Medical management of acute and chronic vomiting in dogs and cats

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Vomiting is a common presentation in small animal practice and can be associated with a wide variety of both gastrointestinal and systemic diseases. A logical diagnostic approach is required to identify the underlying cause to ensure that appropriate therapy can be instituted. Medical management of vomiting can involve drug therapy, fluid therapy and dietary manipulation. This article describes the physiology and pharmacological control of acute and chronic vomiting in dogs and cats.

Processes involved in vomiting

Vomiting is defined as the expulsion of food or fluid from either the stomach or duodenum via the mouth and is a common clinical sign in small animals (Fig 1). The processes leading to vomition include:

- Salivation and nausea, which usually precede vomition;
- Reverse peristalsis, which empties the contents of the upper small intestine back into the stomach;
- Closure of the glottis, which prevents aspiration of expelled material into the trachea;
- Contraction of the muscles of the abdominal wall, which leads to an increase in intra-abdominal pressure;
- Relaxation of the lower oesophageal sphincter;
- Expulsion of the gastric contents via the mouth.

Irritation, inflammation or distension of abdominal viscera, including the stomach, duodenum, pancreas, liver and peritoneum, provides a strong stimulus for vomiting and results in stimulation of the vomiting centre in the brain via a neural pathway (Elwood and others 2010).

Fig 1: Vomiting is a common presentation in small animals

Clinical features

Vomiting is a sign commonly associated with a wide range of both gastric and non-gastric diseases. Hence, a logical diagnostic approach is needed to determine the underlying causes (Box 1). History and physical examination will often yield important clues (eg, history of scavenging, exposure to parvovirus, palpation of an abdominal mass). It is essential to differentiate between vomiting and regurgitation before proceeding with potentially expensive or invasive tests.

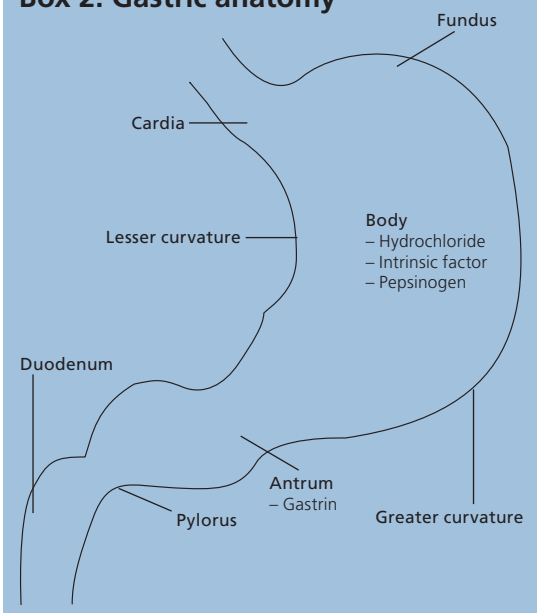
In order to fully understand the complexities of the vomiting reflex and how to suppress it, it is important to consider both gastric anatomy (Box 2) and physiology. Stimulation of the vomiting centre, which is located in the medulla, leads to a vomiting reflex (Fig 2). The cerebral cortex and the gastrointestinal tract (mainly from the stomach and proximal duodenum but also including the pancreas, small intestine, colon, kidneys and peritoneum) is responsible for direct afferent input to the vomiting centre. The vomiting centre also receives indirect stimulation via the chemoreceptor trigger zone (CRTZ). The CRTZ is a small area located outside the blood–brain barrier on the floor of the fourth ventricle in the dorsal medulla, which will result in vomiting if stimulated. The humoral pathway is activated by bloodborne emetogenic substances (eg, uraemic toxins, drugs). Drugs such as morphine can directly stimulate the CRTZ. In addition, input from

Box 1: Causes of vomiting*

- Dietary indiscretion/intolerance/allergy
- Gastric irritation (gastritis/ulceration/neoplasia/motility disorder)
- Intestinal disease (inflammatory bowel disease/neoplasia/bacterial overgrowth)
- Gastric or duodenal distension (obstruction/ileus)
- Drugs (chemotherapeutics/opiates/digoxin/apomorphine)
- Metabolic disease (uraemia/hepatic failure/sepsis/electrolyte imbalance)
- Disorders of other abdominal organs (pancreatitis/peritonitis/pyometra)
- Endocrine disease (hypoadrenocorticism/diabetic ketoacidosis/gastrinoma/hypercalcaemia)
- Motion sickness following stimulation of the vestibular system
- Intracranial disease (neoplasia, encephalitis, raised intracranial pressure)
- Toxins (ethylene glycol, lead)

*This list is not exhaustive

Box 2: Gastric anatomy



- The mucosa in the region of the cardia and pylorus has mucus secreting glands
- Parietal cells are located in the body and fundus, and secrete hydrochloric acid, pepsinogen and intrinsic factor
- Chief cells are also located in the body of the stomach and secrete pepsinogens

the vestibular apparatus mediates vomiting associated with motion sickness and vestibular disease. The CRTZ is rich in dopamine receptors and also has 5 hydroxytryptamine type 3 (5-HT3) receptors.

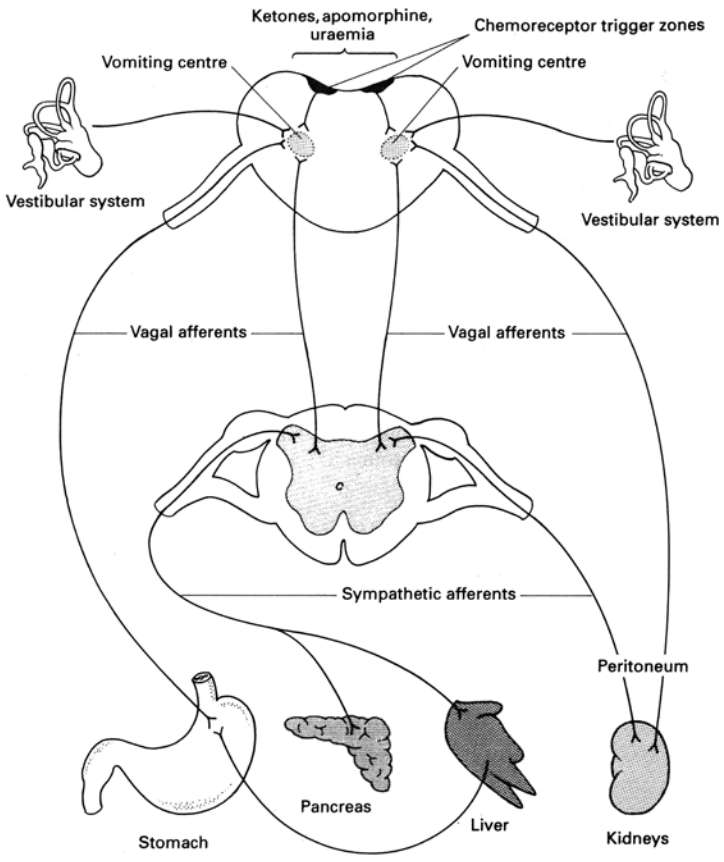


Fig 2: The vomiting centre receives inputs from distant and local sites that can all provoke vomiting. Local receptors in the gastrointestinal tract can initiate vomiting in response to intestinal osmotic load, distension and irritation of the gastric and intestinal mucosa, and inflammation of the peritoneum and other abdominal organs. The chemoreceptor trigger zone, located on the floor of the fourth ventricle in the brain, mediates vomiting associated with many drugs and toxins. Inputs from the vestibular apparatus mediate vomiting associated with motion and vestibular disease. Reproduced, with permission, from Elwood (1995)

Gastric secretions

Control of gastric secretion is complex and involves both neural and humoral mechanisms. The neural component include the vagus nerve while the humoral component involves hormones such as gastrin and gastric inhibitory peptide. There are three phases of gastric acid secretion:

- **Cephalic phase.** The sight, smell and taste of food stimulate gastric secretions via the vagus nerve;
- **Gastric phase.** The distension of the stomach antrum caused by food and the presence of proteins stimulate the release of gastrin;
- **Intestinal phase.** Fats, carbohydrates and acid in the duodenum inhibit gastric acid and pepsin secretion.

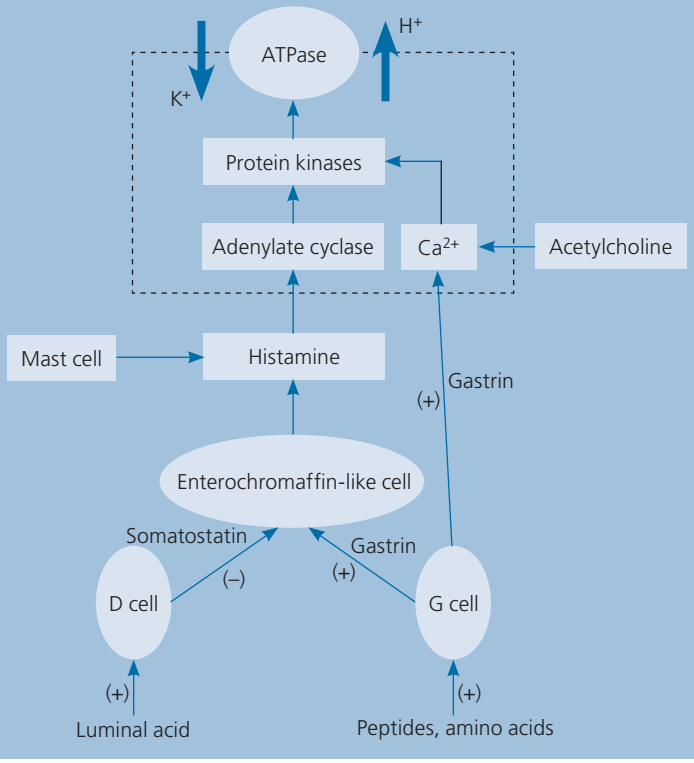
Hydrochloric acid

Acid in the stomach kills ingested bacteria and provides the necessary pH for pepsin to start protein digestion. Acid also stimulates the flow of bile. Parietal cells are responsible for the secretion of hydrochloric acid. Acid secretion is stimulated by acetylcholine and histamine binding to receptors on the parietal cell. Gastrin secretion is also involved in the secretion of hydrochloric acid by stimulating the secretion of histamine from enterochromaffin-like cells (ECL) (Box 3).

Gastrin

Gastrin is released from G cells in the antral mucosa in response to luminal protein and gastric distension

Box 3: Regulation of gastric acid secretion by the parietal cell



(gastrin is also found in pancreatic islets in the fetus). Gastrin is the most potent stimulus of acid secretion and its release is inhibited when antral pH is less than 3. Somatostatin (released from D cells adjacent to parietal cells) inhibits gastrin release. In addition, gastrin has a trophic action on the mucosa of the stomach and intestines, and also stimulates insulin secretion following a protein meal.

Pepsinogen and pepsin

Chief cells in the body of the stomach secrete pepsinogen, which is the inactive precursor of pepsin. Secretion of pepsinogen is stimulated by acetylcholine, histamine and also secretin release from the duodenum. Hydrochloric acid and previously converted pepsin converts pepsinogen to pepsin. Pepsin is responsible for protein degradation and, in turn, stimulates the release of gastrin and cholecystokinin. It has an optimal pH of 2 and is inactivated when the chyme enters the duodenum (neutral pH).

Histamine

Histamine is released from ECL cells following gastrin or acetylcholine binding. Histamine is involved in stimulating pepsinogen secretion by the chief cells.

Secretions are inhibited by:

- Low intraluminal pH;
- Fat;
- Hyperosmolar solutions;
- Somatostatin from D cells;
- Prostaglandins.

Medical management of vomiting includes measures to reduce gastric secretions and increase gastric emptying.

Gastric mucosal barrier

The gastric mucosal barrier separates the gastric juices from the interstitial fluid and comprises:

- Surface epithelial cells;
- A basal membrane;
- A mucus layer;
- A mucosal blood supply.

Surface epithelial cells have tight junctions and phospholipid-rich hydrophobic luminal membranes, which act as a barrier and prevent acid damage in the stomach.

The basal membrane is involved in epithelial restitution. Epithelial cells adjacent to a damaged area migrate over the basement membrane and repair the defect by preventing ulceration and further damage. Mucus is produced by crypt and surface epithelial cells and is composed of glycoproteins and mucopolysaccharides. This is secreted onto the mucosal surface and provides a barrier to prevent proteolytic enzymes digesting the stomach wall. The mucus also contains bicarbonate, which neutralises hydrogen ions. In addition, mucus is viscous and adheres tightly to the epithelial cells.

Mucosal blood supply increases following damage to the gastric mucosa. The increased blood flow supplies bicarbonate-rich plasma, which is taken up by the epithelial cells and secreted into the lumen of the oxyntic gland. The bicarbonate is trapped in the mucus layer and neutralises the surface acid, thus helping to prevent further damage.

Diagnostic approach

If the animal is systemically unwell or has haematemesis or abdominal pain, diagnostic investigations to obtain a minimum database initially are recommended. More specialised or invasive tests may be subsequently required if an underlying cause cannot be determined. Many causes of vomiting will be detected or ruled out if a detailed history is obtained and if a thorough clinical examination, basic laboratory tests and imaging (abdominal radiography or ultrasonography) are performed. If such tests prove negative, endoscopic examination of the stomach and duodenum are advised in order to obtain biopsies. See Elwood (2003) for a full discussion on the approach to the vomiting patient.

Nutritional therapy

The main considerations for dietary management in the vomiting animal include:

- The duration of the clinical signs (acute versus chronic);
- Whether reduced gastric acid secretion would be beneficial;
- Whether manipulation of gastric emptying would be beneficial.

A low-fat diet should be given if a reduction in gastric secretions is considered to be of benefit. Liquid diets empty the stomach faster than solids and should be considered in cases where delayed gastric emptying is thought to be likely.

Acute vomiting

Acute gastroenteritis is the most common gastrointestinal disease encountered in practice and is usually self-limiting. In cases with acute vomiting where the animal remains systemically well, specific diagnostics may not be necessary. Withholding food (and sometimes water) for 24 to 48 hours or until vomiting has resolved is often an effective treatment in both cats and dogs presenting with acute signs. Unabsorbed nutrients in the bowel may contribute to osmotic diarrhoea and a period of bowel rest can help to counteract this. In addition, withholding food reduces antigenic stimulation of the gastric and intestinal mucosa. Following bowel rest, assuming clinical signs have resolved, small volumes of water and a bland, low-fat, highly digestible diet should be introduced and fed for up to two to three days. Small frequent meals are advisable during this time. If the animal appears dehydrated, parenteral fluids should be administered if water is to be withheld.

Chronic vomiting

Dietary rest is not indicated in cases with chronic vomiting. In animals showing mild clinical signs and little evidence of debilitation, therapeutic dietary trials should be considered. Both food allergies and food intolerances should be considered. An allergy

involves an immune reaction to a specific dietary protein, while dietary intolerance is a direct reaction to a specific substance in the diet (eg, gluten). Both dietary allergies and intolerance can lead to gastric inflammation and vomiting. Animals suspected of having a dietary allergy or intolerance should undergo a dietary trial using a hypoallergenic diet for at least two weeks. Both commercial and home-cooked diets can be used.

Hydrolysed proteins with a molecular weight that is below the limit of what can be detected by the immune system can help to prevent dietary sensitisation or reaction. These diets (eg, Hill's z/d Ultra) make ideal elimination diets and can help to manage vomiting caused by reactions to dietary proteins. Alternatively, diets containing a single novel protein source can be used as an exclusion diet.

A more in-depth investigation should always be considered in a vomiting animal that fails to respond to a dietary trial. Both gastrointestinal and non-gastrointestinal causes of vomiting should be considered.

Drug therapies for acute and chronic vomiting

Fluid therapy

Acute vomiting will lead to fluid losses and possible electrolyte imbalances. Initially, lactated Ringer's solution is an appropriate choice in most patients. In more protracted cases, it is useful to assess acid–base status as any changes can be unpredictable. Venous blood gases can be measured using in-house analysers, the results of which can help to tailor fluid therapy. Electrolyte monitoring is also advisable – potassium supplementation is likely to be required even in animals where serum potassium is within reference limits as a total body potassium deficit is often common in cases of chronic vomition.

Antiemetic drugs

Antiemetic drugs should only be used for short-term relief or in cases where the cause of vomiting has been confirmed. The ultimate aim is to determine and address the underlying cause rather than simply suppress any vomiting. Antiemetics should not be used if a foreign body is suspected or confirmed as intestinal perforation can occur in animals where an intestinal obstruction has gone undiagnosed. Patients that continue to vomit despite initial supportive management will however require antiemetic therapy to reduce further fluid losses.

There are several different classes of antiemetic drugs and these are discussed below.

Phenothiazines

Phenothiazines (eg, chlorpromazine) are potent centrally acting antidopaminergics, which act at both the vomiting centre and the CRTZ. They also have antihistamine and anticholinergic properties, but should not be used in dehydrated/hypovolaemic patients as they can cause hypotension through alpha-adrenergic antagonism and arteriolar vasodilation. Phenothiazines usually result in sedation and can potentially lower the seizure threshold in animals with epilepsy. They are no longer commonly used in veterinary medicine due to the availability of other potent antiemetics and are not licensed for use in cats and dogs.

Antidopaminergics

Metoclopramide (Teva UK) has both central and peripheral antiemetic effects. Antidopaminergic effects are responsible for central antiemetic properties at the level of the CRTZ. Cats have fewer dopamine receptors than dogs and so metoclopramide is less effective in this species. Peripherally, metoclopramide stimulates the release of acetylcholine from postganglionic nerves, which leads to increased gastric contractions and raised gastro-oesophageal sphincter pressure. Metoclopramide can result in behavioural changes, including excitement and restlessness. The short half-life of this drug necessitates frequent dosing or constant rate infusions.

Antidopaminergics are indicated in animals with:

- Gastro-oesophageal reflux;
- Oesophagitis;
- Delayed gastric emptying;
- Small bowel motility disorders;

However, they are contraindicated in patients with:

- Intestinal obstruction or perforation;
- Epilepsy.

Serotonin antagonists

Ondansetron (Zofran; GlaxoSmithKline) is a serotonin (5-HT3) antagonist with potent antiemetic activity and is commonly used to control nausea in humans undergoing chemotherapy. It blocks the CRTZ and vagal afferent pathways involved in emesis. Constipation may result with repeated administration but it is the expense of this drug that often precludes its use. Ondansetron can be used in cases with intractable vomiting or before the administration of chemotherapeutic agents.

Mirtazapine

Mirtazapine (Teva UK) (Fig 3) is an adrenergic and serotonergic antidepressant used in humans which can be used as an appetite stimulant and antiemetic agent in cats. It may be a more effective antiemetic than metoclopramide and more potent than cyproheptadine as an appetite stimulant, and can be used in combination with these drugs if required. It is recommended that the dose of mirtazapine is reduced by 30 per cent in the presence of hepatic or renal impairment.

Fig 3: Mirtazapine is a fairly effective appetite stimulant in cats and also has antiemetic properties

Fig 4: Maropitant is a powerful antiemetic agent which is licensed for use in dogs. It acts by antagonising neurokinin-1 receptors

Fig 5: Sucralfate and ranitidine are commonly used drugs in patients with gastrointestinal signs

Neurokin-1 receptor antagonists

Substance P is a neurotransmitter that binds to neurokinin-1 (NK-1) receptors and causes vomiting. It is found in high levels in the vomiting centre and is thought to be the main chemical transmitter involved in vomiting. Maropitant (Cerenia; Pfizer) (Fig 4) is a NK-1 receptor antagonist, which prevents substance P from binding to neurokinin receptors. NK-1 receptors are located throughout the body, including the fundus of the stomach, the medullary vomiting centre and the CRTZ. NK-1 receptor antagonists are much more powerful antiemetics than metoclopramide and are effective in both peripheral and central causes of vomiting (De La Puente-Redondo and others 2007). Maropitant does not appear to have any prokinetic effects. It has a wide safety margin, but is metabolised by the liver and should therefore be used with caution in animals with hepatic disease. Its use in lactating or pregnant bitches has not been evaluated as yet and so cannot be recommended. It should not be used in dogs less than 16 weeks of age as some studies have noted bone marrow hypoplasia in young puppies receiving maropitant. This product is highly protein bound and may compete with other highly bound drugs (eg, phenobarbital or non-steroidal anti-inflammatory agents), which can lead to an increased risk of toxicity. The dose should be reduced in hypoalbuminaemic patients. The manufacturers recommend that, after a five-day course, the drug should be stopped for one day to avoid drug accumulation before treatment is restarted if it is still required.

Maropitant is available as an injectable preparation and oral tablets and is currently the only licensed antiemetic for use in dogs. Dogs often exhibit a transient pain reaction during injection. Although the drug is not licensed for use in cats, published studies have shown that maropitant is well tolerated and effective in this species.

Maropitant is indicated in animals with:

- Vomiting;
- Motion sickness;
- Vomiting induced by chemotherapy.

However, it is contraindicated in cases with:

- Gastrointestinal obstruction or perforation.

Gastric protectants and prokinetic drugs

Sucralfate

Sucralfate (Antepsin; Chugai Pharma UK) (Fig 5) is a sulphated disaccharide. Following oral administration, it forms a gel, which adheres to damaged mucosa, creating a protective barrier and protecting it from further acid damage. Sucralfate stimulates prostaglandin release, increases mucus production and bicarbonate secretion. In addition, sucralfate also binds epithelial growth factor at sites of ulceration and stimulates cellular proliferation. Prolonged administration can cause constipation and can interfere with absorption of other drugs.

Ranitidine, cimetidine and famotidine

Ranitidine (Zantac; GlaxoSmithKline) (Fig 5), cimetidine (Zitac; Intervet UK) and famotidine (Pepcid; Merck Sharp & Dohme) are H_2 receptor antagonists which competitively inhibit acid secretion by the parietal cell in the stomach. Famotidine does not inhibit cP450 and only requires once daily administration. Ranitidine has anticholinesterase activity, which results in some prokinetic activity (unlike cimetidine and famotidine). Ranitidine is more potent than cimetidine with less effect on cP450 and a longer half-life, but cimetidine is currently the only licensed veterinary product.

These products are indicated in animals with:

- Gastric/duodenal ulcers;
- Uraemic gastritis;
- Gastro-oesophageal reflux;
- Oesophagitis;
- Gastrinoma.

Omeprazole

Omeprazole (Losec; AstraZeneca) is a proton pump inhibitor, which irreversibly inhibits acid production by the parietal cell. It is more potent and has longer duration of activity than either cimetidine or ranitidine and also has cytoprotective effects by enhancing prostaglandin synthesis. This drug is often used in cases diagnosed with gastrinoma, but can also be useful in any case with gastric ulceration.

Cisapride

Cisapride promotes the release of acetylcholine in the gut wall, which results in prokinetic activity. It is more potent than metoclopramide at stimulating gastric emptying and increasing lower oesophageal sphincter pressure. This drug also stimulates oesophageal peristalsis in cats in which the distal oesophagus comprises smooth muscle. The canine oesophagus is made up of striated muscle, which means cisapride has no effect on oesophageal function in this species. Unlike other prokinetic agents, cisapride stimulates colonic motility.

Cisapride has no central antiemetic effect and therefore has no effect on nausea or vomiting mediated by uraemia or motion sickness. Overdose can cause abdominal cramps and diarrhoea. This drug has been withdrawn from the human market due to reported dysrhythmias and can only be imported from Europe using a special treatment certificate.

Cisapride is indicated in animals with:

- Gastro-oesophageal reflux;
- Megaoesophagus in cats (not dogs);
- Delayed gastric emptying;
- Small bowel motility disorders;
- Megacolon/idiopathic constipation;

However, it is contraindicated in cases with:

- Gastrointestinal obstruction;
- Gastrointestinal ulceration;
- Risk of gastrointestinal perforation.

Erythromycin

Erythromycin is a macrolide antimicrobial that at low doses (5 mg/kg orally every eight hours) has prokinetic activity. It mimics the action of motilin, which results in accelerated gastric emptying of solids. In addition, erythromycin stimulates motilin receptors throughout the gastrointestinal tract and stimulates gastric, pyloric and duodenal contractions; this can result in large particles of food entering the duodenum which, in some cases, can cause undesired effects. Erythromycin is indicated in animals with delayed gastric emptying.

Summary

The combined use of dietary modification and medical therapies are commonly employed to control vomiting in small animal practice. Although medical therapies are often beneficial in such cases to prevent serious fluid and electrolyte losses, where possible, clinicians should always try to identify and eliminate the underlying cause of vomition rather than simply treat the signs.

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