

## CHAPTER 162

# ANTIEMETICS AND PROKINETICS

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### KEY POINTS

- The medullary vomiting center (MVC) probably is not a focal, discrete area in the brain; rather, it is spread throughout the medulla.
- Centrally acting antiemetics are more effective than peripherally acting antiemetics. Centrally acting antiemetics that work on the MVC typically are more effective than those that act only at the chemoreceptor trigger zone.
- Maropitant (a neurokinin-1 antagonist) is highly effective in dogs and cats with minimal adverse effects other than pain upon subcutaneous injection.
- The serotonin (5-HT<sub>3</sub>) receptor antagonists ondansetron and dolasetron are usually effective in dogs and cats and have few adverse effects.
- Metoclopramide is a dopamine receptor antagonist that works at the chemoreceptor trigger zone and is also a gastric prokinetic. Metoclopramide can sometimes cause abnormal behavior and even vomiting (possibly due to excessive gastric prokinetic activity). It tends to be less effective in cats than in dogs.

- Promazine derivatives (e.g., chlorpromazine, prochlorperazine) are effective centrally acting antiemetics that can cause sedation and hypotension due to  $\alpha$ -adrenergic blocking activity.

### ANTIEMETICS

Antiemetics are indicated primarily when vomiting makes it difficult to maintain energy, fluid, or electrolyte homeostasis or when quality of life is adversely impacted by nausea (Table 162-1). Not every vomiting patient should receive an antiemetic; sometimes it is more appropriate to allow a patient to vomit once or twice a day to assess the effectiveness of treatment for the underlying disease. Typical indications for antiemetics include pancreatitis, gastritis, enteritis, peritonitis, hepatic disease, renal insufficiency, and motion sickness; they are also used in patients at risk of aspiration pneumonia. With

**Table 162-1 Centrally Acting Antiemetics Commonly Used in Dogs and Cats**

Drug	Dosage	Special Considerations
Maropitant	1 mg/kg SC q24h or 2 mg/kg PO q24h 8 mg/kg PO q24h for up to 2 days for motion sickness in dogs; 1 mg/kg SC, IV, PO q24h in cats	Approved antiemetic for dogs and cats
Ondansetron	0.1-1 mg/kg IV, PO q8-12h	—
Granisetron	0.1-0.5 mg/kg IV q8-24h	—
Dolasetron	0.6-1 mg/kg IV, SC, PO q12-24h	—
Metoclopramide	0.1-0.5 mg/kg IV, IM, PO q8-12h or CRI of 1-2 mg/kg/24 h for nausea	Gastric prokinetic Can cause extrapyramidal effects if overdosed Note: for treatment of gastroesophageal reflux/ileus, 0.3 mg/kg/hr IV after a 0.4 mg/kg loading dose IV
Chlorpromazine	0.5 mg/kg IV, IM, SC q6-8h in dogs 0.2-0.4 mg/kg IM, SC q6-8h in cats	Can cause hypotension and sedation
Prochlorperazine	0.1-0.5 mg/kg IV, IM, SC q8-12h	Can cause hypotension and sedation

CRI, Constant rate infusion; IM, intramuscularly; IV, intravenously; PO, per os; SC, subcutaneously.

the exception of the neurokinin-1 (NK-1) receptor antagonists, antiemetic drugs are usually ineffective in patients with gastrointestinal (GI) obstruction. Parenteral administration is typically preferred in actively vomiting patients because oral administration will be ineffective if the drug is vomited before absorption.

### Neurokinin-1 Receptor Antagonists

Maropitant is an NK-1 receptor antagonist that blocks the action of substance P in the central nervous system as well as at peripheral NK-1 receptors in the GI tract.<sup>1</sup> It is approved for use in dogs and cats and is considered a safe and effective drug. Dogs are typically treated with 1 mg/kg subcutaneously (SC) or 2 mg/kg orally (PO) q24h for up to 5 consecutive days. Anecdotally, maropitant has been administered intravenously in patients with poor peripheral perfusion and as a way to avoid the pain associated with subcutaneous administration. This appears to be a safe, effective route, but pharmacokinetic studies are lacking. Maropitant often causes pain when injected and is reported to cause bone marrow hypoplasia when administered to puppies younger than 11 weeks old. The drug undergoes extensive first-pass metabolism in the liver; hence, it has a much higher bioavailability when given subcutaneously (90%) than when given orally (23% to 37%, which is not affected by feeding). It can have nonlinear kinetics as the dose is changed.<sup>2</sup> It is effective in preventing vomiting due to motion sickness,<sup>3</sup> vomiting caused by various spontaneous illnesses,<sup>4</sup> and nausea associated with chemotherapy (doxorubicin and cisplatin)<sup>5</sup> in dogs, as well as motion sickness<sup>6</sup> and xylazine-induced emesis in cats when used at 1 mg/kg SC, PO, or intravenously [IV].

NK-1 antagonists are thought to have many other effects beyond antiemesis (e.g., antiinflammatory, neuroprotectant, hepatoprotectant), although their clinical usefulness for these purposes is as yet unproven.<sup>7</sup> Reduction of diarrhea in patients receiving chemotherapy has been reported, and there is some suggestion that NK-1 antagonists may have antitumor activity. They appear to reduce visceral pain in cats and dogs and reduce the minimum alveolar concentration of sevoflurane during anesthesia if given intravenously.<sup>8,9</sup>

### 5-HT<sub>3</sub> Receptor Antagonists<sup>10</sup>

Ondansetron, granisetron,<sup>11</sup> and dolasetron,<sup>12</sup> were developed to alleviate chemotherapy-associated nausea in people. These drugs are competitive blockers of the serotonin (5-HT<sub>3</sub>) receptors, which are found both peripherally (where they are responsible for intestinal

vagal afferent input) and centrally (in the chemoreceptor trigger zone [CRTZ] and medullary vomiting center [MVC]). Ondansetron has been used off label in veterinary medicine for over a decade and has been anecdotally reported to stop vomiting effectively in patients not responding to metoclopramide or promazine treatment (e.g., puppies with parvoviral enteritis).

Ondansetron is metabolized by the liver and is usually administered at a dosage of 0.1 to 1.0 mg/kg IV q8-12h. It has the unusual characteristic in people of inhibiting emesis at low and high dosages while enhancing emesis at intermediate dosages (the same has been shown for metoclopramide in humans). Dolasetron is metabolized into the active fraction (hydrodolasetron) by the ubiquitous carbonyl reductase. It is eliminated from the body by hepatic P-450 enzymes. It usually is administered to dogs and cats at a dosage of 0.6 to 1 mg/kg SC, IV, or PO q12-24h.

The antiemetic effects of these drugs linger after the drug disappears from the blood; therefore they need to be administered only q8-24h. They are ultimately eliminated in the urine and bile. There is a wide margin of safety in humans, and adverse effects seem to be rare in dogs and cats. Adverse effects in humans may include constipation, diarrhea, and somnolence. Prolongation of the QT interval is reported with dolasetron, but the importance of this in veterinary medicine is doubtful. These drugs have minimal interactions with other drugs. Ondansetron is reported to decrease the efficacy of tramadol.

It has been suggested that because there are many 5-HT<sub>3</sub> receptors in the GI tract, administering dolasetron orally might produce both a peripheral and a central antiemetic effect. Dolasetron is reported to have excellent bioavailability when given orally. Combining dolasetron with metoclopramide is often effective for chemotherapy-induced nausea that is resistant to other antiemetics.<sup>11</sup> Ondansetron is effective in preventing emesis caused by dexmedetomidine when the latter is used as a preanesthetic in cats, but it must be given at the same time as the dexmedetomidine.<sup>13</sup>

### Metoclopramide

Metoclopramide is a popular antiemetic. Its antidopaminergic activity and ability to block 5-HT<sub>3</sub> receptors make it a potent blocker of the CRTZ. However, cats are thought to have a paucity of dopamine receptors, which may explain why the drug seems less effective in that species. Typically given at 0.1 to 0.5 mg/kg IV, SC, or PO, metoclopramide also has gastric prokinetic activity that facilitates gastric

emptying and decreases gastroesophageal reflux, although markedly higher dosages may be required in order to achieve these actions. This combination of mechanisms should be very effective; however, clinical practice has shown that metoclopramide is often inadequate in patients with a strong stimulus to vomit (e.g., severe pancreatitis or renal failure). Its effectiveness can be enhanced if it is administered as a constant rate infusion. Intravenous dose recommendations vary and lower dosages are typically adequate for antiemetic actions (1 to 2 mg/kg q24h), but higher doses are necessary to promote gastroparesis and prevent gastroesophageal reflux (loading dose of 0.4 mg/kg IV, followed by 0.3 mg/kg/hr IV). The drug is sensitive to light, so the intravenous solution should be covered to prevent loss of efficacy. In people undergoing chemotherapy, metoclopramide's effectiveness may be enhanced by concurrent administration of low-dose dexamethasone, but this practice has not been critically evaluated in dogs or cats.

Metoclopramide is excreted by the kidneys, and care must be taken when using it in patients with substantially decreased glomerular filtration. If high blood levels occur due to renal dysfunction or overdosage, extrapyramidal signs (e.g., behavioral changes, apparent hallucinations) may occur. Such patients may display clinical signs similar to those seen with amphetamine intoxication (e.g., hyperactivity, frenzied behavior).

### Promazine Derivatives

Promazine derivatives are broad-spectrum, inexpensive, centrally acting antiemetics<sup>14-16</sup> that are effective against most causes of nausea except inner ear problems. They have antidopaminergic and antihistaminic effects that block the CRTZ and, at higher dosages, the MVC. These drugs also have anticholinergic, antispasmodic, and  $\alpha$ -adrenergic blocking effects. The promazine derivatives used most commonly as antiemetics in small animal veterinary medicine are chlorpromazine, prochlorperazine,<sup>17</sup> and acepromazine. Chlorpromazine typically is used at 0.1 to 0.5 mg/kg IV, SC, or intramuscularly (IM) q6-8h, and prochlorperazine is used at 0.1 to 0.5 mg/kg IV, IM, or SC q8-12h in dogs. The antiemetic effect of these drugs is typically evident at dosages lower than those causing sedation; however, varying degrees of vasodilation may occur, producing hypotension. Therefore caution is necessary in dehydrated or hypotensive patients; concurrent intravenous fluid therapy may be necessary.

Promazine drugs have been reported to increase central venous pressure and change the heart rate (bradycardia or tachycardia), and they possess antiarrhythmic qualities in the dog. These drugs were once believed to lower the seizure threshold, but this is now doubted.<sup>18</sup> The promazines are metabolized by the liver and can cause central nervous system signs in patients with substantial hepatic insufficiency, especially those with congenital portosystemic shunts. It has been suggested that prochlorperazine and perhaps other promazine derivatives not be used concurrently with metoclopramide because these drugs may potentiate extrapyramidal effects. The clinical importance of this is uncertain.

### Anticholinergic Agents

Aminopentamide (0.01 to 0.03 mg/kg IM, SC, or PO q8-12h) is an anticholinergic agent that has been used as an antiemetic in dogs. There are cholinergic receptors in the brain involved in the vomiting center and in the upper GI tract via the vagus nerve. The latter are muscarinic receptors. It is uncertain which receptors aminopentamide affects, but the drug appears to have relatively few of the typical adverse effects that other anticholinergic agents have on the GI tract (e.g., paralysis, distention). Clinically, aminopentamide appears to be less effective than metoclopramide and is certainly inferior to the 5-HT<sub>3</sub> and NK-1 antagonists. Other anticholinergic medications (e.g., atropine, propantheline, glycopyrrolate) tend to be less effective

or have more adverse effects (e.g., greater inhibition of GI motility). Aminopentamide should be used with caution in animals with glaucoma, cardiomyopathy, tachyarrhythmias, hypertension, myasthenia gravis, or gastroesophageal reflux.

### Other Drugs

Trimethobenzamide has antidopaminergic properties but appears to be a relatively weak antiemetic in dogs. Steroids, especially dexamethasone and methylprednisolone, have been used to prevent nausea in humans undergoing chemotherapy or general anesthesia.<sup>19</sup> There are limited data on the efficacy of steroids in cats,<sup>11,20</sup> but their common use and apparent effectiveness in vomiting cats diagnosed with inflammatory bowel disease at least raises the question of whether they have primary antiemetic actions. In humans, steroids are primarily used as an antiemetic in combination with other drugs such as metoclopramide.

Megestrol acetate<sup>21</sup> and gabapentin<sup>22</sup> have been used as adjuncts in people receiving highly emetogenic chemotherapy protocols in whom vomiting is not adequately controlled with other combination antiemetic therapy. Their use for this purpose has not been reported in veterinary medicine but might be considered in severe cases that are resistant to more traditional therapy. Propofol has a variety of nonanesthetic effects, including antiemesis. Its use for induction and/or maintenance of anesthesia has been associated with less vomiting in human patients.<sup>23</sup> Based on the apparent response of some patients with "limbic epilepsy" and sialomegaly to phenobarbital, there is some thought that phenobarbital might have antiemetic activity.<sup>24</sup> No studies clearly confirm or deny this possibility in dogs or cats. Finally, it may be worth noting that acupuncture has been reported to lessen postoperative nausea in people.<sup>25</sup>

### Peripherally Acting Antiemetics

Drugs that soothe inflamed mucosal lesions (e.g., bismuth subsalicylate or barium sulfate) or relieve dyspepsia (e.g., antacid drugs) can be used to alleviate vomiting (see Chapter 161). However, they are typically much less effective than the other drugs that have been discussed.

## PROKINETIC DRUGS

Prokinetic drugs promote the oral to aboral movement of intraluminal contents. In veterinary medicine, they are primarily used to promote gastric emptying and colonic emptying.

### 5-HT<sub>4</sub> Serotonergic Agonists

5-HT<sub>4</sub> serotonergic agonists<sup>26</sup> are the most effective class of prokinetic drugs in veterinary medicine. Cisapride is no longer available for use in people but is available to veterinarians from compounding pharmacies. It has been the primary drug of this class used in veterinary medicine for treating gastroesophageal reflux, poor gastric emptying, and chronic constipation. The drug is well absorbed after oral administration and is primarily eliminated by first-pass metabolism in the liver (hence, elimination may be delayed in animals with severe hepatic insufficiency). Cisapride has approximately 30% bioavailability after oral administration in cats.

Cisapride (0.5 to 1.0 mg/kg PO q8-24h in dogs; 2.5 to 5 mg/cat q8-12h PO in cats) enhances gastric emptying while simultaneously increasing gastroesophageal sphincter pressure.<sup>27,28</sup> It is more effective than metoclopramide in treating patients with gastroesophageal reflux and delayed gastric emptying. Although frequently used to try to enhance esophageal motility in patients with megaesophagus, it is ineffective on striated muscle. The fact that cisapride increases gastroesophageal sphincter tone may make regurgitation worse in such patients (unless gastroesophageal reflux is a major contributing

factor to the patient's regurgitation). Cisapride has been effective in treating idiopathic constipation in cats with mild to moderate disease; however, severe disease responds poorly. Finally, cisapride increases small intestinal motility; however, this effect has not found a major application in small animal medicine, probably because many critically ill postoperative patients cannot tolerate oral medications. Cisapride has been responsible for several human deaths due to its effect on cardiac conduction; however, death has not been reported in dogs or cats. Other adverse effects seem rare.

Mosapride (0.25 to 1 mg/kg PO q12h) has recently become available in Japan.<sup>29</sup> It is somewhat similar to cisapride except that it has minimal effects on colonic motility. It can be administered intravenously, which would be advantageous in many critically ill patients. Tegaserod (0.05 to 0.1 mg/kg PO q12h) and prucalopride (0.01 to 0.2 mg/kg PO q12h) are similar drugs currently available in Europe. Tegaserod primarily enhances colonic motility, whereas prucalopride can increase both gastric and colonic motility. There is currently minimal clinical experience with these drugs in veterinary medicine.

### Cholinomimetic Drugs

Bethanechol, ranitidine, and nizatidine are the primary examples of the cholinomimetic class of prokinetic drugs. Ranitidine and nizatidine inhibit acetylcholinesterase, whereas bethanechol is a true cholinomimetic drug that binds to muscarinic receptors. Bethanechol (5 to 15 mg/dog PO q8-12h) affects motility throughout the GI tract, whereas ranitidine (1 to 2 mg/kg PO or IV q12h) and nizatidine (2.5 to 5 mg/kg PO or IV q12h) seem more effective for promoting gastric emptying than colonic motility.

### Motilin Receptor Agonists

Erythromycin (0.5 to 1 mg/kg PO or IV q8h) stimulates motilin receptors and has been used to promote GI motility in a variety of clinical situations in dogs. It increases lower esophageal sphincter pressure as well as small and large bowel peristalsis.<sup>30</sup> There is some concern that tolerance will develop with sustained use of the drug, rendering it less effective.

### Metoclopramide

Metoclopramide is probably the most commonly used prokinetic in veterinary medicine. It was discussed in detail earlier in the section on antiemetics. Metoclopramide's method of action is somewhat debated and appears to involve more than just dopamine receptors; it may increase the sensitivity of the smooth muscle in the small intestine to the effects of acetylcholine. Its primary use in veterinary medicine is as a moderately effective gastric prokinetic. Cisapride is a more effective prokinetic, but metoclopramide can be administered by constant IV infusion, which is advantageous in some patients. Rather high doses are required to cause prokinesis and reduce gastroesophageal reflux: 0.4 mg/kg IV as a loading dose and then 0.3 mg/kg/hr is recommended for this purpose (note this is higher than typically recommended to prevent nausea: 1 to 2 mg/kg/24 h). Intermittent dosing is also possible (0.2 to 0.5 mg/kg PO, SC, or IM q6-8h).

### Misoprostol

Misoprostol, a prostaglandin E analog, is discussed in Chapter 161. It appears to enhance colonic motility and has been used in patients with nonresponsive constipation.

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