Vomiting

Abstract: Vomiting is the forceful expulsion of stomach contents through the mouth, caused by humoral stimulation of the chemoreceptor trigger zone (CRTZ) or neural stimulation of the emetic center. The CRTZ is activated and controlled by neurotransmitter manipulation at the receptor level. Clinical signs preceding vomiting may include ptyalism, tachycardia, depression, hiding, and yawning. Gastritis, gastrointestinal ulceration, pancreatitis, motion sickness, uremia, chemotherapy, and drug administration are common initiating causes of vomiting. This article reviews the anatomic and physiologic aspects of the vomiting reflex and its neurotransmitters, associated receptors, and rational management.

Emesis, or vomiting, is one of the most common reasons dogs and cats present for medical evaluation. Vomiting is often associated with mild, self-limiting diseases that resolve with minimal diagnostic tests and therapy. However, it can be related to debilitating conditions that have life-threatening consequences. The history obtained from the client should be as detailed as possible because historical details are often helpful in selecting the appropriate treatment and diagnostic plan. Questions to ask during the history should include onset of vomiting, duration of clinical signs, type and frequency of vomiting, relation to food ingestion, characteristics of the vomited contents, diet history, and environment. Questions about known medical conditions and current therapies are also pertinent because these factors may play an active role in the inciting cause.

The Vomiting Reflex
Pathophysiology

The vomiting reflex is a neurophysiologic event that initiates the nonvoluntary process of vomiting. Vomiting is a reflex act that is mediated neurologically by the activation of the bilateral nucleus tractus solitarii, or emetic center, situated in the parvicellular reticular formation in the lateral region of the medulla oblongata. This is the area that initiates, controls, regulates, and organizes the vomiting reflex. The vomiting reflex comprises six fundamental components. The emetic center (1) receives input from (2) the gastrointestinal tract (afferent neurons), (3) the higher centers of the brain, (4) the vestibular apparatus, and (5) the CRTZ. Finally, to coordinate the vomiting reflex, the vomiting center sends signals through (6) the efferent motor neurons. The vagal and sympathetic afferent neurons originate from the gastrointestinal tract, particularly the duodenum, as well as other areas, including the urinary and reproductive system, liver, pancreas, peritoneum, and cardiac vessels. Stimulation of these neurons initiates the impulse that travels directly to the emetic center. The higher centers of the brain, including the cerebral cortex and the limbic system, can trigger emesis through three mechanisms: direct stimulation of the vomiting center by inflammatory diseases, hydrocephalus, or neoplasia; psychogenic stimulation caused by fear, stress, excitement, or pain; and traumatic stimulation related to head injuries and increased intracranial pressure.

The CRTZ is a bilateral set of centers in the brainstem, located on the floor of the fourth ventricle. It possesses free nerve endings that maintain direct contact with the cerebrospinal fluid via ependymal pores or the sheath surrounding fenestrated capillaries. These free nerve endings are activated by the vestibular system or through the humoral pathway by conditions affecting the blood or cerebrospinal fluid (e.g., drug administration, infection, osmolar...
Vomiting

and acid–base disorders, electrolyte derangements, metabolic diseases).\textsuperscript{15}

Finally, to initiate the vomiting reflex, efferent motor signals must be transmitted to the upper gastrointestinal tract through the sensory aspect of cranial nerves V, VII, IX, X, and XII and to the diaphragm and abdominal muscles via the spinal nerves.\textsuperscript{8}

Anatomy

The act of vomiting is composed of three phases: nausea, retching, and expulsion of proximal duodenal and gastric contents.\textsuperscript{6,7,16} Nausea is the conscious recognition of subconscious excitation in an area of the medulla that is closely associated with the vomiting center. This excitation is caused by irritative impulses coming from the gastrointestinal tract, lower brain, or cerebral cortex.\textsuperscript{15,17–19} Ptyalism, tachycardia, nervousness, hiding or seeking attention, shivering, and yawning are all characteristic signs of nausea triggered by general activation of the sympathetic and parasympathetic branches of the autonomic nervous system. Hypersalivation stimulates swallowing, which stimulates relaxation of the gastroesophageal sphincter. The bicarbonate-rich saliva secreted by the salivary glands in the mouth lubricates the esophagus and helps neutralize the stomach’s acidic environment before vomiting.\textsuperscript{8,15} Before retching, aboral gastric and esophageal motility diminishes and the lower esophageal and pyloric sphincters relax.

Retching is the second phase of vomiting and begins with the onset of a retrograde giant contraction.\textsuperscript{20,21} This contraction is a single-phase, retrograde, peristaltic motion that empties the proximal duodenal contents into the stomach.\textsuperscript{20–22} It is followed by deep inspiratory movements, forceful contractions of the abdominal muscles and diaphragm, and closure of the glottis. These actions produce negative intrathoracic pressure and positive intraabdominal pressure, facilitating the movement of gastric contents into the esophagus. Before expulsion, the respiratory center is inhibited and the nasopharynx and glottis close to prevent pulmonary aspiration and nasal regurgitation of the gastric contents. The third and last phase of vomiting is the expulsion of stomach contents through the mouth.

Antiemetics

Antiemetics are drugs that block the vomiting reflex\textsuperscript{9,23,24} by impeding neurotransmission at central (CRTZ, emetic center) and peripheral (gastrointestinal epithelium) receptor sites. These drugs are classified based on the type of receptor they block (Table 1). However, antiemetics have the potential to prolong gastrointestinal infections, predispose patients to such infections, and prevent toxin elimination by decreasing gastrointestinal motility. The use of most of these drugs in animals is off-label, and some dosages are extrapolated from the human medical literature (Table 2).

Phenothiazines

Phenothiazines are broad-spectrum antiemetics that have antihistaminergic and anticholinergic properties at low doses in the CRTZ and anticholinergic effects at higher doses at other central sites, including the emetic center.\textsuperscript{9} These drugs also block norepinephrine at peripheral α-adrenergic receptors. Drugs in this group include chlorpromazine, prochlorperazine, and acetylpromazine. Common adverse effects in small animals, especially dogs, include ataxia, hypotension, and excessive sedation. Generalized central nervous system (CNS) stimulation, aggressiveness, violent behavior, extrapyramidal effects, and seizures are rare. Fluid therapy is indicated in
patients undergoing phenothiazine therapy because of the vasodilatory properties of these drugs.

**Anticholinergics**

Anticholinergic drugs block cholinergic afferent pathway transmission from the gastrointestinal tract (peripheral action) and the vestibular system to the emetic center (central action). Scopolamine and isopropamide are centrally acting anticholinergics that cross the blood–brain barrier. They have a short duration of action and can cause excitement in cats. Peripherally acting anticholinergics include propantheline and methscopolamine. Isopropamide and propantheline are the drugs in this group that are most commonly used in small animals for vomiting related to motion sickness. Side effects reported in humans and small animals include xerostomia (dry mouth), sedation, visual disturbances, drowsiness, dysphoria, confusion, gastrointestinal ileus, and disorientation.

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**TABLE 1 Vomiting Reflex Components, Receptors, and Controlling Neurotransmitters and Medications**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Receptor Agonists</th>
<th>Receptor Antagonists</th>
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<tbody>
<tr>
<td><strong>Chemoreceptor trigger zone</strong></td>
<td></td>
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<tr>
<td>D&lt;sub&gt;2&lt;/sub&gt;-Dopaminergic</td>
<td>Dopamine</td>
<td>Metoclopramide</td>
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<tr>
<td>M&lt;sub&gt;1&lt;/sub&gt;-Cholinergic</td>
<td>Acetylcholine</td>
<td>Propantheline</td>
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<tr>
<td>H&lt;sub&gt;1&lt;/sub&gt;-Histaminergic</td>
<td>Histamine</td>
<td>Diphenhydramine</td>
</tr>
<tr>
<td>α&lt;sub&gt;2&lt;/sub&gt;-Adrenergic</td>
<td>Norepinephrine</td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-Serotonergic</td>
<td>Serotonin</td>
<td>Ondansetron</td>
</tr>
<tr>
<td>ENK&lt;sub&gt;µ&lt;/sub&gt;-Enkephalinergic</td>
<td>Met-enkephalin</td>
<td>Leu-enkephalin</td>
</tr>
<tr>
<td>Neurokinin-1 antagonist</td>
<td>Substance P</td>
<td>Maropitant</td>
</tr>
<tr>
<td><strong>Emetic center</strong></td>
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<tr>
<td>Glucocorticoid receptors</td>
<td>Dexamethasone</td>
<td>Cyproterone</td>
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<tr>
<td>Neurokinin-1 antagonist</td>
<td>Substance P</td>
<td>Maropitant</td>
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<tr>
<td><strong>Vestibular apparatus</strong></td>
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<tr>
<td><strong>Vagal afferents</strong></td>
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<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-Serotonergic</td>
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<tr>
<td><strong>Vagal efferents</strong></td>
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<td>D&lt;sub&gt;2&lt;/sub&gt;-Dopaminergic</td>
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<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;-Serotonergic</td>
<td>Cisapride</td>
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<td>M&lt;sub&gt;3&lt;/sub&gt;-Cholinergic</td>
<td>Acetylcholine</td>
<td>Propantheline</td>
</tr>
<tr>
<td>Motilin</td>
<td>Erythromycin</td>
<td>Motilin</td>
</tr>
</tbody>
</table>

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**QuickNotes**

Vomiting is a neurologically mediated reflex that depends on neural or humoral activation of the emetic center.
Antihistamines
Antihistamines can intercept cholinergic and histaminic nerve transmission responsible for vestibular stimulation of the vomiting center.25 Drugs in this classification include diphenhydramine, dimenhydrinate, and meclizine. These drugs display H 1-antihistaminergic properties and are mainly used to control the clinical signs of motion sickness. Mild sedation, xerostomia, and drowsiness are some of the adverse effects. Meclizine can be teratogenic if administered at high doses.25 Cats do not have histamine receptors in the CRTZ, and antihistaminic drugs do not control their vomiting.27

Serotonin Antagonists
Serotonin antagonists are specific inhibitors of 5-HT-serotonergic receptors. They control vomiting by acting on receptors located on the periphery of vagal nerve terminals and centrally on the CRTZ.25,26 These receptors are normally stimulated by serotonin released from the enterochromaffin cells of the small intestine in response to damage to the gastrointestinal mucosa. Ondansetron, a member of this class of antiemetic drugs, has been shown to control vomiting in dogs28,29 and is used in dogs receiving radiation and chemotherapy when metoclopramide and other antiemetics fail to control vomiting.25,26 Dolasetron, another member of this group, acts on receptors in the CRTZ.25 Both of these drugs are used extensively in human medicine, and they seem to be safe antiemetic alternatives in veterinary medicine.25,31 However, they are not effective in controlling vomiting caused by motion sickness.25,26

Side effects of these drugs that have been reported in people include electrocardiographic changes, including PR and QT prolongation and QRS widening, that are believed to be caused by sodium channel blockage by dolasetron metabolites. Diarrhea, headache, dizziness, and musculoskeletal pain have been reported as well. These medications can be expensive.

Substituted Benzamides
Substituted benzamides exert antiemetic effects through different mechanisms. Some, such as metoclopramide and trimethobenzamide, antagonize dopamine receptors in the CNS and block 5-HT 3-serotonergic receptors when administered at high concentrations.25,26 Metoclopramide is known for its potent dopaminergic antagonism, but trimethobenzamide, which is also a weak antihistamine, has not been a very effective anti-dopaminergic agent clinically. Metoclopramide has more action on D 2-dopaminergic receptors than trimethobenzamide and is 20 times more potent than phenothiazines.7 As a result, metoclopramide should not be used in patients receiving dopamine.12

Cisapride, another substituted benzamide, activates neuronal 5-HT 3 receptors, which facilitates gastric emptying. Metoclopramide also activates neuronal 5-HT 3 receptors and blocks 5-HT 3-serotonergic receptors, increases the lower esophageal sphincter tone, and enhances aboral gastrointestinal motility; therefore, these drugs are classified as prokinetics as well.9 Adverse effects of these drugs include CNS excitement and behavioral changes, especially during rapid intravenous administration or if given at high doses. Metoclopramide controls peripherally induced and humorally mediated vomiting due to numerous conditions, but it should be avoided if gastrointestinal obstruction is suspected because its prokinetic properties could predispose these patients to gastric or intestinal perforation. This contraindication also applies to cisapride.

Butyrophenone and Benzimidazole Derivatives
Butyrophenone derivatives (e.g., haloperidol, droperidol) are potent dopamine antagonists in the CRTZ and are used as tranquilizers.9 Their side effects are very similar to those of phenothiazines. The benzimidazole derivatives antagonize dopamine receptors in the gastrointestinal smooth muscle and display prokinetic properties like those of metoclopramide,22 but their use in veterinary medicine is minimal if any.

Opioids
Enkephalins—endogenous opiates belonging to the endorphin family—are believed to have antiemetic properties. Neurons containing enkephalins have been identified near the CRTZ and the emetic center.35 Evidence suggests that opioid κ and/or μ receptors are present in the vomiting center and are involved in inhibition of emesis in dogs and cats.34 Butorphanol, a pri-
## TABLE 2  Most Common Antiemetics Used in Small Animal Medicine

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Site of Action</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α2-Adrenergic antagonists</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine[4,13]</td>
<td>CRTZ and emetic center</td>
<td>Dogs and cats: 0.1–0.5 mg/kg SC or IM q6–8h</td>
<td>Hypotension, sedation</td>
</tr>
</tbody>
</table>
| Chlorpromazine[4,13,15]       | CRTZ and emetic center       | Dogs: 0.1–0.5 mg/kg SC, IM, or IV q6–8h  
Cats: 0.2–0.5 mg/kg SC, IM, or IV q6–8h | Hypotension, sedation              |
| Yohimbine[4,2]               | CRTZ and emetic center       | Dogs: 0.25–0.5 mg/kg SC or IM q12h     | Hypotension, sedation              |
| **D2-Dopaminergic antagonists**|                              |                                       |                                    |
| Metoclopramide[4,13]         | CRTZ, GI smooth muscle       | Dogs: 0.1–0.4 mg/kg PO, SC, or IM q6h  
Cats: 0.2–0.4 mg/kg PO, or SC q6–8h  
CRI: 1–2 mg/kg/day | Extrapyramidal signs, constipation |
| Trimethobenzamide[2,13]      | CRTZ                         | Dogs: 3 mg/kg IM q8–12h               | Allergic reactions                 |
| **H1-Histaminergic antagonists**|                              |                                       |                                    |
| Diphenhydramine[4,2,13]      | CRTZ                         | Dogs and cats: 2–4 mg/kg PO or IM q8h | Sedation, GI effects               |
| Dimenhydrinate[4,2,13]       | CRTZ                         | Dogs and cats: 4–8 mg/kg PO q8h       | Sedation, GI effects               |
| Meclizine[4]                 | CRTZ                         | Dogs and cats: 4 mg/kg PO q24h        | Sedation, xerostomia, tachycardia  |
| **M1-Cholinergic antagonists**|                              |                                       |                                    |
| Propantheline[4]             | Parasympathetic nervous system | Dogs and cats: 0.25 mg/kg PO q8h       | Gastric retention, ileus, tachycardia |
| Isopropamide[4]              | Parasympathetic nervous system | Dogs and cats: 0.2–0.4 mg/kg PO q8–12h | Gastric retention, ileus, tachycardia |
| **5-HT3-Serotonergic antagonists**|                              |                                       |                                    |
| Ondansetron[4,12]            | CRTZ and vagal afferent neurons | Dogs: 0.11–0.176 mg/kg slow IV push q24h  
Cats: 0.1–0.15 mg/kg slow IV push q24h | Sedation                           |
| Dolasetron[4]                | CRTZ                         | Dogs: 0.6 mg/kg IV q24h or 0.5 mg/kg PO, SC, or IV q24h  
Cats: 0.6 mg/kg IV q12h or 0.6–1 mg/kg PO q12h | Electrocardiogram changes          |
| Mirtazapine[4]               | CRTZ and vagal afferent neurons | Dogs: 0.6 mg/kg PO q24h, not to exceed 30 mg/day  
Cats: 3–4 mg/cat PO q72h | Sedation, ataxia, depression, vocalization |
| **NK1-Neurokinin antagonist**|                              |                                       |                                    |
| Maropitant[40]               | CRTZ and emetic center       | Dogs: 1 mg/kg SC q24h up to 5 days or 2 mg/kg PO q24h up to 5 days | Injection site soreness, ataxia, anorexia, diarrhea |
| **5-HT4-Serotonergic antagonist**|                              |                                       |                                    |
| Cisapride[4,12]              | Myenteric neurons            | Dogs: 0.1–0.5 mg/kg PO q8h  
Cats: 0.1–1.0 mg/kg or 5 mg (total dose) PO q8–12h | None                              |
| **Motilin agonist**          |                              |                                       |                                    |
| Erythromycin[4,2]            | GI smooth muscle             | Dogs and cats: 0.5–1.0 mg/kg IV q8h, up to 5.0 mg/kg PO q8h | Vomiting at antimicrobial doses (15 mg/ kg tid) |
| **Opioid**                   |                              |                                       |                                    |
| Butorphanol[4,13]            | Emetic center                | Dogs: 0.2–0.4 mg/kg IM 30 min before cisplatin infusion | Sedation, ataxia, anorexia, diarrhea |
| **Others**                   |                              |                                       |                                    |
| Propofol[4]                  | CRTZ                         | None reported in veterinary medicine  | Apnea, hypotension, seizurelike signs |
| Dexamethasone[13]            | Emetic center, medulla       | Dogs: 0.1 mg/kg SC or IV before chemotherapy | GI ulceration                      |
| Diazepam[4]                  | Vestibular system suppression | 0.1–0.2 mg/kg PO q6h                  | Sedation                           |

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Phenothiazines are a broad-spectrum antiemetic and antihistaminergic properties in the CRTZ and anticholinergic effects in the emetic center. Mirtazapine is a piperazinoazepine drug used as an antidepressant in people. It antagonizes central presynaptic $\alpha_2$-receptors and blocks serotonin receptors. It is a weak $5-HT_1$ serotonin receptor antagonist, a potent $5-HT_2$ and $5-HT_3$ serotonin receptor antagonist, and an $H_1$-histamine antagonist. It is used to control chemotherapy-associated nausea and vomiting in humans and, more recently, in small animals.

Neurokinin Antagonists
Neurokinin (NK) antagonists are a new group of antiemetics that includes maropitant, an agent developed for dogs that acts as a ligand for the substance P receptors located in many areas of the brain, including the emetic center and CRTZ. It is believed that the substance P–NK$_1$ receptor complex is in the final common pathway of the neural and humoral pathways of the vomiting reflex. Studies in dogs have showed that maropitant prevents vomiting caused by peripheral and central emetogens, including apomorphine, cisplatin, and syrup of ipecac, and clinical conditions such as pancreatitis and gastroenteritis. Maropitant is also effective against vomiting caused by motion sickness. Adverse effects reported with this drug include ataxia, anorexia, diarrhea, and injection site soreness. This drug should not be used in dogs younger than 16 weeks because bone marrow hypoplasia has been reported.

Other Drugs
Other drugs used to control vomiting centrally include yohimbine, diazepam, dexamethasone, propofol, and mirtazapine. Yohimbine, a pure $\alpha_2$-adrenergic antagonist, is a very potent antiemetic used in dogs and cats. It may cause CNS excitement, excessive sedation, muscle tremors, tachypnea, ptysialism, and hyperemic mucous membranes.

Diazepam relieves nausea and vomiting in people. Studies with animal models and clinical trials in human medicine suggest that this drug suppresses the vestibular system. The antiemetic properties of corticosteroids are incompletely understood, but their mechanism involves the activation of glucocorticoid receptors in the medulla, especially the emetic center in cats. Dexamethasone has been shown to be useful in controlling chemotherapy-associated nausea and vomiting in human patients and dogs. Propofol, an alkylphenol derivative, is used as an antiemetic in people with chemotherapy-associated nausea and vomiting that is unresponsive to serotonin antagonists or dexamethasone. It has been proposed that its antiemetic mechanism involves reduction of the serotonin concentration in the CRTZ via $\gamma$-aminobutyric acid activity and $5-HT_3$ serotonin receptor antagonism.

Gastritis or Gastric Ulceration
Treatment to manage vomiting caused by gastritis or gastric ulceration must include proper fluid therapy and gastric mucosal protection. Many clinicians use broad-spectrum antiemetics because they cover local and peripheral receptors. Chlorpromazine, serotonin antagonists, and metoclopramide are good options. Maropitant seems to work extremely well in dogs. If vomiting is associated with gastrointestinal ulceration due to NSAID administration, therapy with misoprostol, a prostaglandin E$_1$ (PGE) analog, may be effective in controlling both the ulcerative lesion and vomiting as a secondary problem. Proton pump inhibitors and $H_2$-histamine antagonists provide more complete inhibition of gastric acid secretion in severe cases of ulceration. If *Helicobacter* spp are the underlying cause of ulceration, appropriate antibiotic therapy and antacids should relieve the clinical signs of the infection.

Patients with neoplastic diseases often have gastrointestinal ulceration. Mast cell tumors of any stage, grade, and size can cause vomiting in dogs by increasing the plasma histamine concentration. Histamine acts on the CRTZ and the gastric mucosa. Mast cell tumor ulceration and its effects are treated with $H_1$-histamine antagonists. Tumor size and histamine release in dogs are controlled with the administration of corticosteroids.

Pancreatitis
Pancreatitis causes ileus due to intestinal inflammation, resulting in direct afferent input to the vomiting center. Metoclopramide is the most common antiemetic used in these patients because it acts centrally and peripherally. In dogs, phenothiazines, $5-HT_3$-serotonergic
antagonists, and maropitant can be useful if metoclopramide fails to control vomiting.

**Chemotherapy and Other Drugs**

Emesis caused by cancer chemotherapy and other drugs (e.g., digitalis) is mediated by 5-HT₃-serotonergic receptors.²,¹²,²⁵ In humans, the chemotherapeutic drugs most commonly associated with vomiting include cisplatin, cyclophosphamide, dacarbazine, and doxorubicin.²⁰ Drugs with 5-HT₃-serotonergic antagonist properties, especially the serotonin antagonists ondansetron, granisetron, dolasetron, block these receptors in the CRTZ in cats and in the vagal afferent neurons in dogs.²⁵,²⁶,²⁸,²⁹,⁵⁷ Metoclopramide is widely used to control chemotherapy-induced vomiting.⁶,⁵⁸ The new agent maropitant is also effective in controlling cisplatin-induced vomiting in dogs, and even though there is coexpression of substance P with 5-HT receptors in the primate brain,³⁷ this has not been documented in dogs or cats.

**Motion Sickness**

Motion sickness, or kinetosis, is generated from the vestibular apparatus.²,⁹,¹¹ Studies in humans have revealed that motion sickness is caused by three mechanisms: (1) conflicting inputs from the visual and vestibular systems; (2) conflicting inputs from the two vestibular systems (the semicircular canals and the otolith organs); or (3) comparison of input from these systems with the individual’s expectations derived from previous experiences.⁵⁹ Vomiting caused by motion sickness involves M₁-cholinergic and H₁-histaminergic receptors,²,¹¹ and treatment should antagonize both receptors. Phenothiazines like chlorpromazine and prochlorperazine can antagonize both receptors at the same time, but diphenhydramine, dimenhydrinate, cyclizine, meclizine, and promethazine are H₁-histamine blocking agents only, and they should be combined with a M₁-cholinergic receptor blocker for effective control of emetic signals originating from the vestibular apparatus. Maropitant prevents kinetosis in dogs by blocking the final common pathways of the vomiting reflex, including signals from the vestibular system.⁴⁰ Scopolamine is a muscarinic M₁-cholinergic antagonist used to treat motion sickness, but results are not consistent.

**Uremia**

Uremic toxins cause decreased gastrin clearance and irritate the gastrointestinal mucosa, resulting in ulcerative lesions and gastritis. When these toxins cross the blood–brain barrier, they stimulate central and peripheral receptors and activate D₂-dopaminergic receptors in the CRTZ.²,¹¹ Dopamine antagonists like metoclopramide and chlorpromazine effectively block these receptors.

Diuresis with appropriate fluid therapy and a proton pump inhibitor or H₂-histaminergic antagonist helps relieve uremia by diminishing the secretion of hydrogen ions into the stomach, providing protection and promoting mucosal healing.

**Gastrointestinal Motility Disorders**

Prokinetics—cisapride, metoclopramide, and erythromycin—should be used to control vomiting due to nonobstructive delayed gastric emptying. These drugs exert their effects on different receptors. Cisapride, the most effective prokinetic agent available,¹¹ lacks direct antiemetic effects but stimulates 5-HT₄-serotonergic receptors.⁶⁰ Metoclopramide’s antagonism of D₂-dopaminergic receptors enables it to stimulate motility in areas where these receptors are present (the higher gastrointestinal tract, lower esophageal sphincter, stomach, and duode-
Erythromycin, a macrolide used for its antimicrobial properties, is useful as a prokinetic at low doses. In dogs, it stimulates the release of motilin, which initiates phase III of the migrating myoelectric complex, the sequence of motor activity during the interdigestive period in the small bowel. This cyclic pattern originates in the gastric antrum and extends over the entire length of the small intestine. The third and final phase of this pattern is generally associated with the propulsion of ingesta. It is unknown whether cats can benefit from this effect.

Dogs that vomit bile in the morning before eating may have *bilious vomiting syndrome*. This is a condition characterized by grass ingestion, vomiting, and lack of other definitive clinical signs. It mostly occurs in the morning and is believed to be commonly associated with gastritis, inflammatory bowel disease, and bile and gastroesophageal reflux. Affected patients usually respond to a single evening dose of cisapride, metoclopramide, or erythromycin.

### Undetermined Etiology

Patients with vomiting of undetermined etiology must be treated with the safest approach possible once systemic diseases (e.g., liver disease, renal disease, endocrine disease) have been ruled out. Patients that are uncomfortable from excessive vomiting or are at high risk for aspiration pneumonia and have not been exposed to a toxic agent should be treated with antiemetics when available. 

#### References

1. Emesis is initiated, controlled, regulated, and organized by the
   a. higher centers of the brain.
   b. CRTZ.
   c. vestibular apparatus.
   d. emetic center.

2. The vomiting pathways are controlled by
   a. neurotransmitter–receptor interactions.
   b. the higher centers of the brain.
   c. the peripheral nervous system.
   d. vestibular neurons.

3. _________ are considered broad-spectrum antiemetics because of their effect on multiple receptors.
   a. Anticholinergics
   b. Phenothiazines
   c. Serotonin antagonists
   d. Opioids

4. Emesis caused by cancer chemotherapy and other drugs is mediated by
   _________ receptors.
   a. D₂-dopaminergic
   b. M₁-cholinergic
   c. H₂-histaminergic
   d. 5-HT₂-serotonergic

5. Which antiemetic is also classified as a prokinetic?
   a. ranitidine
   b. maropitant
   c. metoclopramide
   d. propofol

6. Which condition or pathogen is the least likely to cause gastric ulceration?
   a. Helicobacter spp
   b. mast cell tumor
   c. gastrinoma
   d. ketosis

7. Mirtazapine does not antagonize _________ receptors.
   a. H₁-histaminergic
   b. 5-HT₁-serotonergic
   c. central presynaptic α₁
   d. D₂-dopaminergic

8. _________ can be used for chemotherapy-associated nausea and/or vomiting, especially when patients do not respond to the newer serotonin antagonists and when multiple medication therapy fails.
   a. Propofol
   b. Diazepam
   c. Mirtazapine
   d. Dexamethasone

9. Which antiemetic antagonizes neurokinin receptors in many areas of the brain?
   a. mirtazapine
   b. maropitant
   c. dolasetron
   d. prochlorperazine

10. Select the correct antiemetic–adverse effect pair.
    a. ondansetron; renal toxicity
    b. chlorpromazine; hypotension
    c. metoclopramide; sedation
    d. meclizine; gastrointestinal perforation

3 CE CREDITS

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