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DIFFICULT VOMITING DISORDERS: THERAPY
Robert J. Washabau, VMD, PhD, Dipl. ACVIM
Professor of Medicine and Department Chair
Department of Veterinary Clinical Sciences
College of Veterinary Medicine, 1352 Boyd Avenue
University of Minnesota, St. Paul, Minnesota USA 55108
washabau@umn.edu

Anti-Emetic Therapy
Physiology of Emesis: The essential components of the emetic reflex are visceral receptors, vagal and sympathetic afferent neurons, a chemoreceptor trigger zone (CRTZ) located within the area postrema that is sensitive to blood-borne substances, and an emetic center within the reticular formation of the medulla oblongata receiving input from vagal and sympathetic neurons, CRTZ, vestibular apparatus, and cerebral cortex. An important concept dating from the early 1950’s is that vomiting occurs either through activation of the CRTZ by blood-borne substances (humoral pathway), or through activation of the emetic center by vago-sympathetic, CRTZ, vestibular, or cerebrocortical neurons (neural pathway). Thus, activation of the CRTZ by a variety of humoral emetogenic substances (e.g. uremic toxins, cardiac glycosides, and apomorphine) is abolished by surgical ablation of the area postrema, but not by vagotomy or sympathectomy. In contrast, neural activation of the emetic center by gastric disease (e.g. gastritis) is abolished by vagotomy or sympathectomy, but not by ablation of the area postrema. Many experimental data have been readily explained by this two-component model. Despite contemporary reexamination, there is still good agreement on the two general patterns of emesis, one humoral and one neural. Current therapy is largely based on these assumptions.

Many of the spontaneous vomiting disorders of cats and dogs, particularly those of the primary gastrointestinal tract, are believed to result from activation of the neural pathway. Vomiting associated with primary gastrointestinal tract disease (e.g., inflammation, infection, malignancy, toxicity) results from activation of visceral receptors, afferent neurons, and the emetic center. Efferent information transmitted back to the gastrointestinal tract stimulates the motor correlates of vomiting (retrograde duodenal and gastric contractions, relaxation of the caudal esophageal sphincter, gastroesophageal reflux, opening of the proximal esophageal sphincter, and evacuation of gastrointestinal contents). A neural pathway can also be involved in vomiting associated with motion sickness. Motion within the semicircular canals is transduced to vestibulo-cochlear neurons that ultimately synapse in the CRTZ or emetic center. Cats and dogs experience motion sickness, although the neuroanatomy and pharmacology appear to be somewhat different between the two species. Histaminergic neurons and the CRTZ are involved in motion sickness in the dog, whereas neither are involved in motion sickness in the cat. A neural pathway involving cerebrocortical neurons may be involved in vomiting disorders associated with anxiety or anticipation, but these are probably more important in human beings.

The essential component of the humoral pathway is the chemoreceptor trigger zone (CRTZ) located within the area postrema that is sensitive to blood-borne substances. Receptors within the CRTZ may be activated by many endogenous (e.g., uremic-, hepatencephalopathic-, or endotoxins) and exogenous (e.g., digitalis glycosides, apomorphine) blood-borne substances. Most pharmacological approaches to anti-emetic therapy have been based on neurotransmitter-receptor interactions at the CRTZ, emphasizing the humoral pathway of emesis. The neural pathway has received much less emphasis even though it is a much more important pathway.

Pharmacology of Emesis: Vomiting is initiated through activation of one or more neurons in the CRTZ or emetic center.

Anti-Emetic Classifications
A number of anti-emetic drugs have been formulated based on the aforementioned
neurotransmitter-receptor systems. These drugs may be classified as: α₂ adrenergic antagonists, D₂ dopaminergic antagonists, H₁ and H₂ histaminergic antagonists, M₁ muscarinic cholinergic antagonists, ENK enkephalinergic mixed agonists/antagonists, and 5-HT₃ serotonergic antagonists. The 5-HT₄ serotonergic agonists are not direct anti-emetic drugs *per se*, but may have an indirect anti-emetic effect by promoting gastrointestinal motility.

**Physiology of Vomiting**

<table>
<thead>
<tr>
<th>Cerebral Cortex</th>
<th>Chemoreceptor Trigger Zone</th>
<th>Emetic Center</th>
<th>Gastrointestinal Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety, Anticipation</td>
<td>Apomorphine Uremic Toxins Hepatotoxins Endotoxins Cardiac Glycosides</td>
<td>Motion</td>
<td>Dog</td>
</tr>
</tbody>
</table>

**Pharmacology of Vomiting**

<table>
<thead>
<tr>
<th>Cerebral Cortex</th>
<th>Chemoreceptor Trigger Zone</th>
<th>Oculo Vestibular System</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENK, M₁, N₅, H₁</td>
<td>N₅, NK₁, 5-HT₁₅, RFN</td>
<td>DMV, DM, M₂, NMDA</td>
</tr>
</tbody>
</table>

**Rational Use of Anti-Emetic Agents in the Diagnosed Patient:**

1. **Motion Sickness** - Motion sickness is believed to arise from stimulation of labyrinthine structures in the inner ear. The chemoreceptor trigger zone and H₁ histaminergic receptors are involved in this pathway in the dog, but apparently they are less importantly involved in the cat. Motion sickness in the dog can be treated with histamine H₁ antagonists or neurokinin NK₁ antagonists. Motion sickness in the cat is probably best treated with an α-adrenergic antagonist, e.g., chlorpromazine, instead of a pure H₁ histaminergic antagonist.

2. **Uremia** - Vomiting associated with uremia has both central and peripheral components. The central component of uremic vomiting is associated with activation of CRTZ D₂ dopaminergic receptors by circulating uremic toxins. The central component is best treated with a D₂ dopaminergic antagonist, e.g., metoclopramide. The peripheral component of uremic vomiting is associated with uremic gastritis and is best treated with acid secretory inhibitors (e.g. ranitidine 1–2 mg/kg q 12 h IV; omeprazole 0.7 mg/kg q 12 h PO) to diminish gastric parietal cell H⁺ ion secretion, and with chemical barrier diffusion barriers (e.g., sucralfate 0.25–0.5 grams q 8–12 h PO) to provide a barrier to H⁺ ion back diffusion.

3. **Cancer Chemotherapy** - Certain cancer chemotherapies (e.g. cisplatinum, cyclophosphamide) are associated with a high incidence of vomiting. Chemotherapy-induced emesis is mediated by 5-HT₃ serotonergic receptors, either in the CRTZ or in vagal afferent neurons. Antagonists of the 5-HT₃ serotonergic receptor (e.g. ondansetron, granisetron, tropisetron) abolish the vomiting associated with cisplatinum administration in the cat. Although metoclopramide has some 5-HT₃ antagonistic properties, it has not proved very useful in chemotherapy-induced emesis.

4. **Delayed Gastric Emptying Orders** - Disorders of delayed gastric emptying (e.g. gastritis, metabolic derangements, post-operative gastric dilatation and volvulus) may cause an animal to experience nausea and vomiting. Treatment of these disorders with cholinomimetic agents has been associated with untoward side effects. Contemporary therapy consists of 5-HT₃ serotonergic agonists (e.g., cisapride, metoclopramide), cholinesterase inhibitors (e.g., ranitidine or nizatidine),
and motilin agonists (e.g., low dose erythromycin – dog only). Cisapride is superior to metoclopramide in the treatment of gastric emptying disorders in cats and dogs. Ranitidine and nizatidine inhibit acetylcholinesterase activity in addition to their effects on histamine H₂ receptors in the gastric mucosa. Both drugs (ranitidine and nizatidine) stimulate gastric emptying in the cat and dog. Erythromycin stimulates phase III migrating myoelectric complex (MMC) activity in the dog, but the migrating spike complex (MSC) activity of the cat is under different physiologic regulation.

**Newer Anti-Emetic Therapy - Neurokinin-1 Receptor Antagonists**

<table>
<thead>
<tr>
<th>Examples</th>
<th>Tradename</th>
<th>Pharma</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maropitant</td>
<td>Cerenia</td>
<td>Pfizer</td>
<td>1.0 mg kg SQ SID x 5</td>
</tr>
<tr>
<td>Maropitant</td>
<td>Cerenia</td>
<td>Pfizer</td>
<td>2.0 mg kg PO SID x 5</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>Emend</td>
<td>Merck</td>
<td></td>
</tr>
<tr>
<td>Lanepitant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dapitant</td>
<td></td>
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</table>

**Anti-Emetic Strategies for the UnDiagnosed Patient**

1. NK1 Neurokinin Antagonists
2. 5-HT3 Serotonergic Antagonists
3. α₂-Adrenergic Antagonists
4. D2 Dopaminergic Antagonists

**Irrational Usage of Anti-Emetic Agents**

- Systemic hypotension → Phenothiazines
- Pre-existing epilepsy → Phenothiazines
- G.I. obstruction → Prokinetic agents
- G.I. infection → All Classes
- G.I. toxicity → All Classes
- Prolonged usage → All Classes

**References:**

- **FDA Application** – January 29, 2007 – NADA 141-262 & 141-263 - Maropitant 1.0 mg/kg SQ effective against emesis due to syrup of ipecac, apomorphine, and cisplatin.