/kg sid). The half-life is 13-17 hours (it’s clearance in cats is much slower than dogs), making this drug once daily dosing in the cat as it is in dogs. There is no evidence that there is drug accumulation with repeated dosing. Efficacy studies in cats have shown effectiveness against emesis induced by xylazine (a centrally acting emetogenic agent in cats) and for motion sickness (demonstrated in a Ferris wheel model). The recommended dose based on the pharmacokinetic studies in normal cats is 1 mg/kg sid PO or SQ. A clinical study in cats with acute vomiting showed that <3% of cats vomited days 0 and 1, then no vomiting day 2 (vs. ~20% for placebo).

**Safety Studies:**
The most common adverse events in dogs > 16 wks of age were vomiting, diarrhea, hypersalivation, lethargy, depression, anappetence, weight loss, and injection site reactions. Many of these were not distinguishable from the disorders that resulted in vomiting. In general, though, maropitant was safe and well-tolerated when administered at the oral and injectable label dose to dogs with a wide range of clinical illnesses and when on a variety of concurrent medications. Caution should be used in puppies younger than 11 weeks of age, as histological evidence of bone marrow hypoplasia was seen at
higher frequency and greater severity in puppies treated with maropitant than in control puppies in the preclinical studies. However, these studies were performed in patients with a variety of infectious diseases in stressed conditions, and at dosages much higher than the label dose. When these studies were repeated in a more controlled setting at the label doses in 9 and 10 week old puppies, bone marrow hypoplasia was not seen. Caution should also be used in dogs with hepatic dysfunction since maropitant undergoes hepatic metabolism.

**Clinical Use of Maropitant:**
For the treatment and prevention of acute emesis, the injectable solution should be administered at 1 mg/kg once daily (for up to 5 days). For prevention of acute emesis, the tablets should be given orally at 2 mg/kg once daily (for up to 5 days). For the prevention of emesis due to motion sickness, maropitant should be given orally at a dosage of 8 mg/kg once daily (for up to 2 days). Dogs should be fasted 1 hour prior to administration and dosed 2 hours prior to travel. Tablets may be given with a small amount of food, but not wrapped tightly in fatty food (which may affect dissolution). Injection site stinging can be minimized by refrigerating the vial. When drawn up into a syringe, it should be administered immediately, prior to allowing it to warm up.

The oral dose of 2 mg/kg is generally interchangeable with the injectable dose of 1 mg/kg. A maximum concentration is achieved in 45 minutes after SQ administration, and in 2 hours after oral administration. Feeding has no effect on oral pharmacokinetics. It should be noted that the label states that drug accumulation could occur with chronic dosing due to non-linear pharmacokinetics (clearance is not constant or proportional to the amount of drug administered), presumably due to saturation of transport processes and metabolizing enzymes. The labeled recommendation is that after 5 days of 2 mg/kg orally, maropitant should be stopped for 1 day, and after 2 days of 8 mg/kg orally, maropitant should be stopped for stopped for 2 days. These recommendations were based on pharmacokinetic modeling, but when actual blood levels were measured, drug accumulation was not observed.

**Specific Syndromes to Use Antiemetics**

**Motion Sickness**

Motion sickness is stimulated by receptors in the inner ear. The CRTZ mediates the pathway in the dog, but not in the cat. The most important receptors mediating vomiting in patients with motion sickness are NK-1, M₁-cholinergic and H₁-histaminergic receptors. Therefore, treatment should involve antagonists of these receptors. Antagonism of NK-1 receptors can be accomplished with maropitant. Antagonists of M₁-cholinergic receptors include scopolamine, and prochlorperazine/chlorpromazine (mainly cats). Antagonists of H₁-histaminergic include diphenhydramine and dimenhydrinate. Since histamine is not an important mediator of vomiting in cats, and histamine receptors are not present in the CRTZ of cats, antihistamines are usually ineffective in this species. Rather, maropitant, chlorpromazine and prochlorperazine are more appropriate drugs.
Uremia

Vomiting in uremic patients is initiated through both central and peripheral pathways. Central pathways are mediated through the effect of blood-borne uremic toxins on the CRTZ. There is primarily stimulation of D₂-dopaminergic receptors (mainly dogs, not cats), and treatment should be with maropitant, or D₂-dopaminergic receptor antagonists such as metoclopramide or chlorpromazine/prochlorperazine. Peripheral pathways are mediated through the effect of uremic toxins on the gastrointestinal mucosa, resulting in erosions/ulcers and uremic gastritis. Therefore treatment should be directed towards gastroprotective agents such as drugs that inhibit gastric acid production (H₂-histaminergic receptor antagonists and proton pump inhibitors such as omeprazole) and drugs that act locally on the gastric mucosa (such as sucralfate).

Drug-Induced Vomiting

Many drugs can induce vomiting. These include a variety of chemotherapy drugs, digitalis, and a variety of antibiotics. These drugs may either stimulate receptors in the CRTZ or peripheral receptors. Chemotherapy drugs in particular stimulate 5-HT₃-serotonergic receptors. This occurs peripherally in the dog and in the CRTZ in the cat. Therefore, 5-HT₃-serotonergic receptor antagonists, such as dolasetron, ondansetron and granisetron would be indicated. Maropitant is also very effective for this mechanism of vomiting. Metoclopramide also inhibits 5-HT₃-serotonergic receptors. Metoclopramide’s effect in this regard is much less than that of ondansetron and therefore is less effective, though it is considerably less expensive. When used for chemotherapy-induced nausea, metoclopramide should be used at high dosages (1 mg/kg).

Gastrointestinal Motility Disorders

Vomiting induced by gastrointestinal motility disorders should be treated with prokinetic agents. Cisapride is the most effective prokinetic agent, stimulating gastrointestinal motility from the lower esophageal sphincter to the colon (through stimulation of 5-HT₄-serotonergic receptors). Cisapride has minimal direct antiemetic effects. Metoclopramide is useful to stimulate motility of the lower esophageal sphincter, stomach, and duodenum (through stimulation of D₂-dopaminergic receptors). It is therefore useful for delayed gastric emptying. Tegaserod (Zelnorm®) was a more recently approved 5-HT₄-serotonergic receptor agonist (though it was subsequently taken off the market). It may be indicated in similar conditions as cisapride. Metoclopramide has minimal effect on the remainder of the intestine due to the lack of D₂-dopaminergic receptors beyond the duodenum. Erythromycin may also be useful for delayed gastric emptying due to its effect of stimulating motilin receptors. When used for this purpose, it should be given at low doses (0.5 to 1 mg/kg tid), much lower than doses used for antibacterial purposes. At the latter doses, erythromycin can cause vomiting. When any of these drugs are used for delayed gastric emptying, they should be given 30 minutes prior to eating. These drugs are also used to treat dogs that vomit bile in the morning.
prior to eating (“bilious vomiting syndrome”). In many of these dogs, there is duodenal-gastric reflux resulting in stimulation of the vomiting reflex. Therefore, a single dose of any of these three agents at bedtime is often effective.

**SIDE EFFECTS OF ANTIEMETICS**

Caution should be used with certain antiemetics due to their side effects. Prokinetic agents (cisapride, metoclopramide, and erythromycin) are contraindicated in cases of gastrointestinal obstruction. However, in my experience serious adverse effects have not been seen when these agents are inadvertently given to patients with gastrointestinal obstruction with the exception of animals with linear foreign bodies. Certain drugs, especially chlorpromazine and prochlorperazine, can cause systemic hypotension. These drugs should only be given if the patient is not hypotensive or if there is IV fluid support. These drugs are no longer thought to reduce the seizure threshold and can safely be used in patients with seizure disorders. Many antiemetics can cause unwanted sedation. These include phenothiazines (chlorpromazine and prochlorperazine), antihistamines, and yohimbine. Other behavioral changes are seen with metoclopramide.
Current Concepts in the Diagnosis and Treatment of Acute Pancreatitis

VSH Fall CE 2012

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Pathophysiology:
The pathophysiology of acute pancreatitis (AP) is complex and involves multiple inflammatory pathways. The pancreas is exquisitely sensitive to circulatory and ischemic events and the role of inflammatory pathways, pancreatic microcirculation, and the perpetuation of disease by the intestinal tract in the pathogenesis of AP have all received substantial attention. Intervention in these areas appears to have the most promise in attenuating disease severity.


Pathology:
A recent study looked at the frequency of pancreatic pathology in 101 dogs presented for necropsy for any reason. Of these dogs 92% had histologic lesions in the exocrine pancreas: 80.2% had hyperplastic nodules (questionable pathologic significance); 52.5% lymphocytic inflammation, 49.5% fibrosis, 46.5% atrophy (fibrosis and atrophy are indicators of prior inflammation and damage); 31.7% neutrophil infiltrates; 25.7% pancreatic fat necrosis; 16.8% pancreatic necrosis and 9.9% edema. It is unknown how many of these lesions were significant but exocrine pancreatic lesions were much more common than expected.


Clinical Significance:
Acute pancreatitis is a common clinical disorder. Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis were reported in 70 cases. In this study there was anorexia in 91%, vomiting in 90%, weakness in 79%, abdominal pain in 58%, dehydration in 46%, diarrhea in 33%, icterus 26%, and fever in 21%. A definitive diagnosis of pancreatitis can be difficult because clinical signs, exam findings, and clinicopathologic abnormalities are non-specific. In dogs with acute pancreatitis a history of dietary indiscretion is common and vomiting and abdominal pain are probably the most common presenting complaints. In people the most common symptoms are abdominal pain in 95-97% and fever in 75%. Every patient with pancreatitis would be expected to have abdominal pain. In many dogs and cats with pancreatitis abdominal pain probably goes unrecognized.


Diagnostics:
Ultrasonography:
Common ultrasound findings in patients with pancreatitis are an enlarged irregular hypoechoic/heterogeneous pancreas, hyperechoic peripancreatic mesentery, peripancreatic fluid, and/or a pancreatic mass effect. Ultrasound for pancreatitis has a reported sensitivity of 68% in dogs. Abdominal ultrasound was both sensitive in cats with moderate to severe pancreatitis (80%) and specific in healthy cats (88%). In another study the sensitivity of ultrasound in cats was reported to be 24%. Ultrasound is very operator and machine dependent. With more advanced equipment and more experience with pancreatic imaging the sensitivity of ultrasound for diagnosing pancreatitis might improve.


*Comparison of the Sensitivity of Different Diagnostic Tests for Pancreatitis in Cats. JVIM 2001;15(4):329-33*

**Pancreatic Lipase Immunoreactivity (PLI)**
Pancreatic lipase immunoreactivity has gained widespread acceptance and has been embraced by the veterinary community for the diagnosis of pancreatitis. There are now many reports in dogs and cats demonstrating its diagnostic utility in identifying pancreatic inflammation. Prospective studies critically evaluating the PLI in the clinical setting have not been reported.

**A Multi-Institutional Study Evaluating the Diagnostic Utility of the Spec cPL™ and SNAP® cPL™ in Clinical Acute Pancreatitis in 84 Dogs**

Study evaluating pancreas-specific lipase in dogs as an aid in diagnosing AP in dogs that were rigorously evaluated clinically. The objectives were to describe the variability in dogs with suspected clinical AP and to evaluate the accuracy of the Spec cPL (SPEC) and Snap cPL (SNAP), in diagnosing clinical AP. The hypothesis was that the SPEC and SNAP provide better diagnostic accuracy than serum amylase or total lipase.

Cases were recruited by Comparative Gastroenterology Society (CGS) members from 14 institutions. A total of 84 dogs were enrolled prospectively (27 without AP and 57 with possible AP) and a standard set of data was collected from all dogs. Each dog was then retrospectively classified into groups according to the likelihood of having AP by a consensus of experts blinded to the SPEC and SNAP results.

Sensitivities and specificities respectively were as follows:

- SNAP: 91.5-94.1% and 71.1-77.5%
- SPEC (cutoff value of 200 ug/L): 86.5-93.6% and 66.3-77.0%
- SPEC (cutoff value of 400 ug/L): 71.7%-77.8% and 80.5-88.0%
- Amylase: 52.4-56.0% and 76.7-80.6%
- Lipase: 43.4-53.6% and 89.3-92.5%

**Conclusions:**
SNAP and SPEC have higher sensitivity for diagnosing clinical AP than does the measurement of serum amylase and lipase activity. A positive SPEC or SNAP has a good positive predictive value (PPV) in populations likely to have AP and a good negative predictive value (NPV) when there is a low prevalence of disease.
New Concepts in Treatment

Early Re-feeding

Traditionally patients with AP have been fasted for a prolonged period of time (72-96 hours) due to a concern that early re-feeding would stimulate pancreatic secretion resulting in the worsening of the disease. Pancreatic secretions decrease early in pancreatitis therefore early re-feeding is not expected to potentiate pancreatitis. Studies in humans show that early re-feeding decreases mortality. The current approach is re-feeding with a low-fat or low residue-diet when vomiting is controlled. With the effectiveness of the currently available antiemetics early re-feeding can usually be achieved and placement of a feeding tube is generally not necessary. Some cases may require a short-term NG tube for feeding and scavenging of gastric residual fluid. Placement of a jejunostomy tube, longer term enterostomy tube, and parenteral nutrition are not required in most cases. From clinical experience early re-feeding does not seem to be detrimental. This approach may also results in an earlier discharge from the hospital and cost savings.


Antiemetics used most commonly with pancreatitis:

Cerenia® (maropitant citrate) 1 mg/kg SQ q24h or 2 mg/kg PO q24h
MOA: neurokinin-1 (NK-1) receptor antagonist inhibiting the binding of substance P

Ondansetron (generic, Zofran®) 0.1-1.0 mg/kg PO or IV q8-24h or dolasetron (generic, Anzemet®) 0.5-1.0 mg/kg PO or IV q12-24h
MOA: 5-HT3 receptor antagonist

Metoclopramide as constant rate infusion (2-4 mg/kg/day CRI, 0.2-0.5 mg PO q8h); also a GI prokinetic
MOA: Anti-emetic: dopamine D2 receptor antagonist at CRTZ; gastric prokinetic: cholinergic (Ach) activity and D2 receptor antagonist activity, and 5-HT₄ activity

Pain Management

Abdominal pain occurs in 95-97% of humans with pancreatitis. Although abdominal pain in dogs with pancreatitis is only recognized 50% of the time the presence of pain is likely underestimated and therefore pain management is indicated in all cases of pancreatitis.

Analgesics Most Commonly Used for AP

Hydromorphone 0.05-0.2 mg/kg IV, IM, SQ q2-6hous
Buprenorphine 0.01-0.02 mg/kg IV, IM, SQ q6-12hours
Fentanyl: loading dose 2-5 ug/kg followed by 2-5 ug/kg/hr
FLK: fentanyl 2 mcg/kg, ketamine 0.5 mg/kg and lidocaine 2 mg/kg followed by fentanyl 2-5 mcg/kg/hr, ketamine 0.2 mg/kg/hr, lidocaine 35 mcg/kg/min.
Tramadol 2-4 mg/kg PO q6-12h

The NK-1 receptor and its agonist substance P have been reported in pain pathways at the level of the CNS and peripheral nervous system. The presence of NK-1 receptors
have been reported in visceral tissues such as bladder esophagus and colon. Maropitant citrate (Cerenia®) significantly decreased the anesthetic requirements (MAC) during noxious stimulation of the ovary in dogs, which suggests a potential role for NK-1 receptor antagonists to manage ovarian pain. Further studies on the use of NK-1 antagonistic drugs for visceral pain are needed.

*Effect of maropitant, a neurokinin 1 receptor antagonist, on anesthetic requirements during noxious visceral stimulation of the ovary in dogs. Am J Vet Res 2011;72:1576-9*

Acupuncture is used for pain associated with AP in human patients. Additionally electroacupuncture has been shown to improve intestinal motility, decreasing intestinal permeability and reduce endogenous inflammatory mediators in human AP patients.

**Plasma in AP**

Plasma has been commonly used for the treatment of pancreatitis. Evaluation of the use of fresh frozen plasma (FFP) in canine pancreatitis was recently reported. The mortality rate for those dogs receiving plasma (7 of 20 or 35% died or were euthanized) was higher than those that did not (6 or 57 or 12% died or where euthanized) and plasma administration was significantly related to outcome (P<0.001). Severity of illness scores were difficult to assign, however, preexisting illness, evidence of systemic inflammatory response syndrome, and presence of a coagulopathy were not significantly different between the groups that did and did not receive FFP. There was no benefit for administration of FFP in this report. Further investigation should be performed to confirm these result.


**What is the best way to feed patients with pancreatitis?**

**Summary:**

Nutritional support should be viewed as an active therapeutic intervention that improves the outcome of patients with acute pancreatitis. Enteral nutrition should begin within 24 h after admission and following the initial period of volume resuscitation and control of nausea and pain. Patients with mild acute pancreatitis should be started on a low-fat oral diet. In patients with severe acute pancreatitis, enteral nutrition may be provided by the gastric or jejunal route.

*Curr Opin Crit Care 2009 Apr;15(2):131-8*
TIPS FOR DOGS AND CAT W/ CHRONIC VOMITING

JOHN R. HART, DVM, DACVIM

VOMITING?

• MAKE SURE IT’S VOMITING
• REGURGITATION IS OFTEN MISINTERPRETED
• COMPLETELY DIFFERENT WORK-UP
• DESCRIBE THE DIFFERENCE
• ACT IT OUT

VOMITING VS REGURG

• NAUSEA USUALLY ACCOMPANIES VOMITING
• DEPRESSION, SALIVATION, FREQUENT SWALLOWING, VOCALIZING (CATS)
• ABDOMINAL CONTRACTIONS FOLLOW
• VOMITION IS ACTIVE/FORCEFUL
• REGURG IS USUALLY PASSIVE - BLAHHH
• EXCITEMENT, ACTIVITY CHANGES, BODY POSITION CHANGES
DDX: SYSTEMIC DISEASE

- Diabetes mellitus
- Chronic renal failure
- Liver diseases
- Chronic pancreatitis
- Feline hyperthyroidism
- Hypoadrenocorticism
- Lead poisoning
- Feline heartworm disease
- Systemic mastocytosis
- Drug therapy: NSAID, steroids, other.

DDX: GASTRIC DISEASE

- Chronic gastritis
- Dietary indiscretion
- Hair-induced
- Lymphocytic plasmocytic inflammation
- Eosinophilic inflammation
- Helicobacter
- Foreign body
- Ulcer
- Neoplasia
- Pyloric hypertrophy
- Physaloptera
- Gastric motility disorder

DDX: SMALL INTESTINAL DISEASE

- Inflammatory bowel disease
- Lymphocytic plasmocytic inflammation
- Eosinophilic inflammation
- Partial obstruction-stagnant loop syndrome
- Neoplasia
- Foreign body
- Intussusception
- Extra-luminal obstruction
- Diffuse mucosal lymphosarcoma
- Histoplasmosis
- Ulcer
- Giardia
- Bacterial dysbiosis
HISTORY

- HISTORICAL DISEASES
- DRUGS, SUPPLEMENTS – D/C ANY DRUGS WITH POTENTIAL GI TOXICITY, H2 BLOCKER FOR NSAID/STEROID HX
- TOXIN OR FOREIGN BODY EXPOSURE
- DIETARY INDISCRETION
- RECENT DIET CHANGE

TYPE AND TIMING

- FOOD, QUICK INTAKE, JUST AFTER EATING – THINK OVEREATING OR RAPID INTAKE
- UNDIGESTED OR PARTIALLY DIGESTED FOOD > 8-10 HOURS AFTER EATING - THINK GASTRIC OUTFLOW OBSTRUCTION
- BILE, EARLY MORNING VOMITING BEFORE FEEDING – THINK BILLIOUS VOMITING SYNDROME

MINIMUM DATABASE

- DOGS: CBC, CHEM, UA
- CATS: CBC, CHEM, UA, T4, FELV/FIV, HW (ENDEMIC AREAS)
- ATTEMPTING TO EXCLUDE SYSTEMIC DISEASE
SURVEY ABDOMINAL RADIOGRAPHS

- RARELY HELPFUL
- RADIODENSE FOREIGN BODIES
- YOUNG DOGS OR CATS WITH DIETARY INDISCRETION, FB EXPOSURE
- MOST LESIONS REQUIRE U/S TO EVALUATE
- SAVE YOUR CLIENTS MONEY FOR MORE HELPFUL TESTS

UPPER BARIUM SERIES

- CAN HIGHLIGHT FOCAL LESIONS – MASSES, THICKENINGS, FOREIGN BODIES
- HELPFUL TO ASSESS MOTILITY
- FOCAL LESIONS OFTEN REQUIRE BIOPSY
- FOREIGN BODIES NEED REMOVAL
- CANNOT ASSESS MUCOSAL DETAIL
- NEED TO BE PERFORMED CORRECTLY

BARIUM SERIES

- EXPENSIVE
- INCREASE RADIATION EXPOSURE TO THE STAFF
- SOME PATIENTS ARE NOT CANDIDATES
- CONSIDER ULTRASOUND, ENDOSCOPY OR LAPAROTOMY INSTEAD
ABDOMINAL ULTRASOUND

- Superior to radiographs except for gastric foreign bodies
- Small intestinal FB's 97% vs 70%
- Can rule out focal mid-distal intestinal disease when considering endoscopy
- Can ID diffuse mucosal changes and lymphadenopathy supporting a diffuse intestinal DZ

ABDOMINAL ULTRASOUND

- Lymphadenopathy can be normal in young dogs/cats
- U/S commonly does not help with diagnosis
- Helpful in 27% of cases in one study
- Geriatric canine patients with frequent vomiting and weight loss
- Consider endoscopy or exploratory

UPPER ENDOSCOPY

- Often the highest diagnostic yield
- Allows histologic assessment of lesions/mucosa
- Is an excellent test for small cell LSA
- Even in questionable cases can perform special testing on formalinized tissue
- Consider as a replacement for radiographs and ultrasound
ABDOMINAL EXPLORATORY

- MUST GET MULTILEVEL BIOPSY
- BIOPSY EVEN IF IT LOOKS NORMAL
- GET PANCREATIC TISSUE
- MAKE IT COUNT!
- COMPLICATIONS – SEPTIC PERITONITIS

Spec cPL/fPL Snap cPL/fPL

- MOST SENSITIVE TEST FOR PANCREATITIS – cats 79.4%, dogs >80%
- SPECIFICITY IS NOT 100%
- OFTEN CONCOMITANT WITH OTHER GI DISEASE
- ELEVATIONS WOULD SUGGEST TREATING WITH A LOW FAT EASILY DIGESTIBLE DIET
- SNAP PL TESTING – MORE SENSITIVE BUT LESS SPECIFIC – ID’S IN THE GREY RANGE

TESTING FOR ATYPICAL ADDISON’S

- BASELINE CORTISOL – CHEAP AND EASY
- > 2 MG/DL – NOT ATYPICAL ADDISON’S – 100% specificity
- < 2 MG/DL – CONFIRM WITH AN ACTH STIM 72% specificity
- OFTEN SEE WAXING AND WANING ANOREXIA, LETHARGY AND DIARRHEA
- WITH HYPERKALEMIA OR HYPONATREMIA PROCEED DIRECTLY WITH ACTH STIM
COBALAMIN AND FOLATE

• COBALAMIN – VITAMIN B12, ABSORBED IN THE DISTAL SMALL INTESTINE
• IMPORTANT IN DNA SYNTHESIS, FA SYNTHESIS, ENERGY REGULATION
• LOW WITH BACTERIAL DYSBIOSIS, MALABSORPTION, INTRINSIC FACTOR DEFICIENCY
• DEFICIENCY - POOR APPETITE, WEIGHT LOSS, DIARRHEA, LETHARGY

BACTERIAL DYSBIOSIS

• ALTERED BACTERIAL POPULATIONS – GM + ANAEROBES, CLOSTRIDIUM
• DIRECT MUCOSAL DAMAGE
• HYDROXYLATED BILE ACIDS
• ENDO/EXOTOXINS
• ALTER MOTOILITY
• COMPETING FOR NUTRIENTS

FOLATE = VITAMIN B9

• BYPRODUCT OF BACTERIAL METABOLISM, ABSORBED IN PROXIMAL SI
• NECESSARY FOR DNA SYNTHESIS
• COBALAMIN NEEDED FOR IT’S ACTIVATION
• LOW W/ MALABSORPTION, ELEVATED W/ BACTERIAL DYSBIOSIS, HIGH FOLATE DIETS
• ANOREXIA, DIARRHEA, WEIGHT LOSS, LETHARGY, WEAKNESS
**COBALAMIN/FOLATE INTERPRETATION**

<table>
<thead>
<tr>
<th>Low Cobalamin</th>
<th>Normal Cobalamin</th>
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<tbody>
<tr>
<td>Low Folate</td>
<td>Malabsorption From Diffuse Intestinal Disease</td>
</tr>
<tr>
<td>Normal Folate</td>
<td>Distal Small Intestinal DZ, Bacterial Dysbiosis</td>
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<tr>
<td>High Folate</td>
<td>Bacterial Dysbiosis</td>
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**COBALAMIN AND FOLATE SUPPLEMENTATION**

- Cobalamin (Vitamin B12) – 1,000 ug/ml
- Cats 250 ug sq
- Dogs 250-1000 ug sq
- Weekly for 6 weeks, biweekly for 6 weeks, then monthly
- Oral supplementation – ineffective
- Don’t use B-complex – 100 ug/ml
- Folate 400-800 ug po sid

**CLINICAL TRIALS**

- Ruled out systemic disease – minimum data base
- Stable patient – hydrated, still eating, minimal weight loss
- 1 diet or medication at a time
- Progressive weight loss or anorexia – further diagnostics
DIET TRIALS - BENEFITS

• TREATMENT FOR DIETARY INTOLERANCE
• MAXIMIZE ABSORPTION ACROSS AN ABNORMAL MUCOSA
• NORMALIZE MOTILITY
• REDUCE SUBSTRATE FOR BACTERIAL DYSBIOSIS
• REDUCE OSMOTIC DIARRHEA
• AVOID AN ALLERGEN

DIET TRIALS

• EASILY DIGESTIBLE
• MILDLY TO MODERATELY FAT RESTRICTED
• HIGHLY BIOAVAILABLE SINGLE PROTEIN AND CARBOHYDRATE SOURCE
• MINIMAL ADDITIVES
• PROMOTES PROXIMAL SI ABSORPTION, REDUCES OSMOTIC LOAD, BACTERIA
• MINIMUM 2 WEEK TRIALS

EASILY DIGESTIBLE DIETS

• HOME-MADE – LOW FAT COTTAGE CHEESE OR CHICKEN AND RICE/PASTA/POTATOES
• COMMERCIALY AVAILABLE
• HILL’S PRESCRIPTION I/D
• EUKANUBA LOW RESIDUE
• ROYAL CANIN HE OR LF
• PURINA EN
HYPOALLERGENIC DIETS

- NEED A COMPLETE DIET HISTORY
- CAN BE THE ONLY DIET FED! NO TREATS!
- TRANSITION FROM THE CURRENT DIET
- 4 WEEK TRIALS
- NOVEL PROTEIN AND CARBOHYDRATE SOURCE
- HYDROLYZED PROTEIN DIETS

NOVEL PROTEIN DIETS

- HOMEMADE – PORK, VENNISON, LAMB COMBINED WITH SWEET POTATOE
- ROYAL CANIN LIMITED INGREDIENTS
- HILL’S PRESCRIPTION D/D
- EUKANUBA RESPONSE DIETS (FP, KO)
- BE WARY OF OVER THE SHELF PRODUCTS
- PROTEIN CONTAMINATION

HYDROLYZED DIETS

- PURINA HA
- HILL’S Z/D AND Z/D ULTRA
- ROYAL CANIN HP
- MAY BE BETTER WITH UNKNOWN DIET HISTORY
**ANTI-ACIDS**
- HISTAMINE TYPE 2 BLOCKER
- FAMOTIDINE – BEST CHOICE
- 2 MG/KG PO BID
- GASTRIC/DUODENAL ULCERATION, GASTRITIS
- USE FOR AT LEAST 2 WEEKS
- SIDE EFFECTS ARE RARE
- AVOID RANITIDINE IN DOGS
- PROTON PUMP INHIBITORS - OVERKILL

**ANTI-ACIDS**
- SUCRALFATE
- REQUIRES GASTRIC ACID pH < 4
- ACTS AS A BARRIER - STIMULATES MUCOSAL PROSTOGLANDIN PRODUCTION
- SLIGHT INCREASE IN GASTRIC pH
- ¼ TO 1 GM PO TID
- SEPARATE FROM OTHER MEDICATIONS
- RARE CONSTIPATION OR VOMITING (CATS)

**ANTI-EMETICS**
- NK-1 RECEPTOR INHIBITOR
- MAROPITANT (CERENIA)
- 1 MG/KG CATS AND 2 MG/KG DOGS PO SID
- VERY EFFECTIVE
- MINIMAL SIDE EFFECTS
- CAN USE CHRONICALLY (EXPENSIVE)
- CAN BUY TIME FOR DIET TRIALS TO BE EFFECTIVE
ANTI-EMETICS

- Dopamine Antagonist
- Metaclopramide (Reglan)
- Weak anti-emetic – Maropitant is superior
- Does have pro-motility effects
- 0.2-0.5 MG/KG PO TID
- May be better for billious vomiting syndrome at bedtime

ANTIBIOTICS

- Typically treating bacterial dysbiosis
- Altered bacterial populations
- Direct mucosal damage
- Hydroxylated bile acids
- Endo/exotoxins
- Competing for nutrients
- Targeting gram + and anaerobes

METRONIDAZOLE

- A nitroimidazole
- Primarily anaerobic bacteria
- Anti-protozoal
- Modulates cell mediated immunity
- 10-15 MG/KG PO BID
- Rarely causes anorexia, vomiting or diarrhea, neurologic dz
- Caution w/ hepatic disease
TYLOSIN TARTRATE

• A MACROLIDE ANTIBIOTIC
• PRIMARILY GM= AND ANAEROBIC BACTERIA
• 10 MG/KG PO BID (1 TSP = 325 MG)
• ADVERSE EFFECTS – ANOREXIA AND DIARRHEA – RARE
• UNPALATABLE