



# VET TALK

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American College of Veterinary Pharmacists

## THE HARD TRUTH ABOUT PROKINETIC MEDICATION USE IN PETS

### Introduction

The moving topic of this Vet Talk newsletter will be prokinetic medications. The availability of information on the many prokinetic agents is varied at best so an overall consensus of prokinetic medications will be assessed in this article, hopefully giving better insight to practitioners about which agents to use in their patients.

### Prevalence

Chronic constipation and gastrointestinal stasis are highly debilitating conditions that not only affect human patients but our four legged patients as well! Though this condition is equally widespread amongst our numerous veterinary species, there are a few specific groups who are more at risk. For example, prevalence of constipation is higher in the following dog breeds: English Bulldogs, Boston Terriers, and German Shepherds. Cats who are most affected include Siamese, Domestic Shorthair, and Manx as well as those cats who are middle-aged and male. Horses, rabbits, guinea pigs, and chinchillas may also experience various forms of constipation due to their unique digestive systems.



### Pathophysiology/Etiology

As with most diseases in the veterinary world, the etiology and pathophysiology of constipation are varied depending on the species being discussed, where in their gastrointestinal tract the problem is occurring, and any accompanying comorbid conditions.

**Canines:** In man's best friend, constipation has many origins. A dog's digestive tract itself is complex but ultimately the mass movements and haustral contractions from the large intestine (colon), propel feces into the rectum stimulating the internal anal sphincter to relax. This then signals the diaphragm and abdominal muscles to contract increasing pressure while the external anal sphincter relaxes resulting in defecation. However, various factors can impede this multifaceted process. Such examples include ingesting foreign objects (i.e. socks, garden hoses, shoes), anal sac inflammation, long term opioid use (i.e. tramadol), chemotherapeutic medications (i.e. vincristine), obesity, old age, immobility, and dehydration. However, other more severe underlying physiologic etiologies such as neuromuscular disease, diabetic gastroparesis, or a neoplastic gastrointestinal obstruction may also be attributable to GI stasis.

**Felines:** Cats can also develop constipation from several causes as their process of defecation is fairly similar

to that observed in dogs. It can be due to a trichobezoar, dehydration, obesity, old age, diabetes, immobility, pain from trauma to the low back, bladder infection, or an anal sac infection. In cases that are more chronic, underlying disease such as colitis or Irritable Bowel Syndrome (IBS) may be the culprit. On the other hand, the cause may be idiopathic which is frustrating for both veterinarian and patient since this form is most difficult to treat.

**Equines:** Despite their large size, horses have incredibly delicate digestive systems. Their stomach is relatively small compared to their body size which then passes food through approximately 100 feet of digestive tract to include the small intestine, then cecum, large colon, small colon, and finally rectum.

During times of illness or stress horses may stop eating, drinking, and

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can develop colic which even in the mildest form, results in pain, abnormal motility, and even ileus. Colic has many origins but the forms most likely to cause constipation are impaction colics due to fecal material, parasites, or enteroliths. Other causes for gut immobility include pelvic flexure impaction from food, poor food quality, an inability to access free forage, dehydration, severe hind limb pain or injury, or long term use of anticholinergic medications such as atropine.



**Lagomorphs:** Rabbits and hares have digestive systems that resemble horses, rather than dogs or cats. Perhaps it is for this reason that they too are very prone to GI stasis. The transit time of the small intestine is rapid, and fibrous material is quickly moved to the cecum and large intestine. The cecum is where fermentation by bacteria occurs. Indigestible fibrous particles then accumulate in the colon and are rapidly transported to the rectum for defecation, usually within 4 hours of ingestion. However, a diet low in fiber in turn results in low amounts of fiber in the colon and cecum which reduces the production of volatile fatty acids, increases pH, and destroys natural microflora. A diet high in carbohydrates may result in clostridial overgrowth, while excessive protein can cause increased ammonia which also results in dysbiosis. Obesity, inactivity, spinal trauma, trichobezoars, dehydration, excess fruit or nuts, in combination

with all of the aforementioned reasons, will surely result in a final outcome of poor gastric motility

**Rodents:** Guinea pigs and chinchillas have a high metabolic rate, a monogastric stomach, and an impressive cecum that is so large it takes up approximately ½ of their body cavity. In the cecum, much like in horses and rabbits, there is fermentation by key microflora. If their diets aren't maintained appropriately with high fiber and low carbohydrates (similar to lagomorphs), dysbiosis occurs resulting in GI distress. Other reasons for constipation include dehydration, old age, spinal pain, obesity, excess fatty diet, a lack of exercise, and dental disease than can severely impair eating and drinking.

### **Clinical Signs and Symptoms**

The classical clinical sign of constipation is straining to defecate without production of feces, droppings, or manure. Affected animals can be of either sex, although in cats there is a male predilection, and of any age though often younger or older animals are most affected. Besides straining, there may also be signs of general discomfort, irritability, a decrease in appetite, and a frequent need to want to defecate with posturing and lifted tail. Variations of these physical demonstrations will be species specific. These problems, if not resolved, can become life threatening. Chronic constipation causes severe pain, endotoxemia, decreased blood flow and eventual necrosis of the intestinal tissue that if not medically managed aggressively, may lead to surgery.



### **Summary of Clinical Signs**

1. Increased tenesmus
2. Failure to defecate
3. Fecal matter, if passed, is reduced in quantity and is usually dry and hard
4. Presence of blood in stool
5. Feces that are particularly foul smelling
6. May continuously get in and out of litter box without passing fecal material
7. Circling or pacing the stall with intermittent straining
8. Decreased activity and lethargy likely due to pain
9. Painful and/or bloated abdomen
10. Decreased interest in food
11. Irritability

### **Diagnosis**

The primary means of diagnosing any species with gastrointestinal stasis is through a complete history, thorough physical exam, and careful observation of their patient's behavior. A CBC and Chemistry Panel will be useful for identifying and/or ruling out other disease processes such as diabetes, pancreatitis, or an underlying infection. Abdominal radiographs and ultrasounds both present the practitioner with an even better understanding to what is, or is not, palpated on physical exam. It is very important to discuss with the owner about being vigilant in observing their pet and noting any changes in their diet or daily bathroom habits then recording these and letting their veterinarian know as they make their way through this process with their pet.

### **Diagnostic Algorithm**

1. Assess history, physical exam, and clinical signs
  - a. Auscultation of the abdomen
  - b. Rectal exam and palpation where appropriate
  - c. Perform oral exams on lagomorphs and rodents as this could be affecting their die-

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tary intake

- d. Determine from owners if patient has ingested any foreign objects
2. Rule out iatrogenic disease
  - a. Current or past medications (oral, ophthalmic, otic, topical)
  - b. Exposure to possible household toxins (plants, owner medications, household cleansers)
3. Preliminary Lab Results
  - a. CBC
    - i. Identify a possible underlying infection
  - b. Chemistry Profile
    - i. Serum chemistry profiles may identify a comorbid disease state such as diabetes or renal disease
  - c. Urinalysis
    - i. Helpful to rule out a possible urinary tract infection as the source of pain and straining
4. Radiographs
  - a. Confirm colonic distention with feces
  - b. Identify an area of foreign body impaction, colonic masses, or even fracture
5. Abdominal Ultrasound
  - a. Help identify the size and internal architecture of area of GI stasis
  - b. More detailed view of what is truly going on internally without being invasive

### Diagnostic Tests

In order to avoid surgery, medical treatment must be implicated as soon as possible. Diagnostic testing should be performed to better understand which form of GI stasis the animal is experiencing in order to treat and alleviate symptoms and improve quality of life.

1. Thorough history and physical exam with rectal palpation
2. CBC
3. Chemistry Panel

4. Urine analysis
5. Abdominal Radiographs
6. Abdominal ultrasound



### Treatment

There are several options available for veterinarians to treat constipation and GI stasis in their patients, most of which are focused on the underlying disease such as giving fluids for dehydration or surgically removing an obstruction. We want to keep all our animal patients well hydrated and increase the fiber in their diets and decrease the amount of carbohydrates. However, several of the most successful therapies for treatments of idiopathic constipation (i.e., feline megacolon) have been removed from the US market and are only available through specialty veterinary pharmacies that compound. The choice of therapy must be individualized to the afflicted species specifically and the exact type of gastric distress they are experiencing as diagnosed by their veterinarian. It is also critical to remember pain control in the process of treatment. Ileus and chronic constipation are painful and it will be hard for your patient to relax their abdomen to encourage normal bowel movements if they are tense with severe pain! Surgical therapy, if warranted, can be helpful (i.e. horse with enterolith impaction) but has significant risks, is costly, and often times the underlying cause must still be identified and corrected.

### Mineral Oil

This substance is a lubricant laxative and one of the most basic routes of treatment with which to start. Mineral oil acts as a lubricant to help ease the passage of fecal matter and in-

crease the water content of stool. It is most often used in horses for treatment of constipation and fecal impactions via a properly placed nasogastric tube. Due to the detrimental risk of aspiration, it is administered orally via a stomach tube at 10-50 ml per dog every 12 hours, 10-25 ml per cat every 12 hours and 500-1000ml per horse up to 2-4 liters daily. Rabbits may be given 1-2 ml per day for 3-5 days. A dose for guinea pigs isn't established. For short term use this is a certainly an appropriate option but for chronic constipation, as soon as laxative use ceases, constipation often returns. This product is generally safe in the hands of a practitioner with minimal side effects of oily stool and abdominal cramping. Despite being OTC, this should never be recommended for owners to give to their pets due to the deadly risk of aspiration!

### Lactulose

This is a disaccharide sugar containing both fructose and galactose. It creates a laxative effect by osmosis in the colon as it is a non-absorbed sugar that retains water in the intestine after oral administration. Side effects from excessive use may cause fluid and electrolyte loss. Use with caution in diabetic animals since it carries a risk for hyperglycemia. The dose for dogs is 1 ml for every 4.5 kg every 8 hours. The cat dose is 1 ml per 4.5 kg every 8 hours by mouth. For horses, the dose is 0.25-0.5 ml/kg per day by mouth. In rabbits and rodents this isn't recommended as the side effect of severe diarrhea can be detrimental to their overall health.

### Gallimycin (erythromycin)

This macrolide antibiotic can be given to "restart" the stomach during acute episodes of gastric stasis in which oral intake is not tolerated. Erythromycin induces gastric propulsive contractions via stimulation of motilin receptors to increase smooth muscle activity which then helps to

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unload solid and non-digestible materials out of the stomach. It can also stimulate fundic contractility. The intravenous formulations are erythromycin gluceptate and lactate, but gluceptate is not currently available. The prokinetic dose, which is well below the antimicrobial dose, for dogs and cats is 0.5-1 mg/kg every 8-12 hours either by mouth or IV. In horses, the dose is 1 mg/kg IV. This medication may NOT be given orally to rabbits, guinea pigs, or other rodents. IV use is generally not recommended either as this route of administration is very difficult to attain in this patient subset. Side effects include diarrhea (especially in horses), hyperthermia in foals, and vomiting.

#### ***Zithromax (azithromycin)***

This is another macrolide antibiotic that has been used as an alternative to the aforementioned erythromycin. This medication doesn't appear to have the drug-drug interactions seen with erythromycin and is also associated with less QT prolongation. However, there are limited studies for its use in the treatment of delayed gastric emptying. There is also concern for its higher cost and using it for gastric emptying instead of for antimicrobial treatment of an actual infection that may eventually create the potential for antibiotic resistance. Side effects include vomiting and diarrhea though it is better tolerated than erythromycin. There are no established doses for azithromycin as a prokinetic in animals at the time of this publishing.

#### ***Zantac (ranitidine) & Axid (nizatidine)***

Both of these medications are histamine receptor antagonists aka "H2 blockers." However, they are unique from others in their class in that they have the ability to improve gastrointestinal stasis via their prokinetic cholinergic properties that improve gastric emptying into the proximal GI

tract. Ranitidine dosing for dogs is 2 mg/kg every 8 hours by mouth or IV. For cats, the dose is 2.5 mg/kg every 12 hours IV or 3.5 mg/kg every 12 hours by mouth. For horses, the dose is 6.6 mg/kg every 6 to 8 hours by mouth or 2 mg/kg every 6 to 8 hours IV. In rabbits, the dose is 0.5 mg/kg every 24 hours IV or 2-5 mg/kg by mouth every 8 hours. The dose in guinea pigs is also 2-5 mg/kg by mouth every 12 hours. Nizatidine dosing is only available for dog and cat species at 5 mg/kg by mouth every 24 hours and 2-5 mg/kg by mouth every 24 hours respectively. Side effects are generally mild and noted at higher doses but may include dizziness, nausea, diarrhea, and myalgia.

#### ***Propulsid (cisapride)***

This medication is a non-selective benzamide 5-HT4 receptor agonist and a 5-HT3 receptor antagonist. This drug is recognized for its ability to promote GI motility via the 5-HT4 receptor in the mesenteric plexus of the digestive tract and by increasing acetylcholine release from nerve endings. It is most often associated with success in cats with IBS. However, due to an association with cardiac arrhythmias and death in humans, it is currently not on the market and the only makers in India have recently moved to cease production. The origin of this medication's deadly cardiac profile in people has been isolated to the blockade of potent human Ether-a-go-go gene (hERG) channel which happens to be responsible for the repolarization phase of the cardiac action potential. Blockade of this hERG channel then increases the action potential phase via delay of the repolarization phase. Because this gene is very human specific, perhaps this is why the cardiac profile in our veterinary population appears safer and with less cardiovascular complications. The dose for dogs as a pro-motility agent is 0.1-0.5 mg/kg by mouth every 8 to 12 hours 30 minutes before meals. The dose for cats with

megacolon (often in combination with lactulose and psyllium) is 2.5 mg by mouth for cats up to 10 pounds and if heavier than this, 5mg by mouth given every 8 to 12 hours 30 minutes before food. For rabbits, guinea pigs, or chinchillas needing assistance with motility, the dose is 0.1-0.5 mg/kg by mouth every 8 to 12 hours. Though not used as frequently, the dose in horses with ileus is 0.1-0.25 mg/kg IV over 60 minutes or 0.1 mg/kg IM injection with frequency not noted. Side effects in veterinary patients appear minimal but may include vomiting, diarrhea, and abdominal discomfort.

#### ***Gastride (mosapride)***

Mosapride citrate is a selective benzamide peristaltic stimulating agent that works as a selective 5-HT4 receptor agonist to create prokinetic gastrointestinal movements to alleviate GI symptoms associated with gastritis. Unlike cisapride that works throughout the entire gut, mosapride only works on the stomach and small intestines (i.e. upper GI tract). In dogs, one study recommended a dose of 2 mg/kg by mouth every 24 hours. This study did not find any side effects or changes in blood levels. The feline dose is 5 mg by mouth every 12 hours again with no side effects noted. In horses, the gastric emptying dose is 0.5 mg/kg while the dose for promoting cecal movement is 1.5-2 mg/kg orally every 12 to 24 hours. The only side effect noted in these dosing trials was one case of mild depression. The dose in rabbits and guinea pigs, appears to be in a range of 0.1-1 mg/kg every 8 to twelve hours. This product is not currently available in the U.S. but does come in 2.5 mg and 5 mg tablets.

#### ***Resolor (prucalopride)***

This medication is a serotonin agonist with selective affinity for 5-HT4 receptors. In human clinical trials prucalopride, at 2mg and 4mg, provided daily accelerated whole gut, gastric,

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small bowel and colonic transit times in constipated patients. The dose of prucalopride can be titrated up based on clinical response. Side effects in these studies collectively expressed such adverse events as headache, nausea, abdominal pain or cramps and diarrhea. Cardiac toxicity does not appear to be an issue at this point likely because it does not appear to interact with either the hERG potassium channel linked with cisapride arrhythmias, nor the 5HT<sub>1B</sub> receptors where tegaserod created problems. Prucalopride is available in Europe and Canada, but not in the United States therefore doses are not available at this time of publishing.

### **Reglan (metoclopramide)**

This medication is an antiemetic and prokinetic benzamide that acts as a dopamine antagonist (D<sub>2</sub>) and at higher doses, a serotonin agonist at 5HT<sub>4</sub>. Interestingly, it also antagonizes serotonin receptor 5HT<sub>3</sub>. Metoclopramide ultimately enhances the response to acetylcholine in the upper GI tract tissue which enhances motility and accelerates gastric emptying time. It also increases lower esophageal sphincter tone. However, since it crosses the CNS, restlessness coupled with depression and extrapyramidal side effects, keep the use of this drug limited and the lowest effective dose for each patient should be used. A liquid formulation, as opposed to IV, may allow for improved efficacy coupled with a lower dose since it may work better when it directly contacts the stomach. The dose commonly used in dogs and cats is 0.2-0.5 mg/kg every 6 to 8 hours IV, IM, or by mouth. For horses, commonly a continuous IV infusion is used at 0.125-0.25 mg/kg/hour in order to reduce postoperative ileus. In rabbits the dose is 0.5 mg/kg every 6 to 8 hours by mouth or SC injection. The dose commonly used in rodents is 0.2-1.0 mg/kg every 12 hours by mouth, IM injection, or SC injection although in

guinea pigs, 0.5 mg/kg is traditionally used.

### **Urecholine(bethanechol)**

This medication is considered a cholinergic agonist normally used for urinary retention since it stimulates the parasympathetic nervous system to increase bladder muscle tone. However, since it stimulates the parasympathetic nervous system as a whole, bethanechol not only increases bladder muscle tone but also stimulates gastric motility, increases gastric tone and possibly helps to restore peristalsis. The dose for dogs is 2.5mg to 15 mg (depending on size of dog) every 8 hours by mouth. Cat dosing is 1.25-5mg per cat every 8 hours by mouth. Horses use a dose of 0.025 mg/kg SQ. Doses are not provided for lagomorphs and rodents as side effects restrict their use. These possible side effects may include hypotension, tachycardia, abdominal cramps, diarrhea, nausea, vomiting, salivation, lacrimation, and bronchial constriction.



### **Prostigmin(neostigmine)**

This medication is an acetylcholinesterase inhibitor that is usually used as an antidote for anticholinergic intoxication and for treatment of myasthenia gravis and for urinary retention. However, it also has limited evidence for stimulating intestinal motility. The following doses for dogs and cats are based on the treatment for urinary retention which is 2 mg/kg per animal per day often given in divided doses such as every 12 hours. In horses for prevention of cecal and large colon impactions the dose is 0.0044-0.022mg/kg via IV,

IM or SC injection or 4 mg SC every 6 hours. Due to the vast array of GI side effects, this medication is not recommended for rabbits or rodents. These side effects include bradycardia, AV block, hypotension, convulsions, dizziness, drowsiness, weakness, urticaria, diarrhea, muscle cramps, nausea, salivation, stomach cramps, vomiting, bronchospasm, dyspnea, increased bronchial secretions and lacrimation.

### **Domperidone**

This medication is a dopamine antagonist gastrointestinal agent and is not currently approved by the FDA in the USA but is available in Canada and other countries. There is currently an Investigation New Drug Application at [domperidoneIND@fda.hhs.gov](mailto:domperidoneIND@fda.hhs.gov). It works by stimulating the motility of the upper GI tract likely via dopaminergic effects and by increasing acetylcholine effects. The action of domperidone is to inhibit dopamine receptors, enhance the action of acetylcholine in the GI tract, increase gastric motility, and increase peristalsis to enhance gastroduodenal coordination in order to facilitate gastric emptying and speeding up small bowel transit time. Overall, the efficacy of domperidone in the presence of diabetic gastroparesis appears to be similar to that of metoclopramide. However, unlike metoclopramide, domperidone doesn't cross the blood brain barrier so it doesn't tend to cause the CNS effects noted with metoclopramide. Though not commonly used in dogs and cats for constipation, reference doses were 0.05-0.1 mg/kg by mouth every 12 to 24 hours. The dose in horses is 0.2 mg/kg given IV in order to promote gastric and small intestinal motility. The dose for rabbits is 0.5 mg/kg by mouth every 12 hours. Side effects that may be noted include xerostomia, dizziness, and tachycardia.

### **Amitiza (lubiprostone)**

This medication is a bicyclic fatty acid that acts locally at the apical por-

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tion of the intestine as a chloride channel activator, increasing intestinal fluid secretion and intestinal motility. It is FDA approved for treatment of chronic idiopathic constipation and constipation associated with irritable bowel syndrome in humans. While it is only approved in humans and no studies have currently been conducted in cats, dogs or horses, there was a pilot study that proved its efficacy in reversing opioid induced constipation in guinea pigs. Side effects include headache, nausea, diarrhea, flatulence, abdominal pain, and dizziness. Interestingly it does not appear to alter sodium or potassium concentrations in the blood. With the lack of available products to treat chronically constipated patients, it is being included for sake of completeness.

#### ***Linaclotide***

This is currently an investigational drug that acts as a peptide agonist of guanylate cyclase-C receptor. It is minimally absorbed and via this receptor, it stimulates secretion of intestinal fluid and in theory, increases transit time. Two large human trials showed an improvement in bowel movement from baseline and the final FDA review and approval should be completed by September 2012. The most common and dose-related adverse event was diarrhea. Since this is a new product, the appropriate animal doses and long-term risks of treating chronic constipation with this drug remain unknown.

#### ***Botulinum toxin***

Botulinum toxin when injected into the pylorus has been proposed to improve gastric emptying and associated symptoms. However, a controlled trial in humans found no significant difference in gastric emptying or symptoms when compared with placebo at one month. On the other hand, there were no serious side effects. Despite a lack of animal dos-

ing, since it is a newer therapy, it has been included for sake of completeness.

#### **Prognosis**

Once present, motility problems may or may not continue to be a lifetime problem depending on what is the underlying cause. It is very important to increase your patient's hydration whether this is through wet food for dogs and cats, adding salt to horses diets to increase their natural thirst response, and providing a salt wheel for your rabbit and rodents for the same reasons. It is also key to increase the fiber in their diets and keep the carbohydrate ratio on the lower side. Hay quality for horses, rabbits, and rodents is very important for their digestive health. No matter what the species or their size, good attentive husbandry is key to overall treatment success.

#### **Role of Veterinary Pharmacist**

Treating pets with motility and gastroparetic issues offers a plethora of unique opportunities for veterinary pharmacists as many of these products must be compounded because they are simply not commercially available nor in a dosage form acceptable to our patients. Such examples include cisapride capsules, bethanechol for injection, domperidone capsules, and lower volume and flavored H2 blockers for our smaller patients. In addition to making compounded medications, we also need to provide proper counseling on how to administer these medications and what side effects to look for. Owners may be a little uncomfortable or even queasy about discussing their animal's digestive disorders so we must do our best to make them comfortable and familiarize them with these drugs used to alleviate their pet's uncomfortable symptoms. Cost is another area we must consider. Perhaps lactulose and ranitidine are all they can manage. It is also important to consider dosing intervals; owners that work may only

be able to give once or twice daily dosing. In this way, we can work closely with the referring veterinarian to make sure drug therapy chosen fits both treatment and owner demands. Being supportive and counseling on the various forms of constipation and gastric stasis medications currently managing their situation to the best of our ability is critical in earning and keeping our owners trust!



#### ***\*Further Reading Upon Request***

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